AN FMRI INVESTIGATION OF FRONTAL LOBE FUNCTIONING IN PSYCHOPATHY AND SCHIZOPHRENIA DURING A GO/NO GO TASK

By

ANDRA MARIE SMITH

B.Sc., Carleton University, 1987
M.Sc., Carleton University, 1993

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY in THE FACULTY OF GRADUATE STUDIES Program in Neuroscience

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

September, 1999
© Andra Marie Smith, 1999
In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of Neuroscience

The University of British Columbia
Vancouver, Canada

Date September 30, 1999
Abstract

The prefrontal cortex and its connections with other regions of the brain allow for behaviors and emotions that differentiate human beings from other animals. When a deficit in this brain region arises, many disturbing results can occur. One of these deficits is difficulty in controlling inappropriate behavioral responses. This disinhibition is observed in many psychiatric disorders, including psychopathy and schizophrenia. In this study, functional magnetic resonance imaging (fMRI) and a Go/No Go paradigm were used to investigate neurophysiological processes associated with response inhibition in psychopathic and nonpsychopathic inmates, stable, medicated schizophrenic patients and healthy control participants.

The results indicated that the dorsolateral prefrontal cortex is involved in response inhibition in healthy control participants. There was a significant difference between control participants and psychopathic inmates in this area of the brain. Specifically, there was a negative relationship between the measure of psychopathy (Hare Psychopathy Checklist-Revised) and activity in the dorsolateral prefrontal cortex.

Schizophrenic patients showed a similar level of activation to control participants in dorsolateral prefrontal cortex. However, there was also an increase in activation in the inferior temporal cortex in schizophrenic patients where a reduction in activity occurred in control participants.

The results indicate that the cortical activation normally associated with response inhibition is different in both psychopathy and schizophrenia. However, the way in which the two disorders differ from control participants is significantly different. Psychopaths have attenuated left dorsolateral prefrontal cortex activity compared to control participants suggesting that the disinhibition observed in psychopathy might be related to a deficit in processing information in
this brain region. The schizophrenic patients' increased lateral temporal lobe activity provides further evidence for the hypothesis that there is anomalous coordination of activity of frontal-temporal brain regions in schizophrenia.
Table of Contents

Abstract ......................................................................................................................... ii
Table of Contents .......................................................................................................... iv
List of Tables .................................................................................................................. vi
List of Figures ................................................................................................................ vii
Acknowledgments ......................................................................................................... viii
Dedication ....................................................................................................................... ix
1. Introduction
   1.1 Frontal Lobe Functioning ..................................................................................... 1
   1.2 Disinhibition ......................................................................................................... 4
   1.3 Psychopathy ........................................................................................................ 5
   1.4 Schizophrenia ..................................................................................................... 12
   1.5 Go/No Go Paradigms ......................................................................................... 16
   1.6 FMRI .................................................................................................................. 24
   1.7 Experiment ......................................................................................................... 33
2. Methods and Materials
   2.1 Participants ......................................................................................................... 34
   2.2 Assessment Tools .............................................................................................. 35
   2.3 Go/No Go Task .................................................................................................. 37
   2.4 Imaging .............................................................................................................. 39
3. Analyses
   3.1 Behavioral Data Analyses .................................................................................... 39
   3.2 Statistical Parametric Mapping (SPM) ................................................................. 40
3.3 Image Analyses

4. Results

4.1 Forensic Population and Matched Control Participants
   4.1.1 Demographic
   4.1.2 Behavioral Data
   4.1.3 Imaging Data

4.2 Schizophrenic Patients and Matched Control Participants
   4.2.1 Demographic Data
   4.2.2 Behavioral Data
   4.2.3 Imaging Data

4.3 Psychopathic Inmates and Schizophrenic Patients
   4.3.1 Behavioral Data
   4.3.2 Imaging Data

5. Discussion

5.1 Behavioral Responding
5.2 Response Inhibition Imaging Data
5.3 Psychopathy Brain Imaging
5.4 Schizophrenia Brain Imaging
5.5 Comorbidity

6. Conclusions

7. References

8. Appendix 1 - Abbreviations
List of Tables

Table 1. Demographic data for matched psychopathic and nonpsychopathic inmates and control participants ................................................................. 48

Table 2. Behavioral data for matched psychopathic and nonpsychopathic inmates and control participants ........................................................................... 51

Table 3. Control Participants imaging data for the comparison of the two Go/No Go conditions versus Rest ........................................................................... 53

Table 4. Psychopathic inmates imaging data for the comparison of the two Go/No Go conditions versus Rest ........................................................................... 54

Table 5. Nonpsychopathic inmates imaging data for the comparison of the two Go/No Go conditions versus Rest ........................................................................... 55

Table 6. Demographic data for matched schizophrenic patients and control participants ......................................................................................... 63

Table 7. Behavioral data for matched schizophrenic patients and control participants ......................................................................................... 64

Table 8. Schizophrenic patients imaging data for the comparison of the two Go/No Go conditions versus Rest ........................................................................... 66
List of Figures

Figure 1. Control participants’ functional imaging data superimposed on a structural image for the ‘Press for all letters except X - Press for X comparison’ ................................................................. 57

Figure 2. Psychopathic inmates’ functional imaging data superimposed on a structural image for the ‘Press for all letters except X - Press for X comparison’ ................................................................. 58

Figure 3. Functional imaging data for the comparison of psychopathic inmates and control participants, superimposed on a structural image, for the ‘Press for all letters except X - Press for X comparison’ ................................................................. 59

Figure 4. Functional data superimposed on a structural image showing the negative relationship between total PCL-R score and brain activation for the ‘Press for all letters except X - Press for X comparison’ ................................................................. 61

Figure 5. Functional imaging data for the comparison of schizophrenic patients and control participants, superimposed on a structural image, for the ‘Press for all letters except X - Press for X comparison’ ................................................................. 67

Figure 6. Schizophrenic patients’ functional imaging data superimposed on a structural image for the ‘Press for all letters except X - Press for X comparison’ ................................................................. 68

Figure 7. Control participants’ functional imaging data superimposed on a structural image for the ‘Press for X – Press for all letters except X comparison’ ................................................................. 69

Figure 8. Functional imaging data for the comparison of schizophrenic patients and psychopathic inmates, superimposed on a structural image, for the ‘Press for all letters except X - Press for X comparison’ ................................................................. 71
Acknowledgements

There are so many people to thank for making this experience a good one. The greatest inspiration has come from the unending and unmatched passion that Dr. Hare brings to his research. It has been a pleasure and an incredible learning experience to be exposed to his wisdom and experience. I would also like to thank Dr. Liddle for his enthusiasm, knowledge and the support he has supplied throughout this difficult fMRI research.

Thanks to the fMRI team of Drs. Forster, MacKay, and Whittall for helping to get fMRI off the ground and running so successfully. The MR technologists also deserve a great deal of thanks for their hard work and especially for being so supportive of me. I really have appreciated your friendships Sylvia and Trudy.

Thank you to my lab mates for their help, especially Helen for all the tedious work she did for me. Kent, thanks for being my partner in crime. We did it! Adrianna and Michelle, you helped keep me sane and in touch with the real world – thanks. I would also like to thank the CSC staff and inmates and the security staff at the hospital for making this almost implausible research a reality. Thanks also to Dr. Brink for his contributions and support.

To those of you not so closely related to the project but very close to me personally, I could not have done any of this without you. John, you are an amazing man and I believe you are one of the best things to happen to me during this Ph.D. Thank you for all the time you made for me. Alissa, Julia, Karolina, Sangeeta and Sue thanks for being the best friends anyone could ever ask for. I would also like to thank the Browns for their support. You have been my family away from home. I would especially like to thank my adopted Grandpa who if he hadn’t been a man of his word might well have been graduating with his Ph.D. alongside me. Thanks to the crew at B.C.U.C. too for your support.
By far the most important people in my life and the most supportive of all have been my family. Thank you Mom, Dad, Steph, Tom, Olivia and especially Emily who has been my sunshine on those rainy Vancouver days.

I would not have stayed in Vancouver if it were not for my best friend and partner in life, Jeff. Thank you so much for putting a smile on my face everyday since I met you. You have kept me from letting the big bad world get in the way of laughter and happiness and for that I am eternally grateful.

This research would not have been performed without the generous funding from the British Columbia Medical Services Foundation, The Medical Research Council of Canada and The John Wacker Foundation.

Dedication

I have always wanted a forum where I could finally thank my mother for all her unconditional support and love throughout my life. I think that this is a perfect opportunity for me to do so as I finish my greatest academic accomplishment to date. I certainly would not have done it without my mother. She is an inspiring woman who puts everyone ahead of herself, especially me. She has no idea of the positive effect she has on everyone she comes into contact with but it is beyond that of most. This thesis is dedicated to my mother, the wind beneath my wings.
1. Introduction

1.1 Frontal Lobe Functioning

"The frontal lobes are the seat of all wisdom" (Bailey, 1933).

The frontal cortices are involved in the highest level of cognitive functioning observed in the animal kingdom. This is not surprising in light of the fact that phylogenetically, the frontal lobes are the most recent and are the most developed in humans, occupying up to one quarter the mass of the human brain. Lesion studies, neuroimaging investigations, and animal research have described the functional diversity of the frontal lobes.

Motion, speech, memory, attention, planning and anticipation are a few examples of frontal lobe functions. Several theories have evolved to explain this diversity. Brodmann (1909) attempted to explain the widespread functioning by the anatomical heterogeneity that exists in the frontal lobes. There are granular, dysgranular and agranular layers of cortex in the frontal lobes, including the prefrontal cortex, frontal eye fields and motor cortex, respectively.

Several researchers have suggested that the functional diversity is a result of the widespread neural interconnectedness of the frontal lobes with other cortical and subcortical regions (Stuss and Benson, 1986; Fuster, 1997). Each of the occipital, parietal and temporal sensory association cortices project to either the anterior temporal cortex or the inferior parietal area, which then project to the dorsolateral and orbital frontal cortices. Frontal cortex is, therefore, the only cortical area that receives information directly from all sensory modalities. There are several connections with the striatum and basal ganglia and there are diffuse thalamic and limbic connections. The frontal lobes are in fact the only cortical areas

1
that project to the hypothalamus and the septal region (Nauta, 1971, 1973; Pandya and Barnes, 1987; Stuss and Benson, 1986). Frontal cortex also receives neurons from the three main brainstem projections that arise from the dopaminergic terminals in the ventral tegmental area, the serotonergic neurons in the raphe nucleus and the noradrenergic terminals in the locus coeruleus (Porrino and Goldman-Rakic, 1982; Bannon and Roth, 1983).

While both anatomic heterogeneity and widespread connectedness may explain the functional diversity of the frontal lobes, more recent thought is that the frontal lobes are a complex neural structure devoted to the organization of behavior. This function arises from the advanced development of the prefrontal cortex, just anterior to the premotor cortex, and its connections with the rest of the brain. The percentage of total cortex occupied by prefrontal cortex in humans is approximately thirty percent. This is a considerable amount of cortex relative to other species. For example, the chimpanzee and the dog prefrontal cortices occupy approximately seventeen percent and seven percent of total cortex, respectively (Uylings and Van Eden, 1990). It has also been shown that, although the adult configuration of the prefrontal cortex is present by the seventh month of uterine life, the myelination and full development occur later than any other brain region and are not complete until well into adolescence and beyond (Yakovlev and Lecours, 1967; Rakic, Bourgeois, Zecevic, Echenhoft and Goldman-Rakic, 1986; Creutzfeldt, 1995). The dorsolateral prefrontal cortex develops last, just following the ventromedial prefrontal cortex, and exhibits the greatest differentiation of all brain regions (Flechsig, 1901; Sanides, 1969; Goldman-Rakic and Schwartz, 1982; Pandya and Yeterian, 1985).

The prefrontal cortex has, in general, been linked to the control of executive function, including planning, judgment, decision-making, social conduct, organization,
anticipation, goal establishment, monitoring results and use of feedback. These functions, along with the role that the prefrontal cortex plays in memory, attention, language, and movement, underline why there can be devastating effects from lesions to the prefrontal cortex. Mesulam (1986) has used the term heteromodal cortex to describe the dorsolateral prefrontal cortex because 1) it integrates sensory information from multiple modalities, and 2) when lesioned, it results in deficits in temporal and sensory integration, planning, maintenance of goal-directedness, and behavior flexibility. Damasio (1985) states that the dorsolateral prefrontal cortex is critical for the coherent organization of mental contents on which creative thinking and language depend, and that permit, in general, artistic activities and the planning of future actions.

The ventromedial prefrontal cortex has been termed the paralimbic cortex because of its strong connections with limbic structures (Mesulam, 1986). MacLean (1990) suggested that because of these connections, the ventromedial prefrontal cortex is the ‘only’ place where there can be interplay between intellect and feelings. Damage to this area can, therefore, result in problems with the integration of motivational and emotional processes and can lead to such changes in personality as a puerile, jocular attitude, sexually disinhibited humor, socially inappropriate behavior, and near total self indulgence with a lack of concern for others (Stuss and Benson, 1984).

Although there appear to be separate deficits for different parts of the prefrontal cortex, its extensive anatomical connectivity does not imply that it is a simple functional domain. In summary, current research, indicates that the prefrontal cortex is responsible for the integration and organization of behavior. Prefrontal lesions have a devastating impact on day to day activities that involve the organization and control of action and thought.
1.2 Disinhibition

"He might do almost anything on impulse, feeling nothing much. The logical explanations for his actions, invented at leisure, always came afterwards" (p.108). Kurt Vonnegut (1985), author describing an uninhibited psychopath.

A deficit in the ability to control action and thought can manifest itself as an inability to suppress inappropriate behavior. This "disinhibition" is observed in many patients with damage to the prefrontal cortex. For example, JC suffered bilateral ventromedial prefrontal damage from a motor vehicle accident. He presented with poor impulse control and intermittent explosive behavior. He was unable to perform a simple Go/No Go task, a task that requires a patient to respond to one cue while inhibiting this response to another cue. He also responded impulsively to other cognitive tasks, a disinhibited form of response style characteristic of frontal lobe damaged patients (Malloy, Bihrlle, Duffy and Cimino, 1993).

No discussion of prefrontal cortex damage is complete without mentioning the case study of Phineas Gage, who in 1848 had an accident that sent an iron rod up through his left cheek, piercing the base of his skull and exiting at the top right of his head. His body survived the ordeal but his personality was never the same. His friends, colleagues and family described this change as "Gage was no longer Gage" (Harlow, 1868). He became vulgar, disinhibited, self centered, impatient and unable to finish anything he planned. An interesting observation was that his intelligence seemed to be unscathed. This is true of many patients with frontal lobe lesions (Damasio et al., 1994; Stuss and Benson, 1986; Hebb, 1939; Fuster, 1997). Although these patients show very distinct behavioral changes, they perform at a normal range on classic IQ tests. Damasio (1985) suggests that IQ is not affected by frontal lobe lesions because frontal lobes are critical at the time when new
activities are learned and when active control is required. However, after the behavior is routine, these activities can be handled by other parts of the brain. For example, a positron emission tomography (PET) study of verb generation showed that the anterior cingulate was activated when the participants were generating verbs to a novel list of nouns but that once the participants knew the noun list, this area did not show an increase in blood flow (Raichle, Fiez, Videen and MacLeod, 1994).

Disinhibition does not result only from trauma to the prefrontal cortex. There are several neurological disorders that are characterized by disinhibition, including Tourette’s syndrome, conduct disorder, and mania (Cummings and Frankel, 1985; Routh, 1994; Strik, Ruchsow, Abele, Fallgatter and Mueller, 1998). Disinhibition is also a cardinal feature of psychopathy and the disorganization syndrome of schizophrenia. These disorders have devastating effects on society. This thesis will investigate the neurophysiological mechanisms of disinhibition in psychopathy and schizophrenia.

1.3 Psychopathy

“Until I got caught or shot to death by the police or something like that….I wasn’t thinkin’, I wasn’t plannin’, I was just doin’. It was a damned shame for those two guys.” Texas murderer Gary Gilmore when asked if he would have killed again, had he not been caught (Hare, 1993, p. 58).

Psychopathy is a socially devastating personality disorder defined by a constellation of affective, interpersonal, and behavioral characteristics, including impulsivity, sensation seeking, poor behavioral control, shallow affect, grandiosity, egocentricity, lack of empathy, guilt or remorse and the persistent violation of social norms and expectations (Cleckley,
The disorder affects approximately 1% of the population and as many as 15-25% of male and female prison populations. In spite of their small numbers, psychopaths are responsible for a markedly disproportionate amount of social damage, antisocial behavior, criminality, and violence (Hare, 1996; Cooke, Forth and Hare, 1998; Kosson, Smith and Newman, 1990). Accurate assessment is critical to research on psychopathy. Hare (1991) has provided an assessment tool, the Hare Psychopathy Checklist – Revised (PCL-R), that has been shown to be a reliable and valid instrument for both risk assessments and for research purposes (Hare, 1991; see review by Fulero, 1996). The PCL-R has a factor structure that includes interpersonal and emotional features (Factor 1), and antisocial, sensation-seeking behaviors (Factor 2). A further description of the PCL-R is provided in the methods section, below.

In the latter part of the 19th century, Daniel Hack Tuke (1885) referred to psychopaths as those suffering from the "inhibitory insanity" syndrome, focusing on the psychopath's impulsivity and disinhibition. Shapiro (1965) noted that "the psychopath is the very model of the impulsive style". Gorenstein and Newman (1980) described psychopathy as "the prototypical syndrome of disinhibition". More recently, Hare (1993) stated that the psychopath "has a chronically unstable and aimless lifestyle marked by the need for immediate gratification and satiation and therefore filled with casual and flagrant violations of social norms and expectations" (p. 57).

Many psychopaths commit spontaneous, unplanned crimes and perform day to day activities on the spur of the moment without considering the possible consequences (Hare, 1993). High scorers on the Hare PCL-R consistently demonstrate significant disinhibitory psychopathology that manifests itself as a personality pattern of markedly high impulsivity (Klinteberg, Humble and Schalling, 1992). Recent studies confirm the prevalence of
disinhibition in psychopathy and specify that it is a fundamental feature of psychopathy (Cooke and Michie, 1997; Gridley, 1990; Raine, 1985; Blackburn and Coid, 1998).

Blackburn and Coid (1998) used a factor analysis of personality disorder measures to yield four factors identified as impulsivity, detachment, sensitivity and compulsivity. The PCL-R correlated highly with the impulsivity factor. Shine and Hobson (1997) showed that psychopathy was associated with high levels of overall hostility, extrapunitive hostility and personality characteristics such as psychoticism and impulsivity. Similarly, Stanford et al., (1994) reported that the total score on the PCL-R is significantly related to the number of impulsive behaviors exhibited by a patient. Multiple impulsive behaviors were evident in 88% of the patients and equally present in both the male (87%) and female (89%) subgroups.

The disinhibition observed in psychopathy can, on its own, be destructive. However, the characteristic that separates psychopathy from other forms of antisocial behavior (and that together with disinhibition makes for a destructive combination) is shallow emotions. Cleckley believed that an inability to experience deep emotion was the fundamental characteristic of the psychopath (Cleckley, 1976). Indeed, Hare's PCL-R (1991) includes several characteristics related to the emotional abilities of the psychopath, including shallow affect, lack of empathy and lack of remorse. For the psychopath, emotions are incomplete, shallow, largely cognitive in nature and without the physiological correlates that most people experience.

To date, no one theory of psychopathy can explain both the disinhibitory and the emotional deficits observed in psychopathy. In an attempt to explain the etiology of psychopathy several researchers have provided insight into its disinhibitory aspects. Lykken's fearlessness model suggests that psychopaths suffer from an innate fearlessness
that renders them unable “to learn to avoid antisocial behaviors and to inhibit forbidden impulses, through punishment and the conditioned fear it leaves behind” (Lykken, 1995). This theory was based on results from several early experiments that showed there is a significant “fear-related” autonomic difference between psychopaths and non-psychopaths (Hare, 1968; 1973; 1978; Lykken, 1958). For example, while they awaited delivery of an electric shock, psychopaths showed smaller increases in skin conductance than did non-psychopaths (Hare, 1965). Psychopaths also had a significantly higher detection threshold for electric shock than did non-psychopaths (Hare, 1968). Although this theory can provide some insights into the disinhibition observed in psychopaths, it does not readily explain the Factor 1 characteristics of psychopathy, such as superficial charm, grandiose sense of self worth, and shallow emotions in general.

Similar problems are evident with the Fowles-Gray model of a weak Behavioral Inhibition System (BIS; Fowles, 1980). The BIS is a neurophysiological system that controls an organism’s response to signals of impending punishment or frustrative non-reward. The Behavioral Activation System (BAS) controls responses to signals of impending reward. Negative affect is a result of the arousal of the BIS, which then results in inhibition of motor activity that might lead to the expected punishment or non-reward. Thus, a weak BIS can result in the failure to inhibit activity that may lead to punishment or frustrative non-reward. The Fowles-Gray theory suggests that psychopaths have a weak BIS associated with a deficit in anticipatory anxiety that “produces impulsivity as a result of the failure of cues for potential punishment and frustration to inhibit reward-seeking behavior” (Fowles and Missel, 1994). This theory does not readily incorporate the interpersonal aspects of psychopathy. It has, however, led to further theories of psychopathy, such as the model of deficient response modulation by Patterson and Newman (1993).
Laboratory studies of passive avoidance learning with reward and punishment contingencies have demonstrated that psychopaths have difficulty altering a “dominant response” associated with reward, once the task contingencies change (Waid and Orne, 1982; Newman and Kosson, 1986; Newman, Widom and Nathan, 1985, Newman et al., 1990). Howland, Kosson, Patterson and Newman (1993) suggested that this occurs because of difficulties in orienting attention to the change in contingencies. Similarly, Newman and Kosson (1986) used a Go/No Go paradigm to demonstrate that psychopaths are relatively poor at learning to inhibit reward-seeking behavior that results in monetary punishment. These studies led Newman and Wallace (1993) to theorize that psychopaths have “difficulty in the automatic switching of attention, which in turn, interferes with their ability to assimilate unattended but potentially relevant information while they are engaged in the organization and implementation of goal-directed behavior”. While this theory encompasses both the fearlessness model and the weak BIS model, it does not fully explain the disinhibited actions of the psychopath.

Hare (1998) has suggested that psychopaths have difficulty in processing emotional material, and that they do not readily distinguish between positive and negative emotions. Several electroencephalography (EEG) studies and a single photon emission computed tomography (SPECT) study of psychopathy have revealed that psychopaths do not distinguish psychophysiological or behaviorally between neutral and emotional words (Williamson, Harpur and Hare, 1991; Intrator et al., 1997; discussed further below). Similarly, Patrick (1994) used a startle blink paradigm to reveal that psychopaths are psychophysiological unresponsive to emotional visual stimuli, whether these are positive or negative in valence. This hypo-emotionality, together with a short “fuse” or inability to withhold reactions, can potentially lead to the cruel, remorseless, predatory violence of the
psychopath (Hare, 1993; 1996; 1998).

This very brief review of some of the etiological models of psychopathy points to an underlying neurobiological anomaly - perhaps a deficit - that results in reduced emotionality and low anxiety. According to these models, this is a cause of the psychopaths' disinhibited, irresponsible, and antisocial behavior. To date, there has been no genetic research performed on psychopathy. This avenue of research will undoubtedly prove to be of interest when discussing the etiology of the disorder.

Although the neuropsychological evidence is mixed (Hare, 1984; Hart, Forth and Hare, 1990; Lapierre, Braun and Hodgins, 1995; Harpur, 1991; Raine, 1985), clinical and neuroimaging research has provided evidence that the frontal lobes are the most likely region of the brain where neuroanatomical or neurophysiological differences between psychopaths and nonpsychopaths will be found. Clinical observation for many years has identified the similarities between psychopathic behavior and the behavior of frontal lobe damaged patients (Damasio, 1985; Blumer and Benson, 1975; Gorenstein and Newman, 1980; Gorenstein, 1982). As previously noted, the patient, JC, exhibited poor impulse control and intermittent explosive behavior. This followed a motor vehicle accident that damaged his ventromedial prefrontal cortex bilaterally.

Blumer and Benson (1975) coined the term "pseudopsychopathy" after observing patients with ventromedial lesions who were disinhibited, grandiose and had a disconcern for social standards and other people. Eslinger and Damasio (1985) identified their patients with inferior frontal and anterior cingulate lesions as "acquired sociopaths". Damasio, Tranel and Damasio (1990) found electrodermal similarities between studies of psychopaths and some of these patients with "acquired sociopathy." Moreover, recent studies implicate ventromedial frontal cortex in not only electrodermal activity but also in the control of
emotional processing, aggression, and social cognition (Damasio, Grabowski, Frank, Galaburda and Damasio, 1994; Tranel and Damasio, 1994).

Williamson, Harpur and Hare (1991) recorded EEG while criminal psychopaths and nonpsychopaths performed a lexical decision task (subject must decide whether or not a letter-string is a word). The letter-strings were affective and neutral words, and pronounceable nonwords. Williamson et al., (1991) found that the psychopaths processed and responded to emotional words as if they were neutral words, devoid of affective or connotative significance. Fronto-central event related potentials (ERPs) of the psychopaths were the same for emotional as for neutral words, and returned to prestimulus baseline much more quickly than did the ERPs of the nonpsychopaths.

These EEG results were confirmed and further explained with a SPECT experiment that investigated relative cerebral blood flow (rCBF) in psychopaths and nonpsychopaths while they performed a similar lexical decision task (Intrator et al., 1997). The most striking results involved group differences in the relative activation of anterior and posterior regions of the brain, with psychopaths showing less anterior and more posterior activation than other participants. PET studies of single-word processing indicate that discrimination between visually presented words and pseudowords occurs early in visual processing, at the level of extrastriate cortex, and that anterior regions are involved in higher level processing of the words and their meanings (Peterson, Fox, Snyder and Raichle, 1990). Presumably the anterior activation exhibited by the nonpsychopaths in the SPECT study reflects the increased neural demands associated with these higher-level mental operations. In contrast, the psychopaths showed less anterior and more posterior activation than did the nonpsychopathic participants, suggesting that the former devoted considerable resources to the identification and processing of the stimuli but relatively few resources to their cognitive
elaboration.

Newman and Kosson (1986) used a reward and punishment version of a Go/No Go task and showed that psychopaths made significantly more errors of commission than did the nonpsychopaths. This is consistent with the disinhibition observed in psychopaths, noted above. Similarly, Lapierre, Braun and Hodgins (1995) showed that psychopaths made significantly more errors of commission during a spatial Go/No Go task than did nonpsychopaths. Kiehl, Smith, Hare and Liddle (1999) used ERP technology to show that psychopaths produced significantly different waveforms during the Go/No Go task than did nonpsychopaths. Nonpsychopathic participants showed the expected greater frontal negativity 275 ms following the presentation of the stimulus (N275) for the No Go stimuli than for Go stimuli, whereas the psychopaths did not show this negativity. Similarly, for Go trials, nonpsychopaths showed a larger positive potential at 300 ms following the presentation of the stimulus (P300) than for No Go trials, while the reverse occurred in the psychopaths. Psychopaths showed a larger P300 for the No Go trials than for the Go trials. This supports the hypothesis that the neural mechanisms of response inhibition are different for nonpsychopaths and psychopaths.

1.4 Schizophrenia

“This rudderless state leads to impulsive instinctual activity: there is no planned reflection which suppresses impulses as they arise or directs them into proper channels” (p. 22). Kraepelin (1974) on the essence of schizophrenia as a destruction of conscious volition.

Schizophrenia can be a chronic, severe, disabling psychiatric disorder with widespread ramifications for families, friends and society. Although pharmacological
treatments reduce symptoms in many patients with schizophrenia, not all patients respond to the drugs, and often the side effects of the drugs lead to non-compliance and reoccurrence of the symptoms they are meant to treat.

No one area of the brain is consistently compromised in schizophrenia and thus a full understanding of the pathology of the disorder is yet to be determined. The most consistent theories of the disorder implicate deficits of the frontal lobes (Weinberger, Aloia, Goldberg and Berman, 1994). More specifically, deficits are observed in the prefrontal cortex and its connections with subcortical and posterior brain regions (Goldman-Rakic and Selemon, 1997). Frontal function depends upon an extended brain system involving circuits and loops incorporating basal ganglia and posterior brain regions as well as the frontal cortex (Frith, 1997).

The prospect of localizing schizophrenia to one brain region has all but been abandoned. More common theories involve abnormalities in long-range connectivity, based on, among other things, PET findings of frontal-temporal disconnections in schizophrenic patients (Friston and Frith, 1995). Similarly, functional magnetic resonance imaging (fMRI) has provided evidence of anomalous connectivity, specifically between the prefrontal cortex and the lateral temporal lobe (Yurgelun-Todd, Waternaux and Cohen, 1996; Mendrek, Liddle, Smith, Kiehl, Duty and Stip, 1999).

Goldman-Rakic and Selemon (1997) have contributed to the understanding of the anomalous functional connectivity research on schizophrenia by reviewing results obtained from research using postmortems, the study of cortical architecture, pharmacological, and in vivo anatomical methodologies. Their basic conclusion was that neural dystrophy occurs in schizophrenia. This can affect the integrative processing that occurs in the prefrontal cortex and the rest of the brain. This neural dystrophy, along with a dysfunction in any one of
several neurotransmitter systems (dopamine, gamma-aminobutyric acid (GABA), serotonin) can play a role in profoundly altering the modulation of pyramidal cells, resulting in an inability of the pyramidal cells to integrate its immense number of informational inputs and, therefore, to maintain information "on line". This would affect the timing of information processing, causing fragmentation of the thought processes that guide behavior, resulting in a reliance on automatic responses, prepotent responses, stereotypical responses, and absence of forethought.

This description of a breakdown in timing of information processing is similar to the deficit in temporal organization that Fuster (1980, 1997) attributes to lesions in prefrontal cortex. It is also consistent with the clinical aspects of the disorganization syndrome of schizophrenia. Liddle (1984), Bilder, Mukherjee, Rieder and Pandurangi (1985), Kulhara, Kota and Joseph (1986), Mortimer, Lund and McKenna (1990), Arndt, Alliger and Andreasen (1991), Malla, Norman, Williamson, Cortese and Diaz (1993) and Liddle and Barnes (1990) have been successful at classifying the symptoms of schizophrenia into three sub-syndromes, reality distortion, disorganization and psychomotor poverty. The clinical features of the disorganization syndrome of schizophrenia include an impaired ability to inhibit inappropriate mental activity. This disinhibition is prevalent in thought and speech, emotion and behavior. Intrusions of loosely associated words and ideas enter into the train of thought and result in disorders of the form of thought. Intrusions of affect inappropriate to the circumstance result in incongruous affect, while the inability to suppress actions inappropriate to the situation result in disinhibited behavior (Liddle, 1984, 1987a,b; Malla et al., 1992).

Neuropsychological studies reveal that the disorganization syndrome is associated with poor performance in tasks that entail the inhibition of an inappropriate response.
Liddle and Morris (1991) demonstrated that severity of disorganization is related to impaired performance in tasks that involve the selection of an appropriate response, such as the Stroop Color-Word Task (Stroop, 1935) and the Reitan Trail Making B Test (Reitan, 1958). McGrath (1992) confirmed the association between formal thought disorder and impaired Stroop performance. Frith, Friston, Liddle and Frackowiak (1991a,b) demonstrated that formal thought disorder and incongruity, the cardinal features of the disorganization syndromes, were associated with a failure to inhibit appropriate responses in the Continuous Performance Test. Allen, Liddle and Frith (1993) found that formal thought disorder is associated with selection of unusual words in a word generation task. Hodgins, Cote and Toupin (1998) had schizophrenic patients perform several neuropsychological tasks, including a Go/No Go task, and concluded that patients were significantly impaired when compared to control participants.

In an ERP study, Smith, Kiehl and Liddle (1998) found that schizophrenic patients exhibited different patterns of waveforms than control participants as they performed a Go/No Go task. Control participants exhibited a larger N275 on No Go trials than on Go trials. Schizophrenic patients did not show this N275 difference between the No Go and the Go trials. Similarly, control participants showed a larger P300 potential for Go trials than for No Go trials while the schizophrenic patients did not exhibit this difference.

In a PET study that examined the relationship between symptom profile and regional cerebral activity, Liddle et al., (1992) found that the disorganization syndrome was associated with diminished rCBF in ventral prefrontal cortex and contiguous insula, and with increased rCBF in anterior cingulate. Increased activity in anterior cingulate coincided with the site of maximal activation in normal individuals during the Stroop task (Pardo, Pardo, Janer and Raichle, 1990). Liddle et al., (1992) interpreted their PET findings as
evidence that ventral prefrontal underactivity leads to the tendency for intrusion of irrelevant mental activity into consciousness, leading to pathological overactivity in the anterior cingulate. Ebmeier et al., (1993) replicated the finding of a correlation between rCBF in the right anterior cingulate and severity of the disorganization syndrome.

Most recently, Rubia et al., (1998) conducted an fMRI study of schizophrenic patients and control participants while they performed a Go/No Go task. Schizophrenic patients and control participants showed left posterior and bilateral anterior parietal lobe activation, but control participants showed significantly more activation in anterior cingulate, left posterior parietal and right anterior parietal lobe than schizophrenic patients. Activation in medial frontal cortex was also significantly reduced in schizophrenic participants.

The evidence for neurobiological deficits in several areas of the brain of schizophrenic patients suggests, yet again, that the disorder involves faulty neural connectivity. It is now important to test this hypothesis with functional brain imaging of neuropsychological tests that are known to differentiate between schizophrenic patients and control participants.

1.5 Go/No Go Paradigms

It is clear that disinhibition is present in both psychopathy and the disorganization syndrome of schizophrenia. This disinhibition manifests itself in an inability to suppress inappropriate social behavior. Measuring this disinhibition in a research setting requires a paradigm that mimics the ability of a participant to inhibit a response even when it is the preferred response, i.e. response inhibition. Go/No Go paradigms have been used successfully in both animal and human experiments to assess this inhibitory processing.
Many different versions of the Go/No Go task have been developed, with the standard paradigm incorporating a motor response to a particular stimulus (Go) and no response to a different stimulus (No Go).

Data from lesion studies and brain imaging studies of the Go/No Go task have provided significant insights into the neural mechanisms underlying response inhibition. Several groups of researchers have shown that bilateral lesions of the frontal lobes of monkeys result in the impairment of learning tasks involving successive discrimination of cues in various modalities and the use of approach/non-approach responses (Weiskrantz and Mishkin, 1958; Rosvold and Mishkin, 1961; Wegener and Stamm, 1966; Dabrowska, 1972). Mishkin (1964) suggested that the ventrolateral frontal lobe lesions in monkeys impaired their ability to inhibit inappropriate responses. More specifically, prefrontally ablated animals show impairments on the Go/No Go task, with No Go trials producing more errors than Go trials (Butters, Butter, Rosen and Stein, 1973; Iversen and Mishkin, 1970). Similarly, Petrides (1986) showed that ablation of the bilateral periaqueductal cortices of monkeys impaired performance of the Go/No Go tasks. Periaqueductal cortex in the monkey is approximately homologous to the dorsolateral prefrontal cortex of the human frontal lobe (Petrides and Pandya, 1995). These data lead to the conclusion that the prefrontal cortex is the focal area for this behavioral inhibitory mechanism, involved in withholding overt responses in monkeys (Watanabe, 1986). More recently, Oishi, Mikami and Kubota (1995) injected a GABA-A antagonist, bicuculline methiodide, into certain regions of the monkey frontal lobe as the monkeys performed a Go/No Go task. The results showed that Brodmann areas 8 and 6 of the rhesus monkey brain (dorsolateral surface of the prefrontal cortex) are associated with the correct performance of the Go/No Go task. They concluded that the
monkey frontal association cortex is responsible for the suppression of motor activity for the No Go condition of the Go/No Go paradigm.

Human lesion studies have contributed further to understanding the role of the prefrontal cortex in disinhibition psychopathology (Blumer and Benson, 1975; Damasio et al., 1994; Mazars, 1970; Damasio and Van Hoesen, 1983; Levin and Duchowny, 1991). Behavioral changes in human patients with frontal lesions often include increased impulsiveness, overreactiveness and disinhibited activity (Lezak, 1983). Blumer and Benson (1975) identify these patients as "pseudopsychopathic", while Damasio et al., (1994) refer to these patients as "acquired sociopaths". As noted above, the most widely referenced case of this disorder is Phineas Gage, who following severe damage to his frontal lobes, became socially inappropriate, impulsive and disinhibited. These characteristics have been observed in many human patients, and the changes in personality most often result from damage to the orbital area of the prefrontal cortex or to pathways crossing this region (Blumer and Benson, 1975).

Drewe (1975) studied the Go/No Go task in several humans with discrete unilateral frontal lobe lesions. Patients with medial frontal lobe lesions, left or right, made more errors and more false positive errors than control participants and patients with dorsolateral or orbital lesions. Leimkuhler and Mesulam (1985) studied a patient with a large medial frontal tumor and also found deficits in performance on a Go/No Go task and on Part B of the Trail Making Test, both tests of withholding inappropriate response tendencies (Weintraub and Mesulam, 1985). These deficits were reversed following the excision of the tumor.

It is clear from these animal and human lesion data that no one region can be considered responsible for disinhibition. However, with the development of brain imaging techniques such as EEG, PET, magnetoencephalography (MEG) and fMRI, the ability to
investigate further the neural mechanisms underlying the disinhibitory processes that occur during a Go/No Go task is enhanced.

Sakagami and Niki (1994) used single unit activity to show that the inferior dorsolateral prefrontal cortex of the monkey participates in the conversion of sensory information from different visual channels into behavioral information, specifically information on the upcoming response. This coincides with the results from Tsujimoto, Ogawa, Nishikawa, Tsukada, Kakiuchi and Sasaki (1997) who used PET to measure rCBF of monkeys while they performed a Go/No Go task. The Go/No Go task resulted in a significant increase in rCBF in the principal sulcus (dorsolateral surface of the prefrontal cortex). This activation was related to the activity during the judgment not to execute the movement, and to subsequent motor suppression. They concluded that the dorsal bank of the principal sulcus plays a significant role in the No Go decision and subsequent motor suppression in the Go/No Go task. These results coincided with the findings of Sasaki and Gemba (1986, 1989) and Sasaki, Gemba, Nambu and Matsuzaki (1993) who used chronically implanted electrodes to obtain cortical field potentials and showed that prefrontal cortical activity, specific to the No Go reaction on Go/No Go tasks, was localized in the dorsal bank of the principal sulcus and the rostroventral corner of the prefrontal cortex in both hemispheres contralateral and ipsilateral to the hand used to make the response. This activity was interpreted as representing the decision not to respond to the No-Go stimulus, and also subsequent suppression of the hand movement, which they called the No Go potential.

These results from animal studies correspond with the results from many human brain imaging studies that suggest that neural circuits involving diverse areas of frontal cortex are implicated in the inhibition of responses during No Go trials of a Go/No Go
paradigm. Many EEG (specifically ERP) experiments, have provided evidence for the neural correlates of standard Go/No Go tasks. The two most common ERP components of visually presented Go/No Go tasks include a negative potential between 200 and 300 ms over the fronto-central scalp, termed the N2 potential, and a positive wave peaking between 300 and 600 ms, termed the P3, with a maximum over centro-parietal sites. The N2 is enlarged in the No Go condition compared to the Go condition, while the posterior P3 is larger for Go trials than for No Go trials. Also, the scalp topography of the P3 has a parietal maximum for Go trials and a central distribution for the No Go trials (Karlin, Martz and Mordkoff, 1969; Hillyard, Courchesne, Krausz and Icton, 1976; Simson, Vaughan and Ritter, 1977; Pfefferbaum, Ford, Weller and Kopell, 1985; Pfefferbaum and Ford, 1988; Kok, 1986; Jodo and Inoue, 1990). These morphological and topographical differences in the P3 between Go and No Go trials are thought to reflect late (e.g., 300 ms or later) decision-making processes. The anterior N2 differentiation between No Go and Go trials has been attributed to early response inhibition processes (Simson, Vaughn and Ritter, 1977; Gemba and Sasaki, 1989; Naito and Matsumura, 1994; Pfefferbaum et al., 1985; Kok, 1986; Jodo and Kayam, 1992; Eimer, 1993). Electrical potentials also have been recorded by Ikeda et al., (1996). They used subdural potentials at orbitofrontal and mesial prefrontal areas and showed that these areas play an important role in preparation for cognition and in decision-making during a Go/No Go task.

Attempts to localize the current source for the No Go potential in the human brain have used MEG to show that there are inflows and outflows of magnetic fields over the dorsolateral frontal parts of the head, contralateral and ipsilateral to the operant hand (Sasaki et al., 1993). These magnetic fields were interpreted to be due to current dipoles localized in the dorsolateral parts of frontal lobes in both contralateral and ipsilateral hemispheres. The
authors concluded that No Go decisions and subsequent suppression of voluntary movements are functional features of the human frontal association cortex, as in the case of monkeys (Oishi, Mikami and Kubota, 1995).

Further evidence from both PET and fMRI studies support a role of the dorsolateral prefrontal cortex in response inhibition. Kawashima et al., (1996) used PET and a simple Go/No Go task in which the participants were asked to press when a red light was presented but to withhold pressing when they saw the green light. A control task of pressing for every stimulus was also performed and subtracted from the Go/No Go condition. The areas of activation for this comparison included bilateral middle frontal gyrus, right precentral gyrus, superior occipital gyrus, and insula and left superior frontal gyrus, and inferior frontal gyrus.

A similar pattern of frontal lobe activation was observed in a recent fMRI study of response inhibition. Rubia et al., (1996) used fMRI with a control task and a Go/No Go task. The control task had the participants responding to 100% of trials. The Go/No Go task involved the participants responding to 70% of trials and withholding responding for 30% of trials. They found activation in right supplementary motor area (SMA), right inferior frontal cortex (B45) and anterior and posterior parietal lobes for the Go/No Go task. Casey et al., (1997) used a similar Go/No Go task and found activation in orbital cortex, dorsal prefrontal cortex and in anterior cingulate. In particular, they found a significant negative correlation between activity in the orbital frontal cortex and the number of errors of commission, suggesting that orbital under-activity predisposes a subject to poor inhibition of responses.

Konishi et al., (1998) also used fMRI to investigate the response inhibition function of the prefrontal cortex associated with the Go/No Go task. For the Go trials, a green square was presented and the participants had to respond by promptly pushing a button using their right or left thumbs. In the No Go trials, a red square was presented and participants were
instructed not to respond. They used image data analysis that allowed the transient brain activity in Go and No Go trials to be analyzed separately, and looked for the prefrontal areas in which the brain activity in No Go trials was dominant over that in Go trials. No Go dominant brain activity would therefore reflect the neural processes for inhibiting an inherent response tendency. They found that the No Go dominant foci were in the posterior part of the right inferior frontal sulcus. This was true whether the right or left hand was used. These results suggested to the authors that this region of the prefrontal cortex is related to the neural mechanisms underlying response inhibition.

An event-related fMRI study of a Go/No Go task by Liddle, Smith and Kiehl (1999), produced similar results. Event-related fMRI records the hemodynamic response to each type of event rather than to blocks of events (as in block design fMRI). The Go (Press for the letter X) and No Go (Do not press for the letter K) trials were equally probable, and the degree of difficulty was enhanced by presenting the Go and No Go trials after a count down that heightened the readiness to respond rapidly when a stimulus was presented. During Go trials there was activation of the anterior cingulate, supplementary motor area, contralateral motor cortex, and ipsilateral cerebellum. During No Go trials activation occurred in bilateral parietal cortex, anterior cingulate, and bilateral prefrontal cortex. When activity during No Go trials was subtracted from activity during Go trials, significant activation was observed in the primary and premotor motor cortices, including cerebellum. Bilateral parietal and bilateral dorsolateral prefrontal cortex activation was observed when activity during Go trials was subtracted from activity during No Go trials, suggesting that these areas are related to response inhibition.

As noted above, both psychopaths and schizophrenic patients show different behavioral and electrocortical responses than do control participants during performance of
Go/No Go tasks (Hodgins et al., 1998; Kiehl et al., 1999; Newman and Kosson, 1986; Lapierre et al., 1995). Identifying the cerebral activity in these two groups, as they perform the Go/No Go task, might provide evidence of the mechanisms underlying the disinhibition that is observed in both psychopathy and the disorganization syndrome of schizophrenia. Functional MRI was used in this thesis because of the excellent spatial resolution it provides, and because of the non-invasive nature of the procedure (discussed below).

The design of a Go/No Go task for fMRI is critical and must include comparison tasks that require the same amount of information processing and the same amount of motor activity. It is also important to ensure that the participants are engaged in the task throughout the session. This requires that pathological groups of participants are able to perform the task with reasonable accuracy. For these reasons, the design of the present study included two different conditions of the Go/No Go task, interspersed with rest epochs. The two conditions of the Go/No Go task involved the same information processing and motor activity but differed in the amount of response inhibition required. The first condition, the ‘Press for X condition’, built up a response to the letter X. This was reversed in the second Go/No Go condition when participants were instructed to withhold responding to the X and respond to all other letters ‘Press for all letters except X condition’. This second condition placed more demands on the areas of the brain involved in inhibitory processing as it is more difficult to exclude the presence of a target letter than to identify the presence of that target. Differences between the ‘Press for X condition’ and the ‘Press for all letters except X condition’ of this Go/No Go task should reflect any abnormal cerebral activity related to disinhibition that may be present in both psychopathy and schizophrenia.

Both the Go/No Go conditions were relatively easy, thereby making it likely that all participants would be capable of engagement in both conditions, furthermore, it was
expected that the psychopaths and schizophrenic patients would have a low error rate. Thus, the conditions were designed with the object of allowing a comparison of patterns of cerebral activity in the different participant groups while they were engaged in response inhibition to a slightly different degree. It was not the goal to compare cerebral activity in control participants while they successfully inhibited responses with that in patients while they failed to inhibit responses, as the interpretation of differences between groups when they are engaged in different activities is difficult. Nonetheless, despite the fact that the conditions were easy enough to be performed by all participants, it was expected that if the neural mechanisms for response inhibition are abnormal in either psychopaths or schizophrenic participants, the patterns of cerebral activity would be abnormal in those participants even when the task was performed adequately.

1.6 Functional Magnetic Resonance Imaging

"Even fifteen years ago, we'd have been tempted to sell our souls to the devil to get data like that – images of a living brain in action as it performs different cognitive tasks" (p. 4).

Martha Farah (1998), a well-known neuroscientist, commenting on fMRI.

The development of fMRI has made a considerable contribution to neuroscience and has provided a very effective tool for understanding the neural correlates of cognitive processing. fMRI studies of primary sensory and motor cortical activation have replicated results from previous PET and non-tomographic techniques and have, in addition, provided high quality information concerning the locus and spread of activity in individual participants (Bandettini, Wong, Hinks, Tikofsky and Hyde, 1992; Belliveau et al., 1991; Cao, Towle, Levin and Balter, 1993; Frahm, Bruhn, Merboldt and Hanicke, 1992; Kim et
The basic characteristics of fMRI have now been established and, subsequently, more advanced fMRI studies of subtle evoked or cognitive responses have been successfully performed. Language tasks, including reading, silent and verbal word generation (Rao et al., 1992; Binder et al., 1994; Friston et al., 1995a), semantic decision-making, and rhyme judgement (Hinke et al., 1993; McCarthy, Blamire, Rothman, Gruetter and Shulman, 1993) have produced significant fMRI data. Other fMRI studies involving working memory, spatial orientation, mental rehearsal of complex motor movements (Blamire, McCarthy and Nobre, 1993), pain research (Wen, Wolff and Berman, 1993; Russell, Howland and Jones, 1993) and olfaction (Sobel et al., 1998) have all demonstrated fMRI's ability to provide insights into the mechanisms underlying higher mental activity and to access attentional processes that occur in association cortex as well as primary cortex.

Very simply, the basis for fMRI is that increased neural activity within the cerebral cortex is accompanied by an increase in local blood flow that exceeds the increased rate of oxygen extraction. This leads to an increase in oxygenated hemoglobin and a reduction in capillary and venous deoxyhemoglobin concentration. The paramagnetic properties of deoxyhemoglobin induce a high local magnetic field, creating local field heterogeneities that cause spins to dephase rapidly and result in decreased signal intensity. With increased blood flow, more oxyhemoglobin is present, decreasing the concentration of deoxyhemoglobin and reducing dephasing. This results in an increase in the MR signal intensity. This is called the blood oxygen level dependent (BOLD) effect (Kwong et al., 1992; Ogawa, Lee, Nayak and Glynn, 1990). Using this BOLD technique, fMRI is non-invasive, requires no injection of a contrast material, does not expose participants to ionizing radiation and offers excellent spatial resolution (1-3 mm) and temporal resolution (1-2 seconds). The lower limits on the
effective resolution of fMRI are physiological and are imposed by the spatio-temporal organization of evoked hemodynamic responses (2-5mm and 5-8 seconds). The local increases in neural activity that result in increased oxygenation endures for several seconds. This observed hemodynamic response has been thought of as a smoothed version of the underlying neural activity (Frackowiak, Friston, Frith, Dolan and Mazziotta, 1997).

It is not possible to discuss fMRI without a basic understanding of certain aspects of magnetic resonance (MR) physics. A complete description of MR physics is not essential but the basic summary that follows will provide an elementary understanding of the techniques of MRI and fMRI. MRI provides a non-invasive technique for imaging the whole body, distinguishing different body tissues based on their chemical compositions. The ability of MRI to distinguish gray matter, white matter and cerebrospinal fluid (CSF) in the brain with spatial resolution that is superior to both computerized tomography and PET has allowed for significant progress in detection of brain tumors, multiple sclerosis, and other brain disease (Hashemi, 1997).

MRI is based on the absorption and emission of energy in the radio frequency range of the electromagnetic spectrum. Protons produce a magnetic resonance signal because when exposed to a strong static homogeneous magnetic field, they behave as spinning magnets and develop a net alignment of their spin axes along the direction of the applied field. Because the nucleus of the hydrogen atom contains a single unpaired proton, it has a strong magnetic moment. Furthermore, hydrogen nuclei in water molecules are abundant in living tissue, and therefore provide a very strong magnetic resonance signal. The characteristics of this signal are influenced by the local chemical environment of the water molecules, thereby allowing differentiation between the signal arising from different tissues. Consequently, the MR signals from hydrogen nuclei are widely used to provide images of
human tissues.

To produce the magnetic resonance signal the spin axes of the protons must be disturbed by a radio frequency (RF) pulse applied at the same frequency as the precessing nuclei. This pulse tilts the magnetization away from the z-axis and the magnetic signal is a measure of the projection of the magnetization in the x-y plane after the pulse and following the magnetic field gradients (discussed below). When the RF pulse is turned off, the nuclei return to their original orientation. At a pre-determined time after the RF pulse, the residual magnetization is detected. The strength of this residual magnetization at a particular location is determined by the density of the protons in tissue, and by the rate at which magnetization decays. This rate is a characteristic of the chemical composition of the tissue, and is described by two intrinsic relaxation rate constants, T1 and T2 (Stark and Bradley, 1992).

T1 relaxation is the time required to regain the resting magnetization following the RF pulse and is determined by thermal interactions between the resonating protons and other magnetic nuclei in the surrounding environment (or lattice). These interactions allow the energy absorbed by certain protons during resonance to be dispersed to the other nuclei in the lattice. T2 relaxation is a measure of how long the resonating protons precess in phase following the RF pulse. This spin-spin magnetic interaction between spinning protons cause T2 decay but unlike T1 there is only a change in phase and no energy transfer. These values, T1 and T2, are distinct for different compounds and for different tissue conditions.

MR images provide a map, modulated by spatial variations of relaxation time, of the density of water protons in the brain. For example, T1-weighted images enhance the distinction between gray matter and white matter whereas T2-weighted images are better for enhancing CSF and pathology (Stark and Bradley, 1992).
Another type of relaxation, T2*, is the dominant source of regional differentiation in BOLD fMRI images. T2* relaxation occurs from the interaction of the magnetic moments of spinning protons, T2, plus the local perturbations of the applied magnetic field, T2’. This combination of T2 and T2’ relaxation cause further phase dispersion which results in a more rapid decay of the MR signal at the time constant T2*. T2* has a reversible loss of phase, for example due to field gradients, while T2 has an irreversible loss of phase.

Deoxyhemoglobin in blood has a relatively strong magnetic moment and therefore causes local magnetic field perturbation that increases the rate of de-phasing of nearby resonant protons, resulting in a shorter T2*. When neurons become active there is local vasodilation that temporarily exceeds the increased demand for oxygen, so the proportion of deoxyhemoglobin falls relative to oxyhemoglobin. Consequently, the rate of de-phasing of the resonant protons is slower and the T2* relaxation time increases, thereby resulting in increased strength of the residual magnetization at the point in time when the magnetic field is detected. Thus, local neural activity leads to an increased strength of the detected magnetic signal.

The spatial localization of the MR signals is determined by applying magnetic field gradients, which cause the resonant frequency of protons to vary along the axis of the magnetic field gradient. Magnetic field gradients are applied in three orthogonal axes. The first step in spatially localizing the MR signal is to apply the slice select gradient. The slices in this thesis were acquired in the axial plane and thus it will be assumed for this description of MRI that the slice select gradient is applied in the z-axis. This slice select gradient is applied at the same time as the RF pulse. Because of this gradient, the precession frequency of the protons will vary in the z direction. The frequency of the applied RF pulse will match the precession frequency of the protons only in a thin axial slice. Protons in this slice will
resonate. Thus, the slice select gradient selects a specific axial slice for excitation.

Frequency and phase encoding gradients are employed to impart a distinct frequency and phase to the magnetic signal arising from each voxel within the selected axial slice. The application of the frequency encoding or readout gradient along the x-axis during the measurement of the MR signal causes the resonant frequency to vary along the x-axis (the left-to-right axis). As a result, the resonant frequency will differ in voxels from different coronal planes. This provides spatially encoding of the MR signals in one dimension within the selected slice. The phase encoding gradient maps the sagittal location of the sources of MR signals based on phase. Phase differences are established by applying a single brief magnetic field pulse perpendicular to the axes of slice selection and frequency encoding. This causes resonant frequencies to vary momentarily along this axis resulting in a phase shift that depends on the position along the phase encoding axis. Once the phase encoding gradient pulse has ended, resonant frequencies return to uniformity. This is repeated along the phase encode axis (Mitchell, 1999).

The emitted radio-frequency energy is recorded as a function of time. To localize the data by frequency and phase, it is necessary to decompose the recorded signal into its component frequencies and phases by Fourier transformation. Although the recorded signal is recorded in the time domain, it represents a Fourier transformation of space, because its component frequencies represent spatial locations. The Fourier transformation of space is known as k-space. A spatially varying signal can be considered as a superposition of components arising from different points in k-space. The components of the emitted signal that vary slowly in space are represented near the center of k-space (i.e. represented by k values near zero). The components of the signal that vary rapidly in space are represented near the edges of k-space. The recorded signal at each time point gives the value of the
signal arising from a particular location in k-space.

To produce an image in which each slice contains 128x128 voxels, it is desirable to sample 128x128 locations in k-space. In conventional MRI, the required coverage of k-space is achieved by performing multiple excitations, each with a different value of the phase encoding gradient, for each line of data in k-space. However, this is time consuming, and does not allow measurement of the relatively rapid changes in blood flow that are associated with neural activity. In Echo Planar Imaging (EPI), which is discussed in greater detail below, rapid adjustment of the gradients allows the collection of data from a wide range of values of the phase select gradient, within a period of approximately 40 milliseconds after a single excitation pulse. Thus, k-space can be sampled in sufficient detail to allow reconstruction of the image for a single axial slice in approximately 40 milliseconds. An entire brain volume (typically 23 axial slices, each 4mm thick) can be sampled in a few seconds (Bradley, Chen and Atkinson, 1997).

T1, T2 and T2* relaxation time constants represent the intrinsic sources of contrasts that produce the MR images. There are external parameters that are controlled by the experimenter to optimize the generation of the data for the MR signal of specific types of images. These parameters make up the “pulse sequence”. Examples of these parameters include 1) the time between RF pulses or repetition time (TR), 2) the time from the RF pulse to the midpoint of the echo (TE), 3) the flip angle of the RF pulse, 4) the thickness and 5) number of the slices imaged.

TR is the interval between consecutive repetitions of a pulse sequence. The TR can be considered as the time between consecutive RF pulse sequences or consecutive MR signals to produce one image. Usually, TR is long compared to the time to prepare a MR signal and finish measuring it. The signal to noise ratio (SNR) increases when TR grows
longer. The TR affects the contrast between tissues that have different T1 times. Shortening TR creates more contrast between tissues with different T1 times. The value chosen for TR influences the amount of T1 relaxation between RF pulses (Stark and Bradley, 1992).

To understand the TE parameter in the pulse sequence, it is important to describe the techniques used for reversing the dephasing due to magnetic inhomogeneity thereby producing the echoes. In the spin echo (SE) technique, a refocus pulse is delivered at a certain time, t, after the initial RF pulse. The strength of the pulse is set to produce 180-degree reversal of the spins. As a result of this 180-degree phase shift, the protons that were previously advancing in phase more rapidly because they were at a location where the magnetic field is stronger than average, are now behind in phase but catch up because they are spinning faster. As a result, at time 2t, all protons are in phase again, and the magnetic signal peaks, forming an echo. The gradual decay of the amplitude of this echo over time t provides a measure of T2. Thus, using this spin echo technique provides images that are strongly weighted towards T2. However, these images are not sensitive to the BOLD effect, which influences T2*.  

In the gradient echo (GRE) technique refocus is achieved by application of a bipolar frequency gradient. This refocus does not compensate for dephasing due to field inhomogeneity. Therefore, it is sensitive to the BOLD effect but is also susceptible to other sources of inhomogeneity. Both GRE and SE sequences have benefits and drawbacks that must be considered when proposing a pulse sequence for a fMRI study (Bandettini et al., 1994).

The TE parameter in the pulse sequence is the time from the initial RF pulse to the time when the combination of the MR signals from tissues at different locations form a composite MR signal or echo. MR signals from all tissues become weaker as TE increases.
However there are drawbacks to shorter values of TE. The minimum TE depends on how quickly a MR signal can be created, phase encoded and then measured (Barth, Diemling and Moser, 1997; Menon et al., 1993). During a SE sequence a TE of 40 ms would place the refocusing pulse 20 ms following the 90-degree pulse and the echo would develop another 20 ms later.

To perform whole brain fMRI it is critical to maximize spatial and temporal resolution and minimize susceptibility artifacts. The technique that can acquire whole brain images in a short time compared with the hemodynamic response time of the cerebral vasculature of 6-8 seconds is EPI. EPI uses rapid reversals of the readout gradient that results in a series of gradient echo signals. This allows for the use of only a single RF excitation to sample the whole of k-space. EPI also allows the use of a short TE that minimizes dephasing from flow or magnetic susceptibility variations. However, EPI images are more susceptible to signal loss and distortion from differences in magnetic field inhomogeneities that occur between brain and the air in the paranasal sinuses, and brain and bone in the skull base (Edelman, Wielopolski and Schmitt, 1994).

Development of the optimal pulse sequence for the current thesis involved minimizing this susceptibility artifact and maximizing signal intensity. Many different studies were performed to achieve this goal (Smith et al., 1998; Kiehl et al., 1998). SE, GRE and asymmetric echo (a combination of SE and GRE sequences) pulse sequences were evaluated. Variations of TE, TR, slice thickness and voxel size were also tested. The chosen pulse sequence was a GRE EPI pulse sequence described in the methods section below. Due to restrictions of the scanner itself it was difficult to completely eliminate the susceptibility artifact at the base of the skull. However, this pulse sequence is a compromise between SNR and susceptibility artifact and was necessary to allow for sufficient SNR to
observe the 2-5% blood flow changes that occur during tasks involving association cortex.

1.7 Experiment

Disinhibition is a cardinal feature of both psychopathy and the disorganization syndrome of schizophrenia. Disinhibitory mechanisms have been linked to medial, lateral and ventromedial prefrontal deficits, suggesting that not just one brain region, but rather the widespread connections of the prefrontal cortex may play a key role in the manifestation of disinhibition.

The non-invasive nature of fMRI and the data that have been produced thus far suggest that it is an excellent method for investigating the neural mechanisms of the complicated processing involved in disinhibition, as well as for identifying any differences that may exist between groups of participants. Similarly, the Go/No Go paradigm has been shown to be a useful task in examining response inhibition.

The present study was designed to investigate the cerebral activity that is correlated with performance of a Go/No Go task, more specifically, withholding a pre-established response. This response inhibition was assessed, using fMRI, in four groups of participants, including psychopathic and nonpsychopathic inmates, stable, medicated schizophrenic patients, and control participants. It was hypothesized that there are significant differences in neural activity between psychopaths and control participants, as well as between schizophrenic patients and control participants. The nonpsychopathic inmates provided a control group for the institutionalization of the psychopathic participants. It was expected that their behavioral data and fMRI results would be intermediate between control participants or psychopaths, given that most of these inmates have several psychopathic characteristics, including disinhibition.
A comparison of the results from the schizophrenic patients and the psychopathic participants was also of interest, because of the similarities and differences between the two disorders and because there has been considerable debate about their comorbidity (Rasmussen and Levander, 1996; Gacono et al., 1995; Hart and Hare, 1989; Raine, 1992; Rice and Harris, 1995). The results from this experiment should help to shed light on the neural circuitry of the disinhibition observed in both psychopathy and the disorganization syndrome of schizophrenia.

2. Methods and Materials

2.1 Participants

There were four groups of participants for this study. All participants were right handed (measured by the Annett Handedness Scale, 1970) volunteers who had English as their first and only language. Participants were matched for age, gender and socioeconomic status based on the Hollingshead two factor index of social position (Hollingshead and Redlich, 1958). No participants had a history of head injury or had an Axis I diagnosis of drug abuse for six months prior to scanning. Aside from the group of schizophrenic patients, no participants had an Axis I diagnosis of schizophrenia or had a known relative with the disorder.

Nine control participants (mean age = 32.68, S.D. = 7.25, one female, eight males) were recruited from the general population. The female subject was not included in the comparison of control participants with the inmate groups. The mean age of the eight control male participants was 32.5 (S.D. = 7.73). Psychopathic (n = 8, mean age = 33.88, S.D. = 7.62) and nonpsychopathic (n = 8, mean age = 37.13, S.D. = 7.70) criminals were all males recruited from the Regional Health Center (RHC), a maximum-security psychiatric
prison in Abbotsford, British Columbia, Canada. All inmates were participating in
treatment programs at RHC that required average to above average overall intelligence.

Nine schizophrenic patients (mean age = 31.67, S.D. = 7.58, one female, eight
males) were stable, medicated outpatients from the day program at the University of British
Columbia Schizophrenia Program. Eight patients were receiving treatment with olanzapine
(mean daily dose = 13.93 mg, S.D. = 6.43), and one subject was receiving risperidone (daily
dose 1 mg).

2.2 Assessment Tools

The Hare Psychopathy Checklist-Revised (PCL-R; Hare, 1991) was used to assess
psychopathy in the criminal volunteers. The PCL-R is the instrument of choice for
measuring psychopathy (Fulero, 1996). The PCL-R provides reliable measures for both the
interpersonal/affective (Factor 1) and the social deviance (Factor 2) components of
psychopathy in a prison population (Hare, 1991). The instrument consists of twenty items
each scored on a three-point scale from an extensive semi-structured interview
(approximately one and a half hours) and from collateral institutional file information. The
interviews were videotaped so that the scores of two independent, well-trained raters could
be compared and averaged. Because RHC would not allow inmates with very high PCL-R
scores to participate in the fMRI part of the study, psychopaths were defined as those with a
PCL-R score of 28 or more, rather than the standard cutoff score of 30. Similarly, there was
not a large population of inmates with low PCL-R scores and thus nonpsychopaths were
defined as those with a PCL-R score of less than and including 23.

The Psychopathy Checklist: Screening Version (PCL:SV; Hart, Cox and Hare, 1995)
was administered to the schizophrenic patients and the control participants. The PCL:SV
has been used widely to assess psychopathy in civil psychiatric patients, community residents, and job applicants, as well as in forensic settings where it is necessary to perform a rapid assessment of psychopathy. The PCL:SV includes 12 items and has a maximum score of 24. For research purposes, psychopaths are defined as those with a PCL:SV score of 18 or more (Hart et al., 1995). No participants from these two groups were included in the study if their PCL:SV score was above eight. Cooke, Michie, Hart and Hare (1999) have shown that the PCL-R and the PCL:SV are parallel tests. Thus, scores from the PCL:SV were converted into PCL-R scores (Hart et al., 1995) for comparison of the control participants and schizophrenic patients with the criminal participants.

The Thought, Language and Communication Index (TLC-I; Liddle, 1991) is an instrument that assesses formal thought disorder. This is assessed from eight one-minute speech samples produced when the subject describes each of a set of eight pictures. Scores for two categories of disorders, Impoverishment of Thinking and Disorganization of Thinking, which include within them eight different types of disorders defined similarly to items in Andreasen's (1979) Thought, Language and Communication Scale, are assigned according to a standard protocol. Each subject performed this task prior to or shortly after the imaging session.

Structured Clinical Interview (SCID; Spitzer, 1989) and case-note information were used to assess drug addiction and psychotic symptoms based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). This was used in conjunction with the Signs and Symptoms of Psychotic Illness scale (SSPI; Liddle, 1998), which assesses psychotic symptoms within the week that the subject is imaged.

Both the National Adult Reading Test (NART; Sharpe and O’Carol, 1991) and the Quick test (Ammons and Ammons, 1962) were administered to all participants as measures.
of premorbid and current functioning IQ, respectively. The NART is based on the ability to read aloud a list of 50 words (Sharpe and O'Carol, 1991) while the Quick test assesses the ability to point to the appropriate picture that matches the word that the experimenter reads.

The participants were individually matched for age, gender and parental occupation. The Hollingshead index of social position considers the participants’ parental occupation and parental education; the latter could not be used because few inmates knew their parent’s education. However, the parental occupation score is sufficient to provide a socioeconomic status of the participant (Hollingshead and Redlich, 1958).

On the day of the fMRI, participants were given a Signs and Symptoms of Psychotic Illness (SSPI) interview to measure any psychotic symptoms that were present. Inmates provided a urine sample that was tested with the TRIAGE 7 (Immucor Canada Incorporated, Edmonton, Alberta, Canada) test kit for seven groups of illicit drugs.

2.3 Go/No Go task

The Go/No Go procedure involved the presentation of letters, one at a time on a screen for a period of 75 milliseconds, with an interstimulus interval of 925 milliseconds. Fifty percent of the stimuli were X and the other 50% were other capital letters randomly selected from the remainder of the alphabet. ‘X’ and ‘non-X’ stimuli were presented in random order. The task was made up of two types of Go/No Go conditions interspersed with Rest epochs. In the ‘Press for X condition’, the subject was instructed to press a button with the right index finger when an X was presented, and to refrain from pressing for all other letters. This was reversed for the ‘Press for all letters except X condition’, as the participants were instructed to refrain from pressing for the X and to press for all other letters. In a pilot study with control participants, the reaction time for the correct responses
was longer and the errors of commission were more frequent in the ‘Press for all letters except X condition’ than in the ‘Press for X condition’. This was consistent with the prediction that the ‘Press for all letters except X condition’ placed greater demand on the mechanism for inhibitory processing. Both conditions involve similar processing of information, and a similar amount of motor activity. Both types of Go/No Go conditions were presented in epochs of 20 seconds duration. Each Go/No Go epoch was preceded by a five second instruction epoch and followed by a 20 second rest epoch. During instruction epochs, the instruction “Press for X” or “Press for all letters except X” was presented on the screen. During rest epochs, the word “REST” was presented and the subject was not required to make any motor response.

Stimuli were presented as white letters on a black background on a screen located at the entrance to the magnet bore. Participants viewed this screen via a mirror attached to the head-coil mount while lying supine in the scanner. Button-press responses were recorded via a MRI-compatible fiber optic device (Lightwave Medical, Vancouver, British Columbia, Canada), including reaction times to correct responses, errors of commission and errors of omission.

Before participants entered the scanning room, full instructions were given and a practice session, with 10 stimuli (five from each of the two Go/No Go conditions), was performed. Participants were instructed to press as quickly and correctly as possible and, if they made a mistake, to continue without thinking about the mistakes. While in the scanner, each subject underwent one scanning session of 460 seconds duration. The scanning session began with an initial rest epoch of 10 seconds to allow longitudinal magnetic relaxation (T1 effects) to stabilize. Images collected during this initial rest epoch were not included in the data analysis. Within the scanning session there were five ‘Press for X condition’ and five
‘Press for all letters except X condition’ epochs, presented in a counterbalanced order.

2.4 Imaging

MRI was performed using a standard clinical General Electric 1.5 Tesla Horizon Echo Speed unit (General Electric, Milwaukee, WI). Participants laid supine with their head securely strapped into a custom head holder. A conventional spin echo T1-weighted sagittal localizer was acquired to confirm that the anterior commissure-posterior commissure (AC-PC) line was at right angles to the transverse slice. This localizer was also used to prescribe a subsequent 3D spoiled gradient (SPGR) pulse sequence (TR/TE 11.2/21 ms, flip angle 60, field of view (FOV) 26x26 cm, 256x256 matrix, slice thickness 1.5mm) volume acquisition to provide structural images of the entire brain.

Whole brain echo planar fMRI was performed using a gradient echo pulse sequence (TR 2500 ms, TE40 ms, FOV 24x24, 23 axial slices, 4 mm thick slices, flip angle 90 degrees, 64x64 matrix, bandwidth 62.5 kHz). During each 460 second scanning session, 180 images of the whole brain were acquired and subsequently reconstructed off-line. The lights in the magnet and in the scanning room were off throughout the imaging.

3. Statistical Analyses

3.1 Behavioral Data Analyses

Errors of commission included any response following a No Go stimulus (e.g. stimulus P for the ‘Press for X condition’ and stimulus X for the ‘Press for all letters except X condition’) within 900 ms of stimulus presentation. Omission errors were defined as a failure to respond to a target stimulus within this same time frame. Mean reaction times were calculated for both the ‘Press for X’ and the ‘Press for all letters except X’ conditions.
for all accurate responses occurring within 900 ms of stimulus presentation.

The forensic population and matched control participants’ behavioral data were analyzed using a three group (psychopath, nonpsychopath, and control) X two condition (‘Press for X condition’ and ‘Press for all letters except X condition’) repeated measures analysis of variance (ANOVA). Separate ANOVAs were performed on the reaction time data, errors of commission, and errors of omission. A correlation analysis was also performed with PCL-R score and errors of commission for the ‘Press for all letters except X condition’, based on the hypothesis that errors of commission would increase with increasing scores on the PCL-R.

Behavioral data were analyzed for the schizophrenic patients and matched control participants with a two group (schizophrenic and control) X two condition (‘Press for X’ and ‘Press for all letters except X’) repeated measures ANOVA. Again, separate ANOVAs were performed for reaction times, errors of commission and errors of omission.

3.2 Statistical Parametric Mapping (SPM)

The functional images were reconstructed on a Silicon Graphics workstation (SGI) using customized reconstruction software (B. Mock, General Electric Medical System, Milwaukee, Wisconsin). The data were then processed using the image analysis software package, SPM96 (Statistical Parametric Mapping version 1996; Wellcome Department of Cognitive Neurology, London, UK). SPM is implemented through Matlab (Mathworks, Inc. Sherborn MA, USA), a programming language for computations of matrices.

In general terms, SPM is a comprehensive collection of mathematical, neuroanatomical, biophysical and statistical methods that combine both change distribution analysis and significance probability mapping. Change distribution analysis is a voxel-
based assessment of neurophysiological changes developed for PET activation studies.
Significance probability mapping was developed for the analysis of multichannel EEG data
and involves the construction of interpolated pseudomaps of a statistical parameter
(Frackowiak et al., 1997). The novelty of SPM comes from its ability to spatially normalize
the data and to correct for multiple comparisons (Friston et al., 1995b).

SPM combines these two methods to analyze functional brain imaging experiments
and provide statistical information on neurophysiological activity in regionally specific brain
areas. Prior to the production of statistical parametric maps (SPM) and statistical analyses
of cerebral activation, images must undergo several stages of processing.

The first step of image analysis is to estimate and correct for movement-related
variance. An estimation of the movement, using a least squares analysis, is calculated
relative to the first scan of the time series as movement in one image can affect the signal in
subsequent images. The estimation is then used to realign the images and perform a
correction to remove movement-related components that persist after simple realignment.
Realignment is followed by spatial normalization to facilitate inter-subject averaging and
group comparisons. Spatial normalization uses spatial transformations to transform each
subject's images into a standardized anatomical space, typically the atlas of Talairach and
Tournoux (1988) (Friston et al., 1995a). The next step in image analysis involves the
smoothing or convolving of the data with a Gaussian filter. This procedure increases the
signal to noise ratio of the data. It also conforms the data more closely to a Gaussian field
model, making it easier to perform statistical tests of regionally specific effects. It is also
important to smooth data for inter-subject averaging to ensure that the hemodynamic
changes from subject to subject are assessed on a spatial scale where there is agreement on
functional anatomy. To maximize the signal from the fMRI time series, it is also important
to smooth the data by convolution with the hemodynamic response function (discussed in 3.3 Image Analyses) (Friston et al., 1995b).

The realigned, spatially normalized and smoothed images are now ready to form the statistical parametric maps (SPM) that are used to infer statistical significance. These maps are spatially extended statistical processes that combine the general linear model and the theory of Gaussian fields to make statistical inferences about regionally specific effects in the imaging data. Each voxel of the image is treated individually and using any univariate statistical parametric test, usually a Student’s t-test, the magnitude of the change of interest is compared with the residual variance. These voxel values are, under the null hypothesis, distributed according to a known probability density function that is usually Gaussian. The resulting statistics are assembled into an image SPM(t) that is then interpreted as a spatially presented statistical map.

The SPM(t) is transformed to the unit normal distribution to give a Gaussian field or SPM(Z). Z scores are the numbers from the unit normal distribution that would give the same probability value as the t statistic. If a prediction of activation at a particular brain site is made a priori then the Z value in that region in the SPM(Z) can be used to test the hypothesis. If no a priori prediction is made, then it is necessary to correct for multiple non-independent comparisons. The Gaussian field properties allow for the computation of corrected probability values (p values) that pertain to different levels of inference in terms of a) the number of activated regions b) the number of activated voxels comprising a particular region and c) the p value for each voxel within that region. These p values are corrected for the multiple non-independent comparisons implicit in an analysis. The resulting probability values for specific contrasts are produced by subtraction, parametric or factorial methods.

These methods determine areas of significant differences that are interpreted as
regionally specific effects, attributable to a sensorimotor or cognitive process that has been manipulated experimentally. Both subtraction and parametric designs were used in the present thesis. Subtraction (categorical) is based on the assumption that the difference between two tasks can be formulated as a separable cognitive or sensorimotor component and that the regionally specific differences in brain activity identify the corresponding functionally specialized area. Parametric designs (dimensional) follow the premise that regional physiology will vary monotonically and systematically with the amount of cognitive or sensorimotor processing.

Statistical inferences can be made using either a fixed-effects model or a random-effects model. The distinction between these models relates to the sources of variability in the measurements that are included in the model, and through this feature, the scope over which the inferences can be made. In fixed-effects models it is assumed that subject specific effects are fixed. The inference that can be made from this model is only applied to the participants imaged and not to a larger population. Contrary to this model, the random-effects model takes into consideration that the participants are part of a larger population and have some inherent variability. Therefore, it is possible to make an inference about the population from which the sample was taken, making a random-effects model wider ranging in its ability to comment on differential activations (Frackowiak et al., 1997).

3.3 Image Analyses

Specific to the present thesis, SPM96 was used to realign and motion-correct (Friston et al., 1995a) the 176 whole brain volumes collected for each participant during the Go/No Go task. The motion correction did not exceed 1 mm or 1 degree for any participant. A mean functional image volume was constructed for each participant from the realigned
image volumes. This volume was used to determine the parameters for spatially normalizing the realigned images into the modified Talairach space employed in SPM96. This was accomplished by matching the realigned image volume to the EPI template supplied by SPM96, using the procedure of Friston et al., (1995a). The EPI template is located in a coordinate frame that has its origin at the mid-point of the anterior commissure, y-axis passing from back to front through the posterior and anterior commissures, and x-axis directed from left to right. Following spatial normalization, images were smoothed with an 8mm full-width at half-maximum Gaussian filter for fixed-effects analysis.

To prepare the data for statistical analysis, the observed time course of image intensity in each voxel was temporally filtered to remove frequency components below 0.36 Hz (Holmes, Josephs, Buchel and Friston, in press) and fitted (using the general linear model) to a model hemodynamic response consisting of sequential contributions from sequential epochs. The hemodynamic response to each type of epoch was modelled by a delayed, filtered boxcar waveform commencing six seconds after the commencement of the epoch and subjected to the same high-pass temporal filter as the observed time course (Friston et al., 1995b).

Fixed-effects statistical analyses were used to ensure that all subjects performed the task and produced enough signal to noise to observe neural activation. This analysis was used to compare both Go/No Go conditions with Rest. A within group analysis of this comparison was also performed with a fixed-effects analysis to compare the amplitudes of the fitted waveforms for each type of epoch. In this model the square of differences between fitted amplitudes for the epochs of interest was compared with the variance estimated from the residuals reflecting the discrepancy between the observed and modeled time course. This procedure identified the voxels where there was a significant difference in cerebral activity.
during the Go/No Go epochs compared with the Rest epochs within each group of participants. However, as noted above, the estimate of variance employed in the computation of the z value does not explicitly account for the variance between participants, and thus the fixed-effects model is not appropriate for comparisons between groups. Further, interpretation of the comparison with Rest is uncertain because brain activity during Rest is not precisely specified. There is an ongoing debate to determine what the ideal baseline condition for fMRI studies should include.

For comparisons among the groups of participants, random-effects models were employed, using the SPM random-effects toolkit (Holmes and Friston, 1998). For each participant, all normalized images representing a given type of epoch (the two Go/No Go conditions and Rest) were averaged to generate a single image representing activity during that type of epoch in that participant. These images were smoothed with a 20mm Gaussian filter. The square of the between-group differences in the contrasts between types of epoch was compared with the variance between participants, to identify significant differences between groups in the contrast between types of epoch. More specifically, comparisons were made between both Go/No Go conditions and Rest, and between the two Go/No Go conditions themselves to evaluate the differences between psychopathic, nonpsychopathic inmates and control participants, and between schizophrenic patients and control participants and schizophrenic patients and psychopathic inmates.

The different demands on the neural mechanisms of response inhibition for the two Go/No Go conditions allow for a better measure of response inhibition than comparing both Go/No Go conditions to rest. This involves the subtraction of the ‘Press for X condition’ epochs from the ‘Press for all letters except X condition’ epochs and will be denoted by ‘Press for all letters except X – Press for X comparison’ for the remainder of this thesis.
This provides information on the brain regions with greater activation during the ‘Press for all letters except X condition’ than the ‘Press for X condition’. The ‘Press for X condition’ minus the ‘Press for all letters except X condition’ will determine the contrast revealing the areas of the brain producing more activation during the ‘Press for X condition’ than the ‘Press for all letters except X condition’. ‘Press for X – Press for all letters except X comparison’ will denote this contrast.

For both the fixed-effects and the random-effects analyses, the significance of the differences between types of epochs for each individual voxel was corrected for multiple comparisons employing a Bonferroni-type correction computed using the theory of Random Gaussian Fields as implemented in SPM96. This correction considers the fact that the signal in adjacent voxels is correlated so the number of independent comparisons is substantially less than the number of voxels examined.

In addition to the subtraction comparisons made above, a parametric method was used to determine if there was a correlation between PCL-R total score and the brain activation related to response inhibition. To perform this analysis, one image for each participant was obtained by subtracting the mean image for the ‘Press for X condition’ from the mean image of the ‘Press for all letters except X condition’ and multiplying that image by a grayscale mask. The value in each voxel of this difference image represents the difference in MRI signal between the two conditions. For each voxel, the significance of the regression was tested, predicting MRI signal difference from PCL-R scores. These images, with the NART and Quick test scores as covariates, were also used to determine if IQ had an effect on the relationship between psychopathy and neural activity during the Go/No Go task. Similarly, TLC-I scores were included as covariates to determine if these scores would account for any neurophysiological differences between psychopaths, schizophrenic patients
and control participants.

4. Results

4.1 Forensic populations and matched control participants

4.1.1 Demographic Data

Table 1 summarizes the demographic data from the forensic groups and control participants. Although the results for the NART and Quick tests did not reach significance, (F(2,23) = 3.073, p = 0.068; F(2,23) = 3.312, p = 0.056, respectively), a correlation analysis revealed a significant negative correlation between both PCL-R total score and NART score, and between PCL-R total score and Quick score (Pearson r = -0.4, p = 0.034; Pearson r = -0.46, p = 0.023, respectively). However, this relationship did not influence the significant imaging results; when the NART and Quick scores were included in the image analysis as covariates the activation in middle frontal gyrus (see below) was still observed.
Table 1: Demographic data for matched psychopathic and nonpsychopathic inmates and control participants. PCL-R scores are total scores. National Adult Reading Test (NART) scores are calculated for premorbid IQ equivalents (Sharpe and O’Carol, 1991). Quick scores are current IQ equivalents determined from norms presented in Ammons and Ammons (1962).

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years) Mean (S.D.)</th>
<th>PCL-R Mean (S.D.)</th>
<th>NART Mean (S.D.)</th>
<th>Quick Mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Participants</td>
<td>32.50 (7.73)</td>
<td>2.25 (1.49)*</td>
<td>118.72 (3.7)</td>
<td>114.67 (10.2)</td>
</tr>
<tr>
<td>Nonpsychopathic Inmates</td>
<td>37.13 (7.70)</td>
<td>16.59 (6.0)</td>
<td>115.45 (5.35)</td>
<td>108.00 (5.86)</td>
</tr>
<tr>
<td>Psychopathic Inmates</td>
<td>33.88 (7.62)</td>
<td>31.85 (2.7)</td>
<td>111.19 (7.49)</td>
<td>102.75 (9.91)</td>
</tr>
</tbody>
</table>

* Converted from PCL:SV scores.
Psychopaths showed significantly higher total scores (mean (M) = 3.66, S.D. = 2.35) on the TLC-I than control participants (M = 0.44, S.D. = 0.43), nonpsychopathic inmates (M = 1.0, S.D. = 1.0) and schizophrenic patients (M = 0.97, S.D. = 0.82) (Main effect of group, F(3,26) = 9.009, p = 0.000; psychopaths and control participants, F(1,14) = 14.79, p = 0.002; psychopathic and nonpsychopathic inmates, F(1,11) = 5.60, p = 0.037; psychopaths and schizophrenic patients, F(1,14) = 9.342, p = 0.009). No significant differences were observed between control participants and nonpsychopathic inmates (F(1,11) = 2.22, p = 0.164).

Overall oneway ANOVAs for each disorder of the TLC-I showed that Weakening of Goal was the only item where scores were significantly greater for the psychopathic inmates than all other groups of participants (F(3,26) = 7.52, p = 0.001). As with the NART and Quick scores, inclusion of the TLC-I scores as covariates in the regression analysis did not affect the imaging results.

One psychopathic participant tested positive for a trace amount of opiates in his urine. Imaging analyses were performed with and without the data from this participant. The difference was minimal and thus his data were included in the data analysis.

4.1.2 Behavioral Data

A summary of commission errors and reaction times to correct responses is reported in Table 2 for the forensic groups and control participants. One nonpsychopathic inmate misread the instructions for one of the epochs and thus the data from this epoch are not included in this analysis or the image analysis. An ANOVA performed on errors of commission revealed no overall differences between groups, no difference between conditions, and no group by condition interaction (Main effect of group, (F(2,21) = 1.334, p
main effect of condition, $F(1,21) = 2.022$, $p = 0.170$ and interaction, $F(2,21) = 0.096$, $p = 0.909$). There was a trend for a greater number of commission errors during the ‘Press for all letters except X condition’ with increased PCL-R score, as shown by a one-tailed Pearson correlation of PCL-R total score and errors of commission in each group (Pearson $r = .28$, $p = 0.09$). Omission errors were minimal for all groups and there were no significant group, condition or group by condition effects (all $p$ values were over 0.1) with a three group by two condition analysis.
Table 2: Behavioral data for matched psychopathic and nonpsychopathic inmates and control participants. Mean errors of commission represent responses to No Go stimuli within 900 ms of stimulation presentation. Mean reaction times are measured in milliseconds and include all correct responses within 900 ms of stimulus presentation. Standard deviations are provided for all measurements.

<table>
<thead>
<tr>
<th>Group</th>
<th>Commission Errors</th>
<th>Reaction Time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“Press for X”</td>
<td>“Press for X”</td>
</tr>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
</tr>
<tr>
<td></td>
<td>“Press for all</td>
<td>“Press for all</td>
</tr>
<tr>
<td></td>
<td>letters except</td>
<td>letters except</td>
</tr>
<tr>
<td></td>
<td>X”</td>
<td>X”</td>
</tr>
<tr>
<td>Control Participants</td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
</tr>
<tr>
<td></td>
<td>1.50 (0.54)</td>
<td>387 (38)</td>
</tr>
<tr>
<td></td>
<td>2.13 (1.46)</td>
<td>405 (33)</td>
</tr>
<tr>
<td>Nonpsychopathic</td>
<td>1.62 (1.30)</td>
<td>397 (69)</td>
</tr>
<tr>
<td>Inmates</td>
<td>2.88 (1.73)</td>
<td>414 (57)</td>
</tr>
<tr>
<td>Psychopathic</td>
<td>3.00 (4.21)</td>
<td>381 (69)</td>
</tr>
<tr>
<td>Inmates</td>
<td>3.75 (3.50)</td>
<td>414 (57)</td>
</tr>
</tbody>
</table>
Results from the reaction time data revealed a significant main effect of condition \( (F(1,21) = 18.44, p = 0.000) \). Across all participants, reaction times were slower for the ‘Press for all letters except X condition’ than for the ‘Press for X condition’. The main effect of group \( (F(2,21) = 0.446, p = 0.646) \) and the group by condition interaction \( (F(2,21) = 0.027, p = 0.974) \) were not significant.

4.1.3 Imaging Data

A comparison of both Go/No Go conditions with Rest in a fixed-effects analysis for both inmate groups and control participants demonstrated activation of bilateral dorsolateral prefrontal cortex, as well as sensori-motor cortex and supplementary motor cortex. Bilateral parietal lobe, anterior cingulate and temporal lobe activations were also observed (Tables 3, 4 and 5).
Table 3: Control Participant imaging data for the comparison of the two Go/No Go Conditions versus Rest. Results presented are maximum z-scores for single voxels for each of the significant areas of activation. (L = left; R = right). Note: *** p ≤ 0.001, corrected.

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach Coordinates</th>
<th>z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frontal Lobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. L Medial Frontal Gyrus</td>
<td>-8 4 48</td>
<td>8.93***</td>
</tr>
<tr>
<td>2. L Precentral Gyrus</td>
<td>-41 -19 48</td>
<td>8.92***</td>
</tr>
<tr>
<td>3. R Inferior Frontal Gyrus</td>
<td>52 8 28</td>
<td>8.81***</td>
</tr>
<tr>
<td>4. R Medial Frontal Gyrus</td>
<td>8 4 52</td>
<td>8.53***</td>
</tr>
<tr>
<td>5. L Inferior Frontal Gyrus</td>
<td>-45 8 24</td>
<td>8.47***</td>
</tr>
<tr>
<td>6. R Superior Frontal Gyrus</td>
<td>34 41 32</td>
<td>8.36***</td>
</tr>
<tr>
<td>7. R Insula</td>
<td>38 19 0</td>
<td>8.31***</td>
</tr>
<tr>
<td>8. L Precentral Gyrus</td>
<td>49 0 48</td>
<td>8.31***</td>
</tr>
<tr>
<td>9. L Middle Frontal Gyrus</td>
<td>-38 41 28</td>
<td>8.27***</td>
</tr>
<tr>
<td>10. L Insula</td>
<td>-38 26 0</td>
<td>8.25***</td>
</tr>
<tr>
<td>11. R Middle Frontal Gyrus</td>
<td>34 -4 44</td>
<td>7.76***</td>
</tr>
<tr>
<td>12. R Cingulate Gyrus</td>
<td>11 19 28</td>
<td>7.36***</td>
</tr>
<tr>
<td>13. L Cingulate Gyrus</td>
<td>-11 22 28</td>
<td>7.06***</td>
</tr>
<tr>
<td><strong>Parietal Lobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. L Inferior Parietal Lobule</td>
<td>-49 -34 44</td>
<td>8.82***</td>
</tr>
<tr>
<td>15. L Precuneus</td>
<td>-26 -56 52</td>
<td>8.43***</td>
</tr>
<tr>
<td>16. R Superior Parietal Lobule</td>
<td>34 -60 48</td>
<td>8.33***</td>
</tr>
<tr>
<td>17. L Postcentral Gyrus</td>
<td>-64 -19 20</td>
<td>8.17***</td>
</tr>
<tr>
<td>18. R Inferior Parietal Lobule</td>
<td>49 -38 44</td>
<td>7.92***</td>
</tr>
<tr>
<td>19. R Supramarginal Gyrus</td>
<td>52 -41 36</td>
<td>7.85***</td>
</tr>
<tr>
<td>20. R Postcentral Gyrus</td>
<td>60 -15 20</td>
<td>7.68***</td>
</tr>
<tr>
<td>21. L Supramarginal Gyrus</td>
<td>-49 -45 36</td>
<td>7.21***</td>
</tr>
<tr>
<td>22. L Lingual Gyrus</td>
<td>-26 -60 0</td>
<td>6.54***</td>
</tr>
<tr>
<td><strong>Temporal Lobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. R Superior Temporal Gyrus</td>
<td>68 -34 8</td>
<td>8.01***</td>
</tr>
<tr>
<td>24. R Middle Temporal Gyrus</td>
<td>52 -30 0</td>
<td>7.72***</td>
</tr>
<tr>
<td>25. L Superior Temporal Gyrus</td>
<td>-34 -49 16</td>
<td>7.17***</td>
</tr>
<tr>
<td>26. L Middle Temporal Gyrus</td>
<td>-38 -49 0</td>
<td>6.20***</td>
</tr>
<tr>
<td><strong>Deep Grey</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. R Caudate</td>
<td>11 0 4</td>
<td>7.80***</td>
</tr>
<tr>
<td>28. L Putamen</td>
<td>-26 -8 16</td>
<td>7.77***</td>
</tr>
<tr>
<td>29. R Putamen</td>
<td>26 11 0</td>
<td>7.65***</td>
</tr>
<tr>
<td>31. R Thalamus</td>
<td>8 -19 8</td>
<td>7.22***</td>
</tr>
<tr>
<td><strong>Occipital Lobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32. R Middle Occipital Gyrus</td>
<td>49 -75 0</td>
<td>7.94***</td>
</tr>
<tr>
<td>33. L Middle Occipital Gyrus</td>
<td>-45 -71 4</td>
<td>6.73***</td>
</tr>
</tbody>
</table>
Table 4: Psychopathic inmates’ imaging data for the comparison of the two Go/No Go Conditions versus Rest. Results presented are maximum z-scores for single voxels for each of the significant areas of activation for Psychopathic Participants comparing both Go/No Go conditions with the Rest conditions. (L = left, R = right). Note: *** p ≤ 0.001, ** p ≤ 0.01, * p < 0.05, corrected for multiple comparisons.

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach Coordinates</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Lobes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R Precentral Gyrus</td>
<td></td>
<td>45</td>
<td>-4</td>
<td>52</td>
<td>8.74***</td>
</tr>
<tr>
<td>2. L Medial Frontal Gyrus</td>
<td></td>
<td>-4</td>
<td>-4</td>
<td>52</td>
<td>8.72***</td>
</tr>
<tr>
<td>3. R Superior Frontal Gyrus</td>
<td></td>
<td>4</td>
<td>11</td>
<td>48</td>
<td>8.71***</td>
</tr>
<tr>
<td>4. L Precentral Gyrus</td>
<td></td>
<td>-41</td>
<td>-8</td>
<td>52</td>
<td>8.71***</td>
</tr>
<tr>
<td>5. R Middle Frontal Gyrus</td>
<td></td>
<td>41</td>
<td>45</td>
<td>24</td>
<td>8.33***</td>
</tr>
<tr>
<td>6. R Insula</td>
<td></td>
<td>38</td>
<td>22</td>
<td>0</td>
<td>8.20***</td>
</tr>
<tr>
<td>7. L Insula</td>
<td></td>
<td>-38</td>
<td>22</td>
<td>0</td>
<td>8.00***</td>
</tr>
<tr>
<td>8. R Inferior Frontal Gyrus</td>
<td></td>
<td>45</td>
<td>8</td>
<td>28</td>
<td>7.85***</td>
</tr>
<tr>
<td>9. L Middle Frontal Gyrus</td>
<td></td>
<td>-38</td>
<td>49</td>
<td>28</td>
<td>7.82***</td>
</tr>
<tr>
<td>10. L Inferior Frontal Gyrus</td>
<td></td>
<td>-45</td>
<td>11</td>
<td>28</td>
<td>7.37***</td>
</tr>
<tr>
<td>11. L Cingulate Gyrus</td>
<td></td>
<td>-11</td>
<td>15</td>
<td>36</td>
<td>6.42***</td>
</tr>
<tr>
<td>Parietal Lobes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. R Superior Parietal Lobule</td>
<td></td>
<td>38</td>
<td>-56</td>
<td>56</td>
<td>8.30***</td>
</tr>
<tr>
<td>13. L Inferior Parietal Lobule</td>
<td></td>
<td>-49</td>
<td>-34</td>
<td>48</td>
<td>8.13***</td>
</tr>
<tr>
<td>14. L Precuneus</td>
<td></td>
<td>-26</td>
<td>-71</td>
<td>36</td>
<td>7.90***</td>
</tr>
<tr>
<td>15. L Superior Parietal Lobule</td>
<td></td>
<td>-30</td>
<td>-60</td>
<td>56</td>
<td>7.53***</td>
</tr>
<tr>
<td>16. L Postcentral Gyrus</td>
<td></td>
<td>-60</td>
<td>-22</td>
<td>32</td>
<td>5.34***</td>
</tr>
<tr>
<td>Temporal Lobes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. R Middle Temporal Gyrus</td>
<td></td>
<td>56</td>
<td>-38</td>
<td>4</td>
<td>7.76***</td>
</tr>
<tr>
<td>18. L Middle Temporal Gyrus</td>
<td></td>
<td>-52</td>
<td>-49</td>
<td>4</td>
<td>7.67***</td>
</tr>
<tr>
<td>Deep Grey</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. R Caudate</td>
<td></td>
<td>11</td>
<td>4</td>
<td>8</td>
<td>7.77***</td>
</tr>
<tr>
<td>20. L Putamen</td>
<td></td>
<td>-30</td>
<td>11</td>
<td>0</td>
<td>7.71***</td>
</tr>
<tr>
<td>21. L Caudate</td>
<td></td>
<td>-11</td>
<td>0</td>
<td>8</td>
<td>7.66***</td>
</tr>
<tr>
<td>22. R Putamen</td>
<td></td>
<td>30</td>
<td>11</td>
<td>0</td>
<td>7.26***</td>
</tr>
<tr>
<td>24. R Thalamus</td>
<td></td>
<td>4</td>
<td>-22</td>
<td>8</td>
<td>4.80*</td>
</tr>
<tr>
<td>Occipital Lobes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. L Middle Occipital Gyrus</td>
<td></td>
<td>-49</td>
<td>-75</td>
<td>0</td>
<td>8.22***</td>
</tr>
<tr>
<td>26. R Middle Occipital Gyrus</td>
<td></td>
<td>45</td>
<td>-82</td>
<td>0</td>
<td>7.83***</td>
</tr>
</tbody>
</table>

---

Note: *** p ≤ 0.001, ** p ≤ 0.01, * p < 0.05, corrected for multiple comparisons.
Table 5. Nonpsychopathic inmates’ imaging data for the comparison of the two Go/No Go
Conditions versus Rest. Results presented are maximum z-scores for single voxels for each
of the significant areas of activation. (L = left; R = right). Note: *** p ≤ 0.001, corrected
for multiple comparisons.

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach Coordinates</th>
<th>z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Frontal Lobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R Inferior Frontal Gyrus</td>
<td>49</td>
<td>11</td>
</tr>
<tr>
<td>2. R Superior Frontal Gyrus</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>3. L Precentral Gyrus</td>
<td>-38</td>
<td>-19</td>
</tr>
<tr>
<td>4. R Middle Frontal Gyrus</td>
<td>34</td>
<td>41</td>
</tr>
<tr>
<td>5. R Insula</td>
<td>41</td>
<td>22</td>
</tr>
<tr>
<td>6. L Medial Frontal Gyrus</td>
<td>-4</td>
<td>-4</td>
</tr>
<tr>
<td>7. L Insula</td>
<td>-38</td>
<td>22</td>
</tr>
<tr>
<td>8. L Inferior Frontal Gyrus</td>
<td>-49</td>
<td>19</td>
</tr>
<tr>
<td>9. L Superior Frontal Gyrus</td>
<td>-38</td>
<td>49</td>
</tr>
<tr>
<td>10. L Middle Frontal Gyrus</td>
<td>-34</td>
<td>60</td>
</tr>
<tr>
<td><strong>Parietal Lobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. L Postcentral Gyrus</td>
<td>-56</td>
<td>-26</td>
</tr>
<tr>
<td>12. L Superior Parietal Lobule</td>
<td>-30</td>
<td>-60</td>
</tr>
<tr>
<td>13. R Inferior Parietal Lobule</td>
<td>52</td>
<td>-38</td>
</tr>
<tr>
<td><strong>Temporal Lobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. R Superior Temporal Gyrus</td>
<td>49</td>
<td>19</td>
</tr>
<tr>
<td>16. R Middle Temporal Gyrus</td>
<td>49</td>
<td>-41</td>
</tr>
<tr>
<td>17. L Superior Temporal Gyrus</td>
<td>-64</td>
<td>-41</td>
</tr>
<tr>
<td>18. R Transverse Temporal Gyrus</td>
<td>64</td>
<td>-15</td>
</tr>
<tr>
<td><strong>Deep Grey</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. R Caudate</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>20. R Thalamus</td>
<td>8</td>
<td>-4</td>
</tr>
<tr>
<td>21. L Putamen</td>
<td>-22</td>
<td>15</td>
</tr>
<tr>
<td>22. R Putamen</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td><strong>Occipital Lobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. R Middle Occipital Gyrus</td>
<td>49</td>
<td>-68</td>
</tr>
</tbody>
</table>
Within participants, random-effects analyses of the ‘Press for all letters except X - Press for X comparison’ for control participants showed significant activation at left supplementary motor cortex \((x,y,z = -19 -4 56, Z = 4.44, p = 0.01)\) and left lateral prefrontal cortex \((x,y,z = -45 38 32, Z = 4.09, p = 0.035)\) (Figure 1). This was not observed in the nonpsychopathic or psychopathic inmates (Figure 2). However, nonpsychopaths did show a significant activation in several posterior areas including bilateral temporal lobes \((x,y,z = -41 -56 12, Z = 4.58, p = 0.017; x,y,z = 41 -52 -8, Z = 3.88 p = 0.041)\). This was not likely due to response inhibition.

Group X condition random-effects comparisons between psychopaths and nonpsychopathic inmates for the ‘Press for all letters except X - Press for X comparison’ showed no significant differences. This same comparison between psychopaths and control participants showed significantly greater activation for control participants than psychopaths in a large cluster of voxels in the left middle frontal gyrus \((Z = 3.90, p = 0.033; x,y,z = -49 41 16)\) (Figure 3). Similarly, there was significantly greater activation in a smaller area of the left inferior frontal gyrus \((Z = 4.05, p = 0.04; x,y,z = -56 38 12)\) for control participants when compared to the nonpsychopathic inmates on the ‘Press for all letters except X - Press for X comparison’.
Figure 1. Control participants’ functional imaging data superimposed on a structural image for the ‘Press for all letters except X - Press for X comparison’. The highlighting, with boxes, represents the area of voxels with significantly more neural activity during the ‘Press for all letters except X condition’ than for the ‘Press for X condition’. The left side of the brain is on the left side of images A and B. A) Transverse section with the maximum activation at voxel x,y,z = -45 38 32. The top of the image is the front of the brain. B) Coronal section showing activation at the same coordinates as A. The top of the image is the top of the brain. C) Sagittal section from the left side of the brain showing activation at the same coordinates as A. The right side of the image is the front of the brain.
Figure 2. Psychopathic inmates’ functional imaging data superimposed on a structural image for the ‘Press for all letters except X - Press for X comparison’. The image indicates that there were no brain regions with significantly greater activation for the ‘Press for all letters except X condition’ than for the ‘Press for X condition’. The left side of the brain is on the left side of images A and B.
A) Transverse section at z = 32. The top of the image is the front of the brain.
B) Coronal section at y = 38. The top of the image is the top of the brain.
C) Sagittal section from the left side of the brain at x = -45. The right side of the image is the front of the brain.
Figure 3. Functional imaging data for the comparison of psychopathic inmates and control participants, superimposed on a structural image, for the ‘Press for all letters except X - Press for X comparison’. The highlighting, with boxes, represents the area of voxels with significantly more neural activity for the control participants than the psychopathic inmates for the ‘Press for all letters except X condition’ relative to the ‘Press for X condition’. The left side of the brain is on the left side of images A and B. A) Transverse section with the maximum activation at voxel x,y,z = -49 41 16. The top of the image is the front of the brain. B) Coronal section showing activation at the same coordinates as A. The top of the image is the top of the brain. C) Sagittal section from the left side of the brain showing activation at the same coordinates as A. The right side of the image is the front of the brain.
A further regression analysis of all participants demonstrated that there was a significant negative relationship between total PCL-R score and left lateral prefrontal cortex (x,y,z = -49 38 16, Z = 4.37, p = 0.025; cluster p = 0.017) for the 'Press for all letters except X - Press for X comparison' (Figure 4) with less activation in lateral prefrontal cortex as PCL-R total score increased. The significant cluster of voxels consisted of 488 voxels with a cluster probability value of 0.017 for an area that encompassed the left middle frontal gyrus (x,y,z = -49 38 16) and the left inferior frontal gyrus (x,y,z = -49 41 -12). When the same regression analysis was performed, with removal of the item scores for the disinhibitory characteristics of the PCL-R, (including proneness to boredom, poor behavioral control and impulsivity), the same relationship between psychopathy and left lateral prefrontal cortex was observed.
Figure 4. Functional data superimposed on a structural image showing the negative relationship between total PCL-R score and brain activation for the 'Press for all letters except X - Press for X comparison'. Psychopathic and nonpsychopathic inmates and control participants are included in the analysis. Boxes highlight areas of voxels that show significantly less activation during the 'Press for all letters except X condition' as PCL-R score increases. Control participants show the greatest activity in these areas relative to the higher scoring psychopathic and nonpsychopathic inmates. The left side of the brain is on the left side of images A and B. A) Transverse section with maximum area of activation at x,y,z = -49 38 16. Top of the image is the front of the brain. B) Coronal section showing activation at the same coordinates as A. The top of the image is the top of the brain. C) Sagittal section from left side of brain showing activation at the same coordinates as A. Right side of the image is the right side of the brain.
4.2 Schizophrenic patients and matched control participants:

4.2.1 Demographic Data

There were no significant differences between groups for the NART or Quick Test scores (F(1,16) = 0.024, p = 0.88; F(1,16) = 0.06, p = 0.81, respectively). Table 6 provides a summary of mean scores for age, PCL:SV, NART and Quick scores. TLC-I scores revealed no significant differences between schizophrenic patients and control participants (F(1,15) = 2.84, p = 0.113). A oneway ANOVA showed a significant difference between control participants and schizophrenic patients with SSPI score (F(1,16) = 4.79, p = 0.044). The mean SSPI score for the schizophrenic patients was 4.3 (S.D. = 5.94) with a range from 0 to 18. No control subject scored above 0.

4.2.2 Behavioral Data

Table 7 summarizes the behavioral data for errors of commission and reaction time to correct responses for both schizophrenic patients and control participants. An ANOVA of the errors of commission revealed a significant main effect of condition (F(1,16) = 9.321, p = 0.008) with more errors occurring during the 'Press for all letters except X condition'. This was mainly due to the schizophrenic patients (F(1,8) = 6.78, p = 0.031) rather than the control participants (F(1,8) = 2.588, p = 0.146). However, there was no significant difference between groups or interaction of group by conditions for errors of commission (F(1,16) = 2.435, p = 0.138; F(1,16) = 1.659, p = 0.216, respectively).

Omission errors were rare for both groups and there were no significant group, condition or group by condition effects (all p values were over 0.063). Aside from three schizophrenic patients who had one omission error during the 'Press for all letters except X condition', no other participant made any errors of omission.
Table 6. Demographic data for matched schizophrenic patients and control participants.
PCL-R scores are total scores. National Adult Reading Test (NART) scores are calculated for premorbid IQ equivalents (Sharpe and O'Carol, 1991). Quick scores are current IQ equivalents determined from norms presented in Ammons and Ammons (1962).

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years) Mean (S.D.)</th>
<th>PCL-SV Mean (S.D.)</th>
<th>NART Mean (S.D.)</th>
<th>Quick Mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Participants</td>
<td>32.68 (7.25)</td>
<td>2.11 (1.45)</td>
<td>118.72 (3.7)</td>
<td>114.67 (10.2)</td>
</tr>
<tr>
<td>Schizophrenic Patients</td>
<td>31.67 (7.58)</td>
<td>2.17 (2.64)</td>
<td>111.19 (7.49)</td>
<td>102.75 (9.91)</td>
</tr>
</tbody>
</table>
Table 7. Behavioral data for matched schizophrenic patients and control participants.

Errors of commission are responses to No Go stimuli within 900 ms of stimulation presentation. Mean reaction times are measured in milliseconds and include all correct responses within 900 ms of stimulus presentation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Commission Errors</th>
<th>Reaction Time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“Press for X”</td>
<td>“Press for all</td>
</tr>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>letters except</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X” Mean (S.D.)</td>
</tr>
<tr>
<td>Control Participants</td>
<td>1.30 (0.71)</td>
<td>2.56 (1.88)</td>
</tr>
<tr>
<td></td>
<td>387 (38)</td>
<td>405 (33)</td>
</tr>
<tr>
<td>Schizophrenic Patients</td>
<td>1.44 (1.51)</td>
<td>5.22 (5.17)</td>
</tr>
<tr>
<td></td>
<td>410 (56)</td>
<td>426 (53)</td>
</tr>
</tbody>
</table>
An ANOVA of the reaction times revealed a significantly longer reaction time for the 'Press for all letters except X condition' than for the 'Press for X condition' (Main effect of condition, $F(1,16) = 25.529, p < 0.000$). There was no significant difference between groups ($F(1,16) = 0.003, p < 0.959$) or interaction of group by condition ($F(1,16) = 1.291, p < 0.274$).

4.2.3 Imaging Data

For both schizophrenic patients and for control participants, fixed-effects comparisons of both the Go/No Go conditions with rest revealed activation of dorsolateral prefrontal cortex bilaterally, the supplementary motor cortex, pre-motor cortex and sensorimotor cortex, parietal lobe, anterior cingulate and temporal lobe (Table 3 and 8).

Comparison between participant groups employing the random-effects model revealed significantly greater activation in right inferior temporal gyrus in schizophrenic participants than control participants for the 'Press for all letters except X - Press for X comparison' (Figure 5). Post hoc testing using the random-effects model within each participant group demonstrated that the difference between groups reflected greater activity in this region for the 'Press for all letters except X - Press for X comparison' in schizophrenic patients (at $x,y,z = 56 -19 -16, z = 4.53, p = 0.00001$, uncorrected; $p = 0.014$, corrected) (Figure 6), while there was a trend for increased activity in this region for the opposite 'Press for X - Press for all letters except X comparison' in the control participants (at $x,y,z = 60 -22 -16, z = 3.34, p = 0.004$, uncorrected, $p = 0.321$, corrected) (Figure 7).
Table 8. Schizophrenic patients' imaging data for the comparison of the two Go/No Go conditions versus Rest. Results presented are maximum z-scores for single voxels for each of the significant areas of activation. (L = left; R = right). Note: *** p ≤ 0.001, corrected for multiple comparisons.

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach Coordinates</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frontal Lobes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. L Superior Frontal Gyrus</td>
<td>-4</td>
<td>8</td>
<td>48</td>
<td>9.12***</td>
<td></td>
</tr>
<tr>
<td>2. L Precentral Gyrus</td>
<td>-49</td>
<td>0</td>
<td>48</td>
<td>8.92***</td>
<td></td>
</tr>
<tr>
<td>3. R Inferior Frontal Gyrus</td>
<td>56</td>
<td>11</td>
<td>32</td>
<td>8.62***</td>
<td></td>
</tr>
<tr>
<td>4. R Precentral Gyrus</td>
<td>49</td>
<td>0</td>
<td>48</td>
<td>8.47***</td>
<td></td>
</tr>
<tr>
<td>5. L Inferior Frontal Gyrus</td>
<td>-60</td>
<td>11</td>
<td>24</td>
<td>8.27***</td>
<td></td>
</tr>
<tr>
<td>6. R Superior Frontal Gyrus</td>
<td>34</td>
<td>60</td>
<td>-4</td>
<td>8.08***</td>
<td></td>
</tr>
<tr>
<td>7. Medial Frontal Gyrus</td>
<td>0</td>
<td>-15</td>
<td>52</td>
<td>7.95***</td>
<td></td>
</tr>
<tr>
<td>8. R Insula</td>
<td>41</td>
<td>19</td>
<td>-4</td>
<td>7.77***</td>
<td></td>
</tr>
<tr>
<td>9. L Middle Frontal Gyrus</td>
<td>-49</td>
<td>41</td>
<td>24</td>
<td>7.42***</td>
<td></td>
</tr>
<tr>
<td>10. R Middle Frontal Gyrus</td>
<td>26</td>
<td>52</td>
<td>-12</td>
<td>7.40***</td>
<td></td>
</tr>
<tr>
<td><strong>Parietal Lobes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. R Superior Parietal Lobule</td>
<td>41</td>
<td>-56</td>
<td>52</td>
<td>8.66***</td>
<td></td>
</tr>
<tr>
<td>12. L Postcentral Gyrus</td>
<td>-41</td>
<td>-38</td>
<td>60</td>
<td>8.46***</td>
<td></td>
</tr>
<tr>
<td>13. L Inferior Parietal Lobule</td>
<td>-38</td>
<td>-52</td>
<td>52</td>
<td>8.26***</td>
<td></td>
</tr>
<tr>
<td>14. R Inferior Parietal Lobule</td>
<td>41</td>
<td>-49</td>
<td>40</td>
<td>7.80***</td>
<td></td>
</tr>
<tr>
<td>15. L Precuneus</td>
<td>-26</td>
<td>-68</td>
<td>48</td>
<td>7.57***</td>
<td></td>
</tr>
<tr>
<td>16. R Inferior Parietal Lobule</td>
<td>52</td>
<td>-34</td>
<td>48</td>
<td>7.31***</td>
<td></td>
</tr>
<tr>
<td>17. L Supramarginal Gyrus</td>
<td>-64</td>
<td>-41</td>
<td>28</td>
<td>7.27***</td>
<td></td>
</tr>
<tr>
<td>18. R Postcentral Gyrus</td>
<td>64</td>
<td>-19</td>
<td>20</td>
<td>6.69***</td>
<td></td>
</tr>
<tr>
<td><strong>Temporal Lobes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. R Middle Temporal Gyrus</td>
<td>52</td>
<td>-49</td>
<td>4</td>
<td>8.24***</td>
<td></td>
</tr>
<tr>
<td>20. R Superior Temporal Gyrus</td>
<td>64</td>
<td>-34</td>
<td>20</td>
<td>7.92***</td>
<td></td>
</tr>
<tr>
<td>21. L Transverse Temporal Gyrus</td>
<td>-60</td>
<td>-15</td>
<td>12</td>
<td>7.77***</td>
<td></td>
</tr>
<tr>
<td>22. L Superior Temporal Gyrus</td>
<td>-56</td>
<td>15</td>
<td>-8</td>
<td>7.75***</td>
<td></td>
</tr>
<tr>
<td>23. L Middle Temporal Gyrus</td>
<td>-52</td>
<td>-41</td>
<td>4</td>
<td>5.73***</td>
<td></td>
</tr>
<tr>
<td><strong>Occipital Lobes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. R Middle Occipital Gyrus</td>
<td>49</td>
<td>-68</td>
<td>0</td>
<td>8.59***</td>
<td></td>
</tr>
<tr>
<td>25. L Middle Occipital Gyrus</td>
<td>-49</td>
<td>-71</td>
<td>0</td>
<td>8.32***</td>
<td></td>
</tr>
</tbody>
</table>
Figure 5. Functional imaging data for the comparison of schizophrenic patients and control participants, superimposed on a structural image, for the 'Press for all letters except X - Press for X comparison'. The highlighting, with boxes, represents the area of voxels with significantly more neural activity for the control participants than the schizophrenic patients for the 'Press for all letters except X condition' relative to the 'Press for X condition'. The left side of the brain is on the left side of images A and B. A) Transverse section with the maximum activation at voxel x,y,z = 56,-19,-16. The top of the image is the front of the brain. B) Coronal section showing activation at the same coordinates as A. The top of the image is the top of the brain. C) Sagittal section from the right side of the brain showing activation at the same coordinates as A. The right side of the image is the front of the brain.
Figure 6. Schizophrenic patients' functional imaging data superimposed on a structural image for the 'Press for all letters except X - Press for X comparison'. The highlighting, with boxes, represents the area of voxels with significantly more neural activity during the 'Press for all letters except X condition' than for the 'Press for X condition'. The left side of the brain is on the left side of images A, B and D. A) Transverse section with the maximum activation at voxel $x,y,z = 56 -19 -16$. The top of the image is the front of the brain. B) Coronal section showing activation at the same coordinates as A. The top of the image is the top of the brain. C) Sagittal section from the right side of the brain showing activation at the same coordinates as A. The right side of the image is the front of the brain. D) Transverse section showing activation at $z = 16$. 

A

B

C

D
Figure 7. Control participants’ functional imaging data superimposed on a structural image for the ‘Press for X - Press for all letters except X comparison’. The highlighting, with boxes, represents the area of voxels with significantly more neural activity during the ‘Press for X condition’ than for the ‘Press for all letters except X condition’. The left side of the brain is on the left side of images A and B. A) Transverse section with the maximum activation at voxel x,y,z = 60 -22 -16. The top of the image is the front of the brain. B) Coronal section showing activation at the same coordinates as A. The top of the image is the top of the brain. C) Sagittal section from the right side of the brain showing activation at the same coordinates as A. The right side of the image is the front of the brain.
4.3 *Psychopathic Inmates and Schizophrenic Patients*

4.3.1 Behavioral Data

An analysis of the variance in the number of errors of commission revealed a significant main effect of condition for the two groups of participants with more errors being made during the 'Press for all letters except X condition' than during the 'Press for X condition' ($F(1,14) = 4.59, p = 0.05$). Neither the differences among groups nor the group x condition was significant ($F(1,14) = 2.25, p = 0.154$; $F(1,14) = 0.062, p = 0.81$, respectively).

Similarly, for the reaction time data, there was a significant effect of condition; the reaction times were longer in the 'Press for all letters except X condition' than in the 'Press for X condition' ($F(1,14) = 32.26, p = 0.000$). Neither the differences among groups nor the group x condition interactions was significant ($F(1,14) = 0.211, p = 0.653$; $F(1,14) = 1.176, p = 0.296$, respectively).

4.3.2 Imaging Data

It appeared from the separate analyses reported above that the psychopathic inmates and the schizophrenic patients exhibited different patterns of neural activity during performance of the two Go/No Go conditions. A direct comparison between these two groups was performed for the 'Press for all letters except X - Press for X comparison'. Random-effects analysis did not reveal a significant group difference in activation after stringent correction for the multiple comparisons performed during an analysis of the whole brain. However, right and left dorsolateral prefrontal cortex and inferior lateral temporal gyrus, were significantly more activated in schizophrenic patients than in psychopathic inmates, with z-scores of 3.74, 3.35, and 2.78, respectively (Figure 8).
Figure 8. Functional imaging data for the comparison of schizophrenic patients and psychopathic inmates, superimposed on a structural image, for the 'Press for all letters except X - Press for X comparison'. The highlighting, with boxes, represents the area of voxels with significantly more neural activity for the schizophrenic patients than the psychopaths for the 'Press for all letters except X condition' relative to the 'Press for X condition'. The left side of the brain is on the left side of images A, B and D. A) Transverse section with the maximum activation at voxels $x,y,z = -48\ 38\ 12$ and $x = 46\ 38\ 12$. The top of the image is the front of the brain. B) Coronal section at $y = 38$. The top of the image is the top of the brain. C) Sagittal section at $x = -48$ (left). The right side of the image is the front of the brain. D) Sagittal section at $x = 46$ (right). The right side of the image is the front of the brain.
5. Discussion

5.1 Behavioral Responding

Reaction times were significantly longer in the ‘Press for all letters except X condition’ than in the ‘Press for X condition’, indicating that the ‘Press for all letters except X condition’ was the more difficult condition for all groups of participants. Because the Go/No Go task involved inhibitory processes, it seems reasonable to conclude that this increased difficulty was due to an increase in the inhibitory processing required for response inhibition.

There were no significant differences between the inmate groups and the control participants in the number of errors of commission or omission. However, there was a trend for a negative relationship between PCL-R score and errors of commission; that is, the higher the PCL-R score the greater the number of errors. Several other researchers found that psychopaths made more errors of commission in Go/No Go tasks than did nonpsychopaths (Lapierre et al., 1995; Newman et al., 1987; Newman and Kosson, 1986). It is possible that the relatively small number of subjects in the present study did not provide enough power for behavioral effects to emerge. However, the fact that significant fMRI group differences did emerge suggests that there is less neural activation during inhibition of a simple response in psychopaths than in control individuals.

Task complexity might also be a factor accounting for the fact that other behavioral studies found differences between psychopaths and control participants, whereas the present study did not. The version of the Go/No Go paradigm used by Lapierre et al., (1995) included a spatial component, while Patterson and Newman (1993) used punishment and reward to motivate participants. Given the nature of fMRI procedures, it was not possible to include these particular manipulations in the task. As noted above, the task was purposely
made relatively easy for all participants. It is possible that a more difficult task would allow for the emergence of group differences in behavior (errors of commission) that would match the group differences in neural activation. The schizophrenic patients did not make significantly more errors of commission than did the control participants. However, the schizophrenic patients made more errors of commission during the ‘Press for all letters except X condition’ than during the ‘Press for X condition.’ Other researchers have found schizophrenic patients make more errors of commission than do control individuals on standard Go/No Go tasks or other tasks of response inhibition (Hodgins, Cote and Toupin, 1998; Smith et al., 1998; Frith et al., 1991; McGrath, 1992). The lack of significant difference between the schizophrenic patients and the control participants may have been due to the large variance in the performance of the schizophrenic patients. In addition, the use of small samples probably made it difficult for significant behavioral differences to emerge.

There were no significant behavioral differences between the psychopathic inmates and the schizophrenic patients. Again, more power might have resulted in the detection of significant group differences.

5.2 Response Inhibition Imaging Data

The imaging data were very interesting both for the Go/No Go compared to Rest conditions and for the ‘Press for all letters except X - Press for X comparison’. All groups of participants produced a similar pattern of neural activity for the comparison of the two Go/No Go conditions with Rest conditions using a within-group fixed-effects analysis. The areas of activation were similar to those identified in other imaging studies of Go/No Go tasks (Casey et al., 1997; Rubia et al., 1996; Kawashima et al., 1996), and included the
motor cortex, premotor cortex, supplementary motor cortex, bilateral dorsolateral prefrontal cortex and certain parts of parietal and temporal cortices. These areas correspond to the parts of the brain responsible for several different aspects of the Go/No Go procedure, including, preparation and initiation of movement, movement itself, detection of the stimuli, working memory of the instructions, and attention to the stimuli and instructions.

This comparison with rest does not involve response inhibition alone, but rather includes all aspects of the Go and No Go trials of the Go/No Go conditions. However, comparison of the two Go/No Go conditions with the Rest period may not be the best way to assess group differences in the neural activation associated with response inhibition. The problem is that it is not clear what the most informative baseline task is for fMRI block design studies. It may be more informative to investigate response inhibition by comparing the two Go/No Go conditions.

In general, Go/No Go tasks involve responding to a stimulus and refraining from responding to another stimulus (e.g. green light = Go; red light = No Go). The Go/No Go task used in the present study was designed to ensure that the specific areas of the brain responsible for response inhibition could be identified. This was accomplished by using two conditions of the Go/No Go task. A response set was first established (Press for X) and then that response was withheld while responding to all other letters (Press for all letters except X). This placed heightened demands on inhibitory mechanisms responsible for response inhibition during the ‘Press for all letters except X condition’ and presumably subtracting the ‘Press for X condition’ from the ‘Press for all letters except X condition’ would reveal areas of the brain related to response inhibition. The increased demands were confirmed by the significantly longer reaction times, over all groups of participants, for the ‘Press for all letters except X - Press for X comparison’. The results from the imaging data from the
control participants also confirmed that there was an increase in activation during the 'Press for all letters except X condition', relative to the 'Press for X condition'. This difference was observed in bilateral (greater in the left) dorsolateral prefrontal cortex, providing further evidence that the dorsolateral prefrontal cortex plays a major role in response inhibition (Konishi et al., 1998; Kiehl et al., in press; Liddle, Smith and Kiehl, 1999).

These results correspond to the event related fMRI data observed by Liddle, Smith and Kiehl (1999) who found that there was bilateral dorsolateral prefrontal cortical activation during the No Go trials of a Go/No Go task. Konishi et al (1998) found that there was right dorsolateral prefrontal cortical activation during the No Go trials of a Go/No Go task, using colored squares as stimuli. The use of color may explain why Konishi et al., (1998) found greater right than left dorsolateral prefrontal cortex activation, while the use of letters produced greater left than right dorsolateral prefrontal cortex activation in the present study.

The dorsolateral prefrontal cortex is also involved in other executive cognitive functions, including memory, attention and planning (Petrides et al., 1993; Posner and Dehaene, 1994; Ingvar, 1985). Although both Go/No Go conditions were designed to have a similar amount of motor activity and information processing, including memory and attention, and the task was relatively easy, it is not likely that these functions were completely independent.

Fuster (1996, 1997) suggests that the cortex of the dorsolateral prefrontal convexity provides the cognitive substrate of motor action by sustaining the interdependent functions that are indispensable for the organization and integration of temporally separate items of perception and action into goal-directed thinking and behavior. Response inhibition is one more part of this temporal integration of behavior that now can be localized to the
dorsolateral prefrontal cortex.

In light of the evidence from neuroimaging studies of Go/No Go tasks, it is curious that some clinical observations have emphasized the role of orbital prefrontal cortex insult rather than dorsolateral prefrontal cortex insult in disinhibitory behavior (Damasio, 1985; Eslinger and Damasio, 1985; Blumer and Benson, 1975, Damasio et al., 1990; Tranel and Damasio, 1994). However, the disinhibition that arises from lesions of the orbital prefrontal cortex involves instinctual drives, motivations and emotions, and is fostered by a concomitant loosening of conventional moral restraints and a loss of the capacity to gauge the effects of one’s behavior on the social interactions with others (Fuster, 1997). The task used in this study did not involve much emotion or external motivation, but rather dealt mainly with response inhibition. This study was unable to examine fully the role of the orbital prefrontal cortex because this part of the brain is the most difficult to image with fMRI. The difference in magnetic susceptibility between brain and the air in the paranasal sinuses, and brain and bone in the skull base, leads to significant susceptibility artifact in ventromedial prefrontal cortex (Forster et al., 1998).

Furthermore, most functions of the prefrontal cortex are phenomena of distributed processing rather than the products of isolated cerebral locations. Pandya and Yeterian (1996) have suggested that the bi-directional intrinsic connections interrelating ventral and medial prefrontal cortex areas with lateral regions contribute in various ways to the process of decision-making by providing, for example, response modulation, planning and sequencing behavior, and attentional influences. They propose that the common problem for all organisms in making appropriate and withholding inappropriate responses under changing circumstances (i.e. response inhibition) is controlled by a combination of the ventromedial prefrontal region and lateral prefrontal region. The former serves functions
that are crucial for the adaptability of behavior for survival, including the emotional and motivational formulation of decisions, and the latter provides further elaboration with regard to the decision-making process and the action in response to that decision.

5.3 Psychopathy Brain Imaging

This explanation of the role of the dorsolateral prefrontal cortex in response inhibition helps to understand the data obtained from the psychopathic and nonpsychopathic criminals in the present study. The increased activity in the left dorsolateral prefrontal cortex for the ‘Press for all letters except X - Press for X comparison’ observed in control participants was not observed in the psychopathic inmates. In fact, both inmate groups showed significantly less increase in activity in the left dorsolateral prefrontal cortex than did control participants. However, nonpsychopathic inmates differed from control participants in only one specific voxel (inferior frontal gyrus, p < 0.04, corrected), whereas the psychopathic inmates significantly differed from the control participants in a larger cluster of 735 voxels encompassing both the inferior frontal gyrus and the middle frontal gyrus.

The regression analysis confirmed that with increased PCL-R score, there was a decrease in left dorsolateral prefrontal cortical activation during the ‘Press for all letters except X condition’ relative to the ‘Press for X condition’. It might be expected that this negative relationship between PCL-R score and left dorsolateral prefrontal cortex activation would be accounted for by PCL-R Factor 2, as Factor 2 includes the disinhibitory characteristics of psychopathy. However, it was not possible to separate the two factors because of their high correlation with one another (r = 0.84 for this sample). Nonetheless, it was possible to remove the item scores for three of these disinhibitory characteristics of the
Nonpsychopathic inmates did not reach the PCL-R research criteria for psychopathy, but their PCL-R scores still were relatively high, indicating that they had a substantial number of psychopathic features, including disinhibition. It is clear from these Go/No Go data that although the nonpsychopaths showed a deficit in left lateral prefrontal cortex, it was not nearly as marked as it was in psychopaths. It is important to consider the confounding variable of violence in these two groups of subjects. Both groups of inmates had substantial backgrounds of violent behavior. It will be necessary to further assess the role of violence on these fMRI data.

This left dorsolateral prefrontal deficit might be cautiously extrapolated to the real life disinhibitory characteristics of the psychopath, as well as to the problems observed in the so-called executive functions, including poor planning, and decision-making. It is well known that psychopaths make poor decisions and do not plan ahead or consider the consequences of their actions (Newman et al., 1987; Patterson and Newman, 1993; Hare, 1993). The present data provide a possible neurobiological basis for these aspects of psychopathy.

This is the first fMRI study of well-defined psychopaths and it is the first study that provides clear support for the hypothesis that there is reduced neural activity in the left dorsolateral prefrontal cortex when psychopaths perform a Go/No Go task. Other researchers have attempted to localize a frontal lobe deficit in psychopathy but results have been controversial and inconclusive.

For example, Gorenstein (1982) found that psychopaths performed more poorly than
nonpsychopaths on several frontal tasks, including the Wisconsin Card Sorting Task (WCST), the Necker cube, and a sequential matching memory task. However, Hare (1984) was unable to replicate these findings. Howland et al., (1993) added rewards and punishment to the WCST and found that psychopaths made more perseveration errors than did nonpsychopaths. Raine (1985) found no significant differences between psychopaths and nonpsychopaths on a continuous performance task. Harpur (1991) reported no significant differences between psychopaths and nonpsychopaths on a Stroop task. However, Lapierre et al (1995) found that psychopaths performed more poorly than did nonpsychopaths on a Go/No Go task, the Porteus maze, and a test of smell, all thought to involve ventral frontal cortex.

The differences observed in the current fMRI study were in the neural mechanisms used for response inhibition rather than in performance errors. Behavioral data, including both errors of commission and omission, were similar for the psychopathic, nonpsychopathic inmates and the control participants.

The neuroimaging data from the present study are in line with other evidence that psychopathy is associated with reduced cerebral asymmetry for certain cognitive functions. Most research involving cerebral asymmetry in psychopaths has examined the processing and organization of verbal material. Jutai and Hare (1983), measuring autonomic and electrocortical responses, found that nonpsychopathic criminals exhibited a consistent left hemisphere superiority on verbal tasks involving either simple recognition or semantic categorization of visually presented words. Psychopathic criminals also showed left hemisphere superiority when the task involved simple recognition of the verbal stimuli, but an unexpected right hemisphere superiority when the task involved categorization into a semantic class. It appeared that words were categorized more efficiently by the left
hemisphere in nonpsychopaths, and by the right hemisphere in psychopaths.

Hare and McPherson (1984) used a verbal dichotic listening task to show that psychopaths had a smaller right ear advantage than did nonpsychopaths but did not differ from them in overall performance. This led to the speculation that some language processes are not as lateralized in psychopaths as they are in nonpsychopaths. Raine, O’Brien, Smiley, Scerbo, and Chan (1990) replicated this finding with adolescent psychopaths and nonpsychopaths.

In a subsequent study, Jutai and Hare (1983) found that as language tasks increased in complexity, nonpsychopaths relied more and more on the left hemisphere to process the information, while psychopaths relied more on the right hemisphere (Hare and Jutai, 1988). In a divided visual field (DVF) study, Day and Wong (1996) found that right-handed psychopaths and nonpsychopaths differed in the way in which they processed emotional-neutral pairs of words, one member of the pair presented in the left visual field (LVF) and the other simultaneously in the right visual field (RVF). The task was to determine the side in which the emotional word appeared. Nonpsychopaths, like control participants, performed better (fewer errors, faster reaction times) when negative words were presented in the LVF (directed to the right hemisphere) than when they were presented in the RVF, whereas psychopaths displayed a left hemisphere advantage during the task.

Mills (1995) showed that this differential lateralization is not confined to language. She recorded ERPs during performance of several tasks, including a dichotic listening task. The participants were instructed to attend to the tone presented in a given ear, following which a test series of tones was played in both ears. The participant was instructed to listen to the test tones and to indicate which of the tones previously had been heard in the designated ear. This dichotic “memory for tones” task draws heavily on left hemisphere
resources. Mills found that nonpsychopathic offenders exhibited the expected right ear advantage (correctly identified more tones that had been presented in the right ear than those that had been presented in the left ear), but that psychopathic offenders showed a slight left ear advantage. This difference was significantly correlated with PCL-R total scores ($r = 0.41$) and with Factor 1 scores.

Mills (1995) also presented the offenders with a task in which they had to mentally rotate visually presented material. This mental rotation task taps parietal lobe resources in the right hemisphere. Psychopaths and nonpsychopaths performed the task equally well. However, analysis of the ERP data yielded a surprising finding; the nonpsychopaths used right parietal resources, but the psychopaths used their right frontal cortex.

Kosson (1996) suggested that psychopathy is related to a left lateral frontal lobe deficit. He had psychopaths and nonpsychopaths perform a dual-task paradigm that required a response from either the right hand or the left hand. When the right hand was used, psychopaths displayed a trend toward classifying primary task targets less accurately than nonpsychopaths. When the left hand was used, psychopaths displayed an opposite trend toward greater accuracy.

Additional evidence that psychopaths show unusual asymmetry for processing affective linguistic stimuli comes from a recent SPECT study (Intrator et al., 1997), and from additional analyses of the data (reported by Hare, 1998). Control participants showed anterior asymmetry in rCBF during a lexical decision task, whereas psychopaths showed asymmetry in posterior regions (occipital and extrastriate cortex) but not in anterior regions. The implications of unusual asymmetries are unclear, but Geschwind and Galaburda (1987) have argued that cognitive functions are most efficient when strongly lateralized. Perhaps some aspects of the psychopath’s behavior, including impulse control, is related to
inefficient cerebral distribution of the cognitive and affective processes that control behavior (Hare, 1993; Hare 1998).

Kosson (1996) suggests that limitations in psychopaths' use of left-hemisphere processing resources provide a plausible mechanism underlying their apparent dual task deficits and some of their difficulties in shifting attention. A summary of the attention literature and psychopathy suggests that psychopaths display heightened responsiveness to cues under conditions that produce endogenous allocations of attention (Kosson and Harpur, 1997). Psychopaths may also be prone to greater or more persistent endogenous shifts of attention and/or greater interference associated with allocation of left hemisphere specific resources. Moreover, psychopaths appear to display excessively narrow attention in situations involving multiple contingencies and multidimensional stimuli. Their reduced breadth of attention may help to explain observed deficits in passive avoidance and inter-level shifts of attention (Kosson and Harpur, 1997).

Studies of patients with dorsolateral frontal syndrome have shown that an attention disorder is usually in the foreground of the syndrome (Fuster, 1997). Similarly, brain imaging studies have shown that the dorsolateral prefrontal cortex is involved in attentional processes (Posner, Grossenbacher and Compton, 1994; Hager et al., 1998). It is not likely that the results from the present study simply reflect deficits in attention, as no other attention-related areas of the brain (including anterior cingulate) were activated in the control participants. Several researchers have implicated the anterior cingulate in attention and response inhibition.

Posner and Badgaiyan (1998) stated that the most consistently activated area in attention is the anterior cingulate. Similarly, Shallice (1994) suggests that cingulate activation is central to executive attention. This has been related to situations that require
overcoming habitual responses (Posner and DiGirolmo, 1998). Although activation of SMA, lateral prefrontal cortex and basal ganglia have also been observed in these situations, anterior cingulate is activated whenever one has competing stimuli and must select one response in preference to the other possibilities. Kiehl, Liddle and Hopfinger (in press) used an ERP Go/No Go task in control participants and showed that the left lateral prefrontal cortex and the anterior cingulate are integral components of the error monitoring system of the brain. However, anterior cingulate activation was observed for errors of commission but not for correct responses. The authors concluded that these areas of activation are specific to error-related processes and not due to processes related to motor control. This coincided with the finding by Casey et al., (1997) of a strong positive correlation between the activation of anterior cingulate and the number of errors. Interestingly, Carter et al., (1998) have recently shown that the anterior cingulate is activated not only during trials in which incorrect responses are made, but also during trials in which correct responses are made under conditions involving strong response competition.

In the present study anterior cingulate activation did not occur for any group of participants for the 'Press for all letters except X - Press for X comparison'. It is likely that the task was not difficult enough and that there were too few errors to observe the anterior cingulate activation that might be related to errors of commission.

The significant difference in dorsolateral prefrontal cortex activation between psychopaths and control participants for the comparison of the two Go/No Go conditions might seem contrary to previous clinical evidence that psychopathy is related to orbital frontal deficits (Damasio et al., 1990; Blumer and Benson, 1975; Eslinger and Damasio, 1985). However, a fMRI study of the same inmates used in the present study (Kiehl et al., 1999) found that psychopaths exhibited less neural activity in several areas of the limbic
system and ventral prefrontal cortex during processing or emotional words than did nonpsychopathic inmates.

Taken together, the fMRI studies with psychopathic inmates provide additional support for Fuster's theory of frontal lobe functioning: orbital frontal cortex is related to emotional processing and dorsolateral prefrontal cortex is related to actions motivated by the orbital frontal cortex. The results also provide neurobiological support for Hare's hypo-emotionality theory of psychopathy, in which the cold-blooded behavior of the psychopath is related to faulty inhibitory and emotional processes. As Hare states, “the cortical/cognitive processes that ordinarily help to inhibit behavior are facilitated by intense emotional coloring in most people, but not in psychopaths. For them, the emotional ‘brakes’ on behavior (“conscience?”) are weak, allowing them to engage in predatory, violent acts without compunction” (Hare, 1999).

It is clear from these studies that it is not possible to localize psychopathy to one brain region. However, it is possible to hypothesize that many of the problems with executive functioning of psychopaths, including their disinhibitory behaviors, reflect inefficient neural communication and integration between the medial and lateral portions of the prefrontal cortex, and between these areas and the limbic system. The impact of these putative neurobiological anomalies may not be apparent during performance of standard intelligence and neuropsychological tests, perhaps because alternate neural systems are able to play a compensatory role. However, the lack of neurobiological integrity would make it difficult for psychopaths to inhibit inappropriate behavior in many real life situations.

5.4 Schizophrenia Brain Imaging

All schizophrenic patients demonstrated significant activation in the expected brain
regions during the performance of the Go/No Go task (Konishi et al., 1998; Liddle, Smith and Kiehl, 1999; Rubia et al., 1996; Casey et al., 1997; Kawashima et al., 1996). Bilateral prefrontal cortex, primary motor cortices, and premotor areas, as well as certain parietal and temporal regions were all activated when the Go/No Go epochs were compared with the Rest epochs. Similarly, there were significant differences in lateral temporal cortex for both the control participants and the schizophrenic patients for the ‘Press for all letters except X - Press for X comparison’. However, these differences were reversed for the two groups. The schizophrenic patients showed significantly greater activation in right lateral temporal lobe in the ‘Press for all letters except X condition’ than in the ‘Press for X condition’, whereas the control participants showed a trend for significantly greater activation in this area for the opposite comparison (‘Press for X - Press for all letters except X comparison’). The schizophrenic patients increased the neural activity related to response inhibition in the right lateral temporal lobe and in right inferior frontal gyrus, whereas the control participants showed increases in activity in bilateral dorsolateral prefrontal cortex and left supplementary motor cortex.

There was a significant difference between groups in the right lateral temporal cortex for the ‘Press for all letters except X - Press for X comparison’. This difference suggests that the schizophrenic patients required increased neural activity in right lateral temporal cortex to correctly perform the Go/No Go task. Several imaging studies have shown that response inhibition in control participants is specifically related to prefrontal cortical activity (Konishi, et al., 1998; Kawashima et al., 1996; Casey et al., 1997). However, it is possible that when this area is challenged, it is necessary to recruit other brain regions to assist with the response inhibition required to perform the task. The neuronal connections between the prefrontal cortex and the temporal lobe have been well-defined (Fuster, 1997; Pandya and
Yeterian, 1996), indicating that there is a functional connectedness between these two regions of the brain.

The imaging data from both the within-group and between-group analyses support the growing evidence that in schizophrenia there is aberrant functional connectivity between frontal and temporal cortex (Friston et al., 1996; Liddle, 1995; Liddle et al., 1997; Maguire and Frith, 1996). In the analysis of neuroimaging time series, functional connectivity has been defined as the temporal correlation between spatially remote neurophysiological events or the influence one neuronal system exerts over another (Friston et al., 1996). These results are similar to results from several brain imaging studies in which schizophrenic patients performed frontal lobe tasks. A PET study (Friston and Frith, 1995) of regional cerebral blood flow (rCBF) during various cognitive tasks has provided a starting point for delineating a pattern of functional connectivity in schizophrenia. Frith et al., (1995) demonstrated that the correlation between frontal activity and lateral temporal activity was negative in control individuals and positive in chronic schizophrenic participants, during a word generation task. In a more comprehensive analysis of the same data set, Liddle et al., (1997) showed the same correlation between frontal and temporal lobes, plus a stronger negative correlation between frontal cortex and medial parietal cortex, and weaker correlation between frontal cortex and thalamus, in schizophrenic participants than control participants.

In subsequent studies of word generation in schizophrenia, Yurgelun-Todd et al., (1996) replicated the finding of an inverse relationship between activity in frontal and temporal lobes, while Curtis et al., (1998) replicated the finding of a significantly stronger negative correlation between frontal cortex and medial parietal cortex. The findings of Frith et al., (1995) in neuroleptic-treated, chronically institutionalized schizophrenic participants
have been reproduced in neuroleptic-free, acutely psychotic individuals (Dolan et al., 1995; Fletcher et al., 1996). This replication suggests that a disruption of functional connectivity between the prefrontal and temporal cortex might reflect a core pathophysiology in schizophrenia, independent of clinical and medication status, and as such may represent a trait-marker for schizophrenia.

Several more recent functional imaging studies have added to the evidence provided by word generation studies. In a study of cerebral activity during a word learning task, Fletcher et al., (1998) found that schizophrenic participants exhibited activation of left lateral frontal gyrus but failed to exhibit normal suppression of left superior temporal gyrus. Similarly, a preliminary fMRI study of the coordination of cerebral activity during a version of the N-back working memory task (Gevins et al., 1990) demonstrated that stable, medicated schizophrenic participants with minimal symptoms did not exhibit the inverse relationship between left lateral frontal and left lateral temporal activity that is seen in control participants (Mendrek et al., 1999). Most recently, in a pilot fMRI study employing an auditory oddball discrimination task, stable schizophrenic patients showed reduced activation of right lateral frontal cortex and thalamus, and abnormally large activation of right posterior superior temporal gyrus (Kiehl, Laurens, Duty and Liddle, 1999).

These results, along with the present Go/No Go fMRI results, strongly support the hypothesis that there is an alteration in the functional connections between the frontal and temporal cortices in schizophrenic patients. This difference was present even with a very simple Go/No Go paradigm and with stable, medicated outpatients who scored similarly to control participants on both the IQ tests and the TLC-I.
5.5 Comorbidity

One of the premises of this study was that a comparison of the neural mechanisms of disinhibition in schizophrenic patients and psychopaths would help to shed light on the neural processes involved in the disinhibitory behavior of psychopaths. Although psychopathy and schizophrenia clearly are distinct clinical disorders, there are similarities between the disorganization syndrome of schizophrenia and certain characteristics of psychopathy. The disorganization syndrome of schizophrenia, characterized by formal thought disorder, and difficulty in suppressing inappropriate behavior and inappropriate affect (Liddle, 1987a,b), resembles the impulsive; irresponsible behavior, and subtle thought disorder observed in psychopaths (Williamson, 1991; Hare, 1991; Gillstrom, 1995). This putative comorbidity of psychopathy and schizophrenia has not been consistently supported by studies of psychiatric, forensic, and forensic psychiatric (Rasmussen and Levander, 1996; Gacono et al., 1995; Hart and Hare, 1989; Raine, 1992; Rice and Harris, 1995; Kiehl et al., 1999). On the other hand, the research on the topic is sparse, and the question of comorbidity remains open.

Kallman (1938) used the term “schizoid psychopaths” to describe individuals with predominantly psychopathic features who also possessed schizoid or schizophrenic-like traits. Likewise, Cleckley, in 1941, viewed psychopathy as a type of psychosis. However, Cleckley later (1976) changed his position and included “an absence of delusions and other signs of irrational thinking” in his sixteen traits of psychopathy, although his retention of the title of his book (The Mask of Sanity) implied that psychopaths were far from normal. Nedopil (1998) commented that comorbidity can be observed only if discrete categories of disorders are involved. If psychopathy and schizophrenia are viewed as dimensional, there can easily be an overlap of symptoms. Although there is some empirical evidence that
psychopathy might be a taxon, or a discrete clinical entity (Harris, Rice and Quinsey, 1994), there also is some evidence that it is better viewed as dimensional in nature (e.g., Widiger, 1998). Clearly, this issue of the comorbidity of psychopathy and psychosis is complex.

The present study is the first fMRI study to allow for a comparison of the neural processing that occurs during the same task in the two disorders. The results provide evidence that the neural circuitry involved in response inhibition is not the same for psychopathic inmates and schizophrenic patients. Even though the imaging data from the direct comparison of schizophrenic patients with psychopathic inmates did not produce significant results after correction for multiple comparisons, the areas of the brain that were expected to show differences did have high z-scores for the ‘Press for all letters except X - Press for X comparison’. Schizophrenic patients produced more activation than psychopathic inmates in bilateral dorsolateral prefrontal cortex and inferior temporal gyrus.

The results from the TLC-I also suggest a difference between the groups in cognitive processing, as the psychopathic inmates produced significantly higher total scores on the test than all other groups of participants, including the schizophrenic patients. It was surprising that the psychopathic inmates had higher scores than the schizophrenic patients. However, these patients were stable, medicated outpatients with no disorganization symptoms (assessed by SSPI measures). The significant difference between the psychopathic inmates and the control participants was not surprising. The difference was mostly a result of psychopathic inmates scoring higher than other participants on the Weakening of Goal item within the category of Impoverishment of Thinking. This item reflects a lack of drive in thinking and is manifested in a lack of normal elaboration of ideas, use of uninformative generalizations and empty speech that lacks relevant detail and/or excessive use of vacuous phrases that convey little information (Liddle, 1991). This result is consistent with previous
findings of subtle thought disorder in psychopathy (see Hare, 1998).

Although thought disorder is not a characteristic included in the PCL-R, recent research has suggested that there are anomalies in the thought and language of psychopaths. Williamson (1991) found that psychopaths used language in an odd way, with logical inconsistencies, contradictions and neologisms. Psychopaths’ narratives lacked cohesion and coherence and included derailment, confusing use of referents, and the tendency to set up the listener’s expectations and the failure to deliver. PCL-R and Thought, Language and Communication (TLC; Andreason, 1979) ratings from a criminal population were strongly correlated, and 20 of 21 psychopaths in Williamson’s study met the TLC criteria for thought disorder. Schmitt (1995) replicated these findings.

Gillstrom (1995) has also found that psychopaths performed poorly on the Proverbs Test, a test that reflects a breakdown in thought processes and is sensitive to the thought disorder associated with schizophrenia (Gorham, 1956). More recently, Brinkley et al., (1999) examined the narratives of 39 male inmates, 18 of whom were classified as psychopathic using the Hare PCL-R. As found by Williamson (1991), psychopathy was associated with a tendency to use relatively few cohesive ties per clause. Contrary to Williamson’s findings, psychopaths did not use more incompetent references than did nonpsychopaths. Thus, psychopaths made fewer attempts to make their discourse a unified whole, but when they did, they did so competently.

The results from the TLC-I scores in the present study do suggest a subtle form of thought disorder in psychopathy. However, because of the small number of participants, it is difficult to make any conclusions from these results at this time. A further study of over one hundred inmates who have completed the TLC-I is underway. Their data will be analyzed and compared with a similar number of control participants.
Although it appears that psychopathy and schizophrenia may be comorbid in some cases, this study suggests that they do not share the same neural mechanisms associated with disinhibition.

6. Conclusions

To my knowledge, this is the first study to use fMRI technology to investigate response inhibition in a well-defined group of psychopaths. The results indicate that the psychopaths performed adequately on the Go/No Go task, but that this performance was not associated with a normal increase in neural activity in dorsolateral prefrontal cortex. It is clear that additional brain imaging studies are needed to confirm this finding and to investigate other features of psychopathy that might also be associated with neural anomalies. A step in this direction is the fMRI study of emotional processing conducted with the participants in this study (Kiehl et al., 1999).

The schizophrenic patients performed poorly on the Go/No Go task, but they did not differ from control participants in the prefrontal cortical activation associated with response inhibition. In addition, the schizophrenic patients exhibited an increase in temporal lobe activity during performance of the task, whereas control participants showed a decrease in temporal lobe activity. These findings support the hypothesis that schizophrenia is associated with abnormal temporal-frontal functional connectivity. This dysconnection, rather than diminished connections, may account for the disinhibitory symptoms of schizophrenia.

Although schizophrenia and psychopathy may share several features, including disinhibition, the present results indicate that the neurobiological processes associated with these features are not the same in the two disorders.
7. References


Neuropsychology of Human Emotion, New York: Guilford Press.


Functional topography: multidimensional scaling and functional connectivity in the brain.  
Cerebral Cortex, 6, 156-164.


Psychological Reports, 2, 1-12.


Harlow, J.M. (1868). Recovery after severe injury to the head. Publication of the Massachusetts Medical Society, 2, 327-346.


Kok, A. (1986). Effects of degradation of visual stimuli on components of the event-related potentials (ERP) in Go/No-go reaction tasks. Biological Psychology, 23, 21-


dichotomy in schizophrenia. British Journal of Psychiatry, 157, 41-49.


area 8 and area 6 of the rhesus monkey induces deficits in performance of a visual
discrimination GO/NO-GO task. *Neuroscience Research, 22,* 163-177.

contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magnetic
Resonance in Medicine, 14,* 68-78.

Ogawa, S., Tank, D.W., Menon, R., Ellermann, J.M., Kim, S., Merkel, H. and
brain mapping using MRI. *Proceedings of the National Academy of Sciences USA, 89,*
5951-5955.

Pandya, D.N. and Barnes, C.L. (1987). Architecture and connections of the frontal
lobe. In E. Perecman (Ed.), *The Frontal Lobes Revisited* (pp. 41-72). New York: IRBN
Press.

Pandya, D.N. and Yeterian, E.H. (1996). Morphological correlations of human and

cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm.
*Proceedings from the National Academy of Sciences USA, 87,* 256-259.

Patterson, C.M. and Newman, J.L. (1993). Reflectivity and learning from aversive
events: toward a psychological mechanism for the syndromes of disinhibition.
*Psychological Review, 100,* 716-736.

*Psychophysiology, 31,* 319-330.

Peterson, S.E., Fox, P.T., Snyder, A.Z. and Raichle, M.E. (1990). Activation of
extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science*, 249, 1041-1044.


Berlin.


monkey prefrontal cortex. Experimental Brain Research, 100, 165-169.


Distinct neurophysiological mechanisms for manic and cycloid psychoses: evidence from a P300 study on manic patients. Acta Psychiatrica Scandinavica, 98, 459-66


and Social Psychology, 43, 769-774.


8. Appendix 1

List of Abbreviations

EEG. Electroencephalography.
EPI. Echo planar imaging.
ERP. Event related potentials.
FOV. Field of view.
FMRI. Functional magnetic resonance imaging.
PET. Positron emission tomography.
PCL:SV. Psychopathy Checklist – Screening Version.

‘Press for X condition’. Go/No Go condition requiring participants to “Press for X”.

‘Press for all letters except X condition’. Go/No Go condition requiring participants to ‘Press for all letters except X’.

SMA. Supplementary motor area.
SPGR. Spoiled gradient echo.
SPM. Statistical parametric mapping.
TE. Echo time.
T2. T2 relaxation time constant.
T1. T1 relaxation time constant.
T2*. Relaxation time constant.
TLC-I. Thought, language and communication index.
TR. Repetition time of fMRI pulse sequence.