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An experimental and functional neuroimaging investigation into the effects of nicotine on prepulse inhibition of the startle reflex in schizophrenia.

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Abstract

Prepulse inhibition of the startle reflex (PPI) refers to the reduction of the startle response to a startling stimulus (pulse), when such a pulse is preceded by a stimulus of lower intensity (prepulse). PPI is believed to reflect the working of a sensory gating mechanism, which by limiting excess sensory input, protects information processing. PPI is impaired in psychiatric populations where such inhibitory processes are compromised, including schizophrenia. The excessive rate of smoking seen in people with schizophrenia is thought to reflect an attempt at self-medication. Nicotine increases PPI in animals as well as healthy humans, and combined such observations suggest the possibility that smoking may provide a way of restoring some of the cognitive abnormalities of schizophrenia as indexed by deficient PPI.

This hypothesis was central to the investigations conducted as part of this thesis. The effects of nicotine on PPI were tested in people with schizophrenia and healthy controls. In the first study of its kind the neural correlates of the enhancing effect of nicotine on PPI were studied in both populations using functional magnetic resonance imaging. Similar motivational factors for smoking behaviour in healthy smokers were explored in a longitudinal study of smokers wishing to quit. Finally, a parallel study delved into the psychological significance of PPI by investigating the tenet that PPI reflects an automatic response, a quality particularly useful to schizophrenia research.

Nicotine enhanced PPI in both healthy and schizophrenic subjects. Furthermore the neuroimaging data confirmed this modulatory effect to involve the hippocampus. Startle amplitude, but not PPI, during smoking was found to predict successful smoking cessation in healthy subjects. Finally, supporting evidence was found for the involuntary status of PPI. This thesis lends support to the hypothesis that smoking may represent an attempt to self-medicate symptoms in schizophrenia.

CHAPTER 1

1.0 Introduction to the thesis.

This thesis explores the cross-species phenomenon of prepulse inhibition of the startle reflex (PPI) - widely believed to provide an operational measure of sensorimotor gating - in healthy human subjects and patients with schizophrenia. Sensorimotor gating refers to a process set at the early stages of information processing whereby sensory input is filtered in order to reduce demands on a limited capacity information processing system. PPI is compromised in a number of psychiatric populations characterised by a reduced ability to screen sensory input such as schizophrenia. The investigations performed as part of this thesis span three major areas of interest in PPI research: the modulation via pharmaceutical challenges of PPI in both healthy subjects and psychiatric patients; the quest to find the neural substrates of PPI in humans, and the need to improve our understanding of the psychological meaning of PPI through the testing of the purported involuntary status of PPI. This overview offers a brief outline of the background and rationale to the investigations conducted as part of this thesis.

1.1 Background

The concept of schizophrenia describes a vast range of psychotic disorders characterised by disturbed thought, emotion and behaviour. The heterogeneity of this disorder is perhaps best illustrated by the fact that any two individuals with the diagnosis of schizophrenia might not have a single symptom in common. Historically, considerable efforts have been made to identify a common 'core' deficit which could underlie some, if not all of these varied symptoms. Profound attentional and information processing deficits have long been recognised as key features of schizophrenia (e.g. Kraepelin, 1921; McGhie and Chapman, 1961; Braff et al., 1993). Such disturbances have been hypothesized as resulting from the breakdown of an inhibitory mechanism, which in normal functioning is able to reduce processing

demands on a limited capacity information processing system. This inhibitory mechanism is thought to function at the interface of automatic and controlled processing, and the breakdown of such a process would cause an intrusion into conscious experience of otherwise unconscious (information) processing (e.g. Hemsley, 1987; Gray et al., 1991). In ascribing the abnormal conscious experiences which typify the symptoms of schizophrenia (and which by definition are so uniquely human) to a dysfunction at a preconscious level, it has been possible to develop animal models of this disorder. Such models have proved invaluable to the testing and development of novel antipsychotic agents as well as providing a means of directly investigating neural mechanisms underlying the abberant behaviour characteristic of schizophrenia.

The hypotheses of this thesis have originated from the neuropsychological model of Braff, Geyer and Swerdlow which postulates a sensorimotor gating deficit in schizophrenia. This model describes how the breakdown of such a sensory information filtering system can give rise to the sensory overload and cognitive fragmentation observed in schizophrenic patients, using evidence from animal and human studies of PPI of the startle response. The startle response is thought reflect changes in attentional processes in humans (Anthony and Putnam, 1985), and shows a number of forms of plasticity, of which prepulse inhibition (PPI) refers to the attenuation of the startle response to a startle stimulus (pulse), when such a pulse is preceded by a stimulus of lower intensity (prepulse). Schizophrenic patients show reduced PPI (e.g. Braff et al., 1978; Braff et al., 1992). This failure to show normal PPI has been interpreted as reflecting the inability to filter sensory input due to a malfunctioning sensorimotor gating system (e.g. Braff et al., 1992). In normal functioning, the attenuation of the response to the pulse is thought to reflect the need to devote processing resources to the prepulse; any other incoming information is processed at a reduced level (e.g. McGhie and Chapman, 1961; Braff and Geyer, 1990). PPI is thought to be a largely automatic process, a particularly useful quality in schizophrenia research where inferences of deficits on non-automatic tasks are confounded by illness-related motivational issues. However it remains that the exact

relationship between PPI and information processing and sensory gating is still unclear. Furthermore a number of recent studies have challenged the involuntary status of PPI, suggesting that under certain conditions PPI may be susceptible to attentional modulation.

Animal studies have shown how dopamine agonists can disrupt PPI (review Swerdlow et al., 1992a; Sipes and Geyer, 1994). This effect is reversed by neuroleptic drugs, moreover the capacity of such drugs to restore normal startle inhibition correlates with their antipsychotic potency (Swerdlow et al., 1994a). Accordingly such drug-induced disruption of PPI has been hailed as an invaluable instrument in the evaluation of drugs for the treatment of psychosis. Interestingly, nicotine has been shown to enhance PPI in the rat (Acri et al., 1994) which raises the possibility that nicotine might have anti-psychotic properties and that at least some of the cognitive deficits characteristic of schizophrenia might be normalised or treated succesfully with nicotine. In support of this suggestion nicotine has already been shown to exert a normalising effect on deficient gating of the acoustically elicited P50 wave (a paradigm related to PPI which taps sensory gating) in schizophrenic patients (Adler et al.,1993). Furthermore, research into the effects of nicotine on PPI in humans has revealed that this drug is capable of amplifying PPI in healthy smokers and non-smokers (Kumari et al., 1996; 1997b).

In the light of these findings, this thesis set out to further probe the relationship between nicotine and modulation of the startle reflex in both healthy and schizophrenic populations. The reason for exploring the effects of smoking on startle and PPI in healthy subjects was to address the question of why some people and not others smoke, or indeed why some and not others become addicted to cigarettes. Thus the enhancing effect of nicotine in healthy smokers was explored by testing whether smoking behaviour in some individuals represented a need to restore a trait-like cognitive deficit as indexed by startle and PPI, by conducting a longitudinal study of smokers wishing to quit.

The thesis went on to address the question whether nicotine would also improve PPI in patients with schizophrenia. If this were the case such findings would lend support to the widely held tenet that the excessive smoking behaviour exhibited by the majority of such patients might reflect an attempt at self-medication, and so importantly provide a further impetus to the development of nicotinic agonist treatments for this disorder. Potentially such a treatment strategy would not only prove a useful advance in antipsychotic medicine but also, by providing an alternative to smoking, reduce the harmful effects of excessive chronic smoking in this population.

The prospect of developing nicotinic agonist treatments for schizophrenia would demand a further understanding of the neural basis of the effects of nicotine, therefore a further important investigation of this thesis concerned establishing the neural mechanisms via which nicotine improves PPI (as mentioned above) as these are still unknown. Until the advent of functional neuro-imaging techniques the study of brain mechanisms of PPI had only been possible in animals. Therefore a further aim of this thesis was to deploy functional Magnetic Resonance Imaging (fMRI) to expose the areas of the brain which are involved in the enhancing effect of nicotine on PPI.

Finally, in tandem to these investigations a study was conducted to test the involuntary status of PPI in a paradigm designed to measure the effect of prepulse detection (and thus awareness of the prepulse) on PPI. As mentioned above, a number of reports have challenged the degree to which PPI represents an involuntary response, by demonstrating attentional modulation of PPI. However it has also been claimed that the stimulus onset asynchronies (i.e. time between onset of prepulse and onset of pulse) at which PPI is generated are too short to allow for such conscious modulation of this response. This issue is further complicated by the fact that parametric characteristics of the PPI paradigms used often vary between studies, making direct comparisons problematic. Therefore it was important to investigate whether paying attention to the prepulse would alter PPI as measured by the

paradigms used in this thesis. Clearly any such findings would bear on interpretation of nicotine-induced changes in PPI, particularly given that the attention enhancing effects of this drug are well documented.

1.2 Organization of thesis

The theoretical background to the investigations conducted as part of this thesis are considered in chapters 2, 3 and 4. Thus in chapter 2 the concept of schizophrenia is discussed by first outlining symptoms and diagnostic issues before delving into aetiological accounts of this disorder which span neuroanatomical, neurobiological and neuropsychological explanations. Chapter 3 offers an overview of the PPI paradigm by discussing parametric influences on PPI before considering the observations of abnormalities of PPI in psychiatric populations and schizophrenia in particular. Next the evidence outlining the neural substrates of this response is considered before discussing the impact of pharmacological challenges on PPI in animals and humans. The chapter concludes with a comparison of PPI with the P50 gating response, a paradigm related to PPI. Findings from P50 studies have been influential in developing the hypotheses tested in this thesis. Chapter 4 is dedicated to nicotine, and describes basic pharmacological issues before considering the literature on nicotine and schizophrenia and on nicotine and sensorigating. Finally, in chapter 5 the hypotheses tested in this thesis are described in detail.

Chapters 6,7,8 and 9 describe the investigations performed as outlined above. They are formatted such that each stands alone as a paper as per the requirements of City University. The inevitable consequence of this is that aspects of the individual introductions and methods sections may in some cases be repetitive. The reader is asked to bear this in mind! Thus chapter 6 describes the longitudinal study of the effects of nicotine on startle and PPI in healthy smokers wishing to quit using an acoustic startle paradigm. Chapter 7 is a study into the effects of subcutaneous nicotine on tactile prepulse inhibition in healthy male smokers, non-smokers and schizophrenic patients. A selection of these subjects subsequently underwent the

same experimental procedure in the MRI scanner, which is described in the following chapter 8. Finally chapter 9 considers the effects of prepulse detection on PPI. Prepulse detection had been assessed in both the tactile and acoustic paradigms used in this thesis, but only the latter paradigm allowed a meaningful comparison of occasions on which prepulses had been detected with those when they had not been detected. Therefore the focus of this chapter is on the acoustic paradigm. The tactile data, as well as a comparison of measures obtained from both paradigms, are discussed as a postscript to this chapter.

Chapter 10 offers a summary of the findings from the above investigations before discussing their contributions and future directions within the wider context of PPI and schizophrenia research.

CHAPTER 2: Schizophrenia

2.0 History of the concept of schizophrenia

The current definition of the concept of 'schizophrenia' has evolved from a history of separate and sometimes contradictory lines of research. This chapter will give a brief overview of the medley of past definitions, and how these have led to the most widely used diagnostic tool today.

Kraepelin's first attempts to comprehensively classify mental disorders in the late nineteenth century are still of huge influence today. His system was centred on the belief that psychological problems, like physical problems, are symptomatic of an underlying disease, and he proposed that diagnosis should be based on description of symptoms. Thus Kraepelin in 1896, introduced the term 'dementia praecox' to link three recognised forms of insanity: catatonia, hebephrenia and `dementia paranoides. The term embodied what Kraepelin saw to be the common core of these three disorders: 'dementia' referring to progressive intellectual deterioration and 'praecox' specifying this process took place early, that is not at the expected age. Bleuler's (1908) concept of 'schizophrenia' was a departure from Kraepelin on two counts in that he did not deem early onset nor inevitable descent into dementia to be key features of the disorder. With less emphasis on the course of the disorder, Bleuler aimed to describe what he considered to be pivotal to the condition: the 'splitting apart of mental faculties'. To Bleuler, the fundamental abnormality underlying the varied disturbances of the disorder was that of the 'loosening in the fabric of thought', epitomised by what he considered to be the most essential symptom of schizophrenia: thought disorder. Thus Bleuler's more theoretical approach contrasted sharply with Kraepelin's, in that he tried to explain the mechanisms underlying disturbances of cognition, emotion and volition.

Despite the unifying nature of both classification systems, Bleuler and Kraepelin proposed that most patients showed a predominance for either the paranoid,

hebephrenic, catatonic or simple subtypes during the course of their illness. They also agreed on what they considered to be the universal stages in the time course of schizophrenia. Firstly that the disorder most commonly commenced with a brief spell of symptoms followed by improvement before further symptoms presented. Secondly, that as the disorder progressed, eventually a state of permanent deterioration would be reached. Thus a tentative distinction was drawn between the early or acute stage of the disorder, and the chronic stage, thought to start around two years after initial onset of symptoms. The acute stage was described as the period in which new symptoms (typically delusions and hallucinations) develop as well as existing symptoms worsen. These florid symptoms then tend to decrease in the next, chronic stage of the disorder where they are replaced by apathy, emotional withdrawal and symptoms reflecting the general deterioration and development of deficits characteristic of this stage (Kraepelin, 1913a; International Pilot Study of Schizophrenia,WHO 1979).

Both Bleuler and Kraepelin's conceptualisations of the disorder were mainly descriptive in nature and were of limited diagnostic value. Indeed international comparison studies into diagnostic practices soon exposed vast differences between countries, highlighting a need for operational diagnostic criteria (e.g. Cooper et al., 1972). One of the most influential contributions to this cause was made by Schneider in 1958. From the many symptoms described by Kraepelin and Bleuler, Schneider selected eight which he considered to be of first rank importance. These 'first rank symptoms' were of diagnostic value; in the absence of any overt brain disease, Schneider suggested the presence of any of these symptoms to be strongly indicative of the diagnosis of schizophrenia. He proposed that a lowering of the boundary between the self and the outside world might underlie at least a number of these symptoms, a notion also embraced by Fish (1962) and Sims (1988) in subsequent years. Schneider's criteria were found to be overly stringent, with an international survey of patients with acute schizophrenia showing only 58% to conform to his criteria (WHO 1973). Nonetheless these early attempts at classifying schizophrenia have been fundamental to all later efforts at categorising the symptoms of

schizophrenia, and the three initially proposed by Kraepelin (paranoid, disorganised (hebephrenic) and catatonic subtypes) still feature in the most current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, 1994).

2.1 Symptoms of schizophrenia

The wide diversity of symptoms of schizophrenia has prompted a number of attempts to sub-categorize the disorder according to prevalent symptom clusters. Following many unspecified references to 'positive' and 'negative' symptoms in schizophrenia (e.g. Mayer-Gross et al., 1954; Fish, 1962) Wing and Brown (1970) were the first to formally make this distinction, which has subsequently been honed by such authors as Strauss et al. (1974) and Andreasen (1982a; 1982b). Positive symptoms include those considered abnormal by their presence (i.e. hallucinations, delusions and thought disorder) while negative symptoms refer to the absence of a behaviour normally present (i.e. poverty of speech, avolition, anhedonia). This distinction led a number of theorists to question whether it signified two separate disorders, different levels of severity of the same condition or indeed represents different phases of the disease pattern (e.g. Hemsley, 1988). A number of diagnostic tools were specifically designed to assess these symptom clusters, including the Scales for the Assessment of Positive and Negative Symptoms (SANS and SAPS; Andreasen, 1982b) and Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

An influential contribution was made by Crow (1980), his novel emphasis being on classifying symptoms rather than categorising patients. He proposed the distinction of Type I and Type II schizophrenia and suggested that these subtypes represented distinct pathological processes. Type I primarily featured positive symptoms, such as hallucinations, delusions and incoherence of speech. This subtype was characterised by acute illness, good response to antipsychotic treatment, intact cognitive functioning and was most likely to stem from dopaminergic overactivity. Type 2 schizophrenia featured negative symptoms such as flattening of affect and poverty of

action and speech, all related to cognitive deficits and thought to reflect structural brain abnormalities. Generally there is also poor outcome. Crow did not rule out that patients might show symptoms from both Types, or that there could be a progression from Type I to Type II.

However Crow's classification system was challenged by a number of theorists for being too simplistic (e.g. Mortimer et al., 1990; Manshreeck and Maher, 1991) leading to other approaches. One of these has been the application of factor analysis to test the relationship between symptom clusters (e.g Kulhara et al., 1986; Liddle, 1987b; Mortimer et al., 1990; Toomey et al., 1997). While these studies consistently confirmed the relative independence of positive and negative symptoms and therefore strengthened the validity of this dichotomy, they also revealed a third factor which comprised of inappropriate affect, poverty of content of speech and other aspects of formal thought disorder. Liddle (1987b) named these three factors 'psychomotor poverty' (to correspond with Crow's negative symptoms), 'reality distortion' (to include hallucinations and delusions, i.e. mainly abnormal *experiences*) and 'disorganisation' (including incoherence and incongruity, i.e. abnormal *behaviours* of a positive nature).

2.2 Diagnosis of schizophrenia

DSM IV is the most extensively used diagnostic tool today, closely followed by the definition provided by the International Classification of Disease, 10th edition (1990) (ICD 10). The emphasis of both systems is purely on the description of symptoms, their main purpose being to aid (and unite) clinical practice and communication. Neither system purports to offer aetiological explanations nor insight into the development of the disorders they describe. Diagnosis is based on presenting clinical signs and symptoms, with the emphasis being on psychotic symptoms such as hallucinations and delusions as the defining characteristics of the disorder. Intrinsic to this approach is that it presents a simplified view of the disorder, especially in the

way the significance of negative symptoms is played down. And so while the reliability of diagnoses based on these methods is recognised, their validity remains an issue. For instance, some of the symptoms emphasized by these systems are not exclusive to schizophrenia, such that for example hallucinations as well as delusions also occur in mood disorders and dementias (Andreasen, 2000). The consequence of such a criterion-based approach for schizophrenia research is the inevitable bias towards perhaps atypical patient groups. As well as DSM-IV and ICD 10, diagnostic tools used today include the earlier mentioned interview-based schedules designed to assess psychotic symptoms, such as the PANSS (Kay et al., 1987), SANS and SAPS (Andreasen, 1982b) as well as the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962).

The debate whether schizophrenia is a unitary disorder or represents a group of disorders remains ongoing. None of the above mentioned attempts at separating patient groups in schizophrenia have achieved exclusive clusters or groups. The positive-negative dichotomy has proven to be the most robust, and features in almost all areas of theory and research in schizophrenia. But even this distinction is a symptom based one, patients more often than not suffering symptoms from both groups. Proponents of the 'unitary' disorder model have been faced with a considerable challenge in their pursuit of the fundamental dysfunctions underlying the wide ranging and wildly varying set of symptoms observed in this disorder, a matter not helped by the fact that the most widely used tools for defining the disorder actively encourage fragmentation. The following sections of this chapter offer a review of recent approaches in the quest for the aetiology of this heterogenous disorder.

2.3 Aetiology of schizophrenia

2.3.1 Genetic component

It has been accepted for some time that there is a large genetic component to the lifetime risk of developing schizophrenia. Perhaps the most comprehensive of the many studies providing support for this genetic hypothesis, was the meta analysis performed by Gottesman (1991). Compared to the 1% prevalence of schizophrenia in the general population, this report confirmed an increased risk for developing the disorder as a function of consanguinity: from 2% for third degree relatives (i.e. cousins) to between 35-58% for monozygotic twins (Gottesman 1991). Critically, some of the studies incorporated into this meta analysis had already eliminated the possible effects of a shared environment by investigating the concordance rates of adopted twins reared separately (e.g. Heston 1966; Kety et al., 1976). The most recent twin study to date conducted at the Maudsley Hospital, London (Cardno et al., 1999) has confirmed concordance rates for monozygotic twins to be 42.6 percent with rates for dizygotic twins at 0 per cent, both findings consistent with the range reported by the earlier Gottesman analysis. Nonetheless, as the concordance rate for even genetically identical individuals is much lower than 100%, the most such studies can claim is that a genetic *predisposition* to develop this disorder can be inherited. Accordingly, a study by Gottesman and Bertelsen (1989) showed offspring from non-symptomatic monozygotic twins of probands to show the same risk of developing the disorder as the offspring from the affected twins.

Considerable attempts have been made to identify a specific gene or genes which would predispose to schizophrenia. One such approach is that of linkage where families with a history of schizophrenia are tested for a genetic marker for the disorder. Linkage studies have failed to identify a single gene, implicating a number of 'susceptibility genes' instead (for a review see Kirov and Murray, 1997). A different approach in which specific genes thought to be involved in the disorder are identified and then compared in patients and controls, have suggested some influence

of the the HLA locus on chromosome 6 as well as D3 dopamine and 5-HT2a receptor genes (Wright et al., 1996). In summary, while no single major gene for schizophrenia has been identified, current evidence suggests a polygenic model for the inheritance of this disorder, in other words that a number of genes of small effect are involved.

2.3.2 Structural brain abnormalities

Speculations that brain abnormalities might underlie the symptoms of schizophrenia stem back to Kraepelin and Bleuler's days. The search for such neural abnormalities has since progressed from the early attempts at identifying a single brain region at the heart of the disorder, to recent models implicating many brain regions and which propose disrupted neural circuitry.

Initial attempts to find brain abnormalities linked to the aetiology of the disorder were disappointing, both in terms of the absence of any glaringly obvious abnormalities, and in terms of the poor replicability of any such findings - possibly attributable to the crude measurement tools used at the time (e.g. Jacobi and Winkler, 1928). It was not until the advent of the new technology of in-vivo brain imaging that interest in this field resurged, delineated by a study by Johnstone and colleagues (1976) which confirmed ventricular enlargements in chronic schizophrenia using computerized tomography (CT). Since then many CT investigations followed, with several meta-analyses of these studies confirming dilation of lateral ventricles (Raz, 1993), a finding also upheld with the more recent technology of magnetic resonance imaging (MRI; for reviews: Lawrie et al. 1997; Lawrie and Abukmeil, 1998; Fannon et al., 2000; Shenton et al., 2001). Most notably, longitudinal studies have demonstrated such enlargements to be present before onset of symptoms, and have not shown ventricular enlargement to be progressive (e.g. Gattaz et al., 1991) implying that this abnormality is most likely to be neurodevelopmental (e.g. O'Callaghan et al., 1988; Weinberger, 1988)

The actual meaning of such findings remains somewhat elusive. Firstly ventricle size is not useful in terms of diagnostic value, as there is considerable overlap in this measurement between control subjects and patients. There does not appear to be strong evidence for functional consequences of such differences in brain structure, with virtually equal numbers of studies succeeding and failing to find associations of ventricle size with clinical symptoms. Of those who did, Owens et al. (1985) showed positive correlations between ventricular size and tardive dyskenesia and impaired social functioning, Weinberger et al. (1980) poor response to drug treatment, Andreasen et al. (1982c) an association with primarily negative symptoms and van Os et al. (1995) a correlation with premorbid social adaptation. Therefore while not of diagnostic value, ventricular enlargement may be a useful indicator of long-term therapeutic outcome (e.g. Raz et al., 1993; van Os et al., 1995).

Aided by the superior spatial resolution offered by MRI it has become apparent that such ventricular enlargement (in particular of the left temporal horn section of the lateral ventricles) most likely reflects reduced volumes of the surrounding limbic and temporal lobe structures, such as the amygdala-hippocampal complex and parahippocampal gyrus (for a review of MRI findings in schizophrenia see Shenton et al., 2001). Post mortem and MRI studies have since reported numerous abnormalities throughout the brain. These include findings of reduced whole brain volume in schizophrenia (review Wright et al., 2000) and reports of a reduction in frontal lobe volume, although these have not always been replicated (Wright et al., 1999). Reports of pathological abnormalities in subcortical structures include that of tissue loss in the thalamus via postmortem investigations (Pakkenberg, 1990; Katsetos et al., 1997) and through magnetic resonance imaging averaging (Andreasen et al., 1994a). Findings of enlargements of basal ganglia structures (caudate, putamen, globus pallidus) in schizophrenic patients have been attributed (in contrast to other reported structural differences) to exposure to typical antipsychotic medication (e.g. Chakos et al., 1994; 1995). Irregularities in other brain areas include reports of volume reduction of the cerebellum (e.g. Andreasen et al., 1994b; Levitt et al., 1999), although a number of studies have since shown the opposite effect (e.g.

Seidman et al., 2000). Furthermore the well established cerebral asymmetry (i.e. larger in the left than right hemisphere) of the planum temporale in the normal brain, does not occur in schizophrenic brains. This has led to some speculation of the disorder resulting from a failure to lateralize language to the left hemisphere (Crow, 1997; 2000).

2.3.3 Functional brain abnormalities

Many of the above mentioned structural abnormalities are subtle, and vary considerably between individuals. They are also widespread throughout the brain, defying any potential use in terms of providing diagnostic markers for the disorder. Instead the heterogeneity of these loci draws striking parallels with the heterogenous nature of the disorder. The fact that brain abnormalities in schizophrenia are so widespread not only contests any possibility of a single location underlying the pathology of the disorder, but points to a disturbance of neural circuitry and neurotransmitter systems, suggesting that defective neural connectivity might play a causal role in schizophrenia (e.g. Andreasen et al., 1998; Friston et al., 1996). In abandoning the 'single locus' approach to schizophrenia, recent research has instead progressed from relating structural irregularities to specific symptoms, to more recently, the unveiling of dysfunctional neural circuits underlying the various cognitive dysfunctions of the disorder, greatly aided by the emergence of functional neuroimaging techniques.

Thus the symptom based approach has confirmed hypothesized links between prefrontal cortex abnormalities and negative symptoms (Andreasen et al., 1986; 1992), temporal lobes and hallucinations (Barta et al., 1990; McCarley et al., 1993 and Silbersweig et al., 1995) and the planum temporale and thought disorder (Shenton et al., 1992). Using cognitive activation paradigms, a large number of studies have now compared regional blood flow using fMRI in patients and control subjects (review see Mitchell et al., 2001). In this way Curtis et al. (1999) were able to demonstrate schizophrenia-related abnormalities in the language processing

network by showing hypofrontality, or reduced frontal lobe activation, as well as a comparative increase in activation in the right fusiform gyrus of patients during a verbal fluency task. Intriguingly fMRI has also been used to expose abnormal patterns of activation in patients when compared to controls on tasks in which patients performed normally, consistent with the idea of different neural organisation in schizophrenia (e.g. Ramsey et al.,1999). Such studies highlight the huge potential of fMRI for uncovering irregularities of neural circuitry in the living brain.

2.3.4 Neurodevelopmental vs neurodegenerative disorder?

Initial reports of gliosis (reactive astrocytosis; a marker of neuronal death in neurodegenerative diseases) in schizophrenic brains raised the possibility that such brain structure changes could have occurred at later stages of life, suggesting the disorder could be progressive and neurodegenerative in nature (e.g. Stevens, 1982). However many recent reports have refuted this, in particular a report by Bruton et al. (1990) confirming gliosis only to be present in those patients who also showed separate neuropathological abnormalities, therefore offering support to the neurodevelopmental model. Recent investigations aiming to reveal the neural changes underlying the observable structural findings have focussed on the extended limbic system (i.e. the hippocampus, dorsolateral prefrontal cortex and cingulate gyrus) (for reviews see Bogerts, 1999; Lawrie and Abukmeil, 1998, Nelson et al., 1998; Bachus and Kleinman, 1996). Much of this evidence supports the neurodevelopmental model of schizophrenia, in that the observed abnormalities (specifically disarray of hippocampal neurons and maldistribution of white matter neurons) could only take place in utero. However such findings are far from robust, having failed to be consistently replicated (Harrison, 1999). In contrast other reported cytoarchitectural changes (smaller neurons, e.g. in hippocampus, Zaidel et al., 1997a, and dorsolateral prefrontal cortex (Rajkowska et al., 1998); synaptic and dendritic abnormalities (for a review see Harrison, 1999) could possibly arise at later stages in life.

On the whole the above evidence points to a neurodevelopmental origin of schizophrenia. However this raises the question of the role of these brain structure abnormalities, present at such an early stage, in the manifestation of a disorder in which the symptoms occur so much later in life and typically follow a pattern of relapse and remission.

2.4 Functional neurobiology

2.4.1 Dopamine hypothesis

Certainly one of the most influential aetiological accounts for the symptoms of schizophrenia has been the dopamine hypothesis. This theory proposes that an excess of central dopaminergic transmission underlies the positive symptoms of the disorder (e.g. Gray, 1998). First put forward some 30 years ago, this theory is primarily based on two lines of evidence, namely the correlation between the efficacy of neuroleptic drugs and their ability to block dopamine transmission (specifically D2 receptors, e.g. Creese, Burt and Snyder, 1976; Seeman et al., 1976), and the capacity of dopamine agonists such as amphetamine to induce psychotic symptoms as well as intensify symptoms of schizophrenic patients (e.g. Young and Scoville, 1938; Connell, 1958; Angrist, Lee and Gershon, 1974).

However despite such extensive evidence, the exact mechanisms of this dopamine abnormality remain elusive (Davis et al., 1991; Joyce and Meador-Woodruff, 1997). Conclusions are complicated by the fact that antipsychotic medication itself seriously affects the dopamine system, making interpretations of studies of medicated patients problematic. While D2 receptor numbers are demonstrably higher in schizophrenic patients, studies of drug-naive patients using positron emission tomography (PET) do not show this (Nordstrom et al., 1995), indicating that the observed increased densities in medicated patients must reflect neuroleptic effects (Zakzanis and Hansen, 1998). Other dopaminergic sites have been implicated: increases in D4

receptors in schizophrenia (Seeman et al., 1993) as well as changes in D1 (Okubo et al., 1997) and D3 (Gurevitch et al., 1997) receptors. However these findings have been challenged and so remain contentious.

More recent evidence points towards hyper responsiveness of dopaminergic neurons in schizophrenia. Thus, using positron emission tomography (PET) dopamine synthesis has been shown to be increased in drug-naive schizophrenic patients, relative to controls (e.g. Hietala, 1994). Furthermore, single photon emission computerised tomography (SPECT) and PET studies showed increased release of dopamine in the basal ganglia following amphetamine challenge in drug-naive patients relative to controls (Breier et al., 1997; Abi- Dargham et al., 1998) indicating a presynaptic dopaminergic abnormality in schizophrenia.

2.4.2 5-Hydroxytryptamine

The suggestion that 5-Hydroxytryptamine (5 H-T or serotonin) might play a part in schizophrenia was first put forward in the mid 1950's following observations that serotonin agonists (such as lysergic acid diethylamide, LSD) induced psychosis-like symptoms in normal individuals. Now many of the current atypical antipsychotics feature an anti-serotonergic component, and indeed in a number of these drugs this anti-serotonergic action outweighs any antidopaminergic properties (i.e. clozapine, olanzapine, qetiapine, risperidone, sertindole, ziprasidone; Meltzer, 1999). These drugs appear to be more efficacious, have a broader action, in that they treat negative as well as positive symptoms of schizophrenia, and produce less noxious side effects than typical antipsychotics (Tamminga, 1998). The improved antipsychotic action of such drugs has been attributed to their affinity for the $5\text{-}HT_{2A}$ receptor in particular (Meltzer, 1996; 1999). Further evidence that this particular receptor is involved in schizophrenia comes from studies confirming reduced expression of this receptor in the frontal cortex of schizophrenic patients (e.g. Harrison, 1999b) and findings that polymorphisms of the gene are a risk factor for this disorder (Williams et al., 1997).

2.4.3 Glutamate

Phencyclydine (PCP or 'angel dust'), amongst other antagonists of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor produces a psychosis very similar to schizophrenia (Javit and Zukin, 1991) which has led to the hypothesis of a role for glutamate in schizophrenia. A considerable number of findings support changes in glutamatergic function in schizophrenia, with the majority of evidence pointing to glutamatergic hypofunction (e.g. Halberstadt, 1995; Bachus and Kleinman, 1996). However reports of both reduced expressions of hippocampal non-NMDA (e.g. Kerwin et al., 1990) and increased expressions of cortical NMDA receptor subtypes (Roberts et al.,1997) have made any straightforward conclusions about glutamatergic involvement problematic (Tamminga, 1998).

2.4.4 Acetylcholine

Although there is little direct evidence to implicate abnormal cholinergic transmission in psychiatric disorders, an increased understanding in recent years of the interaction of ACh with other transmitter systems has fuelled speculations of the role of this transmitter in schizophrenia. Cholinergic transmission plays a vital role in the functioning of regions known to be aberrant in schizophrenia, particularly so in the hippocampal formation (Hyde and Crook, 2001). Two subtypes of cholinergic receptors are recognised, on the basis of their selectivity of response to either muscarine or nicotine. Evidence for involvement of the former type in schizophrenia is modest: some of the atypical antipsychotics such as clozapine and olanzapine have known antimuscarinic properties, however it is not clear whether this aspect is directly related to the ability of these drugs to reduce schizophrenic symptoms (e.g. Hyde and Crook, 2001). Post mortem studies have reported abnormal expression of muscarinic receptors in schizophrenic brains, with increased numbers in the putamen and orbital frontal cortex (Owen et al., 1981) coupled with decreased numbers in striatum, hippocampal formation and frontal cortex (Crook et al., 2000; Bennett et al., 1979). While the behavioural effects of this receptor sub-type are known to

include the modulation of functions which are abnormal in schizophrenia, the lack of drugs capable of selective action at individual muscarinic receptor sites has made it difficult to infer how and why these particular receptors might be of influence.

Research testing the possibility of nicotinic-cholinergic involvement in schizophrenia has been largely driven by the observation of excessive rates of smoking in this population. Chapter 4 provides a detailed account of the putative role of the nicotinic cholinergic system in schizophrenia.

2.5 Neuropsychological explanations of schizophrenia

Following Bleuler's early attempts to isolate the basic defect of schizophrenia, considerable effort has been made to identify an abnormality of a basic mental process or pattern of such abnormalities which could underlie the many and varied symptoms of this disorder. Influential examples of this quest are Frith (1987) and Hemsley's (1987) models of abnormal cognitive functioning in schizophrenia. Even more ambitiously, attempts have been made to construct models which integrate both these cognitive and neural aspects of schizophrenia (e.g. Gray et al., 1991; Frith and Done, 1988; Joseph et al., 1979; McKenna, 1987; Swerdlow and Koob, 1987a). The following offers an overview of the most influential of these theories.

2.5.1 Information processing and attention in schizophrenia

One of the main areas such research has focussed on is that of information processing and attention, disturbances of which have been cited in schizophrenia since Kraepelin and Bleuler's days. Thus Kraepelin (1913) noted that patients were unable to sustain attention and appeared to be unable to resist diverting their attention to trivial environmental features. Bleuler saw the main deficit to be one of disturbed association processes, resulting in patients being unable to order their relevant thoughts and ignore irrelevant ones. In keeping with Bleuler's ideas, subsequent

theorists located this deficit to a basic information 'filtering' mechanism, which when faulty could result in the wide range of cognitive and behavioural problems seen in schizophrenia (e.g. Payne, 1959). The following excerpts from the widely quoted compilation by McGhie and Chapman (1961) of often eloquent descriptions by patients themselves, illustrate the actual experience of being schizophrenic:

> *" ..everything seems to grip my attention, though I am not particularly interested in anything…."; "things are coming in too fast. I lose my grip and get lost…."; "I listen to sounds all the time. I let all the sounds come that are there…."; "I am attending to everything at once, consequently I do not attend to anything…"*
> (from McGhie and Chapman, 1961)

McGhie and Chapman confirmed that the common thread in these self reports was one of disturbed attentional and perceptual processes. Significantly, Chapman (1961) suggested that the interference of irrelevant information in schizophrenia was not, as had been suggested previously, a general one, but instead related to difficulties with processing stimuli related to the object of attention.

Subsequent theories of attentional disturbances in schizophrenia have benefitted greatly from the progress made in the development of models of normal information processing, of which the major contributing ones will be briefly outlined here. The prevailing theme of models of normal cognition is that irrelevant or redundant information is prevented from reaching conscious awareness in order to reduce demands on a limited capacity information processing system. Thus Shiffrin and Schneider (1977) put forward the distinction between 'automatic' and 'controlled' processes. Controlled processing would occur when a task or novel situation required conscious, controlled attention. They suggested that through prolonged practice such tasks could eventually be performed 'automatically', thus shifting from controlled to

automatic processing. Automatic processing, in not placing demands on the limited capacity system as it does not require conscious attention, is economical, accordingly many automatic processes may operate at the same time. The capacity for controlled processing on the other hand would be limited. More recent suggestions are of a continuum (e.g. Kahneman and Treisman, 1984) and/ or dynamic interaction (Sternberg, 1996) between these two types of processing.

Another major influence has been Broadbent's (1958; 1971; 1977) model of selective attention. Briefly, Broadbent proposed that parallel streams of incoming information enter the information processing system via a sensory buffer. This system being of limited capacity, the filter mechanism acts as a protective device, only allowing relevant information through, while retaining irrelevant information for later processing. Broadbent distinguished between stimulus set (filtering) and response set (pigeon holing). Filtering would involve the selection of incoming information for attention on the basis of simple characteristics *not* present in irrelevant stimuli. This being a rather crude selection phase, irrelevant features could easily infiltrate the system. At the pigeon holing stage incoming information from the environment is integrated with stored information, which results in 'expectancies' or 'response biases'. Pigeon holing therefore depends heavily on past experiences of the type of context the individual is presently in and in doing so, biases the expectations of possible input from such an environment, according to which potential response patterns are prepared.

The above models have in common a 'filtering' or 'inhibitory' mechanism which is protective of information processing by inhibiting the awareness of irrelevant information. It is the weakening of such mechanisms which is seen by many to be at the core of schizophrenic cognitive abnormalities. In a review of contemporary theories of the cognitive abnormalities of schizophrenia, Hemsley (1987) revealed remarkable similarities in terms of the attribution of the deficit to the failure of inhibitory mechanisms and inability to use stored regularities:

1. The basic cognitive defect.....it is an awareness of automatic processes which are normally carried out below the level of consciousness" (Frith, 1979, p.233)
2. There is some suggestion that there is a failure of automatic processing in schizophrenia so that activity must proceed at the level of consciously controlled sequential processing" (Venables, 1984, p.75)
3. Schizophrenics "concentrate on detail, at the expense of theme" (Cutting, 1985, p.300)
4. Schizophrenics show "some deficiency in perceptual schema formation, in automaticity, or in the holistic stage of processing" (Knight, 1984, p.120)
5. Schizophrenics show a "failure of attentional focussing to respond to stimulus redundancy" (Maher, 1983, p.19)
6. "Schizophrenics are less able to make use of the redundancy and patterning of sensory input to reduce information processing demands" (Hemsley, 1985)
7. "Schizophrenics do not maintain a strong conceptual organisation or a serial processing strategy.....nor do they organise stimuli extensively relative to others (Magaro, 1984, p.202)

Table 2.1: Current views on the nature of schizophrenics' cognitive impairment. Taken from Hemsley (1987)

2.5.2 Frith's (1979, 1987) model

Such hypotheses have focussed mainly on accounting for the positive symptoms of this disorder such as hallucinations, delusions and thought disorder. Thus Frith (1979) suggested that the (positive) symptoms of schizophrenia result from a defective filter, which allows processes which are normally unconscious to reach awareness. In practice such an interference of normally preconscious information would result in the patient being faced with multiple possible interpretations of events or words. Symptoms would reflect an attempt to make sense of such an inundation of input, such that auditory hallucinations would arise from early incorrect interpretations of sounds made at the preconscious level (which are normally rejected), intruding into awareness. Similarly, delusions would represent attempts to rationalise excessive perceptual information which under normal circumstances would be prevented from reaching conscious awareness. Clearly both phenomena

would rely on the patient's ability to construct the complex belief system necessary to enable interpretation of such excessive input, and Frith suggests that premorbid IQ may be a determining factor in the ability to do so. Thought disorder represented the output equivalent, in that at the level of speech production many possible word options would present. The inability to ignore inappropriate options which had penetrated conscious awareness, would lead to the characteristic loss of thread of conversation.

One of the main problems with Frith's theory is that it does not easily account for the observed coherence of the content of patients' hallucinations nor the specificity of their delusions: awareness of preconscious representations of external and internal input would be expected to lead to arbitrary hallucinatory experiences, similarly why should attempts to make sense of such varied input lead to the typically grandiose or paranoid delusions?

Frith (1987) later criticised his early account for its assumption that behaviour could only result from conscious processes, and so reformulated his theory to propose that normally unconscious processes 'interfere' because higher level conscious processes fail to control them. With more emphasis on the output stage, he proposed that positive symptoms were related to an inability to *monitor* the source of self-generated actions, as well as incorporating an aetiological account for negative symptoms in that they reflected an inability to *carry out* such actions. His model demarcates two routes to action: those which are initiated in response to external stimuli, and those which are generated from within by willed action. In the former, a stimulus is encountered and, according to previous experience (i..e. long term memory), it is determined "what implications the stimulus has for action". This route is referred to as 'stimulus intention' and resembles Broadbent's process of 'pigeonholing'. The other route is that of 'willed intention', where the individual has a particular goal according to which an appropriate action or response is decided, again in consultation with previous experience. Between both components he conceptualises a monitor system, which "can detect mismatch between intentions and actions at a very early

stage". This system, when operational, would compare the suitability of actions (as started via the willed intention route) within the current context (as established by the stimulus intention route). A mismatch would result in unsuitable actions being inhibited. Frith believes that the 'monitor'- to - 'willed action' link is impaired in schizophrenia. This would mean two things: inappropriate actions would not be inhibited, and these (unwilled) actions would not be recognised as ones own. According to Frith's view, thoughts and internal speech also arise from the above outlined action system, this enables an explanation of certain positive symptoms, such that the inability to recognise internal speech as ones own could logically give rise to symptoms such as thought insertion and hallucinations.

2.5.3 Hemsley's (1987) model

Hemsley's (1987) explanation has focussed more directly on Broadbent's (1977) concept of pigeonholing. In essence he suggests that: it is a "weakening of the influences of stored memories of regularities of previous input on current perception which is postulated as basic to the schizophrenic condition" (in Hemsley, 1987, p182). This failure of past experiences to influence current perceptions then is the cause of the infiltration of irrelevant or redundant material into consciousness. In terms of Broadbent's model this suggests that schizophrenics are unable to establish response biases, and in terms of Shiffrin and Schneider's model suggests that in schizophrenia the inhibitory processes which normally protect the limited capacity information processing system from redundant, automatic information are deficient.

Hemsley's model accounts for delusions by suggesting that (over-) awareness of irrelevant features would lead the individual to seek explanations for these occurrences. Hallucinations on the other hand are proposed to reflect "intrusions into conscious experience of material from long term memory, this then being attributed to an external source" (Hemsley, 1987). Thought disorder is accounted for by suggesting that the inability to integrate previous information with current context (which effectively causes the intrusion of redundant information by disabling an

inhibitory mechanism) would result in disruption of the flow of thought and indeed discourse. Hemsley's suggestion is that the negative symptoms of schizophrenia represent a coping strategy and therefore are secondary to the positive symptoms, such that by withdrawing, the individual has learnt to lessen the anguish caused by the basic cognitive impairment.

Hemsley (1994) insisted that any model presuming to account for the schizophrenic symptomatology should provide "testable predictions concerning performance in experimental tasks", and in addition that such performances should be unambiguously related to the proposed (cognitive) deficit, i.e. not accountable for by generalised poor performance. Answering to both criteria, he predicted that the schizophrenic impairment in generating response biases could, under certain circumstances, result in better performance compared with control subjects. This prediction has been borne out using a number of paradigms, of which one will be briefly described here. Latent Inhibition (Lubow, 1968) refers to the slowed acquisition of a learned response to a conditioned stimulus (CS) that occurs if that CS had previously been experienced to have no consequence. This retardation in subsequent learning is thought to occur because, due to the previous noncontingent experience, an individual must "unlearn the irrelevance" of the CS, before learning that it now actually predicts an (unconditioned) stimulus. As, in Hemsley's terms, schizophrenic patients do not experience the influence of past regularities (i.e. that the CS has no consequence), the prediction is that they will not show this retardation in learning and instead will learn the new association *faster* than control subjects. This effect has been demonstrated by a number of authors such as Baruch et al. (1988) and Gray et al. (1992). Hemsley's notion of intrusive irrelevant or redundant information in schizophrenia has further been demonstrated in paradigms designed to test inhibitory processes such as negative priming (e.g. Beech et al., 1989) and Kamin blocking (e.g. Jones et al., 1992).

2.6 Animal models of schizophrenia

2.6.1 Gray et al.'s model

Gray et al.'s (1991) model of the neuropsychology of schizophrenia combines evidence spanning neuroanatomical, neurochemical, behavioural and psychological data. In essence it poses that structural abnormalities in the brain (limbic system) cause a functional neurochemical imbalance (hyperdopaminergic state) which disrupts sub-conscious cognitive processes (Hemsley's integration of past regularities of experiences with current context) which results in positive symptoms of acute schizophrenia (necessarily linked to conscious experience). Crucially, by having reduced the positive symptoms of schizophrenia to a core deficit which operates at a preconcious level, Gray achieved an animal model of schizophrenia which not only enabled the direct investigation of brain systems and subserving functions in animals, but also provided a base for the development and testing of novel neuroleptic substances.

Gray's model implicates the septohippocampal system which, as initially outlined in Gray's (1982) neuropsychological model of anxiety, is assigned a 'comparator' function which allows a comparison of actual and expected events. More specifically, it is proposed that input from the entorhinal cortex into the subiculum informs about the present state of the world, where it is compared with predictions of the next state of the world based on previous experience as generated by the Papez circuit. The outcome of this matching process is then transmitted to the nucleus accumbens, where a 'mismatch', equating to an unpredicted or novel event, would result in an interruption of the current ongoing motor programme (which is subserved by an interplay of prefrontal cortex, amygdala, caudate and accumbens). Thus it is proposed that repeated exposure to what initially is a 'novel' event, eventually causes this event to become part of the context-specific prediction as generated by the hippocampus. Consequently, exposure to said event will cause a gradual change in subicular input into the nucleus accumbens from 'mismatch' to a 'match'. In terms

of information processing models it therefore would appear that this subiculo-accumbens projection is crucial to the process of turning controlled processes into automatic processes (see Shiffrin and Schneider above). Gray suggests that in schizophrenia this projection is compromised, as a result of which automatic processing is disrupted. Accordingly information processing is forced to occur at the (limited capacity) controlled or conscious level (the manifestation of which would be an 'overoccurrence' of apparently novel events).

Both psychological models as outlined by Hemsley (1987) and Frith (1987) may be accounted for by Gray's model. He proposes the subiculo-accumbens projection to control ongoing motor programmes via a continuous comparison of (in Hemsley's terms) "stored memories of regularities of previous input with current perception". In other words that this projection, impaired in schizophrenia, subserves the mechanism of 'pigeonholing' proposed by Hemsley to be weakened in schizophrenia. Equally it accounts for Frith's notion that 'willed intentions are not monitored correctly' in that the operation of the ongoing motor programme, equating to Frith's 'willed intentions', is 'monitored' by the subiculo-accumbens output.

Support for Gray's link of psychological processes to the above mentioned neural systems comes from behavioural paradigms such as latent inhibition, Kamin's (1969) blocking effect and the partial reinforcement extinction effect (PREE; Gray 1972). These paradigms are suggested to model the proposed cognitive deficit of schizophrenia (see previous section 2.5.3 for explanation of latent inhibition). These tasks are performed abnormally by schizophrenic patients (e.g. Baruch, Hemsley and Gray, 1988) and such deficits can be induced in animals via pharmacological challenges which result in increased levels of dopamine (e.g. Weiner, Lubow and Feldon, 1981).

2.6.2 Braff, Geyer and Swerdlow

Another influential animal model of information processing in schizophrenia has focussed on sensorimotor gating. The early observations by McGhie and Chapman (1961) stating the need for a mechanism to reduce "the otherwise chaotic flow of information reaching consciousness", as well as Venables' (1960) notion of disruptions caused by "flooding" via inundation of sensory input in schizophrenia, were instrumental in prompting the investigation of filtering or gating of sensory information in schizophrenia. Theoretically, a sensory gating deficit equates to an inability to filter out irrelevant features, therefore it would be expected that affected individuals would show greater distractibility, a prediction which has been confirmed in a number of studies of schizophrenic performance (e.g. Nuechterlein and Dawson, 1984; Oltsman and Neale, 1975). The development of behavioural techniques in the 1970's to measure sensory gating (such as P50 gating, e.g. Freedman et al, 1983) and prepulse inhibition (PPI; e.g. Graham, 1975) provided a means of quantifying gating. Schizophrenic patients show impairments on both tasks, which has been interpreted to reflect a malfunctioning inhibition or sensory gating system. Such a breakdown would be predicted to result in a susceptibility to sensory overload, cognitive fragmentation and thought disorder. Accordingly, deficits in PPI have been correlated with distractibility (Karper et al., 1996) and thought disorder (Perry and Braff, 1994).

The ability to measure PPI across species has enabled the development of animal models of deficient sensory motor gating which have proved invaluable in the elucidation of brain mechanisms underlying this basic information processing function. Thus Swerdlow and Koob (1987) have identified the neural circuitry which modulates PPI as involving limbic system and basal ganglia interactions (as detailed in chapter 3). Lesions as well as neurochemical interventions to various levels of this circuitry result in a disruption of PPI similar to that seen in schizophrenic patients. The ability of substances to restore pharmacologically induced disruption of PPI in animals has been correlated with their antipsychotic potency in man. Thus PPI

provides a powerful tool for developing new drug reatments for schizophrenia. The following chapter gives a detailed account of this paradigm.

CHAPTER 3: Prepulse inhibition of the startle response: The paradigm

3.0 Basic startle response and its plasticity

Most mammals, when confronted with a sudden, strong exteroceptive stimulus (e.g. burst of noise, flash of light), react with a defensive- or startle reflex comprising abrupt muscular flexion and extension responses. In experimental settings this startle reflex is usually measured as whole body jump in animals, e.g. via stabilimeter displacement (Hoffman and Ison, 1992), and as eyelid closure in Man (Graham, 1992). A vast amount of research has been dedicated to exploring the neural mechanisms underlying this basic behavioural response, culminating in Davis et al.'s (1982) identification of the 'primary mammalian acoustic startle circuit'. This circuit is now believed to comprise three synapses which link the auditory nerve to the spinal motor neuron (Davis et al., 1982; Koch and Schnitzler, 1997). The startle reflex shows several forms of plasticity which are remarkably similar in animals and humans (Brown et al., 1951; Grillon et al., 1994; Geyer and Braff, 1982), examples being habituation (Hoffman and Searle, 1968; Geyer and Braff, 1987) and fear potentiation (Brown et al., 1951).

3.1 Prepulse inhibition

A further example of startle plasticity is that the startle response can be modified reliably by presenting a more innocuous stimulus (prepulse) prior to the startle eliciting stimulus (pulse) (Graham, 1975; Hoffman and Searle, 1968; Ison et al., 1973). Providing the time from prepulse onset to pulse onset, or stimulus onset asynchrony (SOA), is between 30 to 500 milliseconds (ms) (e.g. Graham, 1975), such modification will appear as inhibition of the startle reflex, evident as the attenuation of the startle response (see figure 3.1). This phenomenon, known as 'prepulse

inhibition' (PPI), is thought to reflect an automatic 'sensorimotor gating system', in that the weak *sensory* prestimulus or prepulse inhibits the involuntary *motor* response to the startling stimulus (Swerdlow, Braff and Geyer, 2000b). This mechanism is suggested to be protective of the preattentive stage of information processing: while resources are directed at the prepulse, any other incoming information is attended to at a reduced level thereby safeguarding the processing of the initial event (Braff and Geyer, 1990; Graham, 1975, 1980). Accordingly, observations of reduced PPI are interpreted as indicative of a deficit in sensorimotor gating.

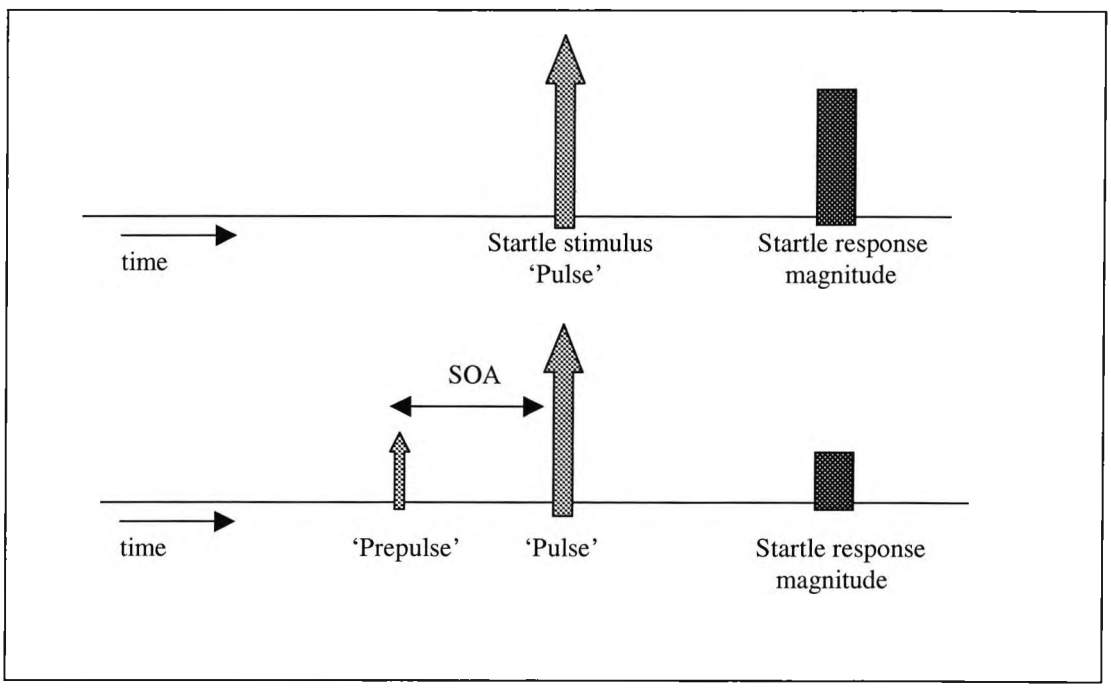

Figure 3 1: Prepulse inhibition of the startle reflex

PPI has been demonstrated using a number of different modalities such as bursts of noise (Blumenthal, 1988), air puffs to the neck (Hackley and Graham, 1987) and flashes of light (Yates and Brown, 1981). Modality of prepulse and pulse can be the same or different for this effect to occur (Blumenthal and Gescheider, 1987; Graham, 1980). PPI is thought to be neither learnt, nor due to conscious behavioural inhibition, as it has been shown to occur on first time trials (Hoffman and Wible, 1970). PPI does not habituate and is resistant to extinction over multiple trials. It

provides a very stable neurobiological measure: Cadenhead et al. (1999) showed high correlations between PPI taken on different occasions over a three month period in healthy male subjects, equally Abel et al. (1998) showed no change in PPI following repeated testing during the same day. PPI occurs at prepulse intervals too short to enable the activation of a conscious response (Swerdlow et al., 1992a), has been shown to occur in sleeping humans (Silverstein et al., 1980) and in decorticate rats (Ison et al., 1991) which confirms that, at least partially, PPI is an automatic process.

3.1.1 Methodological issues: The prepulse

The most widely used PPI paradigm uses acoustic stimuli, where the prepulses and pulses appear among a continuous stream of background noise. Thus the intensity of the stimuli is usually expressed in terms of dB above this background noise (e.g Braff et al, 2001a). The level of this background noise is a major contributing factor to the salience of a prepulse, which is of consequence to the amount of PPI, with stronger prepulses typically generating more inhibition (e.g. Hoffman and Wible, 1970; Swerdlow et al., 1993a). While most studies set background levels at 70 dB of white noise, some have the stimuli emanating from an unspecified 'ambient' background of 30-40 dB. Consequently salience of prepulses between studies may vary hugely, making between-study comparisons problematic.

Prepulse characteristics also vary between studies, in that some paradigms employ discrete prepulses (i.e. there is a gap of background noise between the stimulus and the pulse), while others have used continuous prepulses. The nature of the stimulus can vary: the prepulse either being a pure 'tone', or raised level of (background) white noise. The most effective type in terms of achieving both maximal PPI and effect size differences between patient and comparison groups appears to be the combination of discrete and white noise (e.g. Wynn et al., 2000; Braff et al., 2001a).

3.1.2 Methodological issues: The stimulus onset asynchrony

Although the temporal 'window' for the PPI effect in both humans and rats is when the prepulse precedes the pulse by 30 to 500 ms, most human studies employ SOAs of 30-240 ms with the strongest level of PPI usually achieved at the SOA of 120-ms. SOAs of over 1000 ms have the opposite effect in that they result in startle facilitation (e.g. Hoffman and Wible, 1969; Braff et al., 1978). SOA differentially affects latency to onset and peak of startle, with maximum decrease of latency occurring at the SOA of 30-ms (Graham 1975; Braff et al., 1978; 1992).

3.1.3 Methodological issues: Sex differences

Evidence suggests that PPI is more robust in males than females (e.g. Swerdlow et al., 1993c). Furthermore in females PPI varies according to stage of menstrual cycle such that PPI levels are lowest at mid-cycle (Swerdlow et al., 1997). Braff et al. (2001b) raise the interesting possibility that these cyclical changes might reflect the more general "flexible and less fixed cognitive style" of females. They suggest that this could be related to the observation that females with schizophrenia generally show a less severe manifestation of the illness than do males (e.g. Seeman and Hauser, 1984; McGlashan and Bardenstein, 1990). This sex difference might stem from a relative greater impact of the loss of (more robust) inhibition in males at onset of illness.

3.1.4 Methodological issues: Age and IQ

While PPI has been shown in infants less than 1 year of age (Graham et al., 1981) a number of studies have shown that PPI does not reach 'mature levels' in children until age 8-10 suggesting that the neural circuitry underlying this response are not fully functional until then (e.g. Ornitz et al., 1986; 1991). Braff et al. (2001b) suggest that levels of PPI within any individual may fluctuate throughout childhood and

adolescence as a function of the different rates at which the various brain areas involved in PPI develop. There are mixed reports on the effects of age on PPI in adults, with Swerdlow et al. (1995a) confirming no such effect in a group of adult subjects ranging between 18-48 years of age, and Harbin and Berg (1986) also reporting no age effect in healthy adult subjects. However Cadenhead et al. (2000) have shown increased PPI in older subjects. In PPI paradigms featuring a volitional component (i.e. under instructions to ignore or attend the prepulse) age differences are consistent, with older subjects showing no attentional modulation (e.g. McDowd et al., 1993). No relationship has been established between PPI and IQ (e.g. Perry et al., 1999).

3.1.5 Methodological issues: Laterality

PPI is most often measured via electromyographic (EMG) recordings of the right orbicularis oculi muscles (e.g. Braff et al., 1992), as blink reflex magnitude is generally greater on this side (Hager and Ekman, 1985). The importance of this has become evident in studies where left eyeblink recordings failed to show the differential PPI between psychiatric and healthy populations established by measures taken from the right eye (e.g. Swerdlow et al., 1997b). Braff et al. (2001b) point out that this could potentially arise due to floor effects of weaker left blink responses, or that it could reflect a greater asymmetry in response between right and left blinks in healthy control subjects. Interestingly, the latter suggestion is supported by a recent study by Cadenhead et al. (2000) which reported bilateral blink responses in schizophrenic patients, their relatives, patients with schizotypal personality disorder and healthy controls. This confirmed that healthy subjects showed greater PPI in the right eye compared with the left, furthermore both patients and their relatives only showed a deficit compared with the controls when PPI was measured on the right side. Braff et al. (2001) proposed that this lack of asymmetry in the patient groups may reflect left hemispheric abnormalities in these populations.

3.1.6 Methodological issues: Voluntary component to PPI

Despite the above mentioned characteristics of the paradigm which support PPI as a measure of an involuntary process, evidence from a number of studies suggest that PPI might also be sensitive to attentional or voluntary processes. These studies showed increased inhibition when subjects attended to a prepulse in comparison to trials in which subjects were instructed to ignore the prepulse. Most notably, Filion et al. (1993) showed enhanced PPI at SOAs of 120-ms if prepulses were attended to, which would indicate that at this lead interval PPI can be modulated by attention.

Dawson et al. (1993) extended this study to include schizophrenic patients. The deficit in inhibition as previously observed in this patient group at SOAs of 60 and 120-ms using a no-task paradigm (e.g. Braff et al., 1978, 1992; Grillon et al. (1992) now disappeared in the 'ignore' condition of Dawson's paradigm. The patient deficit in PPI reappeared only in the 'attend' condition of this study at the SOA of 120-ms, again suggesting a more complex process underlying PPI of the startle response. These findings have since been replicated by Dawson et al. (2000).

Using different methods, a study by Norris and Blumenthal (1996) appeared to demonstrate a relationship between increased inhibition and prepulse detection. Subjects were asked to report the presence of a prepulse, and detection accuracy was compared with PPI, the prediction being that if PPI reflected a protective mechanism, then instances in which such a mechanism had been effective should coincide with an enhanced processing of the initial stimulus (prepulse) in comparison to those times when the defense mechanism had failed to protect prepulse processing. They found significantly enhanced PPI in trials where the prepulse had been detected compared to non-detect trials but notably only at SOAs of 30 and 480 ms. No such difference was found at the SOA of 120-ms. The contentious issue of the voluntary component of PPI is discussed in detail in chapter 9.

3.2 PPI deficits in psychiatric populations

Part of the interest in PPI as a measure of preattentive processing has sprung from the observation of impaired PPI in a number of neuropsychiatric disorders characterised by an impairment in cognitive or sensorimotor inhibition. Furthermore, the brain areas identified as regulating startle gating in animal studies, namely the cortico-striato-pallido-pontine circuitry, have also been shown to be part of the pathophysiology of these disorders (Swerdlow et al., 1992a). These include Tourette's syndrome (Castellanos et al., 1996; Swerdlow et al., 2001b), Obsessive Compulsive Disorder (Swerdlow et al., 1993d), Huntington's Disease (Swerdlow et al., 1995b) and schizophrenia (e.g. Braff et al., 1978, 1992, 1999a, 2001a; Bolino et al., 1994; Kumari et al., 1999a; 2000). Deficits in PPI therefore are not specific to a particular disorder, but rather may represent the manifestation of (different) abnormalities in the brain circuitry which regulates this response.

It is important to note that the amount of PPI may vary considerably within any given population. Studies of normal populations alone have described the amount PPI to range from 0 to 100% (e.g. Swerdlow et al., 1995a), similarly PPI fluctuates within psychiatric populations (Swerdlow et al., 2000b). Thus in comparative studies an overlap of this measure in healthy control subjects and psychiatric patients is often observed. Accordingly a deficit in PPI holds no diagnostic value for either psychiatric illness *per se*, or indeed for any *particular* psychiatric disorder. Given this, the study of patterns or changes in PPI within particular populations characterised by specific functional impairments has proved very informative.

3.2.1 PPI deficits in schizophrenia

Schizophrenic patients show a wide range of cognitive impairments when compared with healthy control subjects (for reviews see Hemsley, 1982; Goldstein, 1986). However, inferences of deficits in such (voluntary) tasks are often clouded by the possibility that poor performance may simply reflect the generalised decreased

motivation seen in this population. Such potential confounds are avoided when studying performance on involuntary tasks. The sensory overload and cognitive fragmentation experienced by patients with schizophrenia has been hypothesized to stem from a fundamental deficit in an *automatic* filtering process which serves to exclude irrelevant information and sensory input from a limited capacity conscious processing system (Venables, 1960; McGhie and Chapman, 1961; Braff et al., 1978). As outlined in 3.1 PPI is believed to provide a measure of such gating (e.g. McGhie and Chapman, 1961; Braff and Geyer, 1990). It is this involuntary aspect of PPI, in that it taps processes at an automatic, unconscious level, which has made it so invaluable to schizophrenia research. In particular, it has enabled the development of an animal model of deficient sensorimotor gating to investigate the pathophysiology of this disorder (e.g. Swerdlow and Geyer, 1998) (although note the dispute about voluntary aspect of PPI in 3.1.6).

Impaired PPI has been confirmed in schizophrenic patients using intramodal (acoustic and electrocutaneous) as well as cross-modal (acoustic-tactile) paradigms (e.g. Braff et al., 1978, 1992, 1999a, 2001a; Grillon et al., 1992; Cadenhead et al., 2000; Bolino et al., 1994; Karper et al., 1996; Perry and Braff, 1996; Perry et al., 1998; Kumari et al., 1999a, 2000; Parwani et al., 2000; Weike et al., 2000). The deficit in PPI is also seen in non- medicated, non-psychotic patients suffering from schizotypal personality disorder (Cadenhead et al., 1993) and in healthy first-degree relatives of patients (Cadenhead et al., 1999). This suggests both that the deficit in PPI is independent of the detrimental effects of the illness and/or medication (a finding also confirmed by long term treatment of animals with antipsychotics; e.g. Geyer et al., 2001), and that it reflects a 'trait'.

However despite the wealth of evidence confirming a deficit in PPI in schizophrenia, two studies have shown no such deficit (Dawson et al., 1993; Ford et al, 1999). A contributing factor to the discrepancy between Dawson et al's findings and previous research may have been their introduction of a 'voluntary' component to the paradigm, in that subjects were instructed to actively attend to stimuli, thus changing

the nature of the paradigm considerably. The Ford et al. study featured patients on both typical and atypical medication which could have contributed to their findings (see section 3.2.2).

3.2.2 Neuroleptic medication

Recent evidence indicating a normalising effect of certain antipsychotics on PPI in schizophrenia also support a 'state' component to such impairments (e.g. Kumari et al., 1999a, 2000; Weike et al., 2000). Thus Weike et al. in a comparison of unmedicated patients with medicated patients, showed severly disrupted PPI in the former group, while the latter group showed sizable levels of PPI, albeit still lower than that seen in the healthy control subjects. The Kumari et al. studies investigated the difference between typical and atypical antipsychotics, their findings confirming a superior effect of atypical drugs on PPI. While patients on typical medication showed impaired PPI at 30-ms and 60-ms but not at 120-ms SOAs, patients on atypicals showed comparable levels of PPI to that of controls over all SOAs. It is possible that the ability of typical drugs to restore PPI at 120-ms results from such drugs' positive effects on tasks requiring controlled attention; at 120-ms but not the shorter SOAs it is feasible that some active processing of the prepulse occurs (Kumari et al., 1999a).

But the limitation of these studies is that they - out of necessity - were between-subjects designs. Future investigations into this issue would benefit from within-subject longitudinal comparisons, as the above medication effects may have been confounded by individual differences.

3.2.3 Age of onset

Thus a further contributing factor was exposed in Kumari et al.'s (2000) study, where a relationship was shown between early age of onset of illness (i.e. between age 13-20) and reduced PPI. In contrast, patients with adult onset of illness showed no difference in PPI from the control group. Kumari's survey of previous reports of impaired PPI confirmed that these studies generally involved patient groups with early age of onset. The most plausible explanation for this effect was suggested to be that of a disease-related disruption to a still maturing brain system involved in the modulation of PPI. Interestingly, this study found that patients from the early onset group who were on atypical medication did not reap the above described benefits of this medication on PPI. This is consistent with other reports that atypical medication is less effective in patients with early onset of illness (Meltzer, 1992).

3.2.4. Symptoms

Attempts to establish the relationship between PPI and specific deficits in schizophrenia have confirmed correlations between reduced PPI and increased distractibility (Karper et al., 1996), thought disorder (Perry and Braff, 1994; Perry et al., 1999) and higher scores on rating scales of positive as well as negative symptoms (Braff et al., 1999a; Weike et al., 2000). Using an 'attention-to-prepulse' paradigm, which distinguishes prepulse trials where the prepulse is ignored from those where it is attended, Dawson and co-workers (2000) have shown that PPI deficits on 'attend' trials correlate with increased delusions, conceptual disorganisation, and suspiciousness. No such relationships between PPI amplitude and symptoms were evident on 'ignore' trials (where patients show no deficit).

3.3 Anatomical substrates of PPI

Swerdlow and colleagues (2001a) outlined that the importance of establishing the neural circuitry involved in PPI is threefold: Firstly sensory motor gating reflects an

inhibitory mechanism which enables 'the structure and cohesiveness of thought', thereby playing a crucial and basic role in the process of cognition. Understanding the brain mechanisms underlying sensory gating therefore would help expose the mechanisms underlying basic processes of cognition. Secondly, such knowledge would shed light on brain abnormalities in (psychiatric) populations showing impaired PPI. Third, if PPI is a phenotypic marker (of psychiatric illness) then the understanding of corresponding changes in brain structures could help to inform on the effects of genes on the developing brain.

In animals, methods to locate this circuitry have included ablation (e.g. Swerdlow and Geyer, 1993b; Decker et al., 1995) and selective neurotoxin studies (e.g. Kodsi and Swerdlow, 1997a, 1997c; Seaman, 2000), intracerebral site specific applications of receptor agonists and antagonists (e.g. Swerdlow et al., 1992b; Reijmers et al., 1995), and electrical stimulation (Koch and Ebert, 1998; Li and Yeomans, 2000). In addition the study of selectively bred strains of animals displaying differential PPI has been informative (e.g. Wood et al., 1998; Carter et al., 1999).

In humans inferences concerning PPI circuitry have been made following the observation of impaired PPI in psychiatric populations with specific or hypothesized brain pathology such as for instance Huntington's disease (Swerdlow et al., 1995b); and Tourette's Syndrome (Castellanos et al. 1996; Swerdlow et al., 2001b). PPI being a cross-species phenomenon, such findings have in turn prompted further investigations in animals targetting the corresponding brain regions. Thus, Kodsi and Swerdlow (1997c) showed disrupted PPI in rats following application of a selective neurotoxin to the striatum, an area implicated in Huntington's disease. However despite such similarities in PPI-circuitry a number of findings have also exposed inter-species differences, both in terms of neurochemical regulation of PPI and neural anatomy. Thus, while dopamine and nicotine have similar effects on PPI in animals and humans, glutamatergic antagonists and serotoninergic agonists do not (see Geyer et al., 2001). Connections to the motor area from the nucleus believed to be at the heart of initiating the startle response, the nucleus reticularis pontis caudalis, show

vast interspecies differences (e.g. Holstege et al., 1984; Takeuchi et al., 1979). Therefore it would be inappropriate to assume a single model for PPI circuitry between species. Bearing this caveat in mind evidence from both animal and human studies will be discussed below.

Animal studies have established that PPI is regulated by parallel and sequential neural connections linking the limbic cortex and basal ganglia as well as the thalamus and medial prefrontal cortex (e.g Swerdlow et al., 1992a; Kodsi and Swerdlow, 1997b; Koch and Bubser, 1994).

3.3.1 Limbic system

3.3.1.1 Hippocampus

A vast literature has already implicated the hippocampus as vital for neural control of inhibition processes (e.g. Gray, 1998). PPI is disrupted after infusion of carbachol into the hippocampus (Caine et al., 1991a). Co-administration of the cholinergic antagonist atropine reverses this disruption, which implies that this effect is attributable to the cholinergic agonist properties of carbachol (Caine et al., 1991). The disruption to PPI would seem to be caused by carbachol-induced increases in glutamate release in the nucleus accumbens. This hypothesis is supported by findings of disrupted PPI following intra-nucleus accumbens infusions of glutamate (Swerdlow et al., 1991b). Intra-hippocampal carbachol-induced disruption appears to be independent of the well documented dopamine-agonist induced disruption of PPI, as co-administration of the dopamine antagonist spiperone (at a dose which normally blocks apomorphine-induced disruption of PPI) is ineffective at blocking this effect. Lesion studies of the hippocampus have also confirmed PPI disruption, although such effects are not robust (e.g. Swerdlow et al., 2000a; Caine et al., 2001).

In humans, there is converging evidence for hippocampal involvement in sensory gating as measured by the P50 paradigm. (Freedman et al., 1996 see chapter 4.3). A role for the hippocampus in PPI regulation in humans is supported by findings of impaired PPI in patients with temporal lobe pathology (Morton et al., 1994; Pouretemad et al., 1998).

3.3.1.2 Amygdala

PPI is disrupted following lesions of the amygdala (e.g. Decker et al., 1995; Wan and Swerdlow, 1996). Infusion of either the GABA antagonist picrotoxin or NMDA antagonist dizocilpine into the amygdala also result in disrupted PPI (Fendt et al., 2000). Such disruption is overturned by the dopamine antagonist haloperidol, which suggests that such disruptions, unlike those achieved in the hippocampus, are likely to be mediated via the dopamine system (Fendt et al., 2000).

3.3.2 Basal Ganglia

3.3.2.1 Nucleus Accumbens

The proposed circuitry involved in PPI describes dopaminergic input via the mesolimbic pathway (which originates in area 10 of the ventral tegmental area) to the nucleus accumbens (e.g. Swerdlow and Koob, 1987). Here dopamine is believed to have an inhibitory action on the accumbal Spiny I cells (e.g. Gray et al., 1991) which are GABAergic and project to the ventral pallidum (Swerdlow et al., 1987; Gray et al., 1991). The same accumbal Spiny I cells also receive glutamatergic input from the subiculum which is excitatory (Gray et al., 1991). Swerdlow and Koob (1987) describe how excitatory subicular input serves to activate a specific subset of nucleus accumbens Spiny I cells, the net result of which is a suppression or inhibition of neuronal activity outside the area of immediate interest, thereby providing a means of 'narrowing' the pattern of cortical input onto the target cells in the ventral pallidum.

This more selective input in turn is projected to the thalamus which links back to the limbic cortex, thus providing a feedback loop or mechanism via which a more narrowly focussed pattern of cortical activation is maintained. It is suggested that the role of dopaminergic input to the nucleus accumbens is that of disinhibiting the input to the ventral pallidum, which in effect would enable the establishment of new patterns. Thus in schizophrenia it is suggested the imbalance caused by excessive dopamine input to the nucleus accumbens would cause a disruption of Spiny I - related inhibitory input to the ventral pallidum, which becomes evident as the information processing abnormalities of this disorder such as loose associations and rapid-switching of ideas (Swerdlow and Koob, 1987).

Evidence that dopamine agonist-induced changes in PPI are at least in part mediated by increased dopamine activity in the nucleus accumbens is substantial. Swerdlow et al.(1990) showed the normally disruptive effect of amphetamine on PPI to have vanished after destruction of dopaminergic terminals in the nucleus accumbens. Zhang et al. (2000) showed a correlation between level of amphetamine-induced disruption of PPI and dopamine levels in the nucleus accumbens. Equally, direct infusions of the D2 agonist quinpirole into the nucleus accumbens cause disrupted PPI (Swerdlow et al., 1992b; Wan and Swerdlow, 1994b; Wan et al., 1994a; Reijmers et al., 1995; Kretchmer and Koch, 1998), which can be restored by administering dopamine antagonists systemically (Swerdlow et al., 1994; Wan and Swerdlow, 1994a; Wan et al., 1995). Interestingly studies of untreated rats have revealed an inverse correlation between naturally occurring levels of dopamine in this brain structure with degree of PPI, suggesting that such differences in accumbal dopamine levels underlie individual differences in sensorimotor gating (Feifel, 1999).

3.3.2.2 Striatum

However it is unlikely that the disruptive effects of dopamine agonists are solely mediated by the nucleus accumbens, as Hart et al. (1998) showed that the restorative effect of haloperidol depended on DA blockade in the dorsal posterior striatum as well as in the nucleus accumbens. Studies of rats with 'supersensitive' striatal DA receptors (achieved by intracerebral injection of the neurotoxin 6-hydroxydopamine (6-OHDA) which produces a state of 'supersensitivity' allowing high levels of dopamine receptor activation within a selected receptor population) show disrupted PPI after very low doses of apomorphine (Swerdlow et al., 1986). Animal lesion studies have further confirmed striatal involvement in PPI (Kodsi and Swerdlow, 1995b).

Pharmacological manipulations in humans have also confirmed striatal dopaminergic involvement in PPI regulation: Morton et al. (1995) showed reduced PPI in patients with Parkinson's disease following administration of apomorphine, possibly mirroring the above mentioned effects seen in the 'supersensitive' rat study. Finally patients with Huntington's disease, which has a known striatal pathology, show impaired PPI (Swerdlow et al., 1995b).

3.3.2.3 Pallidum

As described above (3.3.2.1), disrupted PPI following increased dopamine levels in the nucleus accumbens is thought to be related to an associated reduction of GABAergic input to the ventral pallidum (Swerdlow et al., 2001a). This hypothesis is supported by the observation that disruption of PPI following increased DA activity in the nucleus accumbens can be reversed by infusing the GABA agonist muscimol into the ventral pallidum (Swerdlow et al., 1991b; Kodsi and Swerdlow, 1994a), furthermore infusion of GABA antagonists into the ventral pallidum also disrupts PPI

(Swerdlow et al., 1991b; Kodsi and Swerdlow, 1995). Abnormalities of this structure have been reported in schizophrenia (Early et al., 1987; Bogerts et al., 1985).

Output from the pallidum is proposed to reach the main startle circuit via the pedunculopontine nucleus. This nucleus projects to the nucleus reticularis pontis caudalis which has been shown to be instrumental in producing the startle response (Davis et al., 1982). Lesions of the pedunculopontine nucleus result in disrupted PPI (Swerdlow and Geyer, 1993; Kodsi and Swerdlow, 1997b) and this structure has also been reported to be abnormal in some patients with schizophrenia (Karson et al., 1991)

3.3.3 Medial prefrontal cortex

The medial prefrontal cortex (MPFC) is also involved in the regulation of PPI in the rat, which potentially parallels involvement of prefrontal cortex in humans. Manipulations leading to the reduction of dopaminergic activity in this region in the rat result in reduced PPI, possibly modelling the hypofrontality observed in schizophrenic patients (Csernansky et al., 1993; Koch and Bubser, 1994). Infusion of the GABA antagonist picrotoxin into the MPFC (Japha and Koch, 1999) as well as the amygdala (Fendt et al., 2000) disrupts PPI. This disruption is reversed after systemic haloperidol, indicating that these effects reflect dopaminergic changes. The most parsimonious explanation for these findings is that these changes in the MPFC and amygdala cause an increase in subcortical dopamine levels (in particular in the nucleus accumbens) which bring about the changes in PPI, while hippocampal activation-induced changes might involve more elaborate, DA-independent processes (see Swerdlow et al., 2001a).

3.3.4 Thalamus

Although not as intensively investigated, evidence supports the thalamus as essential to the regulation of PPI. Injections of apomorphine into the ventromedial thalamus of the rat cause disruption of PPI (Young et al., 1995), an effect also caused by infusion of the GABA agonist muscimol into the mediodorsal thalamus (Kodsi and Swerdlow, 1997b). A number of studies have reported abnormalities in the thalamus of schizophrenic patients, which are suggested to be instrumental to the disturbances of the disorder (e.g. Hazlett et al., 1999; Andreasen et al., 1994a). Significantly, a recent functional neuroimaging study has confirmed the role of the thalamus in regulation of PPI in human subjects (Hazlett et al., 2001; see below)

3.3.5 Brain imaging studies of PPI

Hazlett et al., 1998 explored the neural correlates of attentional enhancement of PPI by comparing relative glucose metabolic rate (rGMR) patterns between schizophrenic patients and control subjects. Patients failed to show the attentional PPI effect: i.e. they did not show significantly greater inhibition on trials on which the prepulse was attended to versus trials on which the prepulse was ignored. No difference was observed in activation patterns between controls and patients in the frontal motor region, temporal cortex or occipital cortex, which was interpreted as evidence that the behavioural defict observed in patients was not due to anomalies in the auditory or visual association areas. However patients did show less rGMR in the superior, middle and inferior frontal gyrus as well as the parietal cortex consistent with the hypothesized importance of these areas in attentional processes. In the control group, the enhanced PPI associated with attending to a prepulse was accompanied by increased frontal lobe (dorsolateral, BA 8, 10, bilaterally; orbital prefrontal, BA 11 left; and cingulate, BA 24 right) and decreased occipital lobe rGMR. In patients, only increases in rGMR in Brodmann area 10 (left frontal pole) was correlated with an

increase in PPI. One of the problems with interpreting these results is that the measure taken to determine the ability of subjects to distinguish between/attend to the appropriate stimulus revealed a significantly higher error rate for the patient group. This could reflect patients inability or even unwillingness to perform the task properly. Hazlett et al. (2001) have recently adapted the above paradigm for fMRI, and using a region of interest approach they examined the effect of attentional modulation of PPI on blood oxygen level dependent (BOLD) activation in the thalamus and cingulate. Increased PPI on attend trials was paired with greater activation of the thalamus, confirming the involvement of this area in the regulation of PPI, as was previously shown in animal studies. More recent findings from neuro imaging studies of PPI are discussed in detail in chapter 8.

3.4 Pharmacological modulation of PPI

Similar deficits in sensorimotor gating to those seen in schizophrenia can be produced in animals via pharmacological challenges. This has enabled an animal model of this particular dysfunction which in turn has allowed insight into neurobiological mechanisms underlying these deficits as well as providing a useful means of testing efficacy of novel neuroleptic treatments. This section will consider the models based on challenges to the dopamine, serotonin and glutamatergic systems by reviewing such pharmacological manipulations in animals as well as the attempts to replicate these effects in healthy human subjects. Note that the effects of nicotine on PPI in both animals and humans are outlined in chapter 4.

3.4.1 Dopamine models of PPI disruption

Not surprisingly, given the emphasis of early accounts of a hyper functioning dopamine system in schizophrenia, many attempts to recreate a PPI deficit in animals have focussed on the dopaminergic system. In a pioneering study, Swerdlow et al.

(1986) reported disrupted PPI in rats with chemically induced supersensitive mesolimbic dopamine systems after administration of an otherwise ineffective dose of the direct dopamine agonist apomorphine. Using a different approach, Mansbach et al. (1988) not only showed disrupted PPI in normal rats following apomorphine and the indirect dopamine agonist amphetamine, but also confirmed such effects could be reversed by co-administration of haloperidol. These findings have since been replicated by many investigators in both the rat and mouse (for review see Geyer et al., 2001). While a robust phenomenon, the degree of such dopamine agonist induced changes has been found to vary between different strains of rats. It appears most likely that the disruptive effect of dopamine agonists on PPI occur via their interaction with D2 receptors, as selective D2 agonists produce PPI deficits (e.g. Peng et al., 1990), while attempts to recreate this disruption via manipulation of D1, D3 or D4 receptors have been less convincing (Geyer et al., 2001).

In addition to haloperidol's restorative effect on dopamine agonist-induced PPI disruption, atypical antipsychotics have also been shown to counteract such disruption in the rat. In this way clozapine (e.g. Swerdlow et al., 1991a), olanzapine (e.g. Rasmussen et al., 1997), risperidone (e.g. Rigdon and Viik, 1991) and quetiapine (e.g. Swerdlow et al., 1994b) have all been shown to attenuate apomorphine-induced reduction of PPI . As with typical antipsychotics, the ability of such drugs to reverse the effects of dopamine agonists has been linked to their affinity for D2 receptors (Swerdlow et al., 1994a). This suggestion has been supported by the inability of the presumed antipsychotic M100907, a 5-HT_{2A} antagonist with minimal DA affinity, to restore apomorphine-induced disrupted PPI (e.g. Geyer et al., 1999) as well as a number of other psychoactive but non-dopaminergic compounds (see Geyer et al., 2001 for review). These observations have therefore confirmed that while this model has considerable predictive validity in terms of the identification of potential treatments for schizophrenia, it is limited to the identification of compounds which have D2 affinity.

The involvement of D2 dopamine receptors in the modulation of PPI in humans has been confirmed in studies of dopamine agonist treatments in healthy human volunteers. Thus Abduljawad et al. (1998; 1999) showed disrupted PPI in healthy subjects following administration of the D2 dopamine agonist bromocriptine. A 3mg dose of the D2 antagonist haloperidol also caused a reduction in PPI although this effect was much smaller and was not replicated in the subsequent study. The reduction in PPI was blocked after combined administration of haloperidol and bromocriptine. PPI has also been disrupted in healthy subjects following administration of the indirect dopamine agonist amphetamine (Kumari et al., 1998b; Hutchison and Swift, 1999). Hutchison and Swift reported this reduction in a group of non-smokers after 20 mg of amphetamine. Using a much lower dose of 5 mg, Kumari and colleagues found this effect only in their subset of smokers, which they suggested reflected an interaction of nicotine with the dopaminergic system, causing an increased sensitivity to the effects of amphetamine. Interestingly this study also reported a reduction in PPI after 5mg of haloperidol, again only in the smoking group, which was a higher dose than reported in the Abduljawad et al. studies. An interesting extension of these human studies would be to investigate the combined effects of such dopamine agonists and antagonists.

3.4.2 Serotonin

Mansbach and colleagues (1989a) confirmed a role for serotonergic agonists in the disruption of PPI by showing reduced PPI in the rat following administration of MDEA and MDMA (both 5-HT releasers). Since then these findings have been supported by numerous studies using a wide range of compounds all known to cause 5-HT release and whose actions are blocked by pretreatment with serotonin-selective reuptake inhibitors (SSRI's) (see Geyer et al., 2001 for review).

Attempts to specify which serotonergic receptor subtype is involved in this modulatory effect have implicated several. Thus Rigdon and Weatherspoon (1992) showed selective 5-HT_{1A} agonists to decrease PPI in the rat, an effect which is minimised by administration of both non-selective 5-HT 1 (Rigdon and Weatherspoon, 1992) and selective 5 HT_{1A} antagonists (Sipes and Geyer 1995a). A role for the 5 HT_{1B} receptor has also been demonstrated by Dulawa et al. (1997; 1998) using the 5 HT_{1A1B} agonist RU24969. Sipes and Geyer (1994) using the 5-HT2 agonist DOI also showed PPI disruption in the rat, an effect shown to be mediated by the 5-HT_{2A} receptors. Thus DOI induced-disruption is reversed by the a 5-HT_{2A} antagonist M100907 (Sipes and Geyer, 1995b) and D2/ 5-HT_2 antagonists risperidone and amoxapine (Varty and Higgins, 1995a; Wadenberg et al., 2000), while haloperidol does not have this restorative effect (Varty and Higgins, 1995; Padich et al., 1996). Thus in contrast to the predictive validity of the above described model where dopamine agonist induced disruption of PPI is reliably restored by both typical and atypical antipsychotic agents, but not by drugs with no antipsychotic potency, this model is somewhat limited to identifying substances whose clinical potency is due to 5-HT2A effects.

The predictive value of this model is further compromised by the observation of opposite effects of serotonin agonists on PPI to that seen in the rat in mice and men. This way the 5 HT_{1A} agonist 8-OH-DPAT causes an *increase* of PPI in mice (Dulawa et al., 1997; 1998; 2000) however the same substance causes a *decrease* in PPI in the rat (e.g. Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1995a). Vollenweider and colleagues (1999) in comparing the effects of the indirect serotonergic agonist MDMA on PPI in both rats and healthy human subjects, also found interspecies differences despite their efforts to keep the paradigms as similar as possible. Thus while the drug decreased PPI in the rat, it increased PPI in the human subjects. Administration of the highly specific serotonin uptake inhibitor citalopram blocks this disruptive effect of MDMA in the rat (review Geyer et al., 2001) and the enhancing effect of MDMA in humans (Liechti et al., 2001) while ketanserin (a specific 5-HT2 antagonist) does not have this effect. Therefore it appears that while

the effects of MDMA on both humans and rats are mediated by the same neurochemical mechanism, the behavioural consequences are opposite. Liechti et al postulated that MDMA-induced serotonin release might activate 5-HT_{1A} receptors and that the human response pattern to such activation might more closely resemble that of the mouse than the rat.

Similar discrepancies with the hypothesized role of 5-HT in PPI disruption were reported by Gouzoulis-Mayfrank et al. (1998) who investigated the effect of psilocybin, a 5-$HT_{1A/2}$ agonist which causes symptoms resembling acute schizophrenia (such as hallucinations and delusions) in healthy human subjects. Contrary to expectations, they observed an increase in PPI. No reliable effects of psilocybin on PPI in animals have been reported. Following the observations described above, where citalopram, but not the specific $5HT_2$ blocker ketanserin, blocks the MDMA induced increase in PPI, it would seem likely that the effects of psilocybin also involve the 5-HT_{1A} receptors, although this still needs to be confirmed empirically (see Braff et al., 2001).

3.4.3 NMDA/ glutamate antagonists

NMDA antagonists PCP and dizocilpine reliably disrupt PPI in the rat (e.g. Mansbach and Geyer, 1989). Later studies also confirmed such an effect for the NMDA antagonist ketamine (Mansbach and Geyer, 1991). NMDA antagonists also disrupt PPI in the mouse (Dulawa and Geyer, 1996; Curzon and Decker, 1998; Sallinen et al., 1998) and in infra-human primates (Linn et al., 1999; Javitt and Lindsley, 2001). These effects are reversed by administration of atypical antipsychotics but generally not by typical antipsychotics (Geyer et al., 2001). Of the former drug type, clozapine has been the most extensively tested with some studies confirming a restorative effect (e.g Bakshi et al., 1994), while others have failed to replicate this (e.g. Hoffman et al., 1993). Geyer et al. (2001) point out that interpretations of clozapine's effects are made difficult by the drug's ability to

enhance PPI on its own, and furthermore that the mechanisms underlying any such effects are likely to involve multiple receptor sites (Bakshi and Geyer, 1998). Equally treatment with the atypical drug risperidone has yielded mixed results. At least some of these discrepancies are thought to reflect strain differences (Geyer et al., 2001). Interestingly while acute haloperidol has no restorative effect (e.g. Geyer et al., 1990) chronically administered haloperidol does restore PCP-induced disrupted PPI (e.g. Pietraszek and Ossowska, 1998).

Attempts to replicate these findings in human subjects with ketamine have met with mixed success. While the first of such studies (Karper et al., 1995) reported decreased PPI following ketamine subsequent reports have failed to replicate this. Thus van Berckel et al. (1998) showed no effect of ketamine, which they ascribed to an insufficient dose. Duncan et al. (2001) using a higher dose were able to induce psychotic-like changes in their subjects. Nonetheless ketamine did not cause the expected reduction of PPI, but instead caused an *increase* in PPI. While perhaps slightly premature given the paucity of currently available evidence, it would seem that NMDA blockade in humansmay not be an appropriate model for establishing the basis of the impaired PPI seen in schizophrenia. However future studies using different parameters and even different NMDA antagonists might yet yield the changes in PPI as observed in animal studies.

3.5 PPI and P50

Finally, it is important to consider the other extensively reported measure of sensory gating often compared with PPI, the P50 gating phenomenon. P50 refers to an evoked potential wave, which is elicited approximately 50 seconds following exposure to an auditory stimulus. P50 suppression refers to the reduction in P50 amplitude to a second, identical ('test') stimulus, when that stimulus is presented between 75-2000 msec after presentation of the first ('conditioning') stimulus. This inhibitory response is interpreted as reflecting a sensory gating mechanism (Adler et

al., 1982). The P50 response, in contrast with the muscle response measured in PPI, is measured via electroencephalography (EEG). Thus importantly P50, unlike the (PPI) startle paradigm, does not involve a motor response, the distinction between paradigms therefore is one of providing measures of sensory gating and sensori *motor* gating respectively.

PPI and P50 have a number of phenomena in common, which have led to the assumption that they might reflect similar processes and/or be regulated by similar physiological systems. As is the case with PPI, P50 gating has been found to be abnormal in patients with schizophrenia, which lends support to the premise of a fundamental sensory gating deficit in this patient group (e.g. Adler et al., 1982; Bolino et al., 1992; Freedman et al., 1983). Also, brain mechanisms known to be involved in PPI such as the septo-hippocampal system, (e.g. Caine et al., 1992; Koch, 1996; Wan et al., 1996) are implicated in P50 suppression (Freedman et al., 1996). There are neurochemical similarities: for instance antipsychotic medication similarly affects deficient PPI and P50 in schizophrenic patients, in that atypical, but not typical antipsychotic drugs have a normalising effect (Adler et al., 1982; Nagamoto et al., 1996; 1999; Kumari et al., 1999a). Also bromocriptine (a DA agonist) causes a reduction in both PPI and P50 in healthy human subjects (Abduljawad et al., 1997).

However despite the obvious similarities of both paradigms they measure distinct processes. The measurements themselves differ: while PPI is gauged via peripheral muscle activity, P50 reflects a more direct measure of cortical events. Crucially, the inter stimulus periods vary : the optimum for PPI being 60-120 msec, and for P50 75 -500 msec (Nagamoto et al., 1989). While there is considerable overlap in terms of neurophysiological and neurochemical regulation of both responses, differences in basic circuitry and neurochemical regulation have also been reported (e.g. Swerdlow et al., 2000b). One such observation particularly relevant to this thesis is that of *reduced* P50 gating following nicotine (albeit not significantly: Adler et al., 1993) versus *increased* PPI following nicotine (e.g. Kumari et al., 1996; 1997b) in healthy human subjects, both relative to overnight withdrawal. Also the selective D2/D3

agonist 7-OH-DPAT, which disrupts PPI in the rat (Caine et al., 1995), does not have this effect on the rat equivalent to the P50 paradigm (Ellenbroek et al., 1999).

Only two studies so far have compared the behavioural responses from these sensory inhibition paradigms in the same human subjects, both of which showed significant correlations between habituation of startle with P50 suppression (Schwartzkopf et al., 1993; Oranje et al., 1999). While the Schwartzkopf et al. (1993) study showed a moderate trend for an association between PPI and P50 suppression, Oranje et al. (1999) showed a significant correlation between both measures of inhibition. However in an equivalent animal study no such correlation was found between PPI and P50 (Ellenbroek et al., 1999). Clearly the relationship between PPI and P50 warrants more extensive investigation.

Finally, an interesting suggestion put forward by Swerdlow et al. (2000a) is that, as there is converging evidence for a role for the hippocampus in the mediation of P50 and the regulation of PPI is known to involve a much more extensive circuitry, circumstances under which these paradigms yield similar response patterns are likely to reflect circumstances requiring (mainly) hippocampal involvement.

CHAPTER 4 : Nicotine

4.0 Background

Nicotine is extremely addictive. Cigarette smoking, apart from being the most common form of substance abuse, presents as one of the foremost causes of premature death amongst humans (Jaffe, 1990). While over two thousand different compounds have been recognised in cigarette smoke, nicotine is generally acknowledged as the addictive substance accountable for sustained smoking behaviour (Jaffe, 1990, Stolerman and Jarvis, 1995). However the mechanisms underlying nicotine's reinforcing effects are far from clear.

Many different effects of nicotine have been reported. Considerable variation exists however in how individual smokers are affected by the drug. An example is that not all those who have been exposed to nicotine become addicted. Such individual responses to nicotine might be genetically determined; research has shown the heritability estimate for tobacco smoking to be 53% (Hughes, 1986). Genetic factors are also believed to influence the age at which individuals start smoking, and the number of cigarettes smoked per day (Eaves and Eysenck, 1980; Heath and Martin, 1993). The cognitive effects of nicotine may be similarly predetermined: while stress relief appears to be a universal experience (e.g.Wills and Shiffman, 1985), attentional enhancement is not always reported (Heishman et al., 1994; Wesnes and Warburton, 1983) and might only be experienced by individuals with a particular genetic makeup. This implies that there might be a subset of smokers who smoke for these attentional benefits, and others who smoke for other reasons. The possibility of (genetically driven) alternative motivating factors underlying the same drug use, in turn, might explain the variability observed in smoking behaviour.

In recent years a considerable amount of interest has been raised by the observation of dramatically elevated rates of smoking amongst schizophrenic patients. The prevalence of smoking amongst this patient group is estimated to be 40-100% greater

than that of other psychiatric populations, and three times greater than the rate of smoking seen in the general population (Hughes et al., 1986; Glassman, 1993; Ziedonis et al., 1994; Diwan et al., 1998). Furthermore these patients appear to favour stronger cigarettes as well as to extract more nicotine from their cigarettes than other smokers (Olincy et al., 1997). Thus the question has been raised whether the widespread smoking behaviour seen in this patient group is in fact a manifestation of a common underlying physiology, and that these patients smoke in an attempt to self-medicate. Suggestions of beneficial effects of nicotine specific to this population have included that smoking may help to reduce the side effects of antipsychotic medication (Glassman, 1993; Dawe et al., 1995), enhance the therapeutic effect of antipsychotics and alleviate negative symptoms (Glassman, 1993). One of the most convincing lines of evidence however for a self-medicating role for nicotine has come from research looking into the effects of nicotine on sensory gating (Adler et al., 1998). As discussed in chapter 3.5, sensory gating, as measured by the acoustically elicited P50 wave, and sensorimotor gating, as measured by PPI, is deficient in schizophrenic patients (Adler et al., 1993; Braff et al., 1978; 1992). Such deficient gating may in turn underlie some of the symptoms of this disorder. Converging evidence has shown nicotine to enhance inhibitory responses in both paradigms, which suggests that the excessive rate of smoking seen in schizophrenia may reflect an attempt to remedy otherwise deficient gating. Following a summary of the known neuropharmacology of nicotine, this chapter will consider the potential benefits of nicotine for patients with schizophrenia, with particular emphasis on the evidence of nicotine's effects on sensory gating from studies on animals, healthy human volunteers and schizophrenic patients.

4.1 Pharmacology of nicotine

Many factors are known to contribute to the reinforcing effects of tobacco smoking. Thus physiological sensations such as taste and smoke-induced stimulation of the respiratory pathways as well as psychological factors including mindset and milieu

all significantly feature. The consensus however is that the maintenance of smoking behaviour is achieved by nicotine, even though the effects of nicotine on its own might not always be identical to those of cigarette smoking (Jaffe, 1985). The pharmacological actions of nicotine are complex, affecting a number of neurotransmitters, and not yet fully understood.

Nicotine is the major alkaloid of tobacco, first isolated by Posselt and Reiman from tobacco leaves in 1828 (Goodman and Gilman, 1980). The most common method of nicotine administration is via inhalation of cigarette smoke. Following inhalation, nicotine is quickly absorbed into the systemic circulation via which it acts on almost every physiological system. The pharmacologically active form of nicotine closely resembles the acetylcholine (ACh) molecule, although nicotine is less flexible and only binds to one type of cholinergic receptor. This specific site of action was identified by Dale in 1914, when comparing the effects of the neurotransmitter ACh with those of nicotine and the alkaloid muscarine. Both alkaloids mimicked separate effects of ACh, implicating that ACh had two sites of action. Subsequently the notion of two subtypes of cholinergic receptors was introduced, named muscarinic and nicotinic, after their relative selectivity of response to these substances.

4.1.1 Distribution of neural nicotinic receptors

Nicotine affects most bodily systems, however only the sites of action within the central nervous system will be discussed here for the purpose of brevity. Nicotinic acetylcholine receptors (nAChRs), being the main sites via which nicotine exerts its behavioural and psychological effects, are found in many areas of the brain and a number of studies have attempted to map their distribution. Animal studies using autoradiographic methods have located highest nicotine uptake in the hypothalamus, hippocampus, thalamus, midbrain, brainstem and areas of cerebral cortex (Clarke et al., 1984; London et al., 1985). Imaging studies of human subjects using PET, located the most notable nicotine binding sites in the frontal, cingulate and insular

lobes, as well as in the thalamus and basal ganglia (Nyback et al., 1989). Using similar methods Nagata et al., 1995 showed increased bloodflow in the cerebellum and frontal lobes. A recent fMRI study by Stein et al., (1998) used different doses of intravenous nicotine on 16 non-abstinent smokers. Greatest activation was observed in the cingulate and frontal lobe regions including the dorsolateral, orbital and mediofrontal areas. These areas have all been implicated in working memory, attention and motivation (Sawaguchi and Goldman-Rakic, 1994), behaviours which are all susceptible to the modulating effects of nicotine (Warburton, 1990). In addition, areas which have been consistently put forward as mediating the rewarding effects of nicotine - the nucleus accumbens, amygdala and limbic thalamus - were activated by nicotine in this study.

4.1.2 Nicotinic receptor sub units

NAChRs are part of a superfamily of the ligand-gated ion channel class of neurotransmitter receptors, which also include glycine, serotonin 3 (5-HT3) and γ-aminobutyric acid (GABA) (Zang and Nordberg 1995 and others). NAChRs consist of 5 subunits which cluster together to form an ion channel which opens once the related ligand binds to the appropriate site. Two varieties of neuronal nicotinic receptor subunits have been identified, namely α and β, each of which have a number of subtypes which are all encoded by a separate gene (α2–α9 and β2–β4 (Clarke, 1993; Decker et al., 1995)). Nicotinic receptors are distinguishable from each other by their own specific combination of subunits. These differently composed receptors are pharmacologically and functionally distinct as they present with different levels of affinity and sensitivity to various nicotinic agonists and antagonists (Patrick et al., 1993; Sargent, 1993). Autoradiographic binding studies in animals and humans have shown that there are at least three different types of neural nicotinic receptors, appearing at different sites in the brain.

The most common receptor (90% of nicotinic receptors) binds labeled agonists such as ^{3}H-nicotine with high affinity, while not binding α-bungarotoxin. Although there is some variability in the subunit composition of this receptor, it always features α4 and β2 subunits (McGehee and Role, 1995), appears in large quantities in the striatum and substantia nigra, and only in small quantities in the neocortex and hippocampus (Sugaya et al.,1990; Perry et al., 1992; Rubboli et al., 1994 a,b ; Adem et al., 1989). The nicotinic receptor which has a high affinity for the snake toxin α-bungarotoxin is composed of five α7 subunits (McGehee and Role., 1995), and appears mostly in the midbrain, neocortex, thalamus and hippocampus, with lower levels in the striatum (Freedman et al., 1993; Sugaya et al., 1990; Rubboli et al., 1994 a,b). The third type binds neuronal bungarotoxin, contains α3 and β2 subunits (although, as with the most common α4β2 receptor, there is some variability amongst the other subunits) (Schulz et al., 1991), and is abundant in the hippocampus and in much smaller levels in the midbrain (Schulz et al., 1991; Sugaya et al., 1990).

The existence of so many different types of nicotinic receptor has important consequences for the effects gained from smoking. As the multiple receptor subtypes also have different thresholds for nicotine, different doses of nicotine will achieve varied pharmacological effects. The various sub types of nicotinic receptor desensitise rapidly (which refers to receptors becoming insensitive to further (nicotinic) agonists following initial exposure), but do so at different rates (Schoepfer et al., 1990). Given the large diversity of nicotinic receptors in the brain, variation of nicotine absorbed will result in activation of only few or multiple receptors. This way, by titrating the amount of nicotine ingested, specific pharmacological effects can be gained as the dosage allows targeting of those areas of tissue which contain receptors sensitive to that particular concentration of nicotine. The most common method of administration of nicotine lends itself well to such titration, as inhalation of cigarette smoke results in almost immediate absorbtion of nicotine and thus the effects can be monitored by the user. Be it consciously or subconsciously, it may

therefore be possible for a smoker to choose their dose to achieve the desired effect(s).

4.1.3 Nicotine - neurotransmitter interactions

Accordingly, animal studies have shown nicotine to differentially affect the two main dopaminergic pathways to the forebrain. Of these, the mesocorticolimbic system,which is thought to subserve limbic functions, begins in the ventral tegmental area, from which it projects to the nucleus accumbens, cortex, hippocampus, bed nucleus of the stria terminalis and amygdala. The nigrostriatal system, believed to subserve motor functions, begins in substantia nigra and projects to the dorsal striatum, the caudate nucleus and putamen.

The pleasureable and reinforcing effects of nicotine are thought to occur via an interaction of the drug with the mesocorticolimbic system. As is the case with other addictive drugs such as cocaine, these effects are believed to occur via an increase of dopamine levels in the nucleus accumbens (e.g. Henningfield et al., 1985; Wise and Rompre, 1989; Imperato et al., 1986; Corrigall, 1991a; Corrigall et al., 1992, Pich et al., 1997). Some of the evidence for this comes from studies where reduced self-administration was observed following lesions to this pathway, or by infusion of nicotinic antagonists into the ventral tegmental area (Corrigall and Coen, 1991b; Corrigal et al., 1994).

However the nigrostriatal pathway is not affected the same way by nicotine, as evidenced from different rates of dopamine release and metabolism in response to the drug. Studies using acute doses of nicotine in the rat showed increased dopamine release and breakdown in the nucleus accumbens, but not in the dorsal striatum (Andersson et al., 1981; Clarke et al., 1988). Equally, chronic exposure to nicotine resulted in decreased breakdown of dopamine in the dorsal striatum, while not having that effect in the nucleus accumbens (Kirch et al., 1987).

As stated before, it is likely that regional differences in proportions and combinations of nicotinic receptor subtypes might explain such region-specific patterns of nicotinic activation (Dalack et al.,1998). Such receptor differences might not only determine differences of nicotine response between brain areas within an individual, but might also account for the different responses seen between individuals. Given the number of different receptor subunits, potential for unique combinations, each having their own particular pharmacological properties, is extensive. It is therefore possible that differences in combinations of receptor subunits also exist between populations, which might determine characteristic behaviour. Already evidence has been put forward for a differential expression of one such subtype of nicotinic receptor in schizophrenia (Freedman et al., 1997).

Nicotine also has a facilitating effect on glutamate transmission, although the mechanisms involved are less well documented than the drug's interaction with dopamine. It is thought that nicotine exerts this effect by increasing the speed of glutamatergic synaptic transmission in the cortex (Vidal et al., 1993; Gray et al., 1996). This is most likely regulated by the α-bungarotoxin receptor subtype, as studies investigating this particular effect of nicotine in the hippocampus have shown that it can be blocked by administering α-bungarotoxin (Gray et al., 1996). The nicotine-glutamate interaction will be revisited at the end of this chapter.

4.2 Nicotine and schizophrenia

4.2.1 Smoking and side-effects of neuroleptic medication

Some evidence suggests that smoking may help reduce the negative side effects of neuroleptic medication, specifically the Parkinsonian symptoms (Goff et al., 1992; Sandyk, 1993; Decina et al., 1990). Typical antipsychotic drugs such as haloperidol have a strong dopamine blocking action, and it is thought that smoking is able to

provide relief from the related side effects through its efficacy in stimulating dopamine release. Strikingly, McEvoy et al. (1995a) have shown that haloperidol causes a dose dependent increase of smoking in patients, and a study of the effect of haloperidol in healthy smokers similarly found an increase in nicotine intake compared with baseline rates (Dawe et al., 1995). The latter finding was interpreted as reflecting an attempt to restore the haloperidol-induced reduction in dopaminergically mediated reward. Some reports contest the relationship between smoking and neuroleptic induced symptoms however, with reports by Yassa et al. (1987) and Nilsson et al. (1997) finding associations of greater movement abnormalities in patients who smoke than those who do not.

Neuroleptics are also known to adversely affect aspects of cognitive functioning. Levin et al. (1996) found that nicotine administered via a nicotine patch was able to restore some of the haloperidol-induced disruptions in aspects of cognitive functioning such as cognitive slowing , spatial memory impairments and reduced attentiveness as measured by a continuous performance task in schizophrenic patients.

The above mentioned relationship between medication and smoking appears to be specific to the type of neuroleptic used, with reports confirming reduced rates of ad-lib smoking following a switch from typical antipsychotics to the atypical drug clozapine (e.g. George et al.,1995). Similarly McEvoy and colleagues showed that smoking increased following haloperidol (McEvoy et al.,1995a) and decreased following clozapine treatment (McEvoy et al., 1995b) compared with baseline (medication free) smoking levels in two patient groups. The associated changes in nicotine use could mean either that the drugs differ in terms of their side effects or that they differentially affect symptoms. Interestingly, McEvoy and colleagues (1999) have recently demonstrated a relationship between nicotine use and responsivity to clozapine, in that patients who smoke were more likely to gain therapeutic benefits from clozapine than non-smokers. This confirms that the two drugs must target similar pathophysiologic mechanisms such as for instance a sensorigating deficit.

4.2.2 Smoking and symptoms

A number of studies have tried to establish why schizophrenic patients smoke via self-reports. Glynn and Susman (1990) found that in addition to the 'classic' reasons for smoking reported by healthy smokers, a percentage of patients claimed that smoking helped reduce psychiatric symptoms, which some claimed became more severe during withdrawal. Similarly, Dalack and Meador-Woodruff (1996) and Hamera et al. (1995) have reported cases where patients describe a worsening of symptoms during reduced intake or smoking withdrawal.

As mentioned above (4.1.3) nicotine is known to interact with the dopaminergic system, by raising dopamine levels in the nucleus accumbens and prefrontal cortex (e.g. Corrigall 1991a; Lapin et al., 1989). Following from the tenet that hypodopaminergic tone in the frontal cortex (i.e. hypofrontality) might give rise to the negative symptoms of schizophrenia (e.g. Weinberger et al., 1988b; Svensson et al., 1990; Paulman et al., 1990) it has been suggested that by raising dopamine levels in these regions, smoking provides a way of temporarily reducing these negative symptoms (Dalack et al., 1998). Atypical antipsychotics such as clozapine, olanzapine and risperidone might increase cortical dopamine levels, and therefore reduce negative symptoms, in a similar way to nicotine (e.g. Moghaddam and Bunney, 1990; Chouinard et al., 1993). Such drugs, unlike the typical antipsychotics, are known for their ability to reduce negative symptoms. Interestingly, patients switching from typical to atypical drugs such as clozapine reduce their ad lib smoking levels (McEvoy et al.,1995a). Some evidence supports the relationship between smoking and negative symptoms: i.e. Ziedonis et al. (1994) showed that amongst schizophrenic patients, heavy smokers (>25/day) suffered more positive symptoms as well as less negative symptoms compared with light smokers and non-smokers. However Hall et al. (1995) found that patients who had quit smoking showed less negative symptoms than active smokers.

But it is difficult to tease out whether these beneficial effects on negative symptoms such as anhedonia and social withdrawal, explainable in terms of diminished activity in the reward system, reflect nicotine's general effect of bringing about feelings of relaxation and wellbeing, or whether they are specific to the symptoms of schizophrenia per se. After all the rate of smoking in this population far exceeds that seen in any other general or psychiatric population, including depressive illness where the benefits of a reward-system stimulant are obvious. Dalack et al. (1999) monitored symptoms in patients wearing either placebo or active nicotine patches during a three day withdrawal period. While subjects showed the classic symptoms associated with acute nicotine withdrawal, they did not find exacerbations of psychotic symptoms, suggesting that problems patients might have during the early stages of withdrawal are not related to increased psychotic symptoms. Therefore it seems likely that the attraction of nicotine to schizophrenic patients extends to further benefits.

4.3 Smoking and sensory gating

Over the last decade, a number of studies have reported enhancing effects of nicotine on the basic startle response, PPI of the startle response and the P50 response. As outlined in chapter 3, while the basic startle response is thought to provide a measure of reactivity which is sensitive to attentional processes, the two latter paradigms are thought to reflect the working of sensory motor gating and sensory gating mechanisms respectively. Both gating and basic startle are abnormal in a number of neuropsychiatric disorders including schizophrenia. Via pharmacological challenges it has been possible to recreate and subsequently restore these gating deficits in animals and healthy human subjects using both paradigms. As PPI is the main focus of this thesis, of particular interest are observations of such drug induced disruption of PPI using psychotomimetic substances (e.g. amphetamine, apomorphine; for review see Swerdlow et al., 1992a) and demonstrations of reversal of such effects using antipsychotics (clozapine, haloperidol; Swerdlow and Geyer, 1993a). Indeed, the capacity of such drugs to restore normal startle inhibition has been found to be

significantly correlated with their antipsychotic potency. Accordingly it has been put forward that PPI might provide a valuable screening tool for antipsychotic drugs (Varty and Higgins, 1995). Recent observations of nicotine induced enhancement of both PPI and the related P50 response therefore raise the possibility that nicotine might have antipsychotic properties, and that some of the cognitive deficits characteristic of schizophrenia might be normalised or treated successfully with nicotine. The following overview considers the effects of nicotine on PPI within the broader context of nicotinic effects on startle and P50.

4.3.1. Nicotine: Modulating PPI and P50 in animals

Nicotine has been shown to have an enhancing effect on both the basic startle response and PPI. Acri et al. (1991) first reported that a chronic dose of nicotine set at 12mg/kg/day increased amplitude of startle response to acoustic stimuli in rats, which was believed to reflect the attentional enhancing effect of the drug. In an expansion of this study Acri and colleagues (1994) investigated the effects of increasing doses of acute nicotine on startle amplitude as well as PPI. The earlier reported effects of chronic nicotine on startle amplitude were replicated at dosages of .007 and .01 mg/kg. High doses (0.5, 1.0, 2.5 and 5.0 mg/kg) resulted in a significantly decreased startle response. This dose dependent response was thought to reflect nicotine's biphasic, i.e. stimulant and depressant, actions (Taylor, 1985) and mirrors previous findings of dose dependent effects on measures of cognitive performance (e.g. active avoidance paradigm; Oliverio, 1966). In contrast to basic startle amplitude, PPI was enhanced (albeit not always significantly) relative to saline at *all* doses. This enhancement reached significance levels at the dose of .001 mg/kg, at which nicotine had no effect on amplitude, in addition to the doses of .007 and .01 mg. This differential effect of nicotine on startle amplitude and PPI, coupled with observations of other drugs shown to increase startle amplitude but which disrupt PPI, such as apomorphine (Davis et al., 1990) and amphetamine (Davis et al., 1975), indicates the two processes are independent.

Curzon and colleagues (1994), using slightly different doses of acute nicotine, also found that nicotine increased PPI in the rat. In addition to nicotine, the selective $\alpha 4\beta 2$ nicotinic channel blocker mecamylamine was also administered, at the same dose at which this substance had previously been shown to block other effects of nicotine (Collins et al., 1986) . However in this instance mecamylamine was unable to reverse the effects of nicotine, which indicates that the $\alpha 7$ subunit containing receptors rather than the high affinity $\alpha 4\beta 2$ receptors are likely to play a role in the action of nicotine on PPI.

The effects of nicotine on rats are not always consistent, but may be strain dependent (Faraday et al., 1999). Thus Curzon et al. (1994) using Long-Evans rats as opposed to the Sprague Dawley rats tested in the Acri et al. studies, reported no effect of acute doses of nicotine on startle amplitude, but confirmed enhancement of PPI. Faraday and colleagues (1998; 1999) sought to clarify this issue by directly comparing the effects of chronic doses of nicotine between both rat strains. They replicated the earlier findings of the Acri group of enhanced startle amplitude and PPI in Sprague Dawley rats. However in contrast with the Curzon study, Faraday and colleagues found decreased startle and impaired PPI in the Long Evans rats. While methodological differences may have contributed to the different findings of the Curzon and Faraday studies, the employment of identical methods across the two strains within the Faraday experiments confirmed that these strains of rats are differentially affected by nicotine.

Similar strain dependent effects have also been found in mice, using only startle amplitude as a measure (Collins et al., 1988; Marks et al.,1986; Marks et al., 1989). As metabolism of the drug appears to be the same between strains (Marks et al., 1983) it is likely that the distinct behavioural responses reflect differences in central tissue sensitivity, occurring as a result of differences in number or distribution of nicotinic receptors. Indeed Marks et al. (1989; 1986) have confirmed that mice with the greatest behavioural sensitivity to the drug also have a significantly larger number

of nicotinic receptors. Such quantitative differences might also underlie the contrasting reactions to nicotine observed between rat strains.

Nicotine has also been shown to have a modulatory effect on sensory gating as measured by the N40 or paired auditory stimulus paradigm (sensory inhibition of the auditory evoked P20-N40 wave, thought to be the animal equivalent to the P50 wave response in humans – see 3.5 for a description of P50). Rats reared in isolation show a sensory inhibition deficit resembling that shown by schizophrenics (Geyer et al., 1993; Wilkinson et al., 1994). This deficit can be normalised by administering nicotine (Stevens et al., 1997). In a number of inbred mouse strains showing poor inhibition, the intensity of the deficit is correlated with a reduced number of hippocampal α-bungarotoxin sensitive nicotinic receptors (which may contain the α7 nicotinic receptor sub-type) such that mice with low levels of these receptors show more impaired inhibition (Stevens et al., 1996). One such strain, DBA/2 mice, which show no or little sensory inhibition (as measured by the paired auditory stimulus paradigm) showed a brief period of normal inhibition following the administration of nicotine and certain nicotinic agonists. This normalising effect was blocked however by simultaneous administration of α-bungarotoxin. Co-adminstration of mecamylamine (which is a very selective α4β2 nicotinic channel blocker) did not have this effect (Stevens and Wear, 1997), which combined, suggests a pivotal role of the α-bungarotoxin sensitive nicotinic receptors in this behaviour.

Considerable supporting evidence for this specific site of action has been put forward: in normal rats, this sensory gating deficit can be produced by targetting α-bungarotoxin sensitive nicotinic receptors by administering *d*-tubocurarine or α-bungarotoxin (Luntz-Leybman et al., 1992) and by injecting antisense oligonucleotides specific for the α7 nicotinic receptor mRNA (Rollins et al., 1993). Stevens et al. (1998) administered to DBA/2 mice GTS-21, an anabaseine analog which is a selectively partial α7 agonist, and which does not affect α4β2 receptors (Popke et al., 1994). The observed improvements in sensory gating were similar to

those observed when using nicotine in the earlier study (Stevens and Wear, 1997). Both α-bungarotoxin and mecamylamine were administered to establish the site at which the drug was active. As with the nicotine experiment, only α-bungarotoxin reversed the improving effect of the drug, thereby suggesting that the modulatory effect of GTS-21 also was achieved via the hippocampal nicotinic α7 receptors. It is likely that the restorative effects of nicotine work on the same principle as GTS-21. Unlike nicotine however GTS-21 did not cause desensitisation; the inhibition enhancing effect occurred with repeated doses also, whereas with nicotine the effects only occurred after the first dose. It is possible that more rapid metabolism of GTS-21, or the partial agonist nature of GTS-21 results in some receptors remaining 'receptive' while nicotine results in a total block, although such claims must remain speculative for now.

Leonard et al. (1996), using the same N40 paradigm, confirmed that this inhibitory response most likely involves the CA3 and CA4 pyramidal neurons of the hippocampus. As mentioned before, nicotine is believed to increase glutamate release via activation of hippocampal α7 subunit-containing nicotinic receptors. Leonard et al., suggest that gating of sensory input may depend on this interaction: increased glutamate would facilitate GABA release, resulting in inhibition of the CA3 and CA4 pyramidal neurons, the net result being repression of the subsequent response to the next stimulus. Supporting evidence for this hypothesis comes from lesion studies where destruction of cholinergic fibres projecting to the hippocampus resulted in impaired gating (Bickford and Wear, 1995). This deficit was subsequently restored by administration of nicotine.

There is evidence that the effects of nicotine on PPI are regulated via the same mechanisms. In the earlier mentioned Curzon et al., (1994) rat study the enhancing effect of nicotine on PPI was not reversed by co-administration of mecamylamine, implicating α7 rather than high affinity α4β2 receptors in this effect of nicotine. Bullock et al., (1997) investigated the inheritance patterns of PPI characteristics in

mice by comparing levels of PPI in seven mouse strains. A comparison was made between the levels of PPI of these mouse strains and the levels of sensory gating measured with the N40 paradigm in the same mouse strains as previously reported by Stevens et al. (1996). This yielded a significant correlation, implying some overlap in the genetic basis for the two behaviours. Further comparisons between mouse strains also revealed a near significant correlation for α-bungarotoxin binding with PPI levels, which confirmed that strains with fewer hippocampal α-bungarotoxin sensitive nicotinic receptors showed less PPI. Attempts to induce PPI enhancement with selective α7 agonists in DBA\2 mice have produced mixed results, with one report (Kaiser et al., 1998) confirming increased PPI following administration of AR-R-17779 (a selective α7 agonist; Gordon et al., 1998) and one showing no effect of either GTS-21 or AR-R-17779 (Olivier et al., 2001).

In summary, evidence from animal studies suggests that PPI and P50, although distinct, are both enhanced by nicotine. It appears unlikely that these effects are mediated via nicotine's effects on dopamine release, although clearly there is a role for dopamine in the regulation of gating. Instead, this specific modulatory effect is likely to occur via nicotine's interaction with the cholinergic system. As P50 gating is disrupted by a-bungarotoxin but not by mecamylamine, it seems likely that this effect involves the hippocampal α7 receptors. Activation of these receptors facilitates glutamate release, therefore it has been suggested that such nicotine-glutamate interactions in the hippocampus may be critical to the process of sensory gating and could be a site of neurochemical dysregulation in schizophrenia. Evidence for similar mechanisms in the regulation of PPI are less well established.

Importantly, the effect of nicotine on both measures of gating varies between different strains of rats and mice. Such behavioural variations appear to coincide with strain-specific variations in the number of α7 receptors, such that animals with

higher numbers of these receptors also show the greatest levels of response. This then suggests that there may be a genetic basis for this response.

4.3.2. Nicotine: Modulating PPI and P50 in human subjects

Since 1996, research into the effects of nicotine on PPI in humans has been conducted by Kumari and colleagues. The first of these studies established enhanced PPI following the smoking of a cigarette in overnight smoking-withdrawn healthy male smokers (Kumari et al., 1996). This was followed up by Kumari et al.'s (1997b) study into nicotine's effects on healthy non-smokers. Two doses of subcutaneous nicotine were administered, 6 μg/kg and 12 μg/kg, of which the higher dose achieved increased PPI in these subjects. This not only confirms that their previous findings were based on a direct pharmacological action of the drug in that they did not simply reflect the restoration of a withdrawal-induced deficit, but also, as with P50 (see below), suggests a low affinity nicotinic receptor involvement for sensory motor gating.

Kumari et al's 1996 findings have since been replicated by Della Casa et al. (1998) who showed enhanced PPI following cigarette smoking. This study examined the effects of nicotine in both males and females in a between subjects design which compared non-smokers, deprived smokers, deprived smokers allowed to smoke and non-deprived smokers. PPI was increased in both genders under nicotine, however interestingly, while the female group responded in the same way as the subjects in the Kumari study, the male subjects did not show decreased PPI in deprivation. Note however that the Kumari study employed a more sensitive within-subjects design and that the results of the Della Casa study may have been confounded by individual differences in PPI due to the between subjects nature of their design.

The two following studies provide perhaps the closest parallel to the earlier mentioned animal studies outlining strain differences in benefits gained from

nicotine. In the first one Kumari et al. (1999b) demonstrated a relationship between nicotine dependence and PPI. Smokers showing high nicotine dependence as measured by the Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom, 1978) showed less PPI under withdrawal than those smokers who were less dependent on nicotine. It has already been mentioned that, as smokers do not uniformly experience the same cognitive effects following nicotine, an individual's motivation to smoke may be driven by quite distinct experienced benefits. Thus the subset of smokers in this study showing high nicotine dependence might be attempting to access the particular nicotine-induced cognitive attentional benefits indexed by PPI.

As some evidence suggests that PPI is also reduced in normal subjects who score high on measures of psychosis-proneness (Swerdlow et al., 1995a; Simons and Giardina, 1992), Kumari et al.(1997a) set out to establish whether smoking status might interact with such ratings of personality as measured by the Psychoticism scale of the Eysenck Personality Questionnaire (EPQ, Eysenck and Eysenck, 1975). Their prediction that non-smokers who scored highly on this dimension would show lower PPI than smokers with an equivalent score, was borne out, indicating that self administration of nicotine in this population might have a restorative effect on PPI, as is hypothesized in schizophrenia. Thus there appear to be variations in the effects of drugs on PPI in different populations of humans also.

The transient improvement in P50 gating as seen in mice following nicotine (Stevens and Wear, 1997), has been replicated in schizophrenic patients and non-schizophrenic relatives of patients with poor inhibition (Adler et al., 1992,1993). In the first of such studies, the effects of nicotine on P50 gating were tested on first degree relatives of patients (Adler et al., 1992). In order to avoid any confounding effects of chronic exposure to nicotine, the study was restricted to non-smokers. Two doses of nicotine were administered via chewing gum (2mg and 6mg) of which only the higher dose achieved normalisation of the P50 response. The subsequent Adler et al. (1993) study demonstrated impaired P50 gating in patients following overnight smoking withdrawal. This deficiency was normalised following a self-selected dose

of nicotine via ad-lib smoking. This effect, however, was not longlived, only lasting 30 minutes. Normal subjects were tested the same way; nicotine this time had a slight reducing (non-significant) effect on the P50 response.

The findings from both studies suggest that, as both non-affected relatives of schizophrenic patients and the probands show the same deficit in gating which is normalised by nicotine, there may be a genetic basis for the abnormality which is likely to be linked to nicotinic receptor functioning. Furthermore, as only a high dose of nicotine is able to achieve the normalising effect, this restorative effect of nicotine on this measure of sensory gating is likely to be mediated by low affinity nicotinic receptors. This possibility is supported by the following findings: normalisation of deficient P50 gating in relatives of schizophrenic patients following a high dose of nicotine co-administered with mecamylamine (an antihypertensive agent which blocks the high affinity nicotinic receptors; Freedman et al., 1994); decreased levels of the α-bungarotoxin receptor subtype in the hippocampi of schizophrenic patients compared to matched controls (Freedman et al., 1995); and finally the observation of a link between diminished sensory gating and abnormal expression of the gene encoding the α7 subunit (Freedman et al., 1997).

On the basis of such findings the Freedman group have proposed that a reduction or abnormality of α-bungarotoxin receptor subtypes in an individual would result in a decrease of cholinergic activation of inhibitory interneurons which would then result in reduced inhibition (Freedman et al., 1995). This deficient sensory processing might be improved by an increase in cholinergic stimulation of these particular receptors.

Summary: As with animals, nicotine has been shown to enhance both sensory gating and sensory motor gating in humans. While there is evidence that nicotine exerts this effect on the P50 response by targetting the α-bungarotoxin receptor subtypes, it is only possible to speculate about the mechanisms involved in nicotine's effect on PPI in humans for now.

CHAPTER 5: Aims of the thesis

5.1 Hypotheses/ plan of investigation: Investigation 1

A longitudinal study into the effect of smoking and smoking cessation on startle response and PPI in healthy smokers wishing to quit.

Chapter 4 of this thesis provides an overview of current motivational accounts for smoking behaviour. One of the issues raised in this chapter is that the perceived benefits from smoking are varied, ranging from attentional enhancement to stress reduction. Accordingly it is suggested that individuals may indulge in smoking behaviour for quite distinct reasons. The range and differential sensitivity of neuronal nicotinic receptors is consistent with this possibility in that self-dosing of nicotine would allow targetting of specific receptor groups (and effects). Indeed the most common method of nicotine administration is highly compatible with such titration as it allows for an almost immediate monitoring of the effects of nicotine.

It has been suggested that nicotine addiction may have a genetic component: not all individuals who are exposed to nicotine develop an addiction to smoking, indeed Hughes et al. (1996) have estimated the heritability for tobacco smoking to be 53%. Similarly, motivational differences may be genetically determined. The attention enhancing abilities of nicotine have been well documented using a wide range of paradigms in both animals and humans (for a review see Bushnell et al., 2000). Following the previous findings of increased PPI following nicotine by Kumari et al. (1996) in healthy smokers as described in chapter 4.3.2, the aim of this study was to further investigate nicotine-facilitated improvements on aspects of cognitive performance (as indexed by startle response and PPI) in normal smokers, with an aim to gain insights into the motivation underlying this behaviour: is it a restoration of a trait-like cognitive deficit?

The experiment featured a longitudinal design in which the effects of cigarette smoking were considered via a comparison of baseline, withdrawal and one month post-quitting measures of startle and PPI in subjects wishing to quit cigarette smoking. The first measure was taken after subjects smoked their final cigarette prior to quitting. This would provide the baseline level of responses which were expected to reflect the 'normal' levels for each individual. Acquisition of such data would also serve to complement previous findings of nicotine effects on PPI (e.g. Kumari et al., 1996) where comparisons had consisted of withdrawal states with subsequent post-cigarette levels. The second measure was taken 24 hours into withdrawal, with the expectation of reduced PPI (following Kumari et al., 1996). The primary contribution of this study was to be the comparison of both of these measures with those obtained one month post withdrawal where the two possible outcomes were:

a) PPI would be restored to levels observed at baseline, which would indicate that the observed deficit in withdrawal was due to a physical dependence

b) PPI would still be at withdrawal level, which would be interpreted as evidence of an attempt to restore a trait-like deficit, as withdrawal would have disappeared by now.

5.2 Hypotheses/ plan of investigation: Investigation 2

A study into the effect of subcutaneous nicotine on PPI in healthy smokers, non-smokers and patients with schizophrenia

In addition to demonstrating that nicotine enhances PPI in healthy smokers (Kumari et al., 1996), the same group have shown that nicotine, administered via subcutaneous injection, can also enhance PPI in healthy non-smokers, which indicates that the effect in smokers does not merely reflect a restoration of a withdrawal-induced deficit (Kumari et al., 1997b). As outlined in chapter 4.2, the

excessive rate of smoking seen in schizophrenic patients has been postulated to reflect an attempt at self medication. Consistent with this suggestion, nicotine has already been shown to improve deficient P50 gating in this patient group. P50 is related to PPI in that it is believed to measure sensory gating (see chapter 3.5) and as is the case with P50 gating, patients with schizophrenia show impaired PPI (e.g. Braff et al., 1978, 1992, 1999a; Kumari et al., 1999a, 2000; see chapter 3.2.1). Given this evidence it was important to establish whether nicotine also enhanced PPI in this patient group, and if so whether this effect was similar to that already observed in healthy subjects. This study set out to examine this, but using a novel intra-modal tactile startle paradigm specifically designed to cope with the environment of the MRI scanner by Kumari, McAlonen, Geyer and Gray (1998), the ultimate intention being to repeat this experiment as a neuroimaging study.

Therefore there were multiple aims to this study:

i) The first aim was to determine whether the enhancing effect of nicotine on PPI in healthy smokers and non smokers as reported by Kumari et al. (1996;1997b) using an acoustic PPI paradigm, would also occur with the novel intra-modal and fMRI environment-friendly tactile startle paradigm.

In order to accurately control nicotine dose, the method of nicotine administration was chosen as subcutaneous injection of 12 μg/kg bodyweight nicotine base, as this dose had previously been shown to reliably elicit increases in PPI (Kumari et al., 1997b). Again for the purpose of dose monitoring, smoking subjects were asked to refrain from smoking for 12 hours. This overnight withdrawal also served to ensure that the behavioural effects of nicotine would be maximal, which was an important consideration in terms of the planned fMRI study where extreme behavioural contrasts would optimise opportunities for detection of changes in activation patterns.

ii) The second aim was to determine whether the restorative effect of nicotine on P50 gating in schizophrenic patients also extends to PPI. For this purpose, smoking as well as non-smoking patients with a DSM IV diagnosis of schizophrenia were recruited, all of whom were on stable typical antipsychotic medication.

5.3 Hypotheses/ plan of investigation: Investigation 3

An fMRI investigation into the effects of subcutaneous nicotine on prepulse inhibition of the startle reflex in healthy male smokers and schizophnrenic patients.

The aim of this study was to use functional magnetic resonance imaging (fMRI) to investigate the effects of the nicotine challenge as detailed above in Investigation 2 on patterns of neuronal activation caused by PPI. fMRI offers excellent temporal and spatial resolution which enables the exploration of brain areas which are involved in mental activity. Detection of changes in such activity is dependent on the changes in local cerebral blood flow caused by increased neural activation in particular areas of the brain where the consequent increase in oxygenated blood brings an increase in MRI signal.

Evidence from animal and human studies suggest that the modulatory effect of nicotine on P50 gating is mediated by the hippocampal α7 subunit-containing receptors (e.g. Freedman et al., 1995), and animal studies have also confirmed this to be the probable site for this effect on PPI (e.g. Stevens et al., 1998; see chapter 4.3.1). This study represents the first attempt using in-vivo brain imaging techniques to explore the neural correlates of this enhancing effect in in both healthy subjects and schizophrenic patients recruited from the previous study (Investigation 2). Given previous evidence, the expectation is that this modulatory effect would correlate with increased activation of areas rich in α7 subunit-containing receptors such as the

hippocampus and thalamus. Furthermore comparison of activation patterns between the two subject groups will establish whether same brain mechanisms are involved in patients as in control subjects.

The paradigm and procedure were kept identical to that conducted in the previous off-line study. Subjects were selected from the off-line study on the basis of a reliable response to the paradigm as well as the drug. At the time of the fMRI study it was not possible yet to record EMG responses in the scanner due to the metallic content of electrodes, therefore correlations of neural activation and behavioural changes were dependent on the behavioural data acquired for these subjects in the previous study. As PPI has been shown to be extremely stable in individuals over multiple occasions (e.g. Cadenhead et al., 1999; Abel et al., 1998) this was considered an acceptable strategy.

5.1 Hypotheses/ plan of investigation: Investigation 4

The relationship between prepulse detection and prepulse inhibition of the startle reflex

As detailed in chapter 3.1.6 PPI is claimed to tap involuntary processes. This aspect holds particular value for schizophrenia research where findings of impairments on cognitive tasks in patients are potentially confounded by the decreased motivation in this group caused by the generalised deterioration resulting from the disease process. Therefore involuntary tasks such as PPI have an advantage. However recent studies have suggested a voluntary component to PPI which has brought into question the nature of the schizophrenic deficit (Filion et al., 1993; Dawson et al., 1993; Norris and Blumenthal, 1996). The matter is further complicated by the fact that different laboratories have used paradigms which differ in terms of the nature and duration of prepulse stimuli (see chapter 3.1.1) which makes any direct comparisons

problematic. The aim of this study was to explore claims of a voluntary component to PPI by investigating whether conscious awareness of the prepulse affected PPI using the paradigms and specific parametric settings developed and used at the Institute of Psychiatry.

In order to assess this two separate PPI paradigms will be designed (one with acoustic startle stimuli only and one with tactile startle stimuli only) featuring pulse-only trials and prepulse-with-pulse trials with three different stimulus onset asynchronies set at 30, 60 and 120-ms. Trial presentation israndomised. Subjects will be asked after each trial whether they have experienced one or two stimuli, and these responses combined with the EMG recordings of startle responses will provide an insight whether awareness of a prepulse has any modulatory effect on PPI. If so, the expectation is that trials where prepulses have been detected will be coupled with increased PPI compared with trials where there is a failure to detect the prepulse.

CHAPTER 6

Startle Response During Smoking and 24 Hours in Withdrawal Predicts Successful Smoking Cessation

6.1 Abstract

Rationale: The startle response is thought to reflect changes in attentional processes in humans (Anthony and Putnam 1985). The startle response shows a number of forms of plasticity, of which prepulse inhibition (PPI) refers to the attenuation of the startle response to a strong sensory stimulus (pulse), when such a pulse is preceded by a stimulus of lower intensity (prepulse). Recent studies have shown that nicotine modulates startle and prepulse inhibition of the startle reflex in humans and animals. The present study examines individual differences in cognitive benefits obtained from smoking as indexed by startle response and PPI.

Objectives: This study investigated the effects of cigarette smoking via a comparison of baseline and withdrawal measures of startle and PPI in eighteen subjects wishing to quit cigarette smoking using a within-subjects design. The relapse of five of these subjects enabled a between group comparison of these measures with the successful quitters.

Methods: Startle and PPI were measured on three separate occasions: before quitting, 24 hours after quitting and one month post quitting.

Results: The occurrence of a significant drop of startle amplitude in withdrawal relative to baseline factors were found to be predictive of individuals' ability to quit smoking.

Conclusions: The observed response patterns are discussed in terms of individual

differences in commitment to quitting, and self-dosing to manipulate attentional mechanisms as measured by the acoustic startle response. Furthermore it is suggested that these specific response profiles may be predictive of the ability to quit smoking.

6.2 Introduction

Explanations of the underlying mechanisms of smoking dependence have traditionally focussed on neurobiological accounts, such as nicotine's interaction with the dopamine system (positive reinforcement) or in terms of avoidance of withdrawal symptoms (negative reinforcement) (for a review see Shadel et al., 2000). Such accounts have often overlooked the possibility that smoking dependence may result from nicotine's ability to enhance baseline functioning, enabling smokers to cope better with their environment (Hughes, 2001). Of these beneficial effects, the attention enhancing abilities of nicotine have been well documented using a wide range of paradigms in both animals and humans (for a review see Bushnell et al., 2000). Human studies have shown these effects to occur in deprived and non-deprived healthy smokers as well as non-smokers (e.g. Warburton and Arnall, 1994; Warburton and Mancuso, 1998). Furthermore a role for nicotine in the treatment of attentional deficits has been suggested in psychiatric populations with attention deficit/hyperactivity disorder (e.g. Wilens et al., 1999), schizophrenia (e.g. Levin et al., 1996) and Alzheimer's disease (e.g. White and Levin, 1999). The present study investigates the attentional effects of nicotine using a startle paradigm.

Most mammals, when confronted with a sudden, strong exteroceptive stimulus (e.g. burst of noise, flash of light), react with a defensive or startle reflex comprising abrupt muscular flexion and extension responses. In experimental settings this reflex response is usually measured as whole body jump in animals, e.g. via stabilimeter displacement (Hoffman and Ison, 1992), and as eyelid closure in human beings (Graham, 1992). Startle response amplitude is thought to provide a sensitive measure of reactivity to external stimuli (Davis, 1984), as well as reflecting changes in attentional processes in humans (Anthony and Putnam, 1985). The startle response shows a number of forms of plasticity, of which prepulse inhibition (PPI) refers to a reliable modification of this reflex, achieved by presenting a less intensive stimulus (prepulse) prior to the startle eliciting stimulus (pulse). Providing the time from

prepulse onset to pulse onset, or stimulus onset asynchrony (SOA), is short (i.e. between 30 and 150-ms), such modification appears as inhibition of the startle reflex. This phenomenon is thought to reflect an automatic sensory gating system which is protective of the preattentive stage of information processing: while resources are directed at the prepulse, any other incoming information is attended to at a reduced level thereby safeguarding the processing of the initial event (Braff and Geyer, 1990; Graham, 1975, 1980). Accordingly, in terms of day to day functioning, such a gating or filtering system would allow the individual to attend selectively to a pertinent stimulus.

Startle and PPI, in providing measures of basic cognitive processes, have been useful for the evaluation of the effects of various drugs on these processes. For instance numerous studies have documented the modulation of the startle response and PPI via dopaminergic agonists such as apomorphine and amphetamine (for review see Swerdlow et al., 2000b) and antagonists such as clozapine and haloperidol (Swerdlow and Geyer, 1993a; Hoffman and Donovan, 1994). Similarly, these paradigms have proved useful for studying the effects of nicotine. Interestingly, animal studies into the effects of both nicotine administration and nicotine withdrawal on startle and PPI have reported conflicting results (e.g. Acri et al., 1994; Curzon et al., 1994). Faraday and colleagues (1998, 1999) have since established that the most likely explanation for these inconsistent findings may lie in the different rat strains used between studies, and therefore that the modulatory effects of nicotine on both startle and PPI are strain dependent.

In humans the cognitive effects of nicotine may be similarly genetically determined: while stress relief appears to be a universal response to smoking (e.g., Wills and Shiffman, 1985), attentional enhancement is not always reported (Heishman et al 1994; Wesnes and Warburton, 1983) and might be experienced only by individuals with a particular genetic constitution. This implies that there might be one subset of smokers who smoke for these attentional benefits, and another who smoke for other reasons. As nicotine has also been shown to enhance PPI in humans (Kumari et al.,

1996; 1997b) these arguments raise the possibility that some individuals self administer nicotine to access the cognitive attentional benefits indexed by this measure. This may be of particular relevance to schizophrenia. PPI is impaired in this condition (e.g. Braff and Geyer, 1990; Braff, 1993). The excessive rate of smoking observed in such patients may therefore serve as an attempt to alleviate a fundamental deficit (as indexed by PPI) underlying some of their symptoms.

Previous findings in healthy human subjects support trait-dependent differences in the effects of nicotine on measures of startle. Kumari and Gray (1999b) showed a relationship between nicotine dependence and PPI: smokers showing high nicotine dependence, as measured by the Fagerstrom Tolerance questionnaire (FTQ; Fagerstrom, 1989), showed less PPI under withdrawal than smokers who were less dependent on nicotine. It was suggested that the former group might be attempting to access the particular nicotine-induced cognitive attentional benefits indexed by PPI. Furthermore, Kumari et al.(1997a) found an interaction of personality, as measured by the Psychoticism scale of the Eysenck Personality Questionnaire (EPQ, Eysenck and Eysenck, 1975), with smoking status. Their prediction that non-smokers who scored highly on this dimension would show lower PPI than smokers with an equivalent Psychoticism score, was borne out, indicating that self administration of nicotine in this population may have a restorative effect on PPI.

The present study examines further individual differences in cognitive benefits obtained from smoking, as indexed by startle response and PPI, in a group of subjects wishing to quit smoking. Following previous findings we expected to find different patterns of response at baseline (before quitting) and in withdrawal, reflecting different motivations for smoking. Furthermore we aimed to investigate whether such differences might be predictive of individuals' ability to quit smoking. Finally, if smoking served as a means of reversing a trait-like deficit in our subjects, we would expect responses obtained one month after smoking cessation to resemble those obtained in withdrawal. Namely as previous studies have shown withdrawal symptoms to have disappeared after one month (Cummings et al., 1985; Hughes,

1991, 1992) it would no longer be appropriate to attribute the maintenance of withdrawal-level response patterns over such a period to acute nicotine withdrawal; instead such a pattern would suggest a trait-like deficit. To test these predictions, startle amplitude and PPI were measured on three separate occasions: before, 24 hours after and one month after quitting.

6.3 Materials and methods

Subjects

A total of eighteen smokers comprising thirteen females and five males (23-36 years old; mean age 29.28 (standard deviation, 4.40) were recruited by advertisements and by referral from other subjects. Subjects had to agree to go 'cold turkey' (eg. Fiore et al. 1990), and to confirm they wished to quit smoking for at least a month. If successful, they would receive £30 for their time, this amount having been set deliberately low to discourage cheating. The mean number of cigarettes smoked daily was 14.5 (6.24) with the range falling between 6 and 30 cigarettes per day. The average number of years subjects had smoked was 10.72 (4.84). Mean scores on the FTQ (Fagerstrom and Schneider, 1989) were 4.55 (1.85). All subjects participating signed a consent form approved by the Ethical Committee at the Institute of Psychiatry, London.

Startle response measurement

Acoustic startle stimuli were delivered binaurally through a set of headphones (Model Pro-VII; Realistic). Presentation of acoustic startle stimuli and recording of responses were controlled by a commercially available computerised human startle response system (San Diego Instruments, San Diego, California). Measurement of the startle response (eyeblink amplitude) was achieved by recording the electromyographic (EMG) activity of the right orbicularis oculi muscle via two

(6mm) Ag/AgCl electrodes filled with Dracard electrode gel. After preparing the skin surface with Sterets sterile swabs, one electrode was positioned approximately 1 cm lateral to, and 0.5 cm below, the lateral canthus of the subject's right eye, while the second electrode was placed 1.5 cm below and slightly medial to the first electrode, such that both electrodes were equidistant from the centre of the eye. In addition a ground electrode was placed behind the right ear over the mastoid.

Procedure

Subjects were seated comfortably in a softly lit, sound attenuated room after which they were informed of the procedure. The same paradigm as employed in Postma et al. (2001; chapter 9 of this thesis) was used. Sessions started with an acclimatisation period of 3 min to allow subjects to become accustomed to the continuous stream of 70-dB (A) white noise serving as background throughout the experiment. A total of 49 startle eliciting acoustic stimuli were presented over a period of approx. 15 min, with a mean inter-trial-interval of 15 s (range 9-23 s). Following the first pulse-alone trial (a 40-ms presentation of 116-dB [A] white noise) a further 48 trials were presented in four adjoining blocks of 12 each. Per block, three presentations each of four trial types occurred: pulse alone trials, prepulse trials with a 30-ms SOA, the prepulse being a 20-ms presentation of 84-dB (A) white noise, and prepulse trials with 60-ms and 120-ms SOAs. Noise levels were calibrated using a sound level meter. The four trial types occurred in pseudo-random order throughout each block.

All subjects underwent the same paradigm on three separate occasions: before quitting (Occasion 1), 24 hours after quitting (Occasion 2), and one month after quitting (Occasion 3). Time of day effects were controlled for by testing each subject at the same time on the three separate occasions. In addition subjects were monitored every week as well as on the test occasions for non-smoking compliance using an expired air carbon monoxide (ECO) monitor (Bedfont Technical Instruments EC 50).

Statistical Analyses

All analyses were performed using SPSS Windows (version 10). Five subjects, while having had every intention to quit, could not comply with the one month's cessation target: therefore analyses involving all participants cover only the first and second occasion. Compliance with the target (one month's cessation) was added as a between subjects factor (Group: Complied / Not Complied) in these analyses. Thirteen subjects provided data for the third and final occasion (one month after occasion two).

Startle amplitudes over the first 116-dB pulse-alone trials for the first two occasions were analysed via a 2 x 2 [Occasion (occasion 1, occasion 2) x Group (Complied, Not Complied)] analysis of variance (ANOVA) with Occasion as a within-subjects and Group as a between-subjects factor. In order to assess habituation of the startle response, the amplitude data from the pulse-only trials (response on the first pulse-alone trial not being included) were subjected to a 2 x 4 x 2 [Occasion x Block (4 blocks, each consisting of three pulse-alone trials)] x Group analysis of variance (ANOVA). Occasion and Block were entered as within subject factors. This analysis was repeated by entering FTQ scores as a covariate.

Prepulse inhibition was calculated in two ways: (i) as amount of PPI, i.e. the arithmetic difference between mean pulse-alone amplitude and mean prepulse amplitude, and (ii) as percentage PPI, namely as (a-b/a) x 100, where a = pulse alone amplitude and b = amplitude over prepulse trials.

The effect of withdrawal on amount of PPI was examined through a comparison of amount of PPI scores (pulse-alone amplitude means *minus* prepulse amplitude means) which were subjected to a 2 x 2 x 3 (Occasion x Group x Trial type: 30-ms, 60-ms and 120-ms prepulse trials) ANOVA with Occasion and Trial type entered as within subjects factors. The same effect was tested on percentage PPI by a 2 x 2 x 3

(Occasion x Group x Trial type: percentage inhibition on 30-ms, 60-ms and 120-ms prepulse trials) ANOVA.

The effects of longer term smoking cessation on habituation were assessed in the thirteen subjects who had managed to abstain via a 3 x 4 [Occasion (occasion 1, 2 and 3) x Block] ANOVA. Similarly, the effects of longer term abstinence on both amount and percentage PPI were assessed via a 3 x 3 [Occasion (occasion 1, 2 and 3) x Trial type] ANOVA of the difference scores (pulse-alone amplitude means *minus* prepulse amplitude means) and via a 3 x 3 (Occasion x Trial type) ANOVA of percentage PPI.

The effects of withdrawal from cigarette smoking on latency to response peak were considered via a 2 x 2 x 4 (Occasion x Group x Trial type: Pulse-alone, 30-ms, 60-ms and 120-ms prepulse trials) ANOVA with Occasion and Trial type entered as within subjects factors. In order to assess habituation of latency to response peak, the latency data from the pulse-only trials were subjected to a 2 x 4 x 2 [Occasion x Block (4 blocks, each consisting of three pulse-alone trials) x Group] analysis of variance (ANOVA). Occasion and Block were entered as within subject factors. As with the previous measures, the long term effects of smoking cessation on latency to response peak were assessed through comparisons of the data provided by the thirteen successful abstainers via a 3 x 4 [Occasion (occasion 1, 2 and 3) x Trial type] ANOVA.

To investigate possible group differences in nicotine dependence, an independent t-test was performed on FTQ scores between the two groups (Complied/Not Complied). Finally, to establish whether there was a relationship between any changes in startle and FTQ scores, three Pearsons' *r* correlations between FTQ and startle amplitude on occasion 1, occasion 2 and the change in mean amplitudes over pulse alone trials from the first to the second occasion were performed.

6.4 Results

Amplitude and habituation of the startle reflex - withdrawal

We found no effect of either Occasion (1, 2) or Group on startle amplitude of the very first pulse-alone trial (mean: Occasion 1: 937.12 (522.56); Occasion 2: 931.18 (570.72) (in analogue to digit units, each unit = 2.62 μV).

There was significant habituation of startle amplitude within each occasion as evidenced by the main effect of Block [$F(1,16) = 6.75$, $p<.01$]. We found a tendency towards reduced overall startle amplitude on the second (withdrawal) occasion when compared with the first occasion [$F(1,16) = 3.44$, $p<.08$]. However this reduction was present only in the group of subjects who succeeded in quitting for one month; those who did not manage to quit showed a slight increase on the second session, as evidenced by the interaction of Occasion x Group [$F(1,16) = 4.92$, $p< .04$; partial eta squared = .230]. Follow-up t-tests indicated no difference in mean amplitudes at baseline between groups [$t(32) = 1.35$, $p>.05$], nor a difference between groups in withdrawal ([$t(32) = .917$, $p>.05$]. However t-tests showed the drop in amplitude following withdrawal as observed in the 'complied' group to be significant [$t(12) = 3.63$, $p<.003$; Bonferroni corrected $p=.006$; partial eta squared = 0.523], while the increase in amplitude following withdrawal in the 'not complied' group was not significant [$t(4)= .252$, $p>.05$]. (see figure 6.1)

Interpretation of the post-hoc analysis for the not-complied group is limited by the small number of subjects. To throw light on this, a power calculation was carried out, using the mean paired difference observed in the 'complied' group (where a significant effect had been observed) to assess what the chance would be of observing this effect if the number of subjects were reduced to the same number as the not-complied group (i.e. 5). This confirmed a low power (34%) on the basis of which any conclusions re the lack of effect in the not-complied group may be

criticised. However the earlier mentioned interaction of the subject groups with occasion can not be faulted on the basis of power. Therefore we may conclude that the observed differences between the two groups are substantial and robust.

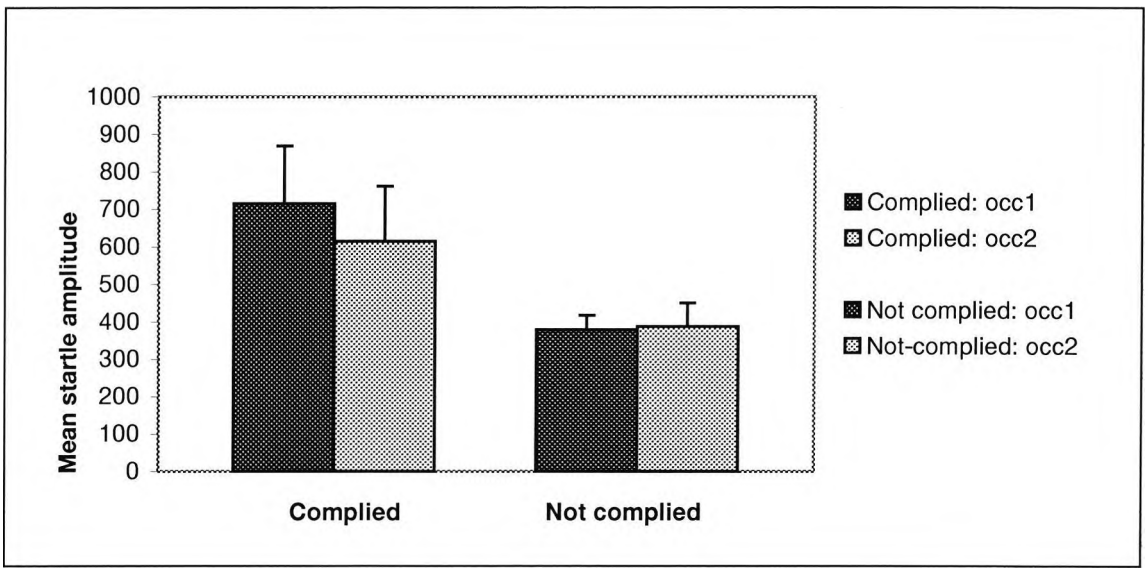

Figure 6.1: Mean startle amplitudes and SEMs on pulse-only trials for 'complied' and 'not complied' groups on Occasions (occ) 1 and 2

Prepulse inhibition (PPI) of the startle reflex - withdrawal

The analysis of amount of PPI revealed main effects of Trial type [F (2,15) = 4.04, p<.04; ; partial eta squared = 0.35] indicating greater inhibition following prepulses at SOAs of 60 and 120-ms than prepulses at a 30-ms SOA. Inhibition was reduced, albeit not significantly, in withdrawal [F (1,16) = 3.41, p<.08; ; partial eta squared = 0.175].

The comparisons involving percentage PPI showed the same effect of Trial type [F(2,15) = 8.98, p<.003 ; partial eta squared = 0.544] and a marginally significant main effect of Occasion [F(1,16) 4.66, p<.05 ; partial eta squared = 0.225],

suggesting a significant reduction in PPI in the withdrawal condition. There were no interactions involving the Group factor (see figures 6.2 and 6.3).

Habituation of the startle reflex - 1 month after cessation

Data from the group of 13 subjects who succeeded in quitting showed habituation over the three occasions, as supported by a significant reduction of mean amplitudes of pulse-alone trials as a function of Block [$F(3,10)=5.92$, $p< .02$; partial eta squared = 0.639]. Overall startle amplitude varied according to occasion, with the lowest mean occurring in withdrawal (Occasion 2) [$F(2,11)=6.66$, $p<.02$; ; partial eta squared = 0.547].

Prepulse inhibition (PPI) of the startle reflex - 1 month after cessation

Changes in amount of PPI for the 'complied' group over the three occasions were not significant [$p> .05$], with the effect of Trial type being maintained [$F(2,11)$ 8.78, $p<.005$; partial eta squared = 0.614]. The reduction in percent PPI was also shown to be temporary: while there was still a main effect of Trial type [$F(2, 11) =15.98$, $p<.001$; partial eta squared = 0.743], Occasion (1,2,3) no longer produced a change ($p>.05$; observed power = 0.179) (see figure 6.3).

Latencies to response peak for pulse-alone and prepulse trials.

Mean latencies to response peak are displayed in table 1. There was a main effect of Trial type [$F(3,14)=6.47$, $p<0.006$; partial eta squared = 0.58] reflecting shorter latencies to response peak in the prepulse as opposed to the pulse-alone trials. The main effect of Occasion (1,2) [$F(1,16) =10.11$, $p<0.006$; partial eta squared = 0.387] indicated slower overall onset of responses on the second, withdrawal occasion. We found no habituation of this measure within each occasion, as was evidenced by no effect of Block [$F(3,14) = 1.28$, $p>.05$]. One month after withdrawal the effect of SOA remained [$F(3,10) = 22.82$, $p< .001$; partial eta squared = 0.872]. Latency to

peak had returned to pre-quitting levels as indicated by a lack of effect of Occasion [p>.05].

	Pulse-alone	30 ms	60 ms	120 ms
Session 1				
Complied	60.08 (1.52)	52.14 (1.61)	52.53 (1.71)	56.38 (2.94)
Not Complied	60.11 (2.70)	55.95 (4.29)	55.26 (2.67)	56.25 (3.12)
Session 2				
Complied	63.05 (1.84)	55.12 (2.09)	55.47 (1.77)	56.51 (2.14)
Not Complied	64.43 (3.72)	66.04 (7.31)	60.96 (4.53)	62.2 (7.96)

Table 6.1: Mean (SD) latencies to response peak (msec) for pulse-alone and 30-msec, 60-msec and 120-msec prepulse trials on occasions 1 and 2 for 'complied' and 'not complied' groups

FTQ and smoking cessation

The number of cigarettes smoked daily by the group of subjects who had succeeded in quitting for one month was significantly lower than by those who relapsed within the month [means 11.84 (SD 4.31) and 21 (SD 6.51), $t(16) = 3.51$, $p<.003$; partial eta squared =0.435]. Equally, the FTQ scores were lower in the former [mean FTQ: 4.08 (1.98)] than in the latter group[mean FTQ: 5.80 (.45)] [$t(14.6)=2.95$, $p<.01$; partial eta squared = 0.373]. There were no significant correlations between FTQ and the measures of startle amplitude (p>.05).

In order to determine the extent to which the observed differences between the complied and not-complied groups in change in startle amplitude following withdrawal were independent of- or could be predicted by smoking dependency, the analysis on startle amplitude was repeated, entering subjects' FTQ scores as a

covariate. Though a change in magnitude of the interaction was observed, the interaction remained significant which served to indicate that the change in startle amplitude was an independent predictor of the ability to quit smoking [$F(1,15) = 4.35$, $p<.05$; partial eta squared = 0.224].

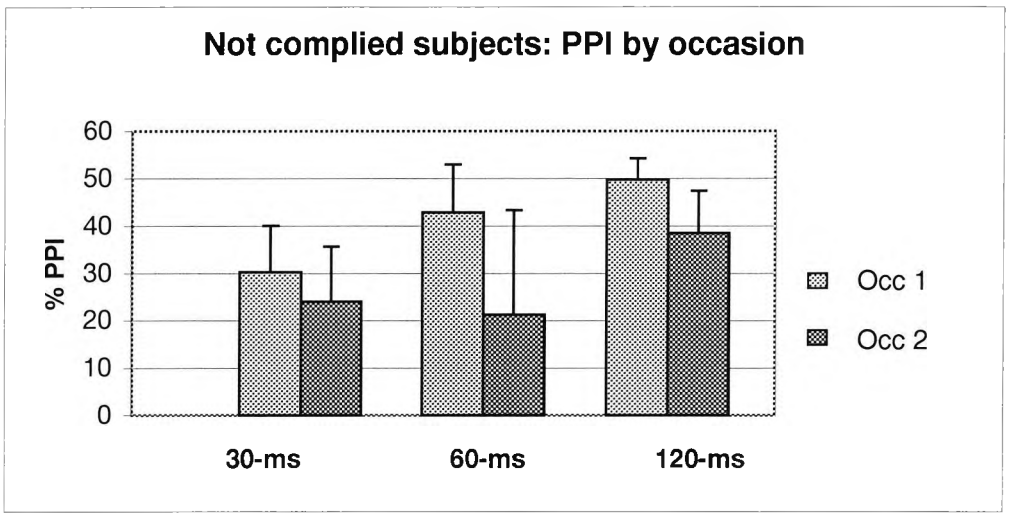

Fig. 6.2: Mean (error bar displays 1 SEM) prepulse inhibition (PPI) of the startle reflex at 30-ms, 60-ms and 120-ms SOAs over occasions 1 (prior to quitting) and 2 (24 hours in withdrawal) for the group of subjects who were unable to comply with smoking cessation.

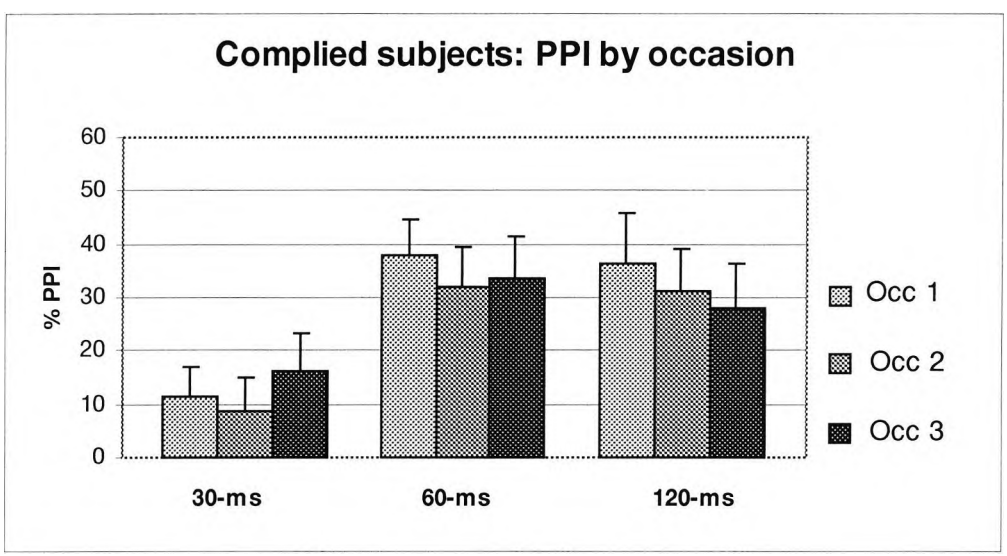

Fig. 6.3: Mean (error bar displays 1 SEM) prepulse inhibition (PPI) of the startle reflex at 30-ms, 60-ms and 120-ms SOAs over occasions 1 (prior to quitting), 2 (24 hours in withdrawal) and 3 (one month post after occasion 1) for the group of subjects who complied with smoking cessation.

6.5 Discussion

This, to our knowledge, is the first study to report the longitudinal effects of cigarette smoking on startle response and PPI in a group of smokers wishing to quit. Startle amplitude in withdrawal relative to baseline was found to be predictive of individuals' ability to quit smoking. Thus the 'complied group' showed a drop in startle amplitude in withdrawal, while the 'not complied' group showed a marginal but non significant *increase* of startle amplitude in withdrawal. Finally, we observed a reduction in PPI 24 hours after withdrawal relative to baseline.

The acoustic startle response is complex and has been shown to reflect arousal and motivational state (e.g. Lang, Bradley and Cuthbert, 1990; Grillon et al., 1991; Bonnet et al., 1995) as well as providing a measure of changes in attentional processes (Anthony and Graham, 1983; Anthony and Putnam, 1985). Interpretations of changes in startle therefore should consider these multiple factors.

The observed changes in startle could have reflected subjects' ongoing emotional states: the aversive effects of withdrawal have been proposed to heighten the state of arousal and thus startle amplitude (Mueller et al., 1998). However our results are not reconcilable with this explanation, as such a motivational account would predict higher startle amplitude in withdrawal relative to during smoking, which is opposite to the findings in either group of the present study.

Nonetheless such motivation-induced arousal may have interacted with nicotine-induced arousal. The two groups differed in dependency as measured by the FTQ, such that the 'complied' group presented with a lower FTQ average, and smoked less cigarettes per day than the 'not complied' group. Consequently the two groups would be expected to differ in severity of withdrawal and thus withdrawal-induced arousal. However arousal is also raised after repeated nicotine inhalation (Knott, Harr and Lusk-Mikkelsen, 1998). It is therefore possible that, as the less nicotine-dependent group experienced less severe withdrawal symptoms (and therefore less withdrawal-

induced arousal), the ensuing comparative reduction in arousal (compared to baseline, chronic nicotine-induced arousal) caused the drop in startle amplitude in this group. This account is problematic, if only for the reason that baseline nicotine levels varied between individuals and were presumably lower in the 'complied' group. Furthermore if severity of withdrawal had been a factor in the observed effects on amplitude, we would have expected FTQ and measures of startle to be correlated, and the interaction of startle amplitude and compliance (Group) to have been abolished after covarying for FTQ. This was not the case.

An alternative account follows observations of differences in (cue) reactivity between smokers who showed different levels of commitment to quitting (McDermut and Haaga, 1998) according to the Stages of Change model (Prochaska and DiClemente, 1983). Briefly this model specifies five different stages of change in an individual's attitude towards a problem behaviour such as addiction, ranging from (1) precontemplation, where no change in behaviour is seriously considered, to (2) contemplation, (3) decision making, (4) active change of the behaviour, to finally (5) maintenance of the new regime. The McDermut and Haaga study showed increased heart rate reactivity to smoking cues for subjects at stage 2 when compared to those at stage 1 of this model, reflecting the former group's increased discomfort. Applied to the present study, our 'complied' group may have been more aroused at baseline compared with withdrawal as they potentially were more committed to quitting, and so this first testing occasion (known to immediately follow the final cigarette) may have appeared more aversive to them than to the group who were less committed. This account might explain the differences between the findings of the current study and other investigations of smokers only asked to quit for experimental purposes. This possibility must remain speculative however and can only be clarified by further studies investigating concurrent levels of arousal.

It is further possible that the observed changes in startle may have reflected nicotine-induced attentional changes. Reports of increases in startle amplitude following

administration of nicotine in the rat have been put forward as evidence for attentional enhancement by nicotine (Acri et al., 1991). In contrast to previous reports of the effects of nicotine on startle amplitude in humans where dosage of nicotine was controlled via exogenous administration (e.g. Kumari et al., 1996, Mueller et al., 1998), this is the first study to compare startle amplitude when nicotine is self-administered via smoking with amplitude following smoking cessation. A considerable amount of research has already aimed to establish whether the differences between smokers in terms of nicotine intake levels reflect individuals' attempts to achieve different physiological effects or constitutional differences between subjects, which require that they ingest different amounts of the drug to achieve the same effect. As subjects presumably were dosing to acquire the individually perceived benefits of the drug, this design should allow one to distinguish subjects aiming to access the attentional benefits (as indexed by high startle amplitude) provided by nicotine from those smoking for other reasons. In the light of these arguments, the observed response pattern in the 'complied' group would suggest that these subjects self-dosed to gain attentional benefits.

As already mentioned, the apparent inconsistency of the data from our 'not complied' group with previous findings, in which similarly high-nicotine-dependent subjects (as established by FTQ scores) showed a reduction of startle amplitude after smoking compared to withdrawal (Kumari et al., 1996, Mueller et al., 1998) may be explained by the unique nature of the present study in studying smokers not quitting for experimental reasons. However another possible explanation of this discrepancy could lie in the influence of the factor of self-applied versus imposed dosing of nicotine. In both previous reports startle amplitude following overnight withdrawal was compared to amplitude following just one cigarette, whereas the present study made this comparison with nicotine levels at optimal/self-desired levels. As Shuh and Stitzer (1995) have shown that heavy smokers usually need two cigarettes to fully relieve withdrawal, it is possible that changes in amplitude seen after one cigarette reflect only partial alleviation of withdrawal. Such a possibility was supported by the Mueller study: after smoking a *second* cigarette the same subjects appeared to show

an *increase* in startle amplitude, which thus returned nearly to withdrawal levels, as was the case in the present study. The possibility that the group differences in startle amplitude may have simply reflected individual differences in startle rather than nicotine-induced differences was ruled out by the lack of difference between groups in startle amplitude during withdrawal, a finding also reported by Kumari and Gray (1999b) in their comparison of high- versus low nicotine-dependent subjects as measured by the FTQ.

Interestingly, the two opposing types of effect on startle amplitude found in the present study have also been reported in rats maintained on chronic doses of nicotine. Thus Acri et al. (1991), using Sprague Dawley rats, reported a decrease and Helton et al. (1993), using Long Evans rats, an increase in startle amplitude following nicotine withdrawal. It is possible that these disparate findings may be explained by strain-dependent responses since Faraday et al. (1998), in a direct comparison of these rat strains, confirmed different sensitivities to acute nicotine (as measured by startle response). This finding, that two rat strains displayed opposing effects from the same dose of nicotine, was proposed as a model of individual differences in sensitivity to nicotine in man. However, it is not clear that this account applies to the present findings, as dosing was clearly not held constant. Our results therefore are more likely to reflect two separate populations who attempt to achieve different physiological effects from self-administered nicotine.

It remains to be clarified *why* startle predicted successful smoking cessation. As seen in previous studies, smokers scoring high on the FTQ were less likely to maintain smoking abstinence than those who scored lower on the FTQ (for review see Fagerstrom and Schneider, 1989), although recent studies have challenged this relationship showing that it is not the *severity* of nicotine withdrawal symptoms which determines the likelihood of successful smoking cessation, but rather the *duration* of such withdrawal symptoms (Piasecki, Fiore and Baker, 1998). As we found no correlation of FTQ with measures of startle, the predictive value of startle for cessation would not seem to reflect levels of dependency or withdrawal severity.

It is however possible that startle indexed motivation as explained by the Stages of Change model, although this needs further investigation. Finally, it has been suggested that benefits gained from smoking such as improved focus on cognitive tasks and increased vigilance may underlie smoking dependence in some individuals (Hughes, 2001). Depending on factors maintaining dependence in different people, smoking cessation might be comparatively less or more problematic.

Following baseline measurements of PPI, we also observed a drop in PPI in all subjects 24 hours after withdrawal. Equivalent findings had previously been reported, but using a between subjects comparison, by Della Casa et al. (1998) and in a study which found increased PPI following the smoking of a cigarette in overnight withdrawn subjects (Kumari et al., 1996). The present study set out to probe whether potential individual differences in such withdrawal induced changes in PPI might distinguish individuals more or less likely to be succesful in smoking cessation. However the absence of any interactions of this change in PPI with Group suggests such changes in PPI not to be predictive of compliance.

Latency to peak response was significantly slower after 24 hours of withdrawal, an observation also made in the Della Casa et al. (1998) study and which these authors attributed to delayed motoric reactions following nicotine withdrawal (Domino and Von Baumgarten, 1969). Changes in peak latency may also reflect prepulse detectability: many studies have shown both improved stimulus detection following nicotine (for a review see Koelega, 1993) and decrements in vigilance during the first few days of abstinence from nicotine (e.g. Warburton, 1992; Gilbert et al., 1992a).

The reduction in startle amplitude relative to baseline in the 'complied' group was still present one month after quitting, although this difference was no longer significant due to a small increase in this measure on the third occasion. The same group of subjects showed no change in percent PPI or amount of PPI over the three occasions (baseline, withdrawal and one month post-cessation).

The present study set out to investigate the effects of smoking cessation and relapse on acoustic startle response and PPI after establishing baseline levels of these measures at optimal/self-desired levels of smoking. A significant drop of startle amplitude in withdrawal relative to baseline appeared to be predictive of individuals' ability to quit smoking. The mechanisms underlying these amplitude changes remain speculative and are suggested to reflect individual differences in either commitment to quitting or perceived benefits from smoking. However the present study is limited by this post hoc interpretation of our findings. Future studies are necessary to confirm the value of startle amplitude in predicting smoking cessation and relapse.

CHAPTER 7

Effects of Nicotine on prepulse inhibition in healthy male smokers, non smokers and schizophrenic patients

7.1 Abstract

The prevalence of cigarette smoking amongst patients with schizophrenia is considerably higher than that seen in any other psychiatric population or indeed general population. It has been hypothesized that this high rate of smoking might reflect an attempt to restore some of the physiological and cognitive deficits of this disorder.

Recent studies have shown that nicotine enhances prepulse inhibition of the startle reflex in humans and animals, a response impaired in a number of psychiatric populations including schizophrenia. Prepulse inhibition (PPI) is defined as the attenuation of the startle response to a startle stimulus (pulse), when such a pulse is preceded by a stimulus of lower intensity (prepulse). PPI is thought to provide an objective measure of sensorimotor gating.

This study examined the effects of 12 μg/kg subcutaneous nicotine on PPI in healthy male smokers, healthy non-smokers and smokers and non-smokers with schizophrenia, using a novel intramodal tactile startle paradigm. Stimulus onset asynchronies (SOA: time from prepulse to pulse) were set at 30, 60 and 120-ms. Nicotine enhanced PPI in all subject groups, irrespective of smoking status. This study provides further support for the premise that the excessive rate of smoking seen in patients with schizophrenia may represent an attempt to improve sensorimotor gating deficits.

7.2 Introduction

The startle response and its several forms of plasticity have enabled the investigation and comparison of very basic cognitive and attentional processes across species. Upon exposure to a strong exteroceptive stimulus such as a burst of noise or flash of light, most mammals react with a startle reflex comprising abrupt muscular flexion and extension which can be measured in animals as whole body jump, e.g. via stabilimeter displacement (Hoffman and Ison, 1992), and in human beings as eyelid closure (Graham, 1992). Startle response amplitude is thought to provide a sensitive measure of reactivity to external stimuli (Davis, 1984), as well as reflecting changes in attentional processes in humans (Anthony and Putnam, 1985). Prepulse inhibition of the startle reflex (PPI) refers to a reliable modification of this startle response which occurs when a startle eliciting stimulus (pulse) is preceded by a less intensive stimulus (prepulse) of subthreshold intensity. Providing the time from prepulse onset to pulse onset, or stimulus onset asynchrony (SOA), is short (i.e. between 30 and 500-ms), such modification appears as inhibition of the startle reflex.

PPI is thought to provide an operational measure of a sensorimotor gating mechanism, which by filtering out sensory input helps to reduce demands upon a limited capacity information processing system (Braff and Geyer, 1990; Graham, 1975, 1980). Consistent with this, PPI is reduced in a number of neuropsychiatric disorders characterised by the inability to screen out excessive sensory information, such as schizophrenia; this fundamental gating deficit has been thought to underlie the sensory overload and cognitive fragmentation experienced by this patient group (e.g. McGhie and Chapman, 1961; Braff and Geyer, 1990). PPI deficits in this patient group as well as in patients with schizophrenia spectrum disorders have been demonstrated using intramodal paradigms featuring acoustic (Braff et al., 1978, 1992, 1999a; Cadenhead et al., 1993, 2000; Grillon et al., 1992; Kumari et al., 1999a; 2000) and electrocutaneous (Bolino et al., 1994) stimuli. Deficits have also been demonstrated with a cross-modal paradigm comprising acoustic prepulse and tactile pulse stimuli (Braff et al., 1992). Furthermore, the brain areas identified as regulating

startle gating in animal studies, namely neural pathways linking the limbic system and the basal ganglia, have also been shown to be part of the pathophysiology of schizophrenia (Swerdlow et al., 1992a). Accordingly impaired PPI has been put forward as a useful biological marker for schizophrenia and related disorders, although the exact relationship between PPI and sensory gating is not yet clear (Cadenhead et al., 1993).

PPI has proved valuable for the evaluation of the effects of various drugs on sensorimotor gating. For instance numerous studies have documented the disruption of PPI via dopaminergic agonists such as apomorphine and amphetamine in animals (for review see Swerdlow et al., 2000) where the capacity of antipsychotic substances to restore normal PPI in these animals has been correlated with their antipsychotic potency in man (e.g. Swerdlow et al., 1994a). Consequently in a number of laboratories PPI is considered a valuable instrument in the screening of such drugs (e.g. Hoffman et al., 1993). Interestingly, nicotine enhances PPI in the rat (Acri et al., 1994) as well as healthy human smokers and non-smokers (Kumari et al., 1996, 1997b; Della Casa et al., 1998; Duncan et al., 2001) which raises the possibility that nicotine might have anti-psychotic properties in Man and that at least some of the inhibitory deficits characteristic of schizophrenia might be normalised via nicotine. Indeed the prevalence of smoking in schizophrenia far exceeds that seen in the general and any other psychiatric population (Hughes et al., 1986) which has led to the suggestion that this excessive rate of smoking might reflect an attempt at some form of self-medication (e.g. Dalack et al., 1998). Consistent with this Adler et al. (1993) showed impaired sensory gating of the P50 wave, a paradigm closely related to PPI, to be restored in schizophrenic patients following nicotine. Equally, recent findings by Kumari and colleagues (Kumari, Soni and Sharma, 2002) have confirmed an enhancing effect of nicotine on acoustic PPI in this patient group.

To date the effects of nicotine on PPI in humans have been examined using an acoustic startle paradigm. The present study sought to establish whether the inhibition enhancing effect of nicotine also occurred using a novel, intramodal tactile

startle paradigm, specifically designed for the MRI scanner by Kumari et al. (1998), in healthy smokers and non-smokers. Using the same paradigm we set out to investigate whether the reduced PPI seen in people with schizophrenia is restored via nicotine administration. Confirmation of such an effect would strengthen the argument that the excessive smoking seen in this patient group is done for a specific pharmacodynamic effect.

7.3 Materials and methods

Subjects

Twenty-one healthy male non-smokers and nineteen smokers were recruited via advertisement and from referrals by other subjects. Fourteen male schizophrenic patients with a DSM IV (First et al., 1999) diagnosis of schizophrenia were recruited via the in- and outpatient services of the Maudsley hospital, London of whom ten were smokers, and four were non-smokers. All patients had been on stable typical antipsychotic medication for a minimum of six weeks prior to taking part in this study.

Control subjects were screened by a clinician using the Structured Clinical Interview for DSM-IV axis I disorders, non patient edition (SCID – I/NP; First et al., 1996). Exclusion criteria included any history of significant medical illness and loss of consciousness as well as history of psychiatric illness in subjects or their first degree relatives. All subjects were right-handed and were screened for illicit drug abuse via urine analysis (none were excluded). Smoking dependence in the smoking controls and patients was established using the Fagerstrom tolerance questionaire (FTQ; Fagerstrom and Schneider 1989) (see table 7.1 for demographic characteristics of participant groups).

	Patients	Smokers	Non-smokers
Age	34.88 (14.08) range 20-54	31.83 (7.9) range: 23-50	27.75 (9.82) range: 20-51
Bodyweight	73 (13.75)	77.15 (11.22)	79 (9.57)
PANSS*: Positive Symptoms	9.33 (3.31)	n/a	n/a
PANSS*: Negative Symptoms	12.77 (3.7)	n/a	n/a
PANSS*: General Psychopathology	24.66 (4.38)	n/a	n/a
Age at onset of illness	24.44 (6.36)	n/a	n/a
Medication dose: *Chlorpromazine* *equivalents*	164.65 (81.15)	n/a	n/a
FTQ	8.14 (1.67) (n=7)	6.91 (1.78)	n/a

*Table 7.1: Demographics of participant groups (*Positive and Negative Syndrome Scale Kay et al., 1987)*

All subjects gave written informed consent. This study was approved by the ethics committee of the Institute of Psychiatry and Maudsley Hospital, London.

Experimental design

Subjects were tested (double-blind) on two separate occasions a fortnight apart:
(i) once after receiving 12 microgrammes/kg bodyweight of nicotine, and

(ii) once after receiving saline (placebo). This dose of nicotine has been shown to reliably elicit changes in PPI (Kumari et al., 1997b). The appearance of the saline and nicotine preparations was identical. Placebo or nicotine was administered via subcutaneous injection to the triceps region of the left upper arm. The doses of nicotine were prepared as 1mg nicotine base in 1 ml of 0.9% saline with added sodium bicarbonate (2.13g/250ml of prepared solution). Time of day of testing was held constant for each subject. Drug order was randomised such that half the subjects received saline and the other half nicotine on the first occasion. Startle testing commenced ten minutes after injection in order to cover the period of maximum effects of nicotine given via this method (Russell et al.,1990).

Startle response measurement

Tactile stimuli comprised pulse alone trials (a 40-ms presentation of 30 p.s.i. air-puff) and prepulse trials (pulse preceded by a 20-ms presentation of 10 p.s.i. air-puff) delivered via two, 1 cm diameter plastic tubes to the neck above the sternum. Presentation of tactile startle stimuli and recording of responses were controlled by a commercially available computerised human startle response system (San Diego Instruments, San Diego, California). Measurement of the startle response (eyeblink amplitude) was achieved by recording the electromyographic (EMG) activity of the right orbicularis oculi muscle via two (6mm) Ag/AgCl electrodes filled with Dracard electrode gel. After preparing the skin surface with Sterets sterile swabs, one electrode was positioned approximately 1 cm lateral to, and 0.5 cm below, the lateral canthus of the subject's right eye, while the second electrode was placed 1.5 cm below and slightly medial to the first electrode, such that both electrodes were equidistant from the centre of the eye. In addition a ground electrode was placed behind the right ear over the mastoid.

Three 5-minute experiments (experiments 1, 2 and 3) were conducted within which 5 blocks of pulse alone trials were alternated with 5 blocks of prepulse trials (total of

60 trials per experiment). Within each block the inter-trial intervals between the six trials were randomised. This 'box-car'design in which two blocks or conditions are alternated at a regular interval is widely used in fMRI studies and was employed in this investigation as the intention was to repeat the current study in the MRI scanner at a later date. The three experiments were distinguished by the different stimulus onset asynchronies (SOAs; i.e. time from onset of prepulse to onset of pulse) of the prepulse trials, these being set at 30- (experiment 1), 60- (experiment 2) and 120-ms (experiment 3). The experiments were conducted in three orders (1,2,3; 2,3,1 and 3,1,2) to control for order effects. Subjects were not required to make any voluntary response during the experiments.

General procedure

Upon recruitment, subjects were informed about the procedure and were told that the purpose of the investigation was to establish the effects of nicotine on reactivity to air puffs. All subjects were asked to refrain from alcohol 24h before their appointment. Smoking subjects were also requested to abstain from smoking for 12 hours before testing. Subjects were made comfortable on a hospital trolley with the back adjusted so that each subject was half reclining. The procedure was explained again, after which electrodes were positioned. Subjects were told to relax as much as possible, but stay awake. No instructions were given re ignoring or attending to the stimuli. Subjects then received the injection. Ten minutes post injection startle testing commenced. Blood pressure and heart rate were monitored at three timepoints: before injection, after injection and after completion of the test.

Subjects showing low reactivity to the tactile stimuli as measured by eyeblink activity were excluded from the final data analysis. Subjects were deemed 'non-responders' if they failed to show a response (i.e. lower than 40 units: each unit = 2.62 μV) on 40% or more of Pulse only trials.

Statistical Analyses

Effects of nicotine on heartrate were assessed via a 2 x 3 x 2 [Drug x Occasion (before injection, 9 minutes after injection, post-testing) x Smoking Status (smokers/non smokers)] analysis of variance (ANOVA: Greenhouse Geisser). A t-test was performed to determine whether patient and control smokers differed in levels of smoking dependence as measured by the FTQ. Forty-three percent of the non smokers, 37% of the smokers and 36% of the patients were classed as non-responders to the tactile stimuli, leaving 12 healthy non-smokers, 12 healthy smokers and 9 patients (of whom 2 were non-smokers) for the final analysis. A chi square test was performed to determine whether the rate of responding/ non-responding varied between groups. A t-test was used to establish whether the responders differed in average age from non-responders. All analyses were performed using SPSS Windows (version 10).

Habituation of the startle response was assessed by subjecting the amplitude data from the pulse-only trials to a 2 x 3 x 2 x 2 [Drug x Experiment (pulse-only amplitudes from each 5 minute experiment in order of presentation) x Group (patients/ controls) x Smoking Status] ANOVA (Greenhouse Geisser). Drug and Experiment were entered as within subject factors.

Prepulse inhibition was calculated in two ways: (i) as amount of PPI, i.e. the arithmetic difference between mean pulse-alone amplitude and mean prepulse amplitude, and (ii) as percentage PPI, namely as (a-b/a) x 100, where a = pulse alone amplitude and b = amplitude over prepulse trials.

The effect of subcutaneous nicotine on amount of PPI was examined through a comparison of amount of PPI scores which were subjected to a 2 x 3 x 2 x 2 [Drug x Trial type (30-ms, 60-ms and 120-ms prepulse trials) x Group x Smoking Status] ANOVA (Greenhouse Geisser) with Drug and Trial type entered as within subjects factors. This analysis was repeated substituting percent PPI as the dependent variable.

Where relevant, interactions were followed up with paired and independent t-tests. The duration of the study (20 minutes) had been determined in order to exploit the maximum effects of nicotine (Russell et al., 1990). Nonetheless the possibility exists that the pharmacological effect of nicotine may have dissipated as a function of time and possibly at a different rate in different individuals, with the effects being the most pronounced during the first block of trials. Therefore to allow for this, data were also analyzed for the first block of trials only via a 2 (Drug) x 2 (Group) x 3 (Trial type) ANOVA, with Drug entered as a within-subjects factor, and Group and Trial type as between-subject factors.

The effects of subcutaneous nicotine on latency to response peak were considered via a 2 x 4 x 2 x 2 [Drug x Trial type (3 SOAs and latency over Pulse-only trials) x Group x Smoking Status] ANOVA (Greenhouse Geisser) with Drug and Trial type entered as within subjects factors.

7.4 Results

For the effects of nicotine on heartrate we found a significant interaction between Occasion and Drug [F(1.23, 45) = 3.69, p<.031; partial eta squared = 0.091] (see table 7.2), which a follow up t-test confirmed reflected an increase in heartrate 9 minutes after the nicotine injection [t(32)= 2.21, p<.034; partial eta squared = 0.132].

	Baseline	9 minutes post-injection	Post testing
Placebo	68.12 (SD 7.80)	67.09 (SD 9.13)	67.79 (SD 8.35)
Nicotine	68.94 (SD 7.92)	70.75 (SD 8,78)	67.88 (SD 7.80)

Table 7.2: Heartrate over three Occasions by drug

Although the smoking patients showed a higher average FTQ than the smoking controls (see table 7.1) this difference did not reach significance (p>.05). Nine of the 21 non-smokers (43%), 7 of the 19 smokers (37%) and 5 of the 14 patients (36%) were non-responders. There was no difference in responsivity between the patient and control groups to this tactile paradigm (p>.05). The mean age of non-responders (38.28, SD 9.82) was significantly higher than responders (31.18, SD 10.61) [t(52)= 2.47, p<.017 ; partial eta squared = 0.104].

There was significant habituation, as evidenced by the main effect of Block [F (1.34, 39.06) = 22.513, p<.01; partial eta squared = 0.435]. Habituation was not affected by Group, Drug or Smoking Status (p> .05).

The analysis of amount of PPI revealed main effects of Trial type [F (1.31, 38.07) = 6.15, p<0.012; partial eta squared =.174] indicating greater inhibition following prepulses at SOAs of 60 and 120-ms than prepulses at 30-ms. There was no significant effect of drug on amount PPI [F (1, 29) = 3.053, p<.091] and a significant interaction of Trial type and Drug, reflecting the more pronounced effect of nicotine on amount PPI at the SOA of 30-ms [F (1.58, 46) = 4.458, p<.024; partial eta squared =.132].

Analysis of percent PPI also showed main effects of Trial type [F (1.65, 47.85) = 9,853, p< .01 partial eta squared =.244]. Furthermore there was a main effect of Drug [F (1, 29)=9.459, p< .005 partial eta squared =.214]. There was no interaction for Trial type and Drug [F (1.548, 48) = 2.988, p< .072]. However we did observe a three way interaction between Drug x Trial type x Group [F (1.548, 48) = 4.677, p< .021; partial eta squared =.131]. There was no effect of smoking status (p>.05). This interaction was further investigated by assessing the 2 way Drug by Group interactions (against the pooled error terms from the Group by Drug and Group by Drug by Trialtype strata) while holding each of the three levels of Trial type fixed. These comparisons yielded no significant interaction at the 30-ms condition [$F_{(pooled)}$ (1,3) = 1.57, p= .213] which indicates that the apparent reduction in PPI at this interval under placebo in the patient group relative to controls (see fig.7.1) was not significant. Also there was no significant interaction at the 60 ms condition [$F_{(pooled)}$ (1,3) = .09, p= .765]. However at 120 ms this interaction *was* significant [$F_{(pooled)}$ (1,3) = 4.45, p= .038] reflecting opposite effects of nicotine in the two subject groups: in patients, the PPI was greater in the placebo than the drug condition whereas in the controls, PPI was greater in the drug condition than placebo (see fig. 7.1).

Subsequent t-tests further probed the effect of nicotine on PPI in both groups, with nicotine having a significant enhancing effect on PPI at 30-ms for patients [$t_{(pooled)}(8)$ =3.97, p<.004; partial eta squared =.0.66; Bonferroni corrected p = .024] as well as controls [$t_{(pooled)}(23)$ = 3.20, p<.004; partial eta squared =.314; Bonferroni corrected p

= .024]. Patients showed no significant change at the SOAs of 60-ms [$t_{(pooled)}(8)$ = 1.40, p<.198; observed power = .171] or at 120-ms [$t_{(pooled)}(8)$ = .0626, p<.548; observed power = .071]. The control subjects also showed this enhancing effect at the SOA of 120-ms [$t_{(pooled)}(23)$= 4.31, p< .001; partial eta squared =.45; Bonferroni corrected p = .006] but no significant change in PPI following nicotine at 60-ms [$t_{(pooled)}(23)$ = 1.48, p<.15; observed power = .381].

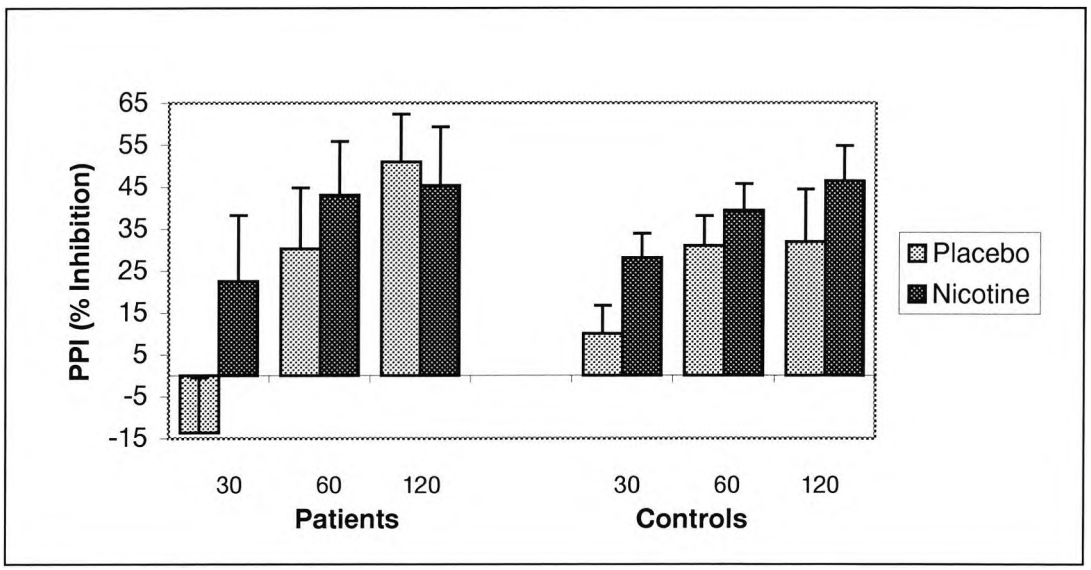

Figure 7.1: Mean (error bar displays 1 SEM) prepulse inhibition (PPI) of the startle response at 30-ms, 60-ms and 120-ms SOAs in patients with schizophrenia and control subjects during placebo and during 12 μg/kg subcutaneous nicotine.

The analysis of percentage PPI data for the first block of trials showed a significant effect of drug [F(1,27) = 8.85, p<.006 partial eta squared =.247], with no further effects or interactions. This suggests that there was an enhancing effect of nicotine on PPI for both subject groups. Furthermore, in contrast to the results from the overall analysis, the absence of an interaction suggests this effect to have been present for all three trial types. However it is possible that this analysis lacked power to detect such an interaction effect (observed power = .207), as only 12 subjects contributed to the 30-ms, 13 to the 60-ms and 8 to the 120-ms condition. The discrepancy between the

results from the overall (within-subjects) analysis and the first block (between-subject) analysis can only be resolved in future studies with more participants.

Analysis of mean latencies to response peak showed a main effect of Trial type [$F(2.142, 66.39)=22.359$, $p<0.01$] confirming shorter latencies over the prepulse conditions compared with pulse only trials, with the greatest facilitation occurring at the 120 ms condition. No other main- or interaction effects were found.

7.5 Discussion

This is the first study to show that acute nicotine enhances PPI in both healthy control subjects and schizophrenic patients using an intramodal tactile startle paradigm. The absence of any effect of smoking status confirmed that this effect occurred in both smoking and non-smoking subjects. The results revealed a differential effect of nicotine between patients and controls: although the patient group showed increased PPI following nicotine on both 30-ms and 60-ms trials, this increase was only significant at the 30-ms condition. In contrast, control subjects showed significantly enhanced PPI on 30-ms and 120-ms trials. The present findings with the novel, intramodal tactile paradigm, are consistent with previous reports of enhanced PPI following nicotine in both healthy smokers and non-smokers using acoustic startle paradigms (Kumari et al., 1996, 1997b; Della Casa et al., 1998; Duncan et al., 2001). Furthermore, the results of the present study confirm that nicotine also has a restorative effect on the impaired sensory gating seen in patients with schizophrenia as measured by PPI.

As is well established with the acoustic startle paradigm, we observed a linear increase of PPI according to SOA with the greatest prepulse inhibition occurring at the SOA of 120-ms. The most notable difference between the paradigm of the present study and the acoustic startle paradigm was the number of non-responders, which was greater in the novel paradigm than is usually observed with the acoustic version in our laboratory (where the exclusion rate has varied between 0-20%). One factor which may have contributed to this was the design of the experiment, in that the (unavoidable) non-random presentation of stimuli may have accelerated the habituation effect in some subjects, to the extent that the predictability of the stimuli caused an extinction of the response. Another factor may have been the age of our overall sample: while the number of non-responders was similar for the different subject groups, the average age of non-responders was greater than that of responders. This is in line with a previous report of reduced responsivity in older subjects made by Ellwanger and Braff (1999) who attribute this phenomenon to an

age-related decline of sensory and/or motor components of the startle reflex, while inhibition of the startle reflex on the other hand appears resistant to the detrimental effects of the ageing process.

The effects of nicotine over the entire subject sample were apparent on both measures of PPI, namely as percentage reduction of non-prepulse trials as well as the calculated arithmetic difference between pulse-only and prepulse trials, although the latter measure only showed a trend for such an effect. This discrepancy may reflect the fact that, unlike percentage PPI, this measure does not take into account baseline variations between subjects (e.g. Kumari et al., 1997b). Nicotine did not cause changes in startle amplitude.

The present findings using tactile stimuli are comparable to those of Kumari et al. (1997b) which, using the same dose and method of nicotine administration as in the present study, showed nicotine to enhance PPI at all SOAs in healthy non-smokers in an acoustic PPI paradigm (Kumari et al., 1997b). Equally the present study confirmed an increase of tactile PPI after nicotine in overnight-withdrawn healthy smokers, as had previously been reported with acoustic PPI paradigms by Kumari et al. (1996), Della Casa et al. (1998) and Duncan et al. (2001). Furthermore there are interesting parallels between our findings in the patient group (i.e. nicotine-induced enhancement of PPI was most pronounced at 30-ms and only marginal at 60-ms) and those recently reported by Kumari et al. (2001). Using a different approach, Kumari and colleagues investigated the relationship between PPI and time elapsed since last cigarette in a group of schizophrenic patients. They reported a significant negative correlation between these two measures for the SOA of 30-ms, with a trend for a similar relationship at 60-ms. The reduced impact of smoking on PPI at longer SOAs was attributed to the effects of antipsychotic medication, as this appears to improve PPI at longer intervals, therefore allowing less margin for improvement (e.g. Kumari et al., 1999a; also see below).

The present study was designed to allow for maximal effects of nicotine by testing the subset of smoking subjects (patients and controls) under nicotine withdrawal on both the placebo and drug occasions. Therefore, performance during placebo in these subjects was assumed sub-optimal due to nicotine withdrawal (e.g. Kumari et al., 1996). Thus an important limitation of the present study is that, as the PPI observed under placebo did not provide a true 'baseline' measure, it was not specifically designed for, and consequently perhaps not as sensitive for detecting deficits in the patient group.

In addition to this design issue, the lack of a significant deficit in the patient group may have been attributable to a reduced sensitivity of the novel tactile paradigm itself for detecting such deficits. For instance Braff et al. (2001a) have shown how manipulation of prepulse characteristics can have a major influence on the ability of an acoustic PPI paradigm to detect such deficits. As this was the first time that this tactile paradigm has been applied to a comparative study, such parameters have not yet been established. Clearly such issues need further investigation.

The present findings may be compared with previous reports of impaired PPI in schizophrenic patients. As stated in the introduction, such deficits have been demonstrated using intra-modal acoustic and cross-modal (acoustic-tactile) paradigms. While most such studies have investigated such effects using the 120-ms SOA only, a number of studies featuring the same range of SOAs as employed by the present investigation showed impaired PPI in patients at SOAs of 30-ms (Kumari et al., 1999a; Braff et al., 1992), 60-ms (Kumari et al., 1999a; 2000; Braff et al., 1992; 1978) and 120-ms (Braff et al., 1992) using acoustic intra-modal paradigms. The precise impact of different classes of antipsychotic medication on such deficits is still unclear. In both studies by Kumari and colleagues such deficits were restricted to the subgroups of patients on typical antipsychotic medication. It was suggested that typical antipsychotics have a selective restorative effect on deficient PPI in schizophrenic patients, in that thus medicated patients showed impaired PPI at short (30-ms and 60-ms) but not at longer (120-ms) SOAs. However, Braff et al. 's (1992)

findings were of deficits at all three SOA's in patients receiving typical antipsychotics. In this context it is interesting to consider the reduction (albeit non-significant) in PPI at 30-ms but not the other SOAs (placebo) observed in the patient group of the present study (see figure 7.1) as it appears to be consistent with Kumari's claims. These authors put forward that the ability of typical drugs to partially restore PPI results from such drugs' positive effects on tasks requiring controlled attention; at longer but not shorter SOAs it is feasible that some active processing of the prepulse occurs (Kumari et al., 1999a). Evidence from a number of studies (Kumari et al., 1999a, 2000; Weike et al., 2000) have confirmed the more comprehensive restorative effects of atypical antipsychotics on PPI deficits, undoubtedly stemming from the broader pharmacological profiles of these drugs. In the context of the present findings of particular interest is the observation that patients receiving the atypical clozapine show a reduction in their ad-lib smoking levels (Buckley et al., 1994; George et al., 1995).

The excessive use of tobacco amongst patients with schizophrenia has been hypothesized as an attempt at some form of self-medication, however the precise nature of these positive effects still remain unclear. Thus the suggestion has been made that patients smoke to reduce the negative side effects of neuroleptic medication (Miller, 1977), however in cultures where such medication is not prescribed, patients are still seen to persist in heavy use of cholinergic agonists such as the betel nut (Burton-Bradley, 1978). The exact benefits are also made elusive by the observation that smoking does not significantly decrease the symptoms of this disorder (e.g. Dalack et al., 1999). The most convincing evidence to-date supports a role for nicotine in improvement of more basic attentional abnormalities of the disorder as measured by paradigms tapping sensory gating (P50 gating: Adler et al., 1993, 1992) and sensori motor gating (PPI : Kumari et al.1996;1997b). The results from the present study add to these findings, showing nicotine to increase gating in patients as well as healthy volunteer smokers and non-smokers. Furthermore they also suggest a restorative effect of the drug on deficient gating, although this claim is

made tentatively given the lack of a pronounced deficit in baseline inhibition levels in the patient group.

In order to control for the confounding effects of varying baseline levels of nicotine all smokers in the present study were in withdrawal. However the observation of increased PPI in both smokers *and* non-smokers indicates that the resulting enhancement in PPI was a 'true' drug effect and not solely a restoration of a withdrawal-induced deficit. This mirrors Kumari et al.'s (1996; 1997b) interpretation of similar findings. Even so, while functionally nicotine appears to affect all groups in a similar way, it is only possible to speculate for now on the mechanisms via which such changes in PPI occur, or if indeed the same mechanisms subserve this response in different populations. Nicotine acts on multiple sites in the brain, interacting with dopaminergic and cholinergic transmitter systems (e.g. Clarke et al., 1984, Gray et al., 1994) both of which have been implicated in the modulation of PPI (e.g. Geyer et al., 2001). Recently compelling evidence has been put forward which suggests that the hippocampal α7 receptors may be the likely site for the inhibition enhancing effect of nicotine on both PPI and P50 gating. The intensity of sensory gating deficits (as measured by N40 - the animal equivalent of P50) in in-bred mouse strains correlates with low levels of hippocampal α7 receptors, and such deficits are temporarily restored by administration of nicotine (Stevens et al., 1996; Stevens and Wear, 1997). Freedman et al. (1995) have confirmed decreased levels of α-bungarotoxin subtype receptors in the hippocampi of schizophrenic patients, and the impaired P50 gating observed in this patient group and their unaffected relatives is restored via nicotine (Adler et al., 1993; Freedman et al., 1994). PPI is increased in the rat following nicotine, an effect which is still intact following co-administration with the selective high-affinity nicotinic receptor blocker mecamylamine, thus implicating low-affinity α7 receptors (Curzon et al., 1994). PPI is enhanced following nicotine in human non-smokers, but only with a high dose, which suggests low-affinity receptor involvement (Kumari et al., 1997b). This being the case it is possible that individuals might self-administer doses of nicotine in order to

specifically target these receptors and the associated behavioural benefits. The most common method of self-administration of nicotine lends itself well to such titration, as inhalation of cigarette smoke results in almost immediate absorbtion of nicotine and therefore the effects can be monitored by the user. Schizophrenic patients who smoke tend to use higher nicotine strength brands and extract more nicotine from their cigarettes when compared with other smokers (Olincy et al., 1997). This could reflect these individuals' attempts to increase sensory gating via targetting of low-affinity receptors. However, given the rapid desensitisation of nicotinic receptors following exposure to nicotine, it would seem likely that any such beneficial effects are temporary, which in turn could explain the inability of cigarette smoking to effectively treat the symptoms of this disorder (Adler et al., 1993).

In conclusion, the present findings, using a novel tactile startle paradigm, are in line with previous reports of enhanced PPI under nicotine in healthy smokers and non-smokers, as well as confirming this effect in schizophrenic patients. Further support therefore has been provided for the premise that the excessive rate of smoking and increased nicotine absorbtion (Olincy et al., 1997) seen in schizophrenic patients serves as a form of self medication, as well as upholding a possible role for nicotinic agonist treatments in schizophrenia. However the mechanisms through which nicotine affects PPI are still unknown. Neither is it yet clear whether the modulatory effect on PPI as seen in patients and healthy subjects is subserved by the same or different mechanisms. Further experiments using functional imaging are currently being carried out in our laboratory aiming to help clarify such issues.

CHAPTER 8

An fMRI investigation into the effects of subcutaneous nicotine on prepulse inhibition of the startle reflex in healthy male smokers and schizophrenic patients.

8.1 Abstract

Nicotine has been shown to enhance prepulse inhibition of the startle response (PPI) in animals and humans. PPI is widely held to be a measure of sensorimotor gating, which is deficient in people with schizophrenia. In a previous study (chapter 7) we established that 12 μg/kg subcutaneous nicotine enhanced PPI using a novel intramodal tactile paradigm in both healthy subjects and schizophrenic patients. The current study set out to explore the neural mechanisms of this enhancing effect using functional Magnetic Resonance Imaging (fMRI).

Six healthy subjects and five schizophrenic patients were selected from the original sample, all of whom were smokers. Subjects were scanned on two separate occasions, once under placebo and once after receiving the above stated nicotine dose, a fortnight apart. Using an A/B box-car design, PPI trials set at three different stimulus onset asynchronies (SOA) of 30, 60 and 120-ms were compared with startle-only trials. Comparison of patterns of brain activation on nicotine versus placebo trials showed increased activation of limbic regions and striatum in both subject groups during nicotine. Furthermore subsequent correlational analyses confirmed the enhancing effect of nicotine on PPI to be related to increased activation of the hippocampus in both groups.

8.2 Introduction

A key feature of schizophrenia is the inability to screen out irrelevant sensory input, and the resulting cognitive overload is thought to give rise to some of the symptoms seen clinically. Prepulse inhibition (PPI) is thought to provide an operational measure of a sensorimotor filtering system, and refers to a reduction in response to a startling sensory stimulus, if that stimulus is preceded shortly by a weak non-startling stimulus (e.g. Graham, 1975). PPI is impaired in patients with schizophrenia (e.g. Braff et al., 1978, 1992, 1999a; Cadenhead et al., 1993, 2000; Kumari et al., 1999a, 2000). Animal models of disrupted PPI have proved valuable for the evaluation of antipsychotic substances: apomorphine and amphetamine-induced PPI deficits in animals (for review see Swerdlow et al., 2000b) can be restored via antispsychotic medication, and the capacity of these substances to restore PPI is correlated with their antipsychotic potency in man (e.g. Swerdlow et al., 1994a).

Interestingly, nicotine enhances PPI in the rat (Acri et al., 1994), as well as in healthy human smokers and non-smokers (Kumari et al., 1996, 1997b; Della Casa et al., 1998; Duncan et al., 2001). Using an intramodal, tactile startle paradigm, we have found that nicotine also enhances PPI in schizophrenic patients as well as non-smoking and smoking healthy subjects. This raises the possibility that nicotine might have anti-psychotic properties in humans and that at least some of the inhibitory deficits characteristic of schizophrenia might be normalised via nicotine. This is consistent with the observation of excessive tobacco use in schizophrenia, which is much higher than that seen in both the general population or in other psychiatric disorders (Hughes et al., 1986), and which is speculated to reflect an attempt at some form of self-medication (e.g. Dalack et al., 1998).

Nicotine also enhances the impaired sensory gating of the acoustically elicited P50 wave in schizophrenic patients (Adler et al., 1993) and their relatives (Adler et al., 1992). P50 and PPI have a number of phenomena in common, which has led to the assumption that they might reflect similar processes and/or be regulated by similar

physiological systems. Yet comparisons of behavioural response patterns have failed to show a strong relationship between these two measures, with some studies confirming only a tenuous relationship (Schwartzkopf et al., 1993; Oranje et al., 1999) and others reporting no such correlation between these measures (e.g. Ellenbroek et al., 1999). Observations from both paradigms have led to the suggestion that schizophrenic patients may smoke in order to improve deficient sensory filtering.

In the rat PPI is regulated via cortico-striatal-pallido-thalamic circuitry (CSPT; Swerdlow et al., 1992a). Challenges to substrates of this circuitry reliably produce deficits in PPI, which is consistent with the hypothesis that the impaired sensory gating seen in schizophrenia may arise from abnormalities in the neural interactions between limbic structures and basal ganglia.

The present study set out to establish the neural correlates of nicotinic modulation of PPI using functional Magnetic Resonance Imaging (fMRI). Brain imaging techniques such as PET and fMRI have enabled in vivo investigations of functional activity in the brain and a number of recent studies have shown how it is also possible to detect drug-induced changes in neural activity by comparing placebo and drug states, thus providing a valuable tool for probing drug mechanisms in living animals and humans by helping to identify the sites of action of such substances. Such human studies have included investigations of neural effects of apomorphine (Grasby et al., 1992: Friston et al., 1992; PET), ketamine (Lahti et al., 1995: PET), cocaine (e.g. Breiter et al., 1997; fMRI; Li et al., 2000; fMRI), heroin (Sell et al., 1997: fMRI; Sell et al., 2000: PET) and nicotine (e.g. Stein et al., 1998; Ross et al., 2001: fMRI).

Extending this approach, an increasing number of studies are investigating the effects of pharmacological challenges on patterns of neuronal activation induced by performance on a cognitive task. Thus, using PET Grasby et al. (1992) have investigated the effects of DA agonists apomorphine and buspirone on free recall, Grasby et al. (1995) the effects of the cholinergic (muscarinic) antagonist

scopolamine on working memory and Ernst et al. (2001) the effects of nicotine on working memory. Using fMRI, Thiel et al. (2001) examined scopolamine- and lorazepam-induced modulation of repetition priming. The above studies were all using healthy volunteers. Recently this approach has also been applied to probe functional abnormalities in psychiatric populations: for example Dolan et al. (1995) used PET to compare brain activation patterns in schizophrenic patients and healthy controls on a verbal fluency task following apomorphine. In exploring the impact of an independent variable (such as a drug) on the neuronal response to performance on a cognitive task, such investigations have provided an exciting way of moving beyond the mainly correlative nature of brain imaging studies of cognitive performance.

Attempts to use in-vivo imaging techniques to elucidate PPI circuitry in humans have involved two distinct approaches. Kumari and colleagues (1998a; 2002b) employed a no-task PPI paradigm, basing their functional comparisons on prepulse versus pulse-only trials. Hazlett and colleagues (1998; 2001) used a paradigm designed to tap attentional modulation of PPI; their functional comparisons centred on attended versus ignored prepulse trials. Both studies by Kumari et al. (1998a; 2002b) used fMRI, the first limited to healthy subjects, and the second offering a comparison of healthy controls and schizophrenic patients and confirming greater activation of striatum, hippocampus and thalamus in the control group. Hazlett et al. (1998) used positon emission tomography (PET) to compare activation patterns in schizophrenic patients and control subjects. Patients showed reduced activation of superior, middle and inferior frontal gyrus and parietal cortex relative to control subjects. However in testing a voluntary component of PPI, this study was complicated by potentially confounding motivational factors. Equally the resolution offered by this technology did not allow for a detailed exploration of the CSPT circuitry believed to modulate PPI. Their subsequent study exploited the superior resolution offered by fMRI to confirm a relationship between increased thalamic activation and increased PPI in healthy subjects.

The present study used fMRI to investigate changes in blood-oxygen-level dependent (BOLD) brain activity co-occurring with the effects of subcutaneous nicotine on PPI. Indirect evidence strongly suggests involvement of hippocampal α7 subunit-containing nicotinic receptors in the nicotine induced improvement of deficient P50 gating in humans (e.g. Freedman et al., 1995). Evidence from animal studies confirms that this may also be the mediating site of this effect in PPI in animals (e.g. Stevens et al., 1998; Bullock et al.,1997).

In order to maximise the modulatory effect of nicotine we examined this effect in overnight-withdrawn healthy smokers and individuals with schizophrenia. Our expectations were that the modulatory effects of nicotine on PPI would be particularly evident in limbic and thalamic structures as these areas are rich in the α7 subunit-containing nicotinic receptors implicated in previous findings.

8.3 Materials and methods

Subjects

Six healthy male control subjects and six male schizophrenic patients (all smokers) with a DSM IV (First et al., 1999) diagnosis of schizophrenia were recruited from the original sample (see Chapter 7) for this study. One of the patients subsequently withdrew from the study, limiting the number of patients to five. All patients had been on stable typical antipsychotic medication for a minimum of six weeks prior to taking part in this study. Subjects gave written informed consent. This study was approved by the ethics committee of the Institute of Psychiatry and Maudsley Hospital, London.

All subjects had previously taken part in the offline equivalent of this study (Chapter 7), and therefore had been subjected to the identical procedure outside the MRI scanner. The data thus obtained from the offline study served as the behavioural data

for analysis in the present fMRI study, as the MRI environment precluded measurement of EMG responses during scanning. As PPI provides a very stable neurobiological measure with high test-retest validity (Cadenhead et al., 1999, Abel et al.,1998) this was not anticipated to impact the findings. Subjects were recruited for the MR study on the basis of their responsivity to the paradigm, and whether their response to nicotine was representative of the overall group response. In order to minimise any discrepancies between the off-line and on-line occasions, the experiments were conducted for each subject in the order in which they had experienced them previously in the off-line study. Subjects were not required to make any voluntary response during the experiments.

Cognitive activation paradigms

Tactile stimuli comprised pulse alone trials (a 40-ms presentation of 30 p.s.i. air-puff) and prepulse trials (pulse preceded by a 20-ms presentation of a 10 p.s.i. air-puff) delivered via two plastic tubes to the neck above the sternum. Presentation of tactile startle stimuli was controlled by a commercially available computerised human startle response system (San Diego Instruments, San Diego, California). Three 5-minute experiments (experiments 1, 2 and 3) were conducted within which 5 blocks of pulse alone trials were alternated with 5 blocks of prepulse trials (total of 60 trials per experiment). Within each block the inter-trial intervals between the six trials were randomised. This A/B 'box-car'design in which two blocks or conditions are alternated at a regular interval is widely used in fMRI studies, enabling a comparison of blood oxygenation level dependent (BOLD) activation between the control condition and condition of interest. The three experiments were distinguished by the different stimulus onset asynchronies (SOAs; i.e. time from onset of prepulse to onset of pulse) of the prepulse trials, these being set at 30- (experiment 1), 60- (experiment 2) and 120-ms (experiment 3).

Experimental design

Subjects were scanned (double-blind) on two separate occasions a fortnight apart:
(i) once after receiving 12 microgrammes/kg bodyweight of nicotine, and
(ii) once after receiving saline (placebo). The procedure was the same as described in the off-line study (Chapter 7). The injection was administered in the clinical room adjacent to the scanning room, immediately after which subjects were positioned in the scanner. Functional scanning commenced ten minutes after injection in order to cover the period of maximum effects of nicotine given via this method (Russell et al.,1990).

Functional magnetic resonance imaging

Gradient echoplanar (EPI) data was acquired using a 1.5 Tesla GE Signa System (General Electric, Milwaukee WI, USA) fitted with advanced NMR hardware and software (ANMR, Woburn MA, USA) in the Department of Neuroimaging at the Maudsley Hospital, London. 100 T2* weighted MR images depicting BOLD contrast (Ogawa et al., 1990) were acquired, at each of 16 near-axial non-contiguous slices parallel to the AC-PC (intracommisural) line. In-plane resolution was 3.3 mm, slice thickness 7 mm and interslice gap 0.7mm, to include the whole brain. TE (Echo time) was 40 ms, TR (Repetition time) = 3 sec. Subjects' heads were placed in a quadrature birdcage coil, which was used for RF (radio frequency pulse) transmission and reception, where head movement was minimised by foam padding and a restraining band across the forehead. Following completion of functional data acquisition, a high contrast, high resolution 3-D inversion recovery prepared spoiled GRASS volume dataset was acquired in the AC-PC plane with TE = 5.3 msec, TI =300 msec, TR =12.2 sec, in-plane resolution = 0.94 mm and 1.5 mm slice thickness.

Data Analysis

fMRI data were analysed using statistical parametric mapping (SPM99; http://www.fil.ion.ucl.ac.uk/spm). Movement related artefacts were corrected by realigning all volumes to the first volume (headmovement was <3mm in all subjects). The mean image produced by the realignment was coregistered with the structural (T1) volume. The resulting images were spatially normalised to conform to the standardised anatomical space of Talairach and Tournoux (1988).The activity at each voxel was scaled, high pass filtered and modelled for each experiment with the co-variate of interest, consisting of 30-sec epochs each convolved with the haemodynamic response function. These data were further analysed by testing the rCBF differences between the Prepulse (experimental) blocks and Pulse only (control) blocks for the placebo condition and nicotine condition for the two subject groups. To identify generic activations respresentative of those found over the entire population of each subject group, a one-way random effects analysis was used (as per table 1a, 1c, 2a, 2c, 3a, 3c in the Results section). The second stage of analysis tested for drug and group effects using repeated and independent measures t-tests ($p<.01$). Finally, a correlational analysis was performed using Spearman's rho (given the low number of subjects this non-parametric test was deemed more appropriate) to test the relationship between the off-line behavioural changes and the on-line activation changes which had been predicted by the hypothesis, i.e. a) the calculated difference in PPI under placebo and nicotine and b) the change in power of activation in the hippocampus and thalamus following nicotine. This analysis was repeated for each SOA.

8.4 Results

Behavioural effects of nicotine

The relevant behavioural data were collected previously in the offline version of this study, using an identical paradigm and procedure (see 8.3). These data are detailed in chapter 7.4.

Brain activation patterns

The initial random effects analyses identified significant changes in BOLD activation during the 'on' condition (i.e. PPI trials) relative to the 'off' condition (Pulse only trials) i.e. those areas involved in the inhibition response. This analysis was performed for each subject group and for both the nicotine and placebo conditions. However, as performance during placebo was assumed sub-optimal due to nicotine withdrawal (e.g. Kumari et al., 1996), the significance of associated brain activation is complex and will not be discussed in order to avoid excessive speculation. For the purpose of completion, these data are displayed in tables 8.1 (a and c), 8.2 (a and c) and 8.3 (a and c). As the intention of this study was to tease out the areas in PPI circuitry which are involved in nicotine-induced modulation of PPI, the discussion of results will focus on the relative changes in activation under nicotine yielded by both the within and between groups comparisons. Therefore, for each SOA condition, the main findings will be discussed in the following order: first results will be described from the within-subjects analyses comparing changes in activation of those areas involved in PPI during nicotine relative to placebo. Second, the findings from the between-subjects comparisons will be reported, which were repeated for the nicotine and placebo conditions.

30-ms condition: within-groups comparison of changes under nicotine relative to placebo

The nicotine-induced increase in PPI in the control group was coupled with significant activation of limbic areas [cingulate (L: Brodmann Area (BA) 23), hippocampus (L; see Fig. 8.1)] and striatum (putamen (R)). In addition there was significant activation of the thalamus (L) and occipital lobe (L: BA19). The patient group also showed hippocampal (L) and thalamic (R; see Fig. 8.2) activation, in addition to cerebellum and precuneus (BA7).

30-ms condition: between-groups comparison under nicotine

Under nicotine patients showed greater activation of the right hippocampal gyrus (see Fig. 8.3) and medial temporal gyrus (L: BA 37) when compared with control subjects.

60-ms condition: within-groups comparison of changes under nicotine relative to placebo

The marginal increase in PPI following nicotine in the control subjects was paired with increased activation of the precuneus (BA 7) and hippocampal gyrus. The patient group, where the inhibitory increase did not reach significance, nonetheless did show relatively greater activation under nicotine in the inferior parietal lobe (BA 40), medial temporal gyrus (BA21) and precuneus (BA 19) as well as the striatum (putamen (R)), thalamus (L) and hippocampal gyrus (R).

60-ms condition: between-groups comparison under nicotine

Between group comparisons showed greater activation for the patient group in the parietal lobe, in addition to the striatum (strong activation in caudate (R; see Fig.

8.4), less so in putamen (R)), hippocampus (R) and thalamus (R). Controls showed comparatively greater activation in the precuneus.

120-ms condition: within-groups comparison of changes under nicotine relative to placebo

Control subjects showed a significant increase in PPI at this SOA, which was paired with activation in the pallidum (R; see Fig. 8.5), superior temporal gyrus (BA 38 (R)), precuneus and hippocampus (R). Patients showed no behavioural change, even so they showed significant activation in striatum (caudate (R)), insular cortex (R), limbic system (cingulate BA 24 (L) and hippocampal gyrus, bilateral), thalamus (L; see Fig. 8.6) and prefrontal cortex (BA 8 and 4 (R)).

120-ms condition: between-groups comparison under nicotine

When compared with controls, patients showed more activation of cerebellum (L), medial frontal and insular areas (R) as well as left hippocampal gyrus (L). We found no increase in activation in the control group relative to the patients.

Correlational analysis of behavioural data with predicted regions of interest

For both subject groups combined, this analysis showed a significant positive relationship between change in percentage PPI following nicotine, and change in power of activation of the left hippocampus following nicotine, at the SOA of 30-ms where the enhancing effect of nicotine on PPI was strongest [Spearman's rho = .738, $p<.01$]. The analysis was repeated for each of the subject groups, showing a trend for this positive relationship in the patient group [Spearman's rho = .700, $p<.09$] and a significant effect for the controls [Spearman's rho = .928, $p<.004$]. No other relationships were found to be significant.

Table 8.1: Brain regions showing a significant change in BOLD response during prepulse inhibition with SOAs of 30 ms (prepulse plus pulse minus pulse only conditions) in healthy control subjects (1a) and patients with schizophrenia (1c) under nicotine and placebo. Regions with significantly greater activation during nicotine than placebo and vice versa are displayed in tables 1b (control subjects) and 1d (patients with schizophrenia). Regions identified through the between-subject analysis as showing significantly greater activation in the control group and in the patient group are displayed in bold, with the corresponding p values in the columns on the right.

Brain Region	*Brodmann Area*	*Talairach Coordinates*	*Side*	*Number of Voxels*	*P*	*Control > Patients*	*Patients > Controls*
1a Control subjects		**Nicotine**					
Hippocampus		-24 –14 –14	L	31	0.001	None	None
Medial temporal gyrus	39	-32 –66 26	L	224	0.001		
Cerebellum		-18 –56 16	L	237	0.001		
Fusiform Gyrus	19	-14 –60 44	L		0.002		
Cingulate (posterior)	31	-20 –54 28	L		0.002		
Thalamus		-12 –20 14	L	60	0.002		
Control subjects		**Placebo**					
Supramarginal gyrus	40	-46 –50 28	L	32	0.001	None	None
Medial Frontal gyrus	11	40 50 –10	R	59	0.001		
Medial Occipital gyrus	18	-28 –90 6	L	44	0.003		
1b Control subjects		**Nicotine>Placebo**					
Putamen		24 -2 –6	R	68	0.001	*None*	*None*
Occipital gyrus	BA 19	-24 -80 32	L	407	0.001		
Cingulate gyrus	BA 23	-12 -54 12	L	242	0.001		
Hippocampus ***(Fig. 8.1)***		-20 –30 -4	L		0.001		
Hippocampal gyrus		-12 –42 4	L		0.001		
Thalamus		-2 -14 10	L	170	0.001		
Control subjects		**Placebo> Nicotine**					
No areas significant						*None*	*None*

Brain Region	*Brodmann Area*	*Talairach Coordinates*	*Side*	*Number of Voxels*	*P*	*Control > Patients*	*Patients > Controls*
1c Schizophrenic Patients		**Nicotine**					
Medial occipital gyrus	19	26 -90 16	R	22	0.001	None	
Medial temporal gyrus	**37**	**-48 –64 6**	**L**	**55**	**0.001**		**0.001**
Hippocampal gyrus		**22 -24 -16**	**R**	**25**	**0.001**		**0.001*(Fig. 8.3)***
Cerebellum		34 -66 –24	R	15	0.001		
Inferior Occipital Gyrus	18	32 –86 -6	R	24	0.001		
Pulvinar (thalamus)		16 -24 8	R	11	0.001		
Schizophrenic Patients		**Placebo**					
Cingulate gyrus	32	12 38 24	R	315	0.001	None	
Cerebellum		**38 –76 –24**	**R**	**265**	**0.001**		**0.009**
Superior temporal gyrus	22	-46 –36 8	L	83	0.001		
Medial temporal gyrus	21	-58 -32 -8	L		0.001		
Supramarginal gyrus	40	46 -46 26	R	30	0.001		
Medial frontal Gyrus	10	-28 54 20	L	56	0.001		
1d Schizophrenic Patients		**Nicotine> Placebo**					
Cerebellum		-16 –46 –10	L	336	0.000	None	None
Hippocampal gyrus	BA19	-20 -54 -4	L		0.000		
Thalamus ***(Fig. 8.2)***		14 -28 4	R	103	0.000		
Precuneus		-12 -66 50	L	169	0.001		
Schizophrenic Patients		**Placebo>Nicotine**					
Medial frontal gyrus	BA 6	42 8 50	R	91	0.000	None	None

Search volume (SV) for 1a: 139,070 voxels; Expected voxels per cluster (EV): 48.77; SV for 1b: 128,469 voxels; EV: 32.989; SV for 1c: 145,439 voxels; EV: 36.447; SV for 1d: 142,136 voxels; EV: 21.037; SV for 1e and 1f: 132,085; EV: 75.495

Table 8.2: Brain regions showing a significant change in BOLD response during prepulse inhibition with SOAs of 60 ms (prepulse plus pulse minus pulse only conditions) in healthy control subjects (2a) and patients with schizophrenia (2c) under nicotine and placebo. Regions with significantly greater activation during nicotine than placebo and vice versa are displayed in tables 2b (control subjects) and 2d (patients with schizophrenia). Regions identified through the between-subject analysis as showing significantly greater activation in the control group and in the patient group are displayed in bold, with the corresponding p values in the columns on the right.

Brain Region	*Brodmann Area*	*Talairach Coordinates*	*Side*	*Number of Voxels*	*P*	*Control > Patients*	*Patients > Controls*
2a Control subjects		**Nicotine**					
Occipital gyrus/Cuneus	**19**	**-30 –80 24**	**L**	**89**	**0.001**	**0.001**	None
Control subjects		**Placebo**					
Caudate		-26 -34 10	L	193	0.001	None	None
Pallidum		-14 2 0	L	210	0.001		
Thalamus		-14 -6 12	L		0.001		
2b Control subjects		**Nicotine>Placebo**					
Precuneus	7	-10 –56 36	L	47	0.006	None	None
Hippocampal gyrus		12 –40 -6	R	74	0.038		
Control subjects		**Placebo>Nicotine**					
Cingulate gyrus	24	24 –42 26	R	1295	0.001	None	None
Medial temporal gyrus	39	42 –66 24	R	246	0.001		
Caudate		-26 –34 14	L	1113	0.001		

Brain Region	*Brodmann Area*	*Talairach Coordinates*	*Side*	*Number of Voxels*	*P*	*Control > Patients*	*Patients > Controls*
2c Schizophrenic Patients		**Nicotine**					
Claustrum		30 18 12	R	170	0.001	None	
Caudate		**22 8 16**	**R**		**0.001**		**0.001*(Fig. 8.4)***
Thalamus	**24**	**12 -16 18**	**R**	**121**	**0.001**		**0.001**
Cingulate gyrus	11	2 -16 34	R		0.001		
Medial frontal gyrus		-20 38 –16	L	89	0.001		
Schizophrenic Patients		**Placebo**					
Cerebellum		18 –60 -20	R	84	0.001	None	
2d) Schizophrenic Patients		**Nicotine>Placebo**					
Inferior parietal lobe	40	-30 –44 42	L	715	0.001	None	
Medial Temporal Gyrus	21	-58 –30 –10	L	146	0.001		
Medial occ gyrus	19	40 –76 –6	R	144	0.001		
Precuneus	**7**	**20 –64 32**	**R**	**53**	**0.001**		**0.001**
Cuneus	18	-6 –94 16	L	76	0.001		
Medial Occipital Gyrus	19	30 –80 12	R	72	0.001		
Putamen		**16 8 –8**	**R**	**39**	**0.001**		**0.004**
Thalamus		-2 –18 2	L	9	0.001		
Hippocampal Gyrus		**24 –14 -22**	**R**	**11**	**0.001**		**0.003**
Schizophrenic Patients		**Placebo>Nicotine**					
No areas significant						None	None

Search volume (SV) for 2a: 135,401voxels; Expected voxels per cluster (EV): 44.857; SV for 2b: 125,634 voxels; EV: 35.942; SV for 2c: 144,777 voxels; EV: 21.219; SV for 2d: 142,521 voxels; EV: 18.915; SV for 2e and 2f: 132,218; EV: 44.050

Table 8.3: Brain regions showing a significant change in BOLD response during prepulse inhibition with SOAs of 120 ms (prepulse plus pulse minus pulse only conditions) in healthy control subjects (3a) and patients with schizophrenia (3c) under nicotine and placebo. Regions with significantly greater activation during nicotine than placebo and vice versa are displayed in tables 3b (control subjects) and 3d (patients with schizophrenia). Regions identified through the between-subject analysis as showing significantly greater activation in the control group and in the patient group are displayed in bold, with the corresponding p values in the columns on the right.

Brain Region	*Brodmann Area*	*Talairach Coordinates*	*Side*	*Number of Voxels*	*P*	*Control > Patients*	*Patients > Controls*
3a Control subjects	**Nicotine**						
Putamen		20 –10 -10	R	53	0.02	None	None
Control subjects	**Placebo**						
Cingulate gyrus	29	-26 –54 8	L	124	0.001		None
Hippocampal gyrus		**-22 –52 6**	**L**			**0.001**	
Putamen		**-24 6 4**	**L**		**0.007**	**0.001**	
3b Control subjects	**Nicotine> Placebo**						
Globus pallidus lateralis *(Fig. 8.5)*		24-10 –6	R	11	0.001	None	None
Sup temp gyrus	38	40 12 –22	R	38	0.001		
Precuneus	7	26–52 52	R	22	0.001		
Hippocampus		32 –22 -12	R	6	0.036		
Control subjects	**Placebo> Nicotine**						
Cuneus	18	-16 –86 4	L	1162	0.001	None	None

Brain Region	*Brodmann Area*	*Talairach Coordinates*	*Side*	*Number of Voxels*	*P*	*Control > Patients*	*Patients > Controls*
3c Schizophrenic Patients		**Nicotine**					
Medial temporal gyrus	21	46 –32 –12	R	101	0.001	None	None
Cingulate gyrus	24	-18 12 32	L	86	0.001		
Prefrontal cortex	10	-24 44 –6	L	168	0.001		
Hippocampus		-34 –24 –8	L	29	0.02		
Schizophrenic Patients		**Placebo**					
Medial frontal gyrus	8/9	-4 26 40	L	468	0.001	None	None
3d Schizophrenic Patients		**Nicotine>Placebo**					
Caudate nucleus		14 10 –14	R	200	0.001	None	
Insula		**42 –12 12**	**R**	**556**	**0.001**		**0.014**
Cingulate gyrus	24	-28 34 –2	L	375	0.001		
Pulvinar (thalamus) *(Fig. 8.6)*		-28 –26 4	L	130	0.001		
Medial frontal gyrus	8	**32 44 –8**	**R**	**130**	**0.001**		**0.006**
Hippocampal gyrus	28	**-18 –16 –14**	**L**	**24**	**0.001**		**0.019**
Precentral gyrus	4	34 –12 50	R	131	0.001		
Hippocampal Gyrus	35	18 –18 –14	R	8	0.003		
Cerebellum		**-20 –88 -6**	**L**	**32**	**0.001**		**0.003**
Schizophrenic Patients		**Placebo>Nicotine**					
Precuneus	7	0 –70 42		213	0.003	None	None

Search volume (SV) for 3a: 141,872 voxels; Expected voxels per cluster (EV): 57.618; SV for 3b: 126,153 voxels; EV: 29.882; SV for 3c: 142,741 voxels; EV: 17.040; SV for 3d: 139,741 voxels; EV: 20.129; SV for 2e and 2f: 131,883; EV: 46.600

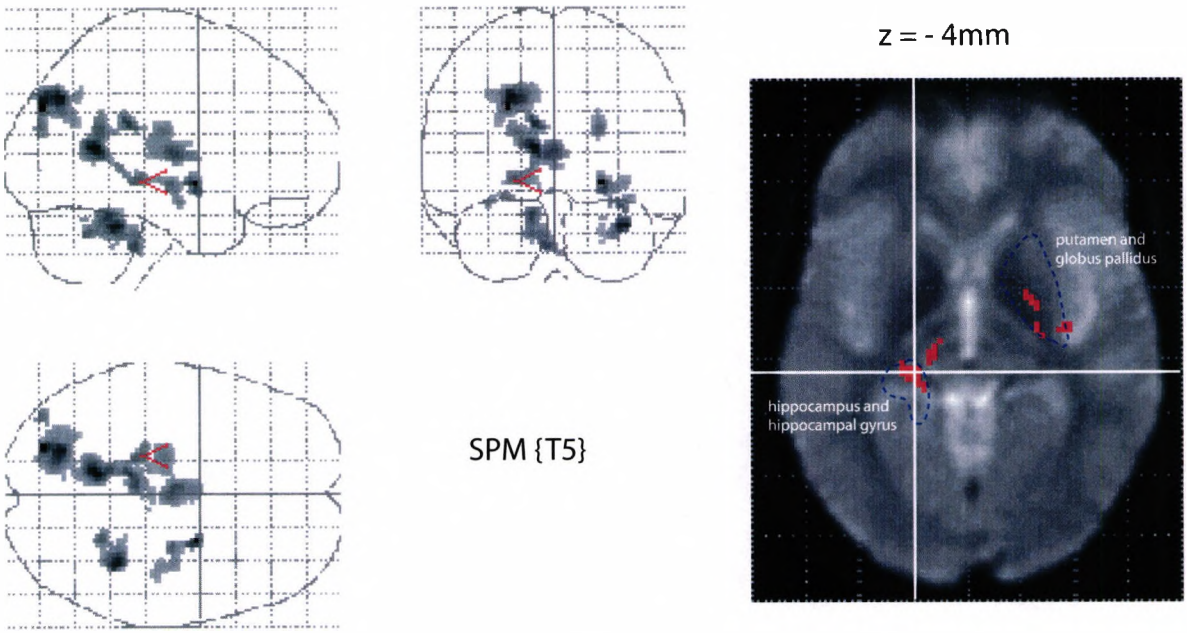

Figure 8.1: Within-subjects comparison for the Control group at 30 ms : areas showing significantly greater activation under nicotine compared with placebo (red; here the hippocampus, -20 -30 -4).
Dashed blue lines outline areas according to Talairach atlas.

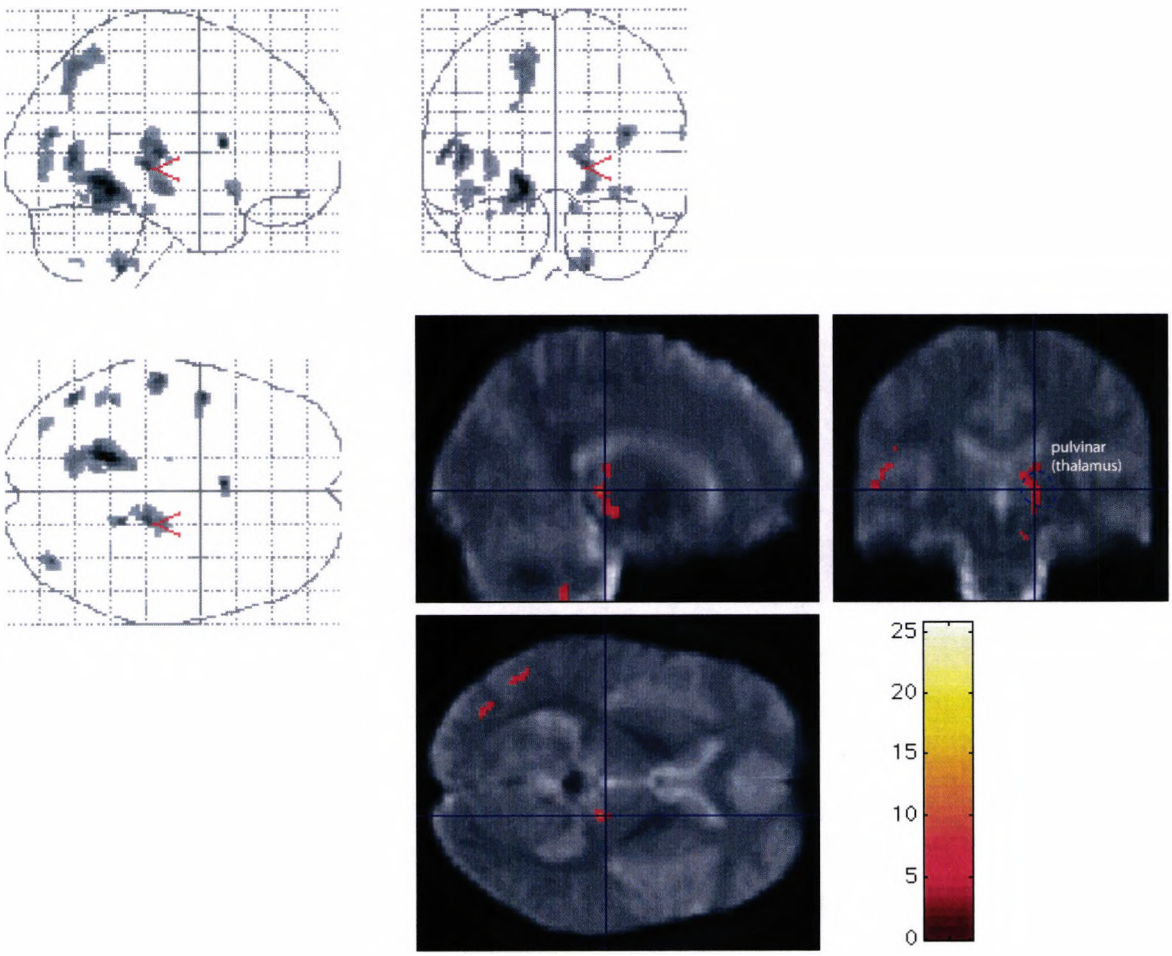

Figure 8.2: Within-subjects comparison for the Patient group at 30 ms : areas showing significantly greater activation under nicotine compared with placebo (red; here the thalamus, 14 -28 4).
Dashed blue lines outline areas according to Talairach atlas.

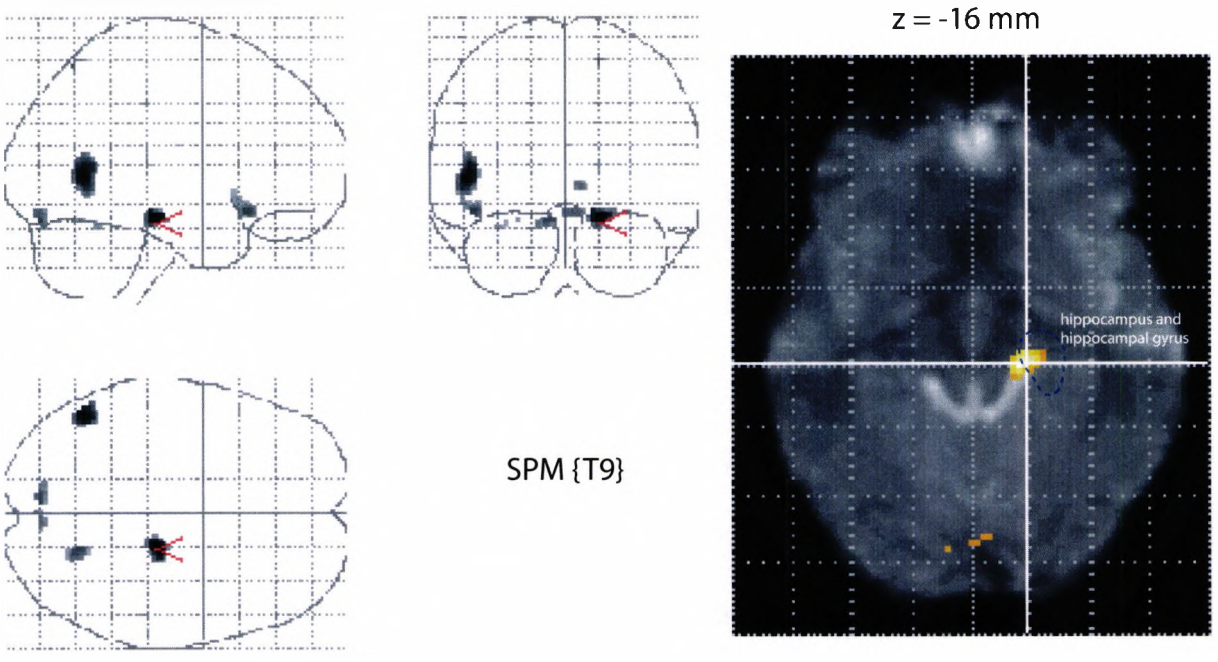

Figure 8.3: Between-subjects comparison for the nicotine condition at 30 ms : areas showing significantly greater activation under nicotine for the patient group compared with controls (orange; here the hippocampal gyrus, 22 -24 -16).
Dashed blue lines outline areas according to Talairach atlas.

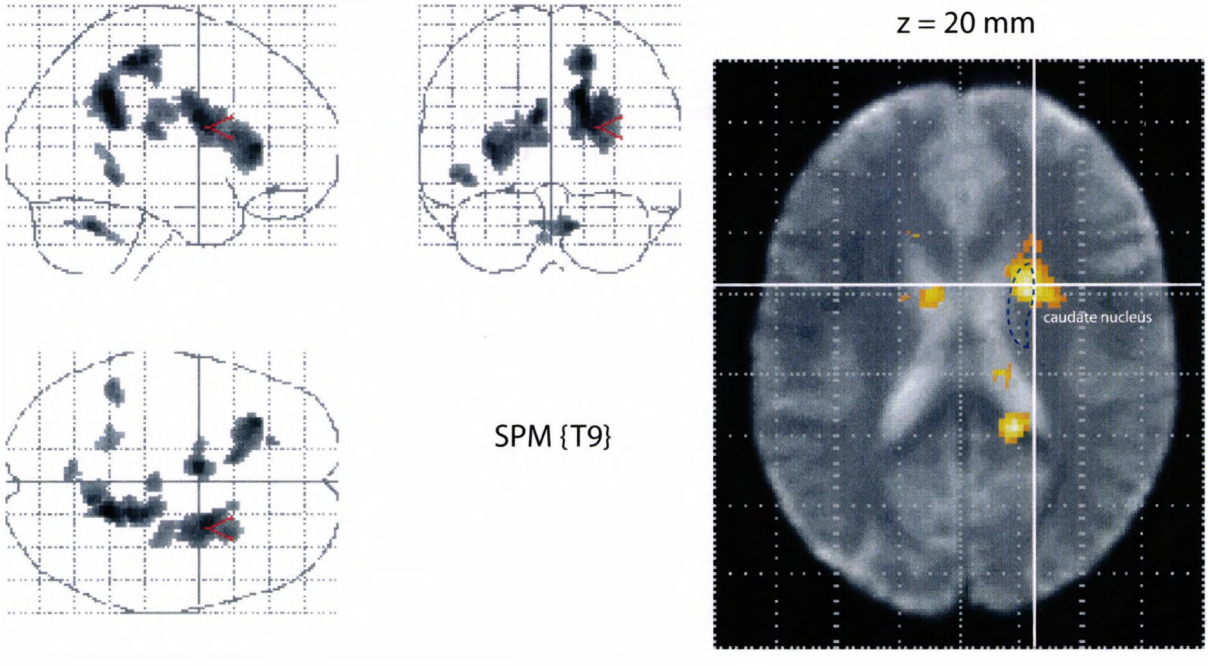

Figure 8.4: Between-subjects comparison for the nicotine condition at 60 ms : areas showing significantly greater activation under nicotine for the patient group compared with controls (orange; here the caudate, 24 4 19).
Dashed blue lines outline areas according to Talairach atlas.

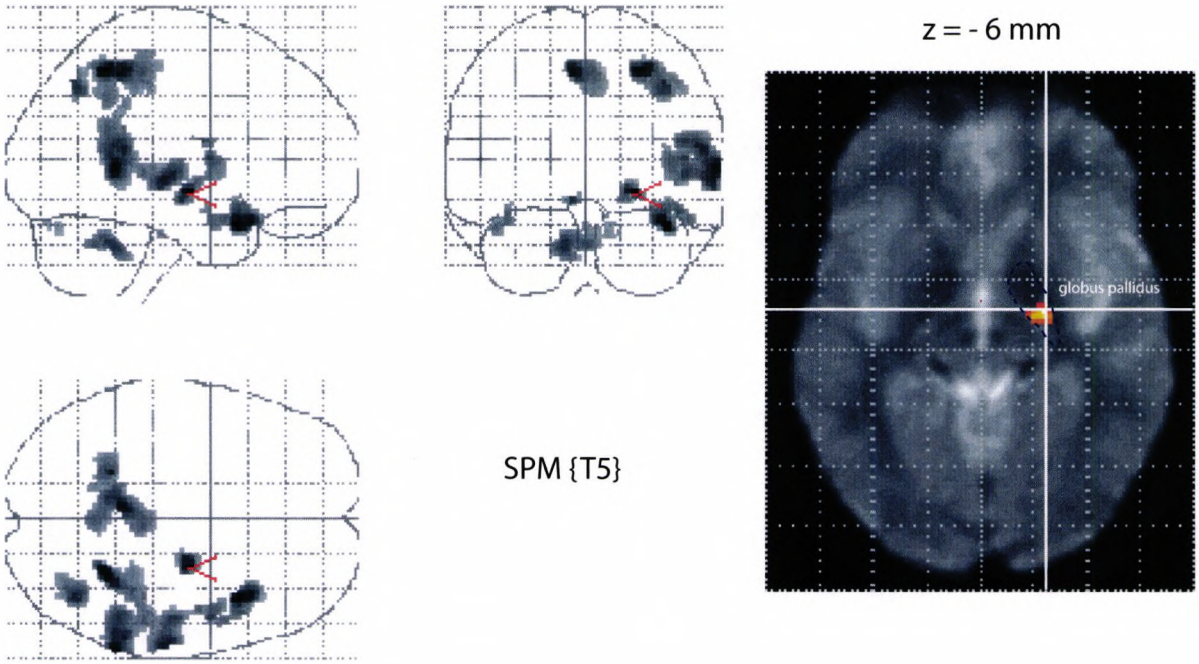

Figure 8.5: Within-subjects comparison for the control group at 120 ms : areas showing significantly greater activation under nicotine compared with placebo (orange; here the globus pallidus, 24 -10 -6).
Dashed blue lines outline areas according to Talairach atlas.

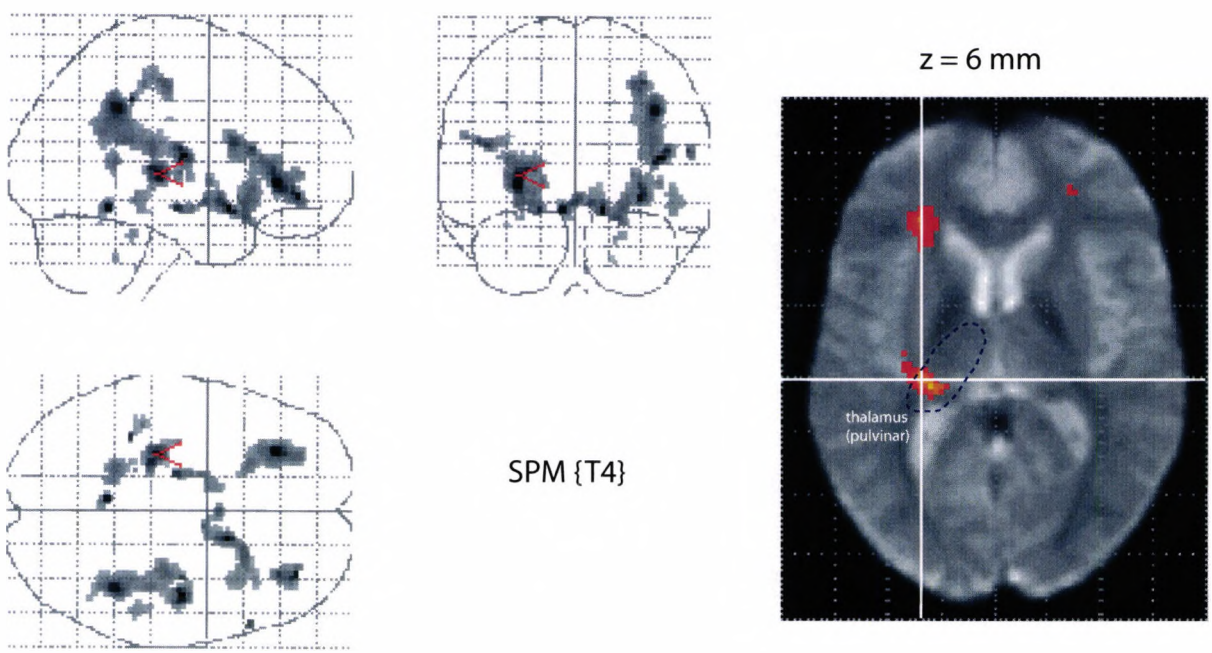

Figure 8.6: Within-subjects comparison for the patient group at 120 ms : areas showing significantly greater activation under nicotine compared with placebo (orange; here the pulvinar, -28 -26 4).
Dashed blue lines outline areas according to Talairach atlas.

8.5 Discussion

The activation patterns in the present study confirm that areas which are known to modulate PPI in animals are also involved in the modulation of PPI in humans. Overall the present findings replicate previously reported patterns of activation from human brain imaging studies of PPI (Kumari et al., 1998a, 2002b; Hazlett et al., 1998, 2001), despite paradigmatic differences precluding direct comparisons. Furthermore, by conducting a correlation analysis between behavioural changes and activated regions of interest, a relationship was confirmed between nicotine-induced increases in PPI and hippocampal activation, suggesting a pivotal role for this structure in mediating the effect of nicotine on PPI in both healthy control subjects and schizophrenic patients. The present results are discussed in the context of the previous animal literature on PPI and nicotine as well as human brain imaging studies of PPI, nicotine and schizophrenia.

Pharmacological and lesion studies in animals have established that the circuitry linking the limbic system and basal ganglia (e.g. Swerdlow et al., 1992a) is crucial for the regulation of PPI, in addition to the thalamus (Kodsi and Swerdlow, 1997b) and medial prefrontal cortex (e.g. Koch and Bubser, 1994). Evidence that these areas are also involved in regulation of PPI in humans has so far mainly come from observations of deficient PPI in certain neuropsychological disorders with known brain pathology. Thus the deficient PPI in Tourette's syndrome has been linked to a disturbance at the level of the basal ganglia (Swerdlow et al., 2001b; Castellanos et al., 1996), whereas the impaired PPI seen in patients with Huntington's disease has been ascribed more specifically to a degeneration of striatal GABAergic cells (Swerdlow et al., 1995b). Temporal lobe involvement is supported by diminished PPI in patients with temporal lobe epilepsy, and patients with non-epileptic seizures (Morton et al., 1994; Pouretemad et al., 1998).

As described in the introduction, only four studies have investigated the neural correlates of PPI in humans to-date. In the first fMRI study of PPI in healthy subjects conducted by Kumari and colleagues (1998a) an identical paradigm to that employed in the present study was used. The three experimental conditions (prepulse trials with SOAs of 30, 60 and 120-ms) yielded significant activation of (30-ms) prefrontal cortex (BA 9, right); (60-ms) insula, dorsolateral prefrontal cortex (BA 9, right) precuneus (BA 7, bilateral), inferior-posterior temporal lobe (BA 37, right) and medial frontal lobe (BA 32, left); and (120-ms) superior occipital gyrus (BA 19, left) and corpus striatum (right). In a subsequent study using the same tactile paradigm Kumari and colleagues (2002b) compared schizophrenic patients and healthy controls during prepulse trials with SOAs set at 120-ms. Relative to the patient group, PPI in the control subjects was coupled with significantly greater activation in the striatum (nucleus accumbens/putamen, globus pallidus), hippocampus and thalamus. Functional neuroanatomical differences during PPI between schizophrenic patients and healthy controls had also previously been confirmed by Hazlett et al. (1998) in a PET study using a paradigm set up to test differences in attentional modulation of PPI (SOA = 120-ms). This study demonstrated a significant relationship between enhanced PPI during attended prepulses and increased activation in dorsolateral prefrontal areas (Brodmann areas 8, 9, 10) and cingulate (Area 24, right) in healthy control subjects. In a subsequent study Hazlett and colleagues (2001), using fMRI, applied a region of interest approach to investigate subcortical involvement in PPI. Attentional modulation of PPI in a group of healthy control subjects was coupled with significant increases in thalamic activation implicating this structure in the modulation of PPI in humans. Even though direct comparisons of the present results with the above findings are problematic given the introduction of a pharmacological component to the present investigation as well as the paradigm differences between this and the Hazlett study, a number of striking parallels were apparent and will be discussed below.

The previous off-line study (Chapter 7.4) showed the most pronounced behavioural effects of nicotine for both patient and control groups on prepulse trials with 30-ms

SOAs. PPI was also enhanced in both groups on 60-ms trials, although this change was not significant. The patient group showed no change at 120-ms while controls showed significantly increased PPI at this interval. Patients were all on typical neuroleptic medication which some claim restores PPI at longer SOAs (e.g. Kumari et al., 2000). It is possible that the absence of change at this interval in the patient group may have reflected higher levels attained during placebo, which would not allow for further enhancement under nicotine. The fMRI study showed significant involvement of limbic regions in the enhancing effect of nicotine on PPI in both patients and control subjects at all SOAs. During the 30-ms condition, where the behavioural data suggested that the effect of nicotine was maximal for both groups, we observed significantly greater left hippocampal gyrus activation relative to the placebo condition in both patients and controls (see Fig. 8.1). In addition the between subjects analysis showed patients to have comparatively greater activation of the right hippocampus than controls (see Fig. 8.3). Under nicotine and in both groups the same region was activated on the right during the 60-ms condition, with the between subjects analysis confirming this effect to be greater in the patients than controls. This imbalance in terms of laterality is consistent with the well-documented lateralisation differences in schizophrenia (e.g. Crow, 2000), but interestingly was reversed in the 120-ms condition. Nicotine induced greater right hippocampal activation during 120-ms trials in control subjects, and increased bilateral activation of this region in the patient group. Notably the between subject comparison at this SOA showed greater activation of the left hippocampal region in controls during placebo, while under nicotine the same region was activated more strongly in the patient group. Over all three experimental conditions, hippocampal gyrus activation was significantly greater in the patient group relative to controls, indicating perhaps a greater sensitivity to the effects of nicotine in the former group.

Under nicotine, activity was observed in the thalamus under all three SOA conditions, although only significantly for the control subjects at the SOA of 30-ms (left), compared to all three SOAs for the patient group (30-ms: right (see Fig. 8.2); 60-ms: right; 120-ms: left (see Fig. 8.6)). However statistically this thalamic

activation was only greater in the patient group compared with the controls at 60-ms. As mentioned above, the thalamus has also been implicated in attentional modulation of PPI in healthy subjects (Hazlett et al., 2001). Interestingly, in the study by Kumari et al. (2002b), where patients and controls were scanned under true baseline conditions (i.e. neither in withdrawal nor under acute nicotine), both the hippocampus and thalamus were activated less strongly bilaterally in patients relative to control subjects, correlating with the behavioural group differences in PPI. Although it must remain purely speculative, as the subject groups from the Kumari and present study are different, it is nonetheless worth noting that the combined findings would suggest hypoactivity of these structures in the patient group which is reversed under acute nicotine.

Both the hippocampal gyrus and thalamus harbour high concentrations of the low affinity nicotinic α7 receptors, which are prominent in the areas near the dentate gyrus and CA3-CA4 region in the hippocampus (Freedman et al., 1993) and the reticular nucleus of the thalamus (Leonard, 1996; Adler et al., 1988). Compelling evidence has already been put forward suggesting that the modulatory effects of nicotine on sensory gating (as measured via the P50 paradigm) and on sensorimotor gating (as measured by PPI) are mediated via these low affinity α7 subunit-containing nicotinic receptors. Post mortem studies have established reduced numbers of this receptor subtype in the hippocampi of schizophrenic patients who show such gating deficits (Freedman et al., 1995). Selectively bred mice with low numbers of these receptors show reduced PPI, which is increased following nicotine administration (e.g. Stevens et al., 1997; Bullock et al., 1997). Furthermore, agonists at this particular nicotinic receptor (3-(2,4)- dimethoxybenzylidine anabaseine; GTS-21,DMXB-A increase sensory gating in the rat and mouse (Leonard et al., 1998a).

The mechanisms via which this modulatory effect occurs have been postulated as resulting from the nicotine-induced increases in glutamate release following activation of the α7 subunit-containing nicotinic receptors. Leonard et al. (1996)

suggest that gating of sensory input may depend on this interaction: increased glutamate release would facilitate release of GABA from interneurons, resulting in inhibition of the hippocampal CA3 and CA4 pyramidal neurons, the net result being suppression of the subsequent response to the next stimulus. On the basis of such findings the Freedman group have proposed that a reduction or abnormality of α-bungarotoxin receptor subtypes in an individual would result in a decrease of cholinergic activation of inhibitory interneurons which would then result in reduced inhibition (Freedman et al., 1995). This deficient sensory processing might be improved by an increase in cholinergic stimulation of these particular receptors. The high concentrations of α7 receptors present in the thalamus implicates this structure in a similar way to the hippocampus in the cholinergic modulation of filtering of sensory input. Abnormalities of the thalamus in schizophrenia are well documented with several studies demonstrating substantial cell loss as well as reduced volume of this structure in schizophrenic brains (Staal et al., 2001; Andreasen et al.,1994a; Pakkenberg, 1990,1992).

We observed increased activation of the striatum under nicotine with strongest activation of these areas occurring at the longer SOAs. The control group showed activation of putamen (right; 30-ms) and pallidum (right; 120-ms; see Fig. 8.5) while patients showed putamen and strong caudate activation (right; 60-ms). Patients showed increased activation compared with controls at 60-ms [caudate (right) see Fig. 8.4 and putamen (right)]. Both previous studies by Kumari et al. (1998a; 2002b) had confirmed right striatal activation during PPI, with this being greater in the control group than in the patients in their comparative study. In the context of the present findings this again would suggest the possibility of a restorative effect of nicotine on otherwise suboptimal functioning of these structures in schizophrenic patients. Animal studies confirming involvement of the striatum in PPI suggest the GABAergic projection from the caudate nucleus to the globus pallidus to be involved in the regulation of PPI (Kodsi and Swerdlow, 1995a, 1995b). Thus, PPI can be disrupted in the rat by lesions of the dorsal posterior caudate nucleus (Kodsi and

Swerdlow, 1995b) and PPI is disrupted in rats with supersensitive DA receptors in the caudate-putamen by injecting doses of apomorphine too low to disrupt PPI in intact rats (Swerdlow et al., 1992). As mentioned above, striatal pathology is also implicated in Huntington's Disease, where there is a loss of PPI (Swerdlow et al., 1991b). We also observed activation in the insula (right), but only in the patient group at 120-ms. Relative to placebo, there was greater activation of the left cingulate gyrus at 30-ms (controls) and 120-ms (patients) during nicotine. The anterior cingulate is part of the cortico-striato-pallido-thalamic circuitry implicated in the modulation of PPI and was also shown in the Hazlett et al. (1998) PET study to be involved in attention-enhanced PPI. However they did not replicate this finding in their subsequent fMRI study.

As mentioned in the methods section, the present investigation was limited by the inability to measure behavioural performance at the time of scanning due to the metal content of the EMG electrodes. This precluded the analysis of choice: namely a factorial analysis in which the interaction term would have informed on those brain regions activated by the (active) PPI condition; where a change in neuronal activation had occurred as a result of the nicotine challenge. Therefore an alternative strategy was adopted in order to substantiate the above findings. A correlational analysis was performed of the off-line behavioural changes with the areas of activation, i.e. a) the difference in PPI under placebo and nicotine and b) the change in amount of activation following nicotine for each SOA. This analysis showed a significant positive relationship between increased PPI and increased activation of the hippocampus at the SOA of 30-ms, where this behavioural change was strongest. After repeating this analysis by subject group this relationship remained significant for the control group but was reduced to a trend for the patient group. This is the strongest evidence to suggest that in humans, as with P50 gating, the enhancing effect of nicotine on PPI is primarily modulated via the hippocampus.

The observed activation patterns may be compared with those seen in previous imaging studies of the sites of action of nicotine in human brain. For example

Nyback et al. (1989) used PET to visualise central sites of nicotine action, confirming large concentrations of binding sites in frontal, cingulate, insular lobe, as well as the thalamus and basal ganglia. Stein et al.'s (1998) investigation of the sites of action of intravenously administered nicotine showed significant activation in cingulate and dorsolateral, orbital and medial frontal regions, all implicated in cognitive processes such as attention and vigilance known to be modified by nicotine (Warburton, 1990). Also activated were those regions known to be involved in the reinforcing effects of nicotine, i.e. the nucleus accumbens, amygdala and thalamus. Visual cortex as well as temporal lobe areas were activated, an effect which was attributed to the extensive projections from the thalamic nuclei (which are particularly rich in nicotinic receptors) to these areas as well as the frontal, cingulate and parietal regions. These authors suggest that much of the cortical activation observed in their study might have reflected intense thalamic nicotinic receptor activation. This may also explain some of the findings of the present study: in addition to the predicted areas of activation described above, nicotine-induced increases in PPI were accompanied by activation of medial and superior temporal, parietal and occipital cortices. The cortical activation observed in our study similarly could have been secondary to an intense thalamic effect.

Patients showed strong cerebellar activation at 30-ms, and at 120-ms significantly greater cerebellar activity than control subjects. McNamara et al. (1990) have observed increases in activity in the cerebellum following nicotine in the rat. Also in humans, a PET study by Nagata et al. (1995) reported strong cerebellar activation following acute nicotine in overnight smoking withdrawn subjects. Such an effect was not reported by Stein et al. (1998) who administered nicotine to non-abstinent subjects which raises the possibility that the cerebellar activation of the former study was related to reversal of nicotine withdrawal. As our subjects were in a similar state to those in the Nagata study this could suggest that the cerebellar effect seen in the present study reflects a restoration of withdrawal-induced lack of tolerance. A suggestion that the cerebellum might be involved in PPI has been made by Stitt et al. (1976) and more recently by Takeuchi et al. (2001); however, other studies have

failed to substantiate such a hypothesis (e.g. Pletnikov et al. (2001). While attempts to identify structural abnormalities in the cerebellum in schizophrenia have met with mixed success (e.g. Heath et al., 1979; Weinberger et al, 1979b) functional imaging studies have confirmed abnormalities of this structure during cognitive activation paradigms (Andreasen et al., 1996). Accordingly Andreasen et al. (1998) proposed an extended dysfunctional neural system underlying the symptoms of schizophrenia, consisting of an interactive circuit linking the prefrontal regions, thalamic nuclei and cerebellum. Although this remains purely speculative, the excessive cerebellar activation seen in the present study might have resulted from an imbalance caused to this already delicate circuit by a strongly activated thalamus.

As was previously reported by Kumari et al. (1998a) significant activation of the precuneus (BA7) was found in both subject groups which is unexpected in terms of its involvement in the modulatory effect of nicotine on PPI. Previous studies have reported activation of this region during the resting stage of block paradigms (Mazoyer et al., 2001), the speculation being that such activation might reflect an affective anticipatory response to impending active task conditions (Simpson et al., 2001). In the current study the comparison condition of 'pulse-only' stimuli served to elicit a strong startle response which was inhibited during the experimental prepulse phase. The increased inhibition under nicotine would have emphasized the contrast between the experimental and comparison conditons which could potentially have increased the anticipatory response to the pulse-only phase, which in turn could explain the increased precuneal activation. It is therefore interesting to note that the Kumari et al. (1998a) study used an identical paradigm to the present one and that no precuneal activation was reported in the Hazlett et al. (1998) study which used an event related design.

The present study is limited by the small number of participants. Even so this small number produced significant activations of predicted areas. Another issue was with the high rate of non-responders to this tactile paradigm, as was evident in the off-line version of this experiment, which calls into question the representativeness of our

final sample as only good responders were selected for the scanning component of the study. Implicit in the box-car design of this paradigm was the non-random presentation of the stimuli, which may have contributed to the relatively high rate of non-responders in the off-line version of this study compared with those of the acoustic randomised paradigm normally employed in our laboratory. In order to overcome such difficulties, an event-related fMRI paradigm using acoustic stimuli is currently being developed by Kumari and co-workers. Finally, the present study was designed to maximise the effects of nicotine on PPI, by comparing the nicotine condition with smoking withdrawal, which consequently did not allow for assessment of neural activation at baseline levels of PPI as the PPI measured during the placebo condition was presumed to be suboptimal (e.g. Kumari et al., 1996). Future studies comparing patients and healthy subjects after self-administered levels of nicotine would be able to provide insight into this.

In conclusion, the findings from the present study confirm involvement of the hippocampus and thalamus in modulation of PPI via nicotine in both healthy control subjects and schizophrenic patients. The correlational analysis between the calculated behavioural enhancement of PPI and change in neural activation following nicotine confirmed the hippocampus as the primary structure for the modulatory effect of nicotine. In addition, we observed basal ganglia involvement although this was not as consistent across all conditions as the hippocampal and thalamic input. Patients showed stronger activation of both hippocampal and thalamic areas across all SOA conditions, which may be interpreted as reflecting a greater sensitivity to the effects of nicotine in this group. Chronic smoking causes upregulation of nicotinic receptors in the hippocampus, caudate and thalamus in healthy smokers, however this upregulation is absent in schizophrenic smokers (Breese et al., 2000). Although rather speculative, it is possible that abnormalities in upregulation may reflect population differences in mechanisms involved in receptor desensitisation. This may explain the differential sensitivity we observed in these structures. Taken together, the results support a role for nicotine in the restoration of deficits in schizophrenia as indexed by PPI.

CHAPTER 9

The relationship between prepulse detection and prepulse inhibition of the acoustic startle reflex

9.1 Abstract

Prepulse inhibition (PPI) of the startle reflex is defined as the attenuation of the startle response to a startling stimulus (pulse), when such a stimulus is briefly preceded by a stimulus of sub-threshold intensity (prepulse). PPI is thought to be neither learnt, nor due to conscious response inhibition, as it occurs at stimulus onset asynchronies (SOAs) too short to enable the activation of a volitional response. The present study explored the latter of these assertions by investigating a) the degree to which human subjects are able to detect prepulses at SOAs of 30, 60 and 120-ms, and b) whether such detection is related to inhibition. Startle eyeblink reflex and detection were measured in 39 participants subjected to an acoustic startle paradigm. Results revealed a significant trend in prepulse detection according to SOA, with highest detection rates at the 120-ms SOA (75%). However, trials on which detection occurred did not differ from trials without detection on measures of startle inhibition. This suggests that PPI is independent of awareness of the prepulse.

9.2 Introduction

Most mammals, when confronted with a sudden, strong exteroceptive stimulus (e.g. burst of noise, flash of light), react with a defensive or startle reflex comprising abrupt muscular flexion and extension responses. In experimental settings this reflex response is usually measured as whole body jump in animals, e.g. via stabilimeter displacement (Hoffman and Ison, 1992), and as eyelid closure in human beings (Graham, 1992).

The startle response can be modified reliably by presenting a less intensive stimulus (prepulse) prior to the startle eliciting stimulus (pulse). Providing the time from prepulse onset to pulse onset, or stimulus onset asynchrony (SOA), is short (i.e. between 30 and 500 milliseconds, ms), such modification will appear as inhibition of the startle reflex, evident as the attenuation of the startle response. This phenomenon, known as prepulse inhibition (PPI), is thought to reflect an automatic sensory gating system which is protective of the preattentive stage of information processing: while the prepulse is being processed, any other incoming information is processed at a reduced level thereby safeguarding the processing of the initial event (Braff and Geyer, 1990; Graham, 1975, 1980). Accordingly, in terms of day to day functioning such a gating or filtering system would allow the individual to attend selectively to a pertinent stimulus. PPI has been demonstrated using a number of different modalities such as bursts of noise (Blumenthal, 1988), air puffs to the forehead (Hackley and Graham, 1987) and flashes of light (Burke and Hackley, 1997).

Part of the interest in PPI as a measure of preattentive processing has sprung from the observation of impaired PPI in a number of neuropsychiatric disorders characterised by the inability to screen out irrelevant sensory information, such as schizophrenia; this fundamental gating deficit has been thought to underlie the sensory overload and cognitive fragmentation experienced by this patient group (e.g. McGhie and Chapman, 1961; Braff and Geyer, 1990). Furthermore, the brain areas identified as

regulating startle gating in animal studies, namely neural pathways linking the limbic system and the basal ganglia, have also been shown to be part of the pathophysiology of schizophrenia (Swerdlow et al., 1992a). Consequently impaired PPI has been put forward as a useful biological marker for schizophrenia and related disorders, although the exact relationship between PPI and sensory gating is not yet clear (Cadenhead et al., 1993).

PPI is thought to be neither learnt, nor due to conscious behavioural inhibition, as it has been shown to occur on first trials (Hoffman and Wible, 1970), and at prepulse intervals too short to enable the activation of a conscious response (Swerdlow et al., 1992a). Also PPI has been shown to occur in sleeping human beings (Silverstein et al., 1980) and in decorticate rats (Ison et al., 1991), observations which confirm that, at least partially, PPI is an automatic process. It is indeed this involuntary aspect of PPI which has made it so valuable to schizophrenia research, as inferences of deficits in this patient group are often clouded by the possibility that poor performance may simply reflect generalised decreased motivation.

Yet evidence from a number of recent studies suggests that PPI may also be sensitive to attentional or voluntary processes (e.g. Dawson et al., 1993; Filion et al., 1993, Bohmelt, Schell and Dawson, 1999). These studies showed increased inhibition when subjects attended to a prepulse in comparison to trials in which subjects were instructed to ignore the prepulse. Most notably, Filion et al. (1993) showed enhanced PPI at SOAs of 120-ms if prepulses were attended to, indicating that at this lead interval PPI can be modulated by attention. Therefore while at lead intervals of 60-ms or shorter PPI is thought primarily to reflect automatic processing, it is likely that PPI at longer lead intervals may also involve controlled attention. Thus PPI at different SOAs may reflect different stages of information processing (Dawson et al., 1997).

A study by Norris and Blumenthal (1996) appeared to demonstrate a relationship between increased inhibition and enhanced processing of the prepulse. In this study

auditory prepulses were set at two different frequencies and subjects were required to report whether they had heard a high or low pitched tone or no tone at all preceding the startling (pulse) stimulus. Following Graham's (1975) theory, the authors predicted that, if PPI reflected a protective mechanism, then those instances in which such a mechanism had been particularly effective should coincide with an enhanced processing of the initial stimulus (prepulse) in comparison to occasions on which the defense mechanism had failed to protect prepulse processing. Thus, increased inhibition should be coupled with accurate identification of the prepulse. Norris and Blumenthal (1996)'s findings confirmed Graham's (1975) predictions.

The present study investigates these issues further. Using an acoustic startle paradigm, we examined to what extent subjects were able to distinguish prepulses from pulses at SOAs of 30, 60 and 120-ms and whether there was an interaction of any such detection on startle amplitude and latency. As well as providing a test for the protection of processing hypothesis, we expected our study to reveal whether explicit awareness of a prepulse would result in changes in PPI. The expectation was that, if there was an association between prepulse detection and startle response, the direction of this association would be towards increased inhibition on trials with detected prepulses.

9.3 Materials and methods

Subjects

Thirty-nine normal subjects consisting of 15 males and 24 females (24-50 years old; mean = 31; SD = 7.86) were recruited via advertisements. Subjects received £5 each for their participation.

Response measurement

Acoustic startle stimuli were delivered binaurally through a set of headphones (Model Pro-VII; Realistic). Presentation of acoustic startle stimuli and recording of responses were controlled by a commercially available computerised human startle response system (San Diego Instruments, San Diego, California). Measurement of the startle response (eyeblink amplitude) was achieved by recording the electromyographic (EMG) activity of the right orbicularis oculi muscle via two (6mm) Ag/AgCl electrodes filled with Dracard electrode gel. After preparing the skin surface with Sterets sterile swabs, one electrode was positioned approximately 1 cm lateral to, and 0.5 cm below, the lateral canthus of the subject's right eye, while the second electrode was placed 1.5 cm below and slightly medial to the first electrode, such that both electrodes were equidistant from the centre of the eye. In addition a ground electrode was placed behind the right ear over the mastoid.

Subjects were required to indicate prepulse detection via a button box measuring 12 x 8 x 5 cm. The box featured two buttons which were labelled '1 click' and '2 clicks' respectively. The button box was linked up to a Personal Computer (Compac Presario 425) which recorded and saved subject's responses.

Procedure

Subjects were seated comfortably in a softly lit, sound attenuated room after which they were informed of the procedure. Instructions were to attend to the acoustic stimuli or 'clicks', and after each of the 49 stimulus presentations to make a response via a button pad to indicate whether they had heard two separate clicks or a single click. We emphasised that this was not a test of subjects' intellectual ability in any way. Subjects were assured that this was not a reaction time task.

Sessions started with an acclimatisation period of 3 min to allow subjects to become accustomed to the continuous stream of 70-dB (A) white noise serving as background

throughout the experiment. A total of 49 startle eliciting acoustic stimuli were presented over a period of approximately 20 minutes. Following the first pulse-alone trial (a 40-ms presentation of 116-dB [A] white noise) a further 48 trials were presented in four adjoining blocks of 12 each. Per block, three presentations each of four trial types occurred: pulse alone trials, prepulse trials with a 30-ms SOA, the prepulse being a 20-ms presentation of 85-dB (A) white noise, and prepulse trials with 60-ms and 120-ms. Noise levels were calibrated using a sound level meter on a monthly basis. The four trial types occurred in pseudo-random order throughout each block. All subjects underwent the same paradigm.

Statistical Analyses

All analyses were performed using SPSS Windows (version 7). In order to assess habituation of the startle response, a within-subjects analysis of variance (ANOVA) was conducted comparing startle amplitudes on pulse-only trials across the four blocks.

Prepulse inhibition was calculated as percentage PPI, namely as (a-b/a) x 100, where a = pulse alone amplitude and b = amplitude over prepulse trials. Use of this measure, in preference to absolute difference scores, minimises the possible effects of individual differences in startle amplitude on PPI (Mansbach et al.,1988). In order to assess the effects of the three different stimulus onset asynchronies (SOAs: trial types 30-ms, 60-ms and 120-ms) on PPI, a within-subjects ANOVA was performed using the data from all 39 subjects. Paired t-tests served as post-hoc comparisons to determine whether each trial type (SOA) elicited a significantly different effect.

Rate of detection was scored as the percentage of detected prepulses per 12 trials for each SOA. As subjects had been asked explicitly to respond after each trial, there were no misses. These detection ratios were then compared to determine the effect of trial type (SOA) on the ability to detect the prepulse using a within-subjects

ANOVA. In addition a signal detection analysis was carried out in which discrimination accuracy for each of the three SOA conditions was determined by calculating d' using SPSS (Stanislaw and Todorov, 1999). This analysis was done in order to achieve the separation of perceptual sensitivity from bias. These d' values were then compared according to SOA using a within-subjects ANOVA on all subjects.

A comparison was made of prepulse detection rates on trials which showed an inhibition response to those of trials where no inhibition occurred. Thus an average was taken of the amplitude of the 12 pulse-only trials. Each individual prepulse trial was then classed as showing inhibition if the amplitude on that given trial was below the average of the pulse-alone trials, or as showing no-inhibition if the given amplitude exceeded said average. Each trial was scored as being a 'detect' or 'non detect' trial. This yielded a 2 (inhibition) x 3 (SOA) matrix in which each cell showed the percentage of prepulse detection rates. For each SOA a comparison was then made between the detection rates for inhibition trials vs no-inhibition trials using paired t-tests. Thus after eliminating those subjects not contributing to both inhibition and no-inhibition cells, this left us with data from 38 (30-ms), 32 (60-ms), and 22 (120-ms) subjects for the analysis. A significant t test would indicate that detection accuracy was different on inhibition trials than no-inhibition trials.

The relation between detection and amplitude was calculated by subjecting the data to a 2 x 3 (detect/not detect x trial type [SOA]) within-subjects ANOVA. As the within-subjects nature of the design dictated that those subjects who did not show both 'detect' and 'not detect' scores on a particular trial type (SOA) had to be excluded from the analysis, this left 18 subjects for the overall analysis. However, when each SOA was considered separately, more data could be preserved. Thus 24 subjects provided data for the 30-ms SOA condition, 34 for the 60-ms condition and 30 for the 120-ms condition. Therefore, to maximise the available data, paired t-tests comparing response amplitudes of the 'detect' versus 'not detect' trials for each SOA were also conducted.

All the above analyses were repeated substituting latency to response onset and latency to response peak as dependent variables (Kumari and Gray, 1999b).

9.4 Results

A significant effect of Block (successive blocks of 12 trials; see Method) on amplitude of startle response was shown in pulse-only trials reflecting a reduction of response amplitude from block 1 to blocks 2, 3 and 4 consistent with strong habituation [F(3,36)=6.44, P<.01].

Mean startle amplitudes (in analogue to digit units, each unit = 2.62 μV) for the 30-, 60-, and 120-ms SOAs were 502.26 (SD 561.71), 403.83 (SD 521.09), and 354.86 (SD 575.71) respectively. The mean amplitude over the pulse-only trials was 526.58 (SD 563.66). Mean (percent) PPI scores were at 30-ms: 5.66% (SD 31.84), 60-ms: 31.48% (SD 28.16) and 120-ms: 47.58% (SD 22.29). A significant effect of Trial Type (SOA) was observed [F(2,37) = 29.53, P< .01] indicating greater inhibition following prepulses at SOAs of 60 and 120-ms than prepulses at 30-ms. Pair-wise comparisons confirmed that greater inhibition occurred at 60-ms than at 30-ms [t(38) = 5.86, P<.01] and at 120-ms than at 60-ms [t(38) = 3.91, P < .01]. The lowest level of inhibition seen in the 30-ms SOA trials was itself significant as compared to startle amplitude measured on pulse only trials [t(38) = 1.63, P<.01].

Using the percentage of correct detections calculation, prepulses were more reliably detected at higher SOAs [F(2,37) = 50.54, P<.01] as illustrated in figure 9.1. Whilst subjects were able to detect prepulses set at the SOA of 120-ms most of the time, these detection rates were still significantly below those at which pulse-only trials were correctly identified [t(38)= 5.39, P<.01]. The signal detection analysis showed increasing values of d' as a function of SOA, with values for the 30-, 60-, and 120-ms SOAs being 0.45 (SD 0.64), 1.34 (SD 0.91) and 2.12 (SD 1.00) respectively. This increase of d' over the three SOA conditions was significant [F(2,37)=47.72, P<.01]. The comparison of detection rates on inhibition trials versus no-inhibition trials yielded no significant effects [30-ms: t (37) = 1.36, p<.183, observed power =

.262; 60-ms: t (31) = 1.65, p< .110, observed power = .357; 120-ms: t (21) = 0, p<.997, observed power = .05]. There were no significant differences in PPI between trials on which prepulses were detected and on which they were not [30-ms: t (24) = 1.03, p<.312, observed power = .168; 60-ms: t (33) = .202, p<.841, observed power = .05; 120-ms: t (30) = .240, p< .812, observed power = .05; figure 9.2, Table 9.1].

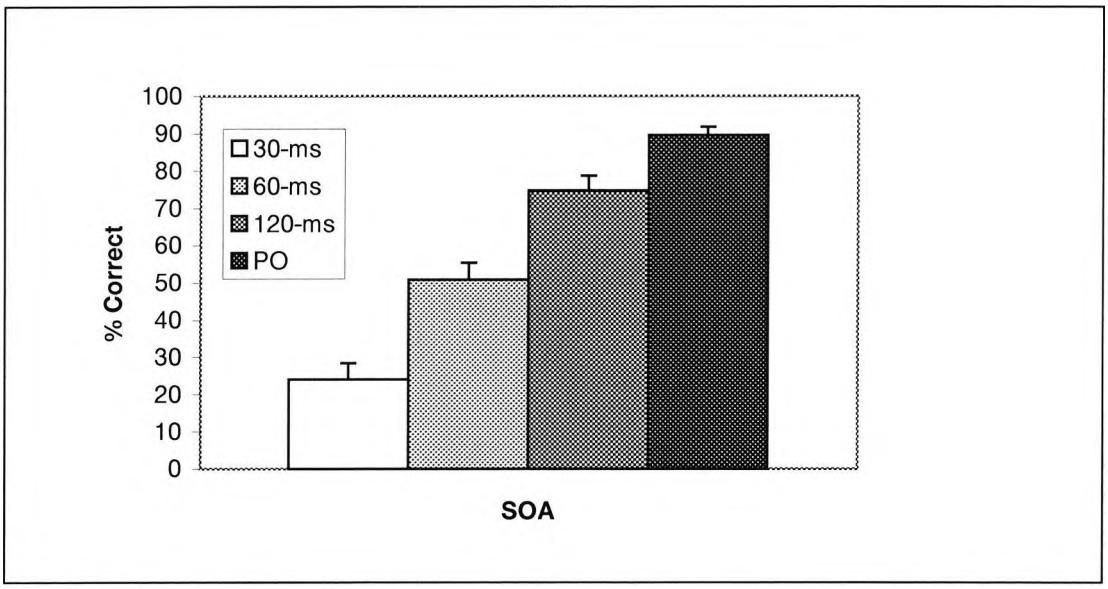

Figure 9.1: Mean (error bar displays 1 SEM) percentage of correct detections as a function of stimulus onset asynchrony (SOA). PO: pulse only trials.

	30-ms		60-ms		120-ms	
	Detect	Nondetect	Detect	Nondetect	Detect	Nondetect
Mean	3.66	-3.79	32.33	30.38	45.86	43.93
Range	-97.38 to 59.72	-126.19 to 48.39	-62.03 to 85.63	-50.53 to 93.23	-3.45 to 93.84	-2.25 to 83.55
SD	35.43	35.50	36.18	29.19	24.10	26.28

Table 9.1: Mean, Range and Standard Deviation of PPI (% inhibition) according to detection

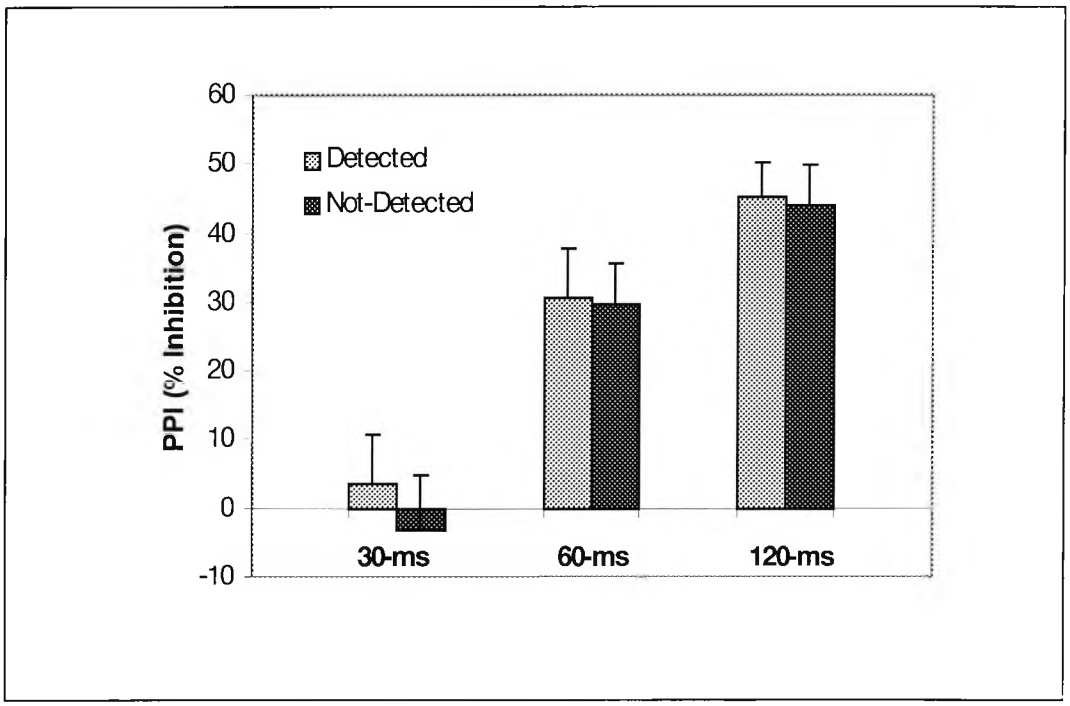

Figure 9.2. Mean (error bar displays 1 SEM) prepulse inhibition (PPI) of the startle response over detected and nondetected trials as a function of stimulus onset asynchrony (SOA).

We found a significant effect of block on detection [$F(3,36) = 40.80$, $p<.01$] for all SOAs and the Pulse only condition which was consistent with a practice effect. Differences in performance occurred mainly between the first and second blocks.

No effect of block on PPI was found.

Latency to response onset was significantly reduced relative to pulse-only trials on the 30-ms and 60-ms trials [$t(38) = 7.95$, $P<.01$; $t(38) = 3.18$, $P<.01$]. There was no significant difference between 120-ms and pulse-alone trials on this measure [$t(38) = 1.08$, $P<.28$]. Prepulse trials also showed significantly reduced latencies to response peak [30-ms: $t(38)=10.93$, $P<.01$; 60-ms: $t(38)=9.19$, $P<.01$; 120-ms: $t(38)=3.37$,

P<.01]. No significant effects were found for detection on latencies to onset or peak [Fs < 1] .

9.5 Discussion

The present study set out to examine the relationship between prepulse inhibition and a measure of conscious perception, namely detection of the prepulse. Our results suggest that the processes of inhibition and detection are separate. A related study had previously been conducted by Norris and Blumenthal (1996; study 1) using a different measure of perception: subjects were required to detect and then identify a prepulse as being either of a low or high pitch. We discuss our findings using the detection paradigm within the context of this earlier discrimination task.

The highest rate of prepulse detection was found, not surprisingly, in the 120-ms SOA condition, where correct responses were recorded on 75% of trials. Detection rates at the 30- and 60-ms SOAs were 24% and 51% respectively. Correct identification rates in the Norris and Blumenthal (1996) study were almost double the detection rates found in the present study for the SOA of 30-ms. It is possible that this reflects a greater difficulty in distinguishing prepulses in the present study, as our prepulses were set at only 15 dB above backgound level as compared to 35 dB (65 dB prepulse over a 30 dB background) in the earlier study.

The data were analysed to assess the relationship between detection and inhibition in which both measures alternately acted as dependent variable. This mirrored the statistical analyses performed by Norris and Blumenthal (1996) and maximised the potential for comparisons of results between the studies given the differences in tasks used. The first comparison addressed the question of how effective inhibition might influence prepulse processing as measured by detection. If PPI were indeed to reflect the working of a preattentive processing protection system, then instances where this system is particularly effective, i.e. instances showing greater inhibition, should be coupled with improved processing of the prepulse. However no difference was found between prepulse detection accuracy on inhibition trials when compared to no-inhibition trials over all SOAs. In contrast, Norris and Blumenthal found increased accuracy of prepulse identification on trials showing inhibition, which they presented

as supporting evidence for the protection of processing hypothesis. Our results fail to support detection as such an indicator of the quality of prepulse processing, as effective inhibition did not predict increased detection rates.

Clearly, while detection was a prerequisite for successful identification of prepulses in Norris and Blumenthal's task, their paradigm made further demands on its subjects than did the present one and might have tapped more extensive cognitive processes. Specifically their task demanded that subjects not only detect the presence of a prepulse (as was the case in the present investigation), but *also* make a discriminatory judgement about the nature of the prepulse, i.e. whether it was a high pitched or low pitched tone. It is possible that a discrimination task with increased demands on processing is more sensitive to the benefits of protection of processing, which could explain the different findings from this earlier and the current study. In the present study 'detection' was meant purely in terms of whether subjects were consciously aware or not of the prepulse, established via a 'presence' (two tones) or 'absence' (one tone) response. However it is possible that subjects used strategies to perform the task which would not necessarily be consistent with the idea of perceiving a separate pre stimulus. This would seriously compromise any subsequent interpretations in terms of effects of 'awareness of prepulses'. One possibility is that the task could have been performed (and indeed a high 'hit' rate achieved) by simply distinguishing between what might have appeared as 'long' tones (prepulse and pulse trials) relative to 'short' tones (pulse-only trials). As no feedback was gathered on performance strategy this remains an issue to be clarified. However it would seem likely that such an approach would have become apparent in a subset of subjects who underwent the experiment with additional trials of SOAs of 200ms (also see further on), where the separation of stimuli was obvious. In the context of such distinct pairs of tones the expectation would be that, if subjects had adopted the 'length of tone' strategy, they would not report 'two tones' during shorter SOAs. This was not the case. Nonetheless the above raised issues of minimum levels of processing needed to (succesfully) perform 'detection' tasks serve to highlight potential confounds in comparisons of studies appearing to tap similar mechanisms. Differences between the

Norris and Blumenthal results and our own should be viewed with this caveat in mind.

Given this, methodological differences other than those already outlined may also have contributed to the different findings between the studies. First, the present study used the average from a total of 12 startle-only trials to establish the baseline startle amplitude against which all prepulse trial amplitudes were compared. In the Norris and Blumenthal study this baseline was deduced from 2 trials only, which may not have always established a truly representative startle amplitude, consequentially affecting the distribution of 'inhibition' and 'no- inhibition' trials. Second, the current analysis was a within-subjects one, while Norris and Blumenthal used a between-subjects analysis.

Analyses for each SOA comparing response measures between detect and non-detect trials failed to show any relation of detection with PPI. These findings therefore suggest that PPI is independent of explicit awareness of a prepulse. Norris and Blumenthal in contrast demonstrated a relationship between increased inhibition and prepulse identification at SOAs of 30 and 480-ms but not at 120-ms. Again it is possible that the use of a between subjects design in the earlier study to compare average amplitude scores on detect and non-detect trials might have contributed to the different findings between the two studies. While this method was presumably adopted to maximise available data (as only 3 to 10 subjects out of 26 contributed to the 'non-detect data set, while 17 to 26 subjects contributed to the 'detect' dataset for the different SOAs), the findings based on such a comparison may have reflected sampling differences in PPI between the resulting groups, rather than changes in amplitude due to detection. In our study, subjects not contributing to both the 'detect' and 'non-detect' data sets were excluded. Our within-subjects analyses were nonetheless based on data from reasonably large samples: 24 subjects (30-ms SOA), 34 subjects (60-ms SOA) and 30 subjects (120-ms SOA).

Given that subjects most likely attended to all stimuli (following from the fact that they made a response after each trial), it is interesting that detection of prepulses occurred on some trials, but not others. As evidence has suggested that the level of attention paid to a particular stimulus directly influences the extent to which we are consciously aware of that stimulus (Crick, 1994; Cowan, 1995), this raises the question whether subjects paid more attention on detected trials than on non-detected trials. As no independent measure of attention was taken, this possibility must remain speculative; it is nevertheless worth considering. For, if detection did reflect or provide a measure of increased attention, then the results of this study suggest that such variations in attention do not affect PPI, as detection did not co-occur with changes in inhibition. In this context it is worth noting that in studies specifically designed to test the effect of attention on PPI, attention to prepulses produces only a limited change in PPI as compared to PPI seen on prepulse-ignore trials (Dawson et al., 1993; Filion et al., 1993, Bohmelt, Schell and Dawson, 1999). However, in these studies the differences between ignored and attended prepulses was investigated using paradigms where prepulses were of much longer duration, so it is difficult to relate our findings to them.

A number of possible limitations to our study, however, need to be considered. First, it is possible that inhibition measures and detection rates might have been affected by backward masking. This possibility could perhaps be eliminated by using a cross-modal design in a future study. Second, as acoustic stimuli set below 84dB have been shown to elicit startle responses, the prepulses in the present study may themselves have been reflexogenic (Hackley, Woldorff & Hillyard (1990); Blumenthal and Goode (1991). However, visual inspection of raw EMG signals did not show evidence of startle response to prepulses in our study. This is possibly attributable to the high level of background noise maintained throughout the experiment, so that the relative 'impact' of the prepulses was only 15 dB. Nevertheless the possibility remains that some of the observed PPI may have reflected refractory effects. Future

studies would therefore benefit from measurements of responses to the prepulse alone to help clarify this issue.

Despite the independence of detection and PPI in our study, we did observe a linear increase in measures of both detection and PPI according to SOA. However this linear trend is unlikely to have been maintained if longer SOAs had been included: in those circumstances detection would be expected to rise to ceiling levels, while PPI on the other hand would be expected to drop, as PPI occurs only between SOAs of 30 and 500-ms, and is optimal at the 120-ms interval. To clarify this, an additional experiment was conducted with a smaller subject sample using the same experimental design as in the current study, only this time with an additional 12 trials set at a 200-ms SOA. Detection rates for this SOA rose to 81% (thereby continuing the linear increase in detection already observed), however PPI dropped to 14%.

The present study was designed to investigate whether detection (and therefore most probably conscious awareness) of a prepulse was a factor in findings of differential inhibition at longer SOAs when compared to SOAs of 60-ms and less, in a large sample size with multiple dependent variables (d'; % correct; blink amplitude; blink latency). Such a possibility was not supported, however, suggesting that while PPI is sensitive to channelling of attention to the stimulus modality at longer SOAs, it is not sensitive to explicit awareness (as indexed by the measure of detection used in the present study) of these stimuli. The current study does not provide direct support for the protection of processing hypothesis. It is however possible that this may have been due to low sensitivity of our measure, detection, to this process and that the postulated protective mechanism benefits tasks with more extensive cognitive demands. This issue can be dealt with only by further empirical studies using multiple measurements of cognitive processing.

9.6 Postscript to chapter 9

The relationship between prepulse detection and prepulse inhibition of the tactile startle reflex

9.7 Methods

Subjects

Eighteen healthy subjects consisting of 8 males and 10 females (24-46 years old; mean = 29.22; SD = 6.05) were recruited via advertisements. All of these subjects had also taken part in the acoustic version of this experiment. Subjects received £5 each for their participation.

Startle response measurement

The tactile pulse stimuli consisted of a 40-ms presentation of a 30 p.s.i. air-puff, which on prepulse trials were preceded by a 20-ms presentation of a 10 p.s.i. air-puff, and delivered via two, 1cm diameter plastic tubes to the neck just above the sternum. All other methodological issues, including the presentation and randomisation of stimuli as well as the recording of EMG and detection responses were identical to those described in the acoustic version of this experiment.

Statistical Analyses

These data were analysed using the same approach as for the acoustic paradigm (9.3).

9.8 Results

We found a significant reduction of response amplitude from block 1 to blocks 2, 3 and 4, confirming habituation of the startle response [$F(3,15)=3.52$, $P<.04$]. Mean startle amplitudes for the 30-, 60-, and 120-ms SOAs were 239.16 (SD 148.61), 233.65 (SD 157.87), and 203.75 (SD 129.52) respectively. The mean amplitude over the pulse-only trials was 260.97 (SD 150.63). Mean (percent) PPI scores were at 30-ms: 9.92% (SD 17.11), 60-ms: 13.88% (SD 21.33) and 120-ms: 24.18% (SD 21.53). There was a significant effect of Trial Type (SOA) [$F(2,16) = 5.197$, $P< .018$] consistent with greater inhibition following prepulses at longer SOAs. However pair-wise comparisons showed this increase only to be significant between the 60-ms and 120-ms conditions [$t(17) = 2.45$, $P < .025$]. The amplitude of the condition with the lowest level of inhibition (30-ms SOA trials) was significantly lower than the startle amplitude measured on pulse only trials [$t(17) = 2.88$, $P<.01$].

A comparison of the percentages of correct detections for each SOA, showed that prepulses were more reliably detected at longer SOAs [$F(2,16) = 4.82$, $P<.023$] as illustrated in figure 9.3. Follow-up t-tests showed no difference in the correct identification of stimuli between 60-ms, 120-ms and pulse only trials. Only at 30-ms were detection rates significantly lower [$t(17)= 2.70$, $P<.015$].

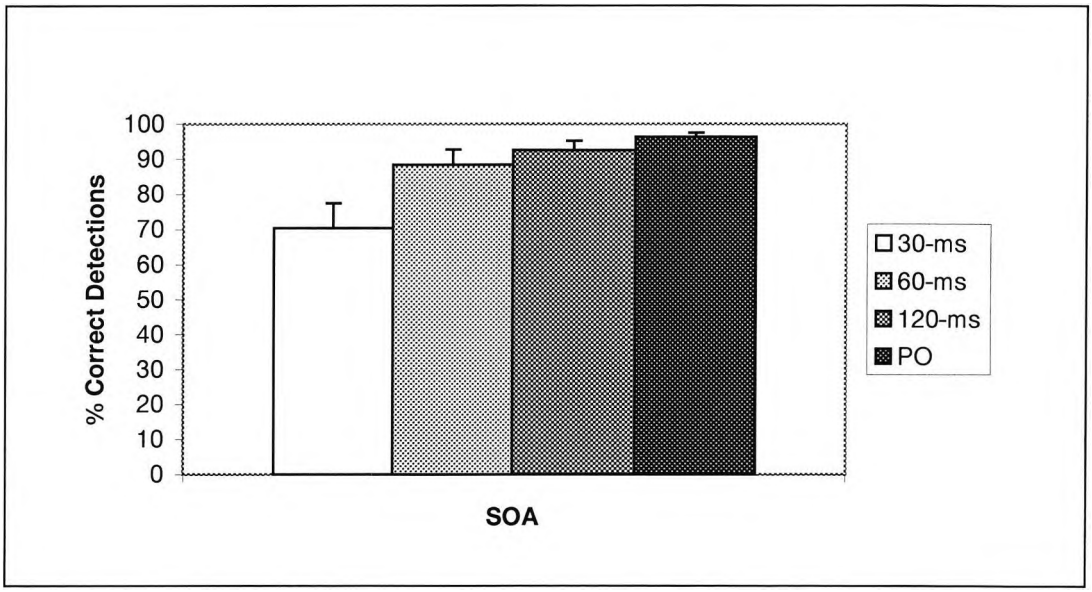

Figure 9.3: Tactile Paradigm: Mean (error bar displays 1 SEM) percentage of correct detections as a function of stimulus onset asynchrony (SOA). PO: pulse only trials

The relative ceiling effects obtained at the longer SOAs made comparisons of detect versus non-detect trials meaningless, therefore such analyses were confined to the 30-ms condition. After eliminating those subjects not contributing to both 'detect' and 'non-detect' cells, this left us with data from 13 subjects for the analysis. This showed no difference in PPI between trials on which prepulses were detected and on which they were not [$t(12)=1.97$, $p>.05$]. All subjects provided data for the comparison of detection rates on inhibition versus no inhibition trials. This comparison yielded no significant effects [30-ms: $t(17)= .545$, $p>.05$].

There was a trend of Trial Type on latency to response peak [$F(3,15)= 3.06$, $p<.06$]. T-tests confirmed that this reflected a reduction of this measure on all prepulse trials relative to pulse-only trials [Pulse vs 30-ms $t(17)=2.71$, $p<.01$; Pulse vs 60-ms $t(17) = 2.59$, $p<.019$; Pulse vs 120-ms $t(17)= 3.05$, $p<.01$].

Within-subjects comparison of tactile and acoustic paradigms

Eighteen subjects provided data on both paradigms, which enabled a comparison of measures. Repeated measures ANOVAs were performed comparing paradigms on startle amplitude, latency to peak response and detection rates for the pulse-only, 30-ms, 60-ms and 120-ms conditions [2 (Paradigm) x 4 (Trial type)]. Habituation was compared via a 2 (Paradigm) x 4 (Block) ANOVA, and prepulse inhibition via a 2 (Paradigm) by 3 (SOA) ANOVA.

Although startle amplitude on prepulse trials varied according to Trial type [$F(3,15) = 8.93$, $p<.01$] there was no significant difference in this measure between paradigms [$F(1,17) = 2.916$, $p>.05$]. Both paradigms showed habituation of the startle response on pulse-only trials [$F(3,15) = 5.67$, $p<.01$] as well as an effect of Paradigm indicating generally lower startle amplitude over the four blocks in the tactile paradigm [$F(1,17) = 4.90$, $p<.041$]. Both paradigms showed equivalent patterns in onset to response peak, i.e. a reduction of this measure over prepulse trials relative to pulse-only trials [$F(3,15)=8.28$, $p<.01$].

There was significant prepulse inhibition with both paradigms [$F(2,16) = 37.41$, $p<.01$], furthermore we observed a significant interaction of SOA and Paradigm [$F(2,16) = 11.15$, $p<.01$]. Follow-up t-tests showed this to reflect greater inhibition of the startle reflex with the acoustic paradigm at SOAs of 60-ms and 120-ms than with the tactile paradigm [$t(17) = 2.37$, $p<.029$; $t(17) = 3.36$, $p<.01$ respectively]. At 30-ms there was no difference between the paradigms in PPI [$t(17) = .921$, $p>.05$].

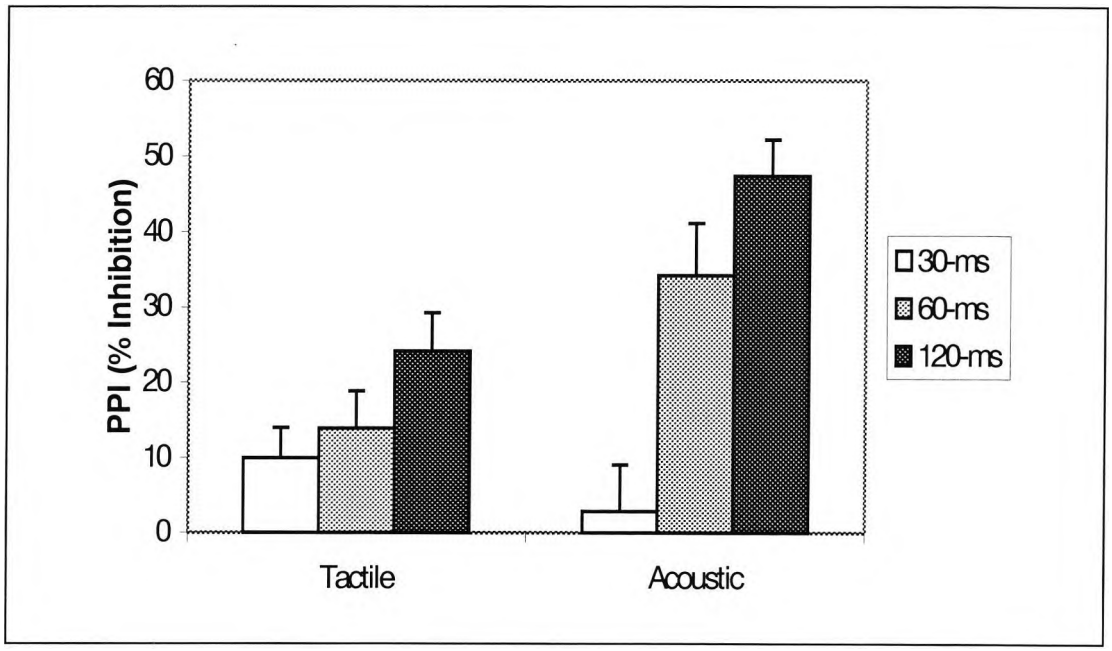

Figure 9.4: Mean (error bar displays 1 SEM) prepulse inhibition (PPI) of the startle response using tactile and acoustic stimuli as a function of stimulus onset asynchrony (SOA).

Detection rates varied significantly across Trial type with the highest detection rates occurring on Pulse Only trials for both paradigms. However the significant effect of Paradigm [$F(1,17) = 44.71$, $p<.01$] as well as the interaction of Trial type with Paradigm [$F(3,15) = 3.96$, $p<.03$] indicated a major difference in detectability of the stimuli between paradigms. Thus pulse-only trials were more reliably identified as such with the tactile stimuli [$t(17) = 2.60$, $p<.018$], similarly tactile prepulses were more easily detected during 30-ms and 60-ms trials than acoustic prepulses [$t(17) = 4.74$, $p< .01$; $t(17) = 4.06$, $p<.01$, respectively] and there was a trend for greater detection of tactile prepulses at 120-ms [$t(17) = 2.03$, $p<.06$].

9.9 Discussion

These data confirmed that, on the whole, the tactile startle paradigm produced similar behavioural effects to the acoustic startle paradigm. Namely it produced significant inhibition of the prepulse at all SOAs, coupled with the same increase in PPI as a function of SOA length, furthermore it produced significant habituation of the startle response, and showed similar effects of latency to onset as observed with the acoustic paradigm. The differences between paradigms were that tactile pulse-only stimuli generally did not elicit as strong a startle response as the acoustic stimuli. This may have been responsible for the comparatively lower levels of PPI observed at the SOAs of 60 and 120-ms with the tactile paradigm, as such lower baseline startle levels would not have allowed the same scope for modulation as was seen in the acoustic paradigm. Tactile prepulses were more readily detected than acoustic prepulses, however as with the latter paradigm, prepulse detection had no effect on PPI. The significance of this observation with reference to attentional modulation of PPI is detailed in the main discussion of this chapter.

CHAPTER 10 Final discussion

The aim of this thesis was to advance current knowledge of the phenomenon of prepulse inhibition of the startle reflex specifically by exploring cognitive aspects and neural mechanisms of the effects of nicotine on PPI. Thus the investigations conducted served to contribute to three major areas of interest within PPI research: namely through exploring the effects of pharmacological challenges on PPI, by using in-vivo functional neuroimaging techniques to explore the neural circuitry involved in PPI, and finally by delving into the psychological significance of PPI. In this chapter the experimental findings from this thesis will be summarized before being considered in the wider context of previous and ongoing investigations into PPI.

10.1 Summary of findings

The study described in chapter 6 set out to investigate the possibility that (at least some) smoking behaviour might be motivated by nicotine's ability to enhance aspects of cognitive functioning as indexed by PPI, a suggestion fuelled by reports of enhanced PPI following nicotine in humans and animals (Kumari et al., 1996;1997b, Acri et al., 1994; Della Casa et al., 1998; Duncan et al., 2001). This study was unique in that it recruited individuals who wanted to stop smoking, whereas most previous related studies had described the effects of nicotine in people willing to quit temporarily for experimental purposes only. Moreover this investigation enabled the testing of some of these individuals after one month of abstinence. The most striking contribution of this study was the ability to compare responses of subjects who did and did not manage to abstain for a month. This enabled the formulation (albeit post-hoc) of a predictor for successful smoking cessation.

In essence, the expectation was of a reduction in PPI under smoking withdrawal compared with baseline. One of the tests of interest was whether this reduction would still be present one month after quitting. If this were the case, it would have

confirmed that smoking was a means of increasing trait-like sub-optimal levels of PPI in these subjects. On the other hand, if PPI levels had been restored to baseline levels, the initial reduction seen under withdrawal would most likely have reflected a temporary withdrawal-induced disruption.

The predicted changes in PPI were observed (i.e.drop after 24 hours), however there were no differences in this change between subjects who succeeded in quitting and those who relapsed. We did observe such a between-group difference in startle amplitude, in that startle amplitude dropped relative to baseline following withdrawal in the group of subjects who succeeded in quitting and not in the five who relapsed. Explanations included the suggestion that this represented a deliberate dosing strategy by the former group to obtain the attentional enhancement thought to be reflected by increased startle amplitude (e.g. Acri et al., 1991), logically suggesting that the latter group did *not* smoke for this effect. Alternatively, it was suggested the observed effect may have been due to between-group differences in commitment (to-quitting) related arousal (as suggested by the 'Stage of Change' model: McDermut and Haaga, 1998). Regardless of *why* these changes in amplitude may have occurred, it was suggested that they could be useful predictors of successful outcome in smoking cessation.

In contrast to the naturalistic nature of the study described above, chapter 7 described a double-blind investigation into the effects of 12 μg/kg nicotine versus placebo on PPI, administered via subcutaneous injection in healthy smokers, non-smokers and people with schizophrenia using a novel, intramodal tactile PPI paradigm. The study confirmed that nicotine enhanced PPI in both healthy subjects and patients, irrespective of smoking status. These findings are consistent with those previously seen in animals (Acri et al., 1994) and healthy human subjects where this effect was reported using an acoustic PPI paradigm (Kumari et al., 1996, 1997b; Della Casa et al., 1998; Duncan et al., 2001). Its novel contribution, in addition to the

demonstration of these effects with a tactile paradigm, was demonstrating this enhancement in schizophrenic patients.

An accumulation of evidence from animal and human studies suggests hippocampal α7 receptors to be the primary site for the enhancing effect of nicotine on both P50 gating and PPI (see chapter 4.3; chapter 8). Confirmation that low affinity nicotinic receptors may also mediate the improving effect of nicotine on acoustic PPI in humans has so far been provided by the observation that only high doses of nicotine achieve this effect (e.g. Kumari et al., 1997b). The same (high) dose used in the Kumari study was used in the experiment described in chapter 7, in which it caused an increase in tactile PPI in healthy as well as schizophrenic subjects. Hence, while such PPI enhancement appears to be dose-dependent, no human PPI study had attempted to directly probe the specific site at which this effect might take place so far.

Therefore a selection of subjects from the study outlined in chapter 7 were subjected to the same procedure in the MRI scanner (chapter 8). This study was the first to examine the neural correlates of nicotine-induced changes in PPI in healthy subjects and people with schizophrenia. Despite the limited number of participants, the results from this study confirmed robust activation of areas implicated in the modulation of PPI. In the rat, these substrates have been described as comprising an interactive circuit of the limbic system and basal ganglia linked with the thalamus and prefrontal cortex (e.g. Swerdlow et al., 1992a; Kodsi and Swerdlow, 1997b; Koch and Bubser, 1994). In addition to these areas, and in view of the evidence for α7 involvement, we predicted that the nicotine-induced increase in PPI would be accompanied by an increase in activation in those areas of this circuitry featuring high concentrations of this receptor subtype. This prediction was borne out with control subjects as well as patients showing increased activation of hippocampal and thalamic regions. Interestingly, while both groups showed increased activation of the hippocampal formation during nicotine, the between subjects comparison revealed that this effect was comparatively stronger in the patient group at all SOAs. While purely

speculative, this difference may reflect a more efficient baseline inhibitory process in the control group.

Finally, chapter 9 aimed to help clarify the functional significance of PPI. Graham (1975) put forward that PPI reflects the working of a sensory gating system which is protective of pre-attentive information processing. The theory proposed that an encounter with a stimulus (i.e. prepulse) triggers two processes: (a) the perceptual encoding of the stimulus, and (b) a parallel protective process which operates by reducing the impact of other input (i.e. pulse) until (a) is complete. A slightly different emphasis is apparent in the influential interpretation outlined by Braff, Geyer and colleagues (e.g. Braff and Geyer, 1990) who propose PPI to reflect an operational measure of sensorimotor gating, which provides an index of the ability to regulate sensory input by - in effect - screening or buffering an otherwise overwhelming flow of information (e.g. Cadenhead et al., 1993). Again this suggests the protection of the early stages of information processing from excessive intrusions. In contrast to Graham (1975), Geyer and colleagues (e.g. 1990) propose this inhibition process to include the buffering of internally generated input (such as thoughts) as well as external stimuli.

The logical prediction from such 'protection of processing' hypotheses is that when such a protective mechanism is successful, processing of information should be optimal. Interestingly, of the numerous studies measuring PPI in the last 25 years which have assumed PPI to reflect a protection of the prepulse, few have actually measured perception of the prepulse. Norris and Blumenthal (1996) did, and appeared to show that occasions when inhibition occurred were indeed coupled with protection of prepulse processing as measured by performance on a prepulse discrimination task.

The study described in chapter 9 investigating the relationship between prepulse inhibition and detection of the prepulse yielded two main findings, of which the first

opposed Norris and Blumenthal's findings in that effective inhibition of the startle response was not related to a superior processing of information as indexed by the ability to detect prepulses. This study thus failed to produce supporting evidence for the protection of processing hypothesis. It was suggested that this may have reflected an insensitivity of the measurement used (i.e. detection) and that the postulated protection only becomes evident in tasks with more extensive demands.

The other issue addressed by this study relates to the involuntary status of PPI: Graham (1975) emphasized this aspect in suggesting that PPI reflected protection of *pre*attentive processing. Equally Swerdlow et al. (1992a) have stated that the intervals at which PPI occurs are too short to allow for the activation of a conscious response. There is strong evidence to support the automaticity of PPI: it occurs in decorticate rats (Ison et al., 1991) and sleeping humans (Silverstein et al., 1980) (also see chapter 3.1.6). In support of this, this study confirmed that conscious awareness of the presence of a reasonably hard-to-detect prepulse did not have an impact on amount of PPI. These results suggest that the SOAs at which PPI was tested (i.e. 30, 60 and 120-ms) were too short to allow for conscious modulation of inhibition, therefore upholding an involuntary status for this response. The above findings related to an intra-modal acoustic PPI paradigm. The postscript to this chapter concerns the results when the same experimental approach was applied to the intra-modal tactile paradigm used in the studies described in chapters 7 and 8. Namely, while tactile prepulses were detected much more readily than acoustic prepulses (such detection rates reaching ceiling levels at 60 and 120-ms and thus ruling out detect vs non-detect comparisons) comparisons at the 30-ms SOA confirmed tactile PPI to be independent of prepulse detection also.

In terms of the psychological significance of PPI, this study did not provide direct support for the protection of processing hypothesis as instances of detection were not paired with increased PPI, thereby contesting the idea that PPI might reflect a process which enables superior processing of information. However, these findings do not rule out the interpretation of PPI as 'protective of information processing' by

virtue of its reflecting the working of a general inhibitory function, which not only serves to limit excess sensory input, but also output.

10.2 General discussion

The issue raised in the final experimental chapter is of crucial importance to the interpretations of results made throughout the thesis and in particular in the investigations involving schizophrenic patients. Claims of deficits in cognitive performance in psychiatric populations are often confounded by the fact that poor performance might merely reflect a lack of motivation to participate in the task. Therefore findings of deficits in tasks tapping involuntary processes are more informative. Chapter 2 describes a number of tasks such as latent inhibition which beautifully avoid this motivational confound as patients (due to a hypothesized fundamental cognitive deficit), are predicted to perform *better* than control subjects (e.g. Gray et al., 1991). Such paradigms have therefore proved particularly useful in understanding abnormalities in schizophrenia. The results from the detection experiment in chapter 9 appear to confirm that the paradigms used in this thesis conformed to the former of these criteria in that they appear to tap an automatic response.

Yet evidence has suggested that under certain conditions PPI *can* be sensitive to volitional processes. As detailed in chapter 9, Norris and Blumenthal found evidence for attentional modulation of PPI during 30-ms (!) and 120-ms trials. The methodological problems of that study are outlined in that chapter. However other studies using more complex tasks than used in either our or the Norris and Blumenthal study have convincingly shown modulation of PPI at SOAs of 120-ms and greater (e.g. DelPezzo and Hoffman, 1980; Hackley and Graham, 1983; 1987; Filion et al., 1993). Therefore while PPI at least in part represents an automatic response, attentional modulation is possible at longer SOAs.

The increase in complexity of some of these paradigms relative to the passive, 'no-task' paradigms used in this thesis is substantial: that developed by Filion, Dawson and colleagues (e.g. Filion et al., 1993) requires detection and discrimination of a specific (high or low tone) prepulse, following which it is classed as either a 'to-be-

ignored' or 'to-be-attended-to' prepulse stimulus, and, if it is an 'attend' trial, sustained attention is required to determine the length of duration of the prepulse stimulus. Attend trials are coupled with greater PPI than ignore trials, which these authors have interpreted as reflecting "the ability to focus on what is important when it is important" (Dawson et al., 2000). This in turn may influence the ability to screen out irrelevant input.

Accordingly (and confusingly) deficits in PPI in schizophrenia have been reported using 'no-task' as well as 'sustained attention' paradigms, which has led to a debate whether such deficits reflect automatic or controlled processing abnormalities. In this way Dawson et al. (1993; 2000) suggest that the impaired PPI observed in schizophrenic patients could reflect a controlled processing deficit only and that automatic sensorigating is intact. Using the above mentioned paradigm developed by Filion et al. (1993), Dawson et al. (1993) found that the patient group failed to show this enhanced PPI in 'attend' trials while interestingly in the 'ignore' condition patients performed at the same level as controls. To clarify this apparent incongruence with earlier studies, which using passive no-task paradigms had shown clear deficits in PPI at SOAs of 60 and 120-ms in the patient group (Braff et al., 1978, 1992; Grillon et al., 1992), Dawson put forward that in those studies differential performances might have reflected control subjects' natural drive to attend to stimuli, the greater PPI in this group being attributable to attentional modulation of inhibition rather than reflecting a deficit in schizophrenics' automatic processing. This effect then disappears when patients also pay a degree of attention to the prepulse (as in ignore trials) but the deficit reappears when sustained attention is required.

However the problem with this claim is that such a controlled processing deficit fails to explain the earlier mentioned deficit observed in schizophrenics at SOAs of 60-ms at which lead interval Dawson and Filion did not show attentional modulation in control subjects. At this interval at least the patient deficit must have reflected an automatic processing problem. Thus it would seem that PPI at different SOAs is

capable of tapping distinct processes. However it remains that the impairment observed by the Dawson group using a paradigm designed to test both automatic and voluntary components of PPI was one of impaired attentional modulation of PPI only (i.e. at 120-ms), while the Braff (1992) findings confirm an automatic sensorimotor deficit. As pointed out by Dawson et al. (2000) the patient populations varied between studies, with the Braff group testing older, more symptomatic patients. The possibility needs to explored that an automatic deficit may reflect a more severe problem associated with worsening of symptoms, while a deficit in attentional modulation of PPI might directly reflect a core deficit in selective filtering of redundant information still evident in relatively remitted patients. Thus in order to fully understand the significance of impaired PPI it would be interesting to use both types of paradigms on patients with a range of illness severity.

Another factor in the expression of PPI deficits at different SOAs and which therefore is potentially linked to automatic/ voluntary processes is that of antipsychotic medication. While some studies have shown patients on typical antipsychotics to show deficits in PPI at intervals of 30, 60 and 120-ms (e.g. Braff et al., 1992) some claim a normalizing action of such drugs on PPI at longer intervals. Thus Kumari and colleagues (1999a) have shown how typical antipsychotic medication partially restores PPI such that patients on these drugs show normal PPI at 120-ms but impaired PPI at shorter intervals. It has been suggested that this partial restoration of PPI at 120-ms may be related to the ability of such drugs to improve attentional processes (and therefore attentional modulation). Equally, the findings reported in this thesis suggest such an automatic impairment in patients on typical antipsychotics, as a reduction was only found relative to the control subjects at the 30-ms SOA (although this was not significant). This was of consequence for the interpretation of subsequent nicotinic effects: as was discussed in chapters 7 and 8 the restorative effect of this medication on PPI at the longer intervals may have induced higher levels of PPI at 60 and 120-ms, thereby limiting the scope for improvement with nicotine. Indeed this study reports how nicotine-induced enhancement of PPI was most pronounced at 30-ms and only marginal at 60-ms.

Using a completely different approach Kumari et al. (2001) had already confirmed similar patterns: they demonstrated a significant impact of smoking on PPI in schizophrenic patients at shorter SOAs, with this relationship being significant at 30-ms, and only a trend at 60-ms. They attributed this to medication-related partial restoration of PPI at longer intervals.

As pointed out in the chapter 7, this study was not specifically designed for detecting PPI deficits (as smoking subjects were in overnight withdrawal and therefore did not provide a true baseline measure), nonetheless patients showed a non-significant reduction in PPI at 30-ms relative to the healthy controls. While the restoring/enhancing effect of nicotine was only significant for the patient group at this interval, control subjects also showed increased PPI at 120-ms intervals. This would suggest that the enhancing effect of nicotine on PPI is less in patients than in controls, which goes against the hypothesis of this thesis. The possibility that this may have reflected antipsychotic medication is outlined above. A more likely possibility is that the dose of nicotine used in this study was not sufficient to induce changes in the patient group, who may have required a higher dose to gain the same effect as seen in the control subjects. As described in chapter 4.2, patients with schizophrenia tend to smoke more and absorb more nicotine from a single cigarette than control subjects (e.g. Olincy et al., 1997) which could reflect a higher tolerance to the drug than in control subjects. There is some indication that such a difference in tolerance levels may be related to typical antipsychotic medication. Dawe et al. (1995) compared nicotine intake in healthy subjects under placebo vs haloperidol. The latter group absorbed significantly more nicotine from a subsequent cigarette as measured by blood nicotine levels. It was suggested that this might have represented a compensatory response in order to achieve normal reinforcement levels. Furthermore this suggestion is supported by findings of decreased smoking levels in patients with schizophrenia who are receiving clozapine relative to those on typical medication (McEvoy et al., 1995a).

Such a dose-related factor may also have contributed to differential effects between control subjects and patient groups in related studies. In a comparison of the effects of self-administered nicotine (via cigarettes) on P50 gating, Adler et al. (1993) showed a transient improvement in impaired P50 gating in schizophrenic patients. However this improvement was not observed in the control subjects. While this potentially could mean that the effects of nicotine on PPI and P50 are quite distinct, it seems more likely that the failure of nicotine to enhance P50 in controls may have been due to a differential dosing strategy. The absorption of nicotine during cigarette smoking is almost immediate and thus allows the individual to monitor the effects. If, as is suggested, patients (also) smoke to improve gating deficits, then circumstances which allow for such self-titration could distinguish between those who smoke for specific (cognitive) benefits and those who smoke for other effects. This possibility is also suggested by the findings in the quit study described in chapter 6 where between group differences in startle response following nicotine withdrawal support a differential dosing strategy between populations. While in the Adler study no difference was observed in number of cigarettes smoked between patients and controls, the amount of nicotine absorbed could nonetheless have been different (e.g Olincy et al.,1997; see above). Note that this study did not measure blood-nicotine levels. In order to facilitate comparisons between the two paradigms, it would be interesting to consider the effects of specified doses of nicotine on P50 gating in patients and controls.

An important issue highlighted by this study as well as a previous investigation by this group (Adler et al., 1992) was the extremely transient nature of the nicotine-induced improvement. The earlier Adler study described an improvement in P50 gating in non-smoking relatives of schizophrenic patients after nicotine, which confirmed that the effect in the subsequent study did not reflect a restoration of a withdrawal induced deficit. Importantly, in both studies P50 recordings were taken at two different time points (5 and 20 minutes after ad-lib smoking commenced) with the improvement in smokers and well as non-smokers being evident only on the first of these occasions. The temporary nature of this improvement was attributed to the

rapid desensitisation of nicotinic receptors. Using a different design, Duncan et al. (2001) showed that smoking after overnight withdrawal increased PPI in healthy smokers, while smoking did not have this effect in non-deprived smokers. This suggests that, as with P50 gating, the rapid desensitisation of nicotinic receptors would limit the timescale of nicotine-induced improvements in sensorimotor gating.
The issue of desensitisation brings us to one of the big challenges facing those attempting to explain the mechanisms via which nicotine might alleviate symptoms in schizophrenia. Desensitisation is not problematic if large numbers of receptors are present and available for activation, as only proportions of these will become desensitised at any one time (Freedman et al., 1995). Chronic smokers show an increase or upregulation of nicotinic receptors, an effect thought to compensate for the otherwise total desensitisation following nicotine use. This increase directly reflects the amount of cigarettes smoked, and is reversible after cessation of smoking (Breese et al., 1997). A comparison of such binding sites in the hippocampus, cortex, thalamus and caudate of postmortem brains showed that, unlike healthy smokers, schizophrenic patients do not show the normal upregulation of nicotinic receptors following chronic nicotine use (Breese et al., 1997). Furthermore animal studies have established that this failure to upregulate is not due to typical neuroleptic medication (Lee et al., 1999). If the number of such receptors is decreased (as is the case in schizophrenia) desensitisation occurs more rapidly and comprehensively. Therefore paradoxically, chronic exposure to nicotine could result in decreased cholinergic transmission (Freedman et al., 1995). This seems to be the most likely reason that the observed beneficial effects of smoking are only transient and might also explain why attempts to use cholinergic agonist treatments for symptoms of schizophrenia have so far been unsuccessful (Berger et al., 1979).

This begs the question whether patients with schizophrenia consciously experience more benefits from smoking following the first cigarette of the day when compared to subsequent cigarettes. Given the above, one would expect to see a worsening of specific symptoms correlated with deficient PPI (i.e. thought disorder; conceptual disorganisation; e.g. Perry and Braff, 1994; Dawson, 2000) after the initial

(beneficial) dose had been absorbed, as repeated exposure to nicotine would cause a reduction in the capacity of the drug to induce its beneficial effects.

In a recent preliminary report, Braff et al. (1999b; abstract) report how patients who smoke show increased PPI compared with non-smoking patients, but it is not clear at what time of day such measurements were taken. One study which has provided some insight into whether nicotine-induced changes in PPI are transient in this patient population is that by Kumari et al. (2001). They reported how, in a group of schizophrenic patients, those who chose to smoke immediately prior to testing showed increased PPI compared with the remaining smokers and non-smokers. However, as the authors point out, any interpretations of their results are limited by the naturalistic design of their study, in that between-group factors other than the subjects' smoking behaviour may have influenced their findings. Clearly such issues need to be clarified, and a future study comparing PPI (and correlated symptoms) after withdrawal and at different time-points during ad-lib smoking would help shed light on this issue.

Given the evidence from P50 gating, it would seem extremely important to pursue the quest for a nicotinic-agonist compound able to induce more permanent beneficial changes. Animal studies have already scored a success in this field: chapter 4.3.1 describes a study by Stevens and Wear (1998) where administration of the selective partial $\alpha 7$ agonist GTS-21 restored impaired sensory gating in DBA/2 mice in a similar way to nicotine. Unlike nicotine, the beneficial effects of GTS-21 persisted with subsequent doses. It was suggested that this might be due to the more rapid metabolism or partial agonist quality of GTS-21, either of which would result in more receptors remaining 'receptive' in contrast to the total block achieved by nicotine.

The study described in chapter 8 is the first in vivo study, using the most up to date neuroimaging techniques, to confirm that the brain circuitry as indicated by animal studies to be important in the modulation of PPI is also evident in humans in a

paradigm which tested the improvement of this response after nicotine. An accumulation of evidence from animal and human studies suggests hippocampal α7 receptors to be the primary site for the enhancing effect of nicotine on both P50 gating and PPI. Neurochemically, this evidence describes the ability of specific nicotinic receptor blockers to interfere with the enhancing effect of nicotine, such that co-administration of α-bungarotoxin (which targets α7 receptors) blocks this effect (e.g. Stevens et al., 1998). In contrast, mecamylamine (a selective high affinity channel blocker) does not affect the improvement caused by nicotine (e.g. Stevens et al., 1998; Curzon et al., 1994). Selectively bred animals with reduced numbers of hippocampal α7 receptors show impaired P50 gating, which is restored following nicotine administration (Stevens and Wear, 1997). Equally in humans evidence has been put forward to support the role of this receptor subtype in the P50 gating response. Thus co-administration of the high-affinity receptor blocker mecamylamine failed to have any effect on nicotine-induced enhancement of deficient P50 gating in relatives of schizophrenic patients (Freedman et al., 1994), furthermore post-mortem studies have confirmed reduced numbers of the α7 subtype receptor in the hippocampi of schizophrenic patients (Freedman et al., 1995). On the basis of this extensive evidence involvement of α7 receptors in nicotine-induced enhancement of PPI was predicted.

This hypothesis was borne out: the most consistently activated areas also featured high numbers of α7 receptors. Therefore it would seem important now to further probe α7 involvement in this response by for instance administrating the selective high affinity receptor blocker mecamylamine in tandem with nicotine. As mentioned above, this strategy was already adopted by Freedman et al. (1994) with P50 gating. A similar outcome with PPI would provide further confirmation of α7 involvement in this effect. The complementary strategy of employing the selective α7 binding α-bungarotoxin in humans is prohibited by the toxicity of this substance. However interestingly, the earlier mentioned α7 agonist GTS-21 is now being used in human trials on patients with Alzheimers disease (Kem, 2000) which opens the possibility of testing the effect of this agonist on PPI in human subjects. Indeed Freedman and

colleagues are currently in the process of planning such studies in human subjects using the P50 paradigm (P.Clarke, pers. comm).

Despite the promising results, there were limitations to the fMRI investigation which need to be considered. As already discussed in chapters 7 and 8 the unavoidable restriction on the design in terms of non-random stimulus presentation (i.e. block design) resulted in rapid habituation which may have caused the high rate of non-responders. Also the inability to measure behavioural responses in the scanner, while not disastrous as PPI has high test-retest reliability, was nonetheless not optimal as this forced the analysis to be restricted to a correlation of the behavioural change measured off-line and the fMRI change. In an attempt to improve on this, a correlational analysis of the drug-induced behavioural changes with changes in power of activation in regions of interest (which showed significantly greater activation under nicotine) was performed. However recent developments have meant that future studies may now benefit from the ability to measure EMG responses on-line, which will allow the exploration of interaction effects during such pharmacological and cognitive challenges and therefore provide a more effective way of determining the site at which nicotine modulates PPI. Furthermore Kumari and colleagues have now developed an event-related PPI paradigm using acoustic stimuli which will avoid the limitations imposed by the tactile paradigm (specifically the high non-response rate to tactile stimuli) in future attempts to replicate the current findings.

This thesis set out to investigate attentional modulation of PPI and the relationship between nicotine and PPI in healthy human subjects and patients with schizophrenia. The PPI deficit in schizophrenia has been put forward as modelling a very basic abnormality at the heart of some of the symptoms of this disorder. It would therefore seem a fitting conclusion to (re)consider the PPI model in the wider context of theories of schizophrenic dysfunction. As described in chapter 2.6 attempts to specify a core cognitive dysfunction underlying the abnormalities of schizophrenia have identified a deficit in inhibitory processes as a prime candidate. The two most

influential animal models (Gray et al. 1991; Swerdlow and Geyer, 1998) have emphasised the role of excess dopamine in the production of such inhibitory disturbances. The evidence in support of dopaminergic hyperactivity is extensive, ranging from the ability of dopaminergic agonists to reproduce abnormalities similar to those observed in schizophrenia in animals as well as bring about psychotic behaviour in humans, to the observed benefits of dopamine antagonists on symptoms of schizophrenic patients (see 2.4.1). Gray et al. describe how structural abnormalities in the projection from the subiculum and/or entorhinal cortex to the nucleus accumbens would lead to hyperactivity of transmission in the ascending mesolimbic dopaminergic pathways, the manifestation of which is a weakening of a mechanism which protects information processing by inhibiting the awareness of irrelevant information. Gray's model is supported by findings from conditioning paradigms such as latent inhibition (LI) which specifically tap the "influences of stored memories of regularities of previous input on current perception" (Gray et al., 1991; p7).

Swerdlow and Geyer's model of sensorigating deficits in schizophrenia focusses on inhibition processes at a much more basic level of information processing than those described by Gray et al. (1991). Their paradigm, PPI, contrasts with Gray's conditioning tasks in that it taps a process which is independent of 'the influence of previous experience', a factor heavily emphasized in both Hemsley's and Gray' theories. Recall that PPI occurs on first time trials and in decorticate rats. No correlation has been found between PPI and such conditioning paradigms in either healthy subjects or schizophrenic patients (e.g. McDowd et al., 1993; Murphy et al., 2001), which implies that while both components of inhibition are impaired in schizophrenia and can be modulated via dopamine agonist and antagonist challenges, they are nonetheless independent. Indeed data from a number of animal studies suggest that the neuronal substrates of LI and PPI are different (Ellenbroek et al., 1996; Broersen et al., 1999). Furthermore, and relevant to this thesis, Thornton et al. (1996) showed nicotine administered either subcutaneously or via cigarette smoking not to affect LI in humans. Thus while both paradigms tap aspects of schizophrenic

dysfunction, the deficit modelled by impaired PPI appears to reflect a much more early information processing problem, while impaired LI seems to refer to a more complex cognitive processing deficit. Interestingly LI abnormalities typically occur in acute schizophrenia and are associated (although not consistently) with positive symptomatology, and are normalised in chronic patients (e.g. Baruch et al., 1988). PPI deficits persist throughout the course of the illness. While this discrepancy may reflect a differential efficacy of neuroleptic medication (PPI is only partly restored by typical antipsychotics) it has also been suggested that the improved LI may reflect the development of an adaptive coping strategy in these patients, who by consciously narrowing their attention are able to avoid some of the associated cognitive overload (e.g. Baruch et al., 1988). PPI deficits in reflecting more automatic and basic processes may be more resistant to adaptive strategies.

In reducing the symptoms of schizophrenia, which by their conscious nature (hallucinations; delusions) are so essentially human, to a neutral level in terms of consciousness by ascribing the aetiology of these symptoms to a dysfunction at a preconscious level, both models have proved invaluable to the furthering of our understanding of this disorder. The advantages of animal models are plentiful: they have allowed the direct investigation of brain structures as well as providing a base for the development and testing of novel antipsychotics. In addition to to proving a valuable measure to predict typical neuroleptic action, PPI is sensitive to atypical antipsychotic properties, which strengthens its worth as a (comprehensive) model of schizophrenic dysfunction. The opportunity granted by the arrival of in vivo neuroimaging techniques has meant that the wealth of evidence already gleaned from animal studies can now be extended immeasurably by investigating the physiological and pharmacological substrates of this phenomenon in healthy human subjects and those with psychiatric illnesses, as has been attempted in the current thesis.

APPENDIX A

The relationship between prepulse detection and prepulse inhibition of the acoustic startle reflex. Psychophysiology, 38 (2001)

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APPENDIX B

Startle Response During Smoking and 24 Hours in Withdrawal Predicts Successful Smoking Cessation. Psychopharmacology, 156 (2001)

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