LIMBIC AND PARALIMBIC CORTEX DYSFUNCTION DURING SALIENT STIMULUS PROCESSING IN SCHIZOPHRENIA

by

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Abstract

Schizophrenia is characterised by difficulties in processing and responding to incoming information. Accumulating evidence suggests that the core problem may represent a difficulty in focusing limited processing resources on salient exogenous stimuli so that an appropriate response to the stimuli can be performed. The present thesis comprises four event-related functional magnetic resonance imaging experiments that are designed to elucidate the neural sites that support the processing of salient exogenous stimuli in healthy individuals, and further, to characterise functional abnormality present during salient stimulus processing by patients with schizophrenia. Experiment One characterises the neural response elicited in healthy participants and patients during the processing of infrequent target stimuli that prescribe a subsequent motor response (Part A) and during the processing of infrequent novel stimuli that automatically reorient processing resources away from the ongoing target detection task (Part B). Experiment Two elucidates the supramodal network of brain areas that supports the processing of frequent target stimuli presented in the auditory and visual modalities in healthy participants. The auditory version of that task is subsequently employed in Experiment Three to compare the healthy participant and patient response during frequent target stimulus processing. Finally, Experiment Four examines the brain response evoked in healthy participants and patients when salient stimuli are processed incorrectly and an error ensues.

The results demonstrate that, in healthy participants, a distributed corticolimbic network of brain areas is active during the processing of salient exogenous events. This network incorporates limbic cortex (i.e., amygdala-hippocampus), paralimbic cortex in the cingulate gyrus and frontal operculum, frontoparietal association cortex, and subcortical structures in the basal ganglia, thalamus, midbrain, and cerebellum. The network is particularly engaged during the processing of stimuli that signal the need to perform an overt behavioural response.

Despite relatively preserved behavioural performance on all tasks, patients with schizophrenia were characterised by functional abnormality throughout the corticolimbic network during both accurate and inaccurate (i.e., erroneous) salient stimulus processing. Particular abnormality was apparent in limbic and paralimbic cortex. Dysfunction within the corticolimbic network during information processing in schizophrenia suggests that there may be insufficient biasing of limited resources to processing salient features of the environment.

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Preface

While the ideas presented in this thesis represent the work of the author (developed in discussion with my Ph.D. supervisor, Professor Peter Liddle), the body of research comprising the thesis was conducted in collaboration with many others whose specific contributions are acknowledged following.

Supervision of the research projects was provided by Professor Peter Liddle and Assistant Professor Elton Ngan. Assistance with patient recruitment was provided by Drs. Adrianna Mendrek, David Irwin, and Elton Ngan, Professor Peter Liddle, Stephanie Caissie, and Tara Cairo. Cameron Anderson, Alan Bates, Izabella Patyk, Lisa Vandenbeld, Athena Vouloumanos, and Dr. Kent Kiehl assisted with healthy participant recruitment. The symptom assessment interviews for patients with schizophrenia were conducted by Elton Ngan and Peter Liddle. Although the author conducted similar symptom assessment interviews as part of her Ph.D. studies, that data does not form part of this thesis.

The novelty oddball paradigm employed in Experiment One was previously developed in research on which the author was a co-investigator (see Kiehl et al., 2001a, 2001b). Similarly, the task used in Experiment Four represented a minor modification to a paradigm designed by Peter Liddle and employed in event-related potential research from our laboratory on which the author was a co-investigator (see Bates et al., 2002). All other experimental design and task programming were the primary responsibility of the author.

Experiment Four (appearing in Chapter 8) was published, in part, as a manuscript appearing in the journal *Brain: A journal of neurology* (citation in full: Laurens KR, Ngan ETC, Bates AT, Kiehl KA, Liddle PF [2003] Rostral anterior cingulate cortex dysfunction during error processing in schizophrenia. Brain 126: 610-622.).

All functional imaging data presented in the thesis were analysed using Statistical Parametric Mapping 99 (SPM99, Wellcome Department of Cognitive Neurology, London, UK. http://www.fil.ion.ucl.ac.uk/spm/). All p values in SPM99 are specified to the third decimal place only. Thus, any p value provided as 0.000 in the text or tables signifies a p value that was smaller than at least $5.0e^{-4}$ (i.e., 0.0005).

Several figures within the thesis are reprinted from published manuscripts and acknowledged here in the format requested by the publishers. Figure 1 is reprinted from Electroencephalography and Clinical Neurophysiology, 106; Halgren E, Marinkovic K, Chauvel P, Generators of the late cognitive potentials in auditory and visual oddball tasks, pp. 156-164, Copyright (1998), with permission from Elsevier. Figure 3 is reprinted by permission from Nature Reviews Neuroscience (Corbetta M, Shulman GL, Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201-215),.copyright (2002) Macmillan Magazines Ltd. Figure 4 is reprinted from Trends in Neurosciences, 23; Brown RG, Pluck G, Negative symptoms: The 'pathology' of motivation and goal-directed behaviour, pp. 412-417, Copyright (2000), with permission from Elsevier. Figure 5 is reprinted from Trends in Cognitive Sciences, 4; Bush G, Luu P, Posner MI, Cognitive and emotional influences in anterior cingulate cortex, pp. 215-222, Copyright (2000), with permission from Elsevier. That figure was adapted from a figure published previously in the Journal of Comparative Neurology, 359; Human cingulate cortex: Surface features, flat maps, and cytoarchitecture, by Vogt BA, Nimchinsky EA, Vogt LJ, Hof PR. Copyright ©1995 Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.. Reprinted by permission of John Wiley & Sons, Inc. Figure 17 is reprinted from Neuroscience and Biobehavioral Reviews, 26; Cardinal RN, Parkinson JA, Hall J, Everitt BJ, Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex, 321-352, (2002) with permission from Elsevier.

Acknowledgements and Dedication

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This thesis is dedicated to my parents, who supported me throughout its inception, development, and realisation.

Chapter 1.0: Introduction

Schizophrenia is a disorder characterised by disruption to multiple facets of mental function. The disturbances span the domains of perception, cognition, language, motivation, emotion, and motor activity, and give rise to a substantial heterogeneity of symptom profile among patients with schizophrenia. Particularly striking abnormalities are observed in the higher mental functions that draw upon multiple affected domains. For example, marked dysfunction is apparent during the selection, initiation, and monitoring of mental activity and behaviour.

A consequence of the symptom heterogeneity among patients has been difficulty in defining the cardinal pathophysiology of schizophrenia. A sizeable body of research has attempted to address the problem by relating particular core symptoms to abnormality in a specific brain region. This research has revealed subtle but diffuse structural abnormalities and functional disturbance in distributed brain systems (e.g., see reviews by Harrison, 1999; Kasai et al., 2002; Liddle and Pantelis, 2003), suggesting that the cardinal pathophysiology in schizophrenia is not a focal abnormality, but rather, a disruption of the connections between neurons that results in an impaired co-ordination of neural activity at spatially remote sites (Friston and Frith, 1995; Bullmore et al., 1998).

Consequently, the last decade has brought a shift towards the examination of integrated brain functions and a search for disruption within distributed neural circuits that support parallel, distributed processing. Concurrently, a number of integrative models have been proposed that characterise the illness in terms of a fundamental abnormality in the co-ordinated processing of information. These models suggest that this core cognitive abnormality, rather than the symptoms, be used to define the phenotype of the illness (Andreasen et al., 1999; Fuller et al., 2003).

1.1 Models proposing information processing disturbances as the core abnormality in schizophrenia

Braff (1993) proposes information processing and attentional dysfunctions as the central feature of schizophrenia, highlighting patients' difficulties in focusing on relevant cues and in avoiding distraction by irrelevant stimuli. Drawing on the results of studies using a variety of experimental paradigms (e.g., prepulse inhibition and P50 gating, event-related potential [ERP] recordings, and reaction time studies), Braff highlights patients' impaired ability to process exogenous information rapidly and efficiently, particularly in the context of distractions and high processing loads. Information processing and attentional abnormalities in schizophrenia are apparent not only on measures reflecting central nervous system function, but also on indices of autonomic system function such as skin conductance and finger pulse volume orienting responses (see Bernstein, 1987 for a review).

Andreasen et al. (1998) describe the central abnormality in schizophrenia as 'cognitive dysmetria', which refers to a disruption in the fluid co-ordination of mental activity. This incorporates disturbance in receiving and processing incoming information, in integrating that information with information that has been previously processed and stored, and in acting to produce a response to that information. The disruption manifests itself in disturbed cognition, emotion/motivation, and behaviour. Andreasen and colleagues posit cortical-subcortical networks as the anatomic substrate for cognitive dysmetria, emphasising particularly a disrupted connectivity between the cerebellum, thalamus, and prefrontal cortex (Andreasen et al., 1996, 1998).

1.2 Rationale for the thesis

Effective cognition and behaviour is predicated in large part on the preferential allocation of limited processing resources to salient features of the environment. Salient events are those that

capture our attention and enter conscious awareness, sometimes at the expense of ongoing thoughts and behaviour. They may be dictated by internal goals (top-down aspects) and/or stimulus-driven (bottom-up) characteristics, and thus include stimuli that have potential relevance for behaviour (i.e., task-relevant or behaviourally-salient events), unexpected or rare events, novel events not previously experienced, intense or potentially dangerous stimuli, and/or stimuli that are motivationally- or emotionally-important. Expanding on the two models described above (Braff et al., 1993; Andreasen et al., 1998), we suggest a revised hypothesis that the fundamental abnormality in schizophrenia may be a difficulty in focusing processing resources on salient stimuli for the purposes of generating an appropriate response to the stimuli.

To date, much of the evidence that suggests the presence of functional abnormality during salient stimulus processing in schizophrenia has derived from ERP research, which provides real-time, millisecond resolution of normal or pathological brain activity elicited by the salient stimulus events. However, one of the main limitations of this technique is a difficulty in localising the neural sources of the recorded brain electrical activity. While positron emission tomography (PET) and single photon emission tomography (SPECT) techniques each provide a means of localising activity within the brain, their temporal resolution does not permit an examination of the activity elicited by individual events. Recent developments in event-related functional magnetic resonance imaging (fMRI) make it possible to characterise the haemodynamic response to distinct stimulus events with a spatial resolution in the order of millimetres (see Josephs et al. 1997; Friston et al., 1998; Buckner and Logan, 2001; Donaldson and Buckner, 2001).

This thesis reports a body of research that aims to characterise the distributed neural circuit(s) that supports the processing of a variety of salient stimuli in healthy participants and to identify functional abnormality within that network during salient stimulus processing in patients with schizophrenia. Each of the studies employs event-related fMRI techniques to localise the

network of brain sites that become active during salient stimulus processing. The first three experiments focus on elucidating the neural response associated with processing salient exogenous stimuli and determining an appropriate response to the stimuli, whereas the final experiment examines the brain response evoked when salient stimuli are processed incorrectly. Due to the risk that any functional abnormality in schizophrenia might arise as a consequence of poor task performance rather than as a consequence of the illness per se (Callicott, 2003), all the paradigms employed were simple cognitive tasks on which patients with schizophrenia and neurologically healthy individuals were expected to show comparable behavioural performance.

1.3 ERP evidence for disrupted information processing in schizophrenia: Target-elicited P3 abnormalities

By far the majority of ERP studies of information processing in schizophrenia have presented stimuli in the auditory modality, largely because it is one of the most affected in schizophrenia (as evidenced by the primacy of auditory hallucinations and pathology in speech/language functions). One paradigm commonly-used to assess the brain abnormalities present in patients with schizophrenia during the allocation of processing resources to salient exogenous stimuli has been the auditory 'oddball' task. During active oddball detection, an infrequent, deviant target stimulus that signals the need for a behavioural or cognitive (e.g., counting) response is presented within a train of homogenous, nontarget background stimuli. In healthy individuals, the salient target stimulus is associated with a large (ca. 5-20 μV) positive P3 (or P300) component waveform that peaks within 250-500 ms following the onset of the task-relevant target tone. Peak latency, which is influenced by variables such as task conditions and subject age, has a mode of about 300 ms when elicited with auditory stimuli in healthy young adults. Explanations of the P3 centre around the basic information processing mechanisms of attentional allocation and immediate memory (Polich and Kok, 1995). P3 amplitude is proportional to the

amount of attentional resources devoted to a given task (Wickens et al., 1983) and is thought to reflect the degree or quality of processing as incoming information is incorporated into memory representations of the stimulus and the context in which the stimulus occurs. The latency of the P3 potential indexes stimulus classification speed and is independent of behavioural reaction time, providing an indication of how rapidly subjects can allocate and maintain processing resources (Polich and Herbst, 2000).

Research employing the paradigm during scalp ERP recordings of patients with schizophrenia has described a relative reduction in the amplitude of the P3 elicited by the task-relevant target tone. After 30 years of research, this auditory-elicited P3 amplitude reduction remains one of the most reliably observed neurophysiological abnormalities in schizophrenia, with less consistent evidence emerging for prolonged P3 latencies in patients (see review by Ford, 1999). The amplitude reduction remains even when patients' performance on the task of detecting the target tones is comparable to that observed in healthy control participants (Ford et al., 1994b, Salisbury et al., 1994a), and unlike in healthy participants, P3 amplitude does not increase in oddball task variants that improve reaction times by increasing target discriminability (Salisbury et al., 1994a).

Accumulating evidence suggests that the auditory P3 amplitude reduction is both a trait and state marker of schizophrenia. The P3 amplitude reduction has been observed not only in chronic medicated patients (e.g., Pritchard, 1986; McCarley et al., 1993; Ford et al., 1994a) and patients withdrawn from medication (Faux et al., 1993; Ford et al., 1994b), but also in first-episode patients (Hirayasu et al., 1998; Salisbury et al., 1998; Demiralp et al., 2002), which suggests that the abnormality is already present early in the illness and prior to the administration of neuroleptic medication. Although atypical antipsychotic treatment may significantly remediate P3 amplitude in patients with schizophrenia (Umbricht et al., 1998), it does not normalise the response to healthy levels. Amplitude improvement is also seen in patients whose

symptoms have improved (Turetsky et al., 1998a), yet even in remitted patients, a reduction in P3 amplitude relative to healthy control participants remains (Rao et al., 1995). Longitudinal evidence suggests that P3 amplitude tracks fluctuating clinical state for both positive and negative symptoms (reflecting an excess/distortion and a diminution/loss of normal function respectively). P3 amplitude decreases with symptom exacerbations and increases with recovery, however, the reduction is present even when patients are least symptomatic (Mathalon et al., 2000).

The P3 amplitude reduction is not specific to schizophrenia, with reductions reported in a variety of neurological and psychiatric populations (see review by Polich and Herbst, 2000). However, the topography and/or the persistence of the abnormality following pharmacological intervention in schizophrenia may distinguish it from the reductions observed in other psychiatric conditions. For example, there is evidence that the P3 amplitude reduction is greater over left temporal lobe sites than sites in the right temporal lobe in patients with schizophrenia (Faux et al., 1993; McCarley et al., 1993) but not bipolar patients (Salisbury et al, 1999). This topographic asymmetry is also present in first-episode psychotic patients with schizophrenia but not first-episode patients with manic psychosis (Salisbury et al., 1998). Whereas the P3 reduction observed in schizophrenia is only partially remediated following treatment with atypical antipsychotic medication (Umbricht et al., 1998), normalisation of the P3 has been observed following antidepressant treatment for patients with major depression (Blackwood et al., 1987; Yanai et al., 1997). This evidence implies that these disorders may be characterised by differential sites or networks of functional abnormality during target stimulus processing.

1.4 Supramodal and modality-specific deficits in the target-elicited P3 in schizophrenia

Considerable neurophysiological and neuroanatomical evidence suggests that multiple intracranial sources contribute to the generation or modulation of the auditory P3 (McCarthy et

al., 1997; Menon et al., 1997; Halgren et al., 1998; Knight and Scabini, 1998; Potts et al., 1998; Kiehl et al., 2001a. 2001b). By implication, the P3 reduction observed during target stimulus processing in schizophrenia might reflect either focal or diffuse abnormality. Studies in healthy participants demonstrate that infrequent target stimuli elicit a P3 response that is maximal over parietal scalp sites across the auditory, visual, somatosensory, and olfactory sensory systems, suggesting that there are supramodal generators of the target-elicited P3 response. However, topographic ERP and magnetoencephalographic studies of healthy participants also reveal modality-specific contributions to the target-P3 (Knight and Scabini, 1998). The P3 amplitude reduction observed in patients with schizophrenia during auditory target detection has been less consistently replicated in the visual modality (Ford, 1999). In studies affording a direct comparison, the auditory P3 amplitude reduction is typically greater or observed more consistently than the visual P3 reduction (see Grillon et al., 1991a; Egan et al., 1994, Ford et al., 1994b, 2001; Pfefferbaum et al., 1989). These results are consistent with functional disturbance within both supramodal and auditory-specific modulators of the P3 response to auditory oddball stimuli in schizophrenia.

1.5 Differentially-affected subprocesses contribute to the auditory P3 abnormality in schizophrenia

An extensive ERP literature in healthy participants and neurological patients suggests that the P3 component elicited by target processing during the oddball task is not a unitary brain potential arising from a discrete brain area or cognitive process. Rather, activation of multiple brain regions may be dissociated depending on the degree of voluntary and involuntary attention allocated to stimulus processing (Knight and Scabini, 1998). Voluntary detection of, and response to, the task-relevant target stimulus described above typically elicits a P3 that is maximal over parietal scalp, termed 'P3b'. A smaller, frontocentrally distributed 'P3a'

component that peaks about 60-80 ms earlier than the P3b in all sensory modalities is generally also elicited by the target stimuli. The P3a component is considered an index of involuntary orienting to the infrequent stimulus for the purposes of conscious stimulus evaluation. Whereas the major determinant of the P3b is the task-relevance of the deviant target stimulus, the P3a is predominantly influenced by the degree of difference between the physical characteristics of the deviant stimulus and the standard (nontarget) tones (Gaeta et al., 2003).

The P3a is sometimes observed more readily (i.e., without being overwhelmed by the larger P3b component) by having participants listen passively to the oddball task, without any requirement for a behavioural or cognitive response to the oddball stimulus. Ford and colleagues (1999, Mathalon et al., 2000) thus distinguish these processes as the 'effortful P3' (P3b) and 'automatic P3' (P3a) respectively, although both subcomponents contribute to the P3 elicited during active oddball target detection. Several groups have differentiated these subcomponents during auditory oddball detection, and report both P3b and P3a amplitude reductions in patients with schizophrenia (Turetsky et al., 1998b; Mathalon et al., 2000).

The P3a component is strongly elicited within an auditory oddball variant that, in addition to the infrequent target and standard nontarget stimuli, incorporates an infrequent distracter stimulus or non-repeating novel stimuli that require no behavioural response (Courchesne et al., 1975). The novel/distracter stimuli evoke a larger P3a response than do target stimuli, and provide a means of examining the brain's response during the involuntary capture of attention away from the ongoing performance of the central task of detecting and responding to the task-relevant target stimulus (Polich, 1998; Friedman et al., 2001; Debener et al., 2002). Few studies have so far made use of the novelty oddball variant to examine whether the P3b and P3a are differentially affected in schizophrenia. Those few studies report a reduction in the amplitude of the P3a elicited by the novel stimuli in patients with schizophrenia relative to healthy participants (Grillon et al., 1990, 1991a; Merrin and Floyd, 1994), suggesting that patients with

schizophrenia allocate a reduced amount of processing resources to both target and novel stimuli (i.e., to salient exogenous stimuli in general).

However, the three studies diverge in terms of whether a greater amplitude reduction in the patient group was observed for the P3 response elicited by the novel or the target stimuli, perhaps related to slight task variations or patient sample differences between the studies (e.g., the sample of patients recruited into the Merrin and Floyd [1994] study were medication free for at least two weeks prior to the study, whereas Grillon et al. [1990,1991a] used a medicated sample of patients). Merrin and Floyd (1994) report that, compared to healthy control participants, the P3 elicited by novel stimuli was further reduced relative to target responses in patients with schizophrenia. Their result suggests that particular dysfunction is apparent in the involuntary orienting of attention to salient stimuli. By comparison, in two studies based on the same sample of patients, Grillon et al. (1990, 1991a) reported a significantly greater reduction in the amplitude of the P3b elicited by target stimuli than the P3a elicited by novel stimuli, suggesting that while both component processes are affected in schizophrenia, particular abnormality is apparent during the processing of the task relevant target stimuli. In healthy participants, the P3b amplitudes elicited by the target stimuli across the midline electrode sites F_Z, C_Z, and P_Z were smaller than the P3a amplitude elicited by novel stimuli by 38.2%, 35.2%, and 12.2% respectively (average 28.5%), whereas in patents with schizophrenia the differences across the three midline sites were 58.7%, 62.6%, and 38.0% respectively (average 52.8%; Grillon et al., 1990). Thus, while both the P3b and P3a amplitudes were attenuated in patients relative to healthy participants, the increased difference between the P3a and P3b amplitudes in schizophrenia relative to healthy participants was interpreted as reflecting an abnormal apportioning of processing resources to the task-irrelevant versus task-relevant stimuli. That is, patients experienced relatively increased distractibility by task-irrelevant novel stimuli, suggesting an inability to filter or 'gate' irrelevant information (Grillon et al., 1990).

Such changes to the P3a component imply that a 'late' gating abnormality may be present when attention is oriented to salient stimuli for the purposes of conscious evaluation. Earlier gating deficits are reflected in disturbance of the 'pre-attentive' ERP component, the P50 (Adler et al., 1982; Freedman et al., 1983), as well as in a diminished prepulse inhibition of the startle response in patients with schizophrenia (Grillon et al., 1992; Braff et al., 2001). In the P50 gating paradigm, two identical rapid-click stimuli separated by 500 ms are associated with a large P50 response to the first click and an attenuated P50 response to the second click in healthy individuals, due to the inhibitory effect of the first stimulus. In patients with schizophrenia, this normal inhibitory process is lost (Adler et al., 1982; Freedman et al., 1983), theoretically leaving patients susceptible to sensory overload and cognitive fragmentation as patients become swamped with stimuli seeking access to higher order cognitive processing resources (McGhie and Chapman, 1961).

1.6 Other ERP component abnormalities indexing disrupted information processing in schizophrenia

Although the P3 component has been the focus of ERP research examining information processing abnormalities in schizophrenia over the last three decades, abnormalities in other stimulus-locked ERP components have been demonstrated during effortful and/or passive performance of the auditory oddball paradigm. Due to the temporal characteristics of the haemodynamic response, these components cannot be distinguished from a P3 response during event-related fMRI, and may thus contribute to any abnormalities observed in schizophrenia during imaging of the auditory oddball paradigm.

In general, early sensory and middle latency responses (i.e., < 50 ms post-stimulus) appear unaffected in schizophrenia (Grillon et al., 1991b; Braff, 1993), whereas disturbed amplitudes and/or latencies have been reported in a variety of later components that precede the P3 potential

and index early-stage information processing, including the N1-P2 complex, N2b and mismatch negativity (MMN) components. Unlike the P3, these components appear to be evoked in a largely automatic, preattentive, and preconscious fashion in healthy participants, (although there is evidence that they may be modulated by selective attention; Michie, 2001; Salisbury et al., 2003).

The N1 and P2. The N1 is a negative brain potential arising approximately 80-100 ms after a sensory stimulus. Although they are functionally independent, the N1 is elicited as part of a complex (N1-P2) in which the N1 is followed by a positive peak (P2) at approximately 175-200 ms (Muller-Gass and Campbell, 2002). These components have been termed 'exogenous' components because their amplitude, latency, and topography seem to depend on the physical properties of sensory stimuli such as their modality and intensity. The exogenous components are distinguished (on a continuum) from 'endogenous' components such as the P3, which depend on the individual's interaction with the stimulus and which vary as a function of factors such as task-relevance, attention, and the processing requirements of the stimulus (Näätänen, 1992; Coles and Rugg, 1995).

The auditory-evoked N1 potential has been localised to bilateral sources in the auditory cortex (at the supratemporal plane) and in the auditory association region of the superior temporal cortex, as well as a possible frontal source reflecting motor-premotor cortex and/or supplementary motor area (SMA)/anterior cingulate cortex contributions (Giard et al., 1994; Muller-Gass and Campbell, 2002). In patients with schizophrenia, N1 and P2 disturbances (generally a decreased N1 amplitude and increased P2 latency) have been reported in research employing the auditory oddball paradigm (Brown et al., 2000, 2002; Bahramali et al., 2001; Ford et al., 2001; Kayser et al., 2001; Williams et al., 2002), suggesting relatively early abnormalities in the processing of incoming information.

Mismatch negativity (MMN). The MMN (or N2a) is a negative component occurring 150-250 ms post-stimulus that is elicited by any discriminable change (i.e., deviance) in a repetitive background of auditory stimulation. Deviant stimuli may differ from the background standard simuli in a simple physical dimension such as frequency, duration, pitch, intensity, or spatial location. The MMN is typically elicited when the passive auditory oddball paradigm is presented while the participant's attention is directed elsewhere (e.g., in reading a book or watching a video). Customarily, the MMN is obtained by subtracting the ERP for the standard events from the ERP for the deviant events. MMN is understood to manifest a comparator mechanism that detects a mismatch between the deviant tone and the standard tone that is represented in auditory sensory memory. More specifically, the component may reflect operations that encode a representation of past stimuli into an auditory sensory memory that is used in the analysis of temporal patterns (Näätänen, 1990, 1993).

The MMN has been sourced to bilateral generators in the auditory cortex, with additional bilateral frontal generators that follow the auditory-cortex activation by a short delay (Giard et al., 1990; Rinne et al., 2000). The frontal mechanism may play a role in the initiation of an involuntary attention switch to changes detected pre-perceptually in the auditory cortices (i.e., it reflects a 'call' to involuntarily orient attention to a potentially significant exogenous event). However, others have argued that the frontal mechanism is reflected in the P3a (or even the N2b; Salisbury et al., 2003) and serves to make the event available to consciousness and behavioural control. That is, where the event is sufficiently deviant, the MMN generated in the temporal lobes is followed by the frontal P3a component (Friedman et al., 2001).

A majority of studies have replicated the initial finding of an attenuated MMN in schizophrenia (Shelley et al., 1991), particularly for duration and frequency changes (see review by Michie, 2001). This abnormality is regarded as reflecting inaccurate formation of the sensory-memory trace rather than abnormally rapid trace decay (Näätänen, 2003). Interestingly,

recent evidence suggests that the frontal generators are generally more affected in patients with schizophrenia than those located in the auditory cortex (Baldeweg et al., 2002; Sato et al., 2003). In light of Friedman et al.'s (2001) assertion that the frontal generator is more closely related to the P3a, the pronounced frontal abnormalities in schizophrenia suggests particular dysfunction in attentional orienting to, and conscious processing of, salient exogenous stimuli.

The N2b. A further component indexing abnormal information processing in schizophrenia during auditory oddball detection is the N2b potential (i.e., a negative component elicited about 200ms post-stimulus). The critical condition for the elicitation of the N2b is that the event which deviates from the prevailing context is task-relevant (Coles and Rugg, 1995). Typically, the N2b covaries with the P3, and has been associated with the process of automatic stimulus discrimination/categorisation for the purposes of subsequent behavioural selection (Ritter et al., 1979, 1982). N2b amplitude, measured as a difference waveform between target and nontarget events during auditory oddball detection, is significantly attenuated in patients with schizophrenia (O'Donnell et al., 1993; Salisbury et al., 1994b; Kasai et al., 1999), suggesting disturbed automatic stimulus classification processes in schizophrenia.

Thus, considerable evidence has amassed from ERP recording of auditory oddball task performance to support the hypothesis that both voluntary and involuntary processing of salient exogenous information is abnormal in patients with schizophrenia. However, little is yet known about the possible site(s) of the functional abnormality underlying these disturbances in salient stimulus processing. The time-course of the neural response to the auditory oddball event has been extensively characterised in healthy populations using scalp-ERP recordings, and source-localisation of dense-array electrode recordings have provided some insight into the brain areas that support the processing of the salient exogenous events (e.g., see review by Friedman et al., 2001). However, the identification of the relevant brain areas (particularly deep structures such as limbic cortex whose activity may not propagate well to surface-recorded ERPs), are more

appropriately inferred from research applying intracranial recordings and event-related fMRI techniques. This research is reviewed in the following sections, along with the results of scalp-ERP recordings made in patients with brain lesions.

1.7 Intracranial recording and lesion evidence for a network of corticolimbic sites mediating the P3 response in healthy adults

Based on pre-surgical intracranial recordings made during auditory and visual oddball detection in patients with epilepsy, Halgren and colleagues (1998) posited a supramodal corticolimbic network that supports the processing of infrequent target stimuli that require a behavioural response (see Figure 1, light shading). This network incorporates the hippocampal and perirhinal (i.e., limbic) cortex in the medial temporal lobes, cortex in the superior temporal sulcus, ventrolateral and orbitofrontal cortex, and superior posterior parietal cortex (i.e., cortex at the intraparietal sulcus). Earlier intracranial work (Halgren et al., 1980) suggested that both the hippocampal formation and the amygdala make an important contribution to processing infrequent stimulus events, in spite of the fact that bilateral medial temporal damage due to hypoxia (Polich and Squire, 1993) or unilateral medial temporal lobectomy (Johnson, 1988, 1989) does not appear to effect the amplitude of the scalp-recorded P3 elicited by target stimuli in either the auditory or visual modality.

Halgren et al. (1998) identified additional brain areas that were active during processing of the task-relevant target events, but not exclusively, including the inferior parietal cortex (at the temporoparietal junction), cingulate cortex, and dorsolateral prefrontal cortex. These areas were active during processing of both the target events and the task-irrelevant novel/distracter events that required no behavioural response, regardless of whether or not they were overtly attended (i.e., during performance of both active and passive oddball paradigms). This system was thus proposed to reflect a sub-network of brain areas specialised for the orientation of attention to

salient stimuli (i.e., commensurate with the scalp-recorded P3a). Figure 1 illustrates the brain areas identified by Halgren et al. (1998) as active only during target processing (light shading, P3b) and those areas active during both target and novel stimulus processing (dark shading, P3a).

Figure 1. Illustration from Halgren et al.'s (1998) report on intracranial recordings of cortical activity made during auditory and visual oddball tasks. The illustration distinguishes the brain areas in which activity was elicited during salient target stimulus processing only (light shading) from the brain areas in which activity was elicited during both salient target and novel stimulus processing (dark shading). Reprinted with permission from Elsevier.

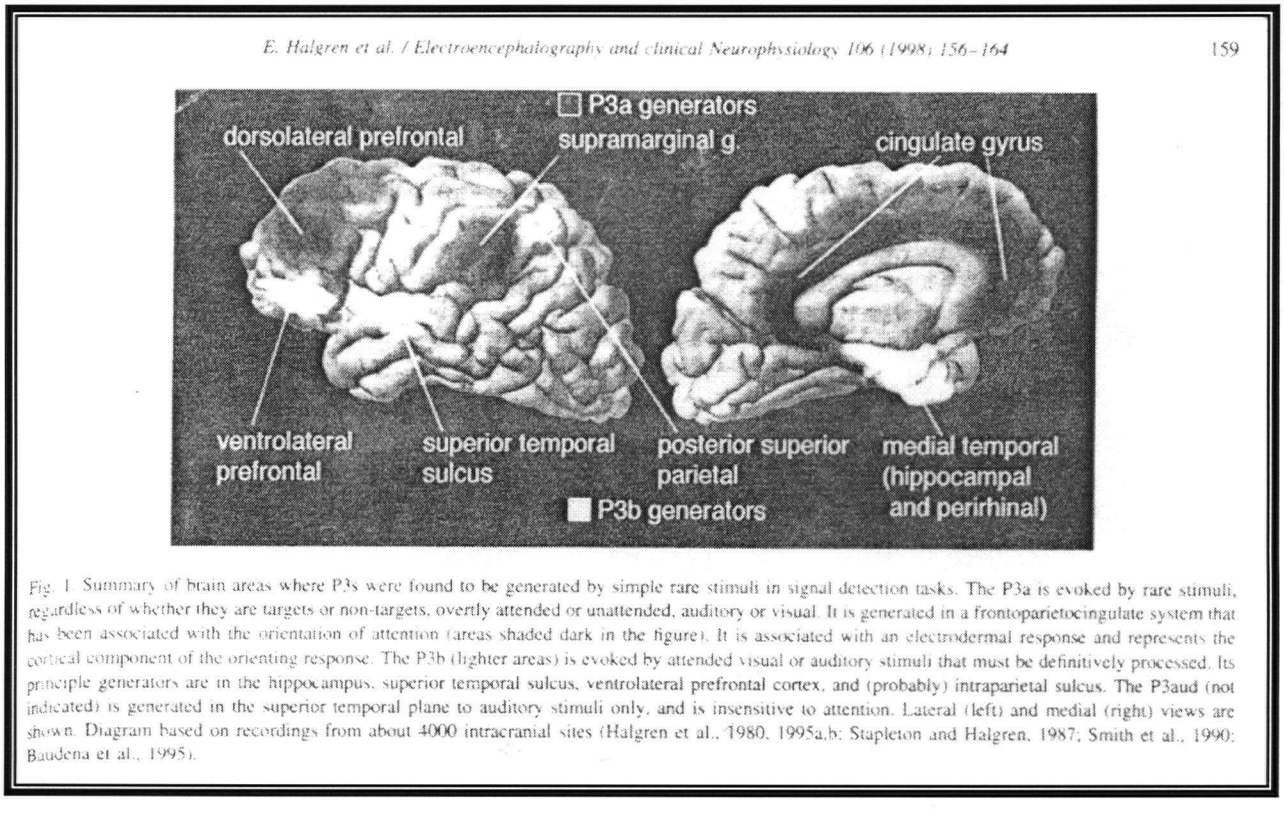


Fig. 1. Summary of brain areas where P3s were found to be generated by simple rare stimuli in signal detection tasks. The P3a is evoked by rare stimuli, regardless of whether they are targets or non-targets, overtly attended or unattended, auditory or visual. It is generated in a frontoparietocingulate system that has been associated with the orientation of attention (areas shaded dark in the figure). It is associated with an electrodermal response and represents the cortical component of the orienting response. The P3b (lighter areas) is evoked by attended visual or auditory stimuli that must be definitively processed. Its principle generators are in the hippocampus, superior temporal sulcus, ventrolateral prefrontal cortex, and (probably) intraparietal sulcus. The P3aud (not indicated) is generated in the superior temporal plane to auditory stimuli only, and is insensitive to attention. Lateral (left) and medial (right) views are shown. Diagram based on recordings from about 4000 intracranial sites (Halgren et al., 1980, 1995a,b; Stapleton and Halgren, 1987; Smith et al., 1990; Baudena et al., 1995).

Lesion studies also provide insight into the sub-networks of brain areas that contribute to the P3 response elicited by salient target and novel stimuli presented in the context of the novelty oddball paradigm. This research has focused on the contribution of cortex at the temporoparietal

junction, prefrontal cortex, and medial temporal limbic structures to the generation of the P3 response elicited by target and novel stimuli. Consistent with the findings of Halgren et al. (1998) damage to the temporoparietal junction results in a marked reduction of the amplitude of both the P3b and P3a across the auditory (Knight et al., 1989) and somatosensory (Yamaguchi and Knight, 1991) modalities, as well as partial reductions within the visual modality (Knight, 1997; see also Verleger et al., 1994). Conversely, prefrontal lesions (comprising predominantly dorsal frontal cortex but extending into ventral frontal areas) differentially affect the P3b and P3a responses. Marked amplitude reductions are observed in the P3a component only, across the auditory (Knight, 1984), visual (Knight, 1997; Daffner et al., 2000), and somatosensory modalities (Yamaguchi and Knight, 1991). Parietal P3 activity generated to the auditory, visual, and somatosensory stimuli shows no significant effect of unilateral posterior hippocampal damage, whereas frontocentral P3 (i.e., P3a) activity elicited by both the target and novel events is reduced by such lesions across all sensory modalities (Knight, 1996; Knight and Scabini, 1998).

Taken together, the lesion studies by Knight and colleagues, and the intracranial work of Halgren and colleagues (see also Baudena et al., 1995; Halgren et al., 1995a, 1995b) suggests that a network of multiple, supramodal corticolimbic sites contributes to the processing of salient exogenous stimuli. That is, while modality-specific effects are observable in the primary sensory and unimodal association cortices, a supramodal network encompassing limbic and cortical structures mediates the P3 response. Knight and Scabini (1998) ascribe particular importance to the limbic contribution to information processing, particularly for novel stimuli. They posit that incoming stimuli are compared against a template of the recent past by neural circuits that are dependent on the hippocampal region. Deviation from the template activates a distributed corticolimbic system that facilitates a behavioural response to the event as well as its integration into memory.

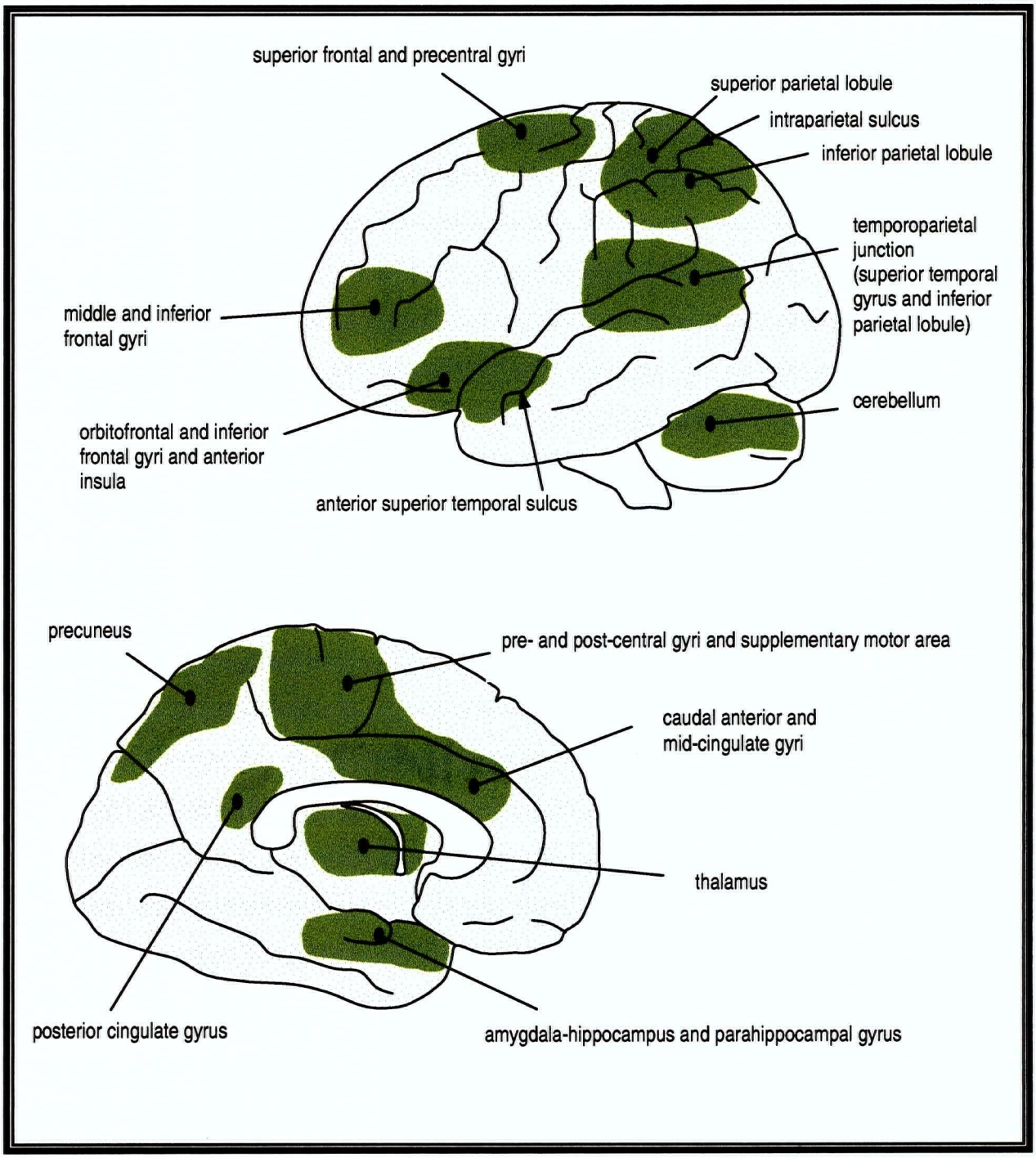
Aside from the problems associated with inferring from lesioned or epileptic brains the areas that contribute to P3 responses, methodological limitations are associated with both techniques. Lesion studies are disadvantaged by damage extending beyond the brain structures of interest, while in intracranial studies, some brain regions are undersampled because they are seldom involved in epileptogenesis and/or are difficult to approach surgically, leaving open the question as to their contribution to the generation or modulation of the P3 potential. These areas include the insular/frontal opercular cortices, dorsal parietal cortex, anterior frontal cortex, and posterior occipital cortex, as well as subcortical structures such as the thalamus, basal ganglia, and cerebellum. The contribution of these sites to salient stimulus processing must be ascertained from studies that have used event-related fMRI techniques.

1.8 Functional MRI evidence for a distributed corticolimbic network mediating salient stimulus processing

Several studies have employed event-related fMRI with neurologically healthy individuals to determine the brain areas that contribute to the processing of infrequent target stimuli presented within the context of the oddball paradigm. These studies report the activation elicited by the infrequent target stimulus relative to a baseline of the frequent nontarget stimulus. Early studies (McCarthy et al., 1997; Menon et al., 1997; Linden et al., 1999) of auditory and/or visual oddball target detection, in which participants were required either to count and/or press a button for each target event, reported activation predominantly in parietal and frontal association cortex. This encompassed activation bilaterally in the inferior parietal lobule (both at the temporoparietal junction and more superiorly at the intraparietal sulcus) and in middle frontal gyrus. Activation was also observed in paralimbic cortex at the anterior insula (i.e., in the frontal operculum), and in the caudal anterior-, mid-cingulate/SMA and posterior cingulate gyri, as well as subcortically in the thalamus.

Ongoing refinements in the application of event-related fMRI techniques have meant that more recent studies not only confirmed the activation of these regions during infrequent auditory and visual target processing but also identified activation in additional brain regions. These additional areas of activation were observed bilaterally in the cerebellum and basal ganglia, in the amygdalo-hippocampal complex, in widespread ventral and dorsal lateral frontal and premotor cortex, and in superior parietal cortex (at the intraparietal sulcus) extending into the precuneus (Clark et al., 2000; Braver et al., 2001; Kiehl et al., 2001a, 2001b; Ardekani et al., 2002). For the purposes of comparison with the Halgren et al. (1998) intracranial data, Figure 2 illustrates a synthesis of the major areas activated by target stimulus processing across the event-related fMRI studies. These results are consistent with those obtained in the intracranial and lesion studies which suggested that a distributed network of corticolimbic sites mediates the response to target stimuli. They also suggest that the cerebellum and subcortical structures (i.e., basal ganglia and thalamus) may form part of this network, although their contribution to salient stimulus processing is more appropriately examined during the processing of stimuli that require no subsequent behavioural response (i.e., when activation in these areas cannot be directly attributed to the motor action).

Figure 2. A stylised depiction of the activation elicited by infrequent target stimulus processing during performance of the oddball task, as revealed by fMRI. The figure illustrates the lateral (top) and medial (bottom) surfaces of the brain. Additional activation occurring subcortically within the basal ganglia is not depicted.



A means of more clearly ascertaining the role of subcortical structures in salient stimulus processing is provided by several whole-brain event-related fMRI studies which employed oddball variants that additionally incorporated infrequent, task-irrelevant novel or distracter stimuli. However, the number of studies to have done so is small, and thus, results are not as coherent as those described for target stimuli. In general, results suggest that association cortex in ventral frontal areas and in or near the temporoparietal junction, as well as paralimbic cortex in the anterior cingulate gyrus and at the frontal operculum (comprising the anterior superior temporal sulcus, anterior insula, and the orbitofrontal cortex), make an important contribution to processing novel/distracter stimuli. Specifically, Clark et al. (2000) reported that a repeating visual distracter stimulus evoked a positive signal change from the nontarget baseline in paralimbic cortex within the rostral anterior cingulate and extending into anterior medial frontal cortex, as well as bilaterally in ventral and dorsal frontal cortex, at the temporoparietal junction, and in the cerebellum and occipital cortex. Research from our laboratory has demonstrated that, relative to the nontarget baseline, visual novel stimuli elicit activation bilaterally in the ventral frontal cortex, at the intraparietal sulcus extending into the precuneus, and at the temporo-occipital junction, as well as in paralimbic cortex at the left frontal operculum, and in sensorimotor cortex and cerebellum, and extensive visual cortex (Kiehl et al., 2001a). In addition to activation of primary auditory and unimodal association cortex, auditory novel stimuli (relative to the nontarget baseline) elicit activation bilaterally at the temporoparietal junction, ventral frontal cortex, and right dorsal frontal cortex, as well as bilaterally in the frontal operculum, in caudal anterior cingulate cortex/SMA, and in bilateral thalamus and cerebellum (Kiehl et al., 2001b). Using an oddball-like task in which participants passively observed novel changes to a continuous background stimulus in the visual and auditory modalities, Downar and colleagues (2002) reported novelty-related signal increases relative to the constant familiar

(baseline) stimulus in the right temporoparietal junction, ventral frontal cortex, and inferior temporal gyrus, as well as in the anterior insula and left anterior cingulate cortex.

These studies demonstrate that many of the areas activated during the voluntary processing of salient target stimuli are also activated during the involuntary capture of attention toward the processing of salient novel/distracter stimuli that require no behavioural response. This suggests that there may be a network of corticolimbic areas that supports the processing of salient exogenous stimuli in general, in order that an appropriate behavioural response (or non-response) may be made to the stimuli. Moreover, these studies suggest that, in addition to their motor-related role in responding to target stimuli, the thalamus and cerebellum form part of the network of brain areas subserving salient stimulus processing. However, in contrast to the intracranial recording and lesion results reviewed above, the fMRI studies demonstrated suprathreshold amygdala-hippocampal activation only during the processing of salient target stimuli and not salient novel/distracter stimuli presented in the context of oddball detection.

Taken together, the event-related fMRI, lesion, and intracranial data suggest that a network of sites mediates the brain's response to salient exogenous stimuli, including both infrequent target and novel stimuli. Although the data derived from the different methodologies show some inconsistencies, on balance, the evidence suggests that this network encompasses limbic and heteromodal association cortex in the frontal, parietal, and temporal lobes. There is also emerging evidence for a contribution from subcortical structures to salient stimulus processing. However, direct comparison of the haemodynamic response elicited by the infrequent target and novel events may provide evidence of modulation of activity within this corticolimbic circuit supporting salient stimulus processing depending on the relative salience of the different stimuli.

1.9 Evidence for modulation of activity within the corticolimbic network by stimulus salience

In the context of active oddball detection, Kiehl et al. (2001a, 2001b) reported greater activation within the network of corticolimbic sites for target relative to novel stimuli (including relatively greater bilateral activation of the amygdalo-hippocampal complex, paralimbic cortex in the frontal operculum, parahippocampal gyrus, caudal anterior cingulate and posterior cingulate cortices, and posterior association cortex at the temporoparietal junction and at the intraparietal sulcus and precuneus, as well as in anterior frontal areas, and the thalamus, basal ganglia, and cerebellum). Novel stimuli showed greater activation relative to target stimuli in primary sensory and unimodal association cortices, as well as some evidence (emerging more strongly in the auditory modality) for greater relative activation in bilateral lateral frontal cortex. These results suggest that the corticolimbic network may be particularly affected by the task-relevance of the incoming stimuli. It would appear that, when the participant's explicit goal is to engage in a behavioural response to the target stimulus, there may be an added motivational component contributing to stimulus salience (in addition to the salience afforded by the infrequency and deviance of the target stimulus).

In the context of a modified oddball paradigm, Downer et al. (2001) also demonstrated that the task-relevance of stimuli may modulate activity within this network. Both active and passive processing of oddball targets presented in the auditory and visual domains elicited activity in association cortex at the intraparietal sulcus and precuneus, at the temporoparietal junction, and in frontal cortex, as well as in paralimbic cortex in the frontal operculum and the caudal anterior and posterior cingulate gyri, and subcortically in the thalamus and cerebellum. However, activity in many of these areas, particularly in the temporoparietal junction, frontal operculum, caudal anterior cingulate, precuneus, thalamus, and cerebellum, was greater for targets that required a subsequent behavioural response than for 'targets' that were passively observed, infrequent deviances from the baseline stimulus.

However, in a subsequent study employing a passive oddball task, Downar et al. (2002) demonstrated that when infrequent 'target' (i.e., deviants) and novel stimuli are only passively observed, areas in the temporoparietal junction, ventral frontal cortex, the frontal operculum, and the caudal anterior cingulate respond relatively more strongly to the infrequent novel stimuli than the passive 'targets'. Thus, sites within the corticolimbic network, although responsive to salient stimuli generally, appear to be modulated according to the task-relevance of the events. Novel stimuli become the more salient stimulus (and thus elicit relatively greater activation within corticolimbic areas) than the infrequent stimulus deviants that have no relevance for behaviour. This suggests that higher level influences such as motivation or goal-related biases exert a critical influence on the processing of incoming exogenous events.

1.10 Top-down modulation of stimulus salience by motivational and affective influences from limbic cortex

The hypothesis that a corticolimbic network supports the processing of incoming sensory information was previously proposed by Mesulam (1998), who suggested that such a network ensured that the attentional spotlight could be shifted towards exogenous events that have motivational and/or affective salience (Mesulam, 1999). Mesulam (1998) describes how information processing proceeds along a core synaptic hierarchy from the primary sensory and unimodal areas, to the heteromodal association, paralimbic, and limbic zones of the cerebral cortex that together are responsible for binding the information into distributed but integrated supramodal representations that can be used to flexibly guide behaviour. Reciprocal connections between the levels allow the higher levels to exert top-down influences upon earlier levels of processing. Thus, the format of the synaptic chain supporting the translation of sensation into action means that identical exogenous stimuli may trigger alternative responses depending on past experience, situational context, present needs, and contemplated consequences.

Motivational and affective influences are core determinates of which exogenous stimuli will receive conscious processing (Zald, 2003). Mesulam (1998) proposes that, under the guidance of the prefrontal cortex, motivational and emotional influences from the limbic cortex in the medial temporal lobes are channelled via paralimbic cortex (incorporating the cingulate gyrus, parahippocampal gyrus, and cortex in the frontal operculum) to the heteromodal association areas that are involved in perceptual elaboration and behavioural planning. In this manner, incoming information may be processed according to its significance (salience) rather than merely according to the surface properties of the stimulus.

Paralimbic cortex provides an important anatomical interface between limbic cortex (in the medial temporal lobes) and the frontoparietal association cortices (Augustine, 1996; Morecraft and Van Hoesen, 1998; Paus, 2001; Mesulam and Mufson, 1982a, 1982b; Mesulam, 1998). Mesulam (1999) and Posner and Petersen (1990) ascribe particular importance to paralimbic cortex in the cingulate gyrus (particularly the anterior portion) in exerting executive control over cortex in the posterior parietal and superior frontal areas in order to bias the processing of salient exogenous stimuli. The anterior cingulate provides a substrate for interactions between cognitive and motivational processes, particularly in relation to the generation of motor output (Vogt et al. 1992). A critical role for the anterior cingulate in detecting and resolving conflict between potential, but incompatible, responses to stimuli has also been proposed (Carter et al., 1998; Botvinick et al., 2001, van Veen and Carter, 2002a), suggesting that the cingulate exerts executive influence over the frontoparietal association areas responsible for processing stimuli and responses.

A recent review of animal research and human neuroimaging studies by Corbetta and Shulman (2002) differentiates the heteromodal association cortices in the frontal and parietal lobes into dorsal and ventral sub-networks that mediate different aspects of attention during information processing (see Figure 3). These authors describe a dorsal frontoparietal sub-

network, embracing the superior frontal cortex and the intraparietal sulcus, that supports the goal-directed (top-down) selection of stimuli and responses. Within this dorsal sub-network, cortex at the intraparietal sulcus may be responsible for identifying the characteristics of salient events (especially their location) and in specifying cognitive plans/intentions that target these events for behaviour (see reviews by Andersen and Buneo, 2002; Gottlieb, 2002). Together with the anterior cingulate cortex, premotor areas in superior frontal cortex play a prominent role in the selection, sequencing, and execution of behaviour (Posner and Petersen, 1990; Posner and Rothbart, 1998; Mesulam et al., 2001), and in resolving conflict between response alternatives (Carter et al., 1998). Bunge et al. (2002) posit that stimulus-response associations are stored in the posterior parietal cortex, and activated in a bottom-up fashion that is driven by the perception of salient exogenous cues. Via top-down inputs to the parietal association areas, the frontal association cortex may then enhance the representation of a task-appropriate motor response relative to task-inappropriate responses in parietal cortex. Thus, the dorsal frontoparietal areas appear specialised for the assembly and co-ordination of stimulus-response mappings, a process which may also contribute to the activation within these areas that has been observed during the online maintenance of information in working memory tasks (Corbetta and Shulman, 2002).

Activity in the dorsal network may be modulated by activity within a predominantly right lateralised ventral frontoparietal network, encompassing the temporoparietal junction and inferior-middle frontal cortex, that is elicited by salient exogenous events. That is, the ventral system acts as a form of 'circuit breaker' for the dorsal system in order to redirect limited processing resources to salient events. The salient events that activate the ventral system include task-relevant target events (Corbetta et al., 2000), but particularly novel and infrequent or unexpected stimuli (see also Downar et al., 2000, 2002). According to Corbetta and Shulman (2002), the ventral frontal areas may be particularly involved in evaluating the novelty of a

stimulus, whereas the temporoparietal junction is more concerned with determining the behavioural significance of the event.

In addition to these cortical components, Mesulam (1999) proposes contributions from the superior colliculus in the midbrain (see also Posner and Petersen, 1990), the thalamus, and the basal ganglia (striatum) to a large-scale distributed network mediating the attentional targeting of salient extrapersonal events. Figure 4 illustrates the interaction between limbic cortex and three of the five striato-thalamo-cortical circuits described by Alexander et al. (1990). This interaction provides both direct and indirect means by which motivational and affective processes may influence the activity of cognitive and motor circuits.

Thus, there is accumulating evidence and theory suggesting that a corticolimbic circuit enables motivational/affective and goal-oriented influences from the limbic cortex to exert influence, via paralimbic cortex (and subcortical structures), on specialised frontoparietal sub-networks during information processing. In this way, limited processing resources may be preferentially allocated to salient features of the environment. Extrapolating from this work in healthy participants suggests that information processing problems in schizophrenia may stem from dysfunction within this corticolimbic network. Such dysfunction may indicate that the information processing abnormalities present in schizophrenia arise more specifically from problems in bringing motivational/affective and goal-directed influences to bear on exogenous stimulus processing. Certainly, there is considerable clinical evidence for disturbed motivation, volition, and affect in schizophrenia, as described in the following section.

Figure 3. Illustration of the specialised dorsal and ventral frontoparietal sub-networks proposed to mediate goal-directed and stimulus-driven aspects of information processing respectively (from Corbetta and Shulman, 2002). Reprinted with permission from Nature Reviews Neuroscience.

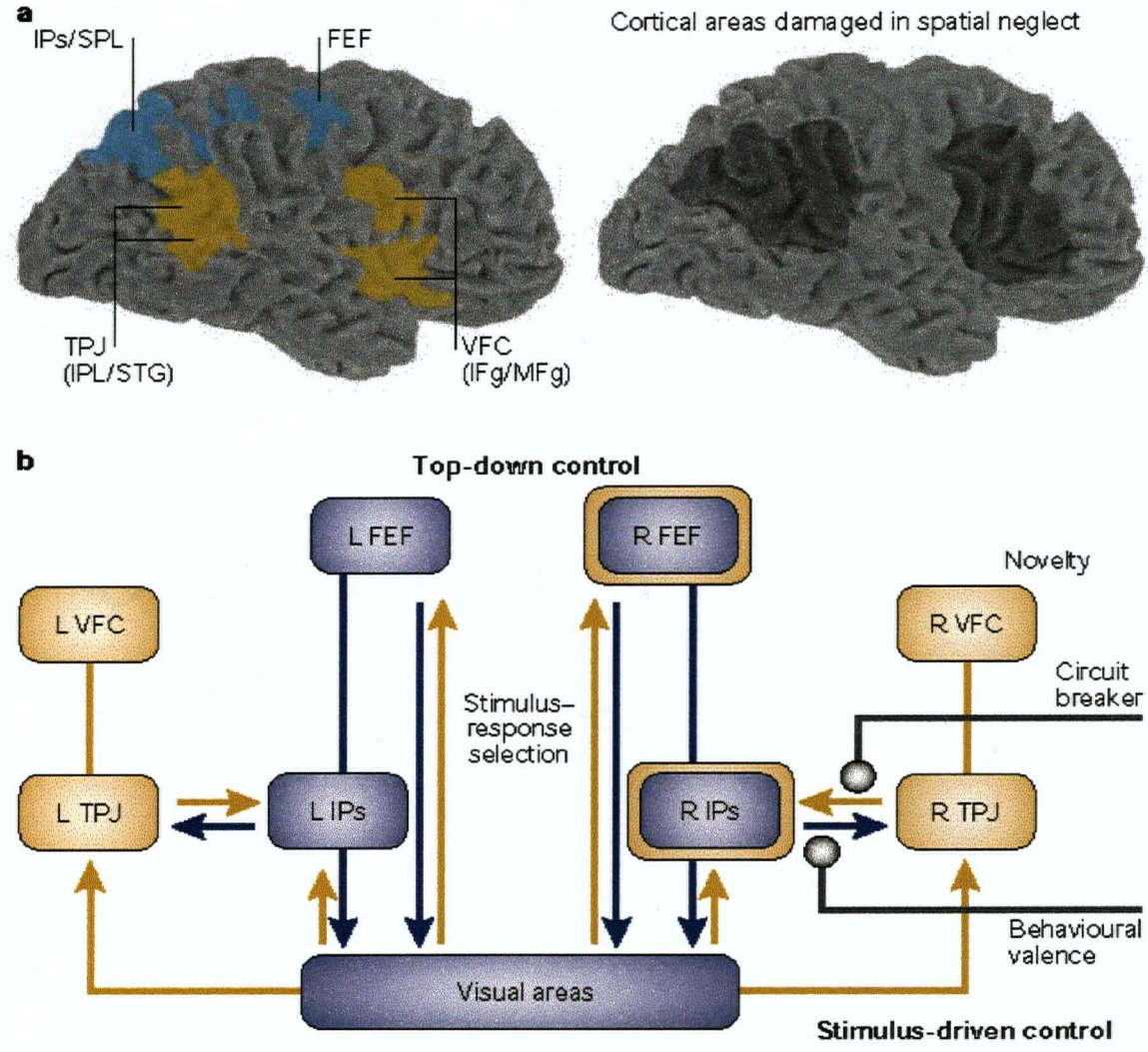


Figure 7 | **Neuroanatomical model of attentional control. a** | Dorsal and ventral frontoparietal networks and their anatomical relationship with regions of damage in patients with unilateral neglect. Areas in blue indicate the dorsal frontoparietal network. FEF, frontal eye field; IPs/SPL, intraparietal sulcus/superior parietal lobule. Areas in orange indicate the stimulus-driven ventral frontoparietal network. TPJ, temporoparietal junction (IPL/STG, inferior parietal lobule/superior temporal gyrus); VFC, ventral frontal cortex (IFg/MFg, inferior frontal gyrus/middle frontal gyrus). The areas damaged in neglect (right) better match the ventral network. **b** | Anatomical model of top-down and stimulus-driven control. The IPs–FEF network is involved in the top-down control of visual processing (blue arrows). The TPJ–VFC network is involved in stimulus-driven control (orange arrows). The IPs and FEF are also modulated by stimulus-driven control. Connections between the TPJ and IPs interrupt ongoing top-down control when unattended stimuli are detected. Behavioural relevance is mediated by direct or indirect (not shown) connections between the IPs and TPJ. The VFC might be involved in novelty detection. L, left; R, right.

Figure 4. Summary of the interaction between limbic structures and the cortico-subcortical loops described by Alexander et al. (1990) for the control of motor, cognitive, and affective/motivational functions (from Brown and Pluck, 2000). Reprinted with permission from Elsevier.

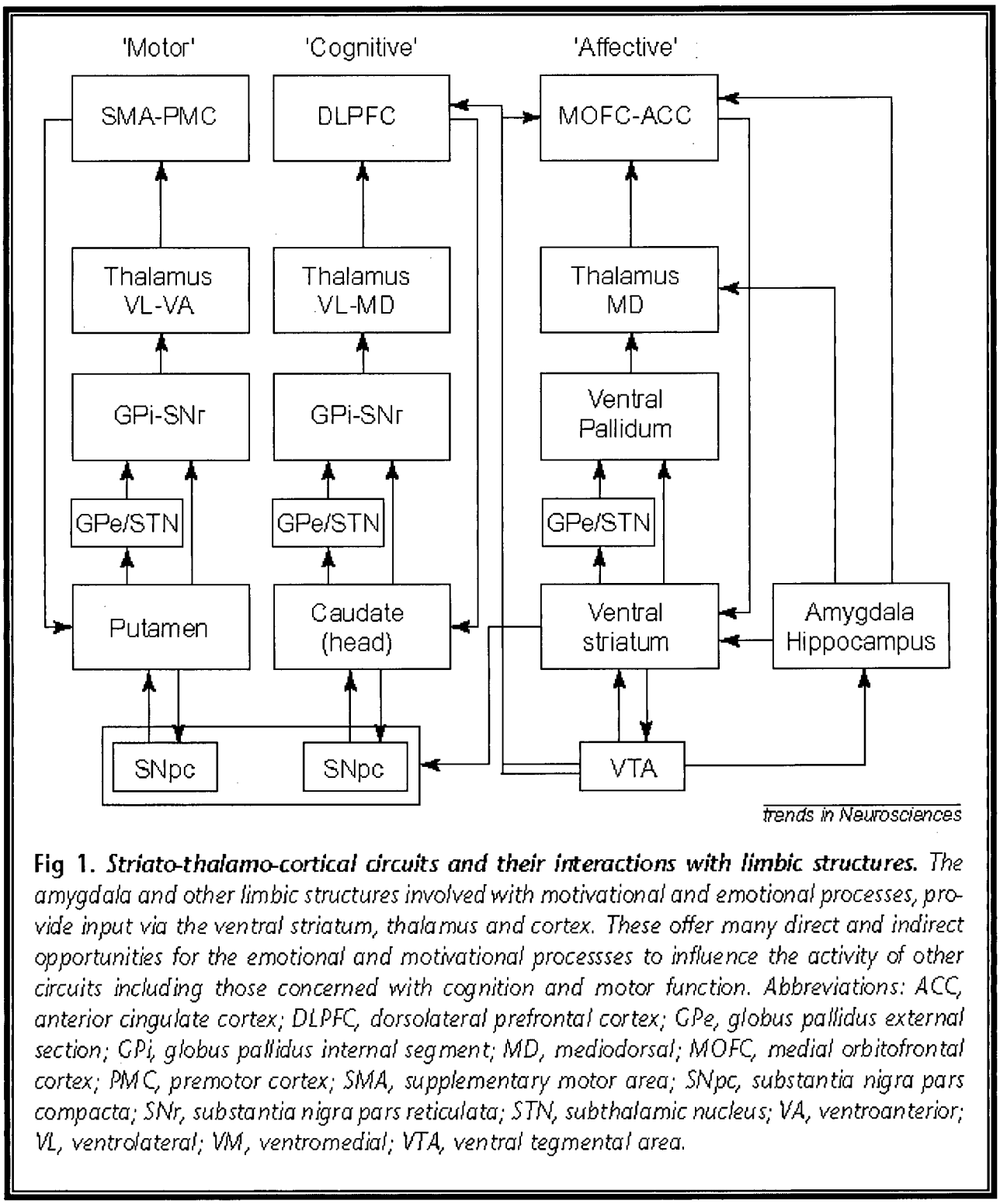


Fig 1. ***Striato-thalamo-cortical circuits and their interactions with limbic structures.*** *The amygdala and other limbic structures involved with motivational and emotional processes, provide input via the ventral striatum, thalamus and cortex. These offer many direct and indirect opportunities for the emotional and motivational processses to influence the activity of other circuits including those concerned with cognition and motor function. Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; GPe, globus pallidus external section; GPi, globus pallidus internal segment; MD, mediodorsal; MOFC, medial orbitofrontal cortex; PMC, premotor cortex; SMA, supplementary motor area; SNpc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA, ventroanterior; VL, ventrolateral; VM, ventromedial; VTA, ventral tegmental area.*

1.11 Clinical evidence for motivational and affective disturbances in schizophrenia

Clinical observation of marked motivational and affective disturbance in schizophrenia dates back to the pioneering descriptions of the illness by Emil Kraeplin (1919) and Eugen Bleuler (1911/1950). Kraeplin (1919) described avolition and affective flattening as central and defining features of 'dementia praecox'. He identified two principal groups of disorders within the illness:

> "On the one hand we observe a weakening of those emotional activities which permanently form the mainsprings of volition.... The result of this highly morbid process is emotional dullness, failure of mental activities, loss of mastery over volition, of endeavour, and ability for independent action.... The second group of disorders consists in the loss of the inner unity of activities of intellect, emotion, and volition.... The near connection between thinking and feeling, between deliberation and emotional activity on the one hand and practical work on the other is more or less lost. Emotions do not correspond to ideas." (pp. 74-75; adapted from Fuller et al., 2003).

Among the 'fundamental symptoms' described by Bleuler (1911/1950) to be present in all patients were 'loss of affective responsiveness, loss of attention, loss of volition, ambivalence and autism'.

While these early conceptualisations of the illness particularly emphasised the negative symptoms of affective and motivational disturbance, modern descriptions of the illness also describe positive symptoms (see e.g., Liddle, 2000). Thus, in contrast to blunted affect (manifest in a decreased responsiveness to emotional events, loss of vocal inflection, and diminished facial expression), affect may also be inappropriate or incongruous to the circumstances (e.g., inappropriate giggling). Similarly, patients may be characterised by disruptions of motivation and will that are either negative or positive. Weakened volition is manifest in long periods of

underactivity, whereas disjointed volition is reflected in poorly organised, ill-judged activities which appear to be prompted by impulse.

The clinical descriptions of motivational and affective disturbances suggest that motivational and affective problems might contribute directly to information processing deficits in schizophrenia, although it may also be the case that they are independent of information processing difficulties but that both emerge out of dysfunction in limbic cortex.

1.12 Functional and anatomical abnormalities in the limbic cortex of patients with schizophrenia

Evidence for functional abnormality within the limbic cortex of patients with schizophrenia is provided by several block-design fMRI studies that have examined limbic function during the processing of affective information. Generally, these studies report decreased task-related activation of the amygdala and/or hippocampus in patients relative to healthy control participants, in spite of efforts to match the groups on task performance and mood state measures.

Schneider et al. (1998) reported that, during the induction of sad mood via the viewing of sad facial expressions, healthy participants, but not patients, showed significant bilateral activation of the amygdala (despite equivalent levels of induced negative affect across the groups). A non-significant trend for group differences was also observed in the hippocampus. Similarly, despite equivalent behavioural performance during the discrimination of positive (happiness) and negative (sadness, anger, fear, and disgust) emotional valence in facial expressions, Gur et al. (2002) reported significantly greater activation of the left amygdala and bilateral hippocampus in healthy participants relative to clinically stable patients with schizophrenia. Two further studies reported relative underactivity of the amygdala in patients with schizophrenia during facial affect labelling (e.g., angry, happy, sad, surprised, disgusted, neutral). Hempel et al. (2003) observed relative underactivity of the amygdala in a sample of patients who were hospitalised and

receiving medication for the first time, even when behavioural performance was matched across the healthy and patient groups. Interestingly, patients showed relative overactivity during the task in the posterior cingulate and bilateral medial frontal gyrus, perhaps reflecting a compensatory response to deficits in more basal limbic functions. Phillips et al. (1999) also report significantly greater activation of the amygdala in healthy participants relative to a group of patients comprising five paranoid and five non-paranoid patients during labelling of fearful faces. Furthermore, during ratings of disgusted expressions, an interesting pattern of activity emerged differentiating the paranoid and non-paranoid patient subgroups. Non-paranoid patients mislabelled the expressions of disgust as either fear or anger more often than paranoid patients, and concurrently demonstrated greater relative activation of the amygdala than paranoid patients.

In contrast to the general pattern of relative underactivity of the amygdala and/or hippocampus in patients, Kosaka et al., (2003) reported relative overactivity of the right amygdala during a task in which participants judged the emotional intensity of facial expressions. The authors suggested their task may have been more cognitively demanding and less emotionally engaging than the tasks in which relative underactivity of the amygdala have been observed. Alternatively, the results may have been influenced by differences in the control conditions against which the task conditions were compared.

There is also evidence that the hippocampus may be characterised by relative underactivity or overactivity in patients depending on the nature of the task. This was demonstrated previously in a PET study by Heckers et al. (1998) which measured regional cerebral blood flow (rCBF) using $[^{15}O]\ CO_2$. They reported that patients exhibited reduced hippocampal activation relative to a resting baseline during conscious recollection of studied words (see also Weiss et al., 2003). However, patients were characterised by relative overactivity of the hippocampus during baseline (in which participants completed unstudied three-letter word stems). This result suggests that patients may be unable to successfully modulate hippocampal activity according to

task demands. Moreover, increased hippocampal activity at baseline and impaired recruitment during episodic retrieval might reflect an abnormal corticolimbic interaction in schizophrenia (Fletcher, 1998). An abnormal encoding-related hippocampal response in schizophrenia has also been demonstrated using fMRI (Eyler Zorilla et al., 2002), with patients characterised by greater activation during blocks of repeated complex pictures than during novel picture encoding, a pattern directly opposite to that observed in healthy participants. In spite of this abnormal encoding-related activity, patients were as capable of later recognising the novel pictures presented during scanning. In two PET-^{15}O water studies, Medoff et al. (2001) also described relative overactivity of the hippocampus in patients compared to healthy participants during a simple tone discrimination task and baseline (rest) condition. The relative elevation of rCBF in the hippocampus at rest was greater when patients were in an unmedicated state than when they were receiving stable doses of the typical antipsychotic haloperidol, suggesting that antipsychotic drugs may help normalise hippocampal function. This is consistent with the result reported by Liddle et al. (2000), who demonstrated that change in glucose metabolism in the left hippocampus of first-episode schizophrenia patients after six weeks' treatment with the atypical antipsychotic risperidone was significantly correlated with a reduction in the severity of delusions and hallucinations after six weeks.

Structural abnormalities in the amygdala-hippocampus are among those most consistently demonstrated in schizophrenia (Harrison, 1999; Wright et al., 2000). Difficulties in differentiating the amygdala and hippocampus has meant that the majority of MRI studies combine the limbic structures into an amygdalo-hippocampal complex (AHC). Volume loss from the AHC is one of the most consistently observed structural abnormalities in schizophrenia, with particular disturbance apparent on the left side (Harrison, 1999; Wright et al. 2000; Shenton et al., 2001). The pattern of AHC asymmetry evident in patients appears to be an exaggeration of the pattern observed in neurologically healthy adults. A meta-analysis by Nelson et al. (1998)

reported significant mean effect sizes for the left and right AHC respectively of 0.67 and 0.72. In the hippocampus alone, mean effect sizes were 0.37 and 0.39 on the left and right respectively, corresponding to a bilateral reduction of 4%. Reduction of the AHC, particularly on the left, is also present in first-episode psychotic patients (Velakoulis et al., 1999), and in high-risk but healthy adolescents with at least two affected relatives (Lawrie et al., 2003), suggesting that the abnormality pre-dates the onset of psychosis. Moreover, longitudinal data from the latter study suggest that further volume reductions may occur with the onset of schizophrenia.

More recently, amygdalo-hippocampal shape differences have been described in patients with schizophrenia (Velakoulis et al., 2001; Csernansky et al., 2002; Shenton et al., 2002). Proton magnetic resonance spectroscopy studies have identified *N*-acetylaspartate (NAA; a metabolite that indexes neuronal mass and integrity) reductions in both medicated (Fukuzako et al., 1995) and neuroleptic-naïve patients (Cecil et al., 1999). Postmortem studies have also reported reduced volume (Bogerts et al., 1985; 1990), reduced cell number (Falkai and Bogerts, 1986), and hippocampal pyramidal cell disarray (Kovelman and Scheibel, 1984; Kuroki and Matsushita, 1998; but see Benes et al., 1991 for a failure to replicate this result).

In their review of 193 MRI studies, Shenton et al. (2001) reported AHC abnormalities in 100% of studies reviewed, frontal lobe abnormalities (particularly in prefrontal grey matter and orbitofrontal regions) in 59% of studies, parietal lobe abnormalities (particularly in the inferior parietal lobule) in 60% of studies, and subcortical abnormalities in the basal ganglia (68% of studies), thalamus (42% of studies), and cerebellum (31% of studies). However, in spite of the consistency with which limbic structural abnormalities are observed in schizophrenia, all the structural abnormalities described in schizophrenia to date are small and subtle in nature, and may be independent of any functional abnormality observed within these structures or their connections.

1.13 Functional abnormality within the corticolimbic network during target processing in schizophrenia

In contrast to the extensive literature describing P3 abnormalities in schizophrenia during ERP recording of the auditory oddball task, very little work has yet employed the task during functional neuroimaging. Although inappropriate for assessing the haemodynamic response associated with individual events, SPECT has indexed areas of sustained abnormality in schizophrenia during performance of the oddball paradigm. Shajahan et al. (1997) measured regional perfusion using SPECT during target counting in a two-tone auditory oddball paradigm. Patients with schizophrenia activated the left superior temporal gyrus (at the temporoparietal junction) and right caudate nucleus during the task. However, relative to the pattern of activation reported in their previous study with neurologically healthy participants (Ebmeier et al., 1995), patients were characterised by hypofrontality during the task (i.e., an absence of activation at the medial frontal site observed in the healthy participants).

More recently, Kiehl and Liddle (2001) published a preliminary report comparing target-related activation elicited during event-related fMRI of the novelty oddball task in 11 clinically stable, medicated patients with schizophrenia and 11 healthy control participants. Due to the small nature of the patient sample, they restricted their search for group differences to 10 regions of interest (ROI; each $20mm^3$) centred on locations that have been demonstrated to be consistently active in healthy participants during the auditory oddball task (see Kiehl et al., 2001a, 2001b; Kiehl and Liddle, 2003). While patients and healthy participants showed equivalent activation of the sensorimotor cortex (associated with motor responding to the target stimulus), multiple sites of reduced haemodynamic activity, both in terms of the extent and the magnitude of activation, were observed in patients relative to healthy control participants during auditory oddball target processing. These included the caudal anterior and posterior cingulate

gyri, right anterior frontal cortex, and bilateral cortex at the anterior superior temporal sulcus, intraparietal sulcus, and temporoparietal junction, as well as in the thalamus. Although limited in scope, these results suggest that schizophrenia may be associated with abnormality throughout a corticolimbic network of brain areas that support target processing.

1.14 Rationale and objectives for Experiment One, Part A:

The results of the Kiehl and Liddle (2001) pilot study are suggestive of widespread dysfunction rather than a single locus of disturbance during target processing in schizophrenia. Their ROI analysis revealed disturbance in paralimbic cortex (within the cingulate gyrus and at the anterior superior temporal sulcus), as well as in heteromodal association cortex (bilaterally at the intraparietal sulcus, temporoparietal junction, and in right anterior frontal cortex). However, a random-effects (between-subjects) analysis in a larger sample of patients is necessary to characterise the full extent of the functional abnormality present in patients during salient target stimulus processing, and particularly to ascertain the presence of functional abnormalities within limbic cortex, association cortex in dorsal and ventral lateral frontal areas, and subcortical structures.

The goal of the first experiment was thus to examine the whole-brain response elicited during auditory oddball target processing in a large sample (n = 28) of chronic, stable patients with schizophrenia. Particular attention was given to determining the activity elicited within the corticolimbic network in healthy individuals during the processing of salient stimuli, especially within the amygdala-hippocampal complex, paralimbic cortex in the frontal operculum and cingulate gyrus, in the dorsal and ventral frontoparietal association networks described by Corbetta and Shulman (2002), as well as in the thalamus, basal ganglia, and cerebellum. Based on Kiehl and Liddle (2001), it was hypothesised that patients would show relatively reduced

activity within these areas, whereas activity within motor-related areas was expected to be comparable in the patient and healthy groups.

Patients with schizophrenia typically respond more slowly to target stimuli in both simple and choice reaction time tasks (Ngan and Liddle, 2000), giving rise to the possibility that reaction time differences between patients and healthy participants may contribute directly to differences observed in the haemodynamic response between groups. In the pilot study of 11 patients, Kiehl and Liddle (2001) did not control for the potentially confounding influence of the significant reaction time (RT) difference between participant groups on the observed differences in haemodynamic activity elicited by target events. Thus, in the present analysis we compared the mean amplitude of the fitted haemodynamic response elicited by target events in the patient and healthy groups with the effect of reaction time removed as a potential confound.

As in Kiehl and Liddle (2001), we employed a novelty variant of the standard two-tone oddball paradigm in which both infrequent, non-repeating novel tones and infrequent target events occurred against the homogenous nontarget stimulus background. This paradigm was adopted so that the brain response elicited during orienting to novelty in patients with schizophrenia might also be characterised (see Experiment One, Part B). Polich and colleagues have demonstrated that the P3 elicited by target stimuli has a similar morphology and topography across three-tone, two-tone, and infrequent single-tone task variants (Katayama and Polich, 1996a; Polich and Margala, 1997). However, in addition to the P3 generators, it is expected that the neural response associated with other ERP components elicited during oddball target processing, such as N1-P2, N2b, and/or MMN, will also contribute to the observed haemodynamic activity. It was not a goal of the present task to differentiate these contributions, but rather, to examine the neural response elicited during the processing of salient target stimuli in schizophrenia. Indeed, the whole-brain analysis used in this larger sample of 28 patients also provided an opportunity to examine the brain response in primary auditory cortex and auditory

association cortex, which have been posited as the brain sites that may underlie the observed MMN reductions in schizophrenia (see Michie, 2001).

1.15 Rationale and objectives for Experiment One, Part B:

Intracranially-recorded ERPs (Baudena et al., 1995; Halgren et al., 1995a, 1995b, 1998), fMRI (Kiehl et al., 2001a, 2001b, Downar et al., 2002), and lesion studies (Knight, 1984, 1996; Knight et al., 1989; Daffner et al. 2000) consistently demonstrate that the processing of novel stimuli presented within the context of oddball target detection elicit widespread activation of heteromodal association cortex, particularly in the prefrontal cortex and cortex at the temporoparietal junction (see also Corbetta and Shulman, 2002). Lesion and intracranial recording studies also suggest a central role for the hippocampus in novelty processing, although fMRI studies employing simple auditory and visual novelty oddball tasks have not reported activation of the limbic cortex during novel stimulus processing (Kiehl et al., 2001a; 2001b). More complex oddball-like paradigms (e.g., a study in which novel stimuli were words that varied in semantic, perceptual, or emotional quality from the baseline words; Strange and Dolan, 2001) have described hippocampal activation during novel stimulus processing. Moreover, hippocampal activation elicited during the explicit (i.e., conscious) encoding of novel verbal and nonverbal materials presented outside of the oddball task context has been reported in meta-analyses of both PET (Lepage et al., 1998) and fMRI studies (Schacter and Wagner, 1999; see also Greicius et al., 2003). Thus, a goal of the present study was to characterise the pattern of activation elicited by simple auditory novel oddball stimuli using a random-effects analysis of a large sample of healthy participants (n = 28). We particularly examined whether salient novel stimuli elicited activation within limbic and paralimbic cortex in addition to the heteromodal association areas located in prefrontal and temporoparietal cortex.

The task also afforded a direct comparison of the activity elicited by infrequent target and novel stimuli within the same participants and relative to the same nontarget baseline. This comparison sought to reveal whether the task-relevant target stimuli and the task-irrelevant novel stimuli elicit activation within distinct corticolimbic areas and/or differential levels of activation within brain areas that are responsive to both types of salient stimulus (see Experiment One, Part C).

Scalp-recorded ERPs in patients with schizophrenia indicate a reduction in the amplitude of the P3a component elicited by novel stimuli presented within the context of the novelty oddball paradigm relative to healthy participants (Grillon et al., 1990, 1991a; Merrin and Floyd, 1994). Thus, in addition to the voluntary orienting abnormalities demonstrated during task-relevant target processing, patients exhibit abnormal involuntary attention capture away from a central task towards salient novel stimuli. The primary goal of the present study was to localise the functional abnormality underlying disturbed involuntary orienting to infrequent, novel stimuli in schizophrenia.

The reduced P3a component elicited to novel oddball stimuli in patients with schizophrenia suggests that decreased haemodynamic activity in patients relative to healthy participants will be observed within a network of corticolimbic areas recruited during novelty processing, particularly in prefrontal, temporoparietal, and possibly limbic cortex. However, evidence that patients with schizophrenia may also experience increased distraction by task-irrelevant stimuli during oddball target detection (Grillon et al., 1990, 1991a) raises the possibility that in at least some cerebral areas, the haemodynamic response elicited during orienting to novel stimuli may be greater in patients with schizophrenia than in healthy control participants.

Previous research has indicated that certain attentional functions are lateralised to the right hemisphere, with maintenance of the alert state suggested to be particularly dependent on right-hemisphere mechanisms (Posner and Peterson, 1990). Clinical evidence from brain lesion

patients demonstrates that right hemisphere lesions elicit more frequent, severe, and lasting contralesional neglect than equivalent lesions in the left hemisphere (see Mesulam, 1999). Based on their review of human and animal literature, Corbetta and Shulman (2002) proposed a predominantly right-lateralised ventral frontoparietal network centred in the temporoparietal junction and ventral frontal cortex that is activated during orienting to salient exogenous events, particularly novel and infrequent stimuli. Thus, it was hypothesised that orienting to the infrequent novel stimuli presented in the context of the oddball paradigm would elicit more widespread activity in the right hemisphere than in the left. By requiring no subsequent behavioural response, the novel stimuli provided a means of assessing hemispheric laterality during the processing of salient exogenous stimuli that was not afforded by the target stimuli which biased hemispheric differences in activity by incorporating a right-handed motor response.

In schizophrenia, there is evidence for a reduction or even reversal (Heckers et al., 2002) in the normal pattern of functional (and structural) cerebral asymmetry, particularly during language and attentional functioning (Crow, 1997; Posner et al., 1998; Hugdahl, 2000). For example, patients with schizophrenia show a decreased right ear advantage on verbal dichotic listening tasks (Sommer et al. 2001), and fail to appropriately modulate their performance on the task as healthy participants do when instructed to shift attention to the left ear (Loberg et al., 1999), suggesting that they experience deficits during both automatic (bottom-up) and controlled (top-down) processing. Neuroimaging studies often reveal left hemisphere hyperactivity in patients with schizophrenia (see review by Gur and Chin, 1999). Thus, while healthy participants were expected to show more extensive activation in the right hemisphere than the left during orienting of processing resources to salient novel stimuli, relative hyperactivity in the left hemisphere was expected to contribute to a reduction or even reversal of this pattern in patients with schizophrenia.

1.16 Rationale and objectives for Experiment Two:

Effective behaviour entails the preferential allocation of processing resources to events that are made salient by their relevance to the organism's goals. In schizophrenia, motivational abnormalities are expected to particularly affect the processing of such task-relevant stimuli (Brown and Pluck, 2000). Research using the oddball target detection paradigm provides some insight into the network of brain areas that may support goal-directed behaviour. Converging evidence from lesion, intracranial ERP recordings, and fMRI studies employing oddball tasks (reviewed above) suggests that infrequent events that have been targeted for a behavioural response elicit activation within a supramodal corticolimbic network of areas, particularly including limbic, paralimbic (frontal opercular and cingulate cortex), and dorsal and ventral frontoparietal heteromodal cortex, as well as subcortical structures (thalamus, basal ganglia, and cerebellum).

However, the ability to infer the brain regions that support goal-directed attention from the comparison of the activity elicited by the target and non-target events in the oddball paradigm is confounded by the attentional capture (i.e., orienting) evoked by the relative infrequency of the target event. That is, the salience afforded to a target stimulus by being relevant to current task goals is confounded by the salience created by the infrequency of the target stimulus. Using ERPs, Polich and colleagues (Katayama and Polich, 1996b; Polich et al., 1996) have demonstrated that the amplitude of the P3 potential elicited by target events increases as target infrequency increases (i.e., target probability decreases). Changes in target probability have also been associated with changes in the haemodynamic response educed during fMRI of the oddball paradigm (Casey et al., 2001; Horovitz et al., 2002). ERP data demonstrate that the involuntary attentional orienting component of the target P3 is reflected in a frontocentral P3a component peaking about 60-80 ms earlier than the parietal (task-relevant) P3b in all sensory modalities

(Knight and Scabini, 1998). However, the temporal coarse evolution of the haemodynamic response does not allow the separation of these components using fMRI.

The comparison of the infrequent target and novel events described above in Experiment One effectively provides some index of the brain areas that support goal-directed processing while removing the influence of stimulus infrequency. In such a comparison, Kiehl et al. (2001a, 2001b) demonstrated that, while many of the areas activated by the target stimuli were also activated by the novel events for which no motor response was required, the activation elicited by the task-relevant target events was significantly greater than that elicited by the novel events in a majority of the activated brain areas. That is, even when comparing events of equivalent infrequency, there appears to be preferential recruitment of a widespread network of areas for stimuli that are relevant to the participant's behavioural goal. However, given that never-experienced novel events are especially salient stimuli that provoke a strong reorienting of processing resources, this comparison also affords a less than ideal means of ascertaining the network supporting goal-directed processing (Downar et al., 2002; Corbetta and Shulman, 2002). A more appropriate means of distinguishing the processing demands associated with a behavioural goal from those associated with the attentional capture elicited by either stimulus infrequency or novelty is to examine the brain response during a task in which a stimulus requiring a behavioural response is equiprobable with a non-novel stimulus requiring no motor response, such as may be done in a Go/NoGo paradigm.

Previous research from our laboratory (Liddle et al., 2001) and others' (Watanabe et al., 2002) have employed equiprobable visual Go/NoGo tasks, however, these studies established a prepotent motor response for Go trials by introducing cue stimuli prior to the presentation of the Go and NoGo trials. In such cases, the salience of the non-target 'NoGo' stimulus (and withholding an inappropriate motor response to that stimulus) is increased relative to the target 'Go' stimulus. Similarly, the findings of Braver et al. (2001) and Menon et al. (2001), who

employed tasks in which Go and NoGo trials were also equally probable, are complicated by the inclusion of multiple NoGo stimuli that may have elicited a frequency-related response.

In the present study, we employed event-related fMRI to examine the neural response, common across the auditory and visual modalities, elicited during the detection of, and motor response to, a Go stimulus relative to an equiprobable NoGo stimulus that required no motor response. To remove the attentional effect of event-infrequency and stimulus novelty, we repeatedly presented only two stimuli, one of which was designated the Go event and the other the NoGo event. The experiment was conducted in healthy participants only in order to define the brain regions active during goal-directed processing of salient target events, regardless of whether the target stimuli were presented in the auditory or visual modality. Based on the activity elicited by target events relative to novel events in the novelty oddball paradigm (Kiehl et al., 2001a, 2001b), we hypothesised that goal-directed allocation of processing resources to the task-relevant Go stimulus would elicit greater activity than the NoGo stimulus in a supramodal network incorporating limbic, paralimbic, and dorsal and ventral heteromodal association areas.

1.17 Rationale and objectives for Experiment Three:

The symptoms of weakened and disjointed volition that are observed in schizophrenia are consistent with there being particular abnormality of function within the network of brain areas that supports goal-directed behaviour. Brown and Pluck (2000) emphasise abnormalities within a limbic-ventral striatopallidal (basal ganglia) system, or 'motive circuit', as central to abnormalities of goal-directed behaviour and the translation of motivation into action in schizophrenia. Limbic cortex, as the source of motivational influences on behaviour, represents a key site in which patients with schizophrenia may be characterised by functional abnormality during the processing of task-relevant target stimuli. Paralimbic cortex, which provides a bridge between the limbic and heteromodal association cortices, is ideally situated to link the

motivational/goal-directed influences from limbic centres with the multimodal perception of stimuli in posterior neocortex and the frontal executive processes that select, initiate, and monitor behaviour. Thus, paralimbic cortex is also a potential site of functional abnormality in schizophrenia. The goal of the present study was to compare the haemodynamic response elicited by task-relevant target events in patients with schizophrenia and healthy participants, particularly within limbic and paralimbic cortex, using the auditory version of the Go/NoGo paradigm employed in Experiment Three. The auditory modality, rather than visual modality, was chosen for consistency with the auditory oddball paradigm employed in Experiments One and Two.

1.18 Rationale and objectives for Experiment Four:

The previous experiments were designed to assess the hypothesis that patients with schizophrenia are characterised by functional abnormality within a network comprising limbic, paralimbic, and heteromodal association cortex, as well as subcortical structures, during the processing of a variety of salient exogenous events, including stimuli that are infrequent, novel, and/or targeted for a behavioural response. In contrast, this final experiment was designed to assess whether schizophrenia is also characterised by functional abnormality when salient exogenous stimuli have been processed incorrectly. That is, Experiment Four examines the brain areas involved in the internal monitoring of stimulus processing and behaviour. Considerable evidence demonstrates that schizophrenia is characterised by disordered monitoring and regulation of self-generated thoughts and behaviour (Frith & Done, 1989; Leudar et al., 1994; Mlakar et al., 1994; Stirling et al., 1998, 2001; Johns et al., 2001). Moreover, research suggests that an impaired ability to monitor internally erroneous responses to stimuli contributes to self-monitoring problems (Malenka et al., 1982, 1986; Frith & Done, 1989). Thus, the present

experiment examined whether patients with schizophrenia are characterised by functional abnormality during error responses.

Evidence for a functional abnormality associated with error monitoring in schizophrenia derives primarily from ERP research investigating a fronto-central negative voltage component termed error negativity (Ne; Falkenstein, et al., 1990, 1991) or error-related negativity (ERN; Gehring et al., 1990, 1993). The Ne/ERN peaks around 50-150 ms after the commission of an erroneous response during tasks that necessitate speeded and accurate response choices, thus providing a physiological marker of internal error monitoring (see Falkenstein et al., 2000, for a review). The Ne/ERN is elicited in situations where participants know the correct answer but fail to execute the correct response (Dehaene et al., 1994), and decreases in amplitude as the participant's confidence in having committed an error decreases (e.g., in tasks in which the quality of the stimulus has been degraded; Scheffers & Coles, 2000). Several ERP studies have demonstrated that the Ne/ERN is attenuated in patients with schizophrenia compared to healthy adults (Kopp & Rist, 1999; Mathalon et al., 2002), even in paradigms in which the correct response is readily apparent and errors are easily identifiable (Bates et al., 2002). These results are consistent with the hypothesis that error responses are processed abnormally in schizophrenia.

The application of error-eliciting tasks during functional magnetic resonance imaging (fMRI) provides further neurophysiological evidence of disturbed brain function in patients with schizophrenia during error commission. Converging evidence from fMRI research (e.g., Carter et al., 1998; Kiehl et al., 2000a; Ullsperger & von Cramon, 2001) and dipole localisation analyses of dense-array ERP data (e.g., Dehaene et al., 1994; Miltner et al., 1997; Holroyd et al., 1998; Luu et al., 2000b) in healthy individuals suggests that the commission of errors, (and the Ne/ERN), is critically associated with activity in the anterior cingulate cortex (ACC). Carter et al. (2001) recently reported attenuation of the haemodynamic response during errors of

commission in patients with schizophrenia compared with healthy participants in the ACC. Taken together, the ERP and fMRI results imply that impaired error monitoring in schizophrenia relates to dysfunction in ACC. However, the nature of the error-related processes purported to underlie the Ne/ERN and ACC activity have been the subject of debate, leaving open the question as to the root of abnormal error-monitoring in schizophrenia.

Early proposals that the Ne/ERN reflects the activity of a rapid, preconscious error-detection system that compares and detects mismatch between representations of the intended response and the actual response (Gehring et al., 1993; Bernstein et al., 1995; Falkenstein et al., 2000; Scheffers & Coles, 2000) have been challenged. Functional MRI evidence that tasks involving strong response competition elicit ACC activation irrespective of response accuracy led others to hypothesise that the ACC functions to detect conflict between incompatible potential responses rather than overt errors (Carter et al., 1998; MacDonald et al., 2000; Botvinick et al., 2001). Other theorists argue that error monitoring incorporates processes related to motivation and/or affective processing of error responses (Dikman & Allen, 2000; Luu et al., 2000a; Vidal et al., 2000). For example, Luu et al. (2000a) demonstrated that the amplitude of the Ne/ERN was larger in participants who reported a propensity to experience negative affect on personality assessment scales than in participants without this propensity, and further, that the amplitude of the Ne/ERN decreased in these participants as they affectively disengaged from the task. Also consistent with the proposal that the error response incorporates a motivational or affective processing component are a number of fMRI studies that localised activity associated with errors of commission to the rostral ACC (Kiehl et al., 2000; Braver et al., 2001; Menon et al., 2001; see also Rubia et al., in press). Activity in the rostral ACC region during errors was dissociated from activity in more superior, caudal ACC that was elicited during both response inhibition and target detection processing that included a degree of response competition. Data from a recent study reporting dipole localisation of error-related ERP components are also consistent with the

idea that caudal ACC activity may reflect a conflict-detection component to error monitoring that is dissociated from an affective component mediated by activity in rostral ACC (van Veen & Carter, 2002b).

Structural and functional dissociation of the ACC into rostral and caudal subregions has been described on the basis of convergent evidence from cytoarchitectural, lesion, electrophysiological, and neuroimaging data (Devinsky et al., 1995; Bush et al., 2000; see Figure 5). The caudal ACC, termed the 'cognitive' subdivision, appears to be responsible for mediating attention and executive functions such as the detection of response conflict via strong reciprocal interconnections with the dorsolateral prefrontal cortex, parietal cortex, and premotor and supplementary motor areas. The 'affective' subdivision in the rostral ACC has connections to limbic and paralimbic areas including the amygdala and hippocampus, and appears primarily involved in assessing the salience of emotional and motivational information, and in regulating emotional responses (see Bush et al., 2000 for a review).

Figure 5. Illustration depicting the segregation of the anterior cingulate cortex into rostral 'affective' (coloured blue) and caudal 'cognitive' (coloured red) subdivisions (from Bush et al., 2000). Reprinted with permission from Elsevier and John Wiley & Sons, Inc..

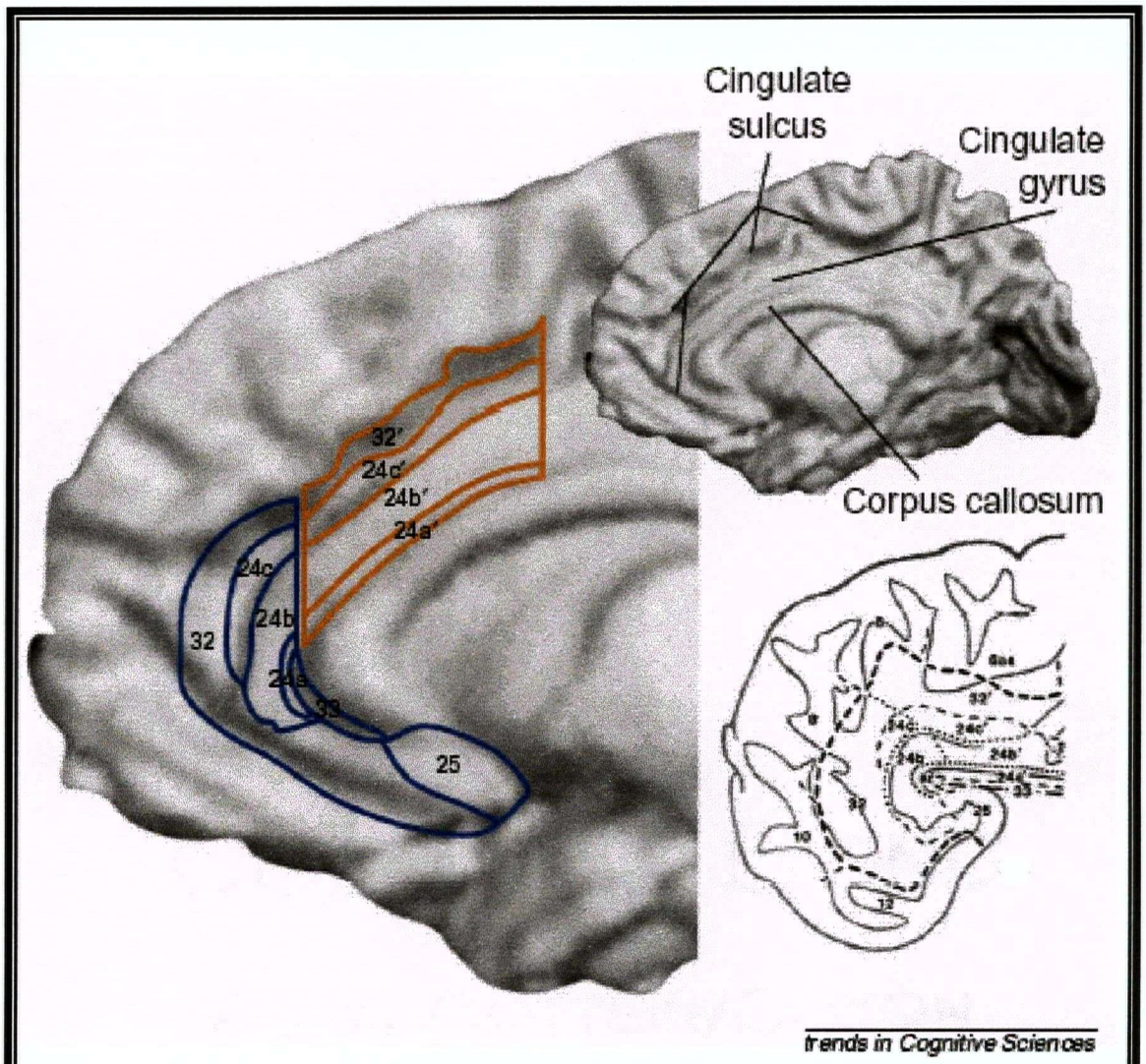


Fig. 1. Anterior cingulate cortex (ACC) anatomy. The upper right part of the figure contains a reconstructed MRI of the medial surface of the right hemisphere of a single human brain (anterior towards the left, posterior towards the right). The cortical surface has been 'partially inflated' to allow simultaneous viewing of gyri and sulci. In this example, a single cingulate gyrus lies between the cingulate sulcus and the corpus callosum. A schematic representation of cytoarchitectural areas (numbered) of ACC is shown on the enlarged section (left). Cognitive division areas are outlined in red and affective division areas are outlined in blue. These simplified localizations are only approximations for illustrative purposes. A schematized flat map of actual anterior cingulate cortical areas is shown in the bottom right panel. The borders of each sulcus appear as thin unbroken black lines, whereas a combination of broken and dotted lines outline cingulate areas. (Adapted, with permission, from Ref. 7.)

Functional subspecialisation of the ACC is also supported by neuroimaging studies that demonstrate reciprocal suppression of rostral ACC and enhancement of caudal ACC activity during attentionally-demanding cognitive tasks (e.g., divided attention, sequential learning, working memory, and response competition tasks; see review by Drevets & Raichle, 1998), as well as the converse condition of suppressed caudal ACC and enhanced rostral ACC activity during tasks employing emotional stimuli (e.g., Whalen et al., 1998). Carter et al. (2001) demonstrated that healthy participants, but not patients with schizophrenia, showed an increase in activity in caudal ACC during the commission of errors in a task that elicited strong response conflict. This result suggests that error monitoring deficits in schizophrenia may be partially associated with a more generalised dysfunction in the detection of response conflict. However, evidence that the amplitude of the Ne/ERN is modulated by the affective or motivational response to errors (Dikman & Allen, 2000; Luu et al., 2000a) implies that the attenuated Ne/ERN in schizophrenia may reflect a disturbance in the affective or motivational component of error monitoring that is related to dysfunction in the rostral ACC.

The idea that disturbed error-related processing in schizophrenia may be related to motivational or affective processing abnormalities is consistent with the clinical presentation of schizophrenia. An extensive range of disorders of emotion occur in schizophrenia, of which blunted affect and inappropriate affect are the most characteristic and tend to be the most persistent (Bleuler, 1911/1950). Disruptions of motivation and will are reflected in weakened or disjointed volition (manifest as extended periods of underactivity and poorly organised, ill-judged, impulsive activities respectively). PET studies have demonstrated a positive correlation between rCBF in the ACC and the severity of disorganisation symptoms (which incorporates inappropriate affect and bizarre, erratic behaviour; Liddle et al., 1992; Ebmeier et al., 1993; Yuasa, et al., 1995). Using ERPs, Bates et al. (2002) reported a significant negative correlation between the psychomotor poverty syndrome (which includes the symptoms of blunted affect and

underactivity) and Ne/ERN amplitude. To the extent that the error-detection signal derives from a motivational or emotional response to errors generated in rostral ACC, these results suggest that the motivational and/or affective response to errors of commission in patients with schizophrenia may be disordered.

The Go/NoGo task used in the present study was previously employed in an ERP study that demonstrated attenuation of Ne/ERN in patients with schizophrenia compared with healthy participants (Bates et al., 2002). In fMRI, the task was shown to elicit robust activation in rostral ACC during errors of commission by healthy participants (Kiehl et al., 2000). In light of the ERP and fMRI evidence, we hypothesised that patients with schizophrenia would fail to show the same magnitude of rostral ACC activity during the commission of errors as is observed in healthy participants. Given the extensive connections between the rostral ACC and limbic and paralimbic structures, we further hypothesised that reduced activation in limbic and/or paralimbic areas would be elicited in patients with schizophrenia relative to healthy participants. To the extent that the Go/NoGo paradigm includes a degree of response conflict, it was also expected that patients with schizophrenia might show an attenuated response compared to healthy participants in caudal ACC during errors.

Chapter 2.0: Experiment One, Part A: Infrequent target stimulus processing

2.1 Method

2.1.1 Participants

Twenty-eight healthy adults (7 female) and 28 patients with schizophrenia (9 female) participated in the experiment and provided written informed consent. An additional patient was recruited but experienced claustrophobia in the scanner and could not complete the experimental task. In each group, all but one participant was right-handed (assessed using the questionnaire of Annett, 1970). All procedures complied with University and Hospital ethical requirements.

Patients were stable, partially-remitted, medicated outpatients recruited from community mental health teams in Vancouver, BC and outpatient programs at the University of British Columbia Hospital. All patients met DSM-IV criteria for schizophrenia (n = 24) or schizoaffective disorder (n = 4), as diagnosed by an institutional or University Hospital psychiatrist, and confirmed by a research psychiatrist on the basis of a clinical interview and case note review (American Psychiatric Association [APA], 1994). Mean duration of illness was 7 years (SD 7.2), with a range spanning 1 to 24 years.

All patients except two received atypical antipsychotics as their primary medication over the 6-month period preceding scanning. Dosages in each patient were constant during that time. The majority of patients received olanzapine (mean dose 17.3 mg/day, range 7.5-30), while seven patients received risperidone (mean dose: 3.4 mg/day, range 2-6), and one patient received clozapine (500 mg/day). Two patients received a second atypical antipsychotic as an adjunctive medication (1 mg/day of risperidone and 50 mg/day of clozapine), while three patients received a typical antipsychotic adjunctive to the atypical medication (5 mg/day of fluphenazine, 5 mg/day of loxapine, and 2 mg/day of trifluoperazine). One patient received only a typical antipsychotic

as their primary medication (10 mg/day loxapine), and one patient received no antipsychotic medication. In addition to antipsychotic medication, several patients were medicated with benzodiazepines (n = 5), anti-cholinergics (n = 6), and anti-depressants (n = 11).

On the day of scanning, a trained psychiatrist evaluated the symptoms experienced by the patients with schizophrenia during the week preceding scanning using the Signs and Symptoms of Psychotic Illness (SSPI) interview schedule (Liddle et al., 2002). The SSPI comprises 20 symptom items scored 0 to 4 according to the severity of the symptom. Mean total score was 12.7 (SD 5.7), with a range of 1 to 23. Syndrome scores were calculated from the items according to the three-syndrome model of schizophrenia described by Liddle (1987a, 1987b). Mean syndrome scores for Reality Distortion (sum of 2 items: delusions and hallucinations), Disorganisation (sum of 3 items: thought disorder, inappropriate affect, and peculiar behaviour), and Psychomotor Poverty (sum of 3 items: blunted affect, poverty of speech, and underactivity) respectively were: 2.8 (SD 2.2; range: 0 - 7), 0.6 (SD 1.0; range: 0 - 4), 3.2 (SD 2.6; range 0 - 9). The low levels of symptomology observed in this sample of patients, (as well as in the samples reported in the subsequent experiments), is consistent with the partially-remitted state of the sample recruited.

Healthy participants were medication-free volunteers without history of neurological or Axis I psychiatric illness. Participant groups did not differ significantly on the demographic variables of age, gender, parental socioeconomic status (Hollingshead & Redlich, 1958), or on estimates of premorbid (National Adult Reading Test [NART]; Nelson, 1982; Sharpe & O'Carroll, 1991) and current (Quick Test; Ammons & Ammons, 1962) intellectual functioning (all tests $p \geq 0.16$; see Table 1 for mean data).

Table 1. Demographic data for patients with schizophrenia and matched healthy control participants.

Variable	Healthy Participants		Patients with schizophrenia	
	Mean	SD	Mean	SD
Age	**28.2**	**8.9**	**31.6**	**10.1**
Parental socioeconomic status (Hollingshead)	**3.0**	**1.3**	**3.2**	**1.5**
Premorbid intellectual functioning (NART)	**116**	**4.6**	**115**	**4.8**
Current intellectual functioning (Quick Test)	**109**	**11.2**	**104**	**11.8**

2.1.2 Procedure

In each of two scanning runs, 244 auditory stimuli were presented to participants using a computer-controlled visual and auditory presentation package (VAPP; http://nilab.psychiatry.ubc.ca/vapp/). During auditory stimulus presentation, participants concurrently fixated a constant visual stimulus, a white rectangle, displayed on a rear-projection screen mounted at the entrance to the magnet bore and viewed by means of a mirror system attached to the head coil. Each auditory stimulus was presented for 200 ms using an MRI-compatible auditory sound-system and noise-attenuating (25dB) headphones fitted with insert earphones. All stimuli were presented at approximately 80dB and each participant reported being able to hear the stimuli and clearly discriminate them from background scanner noise.

Auditory stimuli comprised three classes: Repeating target stimuli were 1500 Hz tones, novel stimuli were non-repeating digital noises (e.g., tone sweeps, whistles), and repeating nontarget stimuli were 1000 Hz tones. Target and novel stimuli (each occurring with a probability of 0.10) were presented against a background of the nontarget stimuli (probability 0.80), with the requirement that between three-to-five nontarget stimuli preceded each occurrence of a target or novel stimulus. Stimuli were presented every 2 s, with the interval between target and/or novel stimuli pseudo-randomly allocated in the range 6-10 s so that those

stimuli were equally likely to occur at 0, 1, and 2 s after the beginning of a 3 s image-acquisition period (i.e., TR). Thus, the haemodynamic response to these stimuli was effectively sampled every second (Josephs et al., 1997).

Participants were instructed to respond as quickly and accurately as possible with their right index finger to each presentation of the target stimulus, and to not respond to either the novel or nontarget stimuli. Responses were recorded using an MRI–compatible fibre-optic response device (Lightwave Medical, Vancouver, BC). Reaction times (RTs) were computed for motor responses committed within 100-2100 ms post-stimulus. Errors of commission included responses to novel and nontarget stimuli within this time window, while errors of omission constituted a failure to respond to target stimuli during this time. Participants performed correctly a block of 12 practice trials prior to scanning.

2.1.3 Imaging parameters

Images were acquired on a standard clinical GE 1.5T system fitted with a Horizon Echo-speed upgrade. A custom head holder was used to minimise movement. Conventional spin-echo T_1-weighted sagittal localising images were acquired to view the positioning of the participant's head in the scanner and to prescribe the functional image volumes. Blood oxygen level dependent (BOLD) contrast images were collected with a gradient-echo sequence (TR/TE 3000/40 ms, flip angle 90°, 24 x 24 cm field of view, 64 x 64 matrix, 62.5 kHz bandwidth, 3.75 mm x 3.75 mm in plane resolution, 5 mm thickness, 29 slices) that effectively covered the entire brain (145 mm axial extent). A total of 142 brain volumes were acquired. Four image volumes collected prior to the presentation of stimuli were discarded from subsequent analyses in order to exclude the effects of the T_1 stabilisation process.

2.1.4 Image processing

Functional images were reconstructed offline, and realigned and motion-corrected using the procedure described by Friston et al. (1995a) and implemented in Statistical Parametric Mapping 99 (SPM99, Wellcome Department of Cognitive Neurology, London, UK. http://www.fil.ion.ucl.ac.uk/spm/). To remove the influence of motion from the data, estimated movement parameters (i.e., three translation and three rotation parameters) were incorporated into the analysis as covariates of no interest (Friston et al., 1996). Moreover, a Group (schizophrenic patients, healthy participants) x Movement (translation, rotation) x Displacement Axis (x, y, z) ANOVA was conducted on the maximal and mean absolute estimated movement parameters to confirm that the participant groups did not differ significantly in extent of head motion.

A mean functional image was constructed in each participant and used to derive parameters for spatial normalisation into the modified Talaraich stereotaxic space implemented in SPM99. Both affine and nonlinear components were used in the spatial normalisation (Friston et al., 1995a). The normalisation parameters for each mean image were then applied to the corresponding functional images for each session, and the images were resampled into isotropic 4mm voxels. The normalised images were smoothed with an 8-mm full width at half-maximum Gaussian kernel to optimise the signal-to-noise ratio and to compensate for intersubject anatomical variation. High frequency noise associated with alterations of the applied radio frequency field was removed using a 0.16 Hz low-pass fifth-order IIR butterworth filter applied to the fMRI time series at each voxel. While all co-ordinates are reported and displayed in the modified Talaraich stereotaxic space implemented in SPM99, a transformation algorithm was applied to these co-ordinates in order to interpret activation patterns within standard Talairach space (i.e., to identify and label functional areas; Talairach & Tournoux, 1998; see http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html for the transformation algorithm).

2.1.5 Image analysis

Statistical analysis was performed within each voxel using the general linear model approach implemented in SPM99. Event-related responses were modelled using a synthetic haemodynamic response function comprised of two gamma functions and their temporal derivatives (Josephs et al., 1997; Friston et al., 1998). The first gamma function modelled the haemodynamic response peak at 6-s post-stimulus, and the second gamma function modelled the small 'overshoot' of the haemodynamic response on recovery. The temporal derivatives of the gamma functions were included to compensate for slight variation in the peak latency of the onset of the haemodynamic response. Event-related responses were modelled separately for five event-types: correct hits to target events ('targets'), correctly-rejected novel events ('novels'), errors of omission on target events ('misses'), errors of commission on novel events ('novel false alarms'), and errors of commission on nontarget events ('nontarget false alarms'). The nontarget events were treated as a baseline and not explicitly modelled. A high-pass filter was applied to remove noise associated with low frequency confounds (e.g., respiratory artifact).

Within-group analyses of target stimulus processing. For each participant, a contrast image summarising the amplitude of the fitted response in each voxel for target stimuli relative to the nontarget baseline was created. These contrast images were then entered into separate second-level, one-sample t-tests (27 degrees of freedom) for each participant group in order to test the null hypotheses that the mean of the observations for target events did not differ significantly from zero in either the healthy participant group or the patient group. The significance of the activation elicited by target events in each group was assessed across the entire brain volume at the cluster level ($p \leq 0.05$ corrected for multiple comparisons, with the height threshold for inclusion in the cluster set at $p \leq 0.005$ uncorrected) according to the method of Friston et al. (1994) implemented in SPM99.

Between-group comparisons of target stimulus processing. The contrast images were also entered into an ANCOVA at the second-level (52 degrees of freedom) to test the null hypothesis that there was no difference between patients with schizophrenia and healthy participants in the mean amplitude of the fitted haemodynamic response elicited by target events, with the effect of reaction time to targets removed as a potential confound (i.e., to ensure that reaction time differences between the healthy and patient groups did not contribute to an activation difference between groups). As for the within-group analyses, the significance of differences between healthy participants and patients with schizophrenia for target events were assessed across the entire brain volume at the cluster level ($p \leq 0.05$ corrected for multiple comparisons, with the height threshold for inclusion in the cluster set at $p \leq 0.005$ uncorrected).

2.2 Results

2.2.1 Behavioural data

Mean reaction times to target stimuli for healthy participants (398 ms; SD 78) and patients with schizophrenia (569 ms; SD 184) differed significantly [$t_{(54)} = -4.517$, $p < 0.0001$]. Healthy participants and patients correctly responded to 99.3% and 95.2% of targets respectively. Both groups committed few error responses: Healthy participants and patients committed false alarms to novel stimuli on 3.0% and 4.3% of novel trials respectively and false alarms to nontarget stimuli on 0.03% and 0.13% of nontarget trials respectively. A Group (healthy participants, patients with schizophrenia) x Inaccuracy (misses, novel false alarms, nontarget false alarms) ANOVA revealed a significant main effect of Group [$F_{(1, 54)} = 5.573$, $p = 0.022$], indicating that patients with schizophrenia performed the task less accurately than healthy participants. While the Group x Inaccuracy interaction failed to satisfy criteria for significance, planned comparisons revealed that patients missed more targets and committed more false alarms to nontarget stimuli

than healthy participants, however, they did not differ significantly from healthy participants on the number of false alarms committed to novel stimuli [$F_{(1,54)} = 1.38$, $p = 0.246$].

2.2.2 Imaging data

The absence of significant main effects and interactions for the Group factor in the ANOVAs examining maximal and mean head motion during scanning suggests that movement did not contribute differentially to the haemodynamic results obtained for healthy participants and patients with schizophrenia. Nevertheless, all results reported in this experiment reflect analyses in which the estimated movement parameters were entered as covariates of no interest so as remove movement-related artefacts from the fMRI time series (Friston et al., 1996).

Target stimulus processing: Healthy participants. The second-level, one sample t-test conducted on data from the 28 healthy participants revealed a single significant cluster of activation encompassing diverse brain regions (11596 voxels, $p < 0.000$ corrected; as explained in the Preface to the thesis, all p values in SPM99 are specified to the third decimal place only). The cluster of activated voxels is illustrated on transaxial brain slices in Figure 6. For many voxels within the cluster, t-statistic values were in excess of 5.72, corresponding to a probability level of 0.05 corrected for multiple comparisons throughout the brain (see Table 2 for voxel-level statistics on selected local maxima within the activated cluster). The random-effects (between-subjects) results closely replicate the pattern of activation reported in the fixed-effects (within-subjects) analysis of data taken from a small sample of 10 healthy participants during auditory target processing (Kiehl et al., 2001a). The cluster incorporates activation in the amygdala-hippocampal complex, in widespread paralimbic cortex at the frontal operculum, rostral ACC, caudal ACC, and posterior cingulate cortex (PCC), and in frontoparietal association cortex at the intraparietal sulcus extending into the precuneus, at the temporoparietal junction, and in dorsal and ventral frontal areas (particularly in the right hemisphere). Other areas of

activation, including in the basal ganglia, thalamus, and cerebellum, are detailed in Table 2 and illustrated in Figure 6.

Target stimulus processing: Patients with schizophrenia. Eight significant clusters of activation were observed for target processing relative to the nontarget baseline in the one-sample t-test conducted on data from the 28 patients with schizophrenia. These clusters are illustrated on transaxial slices in Figure 7, and cluster statistics and voxel-level statistics from selected local maxima within the clusters are provided in Table 3. Consistent with the findings of Kiehl and Liddle (2001), the results suggest that the amount of cortex recruited by patients with schizophrenia during target processing is less extensive than that activated by healthy participants. Several limbic and paralimbic regions that were active in healthy participants at the equivalent significance threshold did not form part of the clusters activated in patients during target processing, including the amygdala-hippocampal complex, rostral ACC, and PCC. However, significant activation was apparent in many brain regions, particularly in caudal ACC and the sensorimotor brain areas typically activated during right-handed responding (e.g., the left postcentral gyrus and anterior SMA). Indeed, the maximal t-score reported for patients in the left postcentral gyrus (i.e., $t_{(27)} = 18.08$, $p < 0.000$ corrected, at co-ordinate x y z = -40 –32 56) was greater than that observed in the left postcentral gyrus for the healthy participant group (i.e., $t_{(27)} = 12.90$, $p < 0.000$ corrected, at co-ordinate x y z = -36 –44 60), demonstrating that the experimental procedure and analysis strategy were capable of identifying reliable activation during target processing in both groups of participants (Callicott et al., 1998). The significant clusters of activation in patients also incorporated paralimbic cortex at the frontal operculum and caudal ACC, as well as heteromodal association cortex in the temporoparietal junction and ventral and dorsal frontal areas. Activation in the intraparietal sulcus was largely restricted to the inferior bank (i.e., the inferior parietal lobule), with little activation apparent in the superior parietal lobule and precuneus, especially in the right hemisphere. Whereas activity in the

dorsolateral prefrontal cortex (Brodmann Areas [BA] 9/10/46) was localised to the right hemisphere in healthy participants, at the equivalent threshold, patients showed bilateral activity in this region. Additional regions activated within the clusters are described in Table 3 and illustrated in the accompanying Figure 7.

Target stimulus processing: Between-group comparisons. The results of the second-level ANCOVA that directly compared the activation elicited in the patient and healthy groups while removing the confounding effect of reaction time differences between the groups are illustrated on transaxial brain slices in Figure 8, and voxel-level statistics for local maxima within the significant clusters of activation are summarised in Table 4. For the contrast assessing regions in which activation elicited in healthy participants was significantly greater than that elicited in patients with schizophrenia, 2 clusters of 3349 and 101 voxels were significant after correcting for multiple comparisons. These clusters encompassed cortex in the amygdala-hippocampal complex, paralimbic cortex in the frontal operculum, rostral ACC, caudal ACC, and PCC, and in heteromodal association areas including bilateral dorsal frontal cortex and cortex at the intraparietal sulcus extending into precuneus, as well as at the right temporoparietal junction, anterior medial frontal cortex, bilateral cortex at the temporo-occipital junction and in the cuneus/lingual gyrus. The greatest relative underactivity was observed in patients compared to healthy participants in the cerebellum bilaterally and in subcortical areas in the thalamus and basal ganglia.

The contrast that tested for regions more strongly activated during target processing in patients with schizophrenia than in healthy participants, revealed no clusters of activation that were significant after correcting for multiple comparisons. The largest clusters of 38 and 56 voxels (corresponding to uncorrected cluster significance levels of 0.011 and 0.003 respectively) were located in the medial-middle frontal cortex (i.e. SMA [BA 6], x y z co-ordinate of voxel of peak activity = -8 –8 60, $t_{(52)} = 4.34$, $p = 0.000$ uncorrected) and in the precentral-postcentral gyri

(i.e., sensorimotor cortex [BA 4/1/2/3], x y z co-ordinate of voxel of peak activity = -44 –16 52, $t_{(52)} = 4.03$, $p = 0.000$ uncorrected).

Figure 6. Illustration of the significant cluster of activation observed in healthy participants during target stimulus processing relative to the nontarget stimulus baseline. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(27)} = 2.77$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The cluster is significant at $p \leq 0.05$ corrected for multiple comparisons.

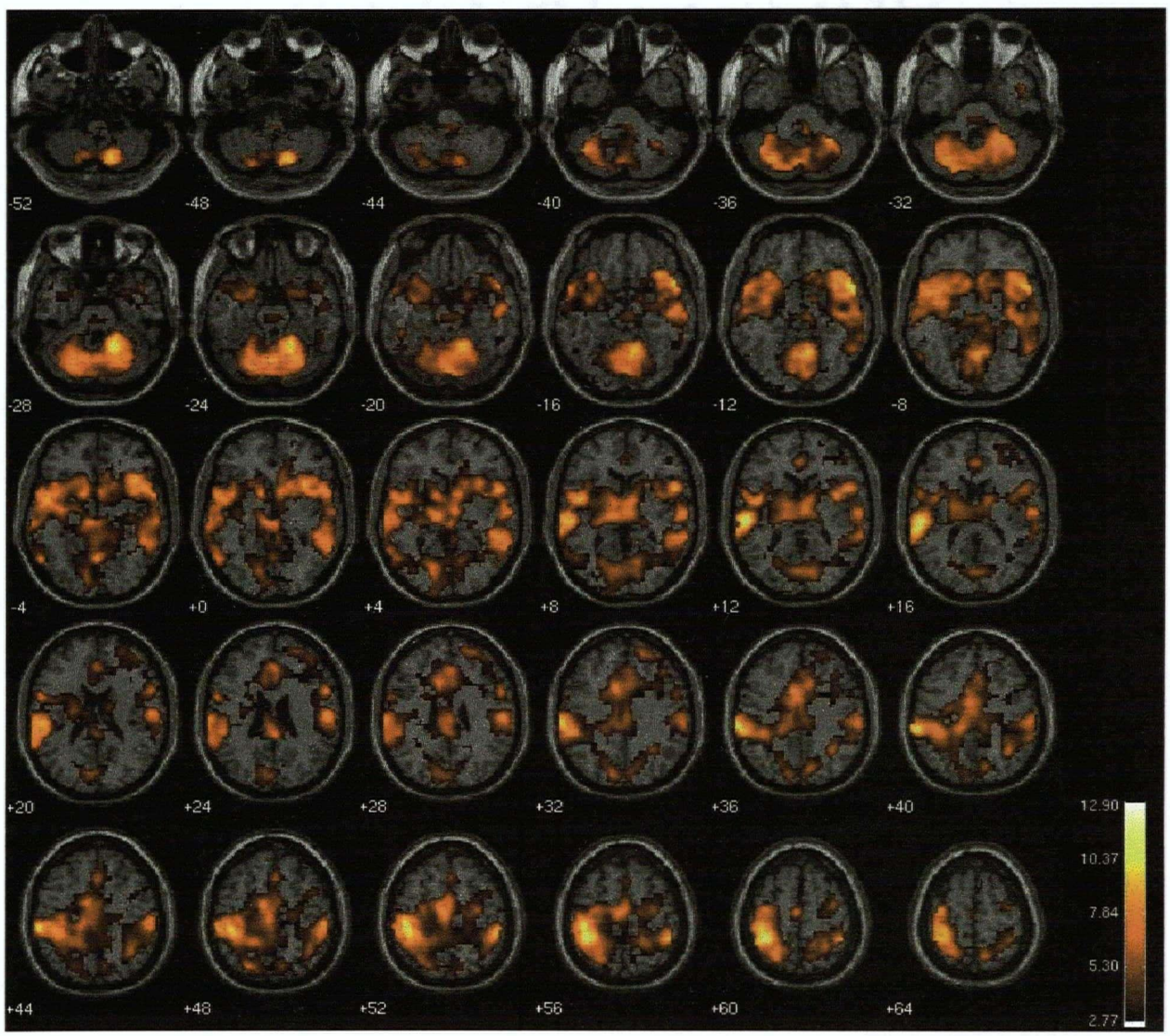


Table 2. Selected local maxima contained within the significant cluster of activation observed in healthy participants during target stimulus processing relative to the nontarget stimulus baseline. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported.

Anatomical Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr} †
	x	y	z			
Limbic – Paralimbic Cortex						
L. Amygdala	-24	-4	20	4.15	0.883	0.000
R. Amygdala	24	0	-24	5.08	0.267	0.000
L. Hippocampus	-16	-12	-20	3.73	0.991	0.000
L. Hippocampus	-32	-24	-12	3.59	0.998	0.001
R. Hippocampus	24	-12	-16	4.57	0.597	0.000
R. Hippocampus	28	-32	-8	4.64	0.544	0.000
L. Anterior Superior Temporal Sulcus (38/22/21)	-56	8	-12	7.98	0.000	0.000
R. Anterior Superior Temporal Sulcus (38/22/21)	52	12	-12	11.22	0.000	0.000
L. Orbitofrontal Cortex (47)	-32	20	-12	7.27	0.001	0.000
R. Orbitofrontal Cortex (47)	36	24	-16	9.56	0.000	0.000
L. Anterior Insula (13)	-44	0	8	10.11	0.000	0.000
R. Anterior Insula (13)	32	16	0	10.15	0.000	0.000
Subcallosal Gyrus (25)	12	24	-12	7.03	0.002	0.000
Rostral Anterior Cingulate Cortex (24/32)	0	36	24	6.81	0.003	0.000
Caudal Anterior Cingulate Cortex (24/32)	-8	12	36	8.47	0.000	0.000
Mid-Cingulate Cortex (24)	-8	-8	48	8.05	0.000	0.000
Posterior Cingulate Cortex (31)	-16	-32	40	6.79	0.003	0.000
Posterior Cingulate Cortex (23/31)	4	-40	24	7.49	0.001	0.000
Posterior Cingulate Cortex (30)	12	-68	8	6.11	0.018	0.000
Temporoparietal Junction						
L. Superior Temporal Gyrus (22/21)	-64	-36	8	8.89	0.000	0.000
R. Superior Temporal Gyrus (22/21)	52	-40	4	8.53	0.000	0.000
L. Inferior Parietal Lobule (40/39)	-60	-48	24	6.27	0.012	0.000
R. Inferior Parietal Lobule (40/39)	64	-36	24	5.96	0.027	0.000
Intraparietal Sulcus						
L. Superior Parietal Lobule (7)	-24	-56	60	8.06	0.000	0.000
R. Superior Parietal Lobule (7)	28	-52	60	6.18	0.015	0.000
L. Inferior Parietal Lobule (40)	-60	-32	40	11.96	0.000	0.000
L. Inferior Parietal Lobule (40)	-36	-52	48	4.60	0.578	0.000
R. Inferior Parietal Lobule (40)	48	-40	56	10.36	0.000	0.000
R. Inferior Parietal Lobule (40)	36	-56	44	6.19	0.015	0.000
L. Precuneus (7)	-24	-72	48	7.42	0.001	0.000
R. Precuneus (7)	12	-76	36	6.10	0.018	0.000
Dorsal and Ventral Frontal Cortex						
L. Middle-Inferior Frontal Gyri (46)	-16	44	12	6.11	0.018	0.000
L. Precentral gyrus (44)	-56	4	20	7.18	0.001	0.000
L. Precentral Gyrus (6)	-36	-16	64	8.49	0.000	0.000
R. Inferior Frontal Gyrus (9)	56	12	24	8.27	0.000	0.000
R. Precentral Gyrus (6)	32	-12	52	6.56	0.005	0.000

continued over...

Table 2 continued.

Anatomical Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Other Neocortex						
L. Postcentral Gyrus (5)	-36	-44	60	12.90	0.000	0.000
R. Postcentral Gyrus (40)	52	-32	52	9.38	0.000	0.000
Medial Frontal Gyrus (6)	-4	-16	52	8.53	0.000	0.000
R. Superior-Middle Frontal Gyri (10/9)	20	52	28	5.88	0.032	0.000
L. Transverse-Superior Temporal Gyri (41/42/22)	-52	-24	12	12.38	0.000	0.000
R. Transverse-Superior Temporal Gyri (41/42/22)	60	-16	8	8.39	0.000	0.000
L. Middle-Inferior Temporal / Middle Occipital Gyri (37/21/19/29)	-56	-64	-4	7.15	0.001	0.000
R. Middle-Inferior Temporal / Middle Occipital Gyri (21/19/37/39)	56	-52	0	8.55	0.000	0.000
L. Cuneus / Lingual-Fusiform Gyri (17/18)	-16	-76	4	7.14	0.001	0.000
R. Lingual-Fusiform Gyri / Cuneus (17/18)	8	-84	-12	7.44	0.001	0.000
Subcortical Structures						
L. Thalamus	-12	-20	4	8.43	0.000	0.000
R. Thalamus	4	-16	8	7.61	0.000	0.000
L. Ventral Striatum	-8	12	-8	7.67	0.000	0.000
R. Ventral Striatum	8	8	-8	5.57	0.075	0.000
L. Caudate	-12	20	-4	6.19	0.015	0.000
R. Caudate	8	8	0	7.35	0.001	0.000
L. Lentiform (Putamen / Lateral Globus Pallidus)	-12	4	0	8.35	0.000	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus)	16	12	0	6.92	0.002	0.000
Midbrain	-4	-28	0	7.98	0.000	0.000
Pons	-4	-24	-32	4.68	0.514	0.000
L. Cerebellum (Uvula)	-28	-68	-36	9.45	0.000	0.000
R. Cerebellum (Dentate)	16	-52	-28	11.17	0.000	0.000
R. Cerebellum (Inferior Semi-Lunar Lobule)	16	-68	-48	9.72	0.000	0.000

Note: L. = Left, R. = Right. All local maxima reported were contained within a single cluster comprising 11596 voxels, which was significant at $p < 0.000$ corrected. †In SPM99, values beyond three decimal places are not provided.

Figure 7. Illustration of the eight significant clusters of activation observed in patients with schizophrenia during target stimulus processing relative to the nontarget stimulus baseline. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(27)} = 2.77$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the clusters are defined in the colourbar located at bottom right. The clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.

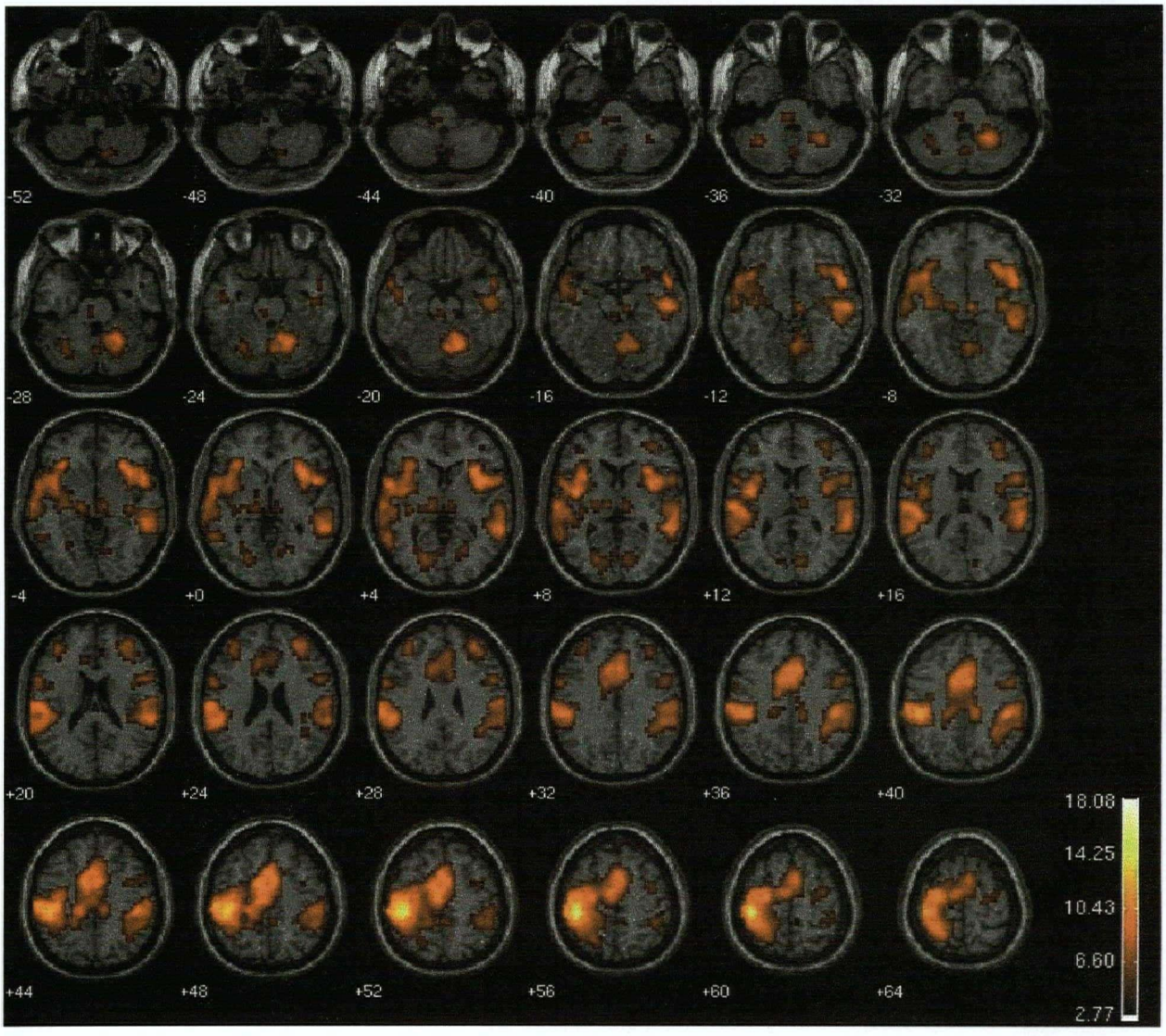


Table 3. Selected local maxima contained within the eight significant clusters of activation observed in patients with schizophrenia during target stimulus processing relative to the nontarget stimulus baseline. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-h) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Anterior Superior Temporal Sulcus (38/21/22) [a]	-56	8	-8	5.71	0.052	0.000
R. Anterior Superior Temporal Sulcus (38/21/22) [b]	52	12	-12	9.09	0.000	0.000
L. Orbitofrontal Cortex (47) [a]	-32	24	-4	6.83	0.003	0.000
R. Orbitofrontal Cortex (47) [b]	28	24	-4	8.13	0.000	0.000
L. Anterior Insula (13) [a]	-44	-4	8	8.91	0.000	0.000
R. Anterior Insula (13) [b]	36	16	0	9.82	0.000	0.000
Rostral Anterior Cingulate Cortex (24/32) [a]	8	36	20	3.00	1.000	0.003
Caudal Anterior Cingulate Cortex (24/32) [a]	8	20	36	8.92	0.000	0.000
Mid-Cingulate Cortex (24) [a]	-8	0	48	10.16	0.000	0.000
Temporoparietal Junction						
L. Superior Temporal Gyrus (22) [a]	-60	-36	12	5.11	0.230	0.000
R. Superior Temporal Gyrus (22) [b]	60	-44	8	7.82	0.000	0.000
L. Inferior Parietal Lobule (40/39) [a]	-64	-24	28	7.96	0.000	0.000
R. Inferior Parietal Lobule (40/39) [b]	56	-36	32	5.45	0.103	0.000
Intraparietal Sulcus						
L. Superior Parietal Lobule (7) [a]	-28	-48	64	8.53	0.000	0.000
L. Inferior Parietal Lobule (40) [a]	-44	-40	48	9.29	0.000	0.000
R. Inferior Parietal Lobule (40) [b]	48	-44	48	5.48	0.094	0.000
L. Precuneus (7) [a]	-12	-44	52	3.69	0.999	0.001
R. Precuneus (7) [a]	4	-44	48	3.52	1.000	0.001
Dorsal and Ventral Frontal Cortex						
L. Middle Frontal Gyrus (10) [f]	-36	44	24	5.33	0.139	0.000
L. Inferior Frontal Gyrus (46) [f]	-36	40	8	3.05	1.000	0.003
L. Inferior Frontal / Precentral Gyri (44) [a]	-60	12	16	5.21	0.193	0.000
L. Precentral / Inferior Frontal Gyri (6/9) [a]	-60	4	28	4.96	0.380	0.000
R. Middle Frontal Gyrus (6) [b]	32	0	56	3.47	1.000	0.001
R. Middle Frontal / Precentral Gyri (9) [b]	52	8	40	4.47	0.783	0.000
R. Middle Frontal Gyrus (46/10) [d]	28	44	24	6.34	0.010	0.000
R. Middle Frontal Gyrus (10/46) [d]	40	44	8	4.08	0.962	0.000
R. Precentral Gyrus (44) [b]	60	8	8	5.37	0.126	0.000
R. Inferior Frontal Gyrus (45/9) [b]	52	12	20	5.13	0.238	0.000

continued over...

Table 3 continued.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates x	y	z	*t* score	P_{corr}	P_{uncorr}
Other Neocortex						
Medial Frontal Cortex (6) [a]	0	12	48	9.01	0.000	0.000
L. Postcentral Gyrus (2) [a]	-40	-32	56	18.08	0.000	0.000
R. Postcentral Gyrus (3) [b]	60	-16	28	5.85	0.035	0.000
L. Superior-Transverse Temporal Gyri (42/22) [a]	-48	-28	16	8.93	0.000	0.000
R. Superior-Transverse Temporal Gyri (42/22) [b]	60	-36	20	7.15	0.001	0.000
L. Middle Temporal Gyrus (21/37) [a]	-56	-56	4	5.35	0.135	0.000
L. Middle Temporal Gyrus (21) [a]	-60	-12	-12	4.45	0.793	0.000
R. Middle Temporal Gyrus (21) [b]	56	-20	-12	7.91	0.000	0.000
L. Cuneus (17) [g]	-20	-72	4	4.66	0.642	0.000
R. Cuneus (18) [c]	12	-80	12	3.97	0.984	0.000
R. Lingual Gyrus (18) [c]	16	-68	-4	3.28	1.000	0.001
Subcortical Structures						
L. Thalamus [a]	-12	-20	4	4.36	0.849	0.000
R. Thalamus [e]	12	-20	8	4.27	0.896	0.000
L. Lentiform (Putamen / Lateral Globus Pallidus) [a]	-28	-8	-4	3.75	0.998	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus) [b]	28	4	8	3.03	1.000	0.003
Midbrain [e / a]	8	-20	-8	5.55	0.079	0.000
Pons [a]	-4	-32	-36	4.19	0.935	0.000
L. Cerebellum [h]	-32	-56	-36	4.44	0.801	0.000
R. Cerebellum (Declive) [c]	16	-60	-20	7.28	0.001	0.000

Note: L. = Left, R. = Right. Cluster **a** = 2997 voxels, $p < 0.000$ corrected; **b** = 1419 voxels, $p < 0.000$ corrected; **c** = 323 voxels, $p < 0.000$ corrected; **d** = 125 voxels; $p < 0.000$ corrected; **e** = 89 voxels, $p < 0.003$ corrected; **f** = 61 voxels, $p < 0.021$ corrected; **g** = 66 voxels; $p < 0.041$ corrected; **h** = 51 voxels, $p < 0.046$ corrected.

Figure 8. Illustration of the two significant clusters of activation in which healthy participants were characterised by a greater haemodynamic response than patients with schizophrenia during target stimulus processing relative to the nontarget stimulus baseline. The effect of the confounding influence of a significant difference in reaction time to target stimuli between the healthy and patient groups was removed in the analysis. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(52)} = 2.67$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The cluster is significant at $p \leq 0.05$ corrected for multiple comparisons.

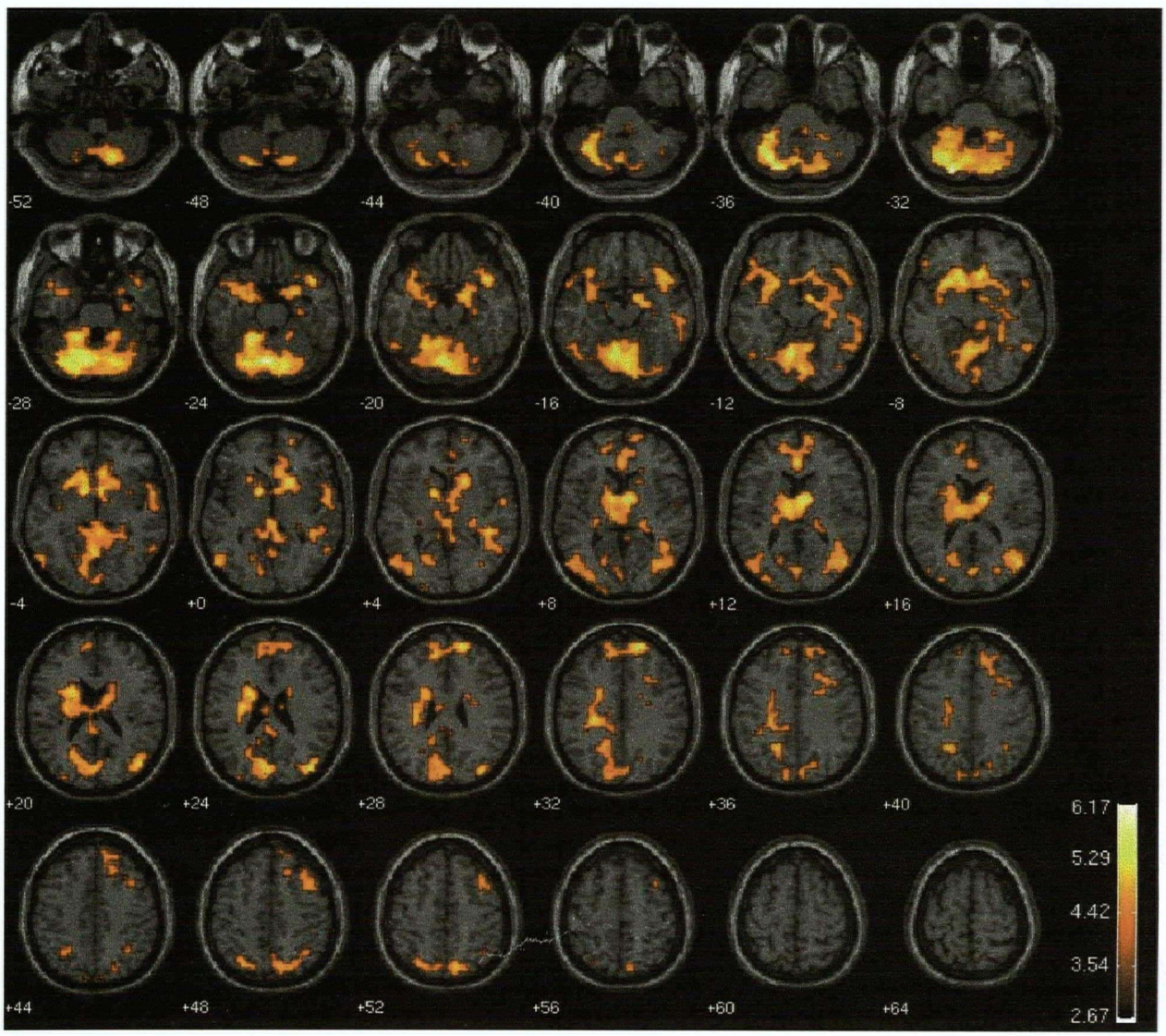


Table 4. Selected local maxima contained within the two significant clusters of activation in which healthy participants were characterised by a greater haemodynamic response than patients with schizophrenia during target stimulus processing relative to the nontarget stimulus baseline. The effect of the confounding influence of a significant difference in reaction time to target stimuli between the healthy and patient groups was removed in the analysis. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-b) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Amygdala [a]	-20	-4	-24	4.13	0.662	0.000
R. Amygdala [a]	24	-12	-16	4.38	0.429	0.000
R. Hippocampus [a]	32	-28	-12	3.48	0.994	0.000
L. Anterior Superior Temporal Sulcus (38/21) [a]	-56	12	-16	3.16	1.000	0.000
L. Anterior Superior Temporal Sulcus (38/21) [a]	-36	12	-20	4.15	0.645	0.000
R. Anterior Superior Temporal Sulcus (38/21/22) [a]	60	4	-4	4.48	0.347	0.000
R. Anterior Superior Temporal Sulcus (38/21/22) [a]	40	16	-20	5.16	0.044	0.000
L. Orbitofrontal Cortex (47) [a]	-32	24	-12	3.98	0.797	0.000
R. Orbitofrontal Cortex (47) [a]	28	24	-20	2.98	1.000	0.000
L. Anterior Insula (13) [a]	-24	16	-8	4.91	0.106	0.000
R. Anterior Insula (13) [a]	40	0	-12	2.91	1.000	0.003
Rostral Anterior Cingulate Cortex (24/32) [a]	0	36	12	5.10	0.054	0.000
Subcallosal Gyrus (25/11) [a]	12	24	-12	4.87	0.122	0.000
Posterior Cingulate Cortex (30/31) [a]	-20	-68	4	3.69	0.961	0.000
Posterior Cingulate Cortex (23/31) [a]	4	-40	24	3.42	0.997	0.000
Intraparietal Sulcus						
L. Superior Parietal Lobule (7) [a]	-28	-68	52	4.34	0.468	0.000
R. Superior Parietal Lobule (7) [a]	28	-68	48	3.16	1.000	0.000
L. Inferior Parietal Lobule (40) [a]	-32	-60	44	2.93	1.000	0.003
R. Inferior Parietal Lobule (40) [a]	36	-56	44	3.26	1.000	0.000
L. Precuneus (7) [a]	-20	-56	36	4.67	0.223	0.000
R. Precuneus (7) [a]	12	-72	52	4.12	0.668	0.000
Dorsal and Ventral Lateral Frontal Cortex						
L. Inferior-Middle Frontal Gyri (47/11) [a]	-48	32	-8	3.36	0.999	0.000
R. Middle-Superior Frontal Gyri (8/6) [a]	40	12	48	3.55	0.988	0.000
R. Precentral Gyrus (9) [a]	40	12	40	3.33	0.999	0.000

continued over...

Table 4 continued.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Other Neocortex						
L. Superior Frontal Gyrus (9) [a]	-12	48	40	3.07	1.000	0.000
L. Medial Frontal Gyrus (10) [a]	-12	44	28	4.66	0.231	0.000
L. Medial-Superior Frontal Gyri (10) [a]	-16	52	12	3.68	0.963	0.000
R. Superior-Middle-Medial Frontal Gyri (9) [a]	20	56	32	4.90	0.109	0.000
R. Superior-Medial Frontal Gyri (10) [a]	20	60	0	3.89	0.861	0.000
R. Inferior-Middle Frontal Gyri (9) [a]	28	20	36	3.66	0.969	0.000
L. Middle-Inferior Temporal / Middle Occipital Gyri (37/20) [a]	-48	-56	-16	3.39	0.998	0.000
L. Inferior Temporal Gyrus (37/19) [b]	-56	-68	-4	4.46	0.362	0.000
L. Middle Occipital / Temporal Gyri (19/18/39) [b]	-32	-88	16	3.41	0.998	0.000
R. Middle Temporal Gyrus (39/19) [a]	48	-72	20	4.52	0.319	0.000
R. Inferior Temporal Gyrus (37/19) [a]	56	-56	-8	3.83	0.902	0.000
R. Superior-Middle Occipital Gyri (19/21) [a]	40	-80	24	4.88	0.118	0.000
R. Middle Occipital / Temporal Gyri / Cuneus (19/39/17/18) [a]	28	-80	12	3.14	1.000	0.000
R. Inferior Occipital Gyrus (19) [a]	44	-76	-12	3.06	1.000	0.000
Cuneus (18/19) [a]	0	-80	20	4.30	0.503	0.000
L. Cuneus (18) [b]	-20	-100	8	3.22	1.000	0.000
L. Lingual Gyrus (18/19) [a]	-12	-76	-4	3.88	0.872	0.000
Subcortical Structures						
L. Thalamus [a]	-12	-8	12	4.40	0.411	0.000
R. Thalamus [a]	8	-4	12	5.21	0.038	0.000
L. Ventral Striatum [a]	-8	12	-8	5.02	0.072	0.000
R. Ventral Striatum [a]	8	12	-8	3.62	0.980	0.000
L. Caudate [a]	-8	4	0	4.02	0.759	0.000
R. Caudate [a]	8	0	12	5.39	0.019	0.000
L. Lentiform (Putamen / Lateral Globus Pallidus) [a]	-12	4	0	5.65	0.008	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus) [a]	20	16	0	4.97	0.085	0.000
Midbrain [a]	0	-28	0	4.34	0.463	0.000
Pons [a]	8	-40	-40	3.06	1.000	0.002
L. Cerebellum (Uvula) [a]	-28	-68	-36	6.17	0.001	0.000
L. Cerebellum (Declive) [a]	-4	-72	-24	6.05	0.002	0.000
R. Cerebellum (Inferior Semi-Lunar Lobule) [a]	16	-68	-52	4.78	0.164	0.000
R. Cerebellum (Declive) [a]	20	-72	-28	4.67	0.225	0.000

Note: L. = Left, R. = Right. Cluster **a** = 3349 voxels, $p < 0.000$ corrected; **b** = 101 voxels, $p < 0.005$ corrected.

2.3 Discussion

This experiment was designed to ascertain the cerebral sites that support the processing of infrequent target stimuli in healthy participants and patients with schizophrenia, and to localise functional disturbance associated with salient target processing in schizophrenia. The data obtained from healthy participants are consistent with previous research from our laboratory conducted using smaller samples and fixed-effects (within-subjects) analyses (Kiehl et al., 2001a, 2001b), and demonstrate that a corticolimbic network encompassing limbic, paralimbic, frontoparietal association cortex, and subcortical areas mediates the processing of infrequent target stimuli. By contrast, and in spite of relatively preserved task performance, patients with schizophrenia showed significant activation in only a subset of the areas active in healthy participants at an equivalent threshold. Most notably absent in the patient group at the adopted threshold was any activation of the limbic cortex (i.e., amygdala and hippocampus).

Consistent with our hypothesis, direct comparison of the participant groups revealed widespread dysfunction throughout much of the corticolimbic network in schizophrenia. Relative underactivity in patients was observed in the amygdala-hippocampal complex, in paralimbic cortex in the frontal operculum, rostral ACC, caudal ACC, and PCC, and in association cortex bilaterally in the dorsal frontal cortex and in the intraparietal sulcus extending into the precuneus, as well as in the inferior aspects of the right temporoparietal junction. Dysfunction was also observed subcortically in the thalamus, throughout the basal ganglia, and in the cerebellum. These group differences were apparent even when the potential effect of RT and accuracy differences between the groups were controlled in the analysis. Thus, the observed dysfunction in schizophrenia is likely due to primary abnormality in this circuitry rather than to the secondary effect of poorer task performance in schizophrenia. Moreover, these widespread

functional abnormalities were observed even in the present sample of chronic, partially-remitted patients who were characterised by quite low levels of symptomology.

These fMRI results augment previous behavioural, autonomic, and ERP evidence for the presence of information processing and attentional dysfunctions in schizophrenia (Bernstein, 1987; Braff, 1993; Bredgaard and Glenthoj, 2000). Abnormal activity was particularly notable in limbic cortex, as well as in paralimbic cortex, and subcortically in the ventral striatum and thalamus (i.e., those brain areas that provide the primary connections between limbic cortex and heteromodal association cortex). Functional abnormality within these areas is likely to contribute to dysfunction in the frontoparietal networks that are specialised for applying goal-directed attention and for re-orienting sustained attention to incoming salient stimuli (Corbetta and Shulman, 2002), thus making it difficult for patients to focus processing resources on the most significant stimuli. Moreover, extrapolating from the theory of Knight and Scabini (1998) to the pattern of dysfunction observed in patients with schizophrenia, abnormality in the hippocampus may contribute to a problem in comparing incoming stimuli with a template of the recent past, thus giving rise to a failure to adequately detect deviation from the template and a subtle but increased difficulty in formulating an appropriate behavioural response to the stimuli. The prominence of the limbic-paralimbic abnormalities observed during task-relevant target stimulus processing are consistent also with the disturbances in motivation and volition that are described clinically in schizophrenia. Although patients performed well at this task and correctly responded to over 95% of target stimuli, the pattern of activation suggests that they and the healthy participants were not equivalently engaged by the exogenous, task-relevant target stimuli.

Other brain areas characterised by a relative reduction in haemodynamic activity in patients compared to healthy participants included the thalamus and cerebellum, where differences between groups were among the most marked. Functional abnormality in these regions during

cognitive task performance has been suggested by Andreasen and colleagues to represent the cardinal pathophysiology of schizophrenia (Andreasen et al., 1998, 1999). That is, dysfunction within cortical-thalamic-cerebellar-cortical circuitry is suggested to disrupt the fluid co-ordination of mental processes and underlie the diverse symptomology expressed in schizophrenia. While the present results are consistent with these areas being particularly impaired during salient information processing in schizophrenia, it must be noted that the present task involved only very simple cognitive operations, and that target processing was associated with a subsequent motor-response that also recruits activity in thalamic and cerebellar regions. Thus, the present task is not well-suited to identifying purely cognition-related functional disturbances in these brain areas. Such abnormalities are more reliably elicited following the processing of stimuli that do not require a behavioural response, as is described in the following section (Chapter 3.0).

It is not possible to ascertain the degree to which medication effects may have contributed to the pattern of differences between the patient and healthy groups. ERP research with previously unmedicated first-episode patients (e.g., Hirayasu et al., 1998; Salisbury et al., 1998; Demiralp et al., 2002) and patients withdrawn from medication (Faux et al., 1993; Ford et al., 1994b) has demonstrated a reduction in the amplitude of the P3 response elicited by auditory oddball target events, implying that at least some of the functional abnormalities observed in this study may be independent of medication status. Preliminary fMRI data from a study conducted in our laboratory using the same experimental task applied in the present study with a sample of eight previously unmedicated first-episode patients demonstrated relative reduction of haemodynamic activity in patients compared to healthy participants in the amygdala-hippocampus, frontal operculum (at the anterior superior temporal sulcus) and PCC, as well as at the intraparietal sulcus and in the cerebellum (Kiehl et al., 2001c). Moreover, data collected in that same patient group following six weeks of treatment with atypical antipsychotic medication indicated

increases in haemodynamic activity relative to the baseline (pre-treatment) scan in the amygdala-hippocampus and PCC. These results suggest that functional abnormalities in at least part of the corticolimbic network are present prior to antipsychotic treatment, and moreover, that medication, at least following a short term of administration, remediates functioning in key areas of the network. Results from the present study suggest that residual functional abnormalities remain within the corticolimbic network mediating the processing of infrequent target stimuli even following persistent medication use.

Significant differences in haemodynamic activity between healthy participants and patients were not observed in the primary and secondary auditory cortices, although a small, non-significant cluster of 7 voxels in the right superior temporal gyrus was comparatively more active in patients than in healthy participants. Significant differences were also not revealed in a supplementary analysis conducted in primary auditory cortex by Kiehl and Liddle (2001), in spite of considerable ERP research suggesting that the function of these areas may be abnormal in schizophrenia during low-frequency, deviant stimulus processing (i.e., as indexed by the reduction in amplitude of the MMN observed in schizophrenia; see Michie, 2001). However, the MMN is typically elicited during passive auditory oddball task presentation. By requiring a motor-response and active processing of the infrequent deviant target stimuli, the active version of the auditory oddball task utilised in the present experiment may not have been sensitive to subtle abnormality in these areas.

Chapter 3.0: Experiment One, Part B: Attentional orienting to salient novel stimuli

3.1 Methods

The novelty processing data reported in this section were acquired in the same scanning runs as the target processing data described in the previous section. The haemodynamic response to target and novel stimuli have been described in separate sections because they address different aspects of the processing of salient exogenous stimuli. Thus, the methods section of the previous section should be referred to for information describing the participants, task procedure, imaging parameters, and image processing procedures. A direct comparison of the haemodynamic response elicited by target and novel stimuli is described in the next section (Chapter 4.0).

3.1.1 Image analysis

Statistical analysis was performed within each voxel using the general linear model approach implemented in SPM99 (Wellcome Department of Cognitive Neurology, London, UK. http://www.fil.ion.ucl.ac.uk/spm/). Modelling of the event-related responses to correctly-rejected novel stimuli were described previously in the target processing section.

Within-group analyses of novel stimulus processing. For each participant, a contrast image summarising the amplitude of the fitted response to novel stimuli relative to the nontarget baseline at each voxel was created. Separate second-level, one-sample t-tests on the contrast images for each participant group (27 degrees of freedom) were conducted to test the null hypotheses that the mean of the observations for novel events in each group did not differ significantly from zero.

Between-group comparisons of novel stimulus processing. The contrast images were also entered into an independent samples t-test at the second-level (54 degrees of freedom) to test the

null hypothesis that there was no difference between patients with schizophrenia and healthy participants in the mean amplitude of the fitted haemodynamic response elicited by novel events. The within-group and between-group tests were assessed for significance at the cluster level across the entire brain volume ($p \leq 0.05$ corrected for multiple comparisons, with the height threshold for inclusion set at $p \leq 0.005$ uncorrected) according to the method of Friston et al. (1994) implemented in SPM99.

Within- and between-group analyses of the functional cerebral asymmetry of attentional orienting processes. To test the hypothesis that healthy participants would show greater extent of activation in the right hemisphere than in the left during novel stimulus processing (i.e., to test the right lateralisation of attentional orienting function), the number of activated voxels that exceeded the height threshold of $p \leq 0.005$ uncorrected for multiple comparisons in the right and the left hemispheres were compared using a repeated measures t-test. This analysis was then also conducted within the patient group. To directly compare the pattern of lateralisation between groups, a laterality index that controls for intersubject variability in absolute brain size [(number of suprathreshold right hemisphere voxels - number of suprathreshold left hemisphere voxels) / total number of suprathreshold voxels] was computed for each participant and entered into an independent samples t-test (see Bullmore et al., 1995 for a discussion of the relative merits of using the laterality index as a measure of cerebral asymmetry).

3.2 Results

3.2.1 Behavioural data

Behavioural results pertaining to novelty stimulus processing were described previously in the target processing section. The ANOVA described in that chapter revealed that, although patients were generally less accurate at performing the task than healthy participants, the planned

comparison comparing the groups on the number of false alarms committed to novel stimuli indicated that patients did not differ significantly from healthy participants [$F_{(1,54)} = 1.38$, $p = 0.246$].

3.2.2 Imaging data

As described for target processing, the results reported in this chapter reflect analyses in which the estimated movement parameters were entered as covariates of no interest so as remove movement-related artefacts from the fMRI time series (Friston et al., 1996).

Novel stimulus processing: Healthy participants. The second-level one sample t-test conducted on healthy participant data revealed five significant clusters of activation elicited during the processing of infrequent, novel auditory events relative to a baseline of frequent, nontarget stimulus processing. Cluster statistics and voxel-level statistics from selected local maxima within the significant clusters are reported in Table 5 and the clusters of activation are illustrated on transaxial slices in Figure 9.

In healthy participants, novelty processing elicited activation in a widespread network of bilateral limbic-paralimbic-association-subcortical areas, including the amygdala-hippocampal complex and parahippocampal gyrus, in the frontal operculum, medial paralimbic cortex in the rostral ACC, caudal ACC, mid-cingulate cortex, and PCC, in heteromodal association cortex at the temporoparietal junction, the intraparietal sulcus extending medially into precuneus, dorsolateral frontal cortex, as well as in the SMA, and subcortically in the thalamus, basal ganglia, midbrain, and cerebellum. At the applied threshold, activation of the ventrolateral frontal cortex was lateralised to the right hemisphere.

The repeated-measures t-test comparing the number of suprathreshold voxels activated in the right and left hemispheres (i.e., those voxels exceeding a height threshold of 0.005 uncorrected)

indicated a laterality effect in healthy participants, with more extensive activation elicited in the right hemisphere than in the left [$t_{(27)} = 2.752$, $p = 0.010$].

Novel stimulus processing: Patients with schizophrenia. Five significant clusters of activation elicited by novelty processing relative to the nontarget baseline were also revealed in the one-sample t-test for patients with schizophrenia. These clusters are illustrated on transaxial slices in Figure 10 and cluster and voxel-level statistics from selected local maxima within the significant clusters are reported in Table 6.

Generally, these clusters encompassed a subset of the regions activated in healthy participants at an equivalent threshold, including association cortex bilaterally at the temporoparietal junction, and dorsal and ventral lateral frontal cortex, and paralimbic cortex in the frontal operculum, caudal anterior- and mid-cingulate gyri (which extended into the SMA). There also appeared to be a limited activation in limbic cortex in the right amygdala-parahippocampal gyrus.

Whereas the activation of ventrolateral frontal cortex was right lateralised in healthy participants, this area was activated bilaterally in patients with schizophrenia. The voxel-level statistics reported for patients in the region of the temporoparietal junction incorporated slightly greater t-score values than observed for healthy participants, indicating strong activation in patients in parts of the network of areas activated in healthy participants during novelty processing. Patients activated more extensive regions of mid-cingulate cortex than healthy participants, yet strikingly failed to activate the limbic cortex in the left amygdala-hippocampal complex, paralimbic cortex in the rostral ACC and PCC, and association cortex bilaterally at the intraparietal sulcus-precuneus, in more superior regions of dorsolateral frontal cortex particularly on the right, and subcortically in the thalamus, basal ganglia, midbrain, and cerebellum.

Figure 9. Illustration of the five significant clusters of activation observed in healthy participants during novel stimulus processing relative to the nontarget stimulus baseline. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(27)} = 2.77$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.

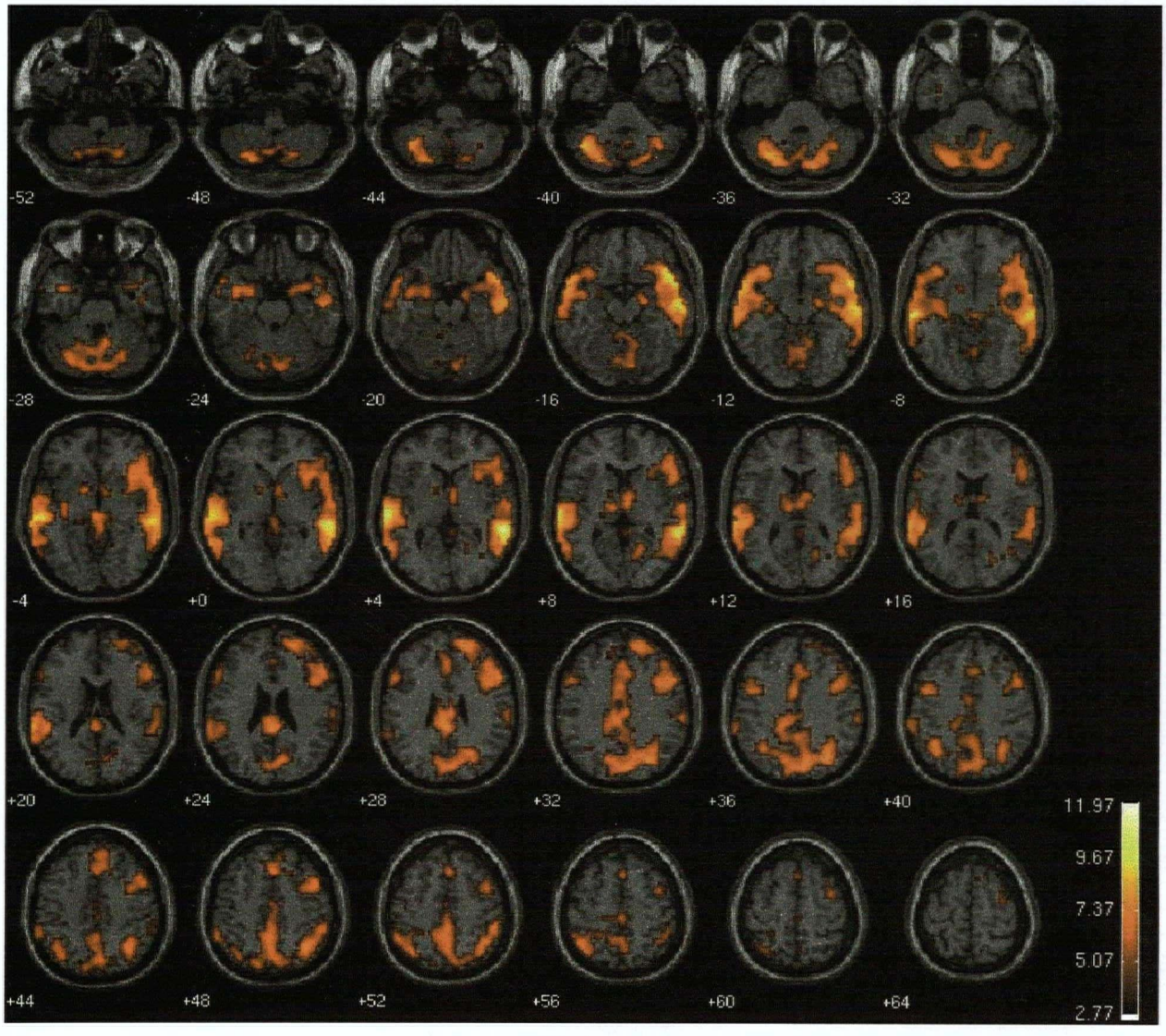


Table 5. Selected local maxima contained within the five significant clusters of activation observed in healthy participants during novel stimulus processing relative to the nontarget stimulus baseline. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-e) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Amygdala [b]	-24	-4	-24	4.79	0.437	0.000
R. Amygdala [a]	20	-8	-16	5.12	0.250	0.000
L. Hippocampus [b]	-28	-20	-12	3.81	0.983	0.000
R. Hippocampus [a]	32	-20	-12	3.08	1.000	0.002
L. Anterior Superior Temporal Sulcus (38/21/22) [b]	-52	12	-16	7.86	0.000	0.000
R. Anterior Superior Temporal Sulcus (38/21/22) [a]	56	8	-12	10.17	0.000	0.000
L. Orbitofrontal Cortex (47) [b]	-36	20	-12	6.83	0.003	0.000
R. Orbitofrontal Cortex (47) [a]	36	16	-4	6.19	0.015	0.000
L. Anterior Insula (13) [b]	-36	16	-12	4.93	0.362	0.000
R. Anterior Insula (13) [a]	40	8	-12	5.52	0.080	0.000
Rostral Anterior Cingulate Cortex (24/32) [b]	0	32	28	4.35	0.747	0.000
Caudal Anterior Cingulate Cortex (24/32) [b]	4	28	36	4.61	0.564	0.000
Mid-Cingulate Cortex (24) [b]	-4	4	36	5.26	0.172	0.000
Posterior Cingulate Cortex (31/23/29/30) [b]	0	-36	28	6.88	0.002	0.000
Temporoparietal Junction						
L. Superior Temporal Gyrus (22) [b]	-64	-36	20	7.80	0.000	0.000
R. Superior Temporal Gyrus (22) [a]	56	-40	4	11.97	0.000	0.000
L. Inferior Parietal Lobule (40/39) [b]	-60	-48	24	3.48	1.000	0.001
R. Inferior Parietal Lobule (40/39) [a]	64	-28	32	4.58	0.591	0.000
Intraparietal Sulcus						
L. Superior Parietal Lobule (7) [b]	-36	-64	52	5.61	0.066	0.000
R. Superior Parietal Lobule (7) [b]	36	-60	48	6.28	0.011	0.000
L. Inferior Parietal Lobule (40) [b]	-36	-56	40	6.31	0.011	0.000
R. Inferior Parietal Lobule (40) [b]	36	-60	44	5.38	0.124	0.000
L. Precuneus (7) [b]	-4	-60	48	4.52	0.635	0.000
R. Precuneus (7) [b]	8	-76	36	6.25	0.012	0.000
Dorsal and Ventral Frontal Cortex						
L. Precentral Gyrus (6) [e]	-46	4	40	4.59	0.590	0.000
L. Inferior-Middle Frontal Gyrus (9) [e]	-48	4	36	4.91	0.362	0.000
L. Inferior-Middle Frontal Gyrus (45) [e]	-56	20	16	3.75	0.989	0.000
R. Precentral Gyrus (44) [a]	52	16	8	5.98	0.025	0.000
R. Inferior–Middle Frontal Gyrus (9) [a]	52	16	28	5.80	0.041	0.000
R. Inferior Frontal Gyrus (46/45) [a]	48	32	8	5.20	0.198	0.000
R. Middle Frontal / Precentral Gyrus (6/8) [a]	48	4	48	5.62	0.066	0.000
R. Middle Frontal Gyrus (9) [a]	48	16	40	4.86	0.392	0.000

continued over...

Table 5 continued.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates x	y	z	*t* score	P_{corr}	P_{uncorr}
Other Neocortex						
L. Transverse-Superior Temporal Gyrus (42/41/22) [b]	-64	-24	4	11.61	0.000	0.000
R. Transverse-Superior Temporal Gyrus (42/41/22) [a]	64	-20	12	5.07	0.272	0.000
L. Middle-Inferior Temporal / Occipital Gyrus (21/39/37/19) [b]	-64	-56	0	6.78	0.003	0.000
R. Middle-Inferior Temporal / Occipital Gyrus (21/39/37/19) [a]	64	-48	-8	6.55	0.026	0.000
R. Postcentral Gyrus (40) [b]	52	-36	52	5.63	0.064	0.000
R. Superior-Middle Frontal Gyrus (10/9) [a]	16	52	28	6.58	0.005	0.000
Medial-Superior Frontal Gyrus (8) [b]	8	40	44	4.54	0.622	0.000
Subcortical Structures						
L. Thalamus (Medial Dorsal Nucleus) [d]	-8	-16	8	4.55	0.612	0.000
R. Thalamus (Medial Dorsal Nucleus) [d]	4	-12	8	5.82	0.038	0.000
L. Lentiform (Putamen / Lateral Globus Pallidus) [d]	-12	4	-4	5.00	0.308	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus) [d]	12	0	-4	3.02	1.000	0.003
Midbrain [a]	0	-24	-4	6.16	0.016	0.000
L. Cerebellum (Tuber) [c]	-40	-60	-40	8.05	0.000	0.000
R. Cerebellum (Uvula) [c]	12	-80	-36	6.34	0.010	0.000

Note: L. = Left, R. = Right. Cluster **a** = 1628 voxels, $p < 0.000$ corrected; **b** = 2145 voxels, $p < 0.000$ corrected; **c** = 636 voxels, $p < 0.000$ corrected; **d** = 113 voxels, $p < 0.003$ corrected; **e** = 79 voxels; $p < 0.021$ corrected.

Figure 10. Illustration of the five significant clusters of activation observed in patients with schizophrenia during novel stimulus processing relative to the nontarget stimulus baseline. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(27)} = 2.77$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.

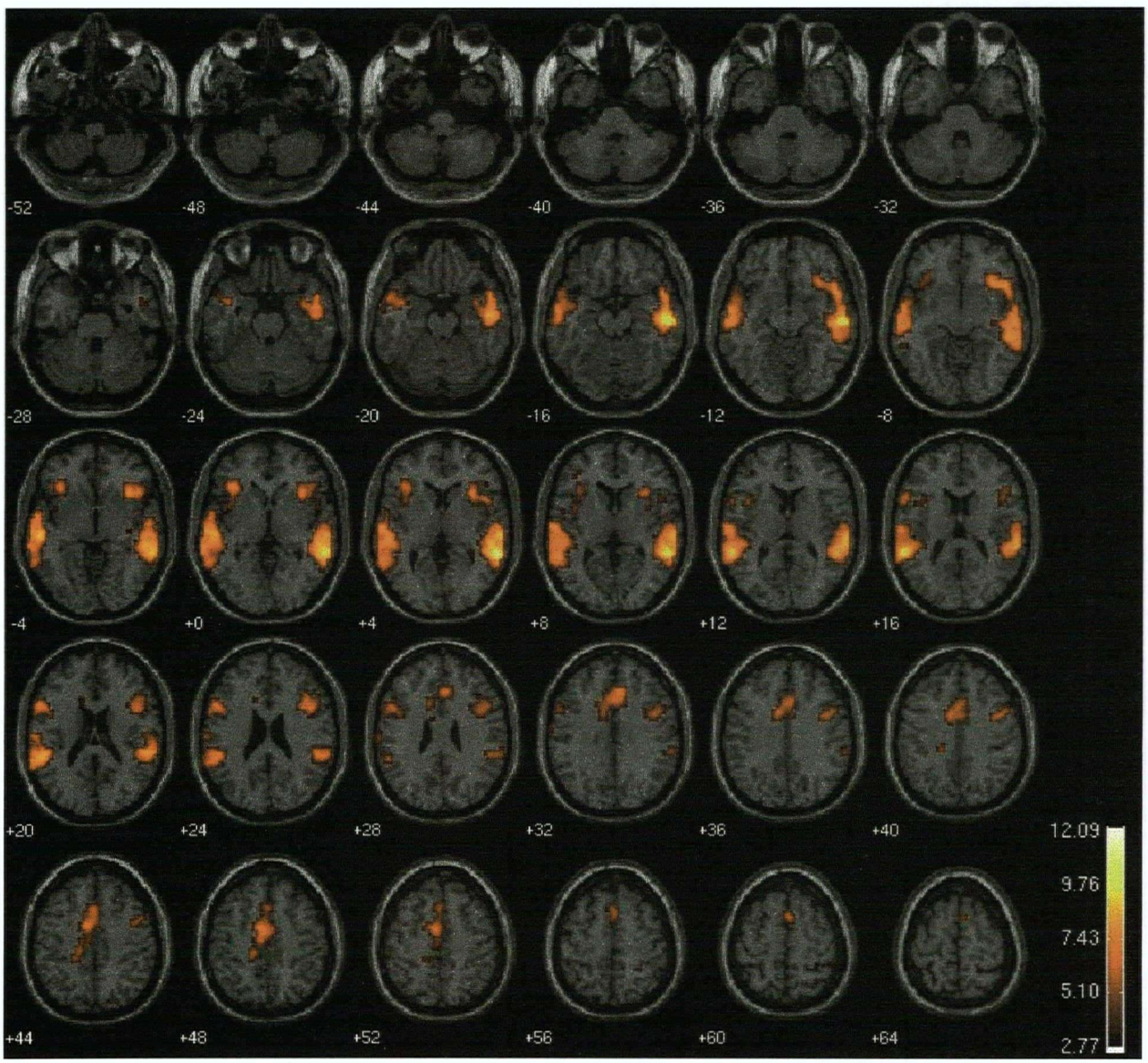


Table 6. Selected local maxima contained within the five significant clusters of activation observed in patients with schizophrenia during novel stimulus processing relative to the nontarget stimulus baseline. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-e) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Anterior Superior Temporal Sulcus (38/21/22) [b]	-52	8	-20	4.07	0.974	0.000
R. Anterior Superior Temporal Sulcus (38/21/22) [a]	52	12	-12	7.62	0.000	0.000
L. Orbitofrontal Cortex (47) [c]	-36	24	0	6.28	0.011	0.000
R. Orbitofrontal Cortex (47) [a]	48	20	-8	7.48	0.000	0.000
L. Anterior Insula (13) [c]	-36	20	4	3.61	0.998	0.001
R. Anterior Insula (13) [a]	36	20	0	5.72	0.045	0.000
Caudal Anterior Cingulate Cortex (24/32) [d]	8	28	32	5.77	0.043	0.000
Mid-Cingulate Cortex (24) [d]	-8	-4	48	6.09	0.019	0.000
Temporoparietal Junction						
L. Superior Temporal Gyrus (22) [b]	-56	-40	16	10.33	0.000	0.000
R. Superior Temporal Gyrus (22) [a]	60	-44	4	12.09	0.000	0.000
L. Inferior Parietal Lobule (40/39) [b]	-60	-44	24	4.48	0.663	0.000
R. Inferior Parietal Lobule (40/39) [a]	64	-32	32	3.26	1.000	0.001
Dorsal and Ventral Frontal Cortex						
L. Inferior Frontal / Precentral Gyrus (45/44/9/6) [c]	-56	16	20	6.14	0.017	0.000
L. Middle Frontal Gyrus (10/46) [c]	-36	40	12	3.23	1.000	0.002
R. Inferior Frontal / Precentral Gyrus (45/9) [e]	44	12	24	4.54	0.753	0.000
R. Middle Frontal / Precentral Gyrus (9/6/8) [e]	40	4	40	4.32	0.888	0.000
Other Neocortex						
L. Transverse-Superior Temporal Gyrus (42/41/22) [b]	-60	-20	12	7.15	0.001	0.000
R. Transverse-Superior Temporal Gyrus (42/41/22) [a]	64	-28	12	7.83	0.000	0.000
L. Middle Temporal Gyrus (21) [b]	-68	-40	0	7.05	0.002	0.000
R. Middle Temporal Gyrus (21) [a]	60	-48	0	7.85	0.000	0.000
Superior – Medial Frontal Gyrus (6) [d]	4	8	60	5.05	0.296	0.000

Note: L. = Left, R. = Right. Cluster **a** = 754 voxels, $p < 0.000$ corrected; **b** = 557 voxels, $p < 0.000$ corrected; **c** = 145 voxels, $p < 0.000$ corrected; **d** = 252 voxels, $p < 0.000$ corrected; **e** = 120 voxels; $p < 0.000$ corrected.

Unlike the result obtained in the healthy participant group, the repeated-measures t-test comparing the number of suprathreshold voxels activated in the right and left hemispheres was non-significant in the patient group, indicating a reduction in the normal pattern of laterality observed in healthy participants [$t_{(27)} = 1.593$, $p = 0.123$].

Novel stimulus processing: Between-group comparisons. Cluster statistics and voxel-level statistics from selected local maxima within the seven significant clusters identified by the two-sample t-test directly comparing the pattern of activation elicited by novel stimuli in the healthy participant and patient groups are reported in Table 7 and illustrated on transaxial slices in Figure 11.

Patients with schizophrenia were characterised by significant relative underactivity compared with healthy participants in diverse brain areas, including the right amygdala-hippocampal complex and parahippocampal gyrus, paralimbic cortex in the right frontal operculum, rostral ACC and PCC, as well as association cortex at the right temporo-parietal-occipital junction, bilateral dorsal frontal cortex, and bilateral cortex in the intraparietal sulcus and precuneus. Subcortically, patients showed highly significant relative reductions of activity in the bilateral cerebellum, with underactivity also apparent in the thalamus and basal ganglia. A further cluster of 36 voxels centred in left posterior hippocampal gyrus in which healthy participants showed greater activation than patients survived only at a cluster significance of $p < 0.05$ uncorrected for multiple comparisons, but is notable given the lesion data suggesting a critical role for posterior hippocampus in novelty detection (Knight, 1996).

No significant clusters were observed in which patients showed greater activation than healthy participants after the criterion for cluster significance of $p < 0.05$ corrected for multiple comparisons was applied. As was observed for target processing, the largest non-significant cluster of 32 voxels ($p = 0.019$ uncorrected) was located in the medial frontal gyrus (i.e., SMA

[BA 6], x y z co-ordinate of voxel of peak activity within the cluster = -8 4 56, $t_{(54)} = 3.96$, p = 0.000 uncorrected).

Though failing to reach significance [$t_{(54)} = 1.304$, p = 0.198], the independent samples t-test comparing groups on the laterality index showed a tendency towards reduced lateralisation in patients relative to controls (healthy mean = 0.21, SD = 0.27; patient mean = 0.11, SD = 0.26).

Figure 11. Illustration of the seven significant clusters of activation in which healthy participants were characterised by a greater haemodynamic response than patients with schizophrenia during novel stimulus processing relative to the nontarget baseline. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(52)} = 2.67$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The cluster is significant at $p \leq 0.05$ corrected for multiple comparisons.

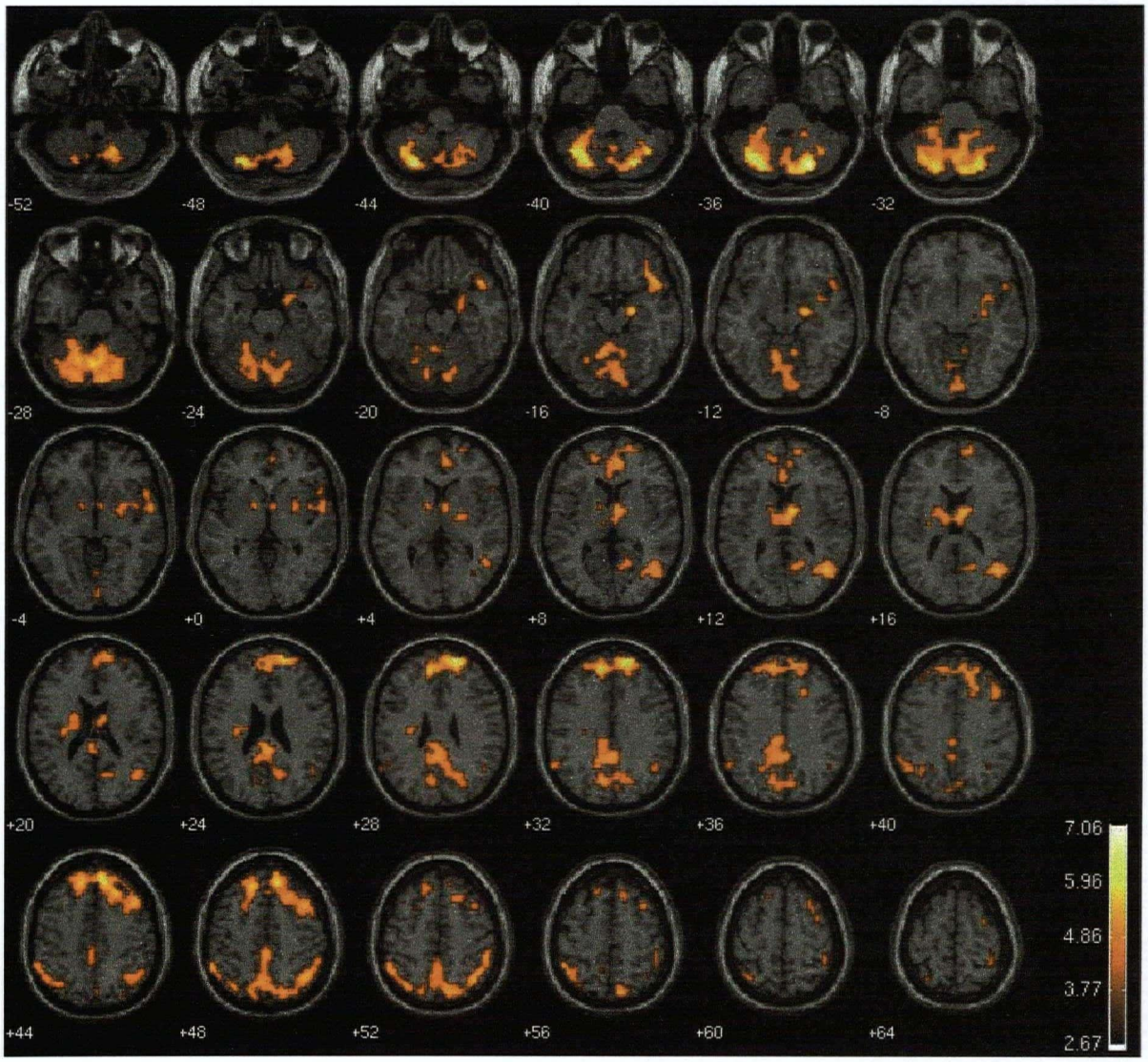


Table 7. Selected local maxima contained within the seven significant clusters of activation in which healthy participants were characterised by greater activation than patients with schizophrenia during novel stimulus processing relative to the nontarget stimulus baseline. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-b) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
R. Amygdala [d]	24	0	-24	4.32	0.466	0.000
R. Hippocampus [d]	20	-12	-16	4.98	0.077	0.000
R. Anterior Superior Temporal Sulcus (38/21/22) [d]	44	16	-20	4.75	0.171	0.000
R. Orbitofrontal Cortex (47) [d]	36	28	-16	4.35	0.434	0.000
R. Anterior Insula (13) [d]	44	0	0	3.19	1.000	0.001
Rostral Ant. Cingulate Cortex (24/32) [b]	8	48	8	4.13	0.639	0.000
Posterior Cingulate Cortex (31/30/29/23) [g]	0	-36	24	4.30	0.477	0.000
	16	-56	8	3.79	0.912	0.000
Intraparietal Sulcus						
L. Superior Parietal Lobule (7) [f]	-32	-68	52	4.70	0.196	0.000
R. Superior Parietal Lobule (7) [g]	40	-60	48	4.58	0.262	0.000
L. Inferior Parietal Lobule (40) [f]	-56	-48	48	4.52	0.302	0.000
R. Inferior Parietal Lobule (40) [e]	42	-56	48	4.49	0.666	0.000
L. Precuneus (7) [g]	-4	-64	48	4.21	0.571	0.000
R. Precuneus (7) [g]	16	-76	52	4.59	0.255	0.000
Dorsal and Ventral Frontal Cortex						
R. Middle Frontal Gyrus (6/8) [b]	44	16	44	4.51	0.638	0.000
	32	12	60	3.61	0.976	0.000
Other Neocortex						
L. Inferior Parietal Lobule (40/39) [f]	-60	-56	32	3.32	0.999	0.001
R. Inferior Parietal Lobule (40/39) [e]	48	-56	32	3.22	1.000	0.001
R. Middle-Superior Temporal / Middle Occipital Gyrus (39/19) [e]	44	-64	12	4.88	0.110	0.000
R. Postcentral Gyrus (40) [g]	52	-36	52	4.01	0.758	0.000
L. Superior-Middle- Medial Frontal Gyrus (9/10) [b]	-12	44	32	5.42	0.016	0.000
	-12	36	48	4.76	0.165	0.000
R. Superior-Middle-Medial Frontal Gyrus (9/10) [b]	16	56	28	6.65	0.000	0.000
	12	40	44	5.78	0.004	0.000
Subcortical Structures						
L. Thalamus (Medial Dorsal Nucleus) [c]	-8	-12	12	3.43	1.000	0.001
R. Thalamus (Anterior Nucleus) [c]	8	-4	12	5.04	0.063	0.000
L. Lentiform (Putamen / Lateral Globus Pallidus) [c]	-12	4	0	4.14	0.631	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus) [c]	28	-8	-8	3.08	1.000	0.002
L. Cerebellum (Pyramis) [a]	-24	-76	-44	7.06	0.000	0.000
R. Cerebellum (Uvula) [a]	28	-76	-36	6.82	0.000	0.000

Note: L. = Left, R. = Right. Cluster **a** = 888 voxels, $p < 0.000$ corrected; **b** = 549 voxels, $p < 0.000$ corrected; **c** = 145 voxels, $p < 0.000$ corrected; **d** = 144 voxels; $p < 0.001$ corrected; **e** = 91 voxels, $p < 0.009$ corrected; **f** = 102 voxels, $p < 0.005$ corrected; **g** = 494 voxels, $p < 0.000$ corrected.

3.3 Discussion

The present experiment employed event-related fMRI during performance of the novelty oddball paradigm in order to localise the functional abnormalities associated with disturbed involuntary orienting to salient novel stimuli in schizophrenia. While patients and healthy participants performed comparably in terms of their accuracy of non-responding to novel stimuli, marked functional differences were nevertheless apparent between the groups. Indeed, the abnormalities elicited during novel stimulus processing in patients appeared more extensive than those described for target stimulus processing, suggesting that reorienting of processing resources to salient novel stimuli may be particularly disturbed in schizophrenia.

In healthy individuals, results converged with existing neuroimaging (Kiehl et al., 2001a, 2001b, Downar et al., 2002), intracranial recording (Halgren et al., 1998), and lesion (Knight, 1984, 1996; Knight et al., 1989; Daffner et al. 2000) data in demonstrating the recruitment of a distributed network of brain sites when attentional resources are involuntarily reoriented away from an ongoing target detection task to incidentally process infrequent novel events. Activation was observed throughout widespread paralimbic and heteromodal association cortex, as well as subcortically in the thalamus, basal ganglia, midbrain, and cerebellum. Moreover, activation was apparent in the amygdala-hippocampus (cf. previous fMRI studies by Kiehl et al., 2001a, 2001b), bringing the fMRI data in line with the lesion and intracranial evidence for limbic involvement in novel stimulus processing.

Many of these brain areas were also active during novelty processing in patients with schizophrenia, with activation apparent bilaterally in heteromodal association cortex at the temporoparietal junction, and ventrolateral and dorsolateral frontal cortex, in paralimbic cortex at the frontal operculum, caudal anterior and mid-cingulate gyri and SMA, and in the right amygdala-parahippocampal gyrus. In the anterior temporoparietal junction, the amplitude of the

fitted response was non-significantly greater in patients than in healthy participants, suggesting that the analysis model was capable of detecting significant activation in both patients and healthy participants, and indicating that hypoactivity in patients with schizophrenia was not generalised throughout the network supporting novelty processing.

However, while function in parts of the corticolimbic circuitry supporting orienting to salient novel stimuli was comparable in patients and healthy participants, multiple loci of dysfunction appear to contribute to the attentional orienting abnormalities observed in schizophrenia during salient novel stimulus processing. Direct comparison of the healthy and patient data revealed relative underactivity in patients bilaterally in heteromodal association cortex at the intraparietal sulcus-precuneus and dorsal frontal cortex, in paralimbic cortex in the rostral ACC extending into medial frontal cortex and in the PCC. Other regions of relative underactivity in patients were observed in the right hemisphere only, including cortex in the frontal operculum, the amygdala-hippocampus-parahippocampal gyrus, and cortex at the temporo-parietal-occipital junction. Subcortically, bilateral areas in the thalamus, the basal ganglia, and the cerebellum were also underactive in patients relative to healthy participants. The observation of relative underactivity during the processing of novel stimuli presented within the context of the oddball paradigm suggests that patients have difficulty reorienting processing resources to salient events that interrupt ongoing attention to the designated target detection task.

ERP research examining novelty oddball processing in brain lesioned patients has emphasised the importance of intact limbic cortex for attentional orienting to novel events, particularly the posterior hippocampal cortex (Knight, 1996). The data obtained in the present experiment in healthy participants suggest that limbic cortex generally (i.e., the anterior amygdala-hippocampal complex and posterior hippocampal cortex), is involved in involuntarily orienting processing resources towards salient novel events. Patients with schizophrenia showed dysfunction within the right amygdala-hippocampal complex and in widespread paralimbic cortex. These extensive

limbic-paralimbic abnormalities imply that patients may be less engaged by the novel stimuli and therefore less inclined to effectively assess their potential significance for ongoing behaviour.

Interesting differences also emerged between the healthy participant and patient groups in the ventral frontoparietal network proposed by Corbetta and Shulman (2002) to be particularly engaged during the processing of salient novel events. Lesions at the temporoparietal junction have been related to a reduction in amplitude of both the P3b elicited during voluntary orienting to task-relevant target events and the P3a elicited by involuntary orienting to infrequent novel and target events (Knight et al., 1989; Yamaguchi and Knight, 1991; Knight, 1997; Verleger et al., 1994). Recent fMRI data imply there may be sub-regions within the temporoparietal junction that are specialised for processing task-irrelevant novel stimuli and task-relevant target events (Downar et al., 2001, 2002). The previous section demonstrated underactivity of the temporoparietal junction in patients with schizophrenia relative to healthy participants during the processing of infrequent target events. Data from the current analysis reveal that the relative underactivity observed in the temporoparietal region during novelty processing by patients lies more posteriorly than that reported for target processing, that is, in the right temporal-parietal-occipital junction. In contrast to lesions in these posterior regions, lesions of the prefrontal cortex differentially reduce P3a and P3b responses, with the former being especially effected (Knight, 1984, 1997; Yamaguchi and Knight, 1991; Daffner et al., 2000). Corbetta and Shulman (2002) posit that ventral frontal areas may function to evaluate the novelty of a stimulus, whereas the temporoparietal junction is more involved in determining its behavioural significance. In the current experiment, the right ventral frontal cortex was extensively activated in the healthy participant group during involuntary orienting to novel stimuli. While activation appeared less extensive in this region in patients, significant differences between patients and healthy participants in the ventral frontal region were restricted to cortex in the right frontal operculum

(i.e., paralimbic cortex incorporating orbitofrontal areas, along with the anterior insula and cortex at anterior superior temporal sulcus). These results may imply that patients retain the ability to evaluate novelty per se, yet experience difficulty in extracting the relevance (or rather, irrelevance) of the novel stimuli for subsequent behaviour.

The contribution of the task context to the present results may be most clearly observed in dorsal frontal and parietal association cortex. In Corbetta and Shulman's (2002) model, the dorsal frontoparietal areas form a system that is involved in preparing and applying goal-directed selection for stimuli and responses. Detection of salient events by the ventral frontoparietal system interrupts activity in that network so as to reorient attention to salient events. In healthy participants, novel stimuli elicited strong bilateral activity in the intraparietal sulcus extending into the precuneus, and in dorsal frontal cortex. On direct comparison of the participant groups, significantly reduced haemodynamic activity in patients relative to healthy participants was observed in both the frontal and parietal areas. A similar pattern of reduced dorsal frontoparietal activity in patients was reported for the infrequent target stimuli in the previous section. The current data suggest that the function of the dorsal frontoparietal areas is disrupted in patients even for salient stimuli that require no subsequent behavioural response. Thus, even though some degree of function was retained in the ventral frontoparietal areas specialised for detecting salient stimuli, patients seem particularly impaired at reorienting processing resources when a salient novel stimulus must interrupt the current task set. That is, there may be a breakdown in schizophrenia of the co-ordinated function of the dorsal and ventral frontoparietal systems that is necessary for orienting to salient stimuli. Given the widespread disturbance observed in patients throughout limbic-paralimbic cortex, it is suggested that a resulting impairment in motivational state may impact on frontoparietal systems and interfere with patients' ability to appropriately assess the relevance of the exogenous stimulus to subsequent behaviour (i.e., there is particular disturbance of the decision/evaluative component of stimulus salience). The idea that a

motivational impairment may contribute to frontal abnormality is consistent with the findings of Daffner et al. (2000), who demonstrated that the P3a elicited by novel stimuli in frontal lobe lesioned patients was markedly reduced in amplitude, and further, that the P3a amplitude attenuation was strongly negatively correlated with measures of apathy (i.e., a reduced P3a amplitude was associated with higher apathy scores).

Cerebellar and subcortical (thalamus and basal ganglia) function were also prominently disturbed in patients during orienting to novel stimuli, in spite of there being no requirement to respond overtly to these stimuli. Andreasen et al. (1998, 1999) place particular emphasis on disordered function of the cerebellum and thalamus in her 'cognitive dysmetria' model of schizophrenia, in which disruption in prefrontal-thalamic-cerebellar connectivity produces difficulties in prioritising, processing, co-ordinating, and responding to information, all of which are relevant to successful performance of the novelty oddball paradigm. The results from the current and previous analyses, however, suggest that dysfunction during the processing of salient exogenous information is more widespread, and in particular, encompasses critical disturbance in higher processing centres located within limbic and paralimbic cortex.

Consistent with research demonstrating a right hemispheric dominance of certain attentional functions in healthy participants (Posner and Peterson, 1990; Mesulam, 1999), suprathreshold activation throughout the right hemisphere was more extensive than in the left. In patients with schizophrenia, this pattern of hemispheric asymmetry during involuntary attentional orienting did not emerge, consistent with previous evidence for a reduction in the normal pattern of cerebral asymmetry (Posner et al., 1998). The nonsignificant trend for group differences in the measure of global hemispheric asymmetry may emerge more strongly in future analyses that could limit the assessment of laterality differences specifically to sites within the corticolimbic network elucidated in the current experiment as mediating the healthy brain's response to salient novel stimuli.

Patients with schizophrenia appear to successfully engage those areas of the brain that have been associated with the automatic/pre-attentive detection of auditory stimulus deviance (as indexed by the MMN), that is, primary auditory and auditory association cortex. Although MMN reductions are among the most consistent ERP abnormalities reported in patients with schizophrenia (Michie, 2001), a recent study indicated that the MMN elicited by novel sounds may be less impaired in schizophrenia than the conventional MMN elicited by repeated rare deviants (Grzella et al., 2001). However, imaging an unattended novelty oddball task is recommended in order to properly characterise any potential group difference in the haemodynamic activity elicited by novel stimulus deviants in brain regions touted as likely generators of the MMN.

The infrequency of committing a motor response in the novelty oddball paradigm renders it unlikely that any pre-potent tendency to respond was established during the task (in the current version, target stimuli represented only 10% of all trials). However, it remains possible that the deviation of both target and novel stimuli from the preponderant nontarget baseline prompted a mobilising of response-related resources that had to be subsequently inhibited for novel trials. Typically, event-related fMRI studies investigating response inhibition create a pre-potent tendency to respond either by presenting a preponderance of trials for which a motor response is required (i.e., targets/Go trials; e.g., Garavan et al., 1999; Braver et al., 2001), or by inserting cue or warning stimuli prior to the presentation of the target/Go or nontarget/NoGo stimuli (e.g., Konishi et al., 1998; Liddle et al., 2001; Watanabe et al., 2002). When the activation elicited by the nontarget/NoGo stimulus is directly compared to that elicited by the target/Go stimulus, inhibition of a motor response that occurs in the context of a pre-potent tendency to respond elicits bilateral activation in dorsolateral (BA 46/9) and ventrolateral (BA 44/45) prefrontal cortex, as well as in cortex at the intraparietal sulcus (encompassing both the superior [BA 7] and the inferior [BA 40] parietal lobules). Thus, to the extent that any need to inhibit a motor

response was created for infrequent novel stimuli in the current task, response inhibition processes may have contributed to the activation apparent in the prefrontal and parietal cortices. By extension, the relatively decreased activity observed in the intraparietal sulcus of patients with schizophrenia compared to healthy participants may be in part attributable to a disturbance in response inhibition processes in patients with schizophrenia (Kiehl et al., 2000b), although imaging studies have typically related response inhibition problems in schizophrenia to the prefrontal cortices (Rubia et al., 2001; Perlstein et al., 2003).

All but one of the patients recruited into the current experiment were medicated with antipsychotics. Thus, it is possible that medication status may contribute to the results obtained in this study. However, ERP research has shown that the amplitude reduction in the P3a elicited by novel stimuli in patients with schizophrenia is not dependent on medication status (Grillon et al., 1991a; Merrin and Floyd, 1994). Future research using previously unmedicated first-episode patients with schizophrenia will provide an opportunity to assess whether a similar pattern of functional abnormality during salient stimulus processing is present prior to the commencement of neuroleptic treatment.

Although patients strongly activated parts of the corticolimbic network that is recruited by healthy participants during orienting to salient novel stimuli, there were no brain areas in which patients were characterised by significantly greater activation than healthy participants. Previous research has suggested that patients with schizophrenia may experience an increased vulnerability to distraction by task-irrelevant stimuli (Braff, 1993; Grillon et al., 1991a). Such abnormality might have been reflected in relative overactivity in patients in parts of the network during novel stimulus processing, even given the comparable performance accuracy between the patient and healthy participant groups on correct non-responses to novel stimuli. However, distraction by task-irrelevant novel stimuli might more appropriately be indexed by measuring the brain's response to infrequent target stimuli presented immediately following the novel

stimuli rather than the response to novel stimuli per se (cf. Grillon et al., 1991a). That is, there may be some further decrement in processing and responding to a target event that immediately follows a novel stimulus relative to a target event that follows a nontarget (baseline) stimulus. In the task design implemented in the current experiment only task-irrelevant nontarget events immediately followed a novel stimulus, so the effect of distractibility by novel events on the task-relevant target events cannot be readily assessed.

However, it is also possible that areas of relative overactivity during novel stimulus processing in the patient group may emerge when the response to the infrequent target and novel stimuli are compared directly. Previous research from our laboratory using the active oddball detection paradigm (Kiehl et al., 2001a; 2001b) demonstrated that, in healthy participants, relatively greater activation is observed for target than for novel stimuli within many of sites activated by both types of salient stimuli (including the amygdalo-hippocampal complex, paralimbic cortex at the frontal operculum, parahippocampal gyrus, caudal ACC and PCC, posterior association cortex at the temporoparietal junction and at the intraparietal sulcus and precuneus, as well as in anterior frontal areas, and the thalamus, basal ganglia, and cerebellum). If patients with schizophrenia experience increased distractibility by the task-irrelevant novel stimuli, then they might not show the same pattern of relatively greater target-related activation within the network of corticolimbic sites. The following section reports the comparison of the participant groups in an analysis that directly compares the activation elicited by target and novel stimulus processing.

Chapter 4.0: Experiment One, Part C: Target and novel stimulus processing comparisons

4.1 Method

4.1.1 Image analysis

Additional contrasts were specified to estimate and test for differences in the amplitude of the fitted haemodynamic response elicited by the target and novel stimuli at each voxel. For each participant, two contrast images were created in which voxel values represented the difference in amplitude of the fitted response for (i) target stimuli relative to novel stimuli, and (ii) novel stimuli relative to target stimuli. Separate one-sample t-tests were conducted within each group to determine whether there were any brain regions in which the mean difference between the stimulus types differed significantly from zero. A two sample t-test was conducted to directly compare the participant groups on the mean difference in amplitude of the fitted response between target and novel stimuli (i.e., to assess whether there was a Group x Stimulus Type interaction). Significant clusters of activation were again assessed at $p \leq 0.05$ corrected for multiple comparisons across the entire brain (height threshold for inclusion at $p \leq 0.005$ uncorrected; Friston et al., 1994).

4.2 Results

4.2.1 Imaging Data

Target relative to novel stimulus processing: Healthy participants. In healthy participants, the second-level, one-sample t-test that tested for brain areas in which the difference in the amplitude of the fitted haemodynamic response for target events relative to novel events was

significantly different from zero revealed a single large cluster of 6306 voxels that was significant after correction for multiple comparisons. This cluster is illustrated on transaxial brain slices in Figure 12, and selected local maxima from within the cluster are reported in Table 8. Incorporated within the cluster are areas of limbic and paralimbic cortex that showed significant activation in healthy participants during both target and novel stimulus processing. Also activated within the cluster are bilateral heteromodal association areas in the intraparietal sulcus, in parietal cortex at the temporoparietal junction, as well as in dorsal frontal/premotor areas and posterior ventral frontal cortex, all of which were significantly activated in healthy participants by both target and novel events. Activation was also observed throughout the basal ganglia, thalamus, cerebellum, and brainstem structures. Thus, although this network of areas was active in healthy participants during orienting to novelty, the areas were activated more strongly by target processing.

The analysis also highlights the difference in haemodynamic activity elicited by auditory target and novel stimuli within the occipital cortex, as was suggested by the comparisons of each stimulus type against the nontarget baseline. That is, whilst auditory target stimuli elicited suprathreshold activation in widespread occipital cortex in healthy participants, salient novel stimuli that required no behavioural response did not.

Target relative to novel stimulus processing: Patients with schizophrenia. In patients with schizophrenia, the one-sample t-test examining the difference in response amplitude for target relative to novelty processing revealed five significant clusters of activation. These clusters encompassed a subset of the areas the were preferentially active in healthy participants for target relative to novel events (see Figure 13 and Table 9). As in the healthy participants, the paralimbic areas that were active in patients during both target and novel stimulus processing were more strongly activated by the target stimuli relative to novel stimuli. Bilateral intraparietal sulcus and parietal cortex in the temporoparietal junction, as well as dorsal frontal/premotor and

posterior ventral frontal areas were also more strongly activated by target stimuli than novel stimuli in patients with schizophrenia.

Although in healthy participants preferential activation for targets relative to novel stimuli in the right anterior superior-middle frontal cortex did not survive stringent correction for multiple comparisons, in patients with schizophrenia, this area was significantly more active during target than during novel stimulus processing. Conversely, in spite of having observed suprathreshold activation in parts of the occipital cortex in the comparison of target, but not novel, stimuli relative to the nontarget baseline, this difference between target and novel stimulus processing did not emerge as significant at the applied threshold.

Novel relative to target stimulus processing: Healthy participants. After correction for multiple comparisons across the entire brain was applied, the second-level, one-sample t-test conducted on data from the 28 healthy participants revealed no brain areas to be significantly more active during novelty processing than during target processing. Two clusters of 42 and 32 voxels were significant only at an uncorrected level ($p = 0.014$ and $p = 0.028$ respectively). The larger of these was located in the left posterior intraparietal sulcus (i.e., encompassing activation in both the inferior parietal lobule [BA 40] and superior parietal lobule [BA7]), and extending further posteriorly into the precuneus (BA 19; xyz co-ordinate of the voxel of peak activation within the cluster = -36 –72 40, $t = 4.58$, $p = 0.000$ uncorrected). The other cluster of activation encompassed the left inferior-middle frontal gyri (BA 9/45/46; xyz co-ordinate of the voxel of peak activation within the cluster = -52 16 24, $t = 4.50$, $p = 0.000$ uncorrected).

Figure 12. Illustration of the significant cluster of activation in which target stimulus processing elicited a greater haemodynamic response than novel stimulus processing in healthy participants. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(27)} = 2.77$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The cluster is significant at $p \leq 0.05$ corrected for multiple comparisons.

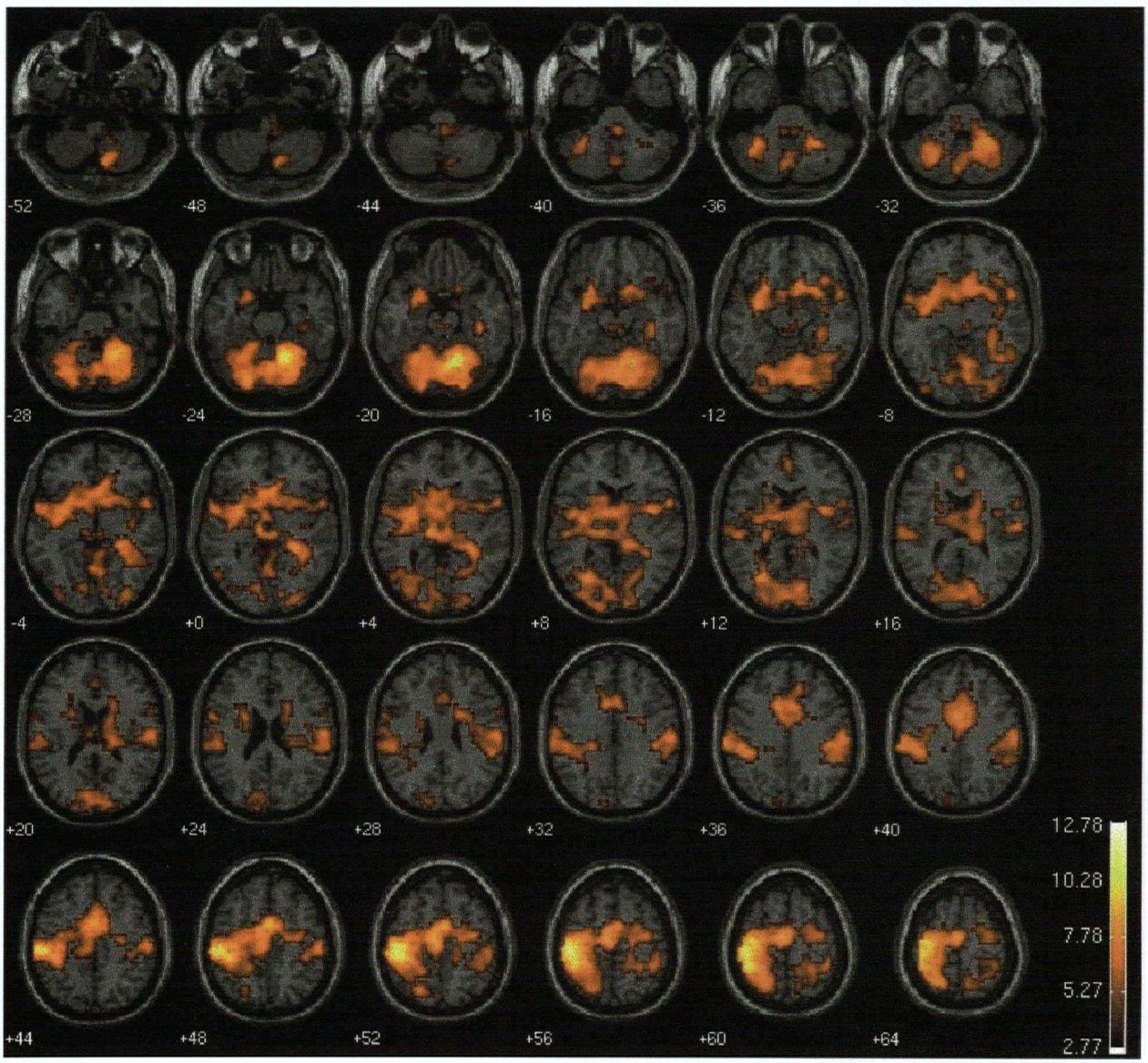


Table 8. Selected local maxima contained within the significant cluster of activation in which target stimulus processing elicited a greater haemodynamic response than novel stimulus processing in healthy participants. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Amygdala	-24	4	-20	5.29	0.155	0.000
R. Amygdala	16	0	-16	3.24	1.000	0.002
L. Hippocampus	-28	-8	-24	2.78	1.000	0.005
R. Hippocampus	28	-40	0	8.30	0.000	0.000
L. Anterior Superior Temporal Sulcus (38/21/22)	-60	4	-4	4.81	0.390	0.000
R. Anterior Superior Temporal Sulcus (38/21/22)	56	8	-8	4.98	0.295	0.000
L. Orbitofrontal Cortex (47)	-24	16	-12	5.99	0.024	0.000
R. Orbitofrontal Cortex (47)	36	24	-12	4.46	0.640	0.000
L. Anterior Insula (13)	-32	0	-12	6.08	0.020	0.000
R. Anterior Insula (13)	28	12	-12	5.90	0.031	0.000
Rostral Anterior Cingulate Cortex (24/32)	0	40	16	4.64	0.505	0.000
Caudal Anterior Cingulate Cortex (24/32)	-8	12	36	6.74	0.003	0.000
Mid-Cingulate Cortex (24)	4	0	48	8.92	0.000	0.000
Posterior Cingulate Cortex (30)	-20	-68	8	4.50	0.603	0.000
Posterior Cingulate Cortex (30)	20	-64	4	3.40	0.999	0.000
Temporoparietal Junction						
L. Inferior Parietal Lobule (40/39)	-56	-28	24	3.84	0.970	0.000
R. Inferior Parietal Lobule (40/39)	56	-36	28	4.82	0.385	0.000
Intraparietal Sulcus						
L. Superior Parietal Lobule (7)	-24	-56	64	7.69	0.000	0.000
R. Superior Parietal Lobule (7)	28	-52	60	3.40	1.000	0.001
L. Inferior Parietal Lobule (40)	-36	-44	56	7.99	0.000	0.000
R. Inferior Parietal Lobule (40)	48	-36	56	4.55	0.571	0.000
L. Precuneus (7)	-20	-68	52	5.05	0.257	0.000
R. Precuneus (7)	8	-60	-64	3.89	0.959	0.000
Dorsal and Ventral Frontal Cortex						
L. Precentral / Inferior Frontal Gyri (6/9)	-56	0	24	4.26	0.784	0.000
R. Inferior Frontal / Precentral Gyri (44/9/6)	60	12	16	3.47	0.999	0.001
L. Precentral / Middle Frontal Gyri (4/6)	-36	-16	60	9.58	0.000	0.000
R. Precentral / Middle Frontal Gyri (6)	32	-12	52	4.96	0.305	0.000

continued over...

Table 8 continued.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates x	y	z	*t* score	P_{corr}	P_{uncorr}
Other Neocortex						
Medial Frontal Gyrus (6)	-4	-12	67	7.86	0.000	0.000
Medial Frontal Gyrus (9)	12	36	36	4.26	0.782	0.000
L. Superior-Transverse Temporal Gyri (42/41)	-48	-24	8	4.51	0.601	0.000
R. Superior-Transverse Temporal Gyri (42/41)	64	-8	12	3.25	1.000	0.002
L. Precentral / Inferior Frontal Gyri (6/9)	-56	0	24	4.26	0.784	0.000
L. Inferior Parietal Lobule (40)	-40	-36	36	6.07	0.020	0.000
R. Inferior Parietal Lobule (40)	64	-36	36	3.64	0.994	0.001
L. Postcentral Gyrus (2/5)	-44	-28	56	12.78	0.000	0.000
R. Postcentral Gyrus (2)	56	-24	48	5.96	0.026	0.000
R. Postcentral Gyrus (40)	60	-16	20	5.30	0.153	0.000
L. Middle-Inferior Temporal / Middle Occipital Gyri (37/19)	-48	-64	4	3.47	0.999	0.001
L. Middle Occipital Gyrus (18)	-28	-72	8	7.40	0.001	0.000
L. Cuneus (18/17)	-16	-100	8	4.78	0.409	0.000
L. Cuneus (19)	-16	-88	28	3.29	1.000	0.000
R. Inferior Temporal Gyrus (37)	52	-56	-8	3.64	0.994	0.001
R. Lingual / Fusiform Gyri (18/19)	16	-76	-16	6.96	0.002	0.000
R. Middle-Inferior Occipital Gyri (18/19)	32	-92	0	4.52	0.597	0.000
R. Cuneus (18/17)	16	-76	12	5.25	0.173	0.000
Subcortical Structures						
L. Thalamus	-12	-24	4	7.69	0.000	0.000
R. Thalamus	8	-24	0	4.95	0.311	0.000
L. Ventral Striatum	-8	8	-8	5.30	0.150	0.000
R. Ventral Striatum	12	12	-8	5.98	0.025	0.000
L. Caudate	-8	12	0	5.03	0.258	0.000
R. Caudate	8	8	4	4.50	0.604	0.000
L. Lentiform (Putamen / Lateral Globus Pallidus)	-32	0	0	6.86	0.003	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus)	12	8	-4	4.74	0.435	0.000
Midbrain	-4	-24	-20	3.99	0.926	0.000
Pons	4	-36	-40	4.21	0.817	0.000
L. Cerebellum (Declive)	-20	-80	-24	7.64	0.000	0.000
L. Cerebellum (Culmen)	-36	-52	-36	6.52	0.006	0.000
R. Cerebellum (Culmen)	16	-56	-24	11.72	0.000	0.000
R. Cerebellum (Inferior Semi-Lunar Lobule)	8	-72	-52	7.00	0.002	0.000

Note: L. = Left, R. = Right. All local maxima reported were contained within a single cluster comprising 6306 voxels, which was significant at $p < 0.000$ corrected.

Figure 13. Illustration of the five significant clusters of activation in which target stimulus processing elicited a greater haemodynamic response than novel stimulus processing in patients with schizophrenia. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(27)} = 2.77$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the clusters are defined in the colourbar located at bottom right. Clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.

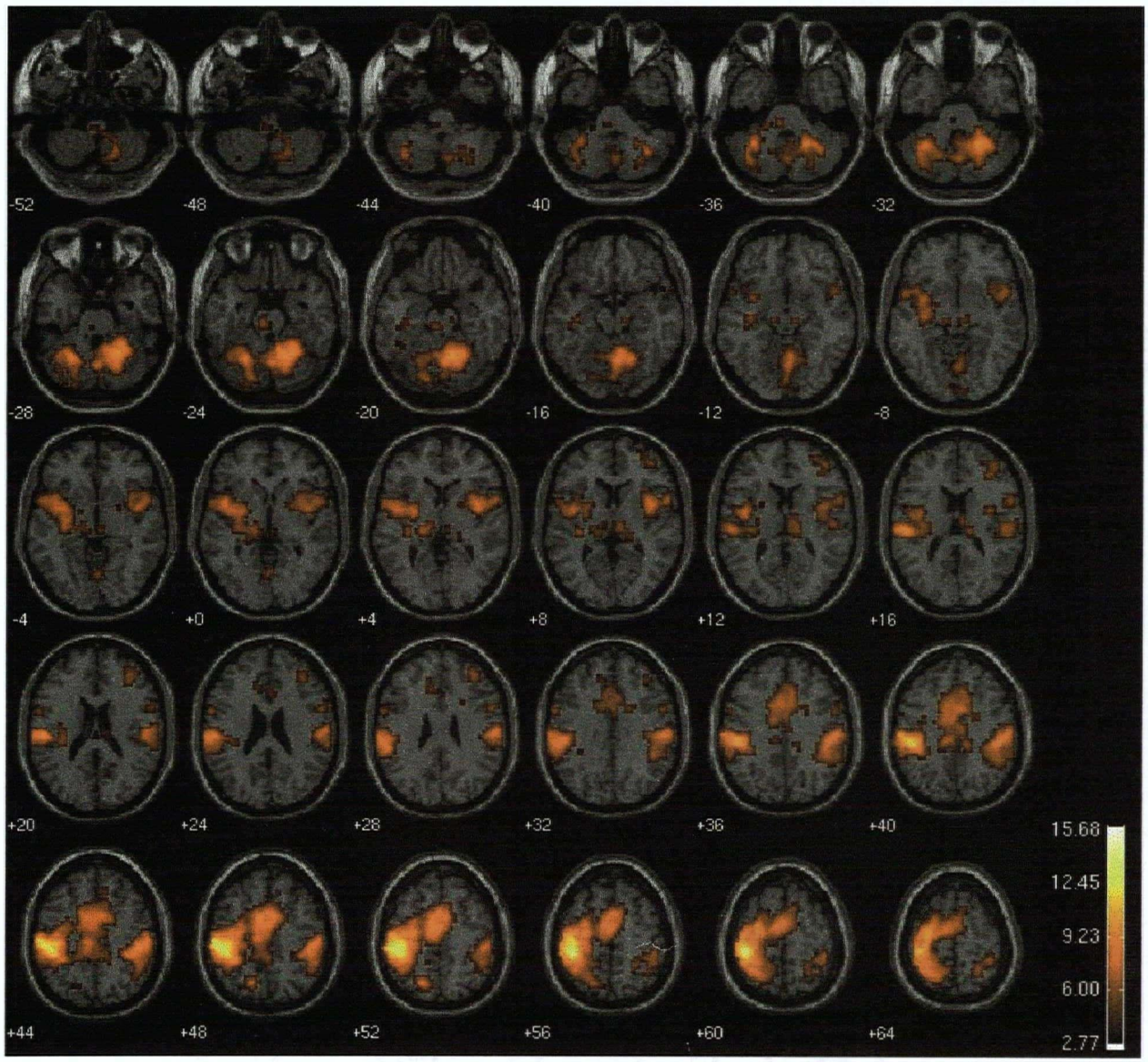


Table 9. Selected local maxima contained within the five significant clusters of activation in which target stimulus processing elicited a greater haemodynamic response than novel stimulus processing in patients with schizophrenia. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-e) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Hippocampus [a]	-32	-20	-12	2.97	1.000	0.003
L. Anterior Superior Temporal Sulcus (38/21/22) [a]	-56	4	4	5.20	0.202	0.000
R. Anterior Superior Temporal Sulcus (38/21/22) [c]	60	8	4	5.16	0.221	0.000
L. Anterior Insula (13) [a]	-44	4	0	5.82	0.038	0.000
R. Anterior Insula (13) [c]	44	0	-4	5.91	0.030	0.000
Rostral Anterior Cingulate Cortex (24/32)[a]	-12	36	28	3.84	0.993	0.000
Caudal Anterior Cingulate Cortex (24/32)[a]	8	8	40	6.47	0.007	0.000
Mid-Cingulate Cortex (24)[a]	-8	0	48	7.89	0.000	0.000
Temporoparietal Junction						
L. Inferior Parietal Lobule (40/39) [a]	-60	-44	28	3.72	0.997	0.000
R. Inferior Parietal Lobule (40/39) [c]	60	-32	24	3.83	0.993	0.000
Intraparietal Sulcus						
L. Superior Parietal Lobule (7) [a]	-28	-48	64	7.23	0.001	0.000
R. Superior Parietal Lobule (7) [c]	36	-56	60	3.55	1.000	0.001
R. Superior Parietal Lobule (7) [c]	28	-48	64	4.40	0.808	0.000
L. Inferior Parietal Lobule (40) [a]	-40	-52	48	4.00	0.972	0.000
R. Inferior Parietal Lobule (40) [c]	36	-36	44	6.30	0.011	0.000
R. Inferior Parietal Lobule (40) [c]	40	-52	56	3.78	0.996	0.000
L. Precuneus (7) [a]	-16	64	52	6.64	0.004	0.000
Dorsal and Ventral Frontal Cortex						
L. Precentral / Middle Frontal Gyri (6) [a]	-28	-20	68	9.88	0.000	0.000
L. Precentral / Inferior Frontal Gyri (6/9) [a]	-60	4	32	4.93	0.410	0.000
R. Inferior Frontal / Precentral Gyri (9/44/45/6) [c]	56	8	28	4.48	0.754	0.000
R. Superior Frontal Gyrus (10) [c]	28	60	8	3.05	1.000	0.003
R. Middle Frontal Gyrus (10) [c]	40	44	28	4.10	0.951	0.000
R. Middle Frontal Gyrus (46) [c]	40	44	12	3.61	0.999	0.001

continued over...

Table 9 continued.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates x	y	z	*t* score	P_{corr}	P_{uncorr}
Other Neocortex						
L. Postcentral Gyrus (2) [a]	-40	-32	60	15.68	0.000	0.000
L. Postcentral Gyrus (40) [a]	-52	-24	16	8.99	0.000	0.000
R. Postcentral Gyrus (2) [c]	48	-28	40	8.26	0.000	0.000
R. Postcentral Gyrus (5) [c]	40	-40	64	5.42	0.112	0.000
R. Postcentral Gyrus (3) [c]	60	-16	28	6.19	0.014	0.000
Medial-Superior Frontal Gyri (6) [a]	-4	-8	52	8.26	0.000	0.000
L. Superior-Transverse Temporal Gyrus (42/41/22) [a]	-64	-28	16	3.21	1.000	0.002
R. Superior-Transverse Temporal Gyrus (42/41/22) [c]	52	-20	12	3.87	0.995	0.000
R. Lingual Gyrus (17) [b]	12	-92	-24	3.54	1.000	0.001
Subcortical Structures						
L. Thalamus [a]	-20	-20	4	4.61	0.657	0.000
R. Thalamus [d]	8	-20	8	4.18	0.922	0.000
L. Lentiform (Putamen / Lateral Globus Pallidus) [a]	-24	-4	0	5.26	0.169	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus) [c]	24	0	0	3.49	1.000	0.001
Midbrain [b/d]	-8	-28	-20	4.58	0.676	0.000
Pons [b]	-4	-32	-36	4.34	0.843	0.000
L. Cerebellum (Declive) [b]	-24	-60	-24	7.44	0.001	0.000
L. Cerebellum (Cerebellar Tonsil) [b]	-40	-60	-44	5.49	0.092	0.000
R. Cerebellum (Declive) [b]	12	-56	-20	9.61	0.000	0.000
R. Cerebellum (Tuber) [b]	40	-60	-40	5.26	0.169	0.000

Note: L. = Left, R. = Right. Cluster **a** = 2412 voxels, $p < 0.000$ corrected; **b** = 904 voxels, $p < 0.000$ corrected; **c** = 778 voxels, $p < 0.000$ corrected; **d** = 64 voxels; $p < 0.021$ corrected; **e** = 78 voxels, $p < 0.008$ corrected.

Novel relative to target stimulus processing: Patients with schizophrenia. In comparison to the healthy participant data, three significant clusters of activation were revealed by the second-level, one-sample t-test conducted on data from the 28 patients with schizophrenia after whole-brain correction was applied. These clusters are described in Table 10 and illustrated on transaxial brain slices in Figure 14. A cluster comprising 64 voxels incorporated, and extended more superiorly than, the nonsignificant cluster reported for the healthy participant group within the left inferior-middle frontal gyri. The other two clusters were located bilaterally in temporal cortex at the temporoparietal junction, and in the right hemisphere, activation extended anteriorly within the middle temporal gyrus.

Group by Task interaction. The two-sample t-test that tested for areas exhibiting a Group x Task Interaction (i.e., areas in which the participant groups showed a differential pattern of activation for target relative to novelty processing and/or for novelty relative to target processing), revealed a single significant cluster of activation comprising 91 voxels (see Table 11 and Figure 15). The cluster incorporated activation in the left amygdala and in paralimbic cortex within the left frontal operculum and rostral ACC, as well as subcortical activation in the basal ganglia. Examination of the data revealed that healthy participants exhibited greater activation in this area during target relative to novel stimulus processing than did patients with schizophrenia. This effect is presented graphically in Figure 16a, which illustrates the mean magnitude of the difference in amplitude of the fitted response for target relative to novel stimuli in the healthy participant and patient groups within selected limbic and paralimbic voxels listed in Table 11. Although not included in the figure, the same pattern of relatively greater activation in healthy participants during target relative to novel stimulus processing was observed in the basal ganglia structures listed in the table.

Although data from the one sample t-tests suggested that patients may be characterised by relatively increased activity in the right anterior superior-middle frontal cortex during target

relative to novel stimulus processing compared with healthy participants, this effect emerged only at an uncorrected significance level (i.e., in the right anterior superior-middle frontal cortex the peak voxel of activity in the Group x Task interaction was at xyz co-ordinate = 40 44 12, t = 2.08, p = 0.021 uncorrected). The mean magnitude of the difference in amplitude of the fitted response for target relative to novel stimuli in the healthy participant and patient groups within this voxel of peak activity is illustrated in Figure 16b.

Likewise, the suggestion that patients may be characterised by relatively increased activity bilaterally in the temporal lobes during novel relative to target stimulus processing compared to healthy controls was also apparent at an uncorrected level of significance only (i.e., in the left temporoparietal junction the peak voxel of activity in the Group x Task interaction was at xyz co-ordinate = -64 –36 0, t = 2.80, p = 0.004 uncorrected; in the right hemisphere, the peak voxel of activation lay more anteriorly in the middle temporal gyrus at xyz co-ordinate = 60 –12 –8, t = 3.40, p = 0.001 uncorrected). The mean magnitude of the difference in amplitude of the fitted response for novel relative to target stimuli for each group within these voxels is illustrated in Figure 16c.

Figure 14. Illustration of the three significant clusters of activation in which novel stimulus processing elicited a greater haemodynamic response than target stimulus processing in patients with schizophrenia. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(27)} = 2.77$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the clusters are defined in the colourbar located at bottom right. Clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.

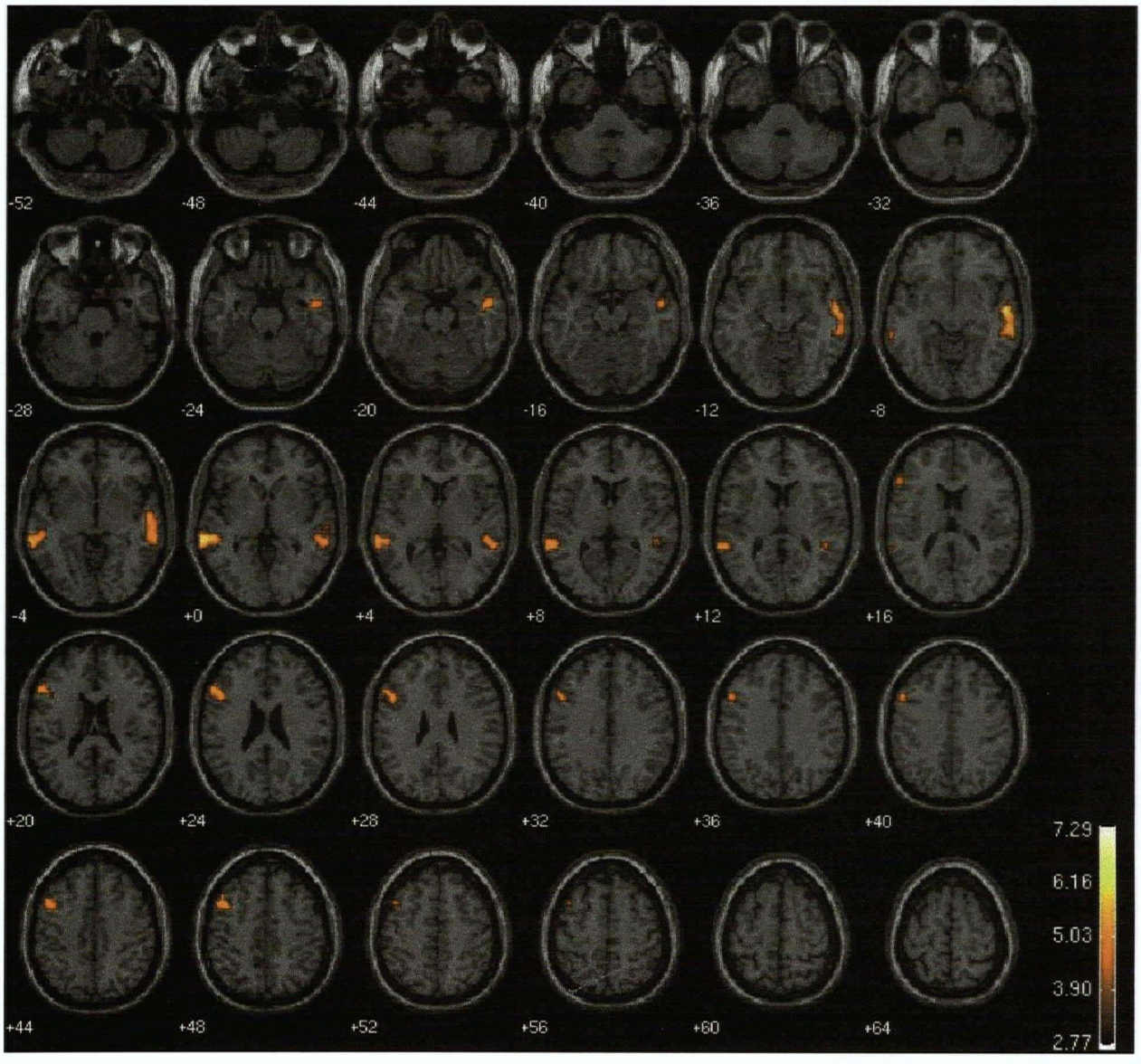


Table 10. Selected local maxima contained within the three significant clusters of activation in which novel stimulus processing elicited a greater haemodynamic response than target stimulus processing in patients with schizophrenia. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-c) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Dorsal and Ventral Frontal Cortex						
L. Middle Frontal Gyrus (9/46) [c]	-56	16	36	4.50	0.737	0.000
L. Middle Frontal Gyrus (8/6) [c]	-44	20	48	4.12	0.945	0.000
L. Inferior Frontal Gyrus (9/45) [c]	-52	20	24	4.29	0.870	0.000
Other Neocortex						
L. Superior Temporal Gyrus (22) [b]	-64	-44	12	4.10	0.950	0.000
L. Middle Temporal Gyrus (21) [b]	-68	-36	0	6.92	0.002	0.000
R. Superior Temporal Gyrus (22) [a]	56	-36	4	3.65	0.999	0.001
R. Middle Temporal Gyrus (21) [a]	56	-12	-8	7.29	0.001	0.000

Note: L. = Left, R. = Right. Cluster **a** = 116 voxels, $p < 0.001$ corrected; **b** = 65 voxels, $p < 0.019$ corrected; **c** = 64 voxels, $p < 0.021$ corrected.

Table 11. Selected local maxima contained within the significant cluster of activation in which healthy participants were characterised by a greater haemodynamic response than patients with schizophrenia during target relative to novel stimulus processing. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Amygdala / Parahippocampal Gyrus	-24	4	-20	2.89	1.000	0.003
L. Orbitofrontal Cortex (47)	-24	24	-12	2.97	1.000	0.002
L. Anterior Insula (13)	-28	12	-8	3.89	0.822	0.000
Rostral Anterior Cingulate Cortex (25)	-4	16	-4	3.59	0.971	0.000
Rostral Anterior Cingulate Cortex (32)	4	20	-8	3.40	0.995	0.001
Subcortical Structures						
L. Ventral Striatum	-8	12	-8	3.84	0.855	0.000
L. Caudate	-8	20	0	3.45	0.992	0.001
L. Lentiform (Putamen / Lateral Globus Pallidus)	-16	12	-8	2.87	1.000	0.003

Note: L. = Left, R. = Right. All local maxima reported were contained within a single cluster comprising 91 voxels, which was significant at $p < 0.014$ corrected.

Figure 15. Illustration of the significant cluster of activation in which healthy participants were characterised by a greater haemodynamic response than patients with schizophrenia during target relative to novel stimulus processing. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(52)} = 2.67$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The cluster is significant at $p \leq 0.05$ corrected for multiple comparisons.

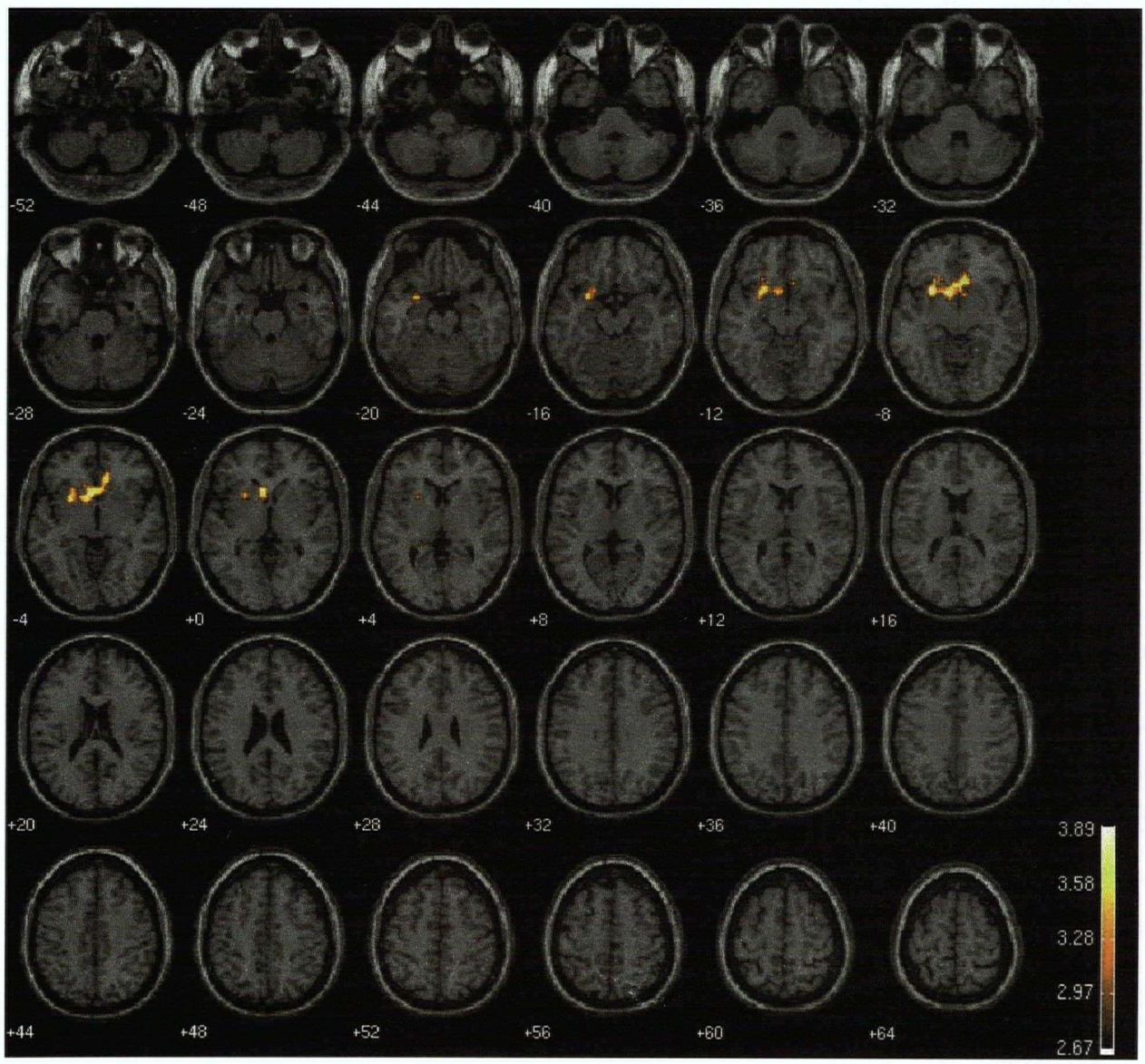
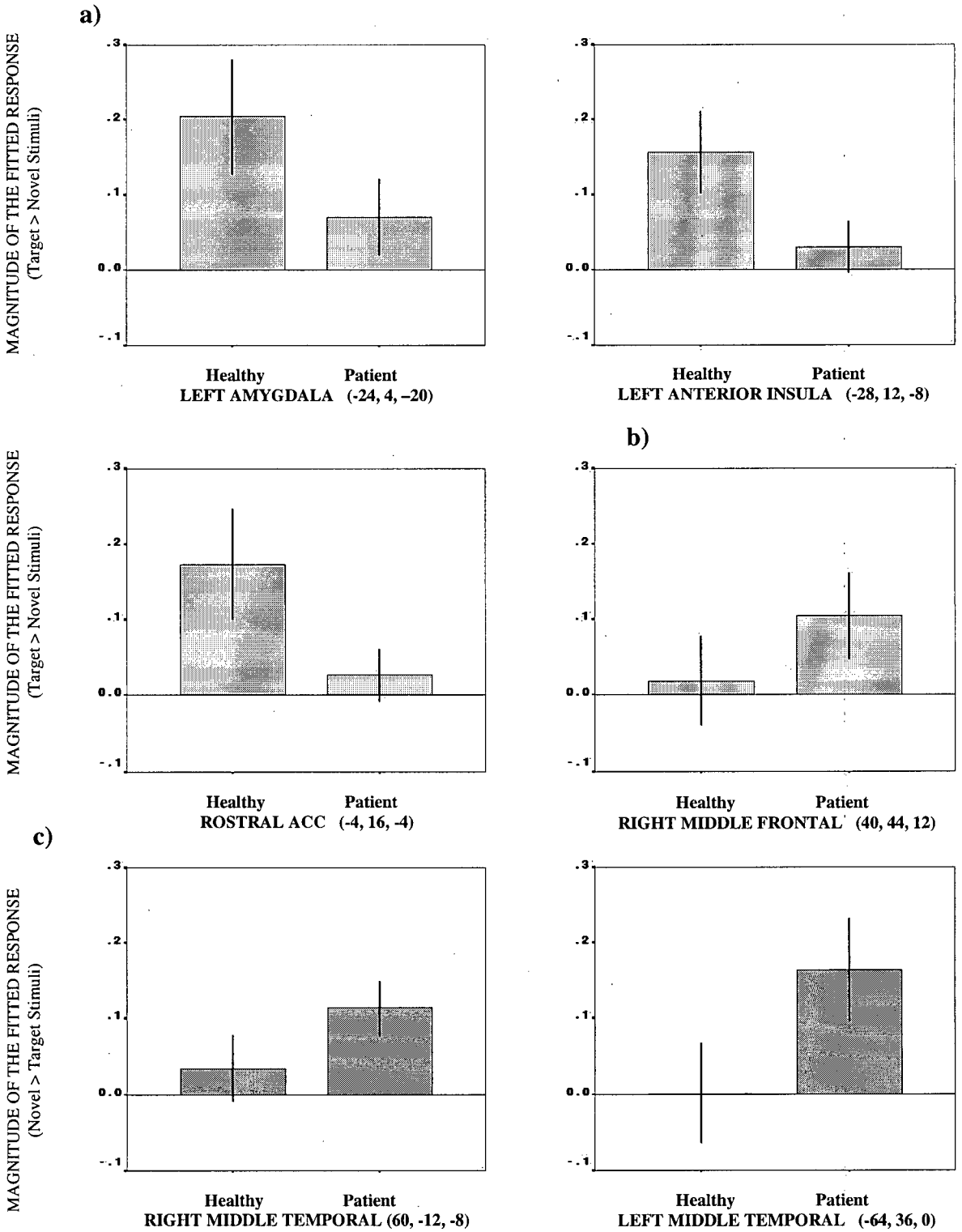


Figure 16. Graphical representation of the mean magnitude (± 2 standard errors) of the difference in amplitude of the fitted response for target and novel stimuli in the healthy participant and patient groups at selected voxels. (a) Selected limbic-paralimbic voxels from within the cluster in which the groups differed significantly on target relative to novel stimulus processing. (b) A right anterior superior-middle frontal voxel in which a trend existed for group differences during target relative to novel stimulus processing. (c) Bilateral middle temporal voxels in which there was a trend for group differences during novel relative to target stimulus processing.



4.3 Discussion

In healthy participants, direct comparison of the haemodynamic response elicited by the infrequent target and novel stimuli revealed relatively greater activity for target events at many sites within the corticolimbic network of areas that was activated during the processing of both salient stimulus types. These areas encompassed limbic-paralimbic cortex, and heteromodal association cortex at the intraparietal sulcus and temporoparietal junction. In frontal association cortex, the relatively greater activation of dorsal and ventral frontal areas by target stimuli was limited to posterior frontal/premotor cortex adjoining sensorimotor cortex. Relatively greater activation for targets was also observed subcortically in the thalamus, basal ganglia, and cerebellum.

Preferential activation for target events in several of these areas (particularly in parietal association cortex, premotor cortex, SMA, and subcortical structures) is commensurate with their role in preparing and applying an overt motor response to target events, an action that was not required for the novel stimuli in the current task paradigm. However, co-activation of these structures with limbic-paralimbic cortex is also consistent with the hypothesis that activity in a widespread corticolimbic circuit is modulated by the relative salience of exogenous stimuli. Thus, in the context of active oddball task performance, infrequent target stimuli are associated with greater activation within the circuit than infrequent novel stimuli that require no behavioural response (see also Kiehl et al., 2001a, 2001b). Conversely, in passive performance of the novelty oddball task, the infrequent 'target' deviants are no longer task-relevant, and are consequently less salient than their infrequent novel counterparts (see Downer et al., 2002).

In healthy participants, the visual cortex was also more active during the processing of auditory target stimuli than during novel stimulus processing. Previous research using the auditory oddball task has also reported activation of the middle occipital gyrus and cuneus

during target relative to novel stimulus processing (Kiehl et al., 2001b). Due to the absence of interconnections linking the unimodal association areas that serve the different sensory modalities (Pandya and Yeterian, 1985), activation within visual cortex during an auditory task may reflect the activity of feedback projections from the heteromodal association cortices which are responsive to both auditory and visual stimuli. It has been suggested that much of the cerebral activity that occurs in healthy participants during target processing in the oddball task is not essential for task performance, but rather, reflects a strategy in which it is advantageous to activate extended brain areas in order to prepare a flexible response to the oddball stimuli (Kiehl and Liddle, 2001; Liddle, 2001).

In general, a similar pattern of relatively greater activity elicited by target compared to novel stimuli was observed in patients with schizophrenia. However, the contrast testing for a Group x Task interaction revealed some important differences between the groups. A significant cluster of activation, reflecting relatively greater activation in the healthy participants compared to patients during target relative to novel stimulus processing, encompassed the amygdala-parahippocampal gyrus, paralimbic cortex at the frontal operculum and rostral ACC, and the basal ganglia (i.e., ventral striatum, caudate, and putamen/globus pallidus). These areas comprise major components of a basal forebrain circuit that modulates behavioural choice, as well as mood, reward assessment, and visceral function (Price, 2003). This circuit, which is illustrated in Figure 17 (Cardinal et al., 2002), comprises the amygdala-hippocampus, ventral striatum (or 'nucleus accumbens' in rodents), ventral pallidum, the orbitomedial frontal cortex, rostral ACC, anterior insula, and the medial thalamus. We suggest that the structures within this circuit play a crucial role in modulating activity within an extended corticolimbic network that processes salient exogenous stimuli in order to determine an appropriate behavioural response to the stimuli. Moreover, the observed difference in activity apparent between the participant

groups in these structures is consistent with the idea that these brain areas are not activated or modulated appropriately in schizophrenia.

Figure 17. Schematic illustration of the basal forebrain circuit that modulates behavioural choice. For simplicity, the hippocampus, although part of the circuit, is not shown (from Cardinal et al., 2002). Reprinted with permission from Elsevier.

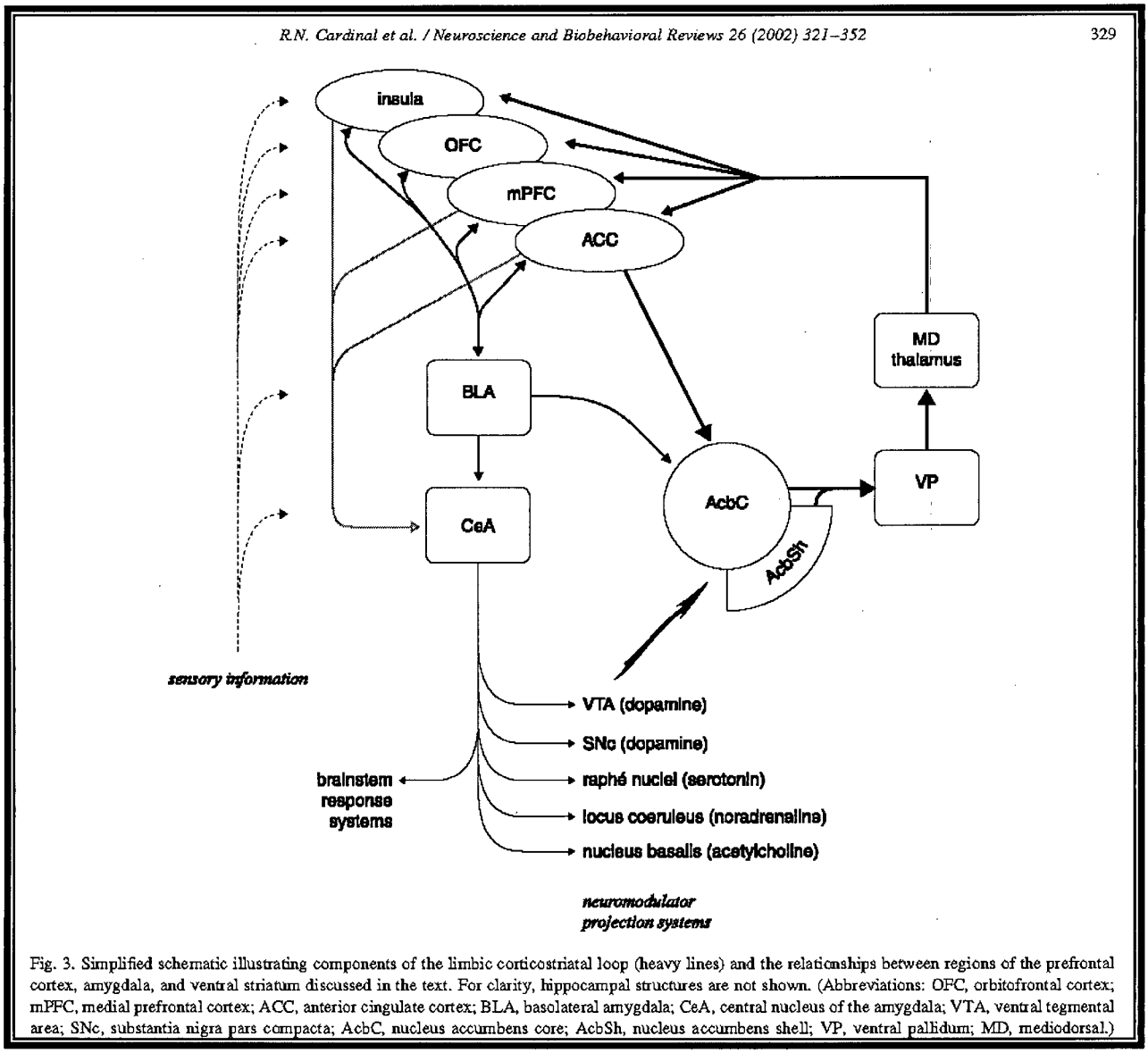


Fig. 3. Simplified schematic illustrating components of the limbic corticostriatal loop (heavy lines) and the relationships between regions of the prefrontal cortex, amygdala, and ventral striatum discussed in the text. For clarity, hippocampal structures are not shown. (Abbreviations: OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; VTA, ventral tegmental area; SNc, substantia nigra pars compacta; AcbC, nucleus accumbens core; AcbSh, nucleus accumbens shell; VP, ventral pallidum; MD, mediodorsal.)

In addition to the relative underactivity of the limbic cortex in patients during target relative to novel stimulus processing, there was also a trend for relative hyperactivity in the right dorsolateral prefrontal area in patients relative to healthy participants. Although many studies have reported task-related hypofrontality in patients with schizophrenia, other studies have demonstrated task-related increases in dorsolateral prefrontal cortex activity (e.g., during working memory task performance; Callicott et al., 2000; Manoach et al., 1999, 2000). In the context of the preserved behavioural performance of patients on the current task, the relatively greater activation observed in the prefrontal cortex of patients during target relative to novel stimulus processing may represent a compensatory mechanism that serves to counteract the relative underactivity observed in limbic cortex and related subcortical areas in the basal forebrain.

There was also a nonsignificant trend for patients with schizophrenia to show relative overactivity bilaterally in the temporoparietal junction during novel relative to target stimulus processing, perhaps indicative of increased distractibility by the task-irrelevant novel stimuli in patients (see Grillon et al., 1991a). This activation lay posterior and inferior to primary auditory cortex, suggesting that this was not an effect caused primarily by a protracted auditory processing of never-experienced auditory events. Corbetta and Shulman (2002) have suggested that the temporoparietal junction is particularly concerned with determining the behavioural significance of a salient event. Thus, overactivity of this cortex during novel relative to target stimulus processing in patients may reflect the assignation of relatively greater processing resources to determining the task-irrelevance of the novel stimuli in this task. That is, the distractibility associated with novel stimuli presented in the context of the novelty oddball paradigm may relate more to problems determining a novel stimulus' behavioural relevance than to difficulties evaluating its novelty per se.

Chapter 5.0: Experiment Two: Supramodal processing of frequent target stimuli relative to nontarget stimuli in healthy participants

The following study was designed in order to ascertain more clearly the impact of task-relevance (i.e., behavioural-salience) on the corticolimbic network that supports infrequent target and novel stimulus processing. We employed a task that removed the salience contributed by stimulus infrequency and stimulus novelty, and allowed a direct comparison of the activity associated with a frequent and familiar stimulus that signalled the need to engage in a behavioural response from an equally-frequent and familiar stimulus that required no subsequent response. In order to characterise the supramodal nature of the healthy brain's response to task-relevant stimuli, the task was conducted in both the auditory and visual modalities with healthy participants only.

5.1 Methods

5.1.1 Participants

Ten right-handed volunteers (mean age 24.4 years, SD 5.1; 5 female) with normal visual and auditory acuity participated in the study (handedness assessed using the questionnaire of Annett, 1970). Participants were medication-free and without history of neurological or psychiatric illness. All procedures complied with University and Hospital ethical requirements, and participants provided written informed consent prior to scanning.

5.1.2 Task

Visual and auditory stimuli were presented to the participant by a computer-controlled presentation system (http://nilab.psychiatry.ubc.ca/vapp/). Visual stimuli were displayed on a

rear projection screen mounted at the entrance to the magnet bore. Participants viewed the screen from a distance of approximately 2 metres by means of a mirror system attached to the head coil. The scanning room and magnet bore were darkened to permit easy visualisation of the stimuli. During both visual and auditory scanning runs, a white 62 x 32 cm rectangular box was presented continuously on the screen to ensure a restricted fixation space during all tasks.

The visual stimuli for the Go and NoGo trials were counterbalanced across participants such that five participants were instructed to respond to the stimulus letter 'X' and to make no motor response to the letter 'K', while the other five subjects responded to the letter 'K' and made no motor response to the letter 'X'. The letters were presented in random order, in white font against a black background, for a period of 200 ms and subtended a visual angle of approximately 6 degrees. Two visual stimulus runs, each containing 35 Go and 35 NoGo trials, were presented to the participant. All trials were presented against a background of no stimulation (i.e., a 'resting' baseline). An ISI of seven seconds ensured that the stimuli had an equal probability of occurring zero, one, or two seconds after the commencement of the three second image volume acquisition period (i.e., TR). Thus, the haemodynamic response to each stimulus type was effectively sampled at one second intervals (Josephs et al., 1997). A constant ISI of 7 seconds was also chosen to minimise any orienting response elicited by unpredictability of the occurrence of a stimulus.

Auditory stimuli were delivered to the participant via insert earphones fitted into 30 dB sound-attenuating MRI-compatible headphones. Five participants were instructed to respond to a 1000 Hz tone and make no response to a 1500 Hz tone, while the other five subjects responded to the 1500 Hz tone and made no response to the 1000 Hz tone. As in the visual paradigm, stimulus duration was 200 ms, with an ISI of 7 seconds. All stimuli were presented at approximately 80 dB, and each participant indicated their ability to hear and discriminate the stimuli from the background noise created by the scanner. Two auditory stimulus runs, each

containing 35 Go and 35 NoGo stimuli, were collected in each participant. The presentation order of the visual and auditory runs was counterbalanced so that half of the participants received the two auditory runs prior to the visual runs.

Across both stimulus modalities, participants were informed of the importance of fast and accurate performance. Participants responded with their right index-finger to the Go stimuli using a commercially available MRI-compatible fibre-optic response device (Lightwave Medical, Vancouver, B.C.). Reaction times to Go events were computed for trials in which the participants responded within 1500 ms of stimulus onset. Failure to respond to a Go event within 1500 ms of stimulus onset constituted an error of omission. Errors of commission were defined as responses that occurred within 1500 ms of the onset of a NoGo stimulus. To ensure comprehension of the task instructions, participants performed a practice block of ten trials prior to scanning.

Post-hoc examination of stimulus presentation order following randomisation revealed that almost 60 percent of trials involved a switch from one stimulus event type to the other on subsequent trials, with only 41 percent of stimuli following a stimulus of the same type. Should participants have become aware of the slight bias towards switching after each trial, the decision to respond or withhold responding to a stimulus may have become slightly easier and evoked a relatively reduced haemodynamic response to the stimulus. While this would make it harder to detect the brain response to the stimuli relative to baseline, it should not have differentially affected the haemodynamic response elicited by the Go and NoGo events.

5.1.3 Imaging parameters

Functional images were acquired in the same manner as outlined previously for the auditory oddball task. For both the auditory and the visual sensory modalities, two scanning runs of 167

functional image volumes were collected, with the initial 4 images excluded from subsequent analyses in order to remove the influence of T_1 stabilisation effects.

5.1.4 Image processing

Functional images were processed and analysed using the Statistical Parametric Mapping 99 software (SPM99, Wellcome Department of Cognitive Neurology, London, UK. http://www.fil.ion.ucl.ac.uk/spm/). Images were reconstructed offline. Each scanning series was independently realigned and motion-corrected using the procedure described by Friston et al. (1996). Corrections for translations and rotations did not exceed 2.5 mm and 3 degrees respectively for any participant. A mean functional image was constructed independently for each scanning series (i.e., 'session') in each participant, and used to derive parameters for spatial normalisation into the modified Talaraich (Talairach and Tournoux, 1988) stereotaxic space implemented in SPM99. Both affine and nonlinear components were used in the normalisation (Friston et al., 1995a). The normalisation parameters for each mean image were then applied to the corresponding functional images for each session, and the images resampled into isotropic 4mm voxels. The normalised images were subsequently smoothed with an 8-mm full-width-at-half-maximum Gaussian kernel to optimise the signal-to-noise ratio and to compensate for intersubject anatomical variation. High frequency noise associated with scanner artefacts was removed using a 0.16 Hz low-pass fifth-order IIR butterworth filter applied to the fMRI time series at each voxel. A high-pass filter was applied to remove noise associated with low frequency confounds (e.g., respiratory artefact).

5.1.5 Image analysis

Statistical analysis was performed using the general linear model approach implemented in SPM99 to estimate and statistically test the effect of the Go and NoGo events on the

haemodynamic response elicited within each voxel. Event-related responses to Go and NoGo stimuli were modelled using a synthetic haemodynamic response function comprised of two gamma functions and their temporal derivatives (Friston et al., 1998; Josephs et al., 1997). The first gamma function modelled the haemodynamic response using a peak latency of 6 s, and the second gamma function modelled the small 'overshoot' of the haemodynamic response on recovery. The temporal derivatives of the gamma functions were included to compensate for slight variation in the peak latency of the onset of the haemodynamic response. Errors of commission and omission were modelled separately from correct responses to Go events and correct non-responses to NoGo events. The confounding effects of fluctuations in global signal intensity between image volumes were removed using an adjusted proportional scaling routine (Desjardins et al., 2001). While all co-ordinates in this study are reported and displayed in the modified Talairach stereotaxic space implemented in SPM99, a transformation algorithm was applied to these co-ordinates in order to localise the activations within standard Talairach space (Talairach and Tournoux, 1988; see http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html for the transformation algorithm).

Conjunction analyses across sensory modalities. Contrasts were specified to estimate and test for differences in the amplitude of the fitted haemodynamic response between Go and NoGo events, and between each of these event types and baseline ('resting') activation, using t-tests at each voxel. Conjunction analyses as implemented in SPM99 (Friston et al., 1999a; Price and Friston, 1997; Price et al., 1997) were performed to identify brain regions that were commonly activated across the auditory and visual modalities. The results from the conjunction analyses form the basis of this paper because they enable the elucidation of supramodal activity, common across the auditory and visual modalities, in a small sample of participants (Friston et al., 1999b). As t-tests were conducted in each voxel across the entire brain, a correction for multiple

comparisons based on the theory of Gaussian fields was applied (Friston et al., 1995b) and all reported voxels satisfy a corrected significance criterion of $p \leq 0.05$.

Random-effects analyses within sensory modalities. To verify the results obtained in the conjunction analyses with analyses that take account of both inter- and intrasubject variability, direct comparisons of the amplitudes of the fitted haemodynamic response to Go and NoGo events were conducted separately within each sensory modality using second-level, random-effects analyses (Friston et al., 1999a). For the auditory and for the visual modality separately, contrast images representing the amplitude of the fitted response in each voxel for (a) Go trials relative to NoGo trials, and (b) NoGo trials relative to Go trials, were computed for each participant. These contrast images were then entered into separate second-level, one-sample t-tests (9 degrees of freedom) for each sensory modality. The resultant SPM{t} in each sensory modality was thresholded at a t-value of 2.82 (corresponding to a significance threshold of $p \leq 0.01$ uncorrected for multiple comparisons), and significant clusters of activation were determined at a cluster significance of $p \leq 0.05$ corrected for multiple comparisons (Friston et al., 1994).

Similar thresholding was applied in further random-effects analyses that tested for modality-specific (i.e., non-supramodal) activations in the direct comparison of Go and NoGo events. Contrast images comparing the response to Go and NoGo events for each subject, separately for each modality, were entered into a second-level, paired t-test (9 degrees of freedom) to elucidate any brain areas in which the Go relative to NoGo comparison was significantly greater in one sensory modality relative to the other.

5.2 Results

5.2.1 Behavioural data

The mean reaction time and percentage of correct hits for Go events was 425 ms (SD 87 ms) and 99.0% respectively in the auditory modality and 402 ms (SD 46 ms) and 99.9% respectively in the visual modality. A paired-samples t-test revealed that mean reaction time did not differ significantly across modalities [$t_{(9)} = 0.973$, $p = 0.356$]. Three of 10 participants made a total of seven errors of omission in the auditory task, and one participant made one error of omission in the visual task. The mean percentage of false alarms to NoGo events (i.e., errors of commission) was 2.1 % (SD 1.18) and 5.7 % (SD 2.75) in the auditory and visual modalities respectively. While errors of omission did not differ significantly across the modalities [$t_{(9)} = 1.765$, $p = 0.111$], participants made significantly more errors of commission during the visual task than during the auditory task [$t(9) = -2.785$, $p = 0.021$].

5.2.2 Imaging data

Go versus NoGo event comparisons – Conjunction analyses across sensory modalities. The results of the conjunction analysis across the auditory and visual sensory modalities, indicating the brain areas in which a significantly greater haemodynamic response was elicited by Go events than by NoGo events, are summarised in Table 12, and illustrated in Figure 18. Go events elicited greater activity than NoGo events in widespread neocortex, including in the limbic cortex, bilateral paralimbic cortex in the frontal operculum, caudal anterior cingulate, mid-cingulate, and posterior cingulate gyri, and in association cortex at the temporoparietal junction, and the anterior intraparietal sulcus extending medially and posteriorly into the precuneus, as well as in bilateral frontal cortex. Other cortical and subcortical (e.g., basal ganglia and thalamus) regions are reported in Table 12.

Figure 18 also illustrates the results of the conjunction analysis that tested for regions in which NoGo events elicited a greater haemodynamic response than Go events. This analysis revealed activation in the rostral extreme of the anterior cingulate cortex (BA 32; x y z co-ordinate of the voxel of peak activation = -8 36 –4, $t_{(9)} = 4.30$, $p < 0.000$ corrected, 12 voxels) and in the left lateral inferior frontal gyrus (BA 45; x y z = -56 24 20, $t_{(9)} = 3.27$, $p < 0.005$ corrected, 2 voxels). Two further single voxels of activation survived correction for multiple comparisons across the whole brain and were located in the superior frontal cortex (BA 6; x y z = -56 –64 40, $t_{(9)} = 3.21$, $p < 0.01$ corrected) and in the posterior aspect of the inferior parietal lobule (BA 39; x y z = -12 12 64, $t_{(9)} = 3.11$, $p < 0.05$ corrected).

Go versus NoGo event comparisons – Random-effects analyses conducted within the sensory modalities. The random-effects analyses conducted separately for the auditory and visual sensory modalities closely replicate the pattern of activity revealed in the conjunction analyses across modalities (Tables 13 and 14 and Figures 19 and 20 respectively). In the auditory modality, nine clusters of activation survived correction for multiple comparisons conducted across the whole brain, while eight clusters survived correction in the visual modality. In both modalities, these clusters incorporated bilateral activation in limbic cortex, in paralimbic cortex at the frontal operculum and in the caudal anterior cingulate and posterior cingulate gyri, and posterior association cortex at the temporoparietal junction and intraparietal sulcus extending medially into the precuneus.

No significant clusters of activation were reported in the random-effects analyses that tested for regions in which greater activity was elicited during NoGo events than Go events. In the auditory modality, a small, non-significant cluster of four voxels was observed in rostral anterior cingulate cortex (BA 32; x y z co-ordinate of the voxel of peak activation within the cluster = -8 36 –8, $t_{(9)} = 3.67$, $p = 0.003$ uncorrected). In the visual modality, the corresponding non-

significant cluster in the rostral anterior cingulate cortex comprised only two voxels (x y z co-ordinate of the voxel of peak activation = -12 36 –8, $t_{(9)} = 3.90$, $p = 0.002$ uncorrected).

Modality of presentation comparisons for Go and NoGo events. The random-effects analyses that directly compared the sensory modalities on the Go relative to NoGo event contrast failed to reveal any brain areas in which the auditory modality was more active than the visual modality. However, a cluster of 37 voxels in medial frontal cortex (BA 10, x y z co-ordinate of the voxel of peak activation = -8 52 20, $t_{(9)} = 6.53$, $p = 0.005$ uncorrected) was significantly more active in the visual modality than in the auditory modality. In light of the behavioural data indicating a larger number of false alarms committed to NoGo events in the visual modality than in the auditory modality, this result suggests that discriminating the Go and NoGo events in the visual modality may have been slightly more difficult than in the auditory task. However, the general paucity of differences between modalities is consistent with the concept of a supramodal network for the processing of and response to stimuli that are task-relevant.

Figure 18. Illustration of the brain regions in which a significantly different amplitude of the haemodynamic response was elicited by Go and NoGo events in healthy participants as revealed by a conjunction analysis of the auditory and visual sensory modalities. Significantly greater activity elicited during Go than during NoGo events is presented in the yellow-red colour range. The converse condition, in which significantly greater activity was elicited during NoGo than during Go events is presented in the blue-purple colour range. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a significance level of $p \leq 0.05$ corrected for multiple comparisons conducted throughout the whole brain. The range of t-score values in each comparison are defined in the colourbars located at right.

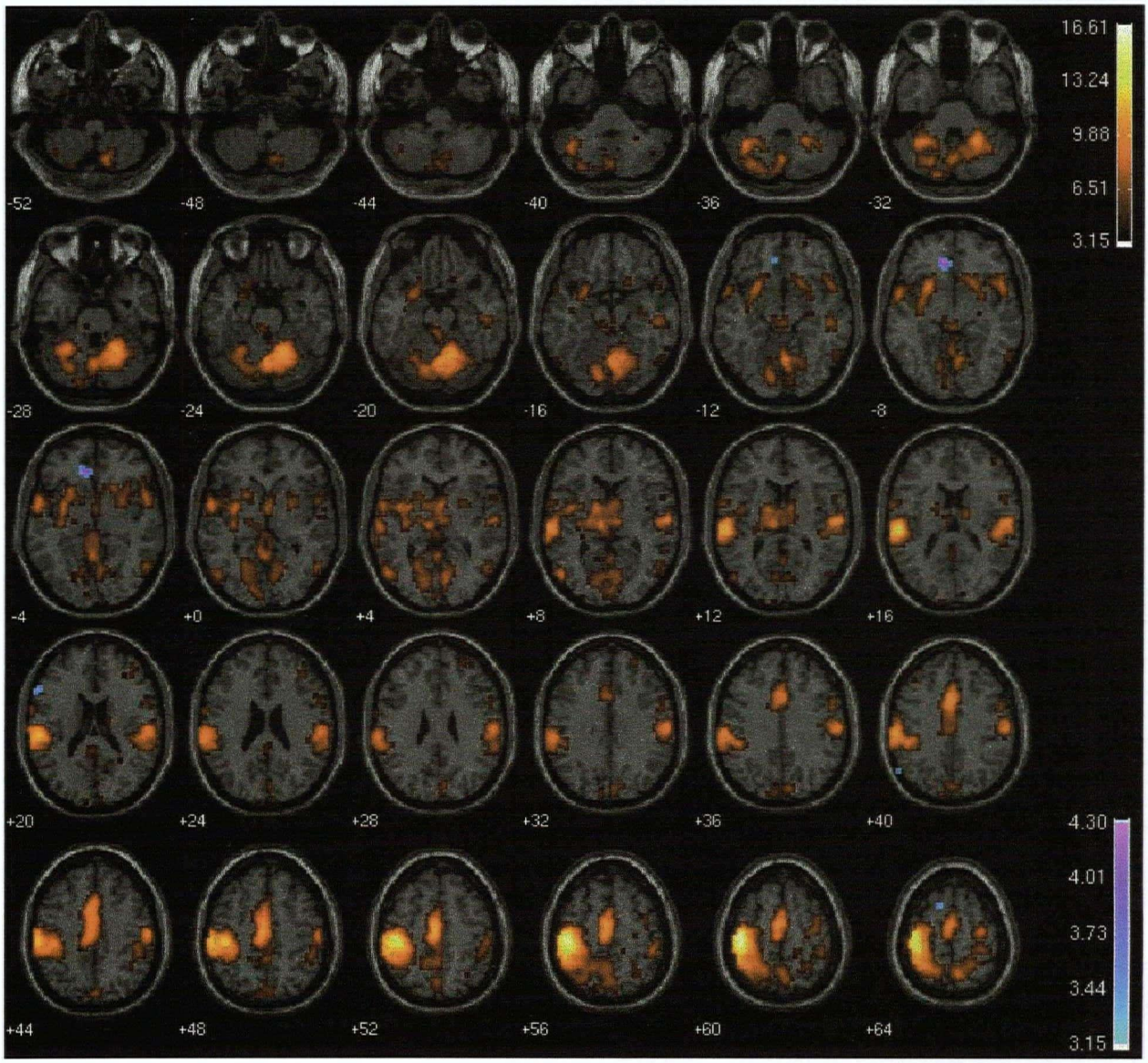


Table 12. Brain regions in which a greater haemodynamic response was elicited during Go events than during NoGo events in healthy participants based on a conjunction analysis of the auditory and visual sensory modalities. The Talairach co-ordinates of each voxel, the *t* score, and the probability of achieving that *t* score when correction for multiple comparisons conducted throughout the whole brain ('P_{corr}') is applied are reported.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}
	x	y	z		
Limbic – Paralimbic Cortex					
L. Amygdala	-28	4	-20	5.27	0.000
R. Hippocampus	32	-16	-16	3.83	0.001
L. Anterior Superior Temporal Sulcus (38/21/22)	-60	4	-4	6.54	0.000
R. Anterior Superior Temporal Sulcus (38/21/22)	52	16	-8	6.32	0.000
L. Orbitofrontal Cortex (47)	-20	16	-24	4.34	0.000
R. Orbitofrontal Cortex (47)	20	16	-16	3.84	0.001
L. Anterior Insula (13)	-44	12	-4	3.45	0.008
R. Anterior Insula (13)	44	16	-8	3.94	0.000
Caudal Anterior Cingulate Cortex (24/32)	0	8	40	8.81	0.000
Mid-Cingulate Cortex (24)	-4	-8	48	9.41	0.000
Posterior Cingulate Cortex (29/30/23)	0	-44	20	3.76	0.001
Temporoparietal Junction					
L. Superior Temporal Gyrus (22)	-64	-36	20	7.10	0.000
R. Superior Temporal Gyrus (22)	56	-40	20	4.65	0.000
L. Inferior Parietal Lobule (40/39)	-60	-40	20	4.97	0.000
R. Inferior Parietal Lobule (40/39)	56	-40	24	4.68	0.000
Intraparietal Sulcus					
L. Superior Parietal Lobule (7)	-16	-56	64	6.03	0.000
R. Superior Parietal Lobule (7)	32	-56	56	3.27	0.024
L. Inferior Parietal Lobule (40)	-52	-36	48	9.71	0.000
R. Inferior Parietal Lobule (40)	44	-40	48	3.15	0.050
L. Precuneus (7)	-12	-52	68	5.59	0.000
R. Precuneus (7)	8	-52	68	5.95	0.000
Dorsal and Ventral Frontal Cortex					
L. Middle Frontal Gyrus (9/8)	-40	32	40	3.36	0.014
R. Middle-Superior Frontal Gyri (10/46)	40	40	24	3.33	0.017
L. Precentral Gyrus (6/4)	-64	0	24	4.46	0.000
R. Precentral Gyrus (6/4)	32	-16	64	6.34	0.000

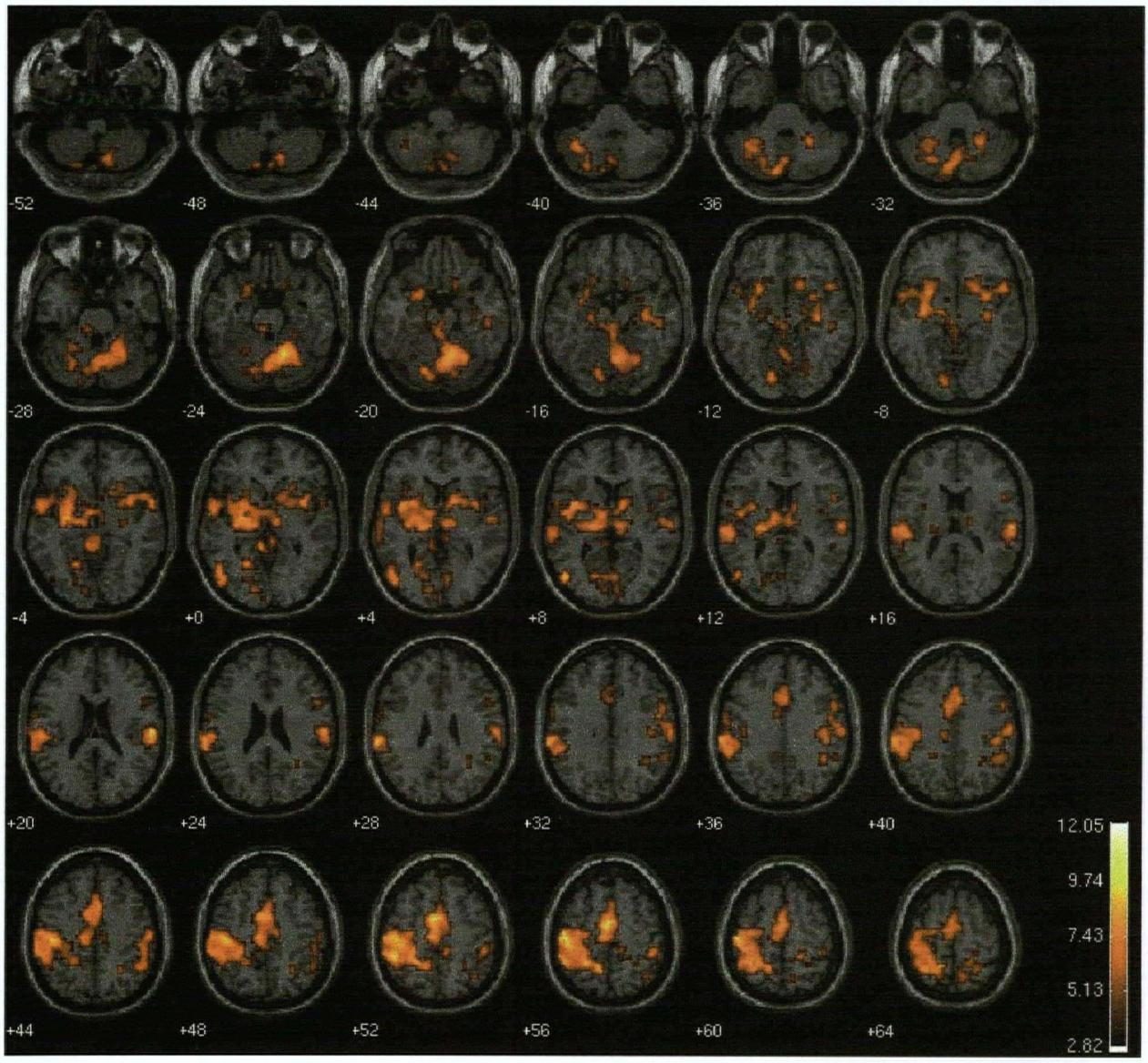
continued over...

Table 12 continued.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates x	y	z	*t* score	P_{corr}
Other Neocortex					
R. Superior Frontal Gyrus (11)	24	56	-12	3.18	0.042
Medial Frontal Gyrus (6)	-4	-20	52	10.83	0.000
L. Postcentral Gyrus (3/2/1/5)	-32	-32	68	14.63	0.000
R. Postcentral Gyrus (3/2/1/5)	24	-32	68	6.01	0.000
L. Superior-Transverse Temporal Gyrus (42/41/22)	-56	-28	16	12.64	0.000
R. Superior-Transverse Temporal Gyrus (42/41/22)	60	-20	8	5.07	0.000
L. Middle-Inferior Temporal / Middle Occipital Gyri (39/19/37)	-48	-72	8	5.63	0.000
R. Middle-Inferior Temporal / Middle Occipital Gyri (39/19/37)	56	-64	-4	5.65	0.000
L. Lingual Gyrus / Cuneus (18/17)	-16	-84	4	4.66	0.000
R. Lingual Gyrus / Cuneus (18/17)	4	-88	8	4.05	0.000
Subcortical Structures					
L. Thalamus	-20	-16	8	5.22	0.000
R. Thalamus	12	-4	12	4.87	0.000
R. Caudate	12	20	-4	3.29	0.021
L. Lentiform (Putamen / Lateral Globus Pallidus)	-28	0	4	5.41	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus)	24	4	0	4.48	0.000
Midbrain	-4	-28	-8	4.20	0.000
Pons	-8	-28	-28	3.21	0.036
L. Cerebellum	-24	-72	-28	5.20	0.000
R. Cerebellum	12	-60	-20	10.15	0.000

Note: L. = Left, R. = Right.

Figure 19. Illustration of the two significant clusters of activation observed in healthy participants in which Go events elicited a greater haemodynamic response than did NoGo events in the auditory sensory modality. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(9)} = 2.82$, corresponding to a significance level of $p \leq 0.01$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The cluster is significant at $p \leq 0.05$ corrected for multiple comparisons.



<u>Figure 20.</u> Illustration of the five significant clusters of activation observed in healthy participants in which Go events elicited a greater haemodynamic response than did NoGo events in the visual sensory modality. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(9)} = 2.82$, corresponding to a significance level of $p \leq 0.01$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The cluster is significant at $p \leq 0.05$ corrected for multiple comparisons.

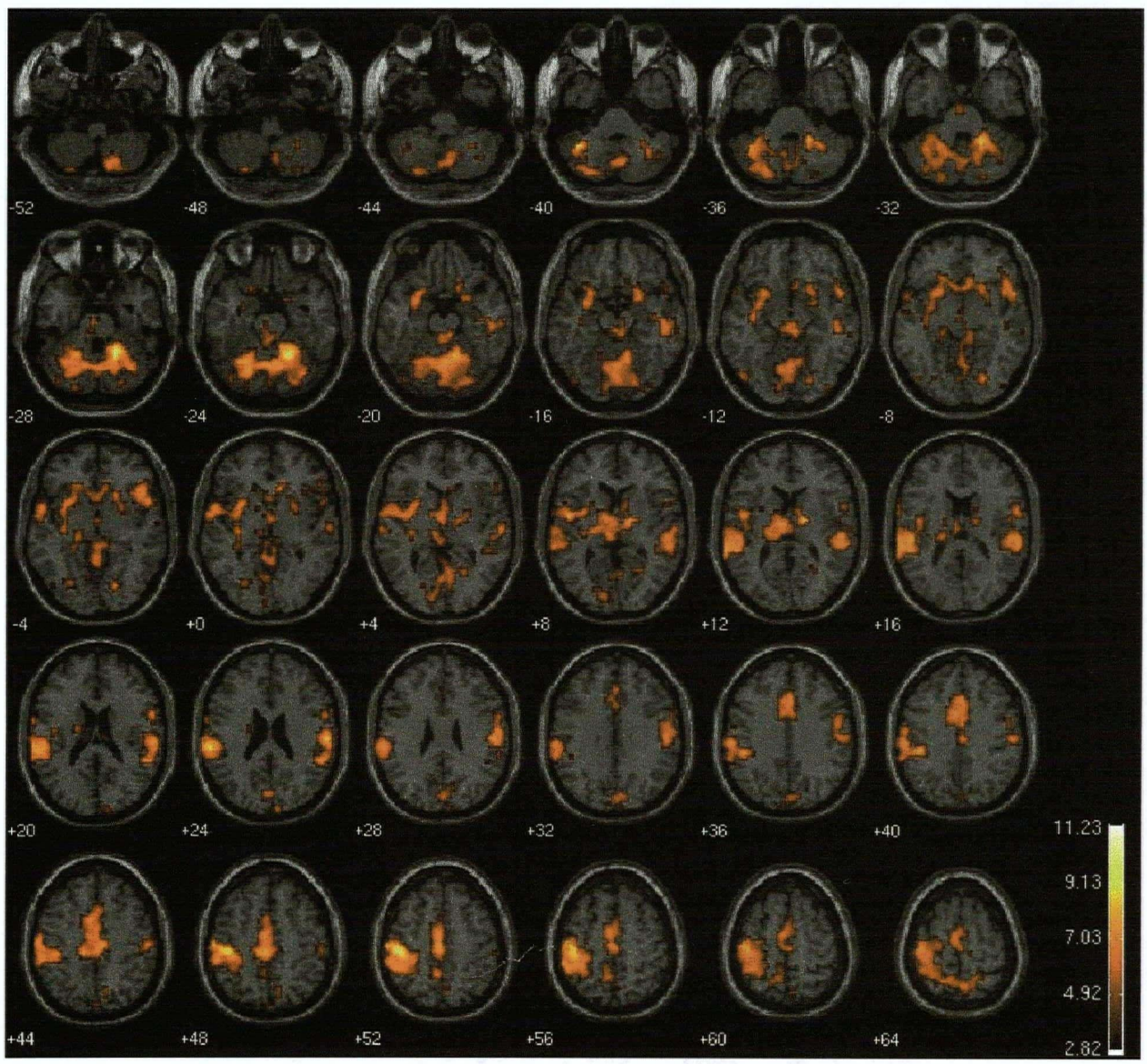


Table 13. Selected local maxima contained within the two significant clusters of activation reported for the auditory sensory modality in which Go events elicited a greater haemodynamic response than NoGo events. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-b) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Amygdala [a]	-20	4	-20	4.76	1.000	0.001
R. Amygdala [a]	28	0	-16	2.85	1.000	0.009
L. Hippocampus [a]	-24	-16	-16	3.41	1.000	0.004
R. Hippocampus [a]	32	-16	-16	3.97	1.000	0.002
R. Hippocampus [A]	36	-20	-12	5.92	0.998	0.000
L. Anterior Superior Temporal Sulcus (38/21/22) [a]	-56	-4	0	5.80	0.999	0.000
R. Anterior Superior Temporal Sulcus (38/21/22) [a]	60	4	-4	6.76	0.966	0.000
L. Orbitofrontal Cortex (47) [a]	-20	20	-16	4.03	1.000	0.001
R. Orbitofrontal Cortex (47) [a]	16	20	-20	3.20	1.000	0.005
L. Anterior Insula (13) [a]	-40	0	0	4.19	1.000	0.001
R. Anterior Insula (13) [a]	42	8	-4	3.46	1.000	0.004
Caudal Anterior Cingulate Cortex (24/32) [a]	4	16	40	6.35	0.990	0.000
Mid-Cingulate Cortex (24) [a]	0	0	44	4.52	1.000	0.001
Posterior Cingulate Cortex (31) [a]	-12	-24	44	6.14	0.995	0.000
Temporoparietal Junction						
L. Superior Temporal Gyrus (22) [a]	-64	-36	8	3.87	1.000	0.002
R. Superior Temporal Gyrus (22) [a]	64	-28	12	2.88	1.000	0.009
L. Inferior Parietal Lobule (40/39) [a]	-64	-32	28	10.65	0.025	0.000
R. Inferior Parietal Lobule (40/39) [a]	64	-28	24	4.50	1.000	0.001
Intraparietal Sulcus						
L. Superior Parietal Lobule (7) [a]	-28	-52	64	7.39	0.500	0.000
R. Superior Parietal Lobule (7) [a]	24	-52	68	4.05	1.000	0.001
L. Inferior Parietal Lobule (40) [a]	-44	-40	52	10.00	0.043	0.000
R. Inferior Parietal Lobule (40) [a]	52	-36	44	5.30	1.000	0.000
L. Precuneus (7) [a]	-12	-52	56	9.18	0.088	0.000
R. Precuneus (7) [a]	12	-64	64	3.91	1.000	0.002
Dorsal and Ventral Frontal Cortex						
L. Precentral Gyrus (6) [a]	-60	0	32	3.61	1.000	0.003
R. Precentral Gyrus (4) [a]	60	-20	44	5.74	0.999	0.000
R. Middle-Inferior Frontal Gyrus (9) [a]	52	8	40	4.73	1.000	0.001
R. Inferior Frontal Gyrus (44/45) [a]	52	12	32	3.04	1.000	0.007
R. Middle Frontal / Precentral Gyri (9/6) [a]	52	12	38	4.28	1.000	0.001

continued over...

Table 13 continued.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates x	y	z	*t* score	P_{corr}	P_{uncorr}
Other Neocortex						
Medial Frontal Gyrus (6) [a]	-4	0	52	11.55	0.013	0.000
R. Postcentral Gyrus (40) [a]	60	-20	20	12.05	0.009	0.000
R. Postcentral Gyrus (3) [a]	20	-40	60	6.06	0.996	0.000
L. Superior-Transverse Temporal Gyrus (42/41/22) [a]	-60	-24	12	5.07	1.000	0.000
R. Superior-Transverse Temporal Gyrus (42/41/22) [a]	60	-28	16	5.20	1.000	0.000
L. Middle Temporal Gyrus (39/37) [b]	-48	-72	8	8.83	0.120	0.000
L. Cuneus / Lingual Gyrus (23/17/18) [a]	-16	-72	8	5.95	0.998	0.000
R. Cuneus /Lingual-Fusiform Gyri (23/18) [a]	4	-72	8	4.17	1.000	0.001
Subcortical Structures						
L. Thalamus [a]	-20	-20	0	7.19	0.622	0.000
R. Thalamus [a]	12	-16	4	5.16	1.000	0.000
R. Caudate [a]	8	8	0	2.84	1.000	0.009
L. Lentiform (Putamen / Lateral Globus Pallidus) [a]	-28	-12	-4	8.93	0.110	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus) [a]	16	4	4	6.12	0.995	0.000
Midbrain [a]	0	-28	-12	4.59	1.000	0.001
Pons [a]	-8	-28	-28	3.02	1.000	0.007
L. Cerebellum (Pyramis) [a]	-8	-80	-36	6.39	0.988	0.000
L. Cerebellum (Uvula) [a]	-28	-68	-32	5.35	1.000	0.000
R. Cerebellum (Culmen) [a]	16	-56	-24	9.64	0.059	0.000
R. Cerebellum [a]	28	-52	-36	4.66	1.000	0.001

Note: L. = Left, R. = Right. Cluster **a** = 3274 voxels, $p < 0.000$ corrected; **b** = 47 voxels, $p < 0.041$ corrected.

Table 14. Selected local maxima contained within the five significant clusters of activation reported for the visual sensory modality in which Go events elicited a greater haemodynamic response than NoGo events. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-e) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Amygdala [a]	-28	0	-16	5.38	1.000	0.000
R. Amygdala [a]	20	4	-20	3.94	1.000	0.002
L. Hippocampus [a]	-36	-20	-16	3.97	1.000	0.002
R. Hippocampus [d]	36	-16	-16	2.88	1.000	0.009
L. Anterior Superior Temporal Sulcus (38/21/22) [a]	-56	4	0	6.29	0.987	0.000
R. Anterior Superior Temporal Sulcus (38/21/22) [c]	56	12	-8	7.36	0.518	0.000
L. Orbitofrontal Cortex (47) [a]	-24	12	-20	5.42	1.000	0.000
R. Orbitofrontal Cortex (47) [c]	48	20	-4	6.27	0.988	0.000
R. Orbitofrontal Cortex (47) [a]	24	8	-16	5.71	0.999	0.000
L. Anterior Insula (13) [a]	-32	8	-4	5.22	1.000	0.000
R. Anterior Insula (13) [c]	42	12	-4	4.47	1.000	0.001
Rostral Anterior Cingulate Cortex (24) [a]	0	32	28	3.28	1.000	0.005
Rostral Anterior Cingulate Cortex (25) [a]	0	16	-4	3.34	1.000	0.004
Caudal Anterior Cingulate Cortex (24/32) [a]	4	16	40	5.28	1.000	0.000
Mid-Cingulate Cortex (24) [a]	8	-20	44	7.38	0.508	0.000
Posterior Cingulate Cortex (31) [a]	-12	-28	44	7.77	0.338	0.000
Posterior Cingulate Cortex (30) [a]	8	-56	4	3.23	1.000	0.005
Temporoparietal Junction						
L. Superior Temporal Gyrus (22) [a]	-64	-36	12	7.07	0.709	0.000
R. Superior Temporal Gyrus (22) [b]	56	-36	8	5.58	0.999	0.000
L. Inferior Parietal Lobule (40/39) [a]	-60	-32	24	9.57	0.062	0.000
R. Inferior Parietal Lobule (40/39) [b]	56	-44	24	6.74	0.958	0.000
Intraparietal Sulcus						
L. Superior Parietal Lobule (7) [a]	-16	-56	64	5.55	1.000	0.000
R. Superior Parietal Lobule (7) [a]	20	-52	64	3.57	1.000	0.003
L. Inferior Parietal Lobule (40) [a]	-52	-40	56	7.55	0.426	0.000
L. Precuneus (7) [a]	8	-56	64	3.04	1.000	0.007
R. Precuneus (7) [a]	4	-60	68	10.11	0.039	0.000
Dorsal and Ventral Frontal Cortex						
L. Precentral Gyrus (4/6) [a]	-60	-16	44	5.89	0.998	0.000
R. Inferior Frontal Gyrus (45) [c]	56	24	4	3.30	1.000	0.005
R. Inferior Frontal / Precentral Gyrus (44/6) [b]	60	4	20	5.82	0.998	0.000
R. Precentral Gyrus (4) [b]	60	-20	40	4.19	1.000	0.001

continued over...

Table 14 continued.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates x	y	z	*t* score	P_{corr}	P_{uncorr}
Other Neocortex						
Medial Frontal Gyrus (6) [a]	-4	-20	52	6.75	0.957	0.000
L. Postcentral Gyrus (2) [a]	-44	-24	52	10.44	0.030	0.000
L. Postcentral Gyrus (40) [a]	-56	-24	16	5.09	1.000	0.000
R. Postcentral Gyrus (2/3) [b]	60	-20	24	8.56	0.155	0.000
R. Postcentral Gyrus (1/2) [b]	56	-28	48	3.85	1.000	0.002
L. Superior-Transverse Temporal Gyrus (42/41/22) [a]	-56	-28	16	5.55	1.000	0.000
R. Superior-Transverse Temporal Gyrus (42/41/22) [b]	56	-24	12	6.94	0.937	0.000
R. Middle-Inferior Temporal Gyri (21) [d]	64	-28	-16	3.15	1.000	0.006
L. Inferior-Middle Occipital Gyri (19/18) [a]	-44	-76	-12	3.28	1.000	0.005
R. Inferior-Middle Occipital /Lingual Gyri (18) [a]	40	-84	-12	3.88	1.000	0.002
L. Cuneus (19) [e]	0	-84	32	4.09	1.000	0.001
L. Cuneus / Lingual Gyrus (17/18/19) [a]	-8	-88	4	3.61	1.000	0.003
R. Cuneus/Lingual Gyrus (19) [a]	24	-76	-8	5.49	1.000	0.000
Subcortical Structures						
L. Thalamus [a]	-8	-12	12	7.14	0.657	0.000
R. Thalamus [a]	16	-8	12	9.05	0.513	0.000
L. Caudate [a]	-4	12	0	2.86	1.000	0.009
R. Caudate [a]	12	24	0	5.85	0.998	0.000
L. Lentiform (Putamen / Lateral Globus Pallidus) [a]	-28	8	0	6.35	0.985	0.000
R. Lentiform (Putamen / Lateral Globus Pallidus) [a]	24	8	0	3.92	1.000	0.002
Midbrain [a]	8	-32	-20	5.22	1.000	0.000
Pons [a]	0	-12	-32	3.46	1.000	0.004
L. Cerebellum (Cerebellar Tonsil) [a]	-40	-52	-40	9.40	0.072	0.000
R. Cerebellum (Culmen) [a]	20	-52	-24	11.23	0.016	0.000

Note: L. = Left, R. = Right. Cluster **a** = 2932 voxels, $p < 0.000$ corrected; **b** = 312 voxels, $p < 0.000$ corrected; **c** = 76 voxels, $p < 0.004$ corrected; **d** = 53 voxels; $p < 0.032$ corrected; **e** = 51 voxels, $p < 0.038$ corrected.

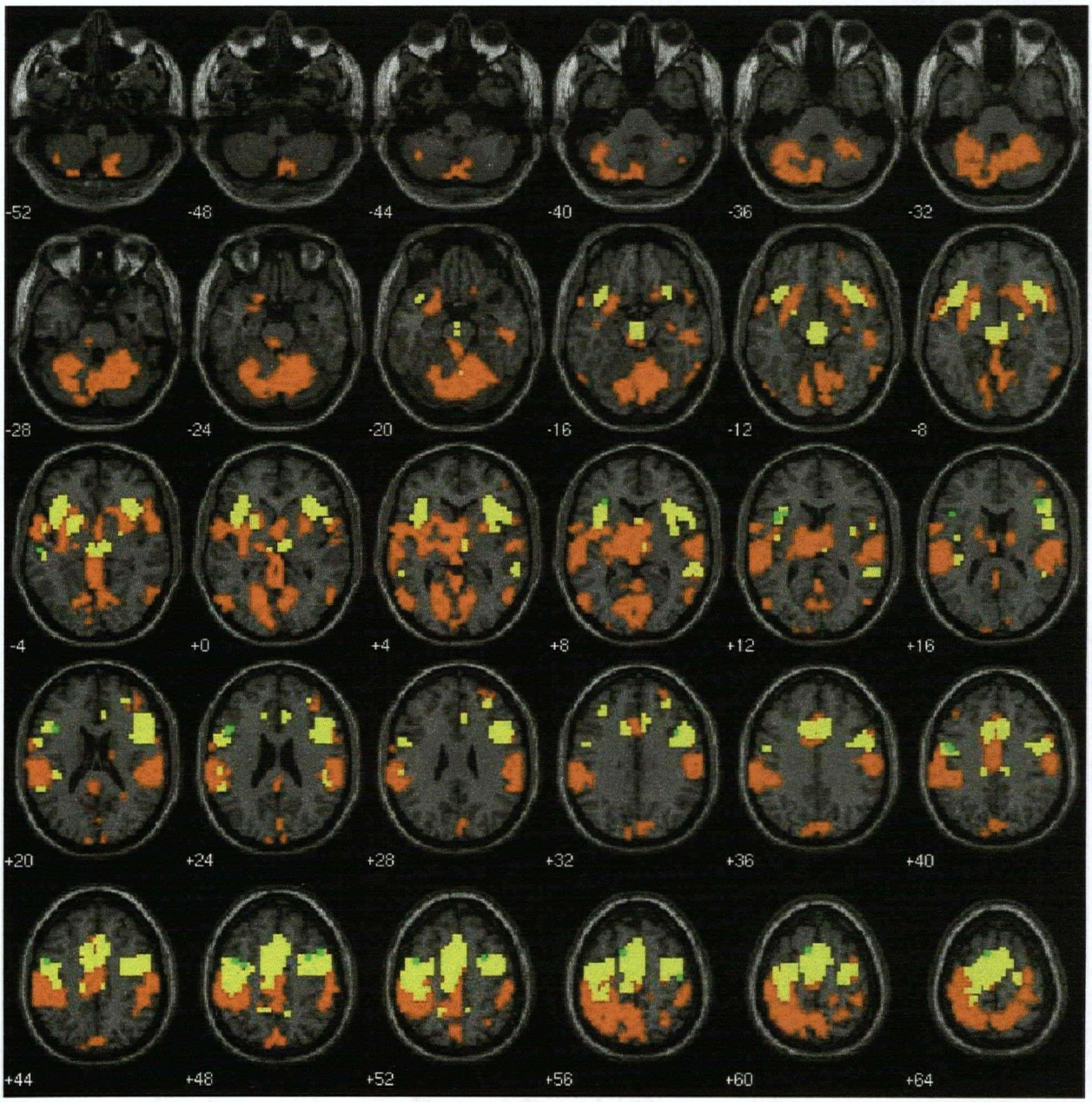
Go and NoGo events relative to baseline. Conjunction analyses conducted across the auditory and visual sensory modalities for Go events relative to a baseline of rest and for NoGo events relative to a baseline of rest revealed several brain regions which were significantly activated in both conditions and which did not show a differential effect for Go and NoGo events (see Figure 21 and Table 15). These areas included superior aspects of the rostral anterior cingulate cortex near to its transition into caudal anterior cingulate cortex, sections of insular cortex bilaterally, and in ventrolateral and dorsolateral prefrontal-premotor cortex, particularly in the right hemisphere.

Table 15. Brain regions activated in the conjunction analysis of the auditory and visual sensory modalities during both Go events relative to a rest baseline and NoGo events relative to a rest baseline but not differentially active during Go and NoGo events. The Talairach co-ordinates of each voxel, the *t* score, and the probability of achieving that *t* score when correction for multiple comparisons conducted throughout the whole brain ('P_{corr}') is applied are reported.

Functional Anatomic Area (Brodmann Area)	Go events versus baseline					NoGo events versus baseline				
	Talairach Co-ordinates			*t* score	P_{corr}	Talairach Co-ordinates			*t* score	P_{corr}
	x	y	z			x	y	z		
L. Rostral Anterior Cingulate Gyrus (24/32)	-12	28	24	3.34	0.015	-12	28	24	3.17	0.044
R. Rostral Anterior Cingulate Gyrus (24/32)	8	28	24	4.88	0.000	8	28	24	4.66	0.000
L. Mid Insula	-40	0	4	5.77	0.000	-40	4	4	3.57	0.003
R. Mid Insula	36	0	8	6.74	0.000	36	0	8	5.30	0.000
L. Inferior-Middle Frontal Gyrus (44/45/9)	-48	16	20	4.22	0.000	-44	16	20	4.54	0.000
R. Inferior-Middle Frontal Gyrus (44/45/9)	48	20	20	7.97	0.000	48	20	20	7.74	0.000
L. Precentral-Middle Frontal Gyrus (6)	-52	-4	40	5.66	0.000	-44	-8	52	7.51	0.000
R. Precentral-Middle Frontal Gyrus (6)	44	-4	52	7.68	0.000	44	-4	52	7.96	0.000

Note: L. = Left, R. = Right.

Figure 21. Illustration of the brain regions significantly activated by both Go and NoGo events and not differentially activated by those events, as revealed by a conjunction analysis of the auditory and visual sensory modalities in healthy participants (indicated in yellow). Red areas are those in which significantly greater activity was elicited during Go events than during NoGo events. Residual areas in which significant activity was elicited during NoGo events only are indicated in green. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a significance level of $p \leq 0.05$ corrected for multiple comparisons conducted throughout the whole brain.



5.3 Discussion

The results of the current experiment confirm that a widespread, supramodal corticolimbic network of brain areas is preferentially recruited during the processing of a target (Go) stimulus that prescribes a subsequent motor response relative to the processing of an equally probable and familiar stimulus for which no motor response is required. This network incorporates limbic cortex (amygdala-hippocampus), paralimbic cortex at the frontal operculum, caudal anterior cingulate, mid-cingulate and posterior cingulate gyri, and association cortex at the temporoparietal junction, anterior intraparietal sulcus extending medially and posteriorly into the precuneus, and dorsal frontal cortex. These results closely replicate the results from the comparison of infrequent target and novel stimuli in Experiment One (Part C; see also Kiehl et al., 2001a, 2001b), which demonstrated greater activation in this extended network for infrequent task-relevant (target) events than for infrequent task-irrelevant (novel) events. However, the current findings indicate that this supramodal network of areas is preferentially engaged by goal-directed processing of behaviourally-salient exogenous stimuli even when the stimuli are neither infrequent nor novel.

Co-activation of widespread limbic cortex and paralimbic cortex in the Go relative to NoGo event comparison is compatible with the idea that a motivational component conferred on the relatively more salient Go event contributes to the difference in brain activation between the Go and NoGo events in the present task. Hitherto, the cingulate gyrus has been considered the main site through which motivational, effortful, and emotional influences are bought to bear on selecting the targets of attention (Mesulam, 1981, 1999; Kim et al., 1999, Maddock, 1999; Paus, 2001; Winterer et al., 2002). The extensive connectivity between limbic cortex and the cingulate gyrus, and output from the cingulate motor cortex to primary and supplementary motor cortex, putamen, and the spinal cord, suggests that the cingulate cortex is ideally situated to mediate

limbic influences on voluntary motor behaviour (Morecraft and Van Hoesen, 1998; Paus, 2001; Vogt et al., 1992). Several studies have described activity in the ACC that is specific to conflict between response options rather than conflict at the level of stimulus identification (Milham et al., 2001; van Veen et al, 2001). By contrast, the PCC may mediate anticipatory attention toward events of intrinsic or experientially-acquired salience (Kim et al., 1999; Hopfinger et al., 2000; Mesulam et al., 2001), and thus provide an site for early motivational biasing of exogenous stimulus processing (i.e., during the stimulus identification phase).

The results of the present study imply that activity in paralimbic cortex around the frontal operculum also contributes to the goal-directed processing of task-relevant stimuli. Paralimbic cortex at the frontal operculum provides an additional interface between limbic cortex in the medial temporal lobes and frontoparietal association cortices (Mesulam and Mufson, 1982a, 1982b; Mesulam, 1998). Cortex at the anterior superior temporal sulcus receives projections from both the dorsal, 'where' visual pathway in posterior parietal cortex and the ventral, 'what' visual pathway in the inferior temporal cortex (Baizer et al., 1991). Likewise, auditory 'where' and 'what' processing streams converge within rostral superior temporal cortex (Rauschecker and Tian, 2000; Karnath, 2001). Cortex at the anterior superior temporal sulcus also receives input from other paralimbic regions (cingulate, insula, and orbitofrontal cortex) and subcortical structures (claustrum, thalamus, and brainstem; Markowitsch et al., 1985; Moran et al., 1987). It is thus ideally situated to link the multimodal perception of stimuli performed in posterior neocortex and the frontal executive processes that select, initiate, and monitor behaviour with the motivational/goal-directed influences from limbic centres.

Work by Karnath and colleagues with patients exhibiting spatial neglect (Karnath, 2001; Karnath et al., 2001) demonstrated a critical role for cortex at the rostral superior temporal sulcus in spatial attention, as was previously reported in non-human primates (Watson et al., 1994). Having observed activation in this region in the present task using foveally-presented visual

stimuli and in the auditory oddball task during bilateral tone presentation (see also Kiehl et al., 2001a, 2001b), we suggest that activity in the anterior superior temporal sulcus extends beyond spatial processes. The anterior superior temporal sulcus may more generally facilitate the selection of stimuli and responses according to the organism's motivational state.

In the present study, greater activation was also elicited by Go stimuli than by NoGo stimuli in subcortical brain areas, including the bilateral putamen and thalamus. However, using the current paradigm, the contribution of goal-directed attention to activation in these areas cannot be distinguished from activation associated with motor responding. The role of these regions in goal-directed attention may be more successfully ascertained using paradigms requiring covert responding to target stimuli (e.g., counting target stimuli).

Many studies have reported right hemisphere dominance in certain attentional processes (see Posner and Petersen, 1990; Mesulam, 1999, Corbetta and Shulman, 2002). In particular, a right frontoparietal network, embracing the lateral prefrontal cortex and the superior parietal lobule is engaged during vigilance tasks in which the participant is required to identify target stimuli embedded in a series of non-target stimuli (Pardo et al., 1991). Consistent with this previous observation, our data revealed that both Go and NoGo stimuli elicited predominantly right-sided activation of lateral prefrontal cortex, while Go stimuli elicited activation of the right superior parietal lobule.

However, in many brain regions, the activation elicited by the Go stimuli was bilateral, and in some instances, there was a tendency towards greater activation in the left hemisphere than the right. As would be expected from the fact that the participants in this study responded with their right index finger, Go stimuli elicited greater activation of the primary sensorimotor cortex, supplementary motor cortex, and thalamus in the left hemisphere than the right (while in the cerebellum, greater activity was observed on the right). However, apparently greater activation in the left (vs. right) temporoparietal junction and mid-cingulate cortex is less readily explained

by the right-handed responding. Braver et al. (2001) observed greater activation of the left mid-cingulate and left temporoparietal cortex during right-handed responses to target stimuli than during right-handed responses in a two-handed response-choice task, and concluded that the observed left hemisphere bias during target detection was unlikely to be due to the handedness of the response. Future research that separates the detection of the Go stimuli from an immediate behavioural response (e.g., by a delayed cue signalling for the commission of a motor response) may provide insight into the laterality of goal-directed attention, as well as information about the time-course in which limbic and paralimbic influences are brought to bear on frontoparietal association areas during goal-directed attention.

In addition to those areas differentially activated by Go and NoGo events, other frontal regions were similarly activated by both event types, including sites in ventral and dorsal frontal cortex, caudal ACC, and regions of insular cortex. Although there were few voxels in which NoGo stimuli elicited greater activation than the Go stimuli, these were mainly located in frontal cortex. In contrast, in the parietal cortex, NoGo stimuli elicited little activation, whereas Go stimuli elicited extensive activation. These observations are consistent with the evidence that the P3 event-related potential elicited by task-irrelevant distracter/novel stimuli is maximal at frontocentral sites and attenuated over posterior cortex, whereas that elicited by target stimuli is maximal over parietal cortex (Katayama and Polich, 1998; Friedman et al, 2001).

Chapter 6.0: Experiment Three: Frequent target relative to nontarget stimulus processing in patients with schizophrenia

In the present experiment, the auditory version of the equiprobable Go/NoGo task was conducted to ascertain whether patients with schizophrenia showed functional abnormality within the corticolimbic network supporting task-relevant stimulus processing during the processing of Go stimuli.

6.1 Methods

6.1.1 Participants

Sixteen healthy adults (11 male) and 16 patients with schizophrenia (13 male) participated in the experiment and provided written informed consent. An additional patient was recruited into the study, but was subsequently excluded due to his inability to clearly discriminate the auditory stimuli during scanning. All healthy participants were newly recruited (i.e., none had formed part of the sample included in the previous experiment). In each group, all but one participant was right-handed (assessed using the handedness questionnaire of Annett, 1970). All procedures complied with University and Hospital ethical requirements, and participants provided written informed consent prior to scanning.

Patients were stable, partially-remitted, medicated outpatients recruited from community mental health teams in Vancouver, BC and outpatient programs at the University of British Columbia Hospital. All patients met DSM-IV criteria for schizophrenia, as diagnosed by an institutional or University Hospital psychiatrist (APA, 1994). Mean duration of illness was 9.9 years (SD 7.4), with a range spanning 2 to 24 years. All patients received stable doses of atypical antipsychotics as their primary medication over the preceding 6-month period. Seven

patients received olanzapine (mean dose 16.4 mg/day, range 7.5-30), five patients received risperidone (mean dose: 3.4 mg/day, range 2-8), two patients received quetiapine (mean dose 350 mg/day, range 300-400), and two patients received clozapine (mean dose 500 mg/day, range 400-600). Two patients also received a typical antipsychotic adjunctive to the atypical medication (1 mg of haloperidol and 25 mg of loxapine). In addition to antipsychotic medication, several patients were medicated with benzodiazepines (n = 2), anti-cholinergics (n = 4), and anti-depressants (n = 10).

On the day of scanning, a trained psychiatrist evaluated the symptoms experienced by the patients with schizophrenia during the week preceding scanning using the SSPI interview schedule (Liddle et al., 2002). Consistent with the partially-remitted status of the patients recruited, overall symptom levels reported were low, with a mean total score on the SSPI of 9 (SD 3.9; range 2 to 15). Syndrome scores were calculated from the items according to the three-syndrome model of schizophrenia described by Liddle (1987a, 1987b). Mean syndrome scores for Reality Distortion (sum of 2 items: delusions and hallucinations), Disorganisation (sum of 3 items: thought disorder, inappropriate affect, and peculiar behaviour), and Psychomotor Poverty (sum of 3 items: blunted affect, poverty of speech, and underactivity) respectively were: 2.4 (SD 2.1), 0.8 (SD 1.2), 1.3 (SD 1.7).

Healthy participants were medication-free volunteers without history of neurological or Axis I psychiatric illness. Participant groups did not differ significantly on the demographic variables of age, gender, parental socioeconomic status (Hollingshead & Redlich, 1958), or on estimates of premorbid (National Adult Reading Test [NART]; Nelson, 1982; Sharpe & O'Carroll, 1991) and current (Quick Test; Ammons & Ammons, 1962) intellectual functioning ($p > 0.05$; see Table 16).

Table 16. Demographic data for patients with schizophrenia and matched healthy control participants.

Variable	Healthy Participants		Schizophrenic Patients	
	Mean	SD	Mean	SD
Age	**28.8**	**6.7**	**30.8**	**10.1**
Parental socioeconomic status (Hollingshead)	**3.3**	**1.6**	**3.5**	**1.5**
Premorbid intellectual functioning (NART)	**118**	**3.3**	**116**	**5.5**
Current intellectual functioning (Quick Test)	**109**	**9.3**	**104**	**10.7**

6.1.2 Task

Auditory stimuli were presented to the participants by a computer-controlled presentation system ('Presentation' version 0.52, Neurobehavioural Systems: http://nbs.neuro-bs.com/). Two stimulus runs were constructed using the task parameters described previously for the auditory runs of the Go/NoGo task presented in Experiment Three. Designation of the 1000Hz and 1500Hz tones as the 'Go' stimulus was counterbalanced across participants such that half the participants from each group responded for the 1000 Hz tone, while the remainder responded for the 1500 Hz tone. Stimuli were presented at approximately 80 dB via insert earphones fitted into 30 dB sound-attenuating MRI-compatible headphones, and each participant indicated their ability to hear and discriminate the stimuli from the background noise created by the scanner.

Reaction times to Go events were computed for trials in which participants responded within 100-2100 ms of stimulus onset. Failure to respond to a Go event within this time constituted an error of omission. Errors of commission were defined as responses that occurred within this time window following a NoGo stimulus. To ensure comprehension of the task instructions, participants performed a practice block of ten trials prior to scanning.

6.1.3 Imaging parameters

Functional images were acquired using the same parameter as were outlined previously for the auditory oddball detection task. Two scanning runs of 173 functional image volumes were collected, with the initial 4 images excluded from subsequent analyses to remove the influence of T_1 stabilisation effects.

6.1.4 Image processing

Functional images were processed and analysed using the Statistical Parametric Mapping 99 software (SPM99, Wellcome Department of Cognitive Neurology, London, UK. http://www.fil.ion.ucl.ac.uk/spm/). Image reconstruction, realignment, and spatial normalisation were conducted as described previously for the auditory oddball task. To remove the influence of motion from the data, estimated movement parameters (i.e., three translation and three rotation parameters) were entered into the analysis as covariates of no interest (Friston et al., 1996). Moreover, a Group (schizophrenic patients, healthy participants) x Movement (translation, rotation) x Displacement Axis (x, y, z) ANOVA was conducted on the maximal and mean absolute estimated movement parameters to confirm that the participant groups did not differ significantly in the extent of head motion. The normalised images were subsequently smoothed with a 12-mm full-width-at-half-maximum Gaussian kernel to optimise the signal-to-noise ratio and to compensate for intersubject anatomical variation. High frequency noise associated with scanner artefacts was removed using a 0.16 Hz low-pass fifth-order IIR butterworth filter applied to the fMRI time series at each voxel. A high-pass filter was applied to remove noise associated with low frequency confounds (e.g., respiratory artefact).

6.1.5 Image analysis

Statistical analysis was performed using the general linear model approach implemented in SPM99 to estimate and statistically test the effect of the Go and NoGo events on the haemodynamic response within each voxel. Event-related responses to Go and NoGo stimuli were modelled using a synthetic haemodynamic response function comprised of two gamma functions and their temporal derivatives (Josephs et al., 1997; Friston et al., 1998). Errors of commission on NoGo events and errors of omission on Go events were modelled separately from correct responses ('hits') to Go events and correct non-responses to NoGo events. The confounding effects of fluctuations in the global signal intensity between image volumes were removed using an adjusted proportional scaling routine (Desjardins et al., 2001).

Replication of the results obtained for Go relative to NoGo processing in the previous Go/NoGo experiment. While this experiment was designed primarily to test for differences between the patient and healthy groups in the processing of task-relevant events, a preliminary random-effects analysis was conducted to corroborate the results obtained in the previous experiment, which demonstrated a supramodal network of brain areas in which greater activity was observed for Go events requiring a subsequent behavioural response than for NoGo events which required no response. Thus, for each healthy participant only, contrasts were specified to estimate and test for differences in the amplitude of the fitted haemodynamic response elicited by Go and NoGo events at every voxel. Significant differences in amplitude for Go and NoGo events were assessed at the cluster level across the entire brain volume ($p \leq 0.05$ corrected for multiple comparisons, height threshold for inclusion at $p \leq 0.01$ uncorrected) according to the method implemented in SPM99 (Friston et al., 1994) .

Between-group comparisons for Go event processing. In order to identify differences between the groups in the magnitude of the activity elicited during the processing of task-relevant events, contrast images were created representing the amplitude of the fitted

haemodynamic response for Go events relative to baseline ('resting') activation at each voxel for each participant. These images were first entered into a second-level, one-sample t-test (15 degrees of freedom) for each participant group in order to test the null hypothesis that the mean of the observations for Go events did not differ significantly from zero in either the healthy participant group or the patient group. The images were subsequently also entered into a second-level ANCOVA (28 degrees of freedom) to test the null hypothesis that there was no difference between patients with schizophrenia and healthy participants in the mean amplitude of the fitted haemodynamic response elicited by Go events, with the effect of reaction time to Go stimuli removed as a potential confound (i.e., to ensure that reaction time differences between the healthy and patient groups did not contribute to an activation difference between groups).

On account of the relatively small sample size employed in the present experiment, in addition to conducting an undirected search for differences between the participant groups across the whole brain, we also tested for group differences using a restricted search of 10 regions-of-interest (ROIs) identified *a priori* (e.g., see method applied in Kiehl et al., 2001d). Based on healthy participant data obtained in the previous experiments, we identified 10 ROIs within limbic and paralimbic cortex that are active during the processing of stimuli that signal the need to engage in a subsequent behavioural response (i.e., Go and Target stimuli). A region was defined as a spherical volume encompassing 555mm^3, which constituted an area corresponding to one resolution element (a measure of the spatial smoothness of the image, and an approximate estimate of an independent observation given the signal correlations that exist between neighbouring voxels in fMRI data). The 10 ROIs were centred on voxels identified in the previous Go/NoGo experiment, including eight voxels in which Go events elicited significantly greater activity than NoGo events (i.e., in the left amygdala, right hippocampus, bilateral anterior STS and orbitofrontal cortex, caudal ACC, and PCC; see Table 12 for co-ordinates), while the remaining two voxels were located in the left and right rostral ACC, where Go and NoGo events

both elicited significant, but statistically equivalent, levels of activity (see Table 15 for co-ordinates). Significant differences between the healthy participant and patient groups within the 10 ROIs were determined at $p \leq 0.05$ after applying a bonferroni correction for conducting multiple ROI comparisons. Because the magnitude of the haemodynamic activity elicited by Go events in the 10 limbic and paralimbic sites was correlated in the previous Go/NoGo experiment, the mean correlation between the sites in that study was entered as a parameter in the calculation of an appropriate bonferroni correction using the method of Simple Interactive Statistical Analysis (SISA, http://home.clara.net/sisa/bonhlp.htm). Specifically, the mean amplitude of the fitted response elicited by the auditory and visual Go events was extracted for each of the 10 healthy participants used in the previous Go/NoGo experiment at each of the 10 sites, and the average correlation between the activity elicited at each site was considered when determining the bonferroni correction to apply when conducting 10 two-tailed t-tests on the current data set. Based on a correlation between the outcome variables of 0.28, to conserve an overall alpha level of 0.05, an alpha level of 0.0097 was adopted for each test.

The significance of differences between healthy participants and patients with schizophrenia for Go events across the entire brain volume were assessed at the cluster level ($p \leq 0.05$ corrected for multiple comparisons, with the height threshold for inclusion in the cluster set at $p \leq 0.01$ uncorrected; Friston et al., 1994).

6.2 Results

6.2.1 Behavioural data

Mean reaction times to Go events for healthy participants (444 ms, SD 79) and patients with schizophrenia (560 ms, SD 131) differed significantly [$t_{(30)} = -3.027$, $p = 0.005$]. However, both participant groups performed the task well, and the groups did not differ significantly on the

accuracy of task performance. On average, healthy participants and patients correctly responded to 99.1% and 98.8% of Go events respectively, and made errors of commission on only 2.6% and 2.5% of NoGo trials respectively.

6.2.2 Imaging data

Go versus NoGo event comparison. The results of the random-effects analysis that examined the difference in the magnitude of the fitted haemodynamic response elicited by Go and NoGo events in healthy participants were largely consistent with the results obtained in the previous Go/NoGo experiment that demonstrated greater activity in a supramodal network encompassing the limbic, paralimbic, and frontoparietal association cortices during the processing of Go events than during the processing of NoGo events (see Figure 22). However, there were several departures from the previous results, presumably due in part to the greater detection power afforded by the increased sample size employed in the present study. Whereas previously the amount of activity elicited by Go and NoGo events in paralimbic cortex at the more superior aspects of the rostral ACC and in parts of the insula did not differ significantly, in the present analysis these areas comprised part of the network of areas in which greater activity was elicited by Go trials than by NoGo trials. Moreover, more extensive activation than previously noted was observed for Go relative to NoGo stimulus processing in bilateral anterior frontal areas. Conversely, whereas Go events had previously elicited significantly greater activity than NoGo events bilaterally in the temporo-occipital junction, this result emerged in the present analysis only when a less stringent correction threshold was applied.

There were no clusters in which significantly greater activity was observed during processing of NoGo trials than during Go trials, even when no correction for multiple comparisons was applied.

Go event processing relative to resting baseline: Within-group analyses. The results of the one-sample t-tests conducted within the participant groups revealed significant activation for Go events relative to resting baseline throughout diverse cortical and subcortical areas in both the healthy participant and patient groups (see Figures 23 and 24 respectively). The figures demonstrate that Go events elicited activation in both groups throughout the paralimbic cortex and in both dorsal and ventral frontoparietal association cortices. However, at the chosen threshold, activation in the amygdala and anterior hippocampus was apparent in the healthy participant group only.

While the activation elicited in healthy participants at this threshold was more extensive than that apparent in the patient group, the largest t-scores were observed within the superior temporal gyrus in the patient rather that the healthy group (BA 22, voxel of peak activation at x y z co-ordinate = 56 4 –8, $t_{(15)} = 12.05$, $p = 0.000$ corrected for multiple comparisons conducted across the whole brain). Thus, the experimental procedure and analysis strategy successfully identified activation in both groups of participants (Callicott et al., 1998).

<u>Figure 22.</u> Illustration of the significant cluster of activation observed in healthy participants in which Go events elicited a greater haemodynamic response than NoGo events. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(15)} = 2.60$, corresponding to a significance level of $p \leq 0.01$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.

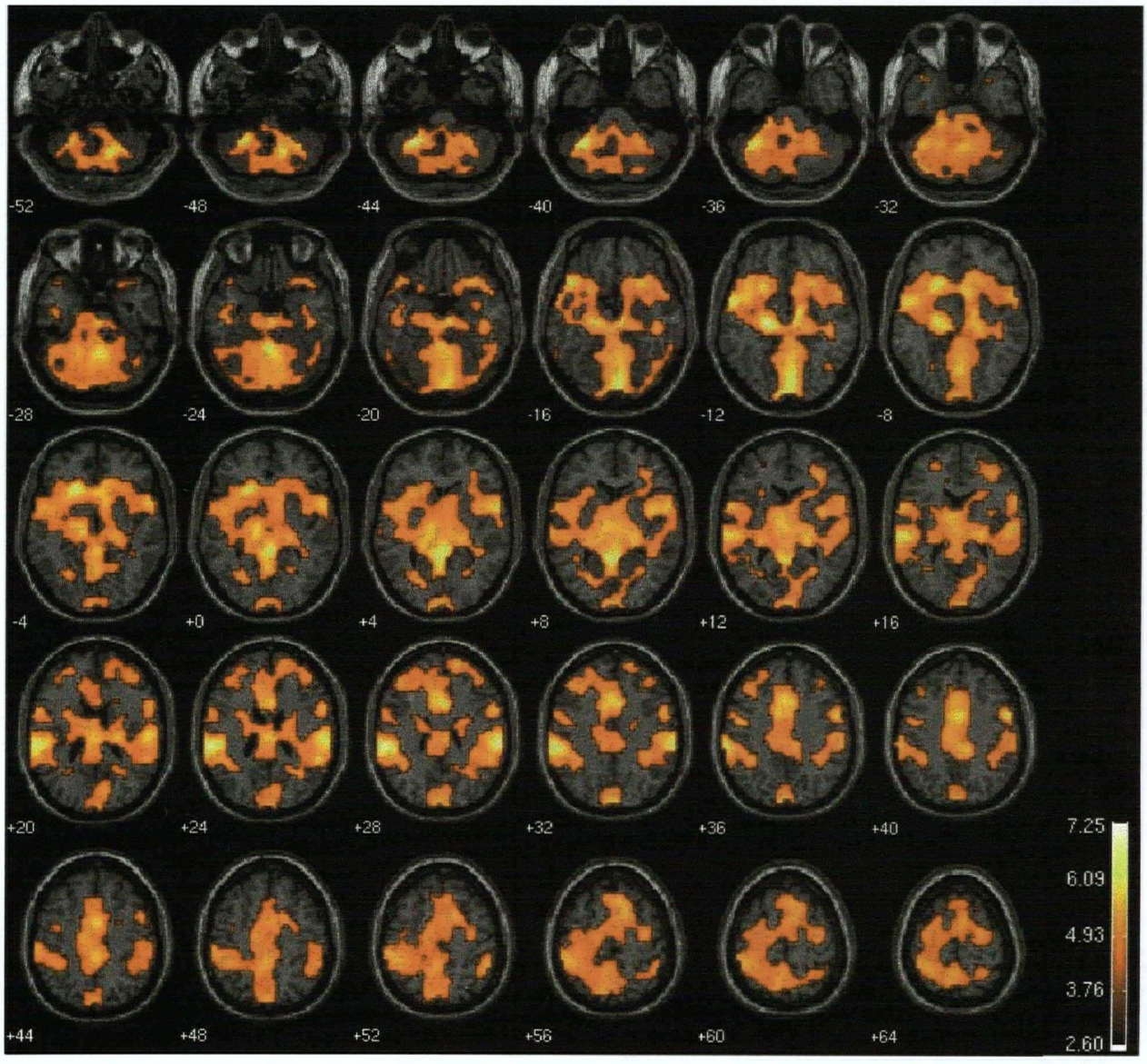


Figure 23. Illustration of the significant cluster of activation observed in healthy participants during Go events relative to a baseline of rest. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(15)} = 2.60$, corresponding to a significance level of $p \leq 0.01$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.

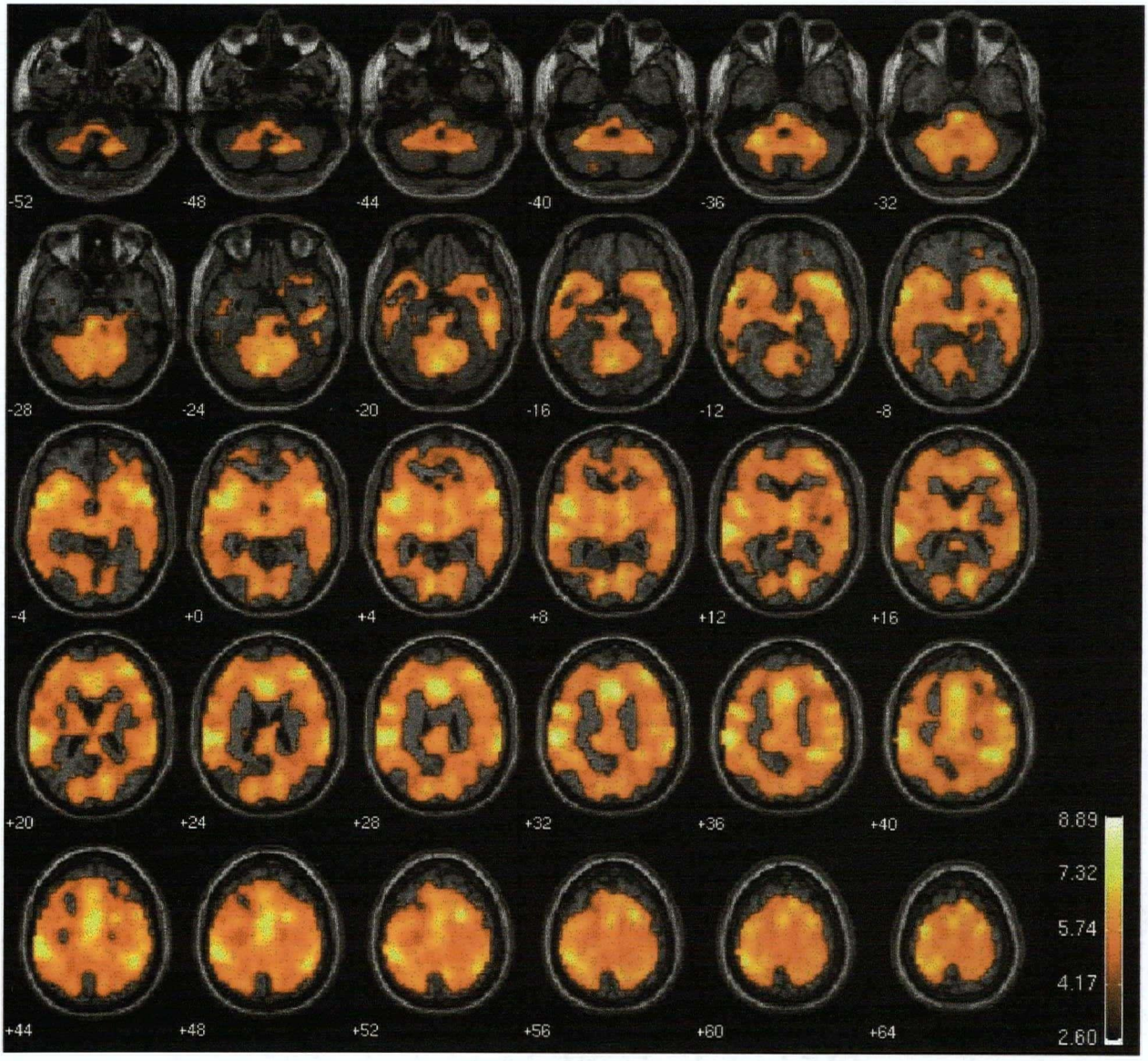
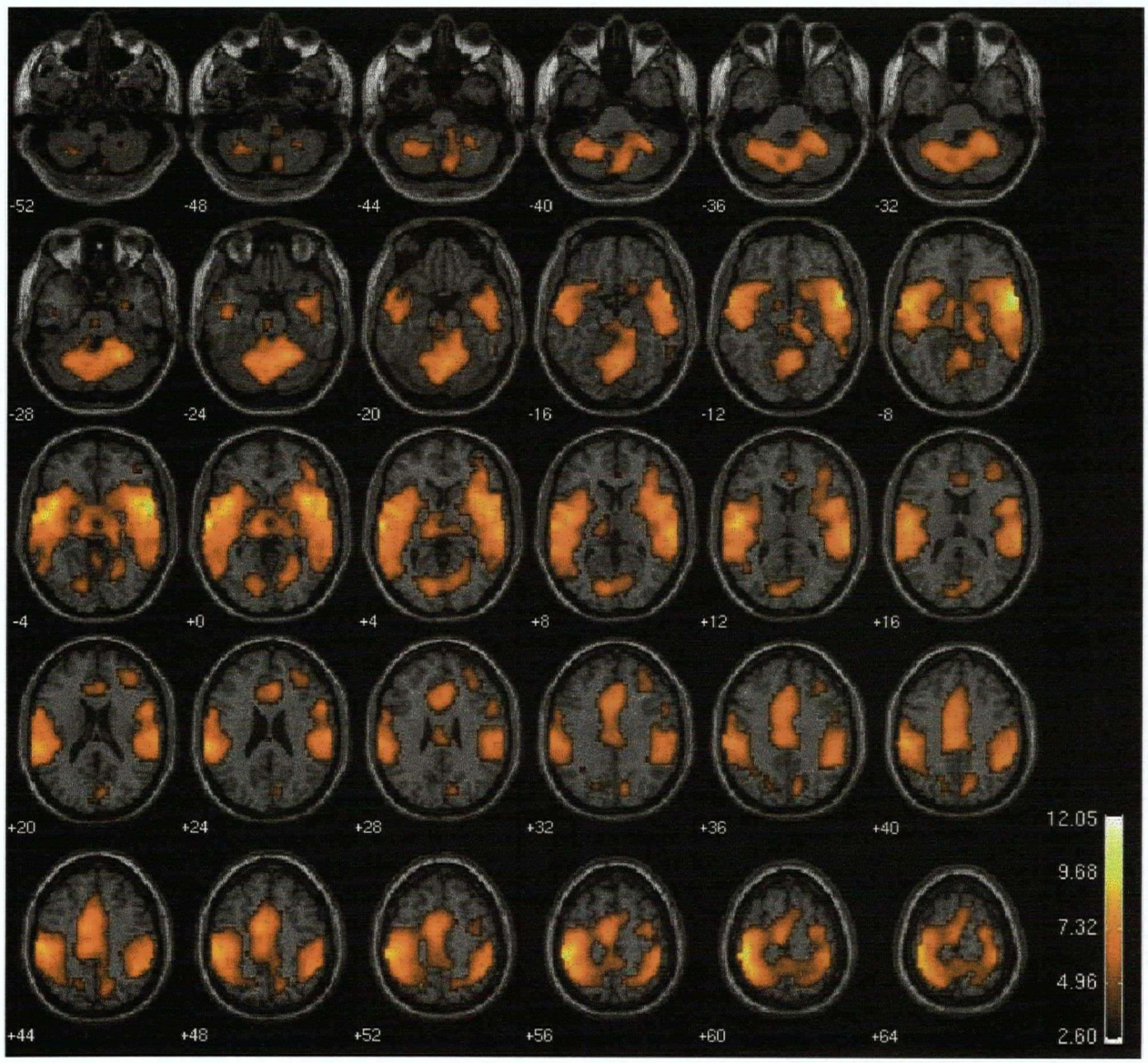


Figure 24. Illustration of the significant cluster of activation observed in patients with schizophrenia during Go events relative to a baseline of rest. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(15)} = 2.60$, corresponding to a significance level of $p \leq 0.01$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.



Go event processing relative to resting baseline: Between-group comparisons. The second-level ANCOVA that compared the mean magnitude of the fitted haemodynamic response elicited by Go events relative to the resting baseline in the patient and healthy participant groups (while removing the confounding effect of reaction time differences between groups), revealed a single cluster in which healthy participants were characterised by significantly greater haemodynamic activity than patients with schizophrenia. The cluster is illustrated on transaxial brain slices in Figure 25 and voxel-level statistics for local maxima within the cluster are summarised in Table 17. The cluster incorporated activation in the PCC, at the left intraparietal sulcus, and in bilateral precuneus-cuneus.

The results of the directed search for group differences during Go event processing relative to resting baseline within the 10 limbic and paralimbic ROIs are summarised in Table 18. After applying a bonferroni correction that set the overall alpha level to 0.05 for two-tailed testing in the 10 regions, significantly greater activation was observed in the healthy participant group than in the patient group in the rostral ACC, PCC, and in bilateral orbitofrontal cortex. A trend for greater activation in healthy participants than patients with schizophrenia was observed in the left amygdala ($p = 0.052$ corrected), right parahippocampus, and left anterior STS (i.e., these areas were significant at $p \leq .05$ if no correction for multiple comparisons was applied). No differences between groups were observed in the caudal ACC or in the right anterior STS, even at an uncorrected level. Figure 26 illustrates the mean magnitude of the fitted response elicited by Go events (solid lines) relative to resting baseline for the healthy participant and patient groups for the voxels listed in Table 18. For comparative purposes, the mean magnitude of the fitted response elicited by NoGo events relative to the resting baseline in each of these voxels is also illustrated for each group (hashed lines).

Figure 25. Illustration of the significant cluster of activation in which healthy participants were characterised by a greater haemodynamic response than patients with schizophrenia during Go events relative to a baseline of rest. The confounding influence of a significant difference in reaction time to Go events between the healthy and patient groups was removed in the analysis. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(28)} = 2.47$, corresponding to a significance level of $p \leq 0.01$ uncorrected for multiple comparisons conducted throughout the whole brain. The range of t-score values within the cluster are defined in the colourbar located at bottom right. The cluster is significant at $p \leq 0.05$ corrected for multiple comparisons.

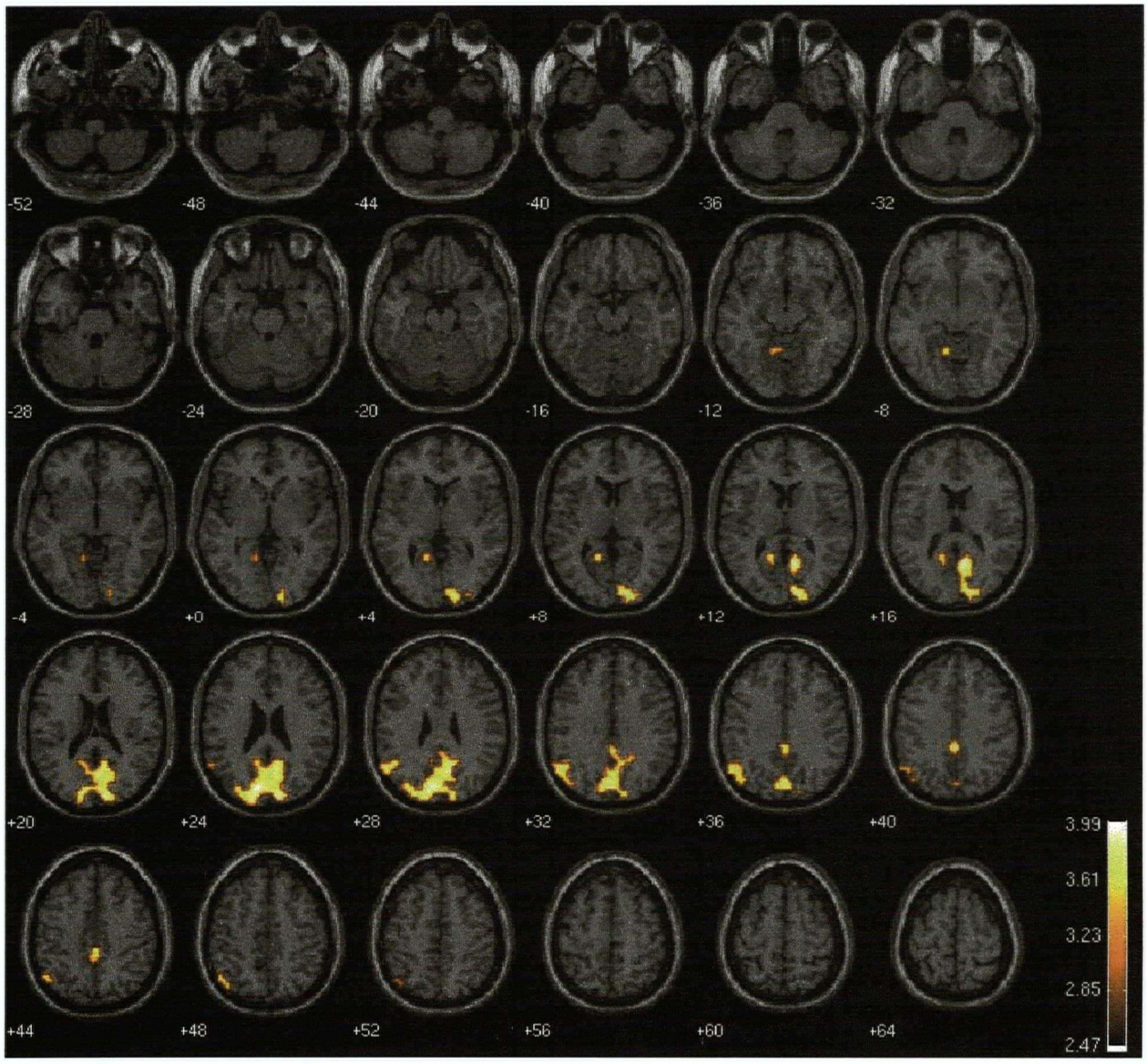


Table 17. Selected local maxima contained within the significant cluster of activation in which healthy participants were characterised by a greater haemodynamic response than patients with schizophrenia during Go events relative to a baseline of rest. The confounding influence of a significant difference in reaction time to Go events between the healthy and patient groups was removed in the analysis. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Paralimbic Cortex						
Posterior Cingulate Cortex (31)	0	-36	40	3.19	0.948	0.002
L. Posterior Cingulate Cortex (30/23)	-12	-52	8	3.11	0.967	0.002
R. Posterior Cingulate Cortex (30/23)	12	-60	12	3.39	0.877	0.001
Intraparietal Sulcus						
L. Superior Parietal Lobule (7)	-48	-64	48	2.91	0.990	0.004
L. Inferior Parietal Lobule (40)	-48	-60	44	2.62	0.999	0.007
L. Inferior Parietal Lobule (40/39)	-56	-60	28	3.17	0.954	0.002
L. Precuneus (7)	-4	-76	32	3.22	0.930	0.002
R. Precuneus (7)	4	-76	36	3.01	0.982	0.003
Other Neocortex						
L. Cuneus (18/19)	-12	-80	24	3.55	0.792	0.001
R. Cuneus (19)	12	-88	24	3.39	0.877	0.001
R. Cuneus / Middle Occipital Gyrus (18)	16	-92	8	3.33	0.901	0.001

Note: L. = Left, R. = Right. All local maxima reported were contained within a single cluster comprising 517 voxels, which was significant at $p < 0.010$ corrected.

Table 18. Voxels of peak activation within the 10 regions of interest in which a significantly greater haemodynamic response was elicited in healthy participants than patients with schizophrenia during Go events relative to a baseline of rest. The confounding influence of a significant difference in reaction time to Go events between the healthy and patient groups was removed in the analysis. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted within 10 ROIs in which correlated haemodynamic activity is observed (two-tailed t-tests; 'P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Limbic – Paralimbic Cortex						
L. Amygdala	-20	4	-16	2.46	0.052	0.010
R. Parahippocampus [a]	32	-20	-28	2.28	0.077	0.015
L. Anterior Superior Temporal Sulcus (38)	-56	16	-8	1.80	0.206	0.040
L. Orbitofrontal Cortex (47)	-28	24	-20	3.99	0.001	0.000
R. Orbitofrontal Cortex (47)	24	20	-16	2.56	0.041	0.008
L. Rostral Anterior Cingulate Cortex	-4	36	28	3.13	0.010	0.002
R. Rostral Anterior Cingulate Cortex	0	36	28	2.88	0.021	0.004
Posterior Cingulate Cortex (23)	8	-52	24	2.79	0.026	0.005

Note: [a] The most significant voxel within the ROI was located inferior to the hippocampus within the paralimbic parahippocampal gyrus. L. = Left, R. = Right.

Figure 26. Graphical representation of the mean magnitude of the fitted response (± 2 standard errors) during Go stimuli (solid lines) and NoGo stimuli (hashed lines) relative to a baseline of rest for the healthy participant and patient groups in the voxel of peak activation within selected limbic and paralimbic regions-of-interest. All voxels were significant at $p \leq 0.05$ uncorrected for multiple comparisons. Underlined voxels indicate those that remained significant after a correction was applied to compensate for conducting tests within 10 regions of correlated activity.

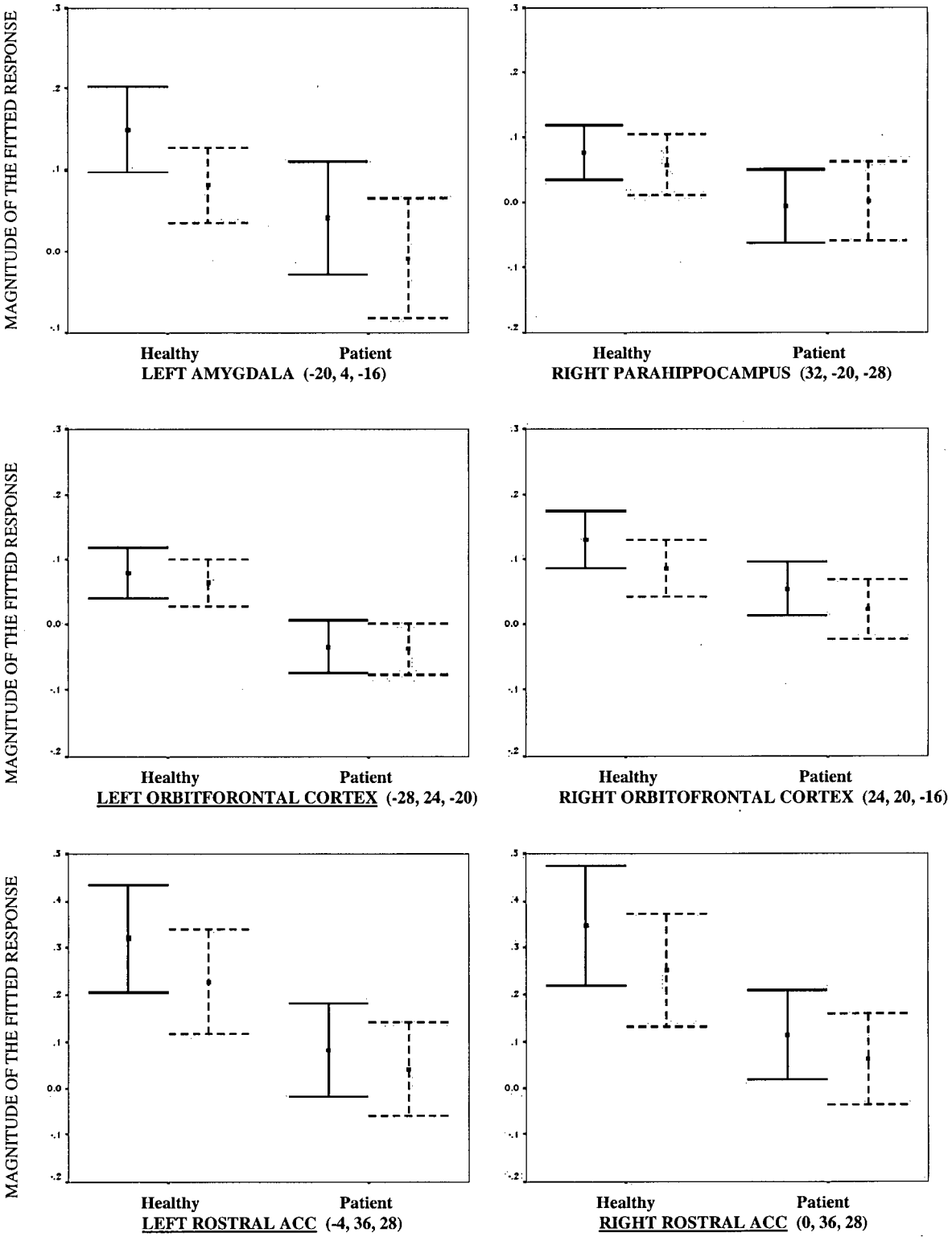
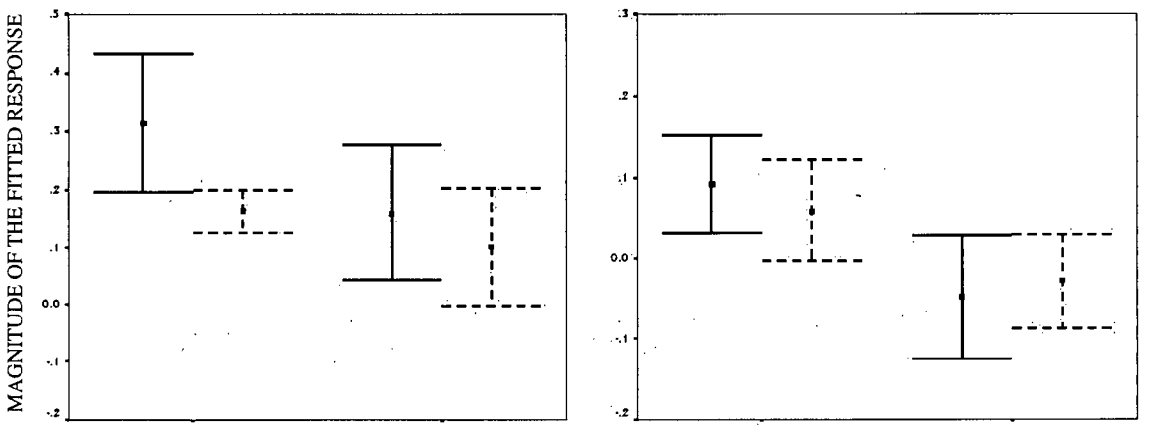


Figure 26 continued.



6.3 Discussion

The results of the current experiment provide further support for the hypothesis that healthy participants recruit a widespread corticolimbic network of brain areas during the processing of task-relevant stimuli. During Go stimulus processing, healthy participants recruited the limbic cortex (i.e., the amygdala-hippocampus), paralimbic cortex at the frontal operculum and throughout the cingulate gyrus, and dorsal and ventral frontoparietal association cortex. Although activation elicited by Go events in patients with schizophrenia was generally less extensive than that apparent in the healthy participants at an equivalent threshold, the processing of task-relevant Go events also elicited activation within the majority of these areas in patients.

However, at the chosen threshold, activation was not apparent in the amygdala and anterior hippocampal gyrus.

An undirected search across the whole-brain for sites in which the participant groups differed in the amount of activity elicited by the Go events revealed a significant cluster within posterior cortex encompassing paralimbic cortex in the PCC and association cortex at the left intraparietal sulcus. The PCC has been ascribed a role in monitoring sensory events and evaluating one's own behaviour (Vogt et al., 1992), and in mediating anticipatory attention toward salient exogenous events (Kim et al., 1999; Hopfinger et al., 2000; Mesulam et al., 2001). Cortex at the intraparietal sulcus, along with dorsal frontal areas, contributes to the assembly and co-ordination of stimulus-response mappings, taking a lead role when these mappings are simple or well-learned, and can be prepared in advance (Corbetta and Shulman, 2002). It functions to characterise salient events and specify cognitive plans that target such events for behaviour (Andersen and Buneo, 2002; Gottlieb, 2002). Thus, the PCC and intraparietal cortex may together facilitate an early, preferential bias in the processing of stimuli that have been targeted for behaviour (i.e., task-relevant exogenous stimuli). In spite of the relatively preserved behavioural performance demonstrated by patients with schizophrenia on this simple task, dysfunction within these areas may imply that the normal motivational salience ascribed to a task-relevant stimulus in less effectively imparted to the Go/target event, such that processing that event is less biased, and the event is thus less efficiently distinguished from the less salient NoGo stimulus.

The motivational influences that bias processing of the task-relevant Go event may be disturbed in schizophrenia due to the widespread dysfunction observed in limbic-paralimbic cortex during Go event processing. Relative underactivity in patients with schizophrenia compared to healthy participants was observed in the rostral ACC, PCC, and in bilateral orbitofrontal cortex, with additional nonsignificant trends for relative underactivity in the left

amygdala, right parahippocampus, and the left anterior superior temporal sulcus. The rostral ACC and orbitofrontal cortex are major routes by which limbic influences are brought to bear on stimulus processing and, in particular, response formulation (Cardinal et al., 2002). Their hypoactivity in patients with schizophrenia implies that insufficient 'late' biasing of stimulus-response mappings may be present in addition to the early biasing problems imparted by posterior cortex (especially PCC) dysfunction.

As in the auditory oddball task, these abnormalities were observed even in a partially-remitted patient sample characterised by low levels of symptomology. This is consistent with the idea that functional abnormality during salient stimulus processing is a core abnormality in schizophrenia. However, future research employing a sample of first-episode, neuroleptic-naïve patients with schizophrenia is needed to ascertain whether the abnormality is present already in early stages of the illness, and prior to the administration of antipsychotic medications.

Chapter 7.0: Experiment Four: Erroneous processing of salient exogenous stimuli

The previous experiments suggest that patients with schizophrenia experience critical dysfunction of limbic and paralimbic cortex during the processing of salient exogenous stimuli, perhaps indexing a problem in focusing processing resources on events of motivational/affective or experiential significance. In schizophrenia, marked abnormalities are apparent not just in the selection and initiation of mental activity and behaviour, but also in the monitoring of that behaviour. This final experiment compares the brain response elicited in healthy participants and patients with schizophrenia when a salient exogenous stimulus is processed incorrectly and an error ensues.

7.1 Methods

7.1.1 Participants

Sixteen healthy adults (12 male) and 10 patients with schizophrenia (9 male) participated in the experiment and provided written informed consent. All participants were right-handed (as assessed using the questionnaire of Annett, 1970), with normal or corrected-to-normal visual acuity. All procedures complied with University and Hospital ethical requirements.

Patients were stable, partially-remitted, medicated outpatients recruited from community mental health teams in Vancouver, BC and outpatient programs at the University of British Columbia Hospital. All patients met DSM-IV criteria for schizophrenia, as diagnosed by an institutional or University Hospital psychiatrist (APA, 1994). Mean duration of illness was 11 years (SD 3.1), with a range spanning 2 to 30 years. All patients received a stable dose of an atypical antipsychotic as their primary medication over the 6-month period preceding scanning. Five patients received olanzapine (mean dose 17.5 mg/day, range 7.5-30), while four patients received risperidone (mean dose: 5.0 mg/day, range 2-8), and one patient received clozapine

(225 mg/day). One patients received a second atypical antipsychotic as an adjunctive medication (75 mg/day of clozapine), while two patients received a typical antipsychotic adjunctive to the atypical medication (5 mg/day of loxapine and 6 mg/day of trifluoperazine). In addition to antipsychotic medication, several patients were medicated with anti-depressants (n = 3) and benzodiazepines (n = 1).

On the day of scanning, a trained psychiatrist evaluated the symptoms experienced by the patients with schizophrenia in the week preceding scanning using the SSPI interview schedule (Liddle et al., 2002). Mean total score on the SSPI was 8.3 (SD 1.6), with a range of 1 to 18. Syndrome scores were calculated from the items according to the three-syndrome model of schizophrenia described by Liddle (1987a, 1987b). Mean syndrome scores for Reality Distortion (sum of 2 items: delusions and hallucinations), Disorganisation (sum of 3 items: thought disorder, inappropriate affect, and peculiar behaviour), and Psychomotor Poverty (sum of 3 items: blunted affect, poverty of speech, and underactivity) respectively were: 2.0 (SD 0.7), 0.9 (SD 0.4), 1.0 (SD 0.5). As in the other experiments reported, the low levels of symptomology observed in patients was consistent with their partially-remitted status.

Healthy participants were medication-free volunteers without history of neurological or Axis I psychiatric illness. Participant groups did not differ significantly on the demographic variables of age, gender, parental socioeconomic status (Hollingshead & Redlich, 1958), or on estimates of premorbid (National Adult Reading Test [NART]; Nelson, 1982; Sharpe & O'Carroll, 1991) and current (Quick Test; Ammons & Ammons, 1962) intellectual functioning ($p > 0.05$; see Table 19).

Table 19. Demographic data for patients with schizophrenia and matched healthy control participants.

Variable	Healthy Participants		Schizophrenic Patients	
	Mean	SD	Mean	SD
Age	**32.3**	**10.6**	**32.9**	**12.9**
Parental socioeconomic status (Hollingshead)	**3.7**	**1.2**	**3.5**	**1.0**
Premorbid intellectual functioning (NART)	**116**	**6.1**	**116**	**7.3**
Current intellectual functioning (Quick Test)[a]	**107**	**9.7**	**101**	**8.2**

Note: [a] Data from one healthy participant was not available.

7.1.2 Procedure

A single scanning run comprising 246 visual stimuli was presented to participants using a computer-controlled visual and auditory presentation package (http://nilab.psychiatry.ubc.ca/vapp/). Stimuli were displayed on a rear-projection screen mounted at the entrance to the magnet bore and subtended a visual angle of approximately 3 x 5 degrees. Each stimulus appeared for 240 ms in white text within a continuously displayed rectangular fixation box. Participants viewed the screen from a distance of approximately 2 metres by means of a mirror system attached to the head coil. The scanning room and magnet bore were darkened to permit easy visualisation of the stimuli.

Participants were instructed to respond as quickly and accurately as possible with their right index finger to each presentation of the Go stimulus (the letter 'X'; occurrence probability = 0.84). They were instructed not to respond to the NoGo stimulus (the letter 'K'; occurrence probability = 0.16). Prior to scanning, participants completed a brief practice session of approximately 10 trials to promote speeded responding to the Go stimulus and thus increase the likelihood of errors of commission.

The SOA between Go stimuli varied pseudorandomly between 1000, 2000, and 3000 ms, subject to the constraint that three Go stimuli were presented within each consecutive 6-s period. In light of the protracted evolution of the haemodynamic response elicited by a single stimulus, it was anticipated that the Go stimuli would generate a sustained, relatively constant baseline haemodynamic activity. The NoGo stimuli were interspersed among the Go stimuli in a pseudorandom manner subject to three constraints: the minimum SOA between a Go and NoGo stimulus was 1000 ms; the SOA between successive NoGo stimuli was in the range 10-15 s; and NoGo stimuli had an equal likelihood of occurring at 0, 1, or 2 s after the beginning of a 3-s acquisition period. Thus, the haemodynamic response to each NoGo stimulus occurred as a perturbation set against the relatively constant haemodynamic response to Go stimuli. By jittering stimulus presentation relative to the acquisition time, the haemodynamic response to the stimuli of interest was effectively sampled at 1-s intervals.

Motor responses were recorded using a commercially available MRI compatible fibre-optic response device (Lightwave Medical, Vancouver, BC). Reaction times to Go events were computed for trials in which the participants responded within 1000 ms of stimulus onset. Errors of commission were defined as responses that occurred within 1000 ms of the onset of a NoGo stimulus. Correctly-rejected NoGo events ('correct rejects') were determined by the absence of a motor response within 1000 ms of the NoGo stimulus.

7.1.3 Imaging parameters

Images were acquired on a standard clinical GE 1.5T system fitted with a Horizon Echo-speed upgrade. A custom head holder was used to prevent movement. Conventional spin-echo T_1-weighted sagittal localising images were acquired to view the positioning of the participant's head in the scanner and to prescribe the functional image volumes. Blood oxygen level dependent (BOLD) contrast images were collected with a gradient-echo sequence (TR/TE

3000/40 ms, flip angle 90°, 24 x 24 cm field of view, 64 x 64 matrix, 62.5 kHz bandwidth, 3.75 mm x 3.75 mm in plane resolution, 5 mm thickness, 29 slices) that effectively covered the entire brain (145 mm axial extent). A total of 142 brain volumes were acquired. Four image volumes collected prior to the presentation of stimuli were discarded from subsequent analyses in order to remove the effects of the T_1 stabilisation process.

7.1.4 Image processing

Functional images were reconstructed offline, and realigned and motion-corrected using the procedure described by Friston et al. (1995a) and implemented in Statistical Parametric Mapping 99 (SPM99, Wellcome Department of Cognitive Neurology, London, UK. http://www.fil.ion.ucl.ac.uk/spm/). Corrections for translations and rotations did not exceed 3.0 mm and 2.5 degrees respectively for any participant. A Group (schizophrenic patients, healthy participants) x Movement (translation, rotation) x Displacement Axis (x, y, z) ANOVA was conducted on maximal estimated movement parameters to ensure that the groups did not differ in extent of head motion.

A mean functional image was constructed in each participant and used to derive parameters for spatial normalisation into the modified Talaraich stereotaxic space implemented in SPM99. Both affine and nonlinear components were used in the spatial normalisation (Friston et al., 1995b). The spatial normalisation parameters for each mean image were then applied to the corresponding functional images for each session, and the images were resampled into isotropic 4mm voxels. The normalised images were smoothed with an 8-mm full width at half-maximum Gaussian kernel to optimise the signal-to-noise ratio and compensate for intersubject anatomical variation. High frequency noise associated with alterations of the applied radio frequency field was removed using a 0.16 Hz low-pass fifth-order IIR butterworth filter applied to the fMRI time series at each voxel. While all co-ordinates in the present paper are reported and displayed in the

modified Talaraich stereotaxic space implemented in SPM99, a transformation algorithm was applied to these co-ordinates in order to localise activation patterns within standard Talairach space (i.e., to identify and label functional areas: Talairach & Tournoux, 1998; see http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html for the transformation algorithm).

7.1.5 Image analysis

Statistical analysis was performed within each voxel using the general linear model approach implemented in SPM99. Event-related responses to both errors of commission (EoC) and correct-rejects (CR) on NoGo stimuli were modelled using a synthetic haemodynamic response function comprised of two gamma functions and their temporal derivatives (Josephs et al., 1997; Friston et al., 1998). The first gamma function modelled the haemodynamic response peak at 6-s post-stimulus, and the second gamma function modelled the small 'overshoot' of the haemodynamic response on recovery. The occurrence of the erroneous motor response determined the timing of EoC (i.e., response-locked timing), whereas the timing of CR corresponded to the presentation of the NoGo stimulus (i.e., stimulus-locked timing). Response-locked timing for EoC was chosen for consistency with standard ERP data analysis methods. The temporal derivatives of the gamma functions were included to compensate for slight variation in the peak latency of the onset of the haemodynamic response. The response to the Go events was treated as a baseline and not explicitly modelled. A high-pass filter was applied to remove noise associated with low frequency confounds (e.g., respiratory artifact). The confounding effects of fluctuations in global signal intensity between image volumes were removed using an adjusted proportional scaling routine (Desjardins et al., 2001).

Two contrast images were specified for each participant, summarising the amplitude of the fitted response in each voxel to: (1) EoC relative to the baseline of motor responding to Go events, and (2) CR relative to the baseline of responding to Go events. These contrast images

were then entered into separate two-sample t-tests at the second-level to test the null hypothesis that there was no difference between patients with schizophrenia and healthy participants in the mean amplitude of the fitted haemodynamic response for either of these event types. The contrast images were also entered into a second-level one-sample t-test for each group to test the null hypothesis that the mean of the observations on each event type did not differ significantly from zero in either healthy participants or patients with schizophrenia.

To test the significance of the a priori hypothesis of reduced activation in rostral ACC in patients with schizophrenia compared to healthy participants during EoC, a correction for multiple comparisons at $p \leq 0.05$ within a predefined 12-mm diameter spherical region-of-interest (ROI) was applied. This ROI was centred on the rostral ACC voxel identified in Kiehl et al. (2000a) as preferentially active in healthy participants during EoC compared to CR on NoGo trials (voxel co-ordinates x y z = -8 45 15). In addition to voxels within the rostral ACC, this ROI also incorporated voxels in the medial frontal gyrus (corresponding to Brodmann area 10).

To ascertain whether patients with schizophrenia showed reduced activation compared to healthy participants in the region of caudal ACC that was preferentially active in healthy participants during EoC compared to CR trials in Kiehl et al. (2000a), a second ROI in caudal ACC was specified (12-mm diameter sphere centred on voxel co-ordinates x y z = 4 22 40).

To examine the specificity of the results to error trials rather than NoGo trials in general, both the rostral and caudal ROIs were also applied to the comparison of patients with schizophrenia and healthy participants on CR trials.

Non-directed searches for differences between healthy participants and patients with schizophrenia on EoC and CR across the entire brain volume were implemented at the cluster level ($p \leq 0.05$ corrected for multiple comparisons, height threshold $p \leq 0.01$ uncorrected) according to the method of Friston et al. (1994) implemented in SPM99.

7.2 Results

7.2.1 Behavioural data

Mean reaction times for correct-hits to Go trials and EoC on NoGo trials for patients with schizophrenia were 393 ms (SD 60) and 349 ms (SD 48) respectively; and for healthy participants were 334 ms (SD 41) and 306 ms (SD 45) respectively. For subsequent reaction time analyses, correct-hits to Go trials were differentiated into three types; those that followed an error of commission to a NoGo trial (EoC-Go), those that followed a correctly-rejected NoGo trial (CR-Go), and those that followed another correct-hit to a Go trial (Go-Go). Mean reaction time and accuracy data for these different categories of correct-hits to Go trials and for EoC on NoGo trials are provided in Table 20.

Reaction time (RT) data were analysed using a Group (healthy participants, schizophrenic patients) x Condition (EoC, EoC-Go, CR-Go, Go-Go) ANOVA. The analysis revealed a significant main effect of Group [$F_{(1, 24)} = 9.18$, $p = 0.006$] indicating that healthy participants responded to the stimuli faster than the patients with schizophrenia. The slowed performance of patients with schizophrenia on this task is consistent with that typically observed on speeded RT tasks (e.g., Ngan & Liddle, 2000).

Table 20. Behavioural data for patients with schizophrenia and matched healthy control participants.

Variable	Healthy Participants		Schizophrenic Patients	
	Mean	SD	Mean	SD
Mean Reaction Time (ms)				
Correct-hits on Go trials				
- Following correctly-hit Go trial	334	44	398	66
- Following error to NoGo trial	321	76	408	100
- Following correctly-rejected NoGo trial	300	50	358	59
Errors of commission on NoGo trials	306	45	349	48
Accuracy (n)				
Correct-hits on Go trials	205	1.2	203	2.6
Errors of commission on NoGo trials	16.6	7.2	16.3	6.4

The main effect of Condition was also significant [$F_{(3, 72)} = 7.40$, $p = 0.0002$], however, a non-significant Group x Condition interaction [$F_{(3,72)} = 1.33$, $p = 0.27$] indicated that patients with schizophrenia responded more slowly than healthy participants across all trial types. The results of post-hoc Scheffé tests conducted on the RT means for the main effect of Condition are reported in Table 21. The RT for Go trials following an EoC were significantly longer than those for Go trials following a correctly-rejected NoGo stimulus, demonstrating that participants modified their response behaviour after committing an error. This was particularly true for patients with schizophrenia. A planned comparison between EoC-Go trials versus CR-Go trials confirmed that the increase in RT following errors was significant within the schizophrenic patient group [$F_{(1,24)} = 7.90$, $p = 0.0097$]. The RT to Go trials following correctly-rejected NoGo trials was less than that to Go trials following other correct Go trials, which may reflect the fact that NoGo trials were always followed by Go trials. As expected, our results replicate previous research demonstrating that EoC are associated with faster responding than occurs on correct-

hits to Go trials, possibly reflecting premature or impulsive response decisions on error trials (e.g., Pailing et al., 2002).

Both healthy participants and patients with schizophrenia correctly identified the majority of Go stimuli (99.6% and 98.7% respectively), although patients responded to significantly fewer Go stimuli than healthy participants [$t_{(24)} = 2.42$, $p = 0.024$]. On NoGo trials, healthy participants and patients with schizophrenia did not differ significantly on accuracy of responding [$t_{(24)} = 0.94$, $p = 0.93$].

Table 21. Significance of post-hoc Scheffé tests on reaction time means for the main effect of Condition.

	Reaction Time Condition			
	Go-Go (Mean: 366 ms)	**EoC-Go (Mean: 365 ms)**	**CR-Go (Mean: 329 ms)**	**EoC (Mean: 327 ms)**
Go-Go		**.9993**	**.0124***	**.0082***
EoC-Go			**.0178***	**.0120***
CR-Go				**.9991**

Note: Condition Go-Go = Correct-hits to Go trials following another correctly-hit Go trial; EoC-Go = Correct-hits to Go trials following an error of commission to a NoGo trial; CR-Go = Correct-hits to Go trials following a correctly-rejected NoGo trial; EoC = Errors of commission on NoGo trials

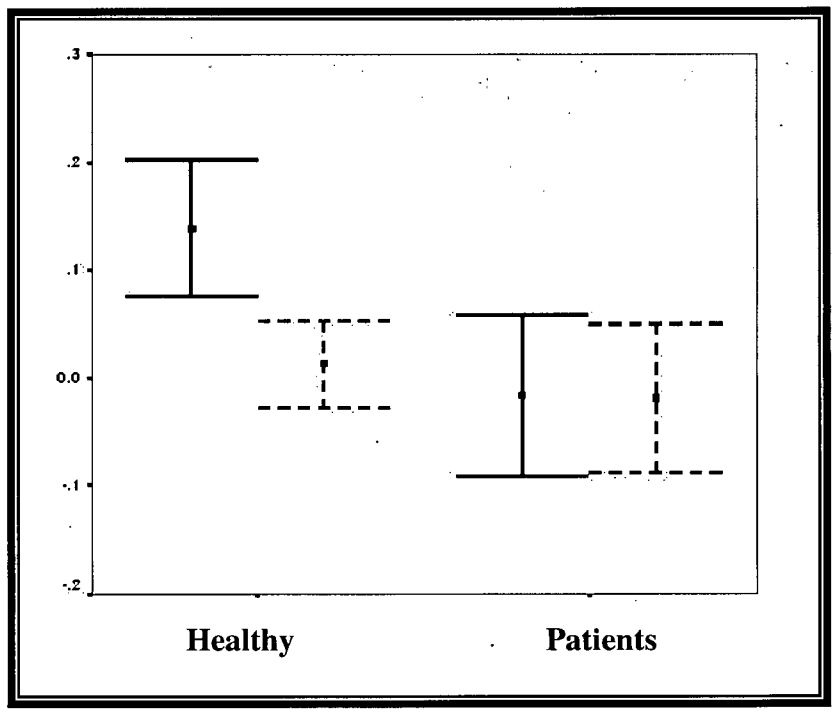
7.2.2 Imaging data

The non-significant main effect and interactions for Group in the ANOVA examining head motion [main effect: $F_{(1,24)} = 0.613$, $p = 0.44$] indicate that the healthy participant and schizophrenic patient groups did not significantly differ on any estimated maximum head motion parameter, which suggests that movement did not contribute differentially to the haemodynamic results across groups.

Errors of commission. Within the ROI centred in the rostral ACC, direct comparison of the magnitude of the fitted response in the two groups during EoC revealed significantly greater activation in healthy participants compared to patients with schizophrenia (co-ordinates of voxel of peak activation: x y z = -8 52 16, $t_{(24)} = 3.11$, $p = 0.043$ corrected for multiple comparisons within the volume of interest). Examination of the magnitude of the fitted response at this peak voxel in the healthy participant and schizophrenic patient groups separately provided clarification of the nature of this effect (see Figure 27, solid lines). Consistent with the findings of Kiehl et al. (2000a), healthy participants showed significant recruitment of the rostral ACC/medial frontal gyrus during EoC (co-ordinates of voxel of peak activation: x y z = -8 52 16, $t_{(24)} = 4.39$, $p = 0.009$ corrected for multiple comparisons within the volume of interest). By contrast, in the patients with schizophrenia, EoC were associated with a failure to activate this region.

Direct comparison of the magnitude of the fitted response in the two groups during EoC in the ROI centred in caudal ACC revealed no significant difference between patients with schizophrenia and healthy participants at $p \leq 0.05$ corrected for multiple comparisons within the ROI volume. Inspection of the magnitude of the fitted response within the ROI for the healthy participant and schizophrenic patient groups separately provided some evidence that both groups recruited caudal ACC during EoC (co-ordinates of voxel of peak activation for healthy participants: x y z = 0 24 36, $t_{(24)} = 1.88$, $p = 0.0392$ uncorrected for multiple comparisons; for patients with schizophrenia: x y z = 8 28 40, $t_{(24)} = 3.20$, $p = 0.0054$ uncorrected). Indeed, there was a trend for patients with schizophrenia to show greater activation than healthy participants within this region of the caudal ACC (co-ordinates of voxel of peak activation : x y z = 8 24 44, $t_{(24)} = 2.18$, $p = 0.0194$ uncorrected for multiple comparisons).

Figure 27. Mean magnitude of the fitted response (± 2 standard errors of the mean) at the voxel of peak activation (x y z co-ordinates = -8 52 16) located within the rostral anterior cingulate cortex/medial frontal gyrus region-of-interest identified in the comparison of errors of commission on NoGo trials relative to a baseline of responding to Go trials. The magnitude of the fitted response is provided for errors of commission to NoGo trials (EoC; solid lines) and correctly-rejected NoGo trials (CR; hashed lines) relative to baseline in patients with schizophrenia (right) and healthy participants (left).



A non-directed search of the entire brain to identify additional regions in which healthy participants demonstrated significantly greater activation than patients with schizophrenia during EoC failed to identify any clusters satisfying the criteria of correction for multiple comparisons. The four largest clusters of activation were located in the posterior cingulate gyrus (24 voxels; peak voxel co-ordinate and statistics: x y z = 0 –44 12, $t_{(24)} = 4.43$, $p = 0.001$ uncorrected for multiple comparisons across the entire brain), the rostral ACC/medial frontal gyrus (24 voxels, peak voxel co-ordinate and statistics: x y z = -12 60 0, $t(24) = 3.18$, $p = 0.001$ uncorrected), the

left hippocampus (14 voxels, peak voxel co-ordinate and statistics: x y z = -32 –20 –12, $t_{(24)}$ = 3.37, p = 0.001 uncorrected), and the left angular gyrus (14 voxels, peak voxel co-ordinate and statistics: x y z = -48 –72 32, $t_{(24)}$ = 3.21, p = 0.002 uncorrected). Although none of these clusters satisfied stringent criteria for significance after correction for multiple comparisons in the entire brain volume, it is noteworthy that the three most significant clusters were located in limbic or paralimbic cortex. These clusters are illustrated in Figure 28 (red colourmap).

In the converse comparison that sought to identify brain regions in which patients with schizophrenia showed significantly greater activation than healthy participants during EoC, two clusters of 165 and 157 voxels respectively were observed (see Table 22 and Figure 28 [blue colourmap]). These clusters were located bilaterally in the intraparietal sulcus and precuneus, with the larger cluster in the left hemisphere extending anteriorly into sensorimotor cortex. To clarify the nature of the difference between the groups, the amplitude of the fitted response in each participant during EoC was determined. Figure 29 illustrates the mean magnitude of the fitted response elicited during EoC in the patient and healthy participant groups for selected local maxima situated within the cluster. The Figure indicates disparate patterns of activation in the participant groups. While patients with schizophrenia show relatively increased activation of these brain areas during EoC relative to the Go stimulus baseline, healthy participants were characterised by a relative decrease in the haemodynamic response during EoC relative to the Go baseline. That is, in spite of a motor response having been made for both trial types, in healthy participants only these brain areas were more strongly activated during Go trials than during EoC.

Correctly-rejected trials. The ROI analysis directly comparing the magnitude of the fitted response in healthy participants and patients with schizophrenia in the rostral ACC for CR trials did not reveal any significant voxel satisfying the correction within the specified small volume of interest. For the purposes of comparison, the magnitude of the fitted response for CR trials at the

peak voxel identified for EoC is provided in the healthy participant and schizophrenic patient groups separately in Figure 27 (hashed lines). The figure indicates that neither the healthy participants nor the patients with schizophrenia showed significant recruitment of the rostral ACC during CR trials.

Similarly, the ROI analysis that directly compared the magnitude of the fitted response between groups in caudal ACC for CR trials revealed no significant voxel satisfying correction within the volume of interest. Neither healthy participants nor patients with schizophrenia showed significant recruitment of this region of the caudal ACC during CR trials.

The non-directed search of the entire brain for regions showing greater activation in healthy participants compared to patients with schizophrenia during correctly-rejected NoGo trials failed to identify any clusters satisfying the criteria of correction for multiple comparisons. However, as for EoC, a large cluster of 34 suprathreshold voxels was located in posterior cingulate gyrus (peak voxel x y z = 0 –52 12, $t_{(24)} = 3.80$, $p = 0.001$ uncorrected for multiple comparisons across the entire brain; see Figure 30 [red colourmap]).

Four clusters were significantly more active in patients with schizophrenia than in healthy controls during CR trials (see Table 23 and Figure 30 [blue colourmap]). As for EoC, two of these clusters were located bilaterally at the intraparietal sulcus, with the two remaining clusters located in the left visual and right premotor cortex. Figure 31 illustrates the mean amplitude of the fitted response for the patient and healthy participant groups in selected local maxima situated within the four clusters. As was apparent for EoC, a differential pattern of responding characterised the patient and healthy groups during CR trials, with only the patient group showing relative activation of these areas relative to the Go stimulus baseline. Healthy participants were characterised by a relative decrease in activity in these areas during CR trials as compared to activity elicited during Go stimulus processing.

Figure 28. Illustration of the clusters of activation in which the amplitude of the haemodynamic response elicited during Errors of Commission relative to the Go baseline differed between healthy participants and patients with schizophrenia. The limbic and paralimbic cortex clusters in which greater haemodynamic activity was observed in healthy participants than in patients are presented in the yellow-red colour range. These clusters were significant only when no correction for multiple comparisons conducted throughout the brain was applied. The two significant clusters of activation in which greater haemodynamic activity was observed in patients than in healthy participants are presented in the blue-purple colour range. These clusters are significant at $p \leq 0.05$ corrected for multiple comparisons. The range of t-score values within the clusters are defined in the colourbars located at right. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(24)} = 2.49$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons.

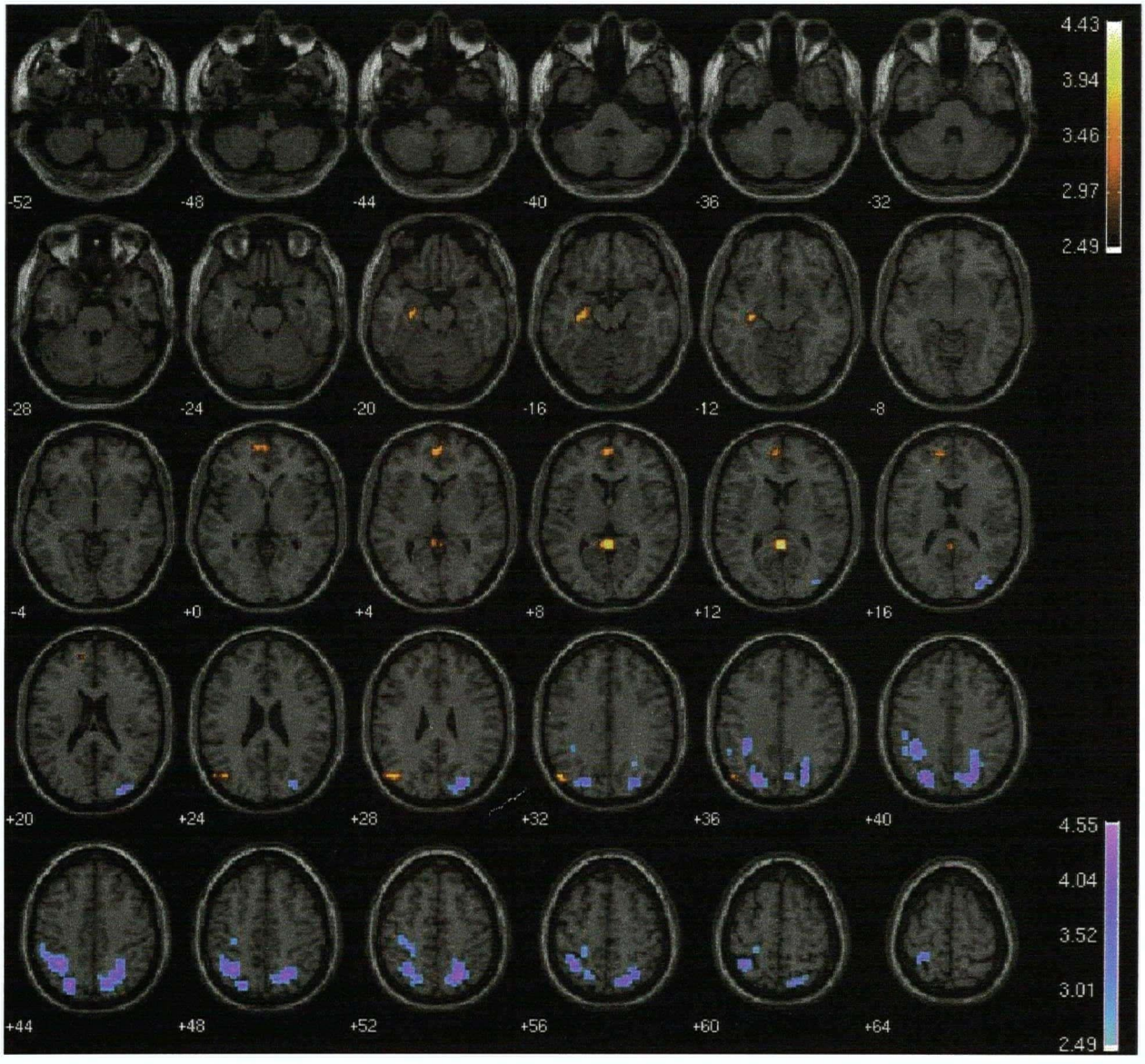


Table 22. Selected local maxima contained within the two significant clusters of activation in which patients with schizophrenia were characterised by a greater haemodynamic response than healthy participants during Errors of Commission relative to the Go stimulus baseline. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-b) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Intraparietal Sulcus						
L. Superior Parietal Lobule (7) [b]	-24	-72	44	4.42	0.888	0.000
R. Superior Parietal Lobule (7) [a]	28	-64	52	3.88	0.996	0.000
L. Inferior Parietal Lobule (40) [b]	-32	-56	48	3.66	1.000	0.001
R. Inferior Parietal Lobule (40) [a]	32	-60	44	3.13	1.000	0.002
L. Precuneus (7) [b]	-20	-64	52	2.92	1.000	0.004
L. Precuneus (7/19) [b]	-24	-76	36	4.01	0.990	0.000
R. Precuneus (7) [a]	20	-64	52	4.55	0.816	0.000
R. Precuneus / Cuneus (7/19) [a]	28	-80	32	3.64	1.000	0.001
Other Neocortex						
L. Precentral Gyrus (4) [b]	-32	-28	52	2.89	1.000	0.004
L. Postcentral Gyrus (2/5/3) [b]	-28	-44	64	3.17	1.000	0.002
R. Superior-Middle Occipital Gyri (19) [a]	32	-84	20	4.14	0.975	0.000

Note: L. = Left, R. = Right. Cluster **a** = 157 voxels, $p < 0.001$ corrected; **b** = 165 voxels, $p < 0.001$ corrected.

Figure 29. Graphical representation of the mean magnitude of the fitted response (± 2 standard errors) during Errors of Commission relative to the Go stimulus baseline for the healthy participant and patient groups in selected voxels in the intraparietal sulci and left sensorimotor cortex. Selected voxels lie within the two clusters in which patients with schizophrenia were characterised by significantly greater activation during error responses than healthy participants (see Table 22).

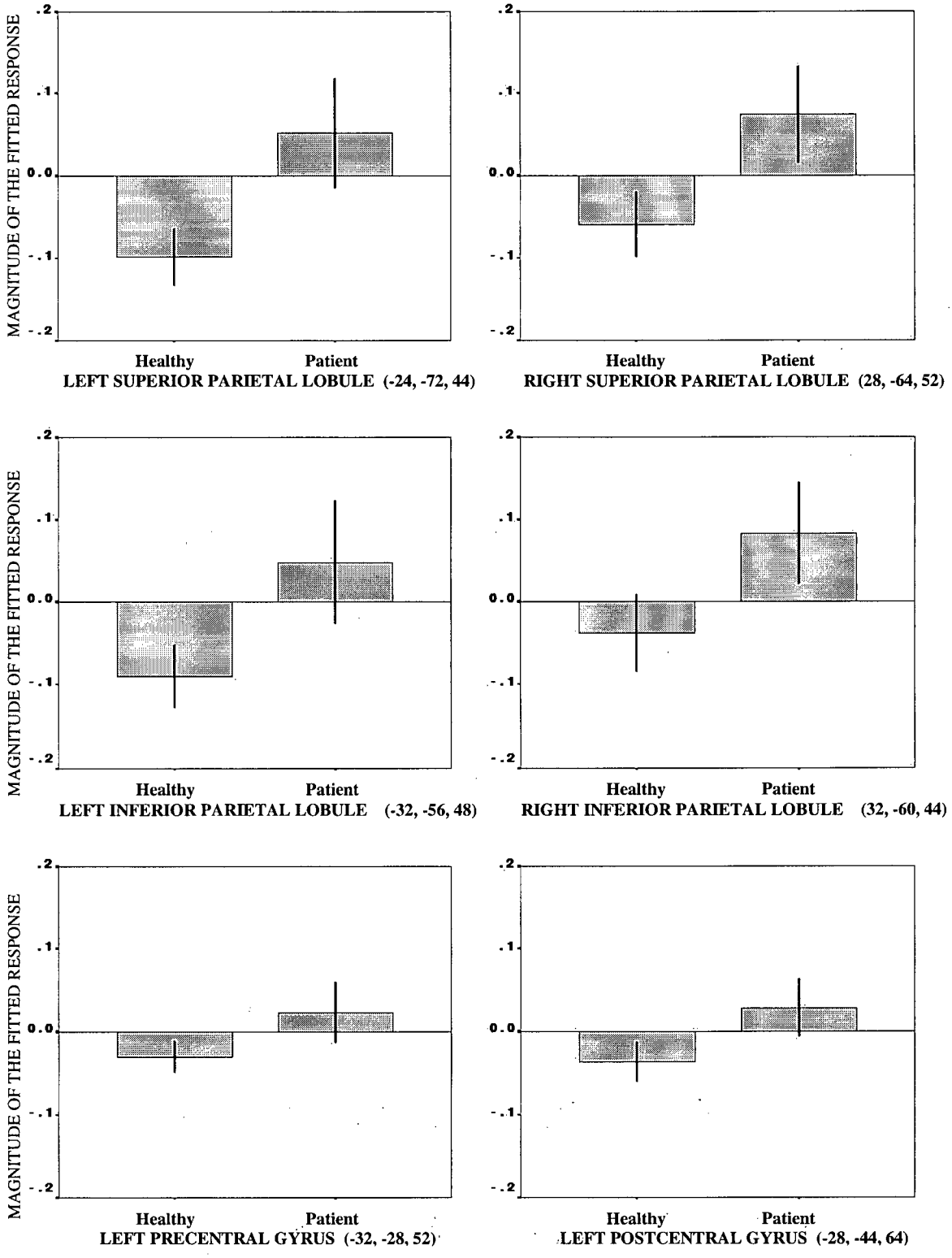


Figure 30. Illustration of the clusters of activation in which the amplitude of the haemodynamic response elicited during Correct Rejects relative to the Go baseline differed between healthy participants and patients with schizophrenia. The posterior cingulate cortex cluster in which greater haemodynamic activity was observed in healthy participants than in patients is presented in the yellow-red colour range. This cluster was significant only when no correction for multiple comparisons conducted throughout the brain was applied. The four significant clusters of activation in which greater haemodynamic activity was observed in patients than in healthy participants are presented in the blue-purple colour range. These clusters are significant at $p \leq 0.05$ corrected for multiple comparisons. The range of t-score values within the clusters are defined in the colourbars located at right. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). Transaxial slices are presented in 4mm increments starting from z = -52 below to z = 64 mm above the AC-PC plane. The image is thresholded at a height of $t_{(24)} = 2.49$, corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons.

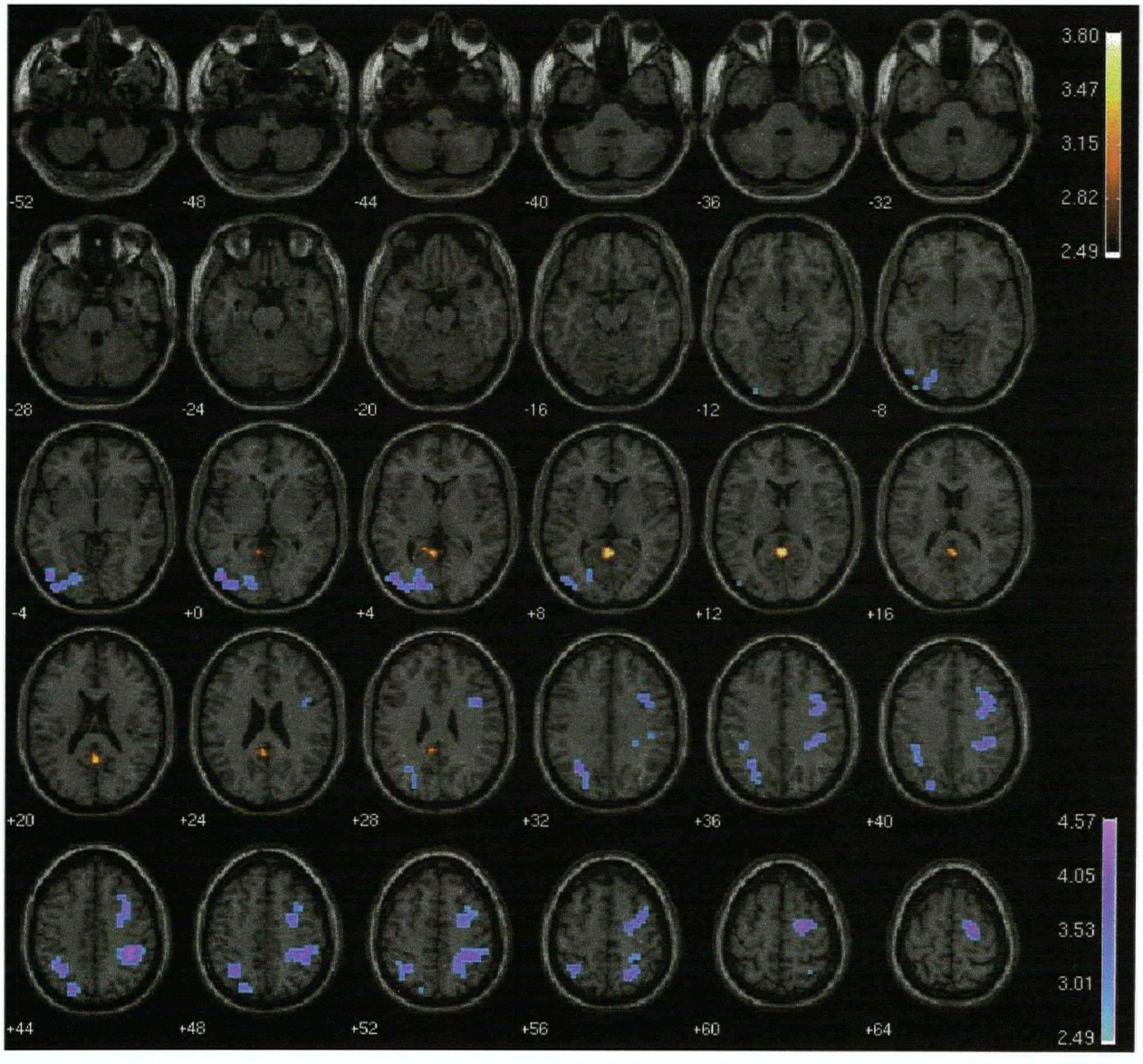
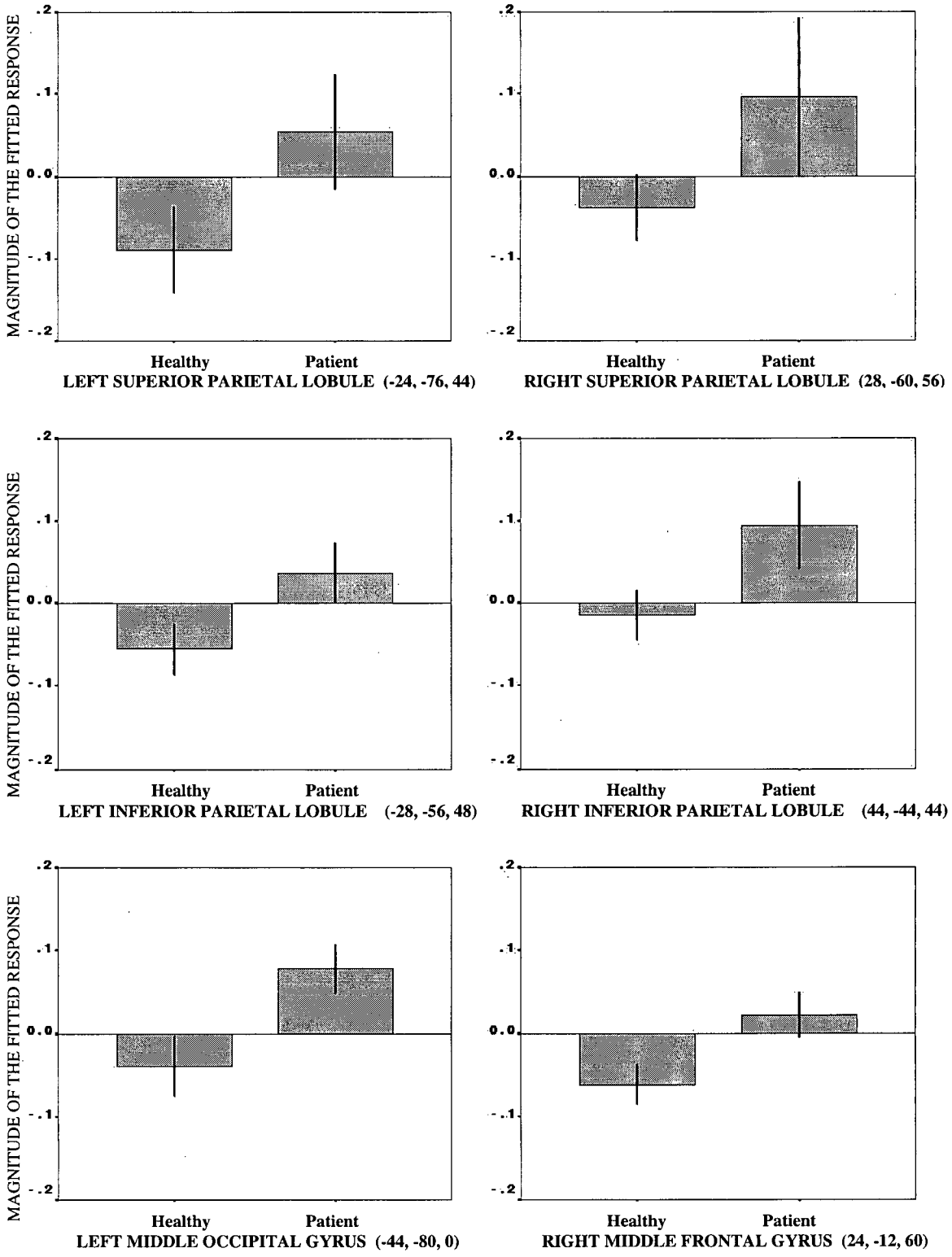


Table 23. Selected local maxima contained within the four significant clusters of activation in which patients with schizophrenia were characterised by a greater haemodynamic response than healthy participants during Correct Rejects relative to the Go stimulus baseline. For each of the local maxima, the Talairach co-ordinates, *t* score, and the probability of achieving that *t* score, both when correcting for multiple comparisons conducted throughout the whole brain ('P_{corr}') and when no correction is applied ('P_{uncorr}'), are reported. Clusters are indicated with a superscript label (a-d) and described at the conclusion of the table.

Functional Anatomic Area (Brodmann Area)	Talairach Co-ordinates			*t* score	P_{corr}	P_{uncorr}
	x	y	z			
Intraparietal Sulcus						
L. Superior Parietal Lobule (7) [d]	-24	-76	44	3.28	1.000	0.002
R. Superior Parietal Lobule (7) [c]	28	-60	56	2.96	1.000	0.003
L. Inferior Parietal Lobule (40) [d]	-28	-56	48	3.82	0.999	0.000
R. Inferior Parietal Lobule (40) [c]	44	-44	44	3.85	0.998	0.000
L. Precuneus (7) [d]	-20	-76	48	3.70	1.000	0.001
R. Precuneus (7) [c]	20	-60	56	3.57	1.000	0.001
Dorsal and Ventral Frontal Cortex						
R. Middle Frontal / Precentral Gyri (6) [b]	24	-12	60	4.44	0.882	0.000
R. Middle Frontal / Precentral Gyri (9) [b]	40	8	40	3.20	1.000	0.002
R. Middle Frontal Gyrus (8) [b]	28	20	44	2.88	1.000	0.004
R. Precentral Gyrus (6) [b]	40	0	36	2.66	1.000	0.007
R. Inferior Frontal Gyrus (9) [b]	40	4	28	3.22	1.000	0.002
Other Neocortex						
L. Inferior Parietal Lobule (40/39) [d]	-32	-60	32	3.95	0.995	0.000
R. Inferior Parietal Lobule / Postcentral Gyrus (40) [c]	40	-36	44	4.30	0.936	0.000
R. Postcentral Gyrus (2/40) [c]	32	-40	52	3.80	0.999	0.000
R. Precuneus / Cuneus (19) [d]	-24	-72	32	3.03	1.000	0.003
L. Middle-Inferior Occipital Gyri (19/18) [a]	-44	-80	0	4.57	0.810	0.000
L. Cuneus (17) [a]	-16	-84	4	3.90	0.997	0.000
L. Lingual Gyrus (18/17) [a]	-20	-80	-4	3.18	1.000	0.002

Note: L. = Left, R. = Right. Cluster **a** = 82 voxels, $p < 0.039$ corrected; cluster **b** = 134 voxels, $p < 0.003$ corrected; cluster **c** = 115 voxels, $p < 0.007$ corrected; cluster **d** = 86 voxels, $p < 0.031$ corrected.

Figure 31. Graphical representation of the mean magnitude of the fitted response (± 2 standard errors) during Correct Rejects relative to the Go stimulus baseline for the healthy participant and patient groups in selected voxels in the intraparietal sulci, right premotor cortex, and left visual cortex. Selected voxels lie within the four clusters in which patients with schizophrenia were characterised by significantly greater activation during correct rejects than healthy participants (see Table 23).



7.3 Discussion

The current study sought to ascertain whether schizophrenia is associated with functional abnormality in the brain response elicited when salient exogenous stimuli are processed incorrectly and an error ensues. Indeed, results demonstrate that schizophrenia is characterised by relative underactivity of the rostral ACC during the commission of errors. Whereas errors elicited increased haemodynamic activity in this region in healthy participants, patients with schizophrenia failed to recruit this area during EoC. Consistent with previous research indicating that this region is specifically involved in error processing (Kiehl et al., 2000a; Braver et al., 2001; Menon et al., 2001), the rostral ACC activation in healthy participants was not observed during correct non-response to NoGo stimuli.

ERP research has demonstrated an attenuation in the amplitude of the fronto-centrally distributed Ne/ERN in patients with schizophrenia relative to healthy participants (Kopp & Rist, 1999; Bates et al., 2002; Mathalon et al., 2002). Our fMRI results suggest that a failure to sufficiently activate the rostral ACC during error commission may contribute to the attenuated Ne/ERN observed in patients with schizophrenia. The observation of aberrant activity in the rostral ACC during EoC is consistent with the hypothesis that patients with schizophrenia experience a disturbed affective and/or motivational response to having committed an error. As an interface between limbic-paralimbic areas and widespread frontal cortex, the ACC is ideally situated to mediate the influence of the motivational and emotional state of an individual on the processing of, and response to, sensory stimuli. Disturbances in affect and motivation are common and persistent symptoms of schizophrenia. Bates et al. (2002) demonstrated that the expression of psychomotor poverty symptoms (including blunted affect and underactivity) is particularly associated with the attenuation of Ne/ERN. Thus, the attenuation of rostral ACC activity during EoC in patients with schizophrenia may reflect a relative diminution of the

affective or motivational response associated with their realisation that an error has been committed.

Relative underactivity in patients with schizophrenia compared to healthy participants was not apparent in the caudal ACC region identified by Kiehl et al. (2000a) as being preferentially active during EoC compared to CR trials in healthy participants. Indeed, there was a trend for patients to show greater activity than healthy participants in this area. This finding contrasts with that of Carter et al. (2001), who demonstrated diminished haemodynamic activity in the caudal ACC of patients with schizophrenia during errors that were elicited using a task that employed degraded stimuli to increase error rates. However, there are notable differences between the present study and that of Carter et al. (2001). As well as impaired caudal ACC function, the patients with schizophrenia in that study exhibited a significantly reduced slowing of RT after error commission. In healthy individuals, RTs typically increase and fewer errors are committed following an erroneous response, which is consistent with the adoption of a more conservative response strategy following detection of an error (Rabbitt, 1966). Carter et al. (2001) interpreted the decreased error-related activity in caudal ACC and the reduced post-error performance adjustment as evidence for impaired internal monitoring function in schizophrenia. In comparison, the present Go/NoGo paradigm employed stimuli that were relatively easier to discriminate than the degraded stimuli employed in Carter et al. (2001), and errors were easily identifiable. Accordingly, the behavioural data obtained using this simple task revealed that patients with schizophrenia exhibited as great an increase in RT as was exhibited by healthy participants for Go trials following EoC relative to Go trials following CR. That is, patients appropriately modified their response behaviour following the commission of an error. This observation implies that they appropriately detected their error responses. Taken together, the results of the present study and those of Carter et al. (2001) suggest that there may be dissociable rostral and caudal ACC contributions to error processing, the relative strength of which may be

modulated by task paradigm. Impairments in an internal monitoring component in schizophrenia might be reflected in caudal ACC underactivity, whereas disturbance in a subjective affective error assessment process may be associated with relative decreases in rostral ACC activity in schizophrenia. In the present experiment, underactivity of the rostral ACC was observed in patients relative to healthy participants in conjunction with a trend for overactivity of the caudal ACC. This pattern of activity is similar to that observed in healthy participants during attentionally-demanding cognitive tasks (Drevets and Raichle, 1998), whereas the converse condition of suppressed caudal ACC and enhanced rostral ACC activity is observed in tasks employing emotional stimuli (Whalen et al, 1998). Thus, the present results suggest that patients may have found the task both more cognitively demanding (calling for relatively greater internal monitoring) and less affectively/motivationally engaging than did the healthy participants.

The question of the relative contributions of rostral and caudal ACC dysfunction to the attenuated Ne/ERN observed in schizophrenia is unresolved. A recent report on source-localisation of high-density ERP data from healthy participants modelled the Ne/ERN as having a caudal ACC generator (van Veen and Carter, 2002b). The rostral ACC was also active during error processing, but later in time, and related to a positive error-related ERP component termed the error-positivity or Pe (Falkenstein et al., 2000). The current temporal resolution of fMRI does not allow the identification of differential Ne/ERN- and Pe-related contributions to ACC activity, and either component might be related to the rostral ACC activity elicited in healthy participants during error responses in the present study. However, previous research has failed to observe differences in Pe amplitude between patients with schizophrenia and healthy participants in spite of detecting a reduction in Ne/ERN amplitude in schizophrenia (Mathalon et al., 2002). Unpublished ERP data from a study in our laboratory that employed the same task as in the present study also failed to identify a difference in Pe amplitude between a small sample of acutely-ill patients with schizophrenia and healthy participants during EoC, in spite of observing

a reduction in Ne/ERN amplitude in patients compared to healthy participants (Bates et al., submitted).

In addition to the error-related failure to activate rostral ACC, there was some evidence for relative underactivity of the hippocampus and PCC in patients with schizophrenia compared with healthy participants during EoC. While these activations in limbic-paralimbic cortex outside the rostral ACC did not satisfy multiple correction criteria across the whole-brain and must be interpreted with caution, they are suggestive of widespread dysfunction within the limbic system in schizophrenia. Relative underactivity in patients in extended limbic cortex provides further support for the hypothesis that the error-related abnormality in rostral ACC function is associated with a disturbed emotional or motivational reaction to errors in schizophrenia. While the hippocampal and rostral ACC underactivity in schizophrenia were associated specifically with EoC, the PCC underactivity was also observed during correct response behaviour (i.e., on correctly-rejected NoGo events). Vogt et al. (1992) proposed a functional dichotomy between the anterior and posterior cingulate cortices, whereby the former is involved with executive functions and the emotional regulation of behaviour and the latter subserves evaluative events such as monitoring sensory events and the organism's own behaviour. Thus, the reported underactivity in PCC in schizophrenia may reflect a generalised impairment in the ability to evaluate infrequent salient stimuli which occur against a background of more common events that signal an alternative behavioural response. Such a breakdown in posterior evaluative functions might be expected to increase the likelihood of error responses.

In addition to observing areas of relative underactivity in patients with schizophrenia, a number of brain areas were characterised by greater activity in patients than in the healthy participants. On NoGo trials, regardless of the accuracy of their subsequent response, patients with schizophrenia showed a relative increase in activity bilaterally around the intraparietal sulcus. This result reflected not only a relative increase in activity during NoGo trials compared

to the Go stimulus baseline in patients with schizophrenia, but also the converse pattern of a relative decrease in activity in this area during NoGo trials compared to Go trials in healthy participants. Unfortunately, the task design employed in this experiment does not permit an examination of the activation of these areas relative to a baseline of rest (i.e., a non-task baseline). Without the capacity to assess NoGo responses against a 'true baseline', it is not possible to determine whether healthy participants actively suppressed these areas when a NoGo stimulus was presented, or whether they simply did not activate them as much as during Go trials. The previous experiments demonstrated that healthy participants strongly activate the intraparietal areas during Go (i.e., target) stimulus processing. Other studies have reported activation of the intraparietal sulcus during response inhibition on NoGo trials that occurred in the context of prepotent responding to Go stimuli (Garavan et al., 1999; Braver et al., 2001; Liddle et al., 2001; Menon et al., 2001). These results imply the intraparietal sulcus area plays an important role in assessing the relevance of incoming stimuli for the purposes of deciding whether or not a behavioural response to the stimuli is required. The current results suggest that patients with schizophrenia fail to modulate activity within this area as required by task demands. Overactivity in the intraparietal sulcus of patients was previously described during performance of a simple, randomly-cued movement task (relative to routine [i.e., predictable] movements) in patients with delusions of alien control (Spence et al., 1997). By implication, in the current study, patients with schizophrenia may have experienced relatively greater difficulty in rapidly deciding the appropriate (non-)behaviour for the infrequent and unpredictable NoGo stimulus. Frith et al. (2000) postulate that overactivity in the intraparietal sulcus results from the lack of an inhibitory signal from the prefrontal cortex. Certainly, the previous experiments, along with a wealth of published literature, demonstrated functional abnormality occurring in the prefrontal cortex of patients with schizophrenia. Moreover, a number of studies have described how the normal co-ordination of prefrontal and parietal activity breaks down in schizophrenia

(see review by McGuire and Frith, 1996). Using a variety of working memory tasks, Quintana et al. (2003) showed that cortex at the intraparietal sulcus may become hyperactive in schizophrenia in order to compensate for disturbed prefrontal function. They further demonstrated that while such a strategy may preserve performance on simple tasks, when this compensatory attempt is unsuccessful, the result can be both prefrontal and parietal hyperactivity. Although evidence of premotor rather than prefrontal abnormality was found in the present study, this does not exclude the possibility of a failure of the prefrontal cortex to inappropriately modulate spatially-remote activity at the intraparietal sulcus during this task.

The other clusters of increased activity in patients with schizophrenia relative to healthy participants during correctly-rejected NoGo trials occurred in right premotor cortex and left unimodal visual association cortex. Premotor cortex is involved in the planning and production of movements, particularly movements guided by external stimuli. The hyperactivated region was ipsilateral to the responding hand and the activation occurred during a trial that involved suppression, rather than commission, of a prepotent motor act. In acts of simple motor responding, patients with schizophrenia are characterised by reduced lateralisation of premotor activation compared to healthy participants (Mattay et al., 1997). Our results suggest that patients with schizophrenia also show a loss of hemispheric specialisation during regulation of motor activity. The explanation for the greater activation in visual association cortex is also uncertain. However, previous neuroimaging research has described an increase in the relative magnitude of signal intensity (Renshaw et al., 1994) and extent of activation (Taylor et al., 1997) in patients with schizophrenia relative to healthy participants in striate cortex during photic stimulation. Our results suggest that abnormalities in visual cortex function may extend beyond the initial processing of sensory stimuli in the context of minimal task requirements (i.e., maintaining fixation on visual stimuli) to disturbed function in areas concerned with evaluating the identity of visual stimuli.

The reported underactivity in rostral ACC and extended limbic-paralimbic cortex during EoC in patients with schizophrenia relative to healthy participants was observed in spite of the low levels of symptomology reported by the patients, who were outpatients living and functioning in the community. Reality distortion symptoms (i.e., delusions and hallucinations) were the most common symptoms reported, with a variable, though relatively low occurrence of disorganised or negative symptoms reported across the patient group. Further research in a larger patient group is needed to clarify the relationship between affective and motivational disturbance (as well as other symptomology) and the relative reduction in rostral ACC activity during error commission in schizophrenia.

This study examined the cortical response to the commission of errors in a medicated patient population, which raises the possibility that some of the observed differences between groups may be attributable to the effects of antipsychotic medication. Previous neuroimaging studies that have examined frontal function in unmedicated patients with schizophrenia have demonstrated both hypofrontality (Andreasen et al., 1992) and hyperfrontality (e.g., Ebmeier et al., 1993) of function, with patient symptomology contributing to variability in the extent of dysfunction. ACC function may be differentially affected by type of antipsychotic medication, as Braus et al. (2000, 2002) report higher levels of neuronal function markers in patients receiving atypical antipsychotics than in those receiving typical antipsychotics. The present study indicates that rostral ACC activity is reduced compared to healthy participants even in a sample of patients who were receiving atypical antipsychotic medication. Further research examining error-related activity in unmedicated patients pre- and post-treatment is required to determine the effect of antipsychotic medication on error processing and internal monitoring in schizophrenia.

Chapter 8.0: General Discussion

8.1 Summary of results

The first three experiments reported in this thesis employed event-related fMRI techniques to characterise the distributed neural circuit that supports the processing of salient exogenous stimuli in healthy participants, and to identify functional abnormality occurring within that network during salient stimulus processing in patients with schizophrenia. Using the same event-related techniques, the final experiment explored whether schizophrenia is additionally characterised by functional abnormality in the brain response elicited when salient exogenous stimuli are processed incorrectly and an error ensues.

The results suggest that, in healthy participants, a distributed corticolimbic network of brain areas is active during the processing of events that are made salient by their relevance to immediate behavioural goals, their infrequency, and/or their novelty. This network incorporates the amygdala-hippocampal complex, paralimbic cortex in the cingulate gyrus and frontal operculum, frontoparietal association cortex, and subcortical structures in the basal ganglia, thalamus, midbrain, and cerebellum. The results suggest further that activity within the network may be modulated by the relative salience of incoming stimuli, with the network particularly engaged during the processing of stimuli that signal the need to perform an overt behavioural response.

In spite of the relatively preserved behavioural performance of patients with schizophrenia on the simple paradigms employed, relative underactivity was observed throughout the corticolimbic network during salient stimulus processing by patients. Particular abnormality was observed in limbic and paralimbic cortex, where dysfunction was apparent regardless of the type of salient stimulus being processed (i.e., infrequent target, infrequent novel, or the frequent target stimulus). Dysfunction was most consistently apparent in the amygdala-anterior hippocampal

complex, the rostral ACC, and the PCC. Relative hypoactivity in limbic and paralimbic areas (specifically, the hippocampus, rostral ACC, and PCC) was also observed in patients during errors of commission to infrequent stimuli that signalled the need to withhold a prepotent motor response.

Abnormality in the dorsal and ventral frontoparietal subnetworks described by Corbetta and Shulman (2002) was also apparent in patients during salient stimulus processing. The more marked dysfunction was observed in the dorsal network that embraces cortex at the intraparietal sulcus and dorsal frontal areas and is purported to support goal-directed selection of stimuli and responses. Within the ventral network, abnormality was predominantly apparent in the temporoparietal(-occipital) junction.

There were several notable differences between the pattern of dysfunction elicited within the frontoparietal association areas and that elicited within limbic-paralimbic cortex. Unlike the generalised abnormality apparent in limbic and paralimbic cortex during the processing of all salient stimulus types, dysfunction within the association areas appeared relatively more dependent on the nature of the salient stimulus being processed. For example, whereas infrequent and frequent target stimulus and infrequent novel stimulus processing were all associated with relative underactivity of cortex in the intraparietal sulcus-precuneus, dysfunction within frontal areas was particularly pronounced during novel stimulus processing. This seems broadly consistent with ERP research demonstrating attenuation in schizophrenia of the frontocentrally-maximal P3a elicited by novel stimuli and of the parietally-maximal P3b elicited by target stimuli (Grillon et al., 1990, 1991a; Merrin and Floyd, 1994). Another difference in the pattern of abnormality apparent in the limbic-paralimbic cortex and the association cortices was that while cortex in the limbic and paralimbic areas were consistently hypoactive in patients relative to healthy participants across all tasks, the pattern of abnormality within the intraparietal sulcus varied across experiments. The pattern of relative underactivity observed in the

intraparietal sulcus during infrequent target, frequent target, and infrequent novel stimulus processing reversed for errors of commission to infrequent NoGo (nontarget) stimuli, with relative hyperactivity apparent during errors in patients compared to healthy participants. Thus, the functional abnormality characterising patients with schizophrenia in intraparietal cortex appears to be a failure to appropriately modulate activity according to the task demands. It is suggested that such a failure may arise as a result of a disrupted co-ordination of activity between this area and the higher brain centres located in limbic-paralimbic areas and frontal cortex which may bias activity in posterior parietal cortex.

8.2 Contribution of the research to understanding the neural basis of salient stimulus processing

Mesulam (1998) proposed that motivational influences arising in the limbic cortex are channelled via paralimbic areas to heteromodal association cortex so that exogenous information may be processed according to its significance rather than solely according to the surface properties of the stimulus. Based on oddball detection studies, Knight and Scabini (1998) ascribed a critical role to the hippocampus in the processing of salient exogenous stimuli. They posited that neural circuits dependent on the hippocampal region allow incoming stimuli to be compared against a template of the recent past. Deviation from the template activates a distributed corticolimbic system that facilitates a behavioural response to the event and its integration into memory. The results obtained in the present studies support this theory, but in addition, imply that the theory must be extended to explicitly incorporate a contribution from the amygdala to the processing of salient exogenous stimuli. In line with the hypotheses of Mesulam (1998), we suggest that the amygdala may contribute to salient stimulus processing through a 'motivated (top-down) biasing' of activity within the corticolimbic network, such that stimuli that have potential relevance for behaviour are processed preferentially. That is, the influence of situational context, past experience, and present and future goals may be brought to

bear on the processing of incoming information and the formulation of an appropriate response via a network of brain areas centred in both the amygdala and hippocampus. For novel and infrequent stimuli, the motivational biasing provided by the amygdala may be relatively automatic, as the brain seeks out never-experienced or unexpected alterations in the environment that may require a change in ongoing behaviour. However, we suggest that activity in this circuit may also be more consciously modulated such that a stimulus targeted to evoke a prescribed behaviour also receives preferential processing.

The motivated biasing of stimulus processing by the limbic cortex is likely to occur via the modulation of activity within the frontoparietal heteromodal association areas that ultimately decipher the nature of the exogenous stimulus and formulate an appropriate behavioural or cognitive response to the stimulus. Paralimbic cortex in the cingulate and frontal operculum, as well as cortico-striato-thalamic and cortico-thalamic-cerebellar circuits, provide a critical means by which the biases arising in limbic cortex are brought to bear on the heteromodal association areas. The paralimbic areas exert dynamic executive control over stimulus processing and response formulation (Posner and Petersen, 1990; Mesulam, 1998), and monitor the accuracy of this process so that remedial action may be initiated as necessary.

8.3 Implications of dysfunction within the corticolimbic network for information processing in schizophrenia

Abnormality within the corticolimbic network in schizophrenia appears to contribute not only to inefficient processing of salient exogenous events, but also, to insufficient consideration of the significance of a self-generated error for ongoing stimulus processing strategies. The disorders of motivation and volition that are described clinically in schizophrenia are consistent with the idea that functional abnormality in the limbic cortex may lead to impairment in the motivated biasing of salient exogenous stimulus processing. Moreover, the low levels of symptomology

reported by the patients recruited to the experiments in this thesis imply that subtle motivational problems may affect information processing even in the absence of marked clinical impairments in motivation or volition. That is, an impaired ability to appropriately focus limited processing resources on salient exogenous stimuli may represent a fundamental abnormality in schizophrenia. An implication of these results is that some normalisation of the brain response in schizophrenia may be achieved if the motivational deficits of the patients can be ameliorated. One approach to testing this might be to examine whether functional changes are elicited when the salience of the exogenous stimuli is manipulated (e.g., by associating particular stimuli with a monetary reward).

Previous research has suggested that the ability of patients to maintain relatively normal task performance (apart from a slowing of reaction time) while concurrently failing to engage large areas of cortex implies that healthy participants typically engage brain areas that are not essential for task performance but simply confer a flexibility in responding to incoming stimuli (Kiehl and Liddle, 2001; Liddle, 2001). The present results imply that what the extended corticolimbic network of areas provides is preferential (biased) processing of salient stimuli. Apparently, what is lacking in schizophrenia is an appropriate modulation of activity in these distributed brain areas so that task performance is at its most efficient. The relative preservation of performance accuracy in patients with schizophrenia may also imply that the functional abnormalities observed in patients were relative and not absolute in nature, and that subthreshold activation within key areas of the corticolimbic network may preserve the ability to perform the task accurately whilst contributing to slowed task performance in patients. That is, the dysfunction contributes to a breakdown in the efficiency of salient stimulus processing, but does not prevent it altogether, at least in these samples of relatively well-functioning, partially-remitted patients with schizophrenia.

Task slowing without an outright inability to perform the task is also consistent with an impaired co-ordination of activity at spatially-remote but connected brain sites in schizophrenia (Friston and Frith, 1995; McGuire and Frith, 1996) . While the diverse brain areas incorporated within the corticolimbic network make specialised contributions to the processing of salient stimuli, efficient information processing should be construed as an emergent property of co-ordinated activity throughout the network. This process appears to be particularly impaired in schizophrenia.

The present work augments previous research positing information processing disturbances as the core abnormality in schizophrenia (Braff, 1993; Andreasen et al., 1998) by identifying functional abnormality within a distributed corticolimbic network during salient exogenous stimulus processing. Even during the performance of tasks that placed relatively low demands on information processing resources, and in spite of ostensibly equivalent levels of performance with healthy participants, patients with schizophrenia were characterised by widespread disturbance. Previous research by Andreasen and colleagues (1996, 1998, 1999; Fuller et al., 2003) suggested that disruption to the connectivity between prefrontal, thalamic, and cerebellar regions lay at the heart of information processing problems in schizophrenia. The present research implies that the fundamental functional abnormality is more widespread, and critically, incorporates dysfunction within limbic and paralimbic cortex in addition to problems in association and subcortical areas.

8.4 Recommendations for future research

The goal of this thesis was to describe the network of brain areas that support the processing of salient stimuli in healthy individuals, and to elucidate functional abnormality in that network during salient stimulus processing by patients with schizophrenia. A series of experiments was performed in order to characterise the brain response elicited by a variety of salient stimuli,

including infrequent target events, infrequent novel events, and frequent target events, as well as erroneous responses committed during salient stimulus processing. In each of the studies, random-effects analyses that accounted for the variability present between-subjects in addition to the within-subject variability were conducted to ensure that the patterns of activity observed in the healthy and patient groups could be considered representative of the populations from which they were drawn. However, all but the first experiment employed relatively small sample sizes and thus afforded less power to reliably detect differences between the participant groups (see Friston et al., 1999b). In Experiments Three and Four, ROIs specified *a priori* enabled an examination of group differences within key sites of the corticolimbic network, however, the analyses examining the response elsewhere in the brain may have been limited by the power afforded by the small patient samples employed. It would be useful to repeat these experiments with larger samples in order to fully characterise the whole-brain response during task performance.

The use of a larger patient sample would also afford an examination of whether particular symptoms are related to an exaggeration of abnormality within different regions of the corticolimbic network. Previous research (summarised in Liddle, 2001), indicates that the major clusters of schizophrenic symptoms (i.e., syndromes) are associated with abnormality in different regions of the corticolimbic network described in this thesis (see Table 24). While the present studies suggest that an impaired ability to appropriately focus limited processing resources on salient exogenous stimuli represents a core abnormality that is present even in partially-remitted patients experiencing relatively few symptoms, this does not preclude a relationship between the syndromes of schizophrenia and more pronounced abnormality within a particular part of the circuit. Determining the existence of a relationship between the syndromes and pronounced abnormality at particular locations within the network would provide further insight into the

specialised roles that the various components of the network perform in supporting the processing of salient stimuli.

Table 24. Summary of the aberrant regional cerebral activity associated with the characteristic syndromes of schizophrenia.

Syndrome	Characteristic Symptoms	Functional Abnormality
Reality Distortion	• Delusions • Hallucinations	**Overactive**: medial temporal cortex, frontal cortex, ventral striatum **Underactive**: posterior cingulate
Disorganisation	• Formal thought disorder • Inappropriate affect • Bizarre behaviour	**Overactive**: medial frontal cortex, anterior cingulate, thalamus **Underactive**: ventral frontal cortex, insula, parietal cortex
Psychomotor Poverty (core negative symptoms)	• Poverty of speech • Blunted affect • Decreased spontaneous movement/Avolition	**Overactive**: basal ganglia **Underactive**: frontal cortex, parietal cortex

The results reported in this thesis suggest that there is an impaired co-ordination of neural activity at spatially-remote sites during salient stimulus processing, that is, a disorder in the 'functional connectivity' between brain areas. An important next step in the development of this

body of research is to explicitly test the integrity of the functional connectivity between the sites within the corticolimbic network in schizophrenia. Functional connectivity is demonstrated by a non-zero temporal correlation between spatially remote neurophysiological (functional) events. Future analyses might use techniques based on Principal Components Analysis (e.g., Friston et al., 1993; Friston, 1994; Woodward et al., submitted) to both elucidate patterns of correlated activity within the distributed corticolimbic network in healthy participants, and to ascertain a breakdown of this connectivity in patients with schizophrenia.

As noted previously in the discussion section to each study, the effect of the patients' medication status on the results obtained cannot readily be ascertained. Future studies could employ these simple paradigms with first-episode, neuroleptic-naïve patients to determine if the functional abnormalities are present already in the early stages of the illness and prior to antipsychotic treatment. Moreover, follow-up scanning of such patients may provide important insight into the relationship between pharmacological intervention, symptom resolution, and normalisation of function within the corticolimbic network. For example, Moore et al. (1999) describe how dysfunction within limbic and prefrontal structures results in the dysregulation of the forebrain dopamine systems, which in turn leads to striking abnormality in cortical-basal ganglia-thalamic circuits and the behaviours mediated by these circuits. Using PET, Liddle et al. (1992) demonstrated overactivity of the ventral striatum and limbic cortex (i.e., the hippocampus-parahippocampal gyrus) in patients experiencing hallucinations and/or delusions (see also Silbersweig et al., 1995). Subsequently, Liddle et al. (2000) demonstrated significant reduction in metabolism within the right ventral striatum immediately following the first dose of risperidone in neuroleptic naïve first-episode patients with schizophrenia. The decrease remained significant after six weeks' treatment. Their study suggests that atypical antipsychotics help to normalise overactivity in key areas of the corticolimbic network in patients with schizophrenia.

The specificity of the functional abnormality within the corticolimbic network to patients with schizophrenia must also be determined. To the extent that motivational and affective problems are also characteristic of major depression and bipolar disorder, and that P3 abnormalities have been previously reported in these groups (see Polich and Herbst, 2000), it is reasonable to expect that these patient groups might also be characterised by abnormality within the corticolimbic network supporting salient stimulus processing. Neuroimaging studies of the mood disorders have demonstrated abnormality within key areas of the network, including in paralimbic ACC, lateral frontal cortex, and the basal ganglia (Bench et al., 1992; Drevets et al., 1992; Mayberg et al., 1994; see also a review by Mayberg, 2003). It will be important to determine whether mood disordered patients demonstrate a pattern of abnormality similar to the widespread dysfunction that is apparent in schizophrenia, or whether functional abnormality within the network is localised within particular structures such as the ACC.

8.5 Conclusion

Effective cognition and behaviour entails the preferential allocation of limited processing resources to salient features of the environment. This thesis demonstrates that salient stimulus processing is supported by a corticolimbic network encompassing limbic, paralimbic, frontoparietal association cortex, and subcortical structures. This network is activated by exogenous events made salient by their infrequency, novelty, and/or by their relevance to immediate behavioural goals, particularly the latter. It is suggested that limbic areas mediate the preferential allocation of limited processing resources to salient stimuli via a 'motivated (top-down) biasing' of activity within the corticolimbic network. In this way, stimuli that (may) have relevance for behaviour are processed preferentially. Patients with schizophrenia are characterised by widespread dysfunction within this network, even when task performance is relatively preserved and when symptom levels are low. Particular abnormality is apparent within

the limbic and paralimbic areas, consistent with the idea that patients experience a disturbance in the motivated biasing of neural activity that sustains the preferential processing of salient stimuli. Problems in processing salient stimuli and in monitoring the responses to such stimuli may constitute a core feature of the illness.

Chapter 9.0: References

Adler LE, Pachtman E, Franks RD, Pecevich M, Waldo MC, Freedman R (1982) Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. Biol Psychiatry 17:639-654.

Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 85:119-146.

Ammons RB, Ammons CH (1962) The Quick Test (QT): Provisional manual. Psychol Rep 11:111-161.

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annu Rev Neurosci 25:189-220.

Andreasen NC, Rezai K, Alliger R, Swayze VW, 2nd, Flaum M, Kirchner P, Cohen G, O'Leary DS (1992) Hypofrontality in neuroleptic-näive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. Arch Gen Psychiatry 49:943-958.

Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Ponto LL, Watkins GL, Hichwa RD (1996) Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. Proc Natl Acad Sci U S A 93:9985-9990.

Andreasen NC, Paradiso S, O'Leary DS (1998) "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr Bull 24:203-218.

Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M (1999) Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biol Psychiatry 46:908-920.

Annett M (1970) A classification of hand preference by association analysis. Br J Psychol 61:303-321.

Ardekani BA, Choi SJ, Hossein-Zadeh GA, Porjesz B, Tanabe JL, Lim KO, Bilder R, Helpern JA, Begleiter H (2002) Functional magnetic resonance imaging of brain activity in the visual oddball task. Brain Res Cogn Brain Res 14:347-356.

American Psychiatric Association [APA] (1994) Diagnostic and statistical manual of mental disorders, 4th Edition. Washington, DC: American Psychiatric Association.

Augustine JR (1996) Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res Brain Res Rev 22:229-244.

Bahramali H, Lim LC, Rennie C, Meares R, Gordon E (2001) ERPs associated with and without an "orienting reflex" in patients with schizophrenia. Int J Neurosci 108:163-174.

Baizer JS, Ungerleider LG, Desimone R (1991) Organization of visual inputs to the inferior temporal and posterior parietal cortex in macaques. J Neurosci 11:168-190.

Baldeweg T, Klugman A, Gruzelier JH, Hirsch SR (2002) Impairment in frontal but not temporal components of mismatch negativity in schizophrenia. Int J Psychophysiol 43:111-122.

Bates AT, Kiehl KA, Laurens KR, Liddle PF (2002) Error-related negativity and correct response negativity in schizophrenia. Clin Neurophysiol 113:1454-1463.

Bates AT, Liddle PF, Kiehl KA, Ngan ET (submitted) State dependent changes in error-related negativity and correct response negativity in schizophrenia.

Baudena P, Halgren E, Heit G, Clarke JM (1995) Intracerebral potentials to rare target and distractor auditory and visual stimuli. III. Frontal cortex. Electroencephalogr Clin Neurophysiol 94:251-264.

Bench CJ, Friston KJ, Brown RG, Scott LC, Frackowiak RS, Dolan RJ (1992) The anatomy of melancholia--focal abnormalities of cerebral blood flow in major depression. Psychol Med 22:607-615.

Benes FM, Sorensen I, Bird ED (1991) Reduced neuronal size in posterior hippocampus of schizophrenic patients. Schizophr Bull 17:597-608.

Bernstein AS (1987) Orienting response research in schizophrenia: where we have come and where we might go. Schizophr Bull 13:623-641.

Bernstein PS, Scheffers MK, Coles MG (1995) "Where did I go wrong?" A psychophysiological analysis of error detection. J Exp Psychol Hum Percept Perform 21:1312-1322.

Blackwood DH, Whalley LJ, Christie JE, Blackburn IM, St Clair DM, McInnes A (1987) Changes in auditory P3 event-related potential in schizophrenia and depression. Br J Psychiatry 150:154-160.

Bleuler E (1911/1950) Dementia praecox or the group of schizophrenias. New York, NY: International Universities Press.

Bogerts B, Meertz E, Schonfeldt-Bausch R (1985) Basal ganglia and limbic system pathology in schizophrenia. A morphometric study of brain volume and shrinkage. Arch Gen Psychiatry 42:784-791.

Bogerts B, Falkai P, Haupts M, Greve B, Ernst S, Tapernon-Franz U, Heinzmann U (1990) Post-mortem volume measurements of limbic system and basal ganglia structures in chronic schizophrenics. Initial results from a new brain collection. Schizophr Res 3:295-301.

Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD (2001) Conflict monitoring and cognitive control. Psychol Rev 108:624-652.

Braff DL (1993) Information processing and attention dysfunctions in schizophrenia. Schizophr Bull 19:233-259.

Braff DL, Geyer MA, Swerdlow NR (2001) Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 156:234-258.

Braus DF, Ende G, Hubrich-Ungureanu P, Henn FA (2000) Cortical response to motor stimulation in neuroleptic-näive first episode schizophrenics. Psychiatry Res 98:145-154.

Braus DF, Ende G, Weber-Fahr W, Demirakca T, Tost H, Henn FA (2002) Functioning and neuronal viability of the anterior cingulate neurons following antipsychotic treatment: MR-spectroscopic imaging in chronic schizophrenia. Eur Neuropsychopharmacol 12:145-152.

Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A (2001) Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cereb Cortex 11:825-836.

Bredgaard R, Glenthoj BY (2000) Information processing and attentional dysfunctions as vulnerability indicators in schizophrenia spectrum disorders. World J Biol Psychiatry 1:5-15.

Brown K, Gordon E, Williams L, Bahramali H, Harris A, Gray J, Gonsalvez C, Meares R (2000) Misattribution of sensory input reflected in dysfunctional target:non-target ERPs in schizophrenia. Psychol Med 30:1443-1449.

Brown KJ, Gonsalvez CJ, Harris AW, Williams LM, Gordon E (2002) Target and non-target ERP disturbances in first episode vs. chronic schizophrenia. Clin Neurophysiol 113:1754-1763.

Brown RG, Pluck G (2000) Negative symptoms: the 'pathology' of motivation and goal-directed behaviour. Trends Neurosci 23:412-417.

Buckner RL, Logan JM (2001) Functional neuroimaging methods: PET and fMRI. In: Handbook of functional neuroimaging of cognition (Cabeza R, Kingstone A, eds), pp 27-48. Cambridge, MA: MIT Press.

Bullmore E, Brammer M, Harvey I, Murray R, Ron M (1995) Cerebral hemispheric asymmetry revisited: effects of handedness, gender and schizophrenia measured by radius of gyration in magnetic resonance images. Psychol Med 25:349-363.

Bullmore ET, Woodruff PW, Wright IC, Rabe-Hesketh S, Howard RJ, Shuriquie N, Murray RM (1998) Does dysplasia cause anatomical dysconnectivity in schizophrenia? Schizophr Res 30:127-135.

Bunge SA, Hazeltine E, Scanlon MD, Rosen AC, Gabrieli JD (2002) Dissociable contributions of prefrontal and parietal cortices to response selection. Neuroimage 17:1562-1571.

Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4:215-222.

Callicott JH, Ramsey NF, Tallent K, Bertolino A, Knable MB, Coppola R, Goldberg T, van Gelderen P, Mattay VS, Frank JA, Moonen CT, Weinberger DR (1998) Functional magnetic resonance imaging brain mapping in psychiatry: methodological issues illustrated in a study of working memory in schizophrenia. Neuropsychopharmacology 18:186-196.

Callicott JH, Bertolino A, Mattay VS, Langheim FJ, Duyn J, Coppola R, Goldberg TE, Weinberger DR (2000) Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cereb Cortex 10:1078-1092.

Callicott JH (2003) An expanded role for functional neuroimaging in schizophrenia. Curr Opin Neurobiol 13:256-260.

Cardinal RN, Parkinson JA, Hall J, Everitt BJ (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev 26:321-352.

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998) Anterior cingulate cortex, error detection, and the online monitoring of performance. Science 280:747-749.

Carter CS, MacDonald AW, 3rd, Ross LL, Stenger VA (2001) Anterior cingulate cortex activity and impaired self-monitoring of performance in patients with schizophrenia: an event-related fMRI study. Am J Psychiatry 158:1423-1428.

Casey BJ, Forman SD, Franzen P, Berkowitz A, Braver TS, Nystrom LE, Thomas KM, Noll DC (2001) Sensitivity of prefrontal cortex to changes in target probability: a functional MRI study. Hum Brain Mapp 13:26-33.

Cecil KM, Lenkinski RE, Gur RE, Gur RC (1999) Proton magnetic resonance spectroscopy in the frontal and temporal lobes of neuroleptic naive patients with schizophrenia. Neuropsychopharmacology 20:131-140.

Clark VP, Fannon S, Lai S, Benson R, Bauer L (2000) Responses to rare visual target and distractor stimuli using event-related fMRI. J Neurophysiol 83:3133-3139.

Coles MGH, Rugg MD (1995) Event-related potentials: an introduction. In: Electrophysiology of the mind: Event-related brain potentials and cognition (Rugg MD, Coles MGH, eds), pp 1-26. Oxford, UK: Oxford University Press.

Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL (2000) Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat Neurosci 3:292-297.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201-215.

Courchesne E, Hillyard SA, Galambos R (1975) Stimulus novelty, task relevance and the visual evoked potential in man. Electroencephalogr Clin Neurophysiol 39:131-143.

Crow TJ (1997) Schizophrenia as failure of hemispheric dominance for language. Trends Neurosci 20:339-343.

Csernansky JG, Wang L, Jones D, Rastogi-Cruz D, Posener JA, Heydebrand G, Miller JP, Miller MI (2002) Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. Am J Psychiatry 159:2000-2006.

Daffner KR, Mesulam MM, Scinto LF, Acar D, Calvo V, Faust R, Chabrerie A, Kennedy B, Holcomb P (2000) The central role of the prefrontal cortex in directing attention to novel events. Brain 123:927-939.

Debener S, Kranczioch C, Herrmann CS, Engel AK (2002) Auditory novelty oddball allows reliable distinction of top-down and bottom-up processes of attention. Int J Psychophysiol 46:77-84.

Dehaene S, Posner MI, Tucker DM (1994) Localization of a neural system for error detection and compensation. Psychological Science 5:303-305.

Demiralp T, Ucok A, Devrim M, Isoglu-Alkac U, Tecer A, Polich J (2002) N2 and P3 components of event-related potential in first-episode schizophrenic patients: scalp topography, medication, and latency effects. Psychiatry Res 111:167-179.

Desjardins AE, Kiehl KA, Liddle PF (2001) Removal of confounding effects of global signal in functional MRI analyses. Neuroimage 13:751-758.

Devinsky O, Morrell MJ, Vogt BA (1995) Contributions of anterior cingulate cortex to behaviour. Brain 118:279-306.

Dikman ZV, Allen JJ (2000) Error monitoring during reward and avoidance learning in high- and low-socialized individuals. Psychophysiology 37:43-54.

Donaldson DI, Buckner RL (2001) Effective paradigm design. In: Functional MRI: An introduction to methods (Jezzard P, Matthews PM, Smith SM, eds), pp 177-195. Oxford: Oxford University Press.

Downar J, Crawley AP, Mikulis DJ, Davis KD (2000) A multimodal cortical network for the detection of changes in the sensory environment. Nat Neurosci 3:277-283.

Downar J, Crawley AP, Mikulis DJ, Davis KD (2001) The effect of task relevance on the cortical response to changes in visual and auditory stimuli: An event-related fMRI study. Neuroimage 14:1256-1267.

Downar J, Crawley AP, Mikulis DJ, Davis KD (2002) A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. J Neurophysiol 87:615-620.

Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992) A functional anatomical study of unipolar depression. J Neurosci 12:3628-3641.

Drevets WC, Raichle ME (1998) Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: Implications for interactions between emotion and cognition. Cogn Emot 12:353-385.

Ebmeier KP, Blackwood DH, Murray C, Souza V, Walker M, Dougall N, Moffoot AP, O'Carroll RE, Goodwin GM (1993) Single-photon emission computed tomography with 99mTc-exametazime in unmedicated schizophrenic patients. Biol Psychiatry 33:487-495.

Ebmeier KP, Steele JD, MacKenzie DM, O'Carroll RE, Kydd RR, Glabus MF, Blackwood DH, Rugg MD, Goodwin GM (1995) Cognitive brain potentials and regional cerebral blood flow equivalents during two- and three-sound auditory "oddball tasks". Electroencephalogr Clin Neurophysiol 95:434-443.

Egan MF, Duncan CC, Suddath RL, Kirch DG, Mirsky AF, Wyatt RJ (1994) Event-related potential abnormalities correlate with structural brain alterations and clinical features in patients with chronic schizophrenia. Schizophr Res 11:259-271.

Eyler Zorrilla LT, Jeste DV, Paulus M, Brown GG (2003) Functional abnormalities of medial temporal cortex during novel picture learning among patients with chronic schizophrenia. Schizophr Res 59:187-198.

Falkai P, Bogerts B (1986) Cell loss in the hippocampus of schizophrenics. Eur Arch Psychiatry Neurol Sci 236:154-161.

Falkenstein M, Hohnsbein J, Hoormann J, Blanke L (1990) Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: Psychophysiological brain research (Brunia CHM, Gaillard AWK, Kok A, eds), pp 192-195. Tilburg, Netherlands: Tilburg University Press.

Falkenstein M, Hohnsbein J, Hoormann J, Blanke L (1991) Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. Electroencephalogr Clin Neurophysiol 78:447-455.

Falkenstein M, Hoormann J, Christ S, Hohnsbein J (2000) ERP components on reaction errors and their functional significance: a tutorial. Biol Psychol 51:87-107.

Faux SF, McCarley RW, Nestor PG, Shenton ME, Pollak SD, Penhune V, Mondrow E, Marcy B, Peterson A, Horvath T, et al. (1993) P300 topographic asymmetries are present in unmedicated schizophrenics. Electroencephalogr Clin Neurophysiol 88:32-41.

Fletcher P (1998) The missing link: a failure of fronto-hippocampal integration in schizophrenia. Nat Neurosci 1:266-267.

Ford JM (1999) Schizophrenia: the broken P300 and beyond. Psychophysiology 36:667-682.

Ford JM, White P, Lim KO, Pfefferbaum A (1994a) Schizophrenics have fewer and smaller P300s: a single-trial analysis. Biol Psychiatry 35:96-103.

Ford JM, White PM, Csernansky JG, Faustman WO, Roth WT, Pfefferbaum A (1994b) ERPs in schizophrenia: effects of antipsychotic medication. Biol Psychiatry 36:153-170.

Ford JM, Mathalon DH, Kalba S, Marsh L, Pfefferbaum A (2001) N1 and P300 abnormalities in patients with schizophrenia, epilepsy, and epilepsy with schizophrenialike features. Biol Psychiatry 49:848-860.

Freedman R, Adler LE, Waldo MC, Pachtman E, Franks RD (1983) Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. Biol Psychiatry 18:537-551.

Friedman D, Cycowicz YM, Gaeta H (2001) The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. Neurosci Biobehav Rev 25:355-373.

Friston KJ (1994) Functional and effective connectivity in neuroimaging: A synthesis. Human Brain Mapping 2:56-78.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS (1993) Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 13:5-14.

Friston KJ, Worsley KJ, Frackowiak RS, Mazziotta JC, Evans AC (1994) Assessing the significance of focal activations using their spatial extent. Hum Brain Mapp 1:214-220.

Friston KJ, Frith CD (1995) Schizophrenia: a disconnection syndrome? Clin Neurosci 3:89-97.

Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RS (1995a) Spatial registration and normalization of images. Hum Brain Mapp 2:165-189.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RS (1995b) Statistical parametric maps in functional imaging: A general linear approach. Hum Brain Mapp 2:189-210.

Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R (1996) Movement-related effects in fMRI time-series. Magn Reson Med 35:346-355.

Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998) Event-related fMRI: characterizing differential responses. Neuroimage 7:30-40.

Friston KJ, Holmes AP, Price CJ, Buchel C, Worsley KJ (1999a) Multisubject fMRI studies and conjunction analyses. Neuroimage 10:385-396.

Friston KJ, Holmes AP, Worsley KJ (1999b) How many subjects constitute a study? Neuroimage 10:1-5.

Frith CD, Done DJ (1989) Experiences of alien control in schizophrenia reflect a disorder in the central monitoring of action. Psychol Med 19:359-363.

Frith CD, Blakemore S, Wolpert DM (2000) Explaining the symptoms of schizophrenia: abnormalities in the awareness of action. Brain Res Brain Res Rev 31:357-363.

Fukuzako H, Takeuchi K, Hokazono Y, Fukuzako T, Yamada K, Hashiguchi T, Obo Y, Ueyama K, Takigawa M, Fujimoto T (1995) Proton magnetic resonance spectroscopy of the left medial temporal and frontal lobes in chronic schizophrenia: preliminary report. Psychiatry Res 61:193-200.

Fuller RLM, Schultz SK, Andreasen NC (2003) The symptoms of schizophrenia. In: Schizophrenia (Hirsch SR, Weinberger DR, eds), pp 25-33. Oxford, UK: Blackwell Science Ltd.

Gaeta H, Friedman D, Hunt G (2003) Stimulus characteristics and task category dissociate the anterior and posterior aspects of the novelty P3. Psychophysiology 40:198-208.

Garavan H, Ross TJ, Stein EA (1999) Right hemispheric dominance of inhibitory control: an event-related functional MRI study. Proc Natl Acad Sci U S A 96:8301-8306.

Gehring WJ, Coles MGH, Meyer DE, Donchin E (1990) The error-related negativity: An event-related brain potential accompanying errors. Psychophysiology 27:S43.

Gehring WJ, Goss B, Coles MG, Meyer DE, Donchin E (1993) A neural system for error detection and compensation. Psychological Science 4:385-390.

Giard MH, Perrin F, Pernier J, Bouchet P (1990) Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. Psychophysiology 27:627-640.

Giard MH, Perrin F, Echallier JF, Thevenet M, Froment JC, Pernier J (1994) Dissociation of temporal and frontal components in the human auditory N1 wave: a scalp current density and dipole model analysis. Electroencephalogr Clin Neurophysiol 92:238-252.

Gottlieb J (2002) Parietal mechanisms of target representation. Curr Opin Neurobiol 12:134-140.

Greicius MD, Krasnow B, Boyett-Anderson JM, Eliez S, Schatzberg AF, Reiss AL, Menon V (2003) Regional analysis of hippocampal activation during memory encoding and retrieval: fMRI study. Hippocampus 13:164-174.

Grillon C, Courchesne E, Ameli R, Geyer MA, Braff DL (1990) Increased distractibility in schizophrenic patients. Electrophysiologic and behavioral evidence. Arch Gen Psychiatry 47:171-179.

Grillon C, Ameli R, Courchesne E, Braff DL (1991a) Effects of task relevance and attention on P3 in schizophrenic patients. Schizophr Res 4:11-21.

Grillon C, Ameli R, Braff DL (1991b) Middle latency auditory evoked potentials (MAEPs) in chronic schizophrenics. Schizophr Res 5:61-66.

Grillon C, Ameli R, Charney DS, Krystal J, Braff D (1992) Startle gating deficits occur across prepulse intensities in schizophrenic patients. Biol Psychiatry 32:939-943.

Grzella I, Muller BW, Oades RD, Bender S, Schall U, Zerbin D, Wolstein J, Sartory G (2001) Novelty-elicited mismatch negativity in patients with schizophrenia on admission and discharge. J Psychiatry Neurosci 26:235-246.

Gur RE, Chin S (1999) Laterality in functional brain imaging studies of schizophrenia. Schizophr Bull 25:141-156.

Gur RE, McGrath C, Chan RM, Schroeder L, Turner T, Turetsky BI, Kohler C, Alsop D, Maldjian J, Ragland JD, Gur RC (2002) An fMRI study of facial emotion processing in patients with schizophrenia. Am J Psychiatry 159:1992-1999.

Halgren E, Squires NK, Wilson CL, Rohrbaugh JW, Babb TL, Crandall PH (1980) Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. Science 210:803-805.

Halgren E, Baudena P, Clarke JM, Heit G, Liegeois C, Chauvel P, Musolino A (1995a) Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. Electroencephalogr Clin Neurophysiol 94:191-220.

Halgren E, Baudena P, Clarke JM, Heit G, Marinkovic K, Devaux B, Vignal JP, Biraben A (1995b) Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. Electroencephalogr Clin Neurophysiol 94:229-250.

Halgren E, Marinkovic K, Chauvel P (1998) Generators of the late cognitive potentials in auditory and visual oddball tasks. Electroencephalogr Clin Neurophysiol 106:156-164.

Harrison PJ (1999) The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 122 (Pt 4):593-624.

Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, Alpert NM (1998) Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nat Neurosci 1:318-323.

Heckers S, Goff D, Weiss AP (2002) Reversed hemispheric asymmetry during simple visual perception in schizophrenia. Psychiatry Res 116:25-32.

Hempel A, Hempel E, Schonknecht P, Stippich C, Schroder J (2003) Impairment in basal limbic function in schizophrenia during affect recognition. Psychiatry Res 122:115-124.

Hirayasu Y, Asato N, Ohta H, Hokama H, Arakaki H, Ogura C (1998) Abnormalities of auditory event-related potentials in schizophrenia prior to treatment. Biol Psychiatry 43:244-253.

Hollingshead AB, Redlich FC (1958) Social class and mental illness: A community study. New York, NY: Wiley.

Holroyd CB, Dien J, Coles MG (1998) Error-related scalp potentials elicited by hand and foot movements: evidence for an output-independent error-processing system in humans. Neurosci Lett 242:65-68.

Hopfinger JB, Buonocore MH, Mangun GR (2000) The neural mechanisms of top-down attentional control. Nat Neurosci 3:284-291.

Horovitz SG, Skudlarski P, Gore JC (2002) Correlations and dissociations between BOLD signal and P300 amplitude in an auditory oddball task: a parametric approach to combining fMRI and ERP. Magn Reson Imaging 20:319-325.

Hugdahl K (2000) Lateralization of cognitive processes in the brain. Acta Psychol 105:211-235.

Johns LC, Rossell S, Frith C, Ahmad F, Hemsley D, Kuipers E, McGuire PK (2001) Verbal self-monitoring and auditory verbal hallucinations in patients with schizophrenia. Psychol Med 31:705-715.

Johnson R, Jr. (1988) Scalp-recorded P300 activity in patients following unilateral temporal lobectomy. Brain 111:1517-1529.

Johnson R, Jr. (1989) Auditory and visual P300s in temporal lobectomy patients: evidence for modality-dependent generators. Psychophysiology 26:633-650.

Josephs O, Turner R, Friston K (1997) Event-related fMRI. Hum Brain Mapp 5:243-248.

Karnath HO (2001) New insights into the functions of the superior temporal cortex. Nat Rev Neurosci 2:568-576.

Karnath HO, Ferber S, Himmelbach M (2001) Spatial awareness is a function of the temporal not the posterior parietal lobe. Nature 411:950-953.

Kasai K, Okazawa K, Nakagome K, Hiramatsu K, Hata A, Fukuda M, Honda M, Miyauchi M, Matsushita M (1999) Mismatch negativity and N2b attenuation as an indicator for dysfunction of the preattentive and controlled processing for deviance detection in schizophrenia: a topographic event-related potential study. Schizophr Res 35:141-156.

Kasai K, Iwanami A, Yamasue H, Kuroki N, Nakagome K, Fukuda M (2002) Neuroanatomy and neurophysiology in schizophrenia. Neurosci Res 43:93-110.

Katayama J, Polich J (1996a) P300 from one-, two-, and three-stimulus auditory paradigms. Int J Psychophysiol 23:33-40.

Katayama J, Polich J (1996b) P300, probability, and the three-tone paradigm. Electroencephalogr Clin Neurophysiol 100:555-562.

Katayama J, Polich J (1998) Stimulus context determines P3a and P3b. Psychophysiology 35:23-33.

Kayser J, Bruder GE, Tenke CE, Stuart BK, Amador XF, Gorman JM (2001) Event-related brain potentials (ERPs) in schizophrenia for tonal and phonetic oddball tasks. Biol Psychiatry 49:832-847.

Kiehl KA, Liddle PF, Hopfinger JB (2000a) Error processing and the rostral anterior cingulate: an event-related fMRI study. Psychophysiology 37:216-223.

Kiehl KA, Smith AM, Hare RD, Liddle PF (2000b) An event-related potential investigation of response inhibition in schizophrenia and psychopathy. Biol Psychiatry 48:210-221.

Kiehl KA, Liddle PF (2001) An event-related functional magnetic resonance imaging study of an auditory oddball task in schizophrenia. Schizophr Res 48:159-171.

Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF (2001a) An event-related fMRI study of visual and auditory oddball tasks. J Psychophysiology 15:221-240.

Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF (2001b) Neural sources involved in auditory target detection and novelty processing: an event-related fMRI study. Psychophysiology 38:133-142.

Kiehl KA, Laurens KR, Mendrek A, Liddle PF (2001c) Improved haemodynamic activity in first episode psychotic patients with atypical neuroleptic treatment: A six week test-retest event-related fMRI study. Neuroimage 13: S1066.

Kiehl KA, Smith AM, Hare RD, Mendrek A, Forster BB, Brink J, Liddle PF (2001d) Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. Biol Psychiatry 50:677-684.

Kiehl KA, Liddle PF (2003) Reproducibility of the hemodynamic response to auditory oddball stimuli: A six-week test-retest study. Hum Brain Mapp 18:42-52.

Kim YH, Gitelman DR, Nobre AC, Parrish TB, LaBar KS, Mesulam MM (1999) The large-scale neural network for spatial attention displays multifunctional overlap but differential asymmetry. Neuroimage 9:269-277.

Knight RT (1984) Decreased response to novel stimuli after prefrontal lesions in man. Electroencephalogr Clin Neurophysiol 59:9-20.

Knight R (1996) Contribution of human hippocampal region to novelty detection. Nature 383:256-259.

Knight RT (1997) Distributed cortical network for visual attention. J Cogn Neurosci 9:75-91.

Knight RT, Scabini D, Woods DL, Clayworth CC (1989) Contributions of temporal-parietal junction to the human auditory P3. Brain Res 502:109-116.

Knight RT, Scabini D (1998) Anatomic bases of event-related potentials and their relationship to novelty detection in humans. J Clin Neurophysiol 15:3-13.

Konishi S, Nakajima K, Uchida I, Sekihara K, Miyashita Y (1998) No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. Eur J Neurosci 10:1209-1213.

Kopp B, Rist F (1999) An event-related brain potential substrate of disturbed response monitoring in paranoid schizophrenic patients. J Abnorm Psychol 108:337-346.

Kosaka H, Omori M, Murata T, Iidaka T, Yamada H, Okada T, Takahashi T, Sadato N, Itoh H, Yonekura Y, Wada Y (2002) Differential amygdala response during facial recognition in patients with schizophrenia: an fMRI study. Schizophr Res 57:87-95.

Kovelman JA, Scheibel AB (1984) A neurohistological correlate of schizophrenia. Biol Psychiatry 19:1601-1621.

Kraeplin E (1919) Dementia Praecox and Paraphrenia. Edinburgh, UK: E & S Livingstone.

Kuroki N, Matsushita M (1998) Pyramidal cell orientation and density in the hippocampus in schizophrenia. Neuropathology 18.

Lawrie SM, Whalley HC, Job DE, Johnstone EC (2003) Structural and functional abnormalities of the amygdala in schizophrenia. Ann N Y Acad Sci 985:445-460.

Lepage M, Habib R, Tulving E (1998) Hippocampal PET activations of memory encoding and retrieval: the HIPER model. Hippocampus 8:313-322.

Leudar I, Thomas P, Johnston M (1994) Self-monitoring in speech production: effects of verbal hallucinations and negative symptoms. Psychol Med 24:749-761.

Liddle PF (1987a) Schizophrenic syndromes, cognitive performance and neurological dysfunction. Psychol Med 17:49-57.

Liddle PF (1987b) The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. Br J Psychiatry 151:145-151.

Liddle PF (2000) Descriptive clinical features of schizophrenia. In: New Oxford textbook of psychiatry (Gelder MG, Lopez-Ibor JJ, Andreasen N, eds). Oxford, UK: Oxford University Press.

Liddle PF (2001) Disordered mind and brain: The neural basis of mental symptoms. London: Gaskell.

Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T, Frackowiak RS (1992) Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry 160:179-186.

Liddle PF, Lane CJ, Ngan ET (2000) Immediate effects of risperidone on cortico-striato-thalamic loops and the hippocampus. Br J Psychiatry 177:402-407.

Liddle PF, Kiehl KA, Smith AM (2001) Event-related fMRI study of response inhibition. Hum Brain Mapp 12:100-109.

Liddle PF, Ngan ET, Duffield G, Kho K, Warren AJ (2002) Signs and Symptoms of Psychotic Illness (SSPI): a rating scale. Br J Psychiatry 180:45-50.

Liddle PF, Pantelis C (2003) Brain imaging in schizophrenia. In: Schizophrenia (Hirsch SR, Weinberger DR, eds), pp 403-417. Oxford, UK: Blackwell Science Ltd.

Linden DE, Prvulovic D, Formisano E, Vollinger M, Zanella FE, Goebel R, Dierks T (1999) The functional neuroanatomy of target detection: an fMRI study of visual and auditory oddball tasks. Cereb Cortex 9:815-823.

Loberg EM, Hugdahl K, Green MF (1999) Hemispheric asymmetry in schizophrenia: a "dual deficits" model. Biol Psychiatry 45:76-81.

Luu P, Collins P, Tucker DM (2000a) Mood, personality, and self-monitoring: negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. J Exp Psychol Gen 129:43-60.

Luu P, Flaisch T, Tucker DM (2000b) Medial frontal cortex in action monitoring. J Neurosci 20:464-469.

MacDonald AW, 3rd, Cohen JD, Stenger VA, Carter CS (2000) Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288:1835-1838.

Maddock RJ, Garrett AS, Buonocore MH (2003) Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. Hum Brain Mapp 18:30-41.

Malenka RC, Angel RW, Hampton B, Berger PA (1982) Impaired central error-correcting behavior in schizophrenia. Arch Gen Psychiatry 39:101-107.

Malenka RC, Angel RW, Thiemann S, Weitz CJ, Berger PA (1986) Central error-correcting behavior in schizophrenia and depression. Biol Psychiatry 21:263-273.

Manoach DS, Press DZ, Thangaraj V, Searl MM, Goff DC, Halpern E, Saper CB, Warach S (1999) Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. Biol Psychiatry 45:1128-1137.

Manoach DS, Gollub RL, Benson ES, Searl MM, Goff DC, Halpern E, Saper CB, Rauch SL (2000) Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. Biol Psychiatry 48:99-109.

Markowitsch HJ, Emmans D, Irle E, Streicher M, Preilowski B (1985) Cortical and subcortical afferent connections of the primate's temporal pole: a study of rhesus monkeys, squirrel monkeys, and marmosets. J Comp Neurol 242:425-458.

Mathalon DH, Ford JM, Pfefferbaum A (2000) Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study. Biol Psychiatry 47:434-449.

Mathalon DH, Fedor M, Faustman WO, Gray M, Askari N, Ford JM (2002) Response-monitoring dysfunction in schizophrenia: an event-related brain potential study. J Abnorm Psychol 111:22-41.

Mattay VS, Callicott JH, Bertolino A, Santha AK, Tallent KA, Goldberg TE, Frank JA, Weinberger DR (1997) Abnormal functional lateralization of the sensorimotor cortex in patients with schizophrenia. Neuroreport 8:2977-2984.

Mayberg HS, Lewis PJ, Regenold W, Wagner HN, Jr. (1994) Paralimbic hypoperfusion in unipolar depression. J Nucl Med 35:929-934.

Mayberg HS (2003) Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. Br Med Bull 65:193-207.

McCarley RW, Shenton ME, O'Donnell BF, Faux SF, Kikinis R, Nestor PG, Jolesz FA (1993) Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. Arch Gen Psychiatry 50:190-197.

McCarthy G, Luby M, Gore J, Goldman-Rakic P (1997) Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. J Neurophysiol 77:1630-1634.

McGhie A, Chapman J (1961) Disorders of attention and perception in early schizophrenia. British Journal of Medical Psychiatry 34:103-116.

McGuire PK, Frith CD (1996) Disordered functional connectivity in schizophrenia. Psychol Med 26:663-667.

Medoff DR, Holcomb HH, Lahti AC, Tamminga CA (2001) Probing the human hippocampus using rCBF: contrasts in schizophrenia. Hippocampus 11:543-550.

Menon V, Ford JM, Lim KO, Glover GH, Pfefferbaum A (1997) Combined event-related fMRI and EEG evidence for temporal-parietal cortex activation during target detection. Neuroreport 8:3029-3037.

Menon V, Adleman NE, White CD, Glover GH, Reiss AL (2001) Error-related brain activation during a Go/NoGo response inhibition task. Hum Brain Mapp 12:131-143.

Merrin EL, Floyd TC (1994) P300 responses to novel auditory stimuli in hospitalized schizophrenic patients. Biol Psychiatry 36:527-542.

Mesulam MM (1981) A cortical network for directed attention and unilateral neglect. Ann Neurol 10:309-325.

Mesulam MM (1998) From sensation to cognition. Brain 121:1013-1052.

Mesulam MM (1999) Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. Philos Trans R Soc Lond B Biol Sci 354:1325-1346.

Mesulam MM, Mufson EJ (1982a) Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. J Comp Neurol 212:1-22.

Mesulam MM, Mufson EJ (1982b) Insula of the old world monkey. III: Efferent cortical output and comments on function. J Comp Neurol 212:38-52.

Mesulam MM, Nobre AC, Kim YH, Parrish TB, Gitelman DR (2001) Heterogeneity of cingulate contributions to spatial attention. Neuroimage 13:1065-1072.

Michie PT (2001) What has MMN revealed about the auditory system in schizophrenia? Int J Psychophysiol 42:177-194.

Milham MP, Banich MT, Webb A, Barad V, Cohen NJ, Wszalek T, Kramer AF (2001) The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on nature of conflict. Brain Res Cogn Brain Res 12:467-473.

Miltner WHR, Braun CH, Coles MGH (1997) Event-related brain potentials following incorrect feedback in a time-production task: Evidence for a 'generic' neural system for error detection. J Cogn Neurosci 9:788-798.

Mlakar J, Jensterle J, Frith CD (1994) Central monitoring deficiency and schizophrenic symptoms. Psychol Med 24:557-564.

Moore H, West AR, Grace AA (1999) The regulation of forebrain dopamine transmission: relevance to the pathophysiology and psychopathology of schizophrenia. Biol Psychiatry 46:40-55.

Moran MA, Mufson EJ, Mesulam MM (1987) Neural inputs into the temporopolar cortex of the rhesus monkey. J Comp Neurol 256:88-103.

Morecraft RJ, Van Hoesen GW (1998) Convergence of limbic input to the cingulate motor cortex in the rhesus monkey. Brain Res Bull 45:209-232.

Muller-Gass A, Campbell K (2002) Event-related potential measures of the inhibition of information processing: I. Selective attention in the waking state. Int J Psychophysiol 46:177-195.

Näätänen R (1990) The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. Behav Brain Sci 13:201-288.

Näätänen R (1992) Attention and brain function. Hillsdale, NJ: Lawrence Erlbaum Associates.

Näätänen R (2003) Mismatch negativity: clinical research and possible applications. Int J Psychophysiol 48:179-188.

Näätänen R, Jiang D, Lavikainen J, Reinikainen K, Paavilainen P (1993) Event-related potentials reveal a memory trace for temporal features. Neuroreport 5:310-312.

Nelson HE (1982) National Adult Reading Test (NART): Test manual. Windsor, UK: NFER-Nelson.

Nelson MD, Saykin AJ, Flashman LA, Riordan HJ (1998) Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry 55:433-440.

Ngan ET, Liddle PF (2000) Reaction time, symptom profiles and course of illness in schizophrenia. Schizophr Res 46:195-201.

O'Donnell BF, Shenton ME, McCarley RW, Faux SF, Smith RS, Salisbury DF, Nestor PG, Pollak SD, Kikinis R, Jolesz FA (1993) The auditory N2 component in schizophrenia: relationship to MRI temporal lobe gray matter and to other ERP abnormalities. Biol Psychiatry 34:26-40.

Pailing PE, Segalowitz SJ, Dywan J, Davies PL (2002) Error negativity and response control. Psychophysiology 39:198-206.

Pandya D, Yeterian E (1985) Architecture and connections of cortical association areas. In: Cerebral cortex (Peters A, EG J, eds), pp 3-61. New York, NY: Plenum Press.

Pardo JV, Fox PT, Raichle ME (1991) Localization of a human system for sustained attention by positron emission tomography. Nature 349:61-64.

Paus T (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nat Rev Neurosci 2:417-424.

Perlstein WM, Dixit NK, Carter CS, Noll DC, Cohen JD (2003) Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. Biol Psychiatry 53:25-38.

Pfefferbaum A, Ford JM, White PM, Roth WT (1989) P3 in schizophrenia is affected by stimulus modality, response requirements, medication status, and negative symptoms. Arch Gen Psychiatry 46:1035-1044.

Phillips ML, Williams L, Senior C, Bullmore ET, Brammer MJ, Andrew C, Williams SC, David AS (1999) A differential neural response to threatening and non-threatening negative facial expressions in paranoid and non-paranoid schizophrenics. Psychiatry Res 92:11-31.

Polich J (1998) P300 clinical utility and control of variability. J Clin Neurophysiol 15:14-33.

Polich J, Squire LR (1993) P300 from amnesic patients with bilateral hippocampal lesions. Electroencephalogr Clin Neurophysiol 86:408-417.

Polich J, Kok A (1995) Cognitive and biological determinants of P300: an integrative review. Biol Psychol 41:103-146.

Polich J, Ellerson PC, Cohen J (1996) P300, stimulus intensity, modality, and probability. Int J Psychophysiol 23:55-62.

Polich J, Margala C (1997) P300 and probability: comparison of oddball and single-stimulus paradigms. Int J Psychophysiol 25:169-176.

Polich J, Herbst KL (2000) P300 as a clinical assay: rationale, evaluation, and findings. Int J Psychophysiol 38:3-19.

Posner MI, Early TS, Reiman E, Pardo PJ, Dhawan M (1988) Asymmetries in hemispheric control of attention in schizophrenia. Arch Gen Psychiatry 45:814-821.

Posner MI, Petersen SE (1990) The attention system of the human brain. Annu Rev Neurosci 13:25-42.

Posner MI, Rothbart MK (1998) Attention, self-regulation and consciousness. Philos Trans R Soc Lond B Biol Sci 353:1915-1927.

Potts GF, Dien J, Hartry-Speiser AL, McDougal LM, Tucker DM (1998) Dense sensor array topography of the event-related potential to task-relevant auditory stimuli. Electroencephalogr Clin Neurophysiol 106:444-456.

Price CJ, Friston KJ (1997) Cognitive conjunction: a new approach to brain activation experiments. Neuroimage 5:261-270.

Price CJ, Moore CJ, Friston KJ (1997) Subtractions, conjunctions, and interactions in experimental design of activation studies. Hum Brain Mapp 5:264-272.

Price JL (2003) Comparative aspects of amygdala connectivity. Ann N Y Acad Sci 985:50-58.

Pritchard WS (1986) Cognitive event-related potential correlates of schizophrenia. Psychol Bull 100:43-66.

Quintana J, Wong T, Ortiz-Portillo E, Kovalik E, Davidson T, Marder SR, Mazziotta JC (2003) Prefrontal-posterior parietal networks in schizophrenia: primary dysfunctions and secondary compensations. Biol Psychiatry 53:12-24.

Rabbitt PM (1966) Errors and error correction in choice-response tasks. J Exp Psychol 71:264-272.

Rao KM, Ananthnarayanan CV, Gangadhar BN, Janakiramaiah N (1995) Smaller auditory P300 amplitude in schizophrenics in remission. Neuropsychobiology 32:171-174.

Rauschecker JP, Tian B (2000) Mechanisms and streams for processing of "what" and "where" in auditory cortex. Proc Natl Acad Sci U S A 97:11800-11806.

Renshaw PF, Yurgelun-Todd DA, Cohen BM (1994) Greater hemodynamic response to photic stimulation in schizophrenic patients: an echo planar MRI study. Am J Psychiatry 151:1493-1495.

Rinne T, Alho K, Ilmoniemi RJ, Virtanen J, Naatanen R (2000) Separate time behaviors of the temporal and frontal mismatch negativity sources. Neuroimage 12:14-19.

Ritter W, Simson R, Vaughan HG, Jr., Friedman D (1979) A brain event related to the making of a sensory discrimination. Science 203:1358-1361.

Ritter W, Simson R, Vaughan HG, Jr., Macht M (1982) Manipulation of event-related potential manifestations of information processing stages. Science 218:909-911.

Rubia K, Russell T, Bullmore ET, Soni W, Brammer MJ, Simmons A, Taylor E, Andrew C, Giampietro V, Sharma T (2001) An fMRI study of reduced left prefrontal activation in schizophrenia during normal inhibitory function. Schizophr Res 52:47-55.

Rubia K, Smith AM, Brammer MJ, Taylor E (in press) Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage.

Salisbury DF, O'Donnell BF, McCarley RW, Nestor PG, Faux SF, Smith RS (1994a) Parametric manipulations of auditory stimuli differentially affect P3 amplitude in schizophrenics and controls. Psychophysiology 31:29-36.

Salisbury DF, O'Donnell BF, McCarley RW, Shenton ME, Benavage A (1994b) The N2 event-related potential reflects attention deficit in schizophrenia. Biol Psychol 39:1-13.

Salisbury DF, Shenton ME, Sherwood AR, Fischer IA, Yurgelun-Todd DA, Tohen M, McCarley RW (1998) First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe. Arch Gen Psychiatry 55:173-180.

Salisbury DF, Shenton ME, McCarley RW (1999) P300 topography differs in schizophrenia and manic psychosis. Biol Psychiatry 45:98-106.

Salisbury DF, Krljes S, McCarley RW (2003) Electrophysiology of schizophrenia. In: Schizophrenia (Hirsch SR, Weinberger DR, eds), pp 298-309. Oxford, UK: Blackwell Science Ltd.

Sato Y, Yabe H, Todd J, Michie P, Shinozaki N, Sutoh T, Hiruma T, Nashida T, Matsuoka T, Kaneko S (2003) Impairment in activation of a frontal attention-switch mechanism in schizophrenic patients. Biol Psychol 62:49-63.

Schacter DL, Wagner AD (1999) Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 9:7-24.

Scheffers MK, Coles MG (2000) Performance monitoring in a confusing world: error-related brain activity, judgments of response accuracy, and types of errors. J Exp Psychol Hum Percept Perform 26:141-151.

Schneider F, Weiss U, Kessler C, Salloum JB, Posse S, Grodd W, Muller-Gartner HW (1998) Differential amygdala activation in schizophrenia during sadness. Schizophr Res 34:133-142.

Shajahan PM, Glabus MF, Blackwood DH, Ebmeier KP (1997) Brain activation during an auditory 'oddball task' in schizophrenia measured by single photon emission tomography. Psychol Med 27:587-594.

Sharpe K, O'Carroll R (1991) Estimating premorbid intellectual level in dementia using the National Adult Reading Test: a Canadian study. Br J Clin Psychol 30:381-384.

Shelley AM, Ward PB, Catts SV, Michie PT, Andrews S, McConaghy N (1991) Mismatch negativity: an index of a preattentive processing deficit in schizophrenia. Biol Psychiatry 30:1059-1062.

Shenton ME, Dickey CC, Frumin M, McCarley RW (2001) A review of MRI findings in schizophrenia. Schizophr Res 49:1-52.

Shenton ME, Gerig G, McCarley RW, Szekely G, Kikinis R (2002) Amygdala-hippocampal shape differences in schizophrenia: the application of 3D shape models to volumetric MR data. Psychiatry Res 115:15-35.

Silbersweig DA, Stern E, Frith C, Cahill C, Holmes A, Grootoonk S, Seaward J, McKenna P, Chua SE, Schnorr L, et al. (1995) A functional neuroanatomy of hallucinations in schizophrenia. Nature 378:176-179.

Sommer I, Ramsey N, Kahn R, Aleman A, Bouma A (2001) Handedness, language lateralisation and anatomical asymmetry in schizophrenia: meta-analysis. Br J Psychiatry 178:344-351.

Spence SA, Brooks DJ, Hirsch SR, Liddle PF, Meehan J, Grasby PM (1997) A PET study of voluntary movement in schizophrenic patients experiencing passivity phenomena (delusions of alien control). Brain 120:1997-2011.

Stirling JD, Hellewell JS, Quraishi N (1998) Self-monitoring dysfunction and the schizophrenic symptoms of alien control. Psychol Med 28:675-683.

Stirling JD, Hellewell JS, Ndlovu D (2001) Self-monitoring dysfunction and the positive symptoms of schizophrenia. Psychopathology 34:198-202.

Strange BA, Dolan RJ (2001) Adaptive anterior hippocampal responses to oddball stimuli. Hippocampus 11:690-698.

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. 3-dimensional proportional system: an approach to cerebral imaging. Stuttgart, Germany: Georg Thieme Verlag.

Taylor SF, Tandon R, Koeppe RA (1997) PET study of greater visual activation in schizophrenia. Am J Psychiatry 154:1296-1298.

Turetsky B, Colbath EA, Gur RE (1998a) P300 subcomponent abnormalities in schizophrenia: II. Longitudinal stability and relationship to symptom change. Biol Psychiatry 43:31-39.

Turetsky BI, Colbath EA, Gur RE (1998b) P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. Biol Psychiatry 43:84-96.

Ullsperger M, von Cramon DY (2001) Subprocesses of Performance Monitoring: A Dissociation of Error Processing and Response Competition Revealed by Event-Related fMRI and ERPs. Neuroimage 14:1387-1401.

Umbricht D, Javitt D, Novak G, Bates J, Pollack S, Lieberman J, Kane J (1998) Effects of clozapine on auditory event-related potentials in schizophrenia. Biol Psychiatry 44:716-725.

van Veen V, Cohen JD, Botvinick MM, Stenger VA, Carter CS (2001) Anterior cingulate cortex, conflict monitoring, and levels of processing. Neuroimage 14:1302-1308.

van Veen V, Carter CS (2002a) The anterior cingulate as a conflict monitor: fMRI and ERP studies. Physiol Behav 77:477-482.

van Veen V, Carter CS (2002b) The timing of action-monitoring processes in the anterior cingulate cortex. J Cogn Neurosci 14:593-602.

Velakoulis D, Pantelis C, McGorry PD, Dudgeon P, Brewer W, Cook M, Desmond P, Bridle N, Tierney P, Murrie V, Singh B, Copolov D (1999) Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. Arch Gen Psychiatry 56:133-141.

Velakoulis D, Stuart GW, Wood SJ, Smith DJ, Brewer WJ, Desmond P, Singh B, Copolov D, Pantelis C (2001) Selective bilateral hippocampal volume loss in chronic schizophrenia. Biol Psychiatry 50:531-539.

Verleger R, Heide W, Butt C, Kompf D (1994) Reduction of P3b in patients with temporo-parietal lesions. Brain Res Cogn Brain Res 2:103-116.

Vidal F, Hasbroucq T, Grapperon J, Bonnet M (2000) Is the 'error negativity' specific to errors? Biol Psychol 51:109-128.

Vogt BA, Finch DM, Olson CR (1992) Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cereb Cortex 2:435-443.

Vogt BA, Nimchinsky EA, Vogt LJ, Hof PR (1995) Human cingulate cortex: surface features, flat maps, and cytoarchitecture. J Comp Neurol 359:490-506.

Watanabe J, Sugiura M, Sato K, Sato Y, Maeda Y, Matsue Y, Fukuda H, Kawashima R (2002) The Human Prefrontal and Parietal Association Cortices Are Involved in NO-GO Performances: An Event-Related fMRI Study. Neuroimage 17:1207-1216.

Watson RT, Valenstein E, Day A, Heilman KM (1994) Posterior neocortical systems subserving awareness and neglect. Neglect associated with superior temporal sulcus but not area 7 lesions. Arch Neurol 51:1014-1021.

Weiss AP, Schacter DL, Goff DC, Rauch SL, Alpert NM, Fischman AJ, Heckers S (2003) Impaired hippocampal recruitment during normal modulation of memory performance in schizophrenia. Biol Psychiatry 53:48-55.

Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, Rauch SL (1998) The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. Biol Psychiatry 44:1219-1228.

Wickens C, Kramer A, Vanasse L, Donchin E (1983) Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. Science 221:1080-1082.

Williams LM, Bahramali H, Hemsley DR, Harris AW, Brown K, Gordon E (2002) Electrodermal responsivity distinguishes ERP activity and symptom profile in schizophrenia. Schizophr Res 59:115-125.

Winterer G, Adams C, Jones D, Knutson B (2002) Volition to Action-An Event-Related fMRI Study. Neuroimage 17:851.

Woodward TS, Takane Y, Hunter MA, Ruff CC, Ngan ETC (submitted) Assessment of cortical connectivity: Application of constrained principal component analysis to fMRI data.

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET (2000) Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157:16-25.

Yamaguchi S, Knight RT (1991) Anterior and posterior association cortex contributions to the somatosensory P300. J Neurosci 11:2039-2054.

Yanai I, Fujikawa T, Osada M, Yamawaki S, Touhouda Y (1997) Changes in auditory P300 in patients with major depression and silent cerebral infarction. J Affect Disord 46:263-271.

Yuasa S, Kurachi M, Suzuki M, Kadono Y, Matsui M, Saitoh O, Seto H (1995) Clinical symptoms and regional cerebral blood flow in schizophrenia. Eur Arch Psychiatry Clin Neurosci 246:7-12.

Zald DH (2003) The human amygdala and the emotional evaluation of sensory stimuli. Brain Res Brain Res Rev 41:88-123.