Investigating the influence of smoking on willed action and cognitive function in individuals with brain injury

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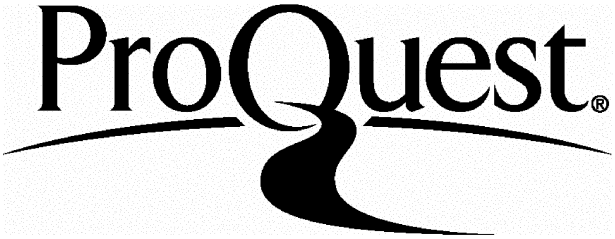

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ABSTRACT

Rationale: Smoking triggers dopamine release, particularly in the mesocorticolimbic dopamine system. Activation of this system has a major overlap with functioning of the frontostriatal circuitry, which has been labelled the 'willed action system'. 'Willed action' describes action that is non-automatic, internally generated, effortful, and involves conscious control. It is implicated in initiation and motivation. There is evidence that abstinence from smoking leads to acute impairments in a range of cognitive and motivational measures, many of which are associated with frontal / frontostriatal functioning.

Aims: The current study aimed to investigate the effects of smoking on willed action in 18 brain-injured smokers.

Method: A within-subjects cross-over design was utilised, to compare performance after an acute (>2 hours) period of abstinence from smoking with performance after smoking. The test battery included measures of reward responsivity (objective and subjective measures of motivation), initiation (verbal fluency), and working memory.

Results: Reward responsivity was enhanced after a cigarette had been smoked compared to the abstinent condition. Additionally, performance on the card sorting task was particularly enhanced after smoking on the first occasion, i.e. when the task was novel. There was no significant enhancement on any other measure.

Conclusion: The results suggest that reward responsivity is modulated by acute smoking status, suggesting a specific effect of nicotine on aspects of motivation. Enhancement of

performance is particularly seen when the task is novel. These conclusions are partially in concordance with a willed action framework. Implications are discussed with reference to routine neuropsychological assessments, and a possible role for nicotine as a therapeutic agent for enhancing motivation after acquired brain injury.

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INTRODUCTION

Smoking is highly prevalent in the general population (around a third of British people smoke), and causes many well-documented health and social problems. There is also a wealth of literature on the physiological, affective and cognitive effects of nicotine consumption, both in animals and humans. Some of this research has focused on constructs such as motivation, reward, pleasure, and higher cognitive processes. There is also considerable research interest in smoking in people diagnosed with schizophrenia, amongst whom there is a noticeably high prevalence of chronic smoking habits (around 90%; Hughes *et al,* 1986), with motivation again central to many of the studies. The current study will look at the effects of acute smoking status on another clinical population, individuals with some form of acquired neurological insult. This population often show motivational impairment caused by the organic brain damage.

I shall first review the literature regarding the concept of motivation, focusing on the constructs of reward responsivity, willed action and executive functioning. The evidence for such constructs from various disciplines, such as neurology, neurobiology, and cognitive psychology, shall be reviewed.

Motivational difficulties, such as apathy, related to acquired brain injury and other disorders will then be described, along with potentially explanatory theories linking

apathy with anatomical damage, neurobiological dysfunction, and executive dysfunction. The emotional / subjective correlates of apathy will also be examined.

There have been many studies claiming that self-administration of nicotine (i.e. smoking) can enhance cognitive abilities. These will also be reviewed, focusing on the evidence that smoking enhances motivation and executive functioning, related to the theoretical frameworks previously outlined. From this, the experimental hypotheses being tested by the current study will be generated and outlined.

PART I: MOTIVATION, REWARD RESPONSIVITY, AND 'WILLED ACTION'

Since classical times, the concept of 'will' has been a central concept to Western thinking. In the Judeo-Christian view, will constituted an autonomous mental function, and during the 19th century this view increased in popularity, including the idea that mental health depended on the free exercise of the will (Berrios and Gili, 1995). In 1890, William James made an influential distinction between those acts that were 'ideo-motor' and those that were 'willed', emphasizing the continuing prominence of this concept.

However, after the turn of the 20th century, the concept of will became increasingly less discussed, possibly due to the increased prominence of psychoanalytic and behavioural views (which could be seen as 'anti-will'), but not because of any crucial research showing that will did not exist (Berrios and Gili, 1995). New concepts attempting to explain internal control of action within different theoretical frameworks have commonly been used in the last century, such as drive, motivation and executive functioning.

Motivation, reward responsivity, and the CARROT

Motivation is a construct that has been described as that which "subsumes the totality of ... goal-related processes" (Duffy, 1997; p.24). Goal-directed behaviour fosters the survival and well-being of an individual, and involves continuous monitoring of the internal and external stimuli that constitute experience, prioritisation based on past,

present and predicted future, and selection of action amongst possible responses. Ultimately, this chain of processes leads to a response, and the monitoring of consequences for reappraisal purposes - the translation of motivation into action (Mogenson *et al,* 1993). Motivation is therefore not really a specific scientific construct, but a framework that brings to together all of the above processes, incorporating systems at the cognitive, affective and sensory levels of functioning. It could be described as representing the dynamic relationship of these distributed and integrated neural systems to the environment (Duffy, 1997).

One of the measurable components of motivation identified is 'reward responsivity'. This construct identifies degree of responsiveness to environmental incentive (Al-Adawi and Powell, 1997). It can be assessed by identifying the degree to which there is enhanced speed or intensity of response from an individual when the potential reward for the given task is increased. Healthy (i.e. 'normally' motivated) individuals should react to personally salient incentives with enhanced responses.

Using this concept, Al-Adawi *et al* (1998) developed the Card Arranging Reward Responsivity Objective Test (CARROT), a card sorting task measuring increased sorting rate when a financial incentive was available (see 'Method' for more detail). Performance on this test was found to correlate extremely highly with a) clinical indices of motivation in individuals, some of whom suffered with varying degrees of apathy after acquired brain injury (Powell *et al,* 1996); b) appetitive motivation (as assessed by personality

questionnaires) in healthy participants (Pickering *et al,* 1998); and c) fluctuations in smoking / abstinence status (purported to be associated with fluctuations in dopaminergic functioning) in 'healthy' smokers (Al-Adawi and Powell, 1997). These observations suggest that the test has good construct validity.

Willed action

'Willed action' is a term adopted by Jahanshahi and Frith (1998) (although Frith had coined the term previously; see Frith *et al,* 1991) in a review of evidence from studies employing converging investigative neurological techniques, such as functional imaging, transcranial magnetic stimulation, and recording of movement-related cortical potentials. They proposed that willed actions are intentional self generated actions, involving functioning of a frontostriatal network. They also claimed that the conceptualisation allows an integrated approach to the study and understanding of cognitive, motor, and motivational deficits in individuals with frontal lobe lesions, schizophrenia, and Parkinson's disease, amongst other conditions (Jahanshahi and Frith, 1998).

Jahanshahi and Frith suggested a number of component processes of willed action, including response selection and preparation, suppression of habitual responses, sequencing and timing of responses, and attention to action. Willed action is seen as involving three aspects: attention and conscious awareness, choice and internal control, and intentionality. However, Jahanshahi and Frith acknowledge that this is a 'common-

sense' distinction, and that there are major problems in designing experimental tasks to engage either willed or externally-generated action in isolation. These criteria for willed action often depend heavily on introspective reports by research participants of being aware that they are selecting or rejecting possible responses.

Nevertheless, many researchers have found evidence to suggest that willed actions are controlled in a way that is partially separate from routine, 'automatic', stereotyped actions that are externally triggered by environmental stimuli. Selective impairment on 'willed action', as opposed to routine, tasks has been demonstrated on a range of tests (both cognitive and motor) in individuals diagnosed with frontal lobe lesions, Parkinson's disease and schizophrenia (Jahanshahi and Frith, 1998).

Attention to action is often used as the defining psychological boundary between the two types of action. James (1890) stated that 'willed' acts involved a conscious element, and that "effort of attention is thus the essential phenomenon of will" (p.522), whereas an 'ideo-motor' act "follows unhesitatingly and immediately ... we are aware of nothing between the conception and the execution" (p.522). Norman and Shallice (1986) further noted that one can be unaware of performing automatic, 'ideo-motor' actions, but 'willed' actions require active, directed attention to the task.

Neurological evidence for a willed action system

To support the hypothesis of a separate system for willed action, a number of studies have identified potentially important neural systems, in particular the frontostriatal circuits.

The frontostriatal circuits

Jahanshahi and Frith (1998) conclude that a network of 5 separate frontostriatal loops provides the anatomical substrate for the concept of 'willed action'. These five circuits were first identified by Alexander *et al* (1986). Each starts at an anatomically separate area of frontal cortex, passes through specific sections of the striatum and the globus pallidus / substantia nigra, projecting back to the original frontal cortical site via distinct thalamic nuclei. The main cortical and subcortical portions of these loops are shown in Figure 1.1.

Each circuit has a direct and an indirect pathway that are considered to have opposing effects on the basal ganglia output nuclei and the thalamic targets of basal ganglia outflow (Miller and DeLong, 1987; Brooks, 1995). These pathways respectively facilitate or suppress activity, creating a system that allows magnification or suppression of activity initiated at the cortical level. This system is therefore ideally suited for the mediation of 'willed' actions (Jahanshahi and Frith, 1998).

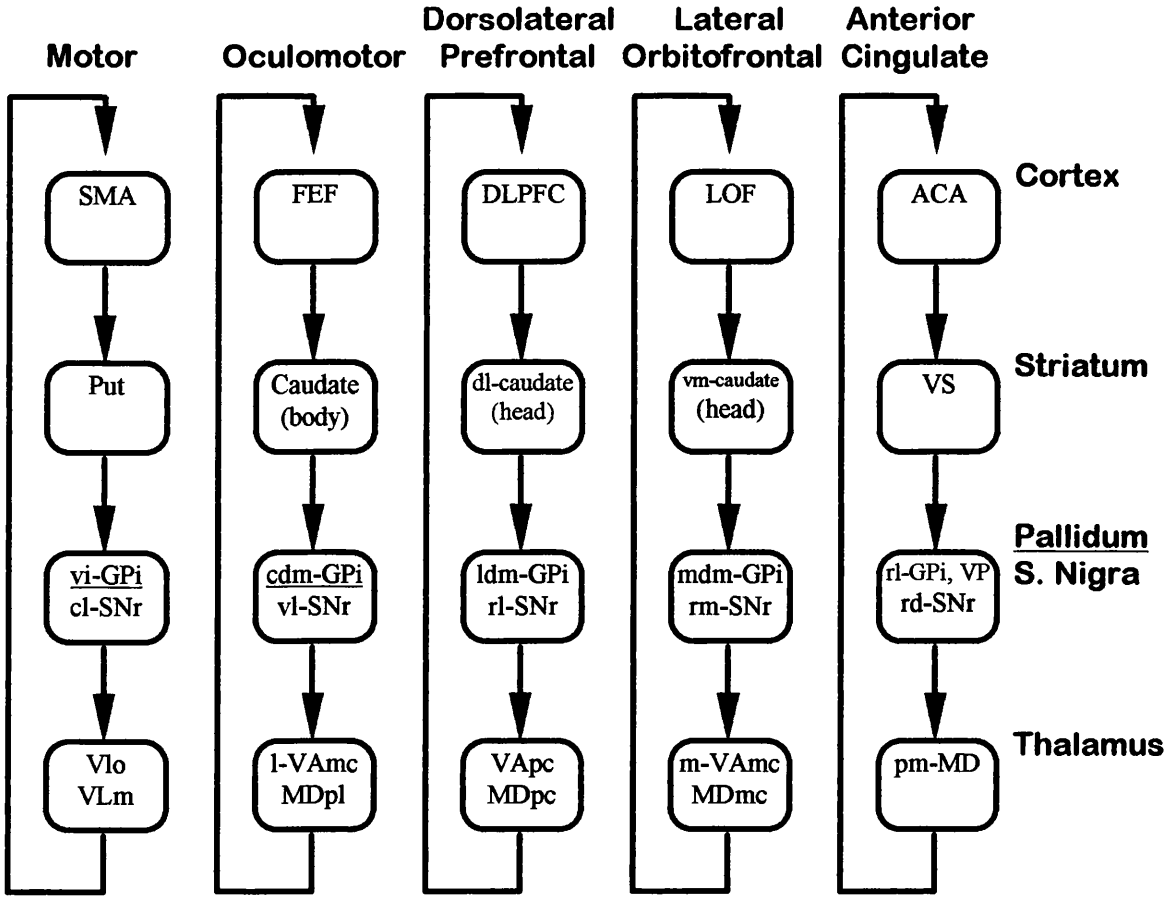


Figure 1.1 The five frontostriatal loops (taken from Jahanshahi and Frith, 1998; adapted from Alexander *et al*, 1986). The circuits project from frontal cortex areas to discrete areas of the striatum, and then back to the same frontal cortex areas via distinct output sections of the basal ganglia and thalamus. Abbreviations used: ACA - anterior cingulate; cdm - caudal dorsomedial; cl - caudolateral; dl - dorsolateral; DLPFC - dorsolateral prefrontal cortex; FEF - frontal eye fields; Gpi - internal segment of the globus pallidus; l - lateral; ldm - lateral dorsomedial; LOF - lateral orbitofrontal cortex; m - medial; mdm - medial dorsomedial; MDpl - medialis dorsalis pars paralamellaris; MDmc - medialis dorsalis pars magnocellularis; MDpc - medialis dorsalis pars parvocellularis; pm - posteromedial; Put - putamen; rd - rostrodorsal; rl - rostrolateral; rm - rostromedial; SMA - supplementary motor area; SNr - substantia nigra pars reticulata; VAmc - ventralis anterior pars magnocellularis; VApc - ventralis anterior pars parvocellularis; vl - ventrolateral; VLm - ventralis lateralis pars medialis; Vlo - ventralis lateralis pars oralis; vm - ventromedial; VP - ventral pallidum; VS - ventral striatum.

It is not clear to what extent the loops are segregated. Evidence is emerging to suggest that each loop, to some extent, plays a specific and distinct role (see Table 1.1). However, there is some indication that there is a degree of convergence between loops. A study of dendritic arborization led Percheron and Filion (1991) to conclude that "the same pallidal or nigral neuron might respond to signals from different parts of the body, and integrate 'motor', 'oculomotor', 'limbic', and two types of 'prefrontal' signal according to context". Alexander and Crutcher (1990) gave the example of simultaneous processing in motor and oculomotor circuits in 'hand-eye' coordination tasks, supporting the idea of some degree of convergence.

There are some pertinent animal studies that support the idea of a neurological system specifically associated with internally generated movements (willed action). Studies with monkeys have suggested that the supplementary motor area (SMA) is essential for movements based on an internal "what to do" decision. For example, Okano and Tanji (1987) showed that cells in the SMA selectively fire just before a self-paced movement of the upper limb, and Funahashi *et al* (1993) found that activity in the dorsolateral prefrontal cortex (DLPFC) is associated with performance on the anti-saccade task, which requires inhibition of strong response tendencies.

Several studies with healthy human participants also support the idea of a specific system for internally generated action. Some have used self-selection of 'random' movements as an experimental task, and have found that such movements are associated with increased

activation in various areas of the frontostriatal circuits (e.g. Frith *et* al, 1991, Playford *et al*, 1992).

There have also been studies showing changing levels of activation in areas of the frontostriatal system as participants become skilled at a task through practice. Jenkins *et al* (1994) found that the DLPFC and the anterior cingulate cortex were only activated during new learning, whereas the SMA was more activated during performance of a prelearned sequence. Passingham (1997), on the basis of imaging studies, suggested that the SMA controlled motor sequences that had become overlearned, and could therefore be performed without external stimuli. A similar effect in the SMA and DLPFC has been shown with a verb generation task (Raichle *et al*, 1994), showing generalization of this increased frontal activation during new learning across different types of task (motor and cognitive). Jueptner *et al* (1997b) also found that the striatum (particularly the caudate nucleus) is differentially active during learning of new motor sequences.

Jueptner *et al* (1997a) found similar results to Jenkins *et al* (1994), and also found evidence that conscious attention to action is at least partly responsible for activation in the DLPFC and anterior cingulate cortex. They asked participants to attend to the motor sequence that they had learned, and found reactivation of the above areas, although this reactivation was not great as the initial activation during new learning. Frith and Dolan (1996) also demonstrated that the maintenance of a representation ('holding it in mind'), often classified as a working memory task, was associated with bilateral activation of the

DLPFC, as well as the relevant distributed neural system (e.g. parietal cortex for a spatial representation).

The above studies suggest that some of the components of the frontostriatal system are involved in new learning, where conscious attention to action is necessary. With practice, tasks become more automatic (i.e. require less attention to their performance), and the frontostriatal systems are no longer engaged to a great extent. In other words, willed action is only necessary for some tasks when they are novel.

Jahanshahi and Frith (1998) also noted that activity of the frontostriatal system has also been associated with:

- precise timing of willed motor actions (particularly the SMA, putamen, and ventrolateral thalamus; Rao *et al*, 1997)
- motor preparation (the SMA, DLPFC, and anterior cingulate; Deiber *et al*, 1996)
- sequential ordering of willed actions (the SMA; Gerloff *et al*, 1997)
- response suppression on a 'go no-go' task (the anterior SMA; Humberstone *et al*, 1997).

Willed action for cognitive tasks

More abstract entities such as words and ideas can also be selected by the proposed willed action (frontostriatal) system. In addition to the study mentioned above (Raichle

et al, 1994), a verbal fluency task has been shown to activate the left DLPFC and the anterior cingulate (Frith *et al*, 1991, Frith and Dolan, 1996), demonstrating the similarity in patterns of brain activation associated with acts with motor and verbal output. The most widely used verbal fluency task requires participants generating as many words as possible beginning with a certain letter, involving a self-directed search of word associative networks to retrieve appropriate words, as well as suppression of inappropriate responses (Jahanshahi and Frith, 1998).

Random number generation, another task involving internally generated response selection and continual monitoring of prior responses to avoid stereotyped responses, has also been shown to involve the DLPFC and the anterior cingulate, amongst other areas, when compared to counting (Jahanshahi *et al*, 1997). Complex cognitive tasks, such as the Tower of London task (Baker *et al*, 1996), where strategies must be generated, and inappropriate ones suppressed, also involve the frontostriatal system (especially the DLPFC). Individuals with Parkinson's disease (where there is impairment of the frontostriatal circuits) exhibit poor performance on all of the above tasks (Taylor *et al*, 1986; Spatt and Goldenberg, 1993; Owen *et al*, 1993), further underlining the importance of these areas for internally generating responses.

Other studies propose a distinction between 'effortful' and 'effortless' cognitive tasks, with frontal cortex implicated in the former type of task. The effortful / effortless

discrimination could be seen as analogous to the 'willed' / automatic distinction in many respects. Schacter *et al* (1996) showed that frontal cortex was activated during an

Table 1.1 Functions or tasks empirically associated with activation of each of the five frontostriatal loops.

Loop	Main (cortical and sub-cortical) structures	Proposed function / task associated with activation	Study
Motor	supplementary motor area (SMA) and the putamen	• motor preparation • response inhibition • precise timing of actions • sequencing of actions	Deiber *et al* (1996) Humberstone *et al* (1997) Rao *et al* (1997) Gerloff *et al* (1997)
Complex	dorsolateral prefrontal cortex (DLPFC) and the caudate nucleus	• internal generation of action / cognition, and its timing • learning new skills • attending to action • working memory • 'executive' functioning, including hypothesis generation • suppression of reflexive responses	Frith *et al* (1991), Jahanshahi *et al* (1997) Jenkins *et al* (1994), Raichle *et al* (1994) Jueptner *et al* (1997a) D'Esposito *et al* (1995) Cummings (1993) Guitton *et al* (1985).
Anterior cingulate	anterior cingulate and the ventral striatum	• motivation • response inhibition • internal generation of action / cognition • learning new skills • attending to action • executive attention • detection of erroneous responding	Cummings (1993) Cummings (1993); Crawford *et al* (1996) Frith *et al* (1991), Jahanshahi *et al* (1997) Jenkins *et al* (1994), Raichle *et al* (1994) Jueptner *et al* (1997a) Posner and Peterson (1990) Dehaene *et al* (1994)
oculomotor	frontal eye fields and the caudate nucleus	• hand-eye coordination (with 'motor' loop)	Alexander and Crutcher (1990)
lateral orbitofrontal	lateral orbitofrontal cortex and the caudate nucleus	• processing of performance feedback • response inhibition	Elliot *et al* (1997) Cummings (1993)

'effortful' but not an 'easy' recall task. Al-Adawi *et al* (1998) suggested that some attention and memory tasks are likely to be related to motivation (perhaps because they require a certain amount of effort), and found evidence for the existence of this relationship, as performance on such tasks correlated with other indices of both 'frontal' function and motivation.

Table 1.1. summarises all of the above studies, as well as the main conclusions of a number of others. This overview suggests that there is some degree functional delineation between the different loops, but that many functions have been associated with different areas by different studies. This could be indicative of a genuine shared functionality on a large number of tasks, but could also reflect the different methodologies of the studies, or a small sample size (e.g. Cummings, 1993, based some of his conclusions on just one case, raising the possibility of a theory based on participant idiosyncrasies).

Neurobiological theories regarding motivation and 'willed action'

Dopamine

Dopamine is a neurotransmitter in the catecholamine sub-class of the monoamine group of neurotransmitters. It is the principal neurotransmitter in both the nigrostriatal and

mesocorticolimbic system, and modulates arousal, motivation, locomotor response, and sensory integration (Le Moal, 1995).

From animal research, it has become clear that dopamine systems are involved in the processing of information related to rewards. Impairments of dopamine transmission lead to deficits in appetitive learning, approach behaviour and the subjective hedonic perception of rewards. The majority of appetitive deficits follow impaired dopaminergic transmission in the nucleus accumbens, whereas impairments in the striatum lead mostly to sensorimotor executive deficits (Schultz, 1997).

Most dopamine neurons are activated in a rather homogenous manner by all primary and conditioned rewards (Schultz, 1997). They depend entirely on the unpredictability of the stimuli, responding only when the reward was unexpected (Mirenowicz and Schultz, 1994), Salamone (1994) suggests that dopamine release mediates activation of goal-directed behaviour (appetitive or avoidant), and is triggered by the experience or expectation of reinforcement. This release may underlie reward responsivity, in that it heightens drive states, making the individual more likely to respond towards incentives in the environment (Powell *et al*, in press). Dopamine neurons become depressed in their activity when an expected reward fails to materialise (Schultz *et al*, 1993).

It therefore seems that dopamine neurons code the deviation between the predicted and actual occurrence of rewarding events (Schultz *et al*, 1995), and the total neuronal

response constitutes a global reinforcement signal that is broadcast to the striatum and many areas of frontal cortex (Schultz, 1997). All of these areas are part of the frontostriatal circuits.

There are many different theories of goal-directed behaviour involving dopamine. The dopamine hypothesis (as labelled by Nader *et al*, 1997) posits that dopamine stimulation itself is a critical link in the reward properties of all stimuli, both necessary and sufficient to produce reward. There is much data to support the involvement of dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens in mediating the rewarding effects of other stimuli (Wise and Rompre, 1989, for a review).

However, there is evidence to suggest that dopamine does not directly mediate the experience of reward, as it is also released in response to aversive stimulation (Thierry *et al*, 1976). There are also a number of examples of dopamine-independent motivated behaviour (e.g. where dopamine antagonists have no effect on ethanol self-administration; Rassnick *et al*, 1993), questioning the dopamine hypothesis, and suggesting that VTA dopaminergic neurons may be only part of an overall reward system. The 'non deprived / deprived' model (as labelled by Nader *et al*, 1997) was put forward to integrate evidence (e.g. Nader *et al*, 1994) that dopamine only mediates the rewarding properties of other stimuli when animals are in a state of deprivation / withdrawal. The 'saliency attribution' model (as labelled by Nader *et al*, 1997) claims that liking (immediate evaluation of how pleasurable a stimulus is) and wanting (a process that mediates our attraction towards

rewarding environmental stimuli) are two separate components of reward, with dopaminergic mechanisms involved in the latter (e.g. Ungersteadt, 1971) but not necessarily in the former, where processes mediating hedonics can respond normally without dopaminergic involvement (Berridge, 1996).

Dopamine release in the nucleus accumbens or VTA (where the mesolimbic / mesocortical dopaminergic pathways originate) may underlie the subjective pleasurable experience elicited by all manner of reinforcers (food, drink, sex,)(Powell *et al*, 1996), and there is much evidence to indicate that recreational drugs exert their addictive properties through dopaminergic mechanisms in the nucleus accumbens and frontal cortex (e.g. Wise, 1996); again, these are areas involved in the frontostriatal circuits.

Dopamine and the frontostriatal circuits

Some of the evidence showing that dopamine acts upon areas of the frontostriatal circuits has already been referred to above. Dopamine therefore appears to play a key role in modulation of these circuits, although its precise role has yet to be established. Indications as to the extent and nature of dopamine's relationship with willed action comes from studies looking at neuroanatomy, neuroimaging, effects of dopamine agonists, schizophrenia, and Parkinson's disease.

Moore (1982) found that projections from the substantia nigra to striatal structures use dopamine, and that there are dopaminergic projections to the septal area, amygdala, medial frontal cortex, and the anterior cingulate cortex. Current models of basal ganglia functioning suggest that striatal dopamine release inhibits basal ganglia output, therefore increasing activity of thalamocortical projections, and facilitating cortically initiated action (Gerfen, 1995).

Some studies have shown a direct association of dopamine transmission (via neuroimaging) with certain facets of willed action. For example, Pedro *et al* (1994) found that stereotypy on a two-choice guessing task (a task involving strategy generation and monitoring; Frith and Done, 1992) was associated with dopamine D2 receptor binding. Sawaguchi and Goldman-Rakic (1991) showed that local blockade of D1 receptors in the DLPFC produced impaired performance on a working memory task in primates (see below for explanation of the theoretical association of willed action and working memory).

Other studies have found evidence that dopamine agonists enhance performance on neuropsychological tests purported to tap facets of willed action. Newman *et al* (1984) demonstrated that levadopa (a dopamine precursor) facilitated recall on an effortful, but not an automatic memory task, in a sample of normal elderly volunteers. Other studies have shown that bromocriptine (e.g. Powell *et al*, 1996; McDowell *et al*, 1998) and methylphenidate (e.g. Watanabe *et al*, 1995; Mehta *et al*, 2000) improved performance

on such tasks. It has also been shown that goal-directed behaviour is compromised in several conditions (e.g. depression, Parkinson's disease, and negative symptoms of schizophrenia) where there is evidence that dopamine transmission is disrupted. Dopamine agonists remediate certain behavioural deficits to some degree (Al-Adawi and Powell, 1997).

It is important to note that although dopamine appears to be important in willed action functioning, there are a multitude of neurotransmitters that interact in complex ways, with dopamine modulating, and being modulated by, other neurotransmitters. It is unlikely that any single neurotransmitter dysfunction underlies complex disorders such as schizophrenia.

Willed action and schizophrenia

The exact physiological basis of schizophrenia is unknown. Robbins (1990) suggests that schizophrenia may reflect dysfunction of the frontostriatal network. This concurs with Frith's (1987) proposed cognitive model of schizophrenia, which again involves a distinction between willed action and stimulus driven action as two routes to action. Disconnections at various points of these two routes are considered to be responsible for positive (e.g. hallucinations, delusions) and negative symptoms (e.g. anhedonia, flat affect, poverty of action, stereotyped action and inattention), with the latter reflecting a dysfunction of willed action.

These negative symptoms are very similar to those commonly observed in individuals with neurological damage in frontal, sub-cortical, or right hemisphere areas. Electrodermal responsiveness studies show that these symptoms, in individuals with both psychotic and neurological aetiology, are associated with electrodermal non-response. This is thought to reflect frontal-subcortical dysfunction (Andersson and Finset, 1999).

Dopamine appears to play an important role in schizophrenia, as drugs that modulate the dopamine system have a marked effect on psychotic symptoms (e.g. Creese *et al*, 1976), and post-mortem studies have found a correlation between increased numbers of dopamine receptors and previous experience of positive symptoms (Crow *et al*, 1984). Crow (1980) suggested that positive symptoms reflect mesocortical dopamine overactivity, and negative symptoms reflect underactivity. There is also a great deal of evidence that reduced dopaminergic activation produces many of the 'executive'-type deficits seen in individuals with schizophrenia (Cohen and Servan-Schreiber, 1992).

Willed action and Parkinson's disease

The importance of dopamine in the frontostriatal system is also illustrated by symptoms of Parkinson's disease, and their conceptualisation within the 'willed action' framework (Jahanshahi and Frith, 1998). Parkinson's disease is a movement disorder relating to degeneration of dopamine-producing neurons in the substantia nigra, resulting in

dopamine deficiency in the striatum, particularly the putamen (Brooks *et al*, 1990). The substantia nigra and the striatum are involved in all 5 frontostriatal circuits.

The main symptoms of Parkinson's disease are akinesia (poverty of spontaneous movement), bradykinesia (slowness of movement), tremor and rigidity. Akinesia has been referred to as 'paralysis of the will' (Wilson, 1925), and there is converging evidence to suggest that the main deficit is in translating willed intention into action, whilst still being able to respond to external stimuli to an extent. Firstly, there is co-existing contralateral bradykinesia and normal movement in individuals with hemi-parkinsonism (Jahanshahi and Frith, 1998). Secondly, there is self-report of patients 'knowing what to do, but not being able to do it' (Frith, 1992). Thirdly, there is observation of 'paradoxical kinesis' where an extraordinary external stimulus (e.g. a fire) can lead to a normally immobile person responding (e.g. running to safety).

Studies using functional imaging show underactivation of the cortical targets of the frontostriatal circuits in individuals with Parkinson's disease during performance of random (i.e. 'internally generated') joystick movements, but normal activation with externally triggered actions (e.g. Jahanshahi *et al*, 1995). Jahanshahi and Frith (1998) identify evidence from a number of experimental paradigms suggesting that willed action is more impaired than routine action. These studies tested participants when off dopaminergic medication; evidence from other research shows that the above

underactivation is ameliorated to a large extent by such medication (e.g. Jenkins *et al*, 1992).

In summary, there appears to be a wealth of evidence to suggest a major overlap between the 5 frontostriatal circuits and the nigrostriatal and mesocorticolimbic system dopamine systems.

Cognitive models of goal directed behaviour

There are also a vast number of studies in the fields of cognitive psychology and cognitive neuropsychology that have contributed to the available literature regarding goal-directed behaviour from a cognitive perspective, with models often referring to 'executive' functioning as controlling behaviour.

Early work in attempting to reveal the basic functions of the frontal lobes was undertaken by A.R. Luria. After 30 years of research, including extensive study of individuals with lesions of the frontal lobes, Luria (1973) concluded that:

" ... the frontal lobes play an essential part in the higher forms of regulating the states of activity. They control the active state of the cortex, which is necessary for the accomplishment of complex tasks, and play an important role also in the execution of intentions that determine the direction of human activity and impart to the latter an elective and purposive character. Numerous observations have also revealed the role of

the frontal lobes in the execution of complex programs of activity, the formation of the orienting basis of action, and the organization of its strategy. Further, their role in the process of matching the effect or consequence of action to the initial intention which is the basis of the highly important function of the modification of action." (p. 22)

Luria's formulation of frontal lobe function shows a good degree of overlap with the concept of willed action, and also with a construct later proposed by Norman and Shallice (1986), which they labelled the 'supervisory attentional system' (SAS).

The 'supervisory attentional system'

This model is strongly related to the concept of willed action, as it accounts for the role of attention in action, and supports the concept of a distinction between controlled and automatic processes.

Norman and Shallice propose two complementary processes that operate in the selection and control of action. One is these is sufficient for automatic action (simple, well-learned acts) and the other allows for conscious attentional control to modulate performance. They posit that this occurs through the mechanism of 'contention scheduling' (McClelland and Rumelhart, 1981), which functions by activating supporting schemas and inhibiting conflicting ones.

In the case of automatic action, simple, well-learned action sequences are represented by action schemas. Each schema has an activation value, and is selected when particular trigger conditions cause activation to rise above a threshold level. No direct attentional control of selection is required. Contention scheduling is a process where schemas compete with one another (i.e. when several are potentially activated) to determine activation threshold values, and subsequently become selected on the basis of this value. Competition between schemas for limited processing resources occurs through lateral activation and inhibition amongst activated schemas. Activation values of a controlling schema can become lower with use, and with practice, these schemas become more specialized, reducing the need for mutual inhibition of other schemas.

Occasionally, an additional control structure is necessary, and it is here that the SAS becomes involved. Tasks that involve the SAS (i.e. deliberate attentional resources) can:

- involve planning or strategy generation
- involve decision making, i.e. strategy selection
- involve aspects of 'trouble-shooting', including self-monitoring
- contain novel sequences of actions
- be judged to be dangerous or technically difficult
- require inhibition (overcoming a habitual response, resisting temptation).

The SAS operates through the temporary application of extra activation and inhibition to schemas, in order to bias their selection. It is proposed that this reflects deliberate

conscious control of action. Norman and Shallice also adopted the term 'will' to describe this control, and define it as "a quantitative dimension corresponding to the amount of activation or inhibition required from the supervisory attentional mechanisms" (p.15). Motivational factors are assumed to supplement the activational influences of the SAS, biasing the contention-scheduling mechanisms towards the long-term goals of the individual. In fact, it was suggested that a willed act depends on the conscious identification of a particular end to be achieved. Potential positive consequences are more likely to lead to activation of source schemas, and negative consequences to inhibition.

Robbins (1991) proposed that dopamine may play a part in setting the threshold for the triggering of schemas in selection of action, and Robbins and Sahakian (1983) argued that increased dopaminergic release increases the number of action schemas activated above the threshold.

Norman and Shallice note that the so-called 'frontal syndrome' involves many deficits one would predict from a dysfunctional SAS, in areas such as planning, error correction, new learning, response inhibition, and perseveration. They also posited that it is very difficult to find 'non-willed' tasks, stating that the SAS is needed to a certain extent for every task; one can only say that there is 'near-zero' attentional activation of schemas.

In summary, the SAS analyses and directs ongoing behaviour with respect to desired outcomes, i.e. goal-directed behaviour. It is clear that the constructs of the SAS and willed action have degrees of overlap in many areas; a) they are made up of similar components, b) attention to action is required for both, c) both implicate the frontal lobes, d) both implicate a key role for dopamine, and e) both produce goal-directed behaviour according to an internal plan / goal / knowledge rather than responding to immediate external stimuli. The co-existence of these constructs could be seen as two different research disciplines (willed action derived from neurological data; the SAS derived from cognitive data and computer models) converging on a very similar model, which supports the idea that the models are valid.

Working memory

Another relevant cognitive models of frontal / executive function is working memory. This could be described as a process where " ... cognitive representations are sustained, prolonged, or maintained in the face of varying degrees of interference, distraction or "noise" that might otherwise disrupt the representations. The process of sustaining these cognitive representations makes them available to ... "mental manipulations" ... " (Fleming *et al,* 1994; p.204).

Baddeley's (1992) model of working memory involves at least two components; the central executive (responsible for overall co-ordination of information processing, with

access to longer term memory), and slave systems (modality-specific processes for 'holding things in mind', involving a store and a rehearsal mechanism). Investigations have found possible neurological substrates paralleling this model, emphasizing the interactions between DLPFC (central executive) and modality specific posterior areas (slave systems)(Goldman-Rakic, 1987; Frith and Dolan, 1996). Baddeley has utilised the model of the SAS put forward by Norman and Shallice to help explain the functioning of the central executive component of working memory.

Fuster (1989) has also posited a theory similar to working memory that he associated with prefrontal cortex functioning, calling it 'active memory'. Active memory bridges a temporal gap in the course of behavioural action, and involves three functions: a retrospective short-term store, a prospective function / preparatory motor set, and a control / inhibitor of interference.

PART II: IMPAIRMENTS OF INITIATION AND MOTIVATION AFTER BRAIN INJURY

Individuals with brain injury (especially to the frontal lobes) will often have neurological damage to one or more of the 5 frontostriatal loops, which are implicated in deficits in motivation and initiation (i.e. willed action). Apathy is a common neurobehavioural sequelae, with hypofunction of dopaminergic systems has been postulated to have a central role (Marin, 1990). The existence of such deficits is one of the best predictors of poor psychosocial outcome after brain injury (Vikki *et al*, 1994), commonly impeding rehabilitation and resulting in social alienation.

Initiation and motivation problems are often labelled as abulia. The term was coined over a century ago, and means 'lack of will'. Bhatia and Marsden (1984) define abulia as a "loss of drive or apathy including loss of spontaneous motor activity, loss of emotional affective expression and reduction of spontaneous thought content and initiative". Similarly, Blumer and Benson (1975) identified a "pseudodepressive syndrome", characterized by passivity, flattening of affect, reduction of verbal output, poor initiation, and slowness to respond.

It should be noted that very few researchers have attempted to quantify and further investigate motivation problems after acquired brain injury, and the literature tends to rely on clinical descriptions such as those mentioned above. However, Marin (1997a)

considers apathy to be a valid construct as a symptom, a syndrome, or a behavioural dimension, of which abulia is a severe form. He defined apathy as "impairments in ... overt behavioural (motor), cognitive, and emotional aspects of goal-directed behaviour" (Marin, 1997b; p.31). Here, motor aspects involve diminished activity, cognitive aspects involve a lack of goals and plans for the short and long term future, and emotional aspects include flat affect and indifference. Importantly, these impairments should not be attributable to diminished consciousness, cognitive impairment, emotional distress, or major depression. Marin developed the Apathy Evaluation Scale (Marin, 1991, Marin *et al*, 1991), a reliable and valid measure of the construct.

A neuroanatomical basis for apathy

Different researchers have suggested that damage to different areas of the frontostriatal system mediate motivational impairment. Blumer and Benson (1975) suggested that the damage to the DLPFC was responsible for their "pseudodepressive syndrome". Other studies concur with this finding (e.g. Stuss and Benson, 1984), commonly citing a lack of initiative with low motivation, alongside blunted affect, associated with this type of damage.

Cummings (1993) proposed that specific behavioural syndromes are related to dysfunction of different frontostriatal circuits. Damage to the dorsolateral prefrontal circuit was seen as responsible for 'executive' dysfunction, although this notably included

'generating hypotheses', as well as problems on verbal and visual fluency tasks; both of these could be seen as problems of initiation. Damage to the orbitofrontal circuit resulted in problems with response suppression (disinhibition), although Cummings noted that Logue *et al* (1968) had found that a large proportion of individuals with lesions of this circuit showed 'alterations in interest, initiative, or conscientiousness'. Damage to the anterior cingulate circuit was related to akinetic mutism (which involves profound apathy) and failure of response inhibition on go-no go tests. Syndromes related to this circuit were acknowledged to be under-researched. A related finding is that damage to the SMA (part of the 'motor' loop) is associated with decreased spontaneous limb movement and partial mutism (e.g. Damasio and Van Hoesen, 1980). It can therefore be seen that there is evidence that apathy is related to damage to 4 out of 5 of the frontostriatal loops.

Initiation and motivation deficits (as well as other so-called 'frontal' deficits) are also found after damage to other parts of the frontostriatal network (e.g. globus pallidus, thalamus) (Cummings, 1993). For example, Bhatia and Marsden (1984) found abulia to be the most common behavioural disorder following basal ganglia lesions, and Mendez *et al* (1989) found dorsal caudate nucleus lesions (likely to involve the 'complex' loop) to be associated with a 'disinterested' presentation.

In summary, researchers have found associations between initiation and motivation problems and damage to many areas of the frontostriatal circuits.

A neurochemical basis for apathy

If it is the mesolimbic and mesocortical dopaminergic systems (assumed to have a major overlap with the frontostriatal circuits) that are disrupted, e.g. through organic brain injury (either structural damage to the pathways or disruption to the synthesis, release or metabolism of dopamine itself), one could predict that there may be some failure to respond to normally motivating events, i.e. reduced goal-directed behaviour. This could be either due to reduced capacity for experiencing pleasure, or reduced ability to respond to available rewards in the environment (Powell *et al*, 1996). Powell *et al* also suggested that these dopamine systems are involved in initiation, planning, and monitoring of goal directed behaviour (i.e. executive functions), and damage to these systems would result in executive deficits. These deficits may underlie apathy and abulia.

There are several observations in support of this. Firstly, damage to the frontostriatal network results in apathy, and dopamine appears to modulate activity in this network. Secondly, there are a number of studies showing some amelioration of apathy symptoms (associated with a variety of diagnoses) and associated cognitive abnormalities with dopamine agonists, as well as improving response to incentive (e.g. Weddell and Weiser, 1995; Levi-Minzi *et al,* 1991). Powell *et al* (1996) reported significantly improved scores on an empirically developed measure of motivation (the CARROT), as well as on tests of willed action such as verbal fluency, following administration of bromocriptine to individuals with varying degrees of abulia following brain injury. There were also

concurrent clinical improvements in session participation, spontaneity (reduction in prompting necessary) and motivation during rehabilitation. It is interesting to note that these improvements were maintained even after bromocriptine was discontinued, which does not concur with the idea that it is solely increased dopaminergic transmission that causes increased goal directed behaviour. Powell *et al* suggest that the bromocriptine facilitated either structural adaptations, or neurobehavioural interactions where the increased behavioural output led to increased opportunities for reward, which then further stimulated dopaminergic functioning.

Thirdly, psychophysiological theories of motivation and reward (e.g. Gray, 1987) strongly implicate the role of dopamine in a behavioural activating system (BAS), where negative symptomatology reflects a dysfunctional BAS.

A cognitive basis for apathy

The model of the SAS readily explains behavioural passivity. If an individual has a goal, but cannot generate or activate the appropriate goal-directed behaviour, then they will appear passive and poorly motivated. Frith (1992) proposed that an inability to generate behaviour aligned to a strategy can result in a lack of behavioural output, or perseverative or stereotyped behaviour.

Robbins and Sahakian's (1983) observation that increased dopamine release leads to increased activation of action schemas is relevant here. If one infers that the opposite is true, i.e. decreased dopamine leads to decreased activation of schemas, then any damage to the mesolimbic and mesocortical dopaminergic systems / frontostriatal circuits might lead to decreased activation, and (one assumes) decreased behavioural output, i.e. passivity and initiation deficits.

The above three explanations (neuroanatomical, neurochemical and cognitive) are not mutually exclusive. They can all co-occur, as three levels of explanation of the same phenomena.

Apathy's relationship to other cognitive deficits (e.g. 'frontal' functioning)

There is further evidence for the importance of the frontal cortex in motivational deficits in individuals with frontal lobe lesions. In terms of performance on neuropsychological tests, apathy has been found to be significantly related to impaired performance on verbal fluency (e.g. Perrett, 1974; Starkstein *et al*, 1992), random number generation (another task involving internally generated response selection; Spatt and Goldenberg, 1993), and Reitan's (1958) Trail Making Test Version B (Starkstein *et* al, 1992). Levin et al (1987), when developing the Neurobehavioural Rating Scale, also noted that ratings of motivation were associated with a reverse serial 7's task. The above tests are all commonly acknowledged to assess frontal lobe functioning.

Powell *et al* (1996) found that clinical measures of motivation and an experimental measure of reward responsivity (the CARROT) were related to verbal fluency, the Buschke Selective Reminding Test (a test seen as effortful and requiring strategy generation and use; Buschke and Fuld, 1974), and Digit Span (Wechsler, 1986). The latter finding was interpreted as being due to performance being partially determined by levels of motivation and effort. This relationship was observed using a within-subjects design, varying motivation through administration of a dopamine agonist.

Al-Adawi *et al* (1998), when comparing a clinical index of motivation with a variety of neuropsychological tests, made some notable observations. Firstly, a principal components analysis found two factors that made significant contributions to the variance in clinical motivation, in particular 'initiation-motivation' (comprised on performance on the CARROT, verbal fluency, an enjoyment questionnaire (EQ), planning and execution times on the Tower of London, and the BSRT), as well as 'reasoning ability'. The orthogonality of these two factors suggests a functional separation between response initiation (latency, speed, and volume of output) and strategic problem solving (including response monitoring). Further analysis of clinical motivation scores suggested that poor response initiation (and not psychomotor slowness) was linked to passivity in clinical sessions rather than inappropriate or disorganized behaviour.

Secondly, they found that Digit Span Forwards and Digit Span Backwards were both related to clinical measures of motivation. Thirdly, although performance on the Wisconsin Card Sorting Test was not significantly related for the sample, there was evidence that participants with low motivation were less likely to persist with this task, or complete it within the time limit. Starkstein *et al* (1992) also noted that apathetic individuals were poorer on time limited tasks.

As the above tests are all hypothesized to involve frontal lobe functioning, it seems likely that measures of motivation / reward responsivity are associated with frontal lobe functioning. This could be conceptualised as being because these 'frontal' tasks require effort, or because executive functions are cognitive prerequisites for goal-directed behaviour, especially if motivation is seen as a wide-ranging concept describing the integration of numerous cognitive (i.e. executive), affective and sensory levels of functioning.

Many studies have found lower frontal cortex activation in individuals with schizophrenia, especially associated with negative symptoms (Jahanshahi and Frith, 1998). There is also corresponding poorer performance on 'frontal' tests, such as planning (e.g. Tower of London; Pantellis *et al*, 1997), and verbal fluency, where the significant association with negative symptoms is considered indicative of poverty of willed action (Allen *et al*, 1993). Individuals diagnosed with schizophrenia show poor performance on other

experimental tasks associated with internally generated action (see Jahanshahi and Frith, 1998).

A subjective correlate of apathy - how does it feel to have low reward responsivity?

Al-Adawi *et al* (1998) proposed enthusiasm for enjoyable activities as a subjective correlate of motivation. This hypothesis was tested by using the Enjoyment Questionnaire (EQ), which assesses whether an individual feels that he/she will enjoy various normally pleasurable activities, i.e. a possible subjective measure of reward responsivity. A significant correlation was found between scores on the EQ and a clinical measure of motivation. Additionally, Powell *et al* (in press) found that reduction in reward responsivity (as measured by the CARROT) following abstinence from smoking paralleled reduction in hedonic tone (as measured by the Snaith Hamilton Pleasure Scale).

On the other hand, it has been shown that motivation and the ability to subjectively discriminate the reasons for that motivation do not necessarily co-exist. Lamb *et al* (1991) found that recovered opiate addicts would press a lever for administration of a dose of morphine small enough so that they could not introspectively detect it.

In terms of a subjective correlate of apathy, it is widely assumed that people with apathy problems with an organic basis feel indifferent, rather than depressed (Marin, 1997b),

although there is a strong overlap between the two states. The relationship between apathy and depression will now be briefly expanded upon.

Apathy and depression

Blumer and Benson (1975) described initiation / motivation deficits as a "pseudodepressive" syndrome. However, this may be a misnomer, as converging evidence indicates that apathy is a clinically distinct state from depression. Starkstein *et al* (1992) found that, of the 42% of their sample of patients with Parkinson's disease that scored above a cut-off level for apathy, 40% did not show significant levels of depression. Starkstein *et al* (1993) found that, in a sample of individuals with cerebrovascular lesions, apathy was significantly associated with major, but not minor, depression, and other studies have also found motivation to be independent of measures of depression in a brain-injured sample (e.g. Al-Adawi *et al*, 1998). Levy *et al* (1998) found that apathy and depression have different concurrent neuropsychiatric symptoms, with apathy correlated with disinhibition and aberrant motor behaviour, and depression correlated with anxiety, agitation, irritability, and hallucinations. Marin (1997b) notes a different emotional profile, in that apathy is characterized by lack of effort, concern or interest, and for some individuals there are no negative thoughts about the self and future, and no dysphoric mood.

Further evidence comes from Powell *et al* (1996), who showed improvements in motivation according to both experimental and clinical measures, and also in 'frontal' tests, after low doses of bromocriptine. None of the participants had motivation problems obviously secondary to low mood, and the mean baseline scores for anxiety and depression were lower than the cut-off scores indicating clinical significance (i.e. as a group, they were not anxious or depressed). There was no concurrent improvement in either anxiety or depression levels in the sample, i.e. motivation was independent of these variables, although this may be partially due to a floor effect.

This suggests that apathy can be a purely motivational deficit contributing to the impairment in willed action noted in a number of disorders. Nevertheless, apathy is a common feature of depression, and often co-exists with other psychiatric disorders such as schizophrenia (Marin, 1997a, b). Some studies have also illustrated a large overlap in the symptoms of apathy and depression, including in a sample with acquired brain damage, whilst still noting that apathy can occur without depression (Andersson *et al,* 1999). It should be noted that Baxter *et al* (1985) showed (via positron emission topography) that individuals with idiopathic unipolar depression show diminished metabolism in the prefrontal cortex and caudate nuclei, suggesting that there may be some neurobiological overlap between areas associated with a type of depression, and those associated with apathy.

Some of the apparent overlap between apathy and depression may be due to depression measures commonly containing items sampling apathy. Another explanation is that similar circuits could be involved with both sets of symptoms, but differ in the degree of neurotransmitter involvement. A relevant observation here is that serotonergic agents frequently relieve depression but increase apathy, whereas dopamine agonists relieve apathy but are ineffective antidepressants (Levy *et al*, 1998).

The apathetic component of depression may be separable from emotional and somatic symptoms. Al-Adawi *et al* (1998) suggest that this might not be expected, as reduced appetitive behaviour should lead to diminished frequency of reward, and subsequent lower mood (e.g. Seligman, 1981). It may be that external events may need to be linked to depressive cognitions for a consequent lowering of mood.

Seligman (1992) describes lowered initiation of responses as a main feature of helplessness, a response to uncontrollable stress. Consequently, one could understand apathy either as a neurobehavioural and / or a psychological syndrome.

PART III: SMOKING AND ITS EFFECT UPON MOTIVATION AND COGNITIVE FUNCTION

For the purposes of this study's working hypothesis, nicotine is conceptualised as an indirect dopamine agonist that people regularly administer through smoking. At the same time, it is important to acknowledge that nicotine has complex effects on other neurotransmitters as well. There is also considerable evidence of modulation of cortical glutamatergic cells (Dalack *et al*, 1998), combination of nicotine with nicotinic acetylcholine receptors (Ashton, 1992), and augmentation of the release of serotonin, norepinephrine, and gamma-aminobutyric acid (Quattrocki *et al*, 2000).

The neurobiological effect of smoking

Neurobiological models of smoking strongly implicate the mesocorticolimbic dopamine system (e.g. Wise, 1998), which comprises projections from the ventral tegmental area to forebrain structures such as the nucleus accumbens, amygdala, anterior cingulate and prefrontal cortex. This system comprises the supposed 'reward pathways' of the brain, with a major overlap with the frontostriatal circuits.

There is direct evidence from studies with animals (e.g. Corrigal *et al*, 1994) showing that nicotine produces excitation of neurons in the mesolimbic dopamine system. Nicotine acts by attaching to acetylcholine receptors on neurons which link the ventral tegmental

area with the nucleus accumbens, which subsequently increases dopamine release in the shell of the nucleus accumbens (Gamberino and Gold, 1999). Furthermore, Dalack *et al* (1998) reviewed a number of studies (e.g. Vezina *et al*, 1992; Whiteaker *et al*, 1995) noting differential patterns of nicotine-stimulated dopamine release in cortical and subcortical structures, due to different nicotinic receptor properties.

There is also indirect evidence that nicotine triggers dopamine release in humans. Dawe *et* al (1995) administered the DA blocker haloperidol to habitual smokers, and found a decrease in dopaminergically mediated reward (i.e. the subjective, positive reinforcing aspect of smoking, independent of nicotine withdrawal symptoms), and a compensatory increase in nicotine intake, perhaps to maintain levels of subjective reward. Caskey *et al* (1999) described similar findings, and also found that smoking rate is decreased when there is concurrent administration of bromocriptine (a dopamine agonist).

The influence of nicotine on motivation

As smoking appears to trigger dopamine release in the frontostriatal system, one can hypothesize that it will be associated with alterations in motivation, and that this can be assessed through measures of reward responsivity and goal-directed behaviour. There could be a simple enhancement of motivation after acute smoking, abstinence from a chronic pattern of smoking could manifest as a deficit during abstinence due to previous neural adaptations to smoking, or pre-existing (i.e. pre-dating the smoking habit)

disturbances of dopamine transmission (expressed behaviourally as a motivational disturbance) could be redressed by smoking (Al-Adawi and Powell, 1997).

Animal studies support the hypothesis that smoking enhances motivation (compared to abstinence). For example, Helton *et al* (1993) showed that abstinence from chronic nicotine administration disrupts operant behaviour in rats in similar ways to reductions in reward magnitude, suggesting an impact on the dopaminergic reward system.

In humans, Al-Adawi and Powell (1997) found that smokers showed significantly less reward responsivity (measured with the CARROT) when abstaining for at least a few hours. Subsequent smoking of a single cigarette effectively restored reward responsivity to within normal limits. They also found that smoking a cigarette (after a period of abstinence) restored levels of verbal fluency, a task associated with willed action. However, this effect was significant with heavier smokers; a similar subsequent study with lighter smokers (Powell *et al*, in press) found no significant effect of smoking on verbal fluency or Digit Span (another task related to executive functioning where performance had been previously shown to be impaired in heavier smokers; Al-Adawi and Powell, 1997).

Al-Adawi and Powell also found evidence to suggest that withdrawal from smoking specifically and directly impairs reward responsivity. An alternative explanation for the aforementioned poor performance after abstinence is that it is a consequence of other

withdrawal symptoms (poor concentration, physical discomfort). However, self-reported withdrawal symptoms only correlated with task performance on some of the tasks (reward responsivity on the CARROT, and a measure of stereotypy). Furthermore, Powell *et al* (in press) found that differences in reward responsivity across smoking / abstinence were significant even when subjectively rated withdrawal symptoms were controlled for. These observations imply that the observed cognitive and motivational impairments are withdrawal symptoms in their own right, and not secondary to a general discomfort of withdrawal.

There are a number of other studies showing that smokers' cognitive performance after a cigarette is equivalent to that of non-smokers, but when abstinent, the performance is decreased (e.g. working memory; Blake and Smith, 1997).

Altogether, the above evidence suggests that dopamine functioning is decreased during abstinence, making individuals less likely to respond to incentives, and negatively affecting performance on tests of cognitive function thought to be influenced by on dopamine activity.

The influence of nicotine on cognitive functioning

If there is increased dopamine release in the frontostriatal system, there should be a change in cognitive functions in the relevant frontal areas. There is clear biological

importance in increased cognitive capability when incentive stimuli are detected, e.g. planning can then take place in order to acquire and consume the stimulus (Powell *et al*, in press). This cognitive enhancement may also result in improved performance on certain neuropsychological tests, i.e. those utilising these cognitive processes.

Numerous studies have shown improvements in a range of cognitive functions in humans after smoking (compared to abstinence), including:

- attentional vigilance, selected attention, and information processing speed (Rusted and Warburton, 1991)
- sustained, divided and focused attention (Kassel, 1997)
- inhibition of incorrect responses (Hatsukami *et al*, 1989)
- working memory, as measured by a Digit Span test (e.g. Levin and Rose, 1995, Al-Adawi and Powell, 1997)
- associative attentional processing required for memory encoding (Warburton et al, 2001)

Many of the above functions are associated with central executive functioning, i.e. those which require effective and controlled allocation of attentional resources, often seen as requiring cognitive 'effort'.

The blocking of nicotinic transmission with antagonists has been found to reduce working memory performance, further confirming the modulating effect of nicotine on this

function (Newhouse *et al*, 1992). However, Powell *et al* (in press) found no significant effect of smoking on Digit Span with lighter smokers, and there are other contradictory findings regarding the influence of nicotine on cognitive functioning (Al-Adawi and Powell, 1997), leaving no clear consensus.

It is possible that these improvements in various cognitive abilities may reflect variation in dopamine activity, with better information processing leading to more effective goal-directed (motivated) behaviour. However, the opposite direction of causation could be also be in effect, i.e. improved performance on the tasks is at least partly due to increased motivation (Al-Adawi and Powell, 1997). Ashby *et al* (1999) note that mood may be relevant, as there is activation of dopamine projections to frontal cortex during positive mood states. Indeed, many studies have noted that induction of positive mood leads to enhanced performance on 'frontal' tests such as verbal fluency (Greene and Noice, 1988) and creative problem-solving (Isen *et al*, 1987).

Animal studies show that cognitive deficits resulting from frontal lesions can be partially reversed by administration of nicotine (e.g. Tung *et al*, 1990), and that lesions producing working memory deficits can be ameliorated by a high dose of nicotine (Tilson *et al*, 1988). However, as far as the author is aware, there are no studies with humans that investigate the effect of nicotine on impaired cognitive functioning after brain injury.

Smoking and schizophrenia

In a relatively large sample of a young adult, outpatient psychiatric population, Hughes *et al* (1986) found that 88% of patients with a diagnosis of schizophrenia smoke, with similar levels reported by other studies (Dalack *et al*, 1998). This is nearly three times the rate for the general population, with the difference being independent of effects of age, gender, socioeconomic status, and concurrent alcohol use (Hughes *et al*, 1986). Olincy *et al* (1997) also found that people with schizophrenia are heavier smokers than smokers without psychiatric disorder, although there are contrary findings (Dalack *et al*, 1998).

These findings probably reflect that people with a schizophrenia diagnosis are more likely to be addicted and less likely to quit. The extremely high prevalence raises the possibility that nicotine use and schizophrenia share underlying neurobiology, either through modulation of the symptoms of the illness, the side effects of anti-psychotic medication, or a combination of the two.

Many researchers feel that the much greater prevalence of smoking in individuals with schizophrenia indicates that it is a form of self-medication. Dalack *et al* (1998) suggest the possibility that smoking either activates or desensitizes different types of nicotinic receptors, leading to a reduction of the hypofrontality and cortical-subcortical

dysregulation in individuals with schizophrenia hypothesized by Davis *et al* (1991). By generalizing from models generated from animal studies, Dalack *et al* suggests that smoking stimulates cortical activity without altering subcortical activity. In terms of symptomatology, they speculate that, as smokers with schizophrenia have more negative symptoms than equivalent non-smokers, they are smoking in an attempt to self-medicate for their abnormal reward-reinforcement system (e.g. ameliorate cortical hypoactivity), which is producing their anhedonic, amotivational negative symptoms (Glassman, 1993). It should be noted that these negative symptoms share great similarity with the apathy that can follow acquired frontal lobe injury. Alternatively (or additionally), people diagnosed with schizophrenia may be smoking to overcome medication-related accumbens dopaminergic blockade (Dawe *et al*, 1995).

Levin *et al* (1996) also found that nicotine enhanced sustained attention in individuals diagnosed with schizophrenia, especially in those individuals on higher, more anticholinergically potent doses of haloperidol, and who had more significant cognitive impairment overall. Tracy *et al* (2000) confirmed this finding, additionally finding a subtle improvement in selective attention in this type of individual.

Possible causes of abstinence-related deficits in dopaminergic function

If one assumes that acute abstinence from a chronic pattern of smoking leads to a deficit in dopaminergic function, executive function and motivation (as opposed to acute

smoking producing a simple enhancement in these areas), it raises the question of whether this abstinence effect is due to previous neural adaptations to smoking, or pre-existing disturbances of dopamine transmission (i.e. pre-dating the smoking habit). This applies not just to smokers diagnosed with schizophrenia, but to any smoker.

Evidence for pre-existing dopaminergic deficits constituting a risk factor for nicotine addiction

There is some evidence that there are dopamine transmission differences between smokers and non-smokers pre-dates their first cigarette, including genetic evidence that smokers have low levels of dopaminergic function prior to dependency, and are therefore more vulnerable to addiction (Noble *et al*, 1994). One mechanism by which this vulnerability could manifest is that those with low dopaminergic functioning would subjectively enjoy smoking, or another dopamine agonist, more than those with 'normal' functioning. In support of this, Volkow *et al* (1999) found that those drug naive participants with low dopamine D2 receptor levels administered enjoyed methylphenidate (a stimulant with dopaminergic and noradrenergic properties) more than others. However, there are also contradictory genetic findings (e.g. Singleton, 1998).

Evidence for neurobiological adaptation when developing a chronic smoking habit

There are two current neuroadaptive models that have been conceptualised to explain changes during the development of substance dependence: counteradaptation and sensitization (Koob and LeMoal, 1997). Both implicate changes at the neurochemical level, involving neurotransmitters associated with the reinforcing effects of drug intake. Counter-adaptation includes processes where there are changes in dopaminergic and serotonergic neurotransmission in the nucleus accumbens during withdrawal, and a change in 'hedonic set point' (a threshold for the efficacy of reinforcers). Withdrawal from drugs of abuse reduces dopamine transmission in the ventral striatum, an effect opposite to that of the drug (see Altmann *et al,* 1996, for a review). Sensitization appears to involve a time-dependent chain of adaptations within the mesolimbic dopamine system that leads to long-lasting changes (see Koob and LeMoal, 1997, for a review).

Fowler *et al* (1998) used PET techniques to show that smokers have reduced levels of monoamine oxidase B (an enzyme that metabolizes dopamine), whilst ex-smokers had similar levels to non-smokers, suggesting that smoking itself had altered the dopamine system, and that this could possibly be reversed.

Summary

In summary, there have been a number of studies showing enhancement of cognitive function and motivation after smoking (compared to abstinence), although the precise mechanisms are unknown, and there are contradictory findings. There have been a number of studies looking at smoking in participants with schizophrenia, with some concluding that smoking in such individuals could be seen as self-medication. To the author's knowledge, there are no equivalent studies looking at the acute effects of smoking on cognitive and motivational functioning in a sample of brain-injured participants.

The current study

The current study will address two main questions:

1. Does abstinence from smoking decrease functioning of the willed action system (particularly reward responsivity and initiation) in people with brain injury?
2. If smoking status is found to affect the functioning of any aspects of willed action, is the size of this effect related to identifiable factors, including a general measure of intellectual functioning? For example, do the largest differences attributable to smoking status occur in those with 'better' intellectual functioning, or in those whose functioning is poorer (possibly due to acquired impairment)?

The main hypothesis concerns question 1, in that individuals with brain injury will show decreased functioning on tasks measuring initiation, reward responsivity and executive functioning when abstinent from their chronic smoking habit. If confirmed, this would be comparable to the findings of Al-Adawi and Powell (1997), who asked non-injured participants to complete a similar battery of tasks.

Because of the number of unresolved issues involved in question 2 (e.g. whether smoking enhances or abstinence decreases functioning) and the lack of previous research regarding smoking in individuals with acquired neurological deficits, no specific prediction can be made.

METHOD

Participants

Every smoker with a brain injury who 1) attended Banstead Place Rehabilitation Centre, 2) attended the Regional Neurological Rehabilitation Unit (RNRU) at Homerton Hospital, 3) was in contact with the RNRU Outreach team, or 4) attended Headway House East London, between August 2000 and April 2001 was identified by relevant staff. They were invited to participate if they met the following inclusion criteria:

- they smoked at least 8 cigarettes a day
- they were behaviourally and cognitively capable of engaging in 35 minutes of cognitive testing, as judged by staff familiar with the participant.
- they had no gross perceptual problems (e.g. extrapersonal neglect)
- they had no gross expressive or receptive aphasia, and no severe dysarthria (i.e. they needed to be able to understand the test instructions, and have speech that is intelligible enough so that they could be understood)
- they spoke English

Design

A within-subjects cross-over design was utilised, with two conditions for each participant:

1. Testing on a battery of measures after a period of abstinence from smoking (ABS).
2. Testing on these measures after smoking (concurrent with the participant's typical smoking pattern)(CIG).

The order of conditions was counterbalanced across participants to control for practice effects.

Changes in performance between smoking and abstinent conditions on measures of 'willed action' were compared with changes in performance on measures of 'non-willed' action. These latter measures functioned as 'control tasks', so that a specific action of nicotine on a theoretically discrete system may be identified, thus suggesting a more specific consequence of cigarette smoking. For the current study, tasks requiring little initiation and motivation (e.g. sub-tests of the Visual Object and Space Perception Battery; Warrington and James, 1991) and a stem completion task measuring unconscious (and therefore effortless) memory was used.

Procedure

Ethical approval was granted by the East London and City Health Authority Research Ethics Committee and the East Surrey Local Research Ethics Committee.

Initially, background information regarding age, education (in number of years), nature of brain injury and time since brain injury was assessed. Participants were also asked to briefly describe, in their own words, their own personal reasons for smoking. If they simply replied that it was 'just a habit' or similar, a follow-up question asked if there was any aspect of smoking that they liked.

For the smoking condition (CIG), subjects were administered the test battery after having smoked a cigarette in the previous 2 hours, as part of their normal smoking pattern. For the abstinent condition (ABS), participants were asked to abstain from smoking for a minimum of two hours before completing the test battery. If possible, participants were asked to complete the tests in the morning before their first cigarette of the day, to ensure the greatest possible convenient period of abstinence.

The two conditions took place on separate days, between 3 and 14 days apart. The tests were administered in the same order on each day, and at a similar time of day across conditions for each participant, especially in relation to mealtimes (e.g. a post-lunch testing would be repeated for the second condition).

Throughout testing, participants were encouraged to fill in written questionnaires themselves; however, many did not wish to or could not do this for various reasons (e.g. poor literacy, motor control). In these circumstances, the questions and response options were also presented verbally. If this questionnaire was part of the experimental conditions (i.e. it was administered twice), participants who completed the form independently did so for both conditions, and those needing help received it both times.

Other assessments included the Hospital Anxiety and Depression Scale (HADS; Snaith and Zigmond, 1994) and the Ravens Coloured Progressive Matrices (RCPM; Raven *et al*, 1998). These were administered only once, at the beginning of the first testing session (regardless of smoking status), to give a measure of anxiety and depression, and a general estimate of intellectual functioning. These assessments were not part of the experimental conditions (CIG / ABS).

A member of staff who was familiar with each participant was recruited to complete the Apathy Evaluation Scale.

Measures

'Background' measures

The following measures were administered in order to assess relevant areas of functioning and other background information for each participant:

Nicotine dependence

Fagerstrom Test for Nicotine Dependence (FTND; Heatherton *et al*, 1991). This widely used written questionnaire assesses current tobacco dependence based on cigarette consumption (amount and pattern), time before first cigarette of the day, and difficulty in abstaining. The maximum score (i.e. a very dependent smoker) is 10. It should be noted that there may be limitations in accuracy of self-report in a brain-injured population. For example, memory and/or estimation difficulties may preclude accurate report of cigarette consumption.

Mood

Hospital Anxiety and Depression Scale (HADS; Snaith and Zigmond, 1994). This a self-report written questionnaire designed to assess anxiety and depression, originally intended for use in non-psychiatric hospital departments. Participants were instructed to complete the questionnaire with relation to 'how they have felt in the last week'.

Non-verbal intellectual reasoning

Raven's Coloured Progressive Matrices (RCPM; Raven *et al,* 1998). It was not feasible to gather comprehensive data regarding the cognitive functioning of all the participants, for logistical reasons (i.e. time constraints, with other tasks taking precedence with respect to the experimental hypothesis). However, the Ravens Matrices were employed to provide a measure of non-verbal reasoning.

This task requires the individual to select the missing section to a pattern or matrix from an array of 6 possible answers. It does not necessarily require a verbal response. There are 36 items presented on 36 consecutive pages of a stimulus booklet. The first item is an example, and the correct answer was given by the researcher, accompanied by an explanation of why it was correct, and why each of the alternatives were incorrect. If either of the subsequent two items were answered incorrectly, the researcher could go back to item 1 and explain the task again (this was not necessary with any of the participants). They were then presented with the remaining items, and their responses (verbal and/or pointing) were recorded by the researcher.

Clinical motivation / apathy

Apathy Evaluation Scale (AES; Marin *et al,* 1991). Marin considered apathy to be a valid construct as a symptom, a syndrome, or a behavioural dimension, and developed a scale which establishes a clinical, 'everyday' picture of motivation. An abridged, simplified version, as used by Starkstein *et al* (1992), was employed. Healthy subjects

were reported to score 3.2 ± 3.6, with 95% scoring below 9 points (as reported in Starkstein *et al,* 1993). This self-report scale was reworded so that it could be completed by a staff member who was familiar with each participant. There was one exception - the final item 'Would you consider yourself apathetic?' was answered by the participant directly (see Appendix 3).

It was thought that staff report would be a more reliable indicator than self-report, as many of the participants had a frontal lobe injury, which is associated with poor insight into one's own difficulties and underestimation of behavioural problems (Levin *et al,* 1987). Wilson *et al* (1998) found that self-report underestimated the degree of 'everyday' functional impairment caused by executive problems, and used a close relative or carer's report when assessing the validity of the Behavioural Assessment of the Dysexecutive Syndrome (BADS). This relative or carer's rating was found to correlate highly with test performance. As apathy is part of the dysexecutive syndrome, this finding informed the above decision not to use self-report.

As Marin's original scale has been abridged and reworded, there is no evidence that the version used here remains valid and/or reliable (including issues of inter-rater reliability). It was therefore only used as a correlational variable in a post-hoc analysis of any significant effects of abstinence from smoking, in order to identify possible sources of variance of that effect.

'Experimental' measures

The following measures were administered in the order given for both abstinent and smoking conditions, in order to assess short-term effects of abstinence:

1. Expired carbon monoxide (CO) levels

This was measured using a simple non-invasive hand-held 'smokerlyser' (the Bedfont EC50 Micro Smokerlyzer), requiring participants to fill their lungs completely and hold for 15 seconds, before breathing out. It should be noted that one of the participants was not able to do this, as they could neither fill their lungs nor hold their breath due to their medical difficulties. In the case of this individual, prolonged and constant observation coordinated between unit staff and the researcher was able to confirm abstinence.

To confirm abstinence, CO levels were measured just before administration of tests in the ABS condition. If CO levels were not at least 6 parts per million (ppm) below that of the smoking condition (CIG), or there had not been constant observation verifying abstinence, the ABS condition was postponed to a later date (as was the case with participants 1, 6 and 18).

2. Emotional and physical symptoms of nicotine withdrawal

Mood and Physical Symptoms Questionnaire (Hughes and Hatsukami, 1986), plus selected items from the *Profile of Mood States* (McNair *et al*, 1971). This 12-item scale was used by Al-Adawi *et al* (1997), and was administered as a written questionnaire in order to explore the relationship between test scores and subjective withdrawal symptoms. Participants used five point scales to specifically assess constructs such as depression, irritability, anxiety, restlessness, hunger and concentration, with a total score of up to 48 given. The higher the score, the greater the symptoms of withdrawal.

3. Verbal fluency

Controlled Oral Word Association Test (COWAT; Benton and Hamsher, 1989). This is a commonly used measure of internal generation of verbal material. Participants are asked to say aloud as many words as possible within one minute, beginning with each specified letters. They are instructed to exclude proper nouns and avoid using the same word with a different suffix, e.g. big, bigger, biggest). If they did not understand these exclusion criteria, examples and further explanation was given until they did understand. The researcher started a stopwatch as he presented the letter, and recorded generated verbatim for later verification of the word's existence, and to check for repetitions.

The letters F, A and S were used on first administration, and equivalent letter combinations (D, O, and T) used for the second occasion (the counterbalancing of CIG and ABS conditions ensured that an even number of FAS and DOT combinations were administered in each condition).

Performance on the COWAT is often impaired after frontal lobe damage, and the task has been shown to involve areas associated with 'willed action' (left DLPFC, anterior cingulate; Frith *et al*, 1991).

4. Visual perception (a 'control task')

Visual Object and Space Perception Battery (VOSP; Warrington and James, 1991). The Object Decision and Cube Analysis sub-tests were selected as control tasks as they a) involve simple, almost effortless, object perception (i.e. little SAS involvement), b) they were the sub-tests with the greatest discrepancy between mean and maximum scores, i.e. there was a lower risk of encountering a 'ceiling effect'.

In the Object Decision task, the participant was instructed that he would see a series of four "silhouettes or shadows", one of which of was a real object, as opposed to the other three, which were invented shapes. He / she was required to select the real object (by pointing). There were 20 sets of 4 silhouettes in all.

In the Cube Analysis task, the participant was asked to analyse a line drawing of a stack of cubes, and count the cubes. He / she was informed that with some of the stacks there would be some cubes that were necessarily there but were obscured from view, and that these should also be counted. All participants were able to give a verbal response.

5. Reward responsivity

Card Arranging Reward Responsivity Objective Test (CARROT; Powell *et al*, 1996). This is a simple psychomotor task. As performance is affected by financial incentive, this test has been shown to have validity as an objective measure of reward responsivity.

Participants are given a stack of approximately 100 laminated cards, each of which has five digits printed on it. One, and only one, of these digits is either a 1, 2 or 3. They are then instructed to sort the cards into three piles in front of them, corresponding to which of the three digits is shown. Participants were told to sort the cards as quickly as possible.

There were four trials in all. The first trial (T1) constituted a practice trial, and established baseline speed for sorting exactly 60 cards. This individual time acts as a personal time limit for subsequent trials. This is particularly important in a brain-injured population, as many have poor motor functioning (including having to use a non-preferred hand due to hemiparesis) and/or slow information processing. In trials T2-T4, participants were again asked to sort the cards in an identical fashion as quickly as possible, and the total number of cards sorted for each trial was recorded. T3 differed from T2 and T4 in that participants were informed that they were again to sort the cards in an identical fashion, but that this time they would be rewarded with 10p for every five cards sorted. The coins were placed on the table in full view after every fifth card was laid.

A reward responsivity score was calculated by subtracting an average of T2 and T4 from T3 (i.e. T3 - [[T2 + T4]/2]). In effect, this provided an index of how much the participant increased (or decreased) their sorting speed when financial incentive was available.

6. Hedonic tone (the ability to experience pleasure)

The Snaith-Hamilton Pleasure Scale (SHPS; Snaith *et al,* 1995). This written questionnaire assesses the participant's ability to experience pleasure in various domains such as social interaction, food and drink, sensory experience, and pastimes. Statements are made about 14 items commonly experienced as pleasurable, and respondents answer using a 4-point scale, ranging from 'strongly disagree' to 'strongly agree'. In Snaith et al's original paper, either 'disagree' response was scored as 1, and either 'agree' response scored 0. However, for the purposes of the current study, it was felt that a 4-point scoring system (0-3, where 'strongly agree' = 3) would identify more subtle changes in hedonic tone across experimental conditions.

Snaith *et al* found that the scale correlated with hedonic tone but not depressed mood, further supporting a distinction between the two constructs. It is hypothesized that this scale may be sampling a subjective correlate of reward responsivity.

7. Working memory

Digit Span (Wechsler, 1986). This was administered to assess working memory functioning, and was split into two parts. Participants were required to repeat different strings of digits of increasing lengths (Digits Forwards), and then a different set of digit strings were read out, and the participant had to repeat them back in reverse order (Digits Backwards). The researcher verbalized each string at an even pace, at one digit per second. Total scores for each section were recorded (one point for each string correctly repeated). The task was discontinued when both strings of a certain length were incorrectly recalled.

Digit Span Backwards is often seen as a measure of 'executive' functioning (in terms of Baddeley's 1992 model), in that it necessitates manipulation of the material held 'on-line' (Fleming *et al,* 1994), and requires a more extensive involvement of the processing resources of the central executive than Digit Span Forwards (Carlesimo *et al*, 1994). Goldman-Rakic (1987) observed that central executive functioning appears associated with DLPFC activation, which is also an area associated with willed action.

A recent meta-analysis by D'Esposito and Postle (1999) suggested that the Digit Span Forwards task is unaffected by prefrontal dysfunction, suggesting that it may not involve the 'willed action' circuits. However, the task is included in the battery as a) performance on this task has improved after nicotine intake in previous studies (e.g. Al-Adawi and Powell, 1997), and b) Digit Span Backwards is a subsection of the full Digit

Span test, with Digits Forwards administered first during standardisation studies (Wechsler, 1986).

8. Implicit memory

A stem completion task. The version used by Shimamura *et al* (1987) was employed. This task is a test of implicit verbal memory. Implicit memory is the phenomenon where previously encoded information affects performance on a task without the individual consciously recalling the information. This effortless, automatic retrieval contrasts with the conscious, effortful retrieval required by a recall task. For this reason, it is included in the current study as a 'control task', as it requires little or no motivation.

Participants were required to read 16 words from 'flashcards', presented for 3 seconds each, and were asked to rate how much they liked each word on a 5-point scale (1 = dislike extremely, 5 = like extremely). This 'distracter' task had face validity as other tasks in the battery (e.g. SHPS) had similar themes regarding pleasure / displeasure. Using this procedure, words can be presented for study without explicitly telling the participants to memorize them. Following a single presentation of the words, plus a brief informal conversation around an unrelated subject, 16 three letter word stems were revealed, one at a time. These comprised the first three letters of all of the target words, in order. Participants were asked to report the 'first word that comes into your head that starts with these three letters'.

Equivalent word lists were used for the CIG and ABS conditions (see Appendix 6 for lists); again, the counterbalancing of conditions across participants ensured that an even number of each word list was administered in each condition.

Statistical analysis

To examine whether there was any significant difference in performance (including 'control' tasks) across conditions, a repeated measures analysis of variance (ANOVA) was employed for each experimental measure, with scores on tasks acting as the dependent variable. All analyses had CONDITION (CIG or ABS) as a within-subjects factor, and a between-subjects factor of ORDER (order of presentation; CIG/ABS or ABS/CIG).

For analysis of sorting rates on the CARROT, there was an additional within-subjects factor of REWARD (rate given financial incentive, REW, versus rate given no financial incentive, NREW). With respect to the first experimental hypothesis (that reward responsivity increases after smoking a cigarette compared to when abstinent), it was the CONDITION x REWARD two-way interaction that was most pertinent, where a significant interaction indicates a difference in reward responsivity between the two conditions, CIG and ABS. A three-way interaction (CONDITION x REWARD x ORDER), if significant, would signify an effect of ORDER (of presentation) on this interaction.

The exception to using an ANOVA was the analysis of performance on the VOSP Cube Analysis task . There was a clear ceiling effect for both conditions, with the majority of scores being at maximum (10/10), violating the ANOVA assumption of a normal

distribution. Here, scores on each condition were categorised as maximum (10) or less than maximum ($\leq$10), and Fisher's Exact Test was used for analysis, to investigate possible significant difference in proportions (between maximum and non-maximum scores) across smoking and abstinent conditions.

In terms of confidence levels for a significant finding, the specifically predicted interaction of CONDITION x REWARD on the CARROT has been observed in a number of previous studies, both with normal and brain-injured participants, and has cohesive theoretical background within which to make this prediction. In this case, it does not seem necessary to apply a Bonferroni correction to ANOVA results from the CARROT in order to reject the null hypothesis at the 95% confidence level. For similar reasons, no correction will be applied when looking at the effect of condition on i) scores on the Mood and Physical Symptoms Questionnaire, and ii) exhaled CO levels.

However, there have been inconsistent results from previous studies regarding the effect of smoking on Digit Span tests, and verbal fluency (COWAT), especially if the sample constitutes less than heavy smokers. Additionally, the control tasks have been chosen as they involve apparently little or no involvement from 'willed action' / SAS systems. For these reasons, it is appropriate for a Bonferonni correction to be applied for these 6 tests, meaning that a p value of less than 0.05/6 (= 0.0083) is necessary in order to reject the null hypothesis

As the post-hoc set of correlations attempting to identify a variable which predicts larger enhancement effects of smoking in particular individuals is entirely exploratory, it is appropriate to apply a Bonferonni correction, dividing a p value of 0.05 by the number of independent correlations (three) to ascertain the p value necessary to reject the null hypothesis at the 95% confidence level ($p < 0.017$).

RESULTS

Demographic data

20 of the 23 invited participants took part in the study. Of these, 2 had to be excluded from the analyses. When tested using the CO smokerlyser, one participant only showed an increase of 1 ppm above his reading in the ABS condition, despite having just finished a cigarette at time of testing. Staff could not give assurance that he had been constantly observed in the preceding two hours before the ABS condition to confirm abstinence. The other participant was excluded as he could not score at all on VOSP Cube Analysis, Digit Backwards, and the COWAT, and his inability to understand the instructions for the CARROT cast doubt upon his comprehension of many of the other instructions.

The localization of brain damage was identified, and is summarized for each remaining participant in Table 3.1.

14 (78%) of the eligible participants were male, and 4 (22%) were female. All had sustained some type of neurological insult from 11 months to 9 years previously, with 8 participants (44%) being the victims of road traffic accidents, 4 (22%) being the victims of assault, 4 (22%) having suffered a cerebrovascular accident, one (6%) having had a spontaneous haemorrhage, and one (6%) having had an abscess surgically removed.

Table 3.1 Type of neurological damage sustained by each participant, time elapsed since damage, and (where known) localisation of damage.

Participant no.	Type of (and time since) neuropsychological insult	Area of damage
1	Motorbike crash (11 months)	Left frontal and temporal contusions
2	Spontaneous sub-arachnoid haemmorhage (2 years)	Low attenuation in the left occipital lobe.
3	RTA (3 years)	Skull fracture in left parietal area, diffuse damage (self-report)
4	Run over by a car (4 years 6 months)	Multiple small contusions bilaterally.
5	Assaulted (4 years 1 month)	Unknown
6	Assaulted? (found unconscious) (3 years 11 months)	Right temporal lobe contusions, small left frontal haemorrhage, bilateral temporal swelling.
7	RTA (1 year 10 months)	Left parietal contusions, air in CSF spaces, ventricles shifted to the right.
8	Assault (1 year 3 months)	Left frontal and left parietal damage.
9	Hit by car (3 years 6 months)	Left parietal, right motor cortex, and right frontal lobe damage
10	Sub arachnoid haemmorhage (stroke) (11 months)	Left middle artery.
11	RTA (8 years)	Patchy haemmorhagic changes at left basal ganglia + small parietal and frontal contusions.
12	Motorbike crash (4 years 6 months)	Basal ganglia bleed, extending into corona radiata and lentiform nucleus (self-report)
13	RTA (2 years 4 months)	Left fronto-parietal, left tempero-parietal, and right frontal damage
14	Abscess surgically removed (4 years 8 months)	Right frontal lobe.
15	Cardio-vascular accident (3 years)	Unknown (short term memory affected)
16	Assault (9 years)	Right hemisphere (parietal / frontal) (self-report)
17	Aneurysm (3 years 4 months)	Bilateral frontal damage (self-report)
18	Brain haemmorhage (1 year 2 months)	Unknown

The participants were aged between 17 and 51 years, with a mean age of 33 years and 5 months. They had spent between 8 and 18 years in education (mean = 11.7 years, s.d. = 2.4).

The mean score (and standard deviation) for current non-verbal reasoning as assessed by Raven's Coloured Progressive Matrices was 30.0 (± 5.7), equivalent to the mean for children aged 10.

Current mood status was assessed using the Hospital Anxiety and Depression Scale (Snaith and Zigmond, 1994). The mean scores (and standard deviations) were 6.6 (± 3.2) for the Anxiety scale, and 5.9 (±3.4) for the Depression scale, both of which are below the cut-off score of 8 for a classification of 'normal'. In fact, 5 participants scored above cut-off for the Anxiety scale, with 2 scores indicating mild, and 3 indicating moderate anxiety levels. 7 participants scored above cut-off for the Depression scale, with 5 scores indicating mild, and 2 indicating moderate levels of depression. 3 participants scored above cut-off levels on both scales (one mildly anxious and depressed, and two moderately anxious and mildly depressed).

The mean score for the Fagerstrom Test of Nicotine Dependence was 3.5 (s.d. = 2.09), with the approximate mean number of cigarettes smoked per day being 15. This indicates that the sample could be described as light to moderate smokers, if compared

with a sample of 'relatively light smokers' from a study by Etter et al (1999), who averaged 1.84 on the FTND, and 12 cigarettes a day.

The mean score for the revised, abridged Apathy scale was 17.6 (s.d. = 6.3). This cannot be directly compared with Starkstein *et al*'s (1992) study, as that used the same scale but incorporated self-report. However, the cut-off score of 9 (denoting the 5th percentile and below) from that study can be used as a guide when describing the current sample, with 17 of the 18 participants scoring 9 or over.

Experimental variables

1. Smoking status - exhaled CO levels and withdrawal symptoms

The means for exhaled CO levels and withdrawal symptoms across conditions are listed in Table 3.2. ANOVA confirmed a highly significant difference in exhaled CO levels across conditions ($F_{1.15} = 43.24$; $p < .00001$) and no significant CONDITION x ORDER interaction ($F_{1.15} = .076$; ns).

Table 3.2: Summary of mean levels for two markers of smoking status.

Measure	CIG condition (Mean ± s.d.)	ABS condition (Mean ± s.d.)
Exhaled CO levels (parts per million)	25.59 ± 12.09	14.29 ± 7.68
Mood & Physical Symptoms Questionnaire	9.50 ± 4.59	10.00 ± 6.62

There was no significant difference across conditions for self-reported nicotine withdrawal symptoms on the Mood and Physical Symptoms Questionnaire ($F_{1,16} = .040$; ns) and no significant CONDITION x ORDER interaction ($F_{1,16} = 2.64$; ns).

Table 3.3: Summary of mean scores (and standard deviations) for each experimental measure.

Measure	CIG condition (Mean ± s.d.)	ABS condition (Mean ± s.d.)
CARROT (non-rewarded rate - cards/sec)	0.87 ± 0.30	0.84 ± 0.29
CARROT (rewarded rate - cards/sec)	0.89 ± 0.30	0.83 ± 0.28
Snaith Hamilton Pleasure Scale	31.44 ± 5.25	29.83 ± 4.99
Verbal fluency (COWAT)	21.67 ± 9.93	23.39 ± 9.38
Digit Span Forwards	8.89 ± 2.37	9.06 ± 2.92
Digit Span Backwards	5.00 ± 2.25	4.44 ± 2.09
VOSP Object Decision	18.39 ± 1.65	18.1 ± 1.37
VOSP Cube Analysis	9.22 ± 1.00	9.67 ± 0.69
Stem completion task	6.18 ± 3.81	5.53 ± 2.62

2. Reward responsivity

2a. CARROT

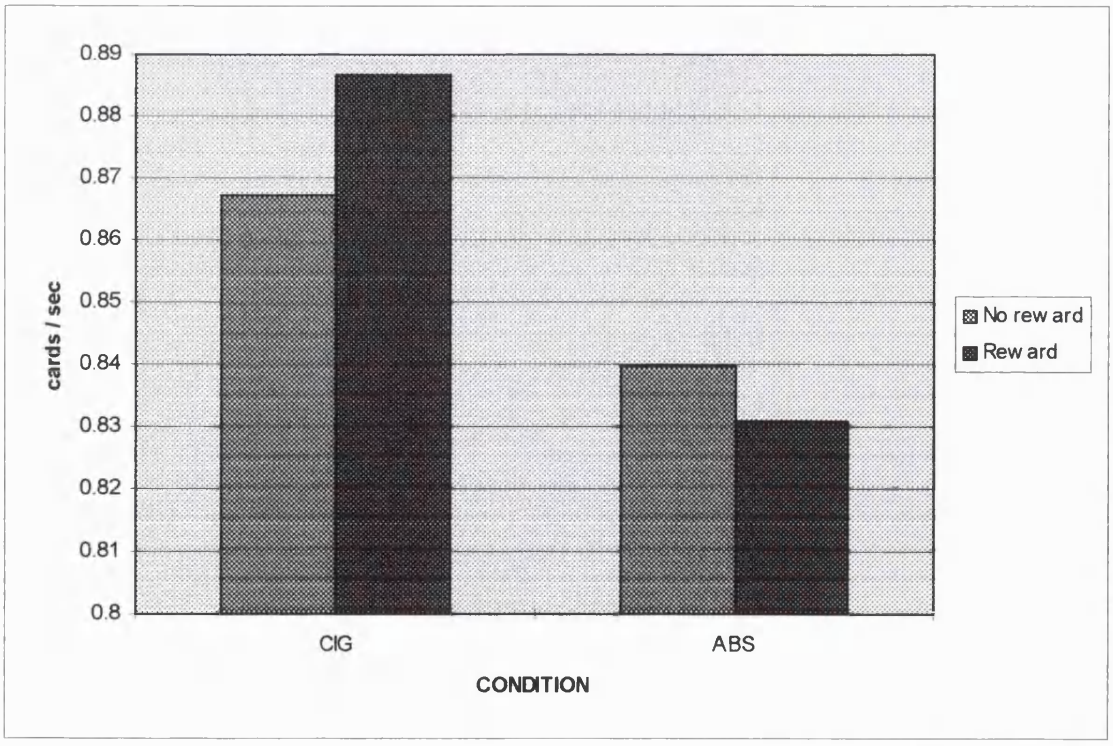
The mean card sorting rate (and standard deviation) for each trial are shown in Table 3.4. This shows that mean rates of sorting increased across the 4 trials, suggesting a within-session practice effect.

For each participant, the mean rate from trials T2 and T4 was calculated to produce a non-rewarded sorting rate. Rates for T3 trials represented the rewarded sorting rate. Fig. 3.1 shows the mean sorting rate for each condition, for rewarded and unrewarded trials.

Table 3.4: Descriptive data for rate of card-sorting across trials in both CIG and ABS conditions, split across ORDER of presentation groups. Figures shown are rates of sorting in cards per second.

Condition Trial number	T1 (mean ± s.d.)	*Non-rewarded* T2 (mean ± s.d.)	*Rewarded* T3 (mean ± s.d.)	*Non-rewarded* T4 (mean ± s.d.)
CIG/ABS presentation order				
CIG	0.74 (± 0.31)	0.81 (± 0.31)	0.86 (± 0.31)	0.90 (± 0.32)
ABS	0.83 (± 0.31)	0.89 (± 0.329)	0.90 (± 0.32)	0.95 (± 0.33)
ABS/CIG presentation order				
ABS	0.65 (± 0.18)	0.69 (± 0.19)	0.75 (± 0.21)	0.79 (± 0.23)
CIG	0.77 (± 0.27)	0.86 (± 0.30)	0.92 (± 0.29)	0.90 (± 0.30)

Fig 3.1: Mean sorting rates across CONDITION (CIG or ABS) and REWARD status (rewarded or not rewarded).



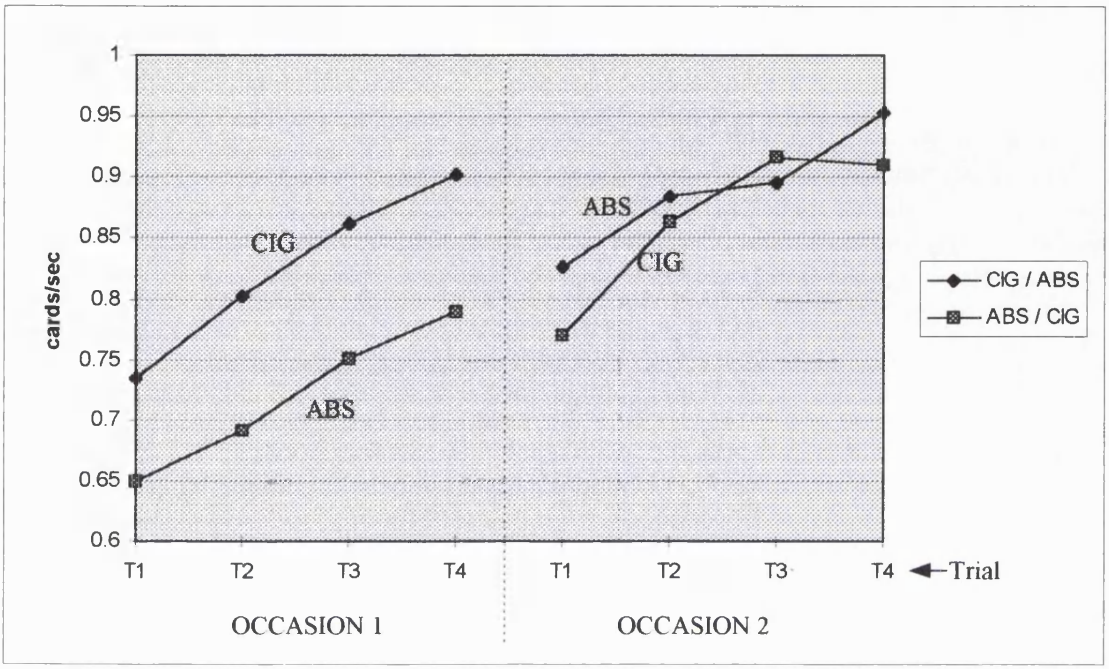
An ANOVA revealed a significant two-way interaction of REWARD x CONDITION ($F_{1.16} = 5.369$; $p < 0.05$), as predicted by the first experimental hypothesis. Here, sorting speed in the CIG condition increased by about 2.5% given financial incentive, whereas there was a marginal decrease in speed in the ABS condition. The three-way interaction of REWARD x CONDITION x ORDER was non-significant ($F_{1.16} = .352$; ns), i.e. there was no effect of order of presentation upon the predicted two-way interaction.

There was also a significant two-way interaction of CONDITION x ORDER ($F_{1.16} = 26.278$; $p < 0.0005$). Although the means for both CIG/ABS and ABS/CIG presentation orders showed improvement on the second testing occasion (a possible between-conditions practice effect), this difference was considerably greater for those in the ABS/CIG presentation order, who sorted cards at a much slower rate on the first testing occasion (i.e. when abstinent)(see Fig. 3.2).

A significant two-way interaction of REWARD x ORDER was also identified ($F_{1.16} = 4.976$; $p < 0.05$). Those participants who were abstinent on the first testing occasion (ABS/CIG) sorted cards faster when given financial incentive, whereas those who were abstinent on the second testing occasion (CIG/ABS) showed a marginal decrease in sorting speed when rewarded, compared to non-rewarded trials.

There was a significant main effect of CONDITION ($F_{1.16} = 7.042$; $p < 0.05$), with sorting speeds being faster in the CIG condition. There was no significant main effect of REWARD ($F_{1.16} = 1.309$; ns), and no significant main effect of ORDER ($F_{1.16} = .181$; ns).

Fig 3.2: The mean sorting times for each trial of the CARROT, grouped by ORDER (of presentation). The individual trials are labelled T1-4 for each testing occasion.



2b. Snaith-Hamilton Pleasure Scale

The mean scores across conditions are listed in Table 3.3.

ANOVA revealed a non-significant trend for the main effect of CONDITION ($F_{1,16} = 3.57$; $p < 0.10$), with a non-significant trend for the interaction of CONDITION x ORDER ($F_{1,16} = 4.21$; $p < 0.06$),. Those who had been abstinent for the first administration of the questionnaire (ABS/CIG) showed little difference in responses across conditions, whereas those who were abstinent for the second administration (CIG/ABS) showed lower hedonic tone under this condition.

3. Cognitive tests of 'willed action' / working memory

The mean scores across conditions are listed in Table 3.3.

ANOVA revealed that performance on all three cognitive tests of 'willed action' / working memory did not differ significantly across condition, and there were no significant CONDITION x ORDER interactions (see Table 3.5). There was also a significant main effect of ORDER on the Digit Span Backwards task, with participants in the CIG/ABS order of presentation scoring significantly higher (before Bonferonni correction; this must be considered as a statistical trend post-correction).

However, there was a non-significant trend for the main effect of CONDITION on the Digit Span Backward task, with an increased mean score under the CIG condition compared to the ABS condition.

Table 3.5 ANOVA results for the cognitive tests of 'willed action' / working memory.

Cognitive test	Effect analysed for	F value & significance level
COWAT	CONDITION	$F_{1.16} = 1.430$; ns
	CONDITION x ORDER	$F_{1.16} = .310$; ns
Digit Span Forwards	CONDITION	$F_{1.16} = .101$; ns
	CONDITION x ORDER	$F_{1.16} = .909$; ns
Digit Span Backwards	CONDITION	$F_{1.16} = 3.408$; $p = 0.100$
	CONDITION x ORDER	$F_{1.16} = 1.354$; ns
	(ORDER)	($F_{1.16} = 5.158$; $p < 0.05$)

It should be noted that the mean score across conditions for the COWAT was 22.53, which is below the 5th percentile for the population, indicating that, as a whole, the sample of participants was impaired on a task indicative of 'willed action'. The mean scores on Digit Span Forwards and Backwards (8.97 and 4.72 respectively), when added, roughly equate to test performance around the 20th-35th percentile, i.e. low average.

4. 'Control' tasks

4a. VOSP Object Decision

The mean scores across conditions are listed in Table 3.3.

It should be noted that the mean for the current sample (18.39, CIG condition; 18.1, ABS condition) on this task was comparable with the mean (18.6) for the control (non brain injured) group from the original standardisation study, where 39.5% scored 18 or less (Warrington and James, 1991).

As the data were significantly negatively skewed for the CIG condition (Skewness Z score = -2.64; $p < 0.05$), the following transformation was performed on all scores on this test (both CIG and ABS conditions):

TRANSFORMED SCORE = SQRT ((ORIGINAL SCORE x -1)+20)

None of the transformed scores differed significantly from a normal distribution (all Skewness Z scores $< \pm 1.52$; ns).

ANOVA revealed no significant difference across conditions for these transformed measures ($F_{1.16} = 1.265$; ns) and no significant CONDITION x ORDER interaction ($F_{1.16} = .112$; ns).

4b. VOSP Cube Analysis

The mean scores across conditions are listed in Table 3.3.

As with the Object Decision task, the mean for the current sample (9.22, CIG condition; 9.67, ABS condition) on this task was comparable with the mean (9.3) for the control (non brain injured) group from the original standardisation study, where 37.5% of the normal sample scored 9 or less (Warrington and James, 1991).

As the scores showed a clear 'ceiling effect', they were partitioned into two categories: 'maximum' or 'less than maximum' (see Table 3.6). 10 participants achieved a maximum score in both conditions, 4 achieved a less than maximum score in both conditions, and 4 achieved a maximum score only in the abstinent condition.

Fisher's Exact Test showed a difference in proportions between 'maximum' and 'less than maximum' scores across conditions (Exact 2-sided significance = 0.38). This should be considered a statistical trend after the Bonferonni correction. Analysis of the raw data revealed that of the 4 participants with a higher score (i.e. maximum) in the ABS condition, three were completing the task for the second time (CIG/ABS), and one for the first time (ABS/CIG).

Table 3.6 Frequencies of 'maximum' and 'less than maximum' scores across experimental conditions for the VOSP Cube Analysis task.

		ABS condition		
		Less than maximum (<10)	Maximum (10)	Total
CIG condition	Less than maximum (<10)	4	4	8
	Maximum (10)	0	10	10
	Total	4	14	

4c. Stem completion

The mean scores across conditions are listed in Table 3.3.

One participant (no.18) did not complete this task. His spoken comprehension and expression was good, but reported that learning to read and write in English had been difficult because of the reverse of reading direction (his first language was Hebrew).

ANOVA revealed no significant difference in performance across conditions ($F_{1.15} = .707$; ns) and no significant CONDITION x ORDER interaction ($F_{1.15} = .495$; ns).

Self-reported reasons for smoking

Table 3.7 summarises the themes expressed by the participants.

Table 3.7: Themes expressed, and the numbers of participants who expressed them. Participants often mentioned two or more themes.

Theme	No. of participants mentioning theme
It's a habit	6
It's relaxing / reduces stress	6
Out of boredom	6
Liking it / for enjoyment	4
Social reasons (joining in / socialising / to impress)	4
To think or concentrate better	2
For a "buzz" / "moment of serenity"	2
Goes with other things (food / coffee / chocolate)	2
Couldn't identify a reason for smoking	2

No statistical or formal qualitative analyses were employed in relation to the participants' comments. See Appendix 10 for the full list of participants statements.

Post-hoc analysis of potential factors related to size of effect of nicotine on the CARROT

For the measure where a significant difference was found between conditions (reward responsivity on the CARROT), the difference between scores in the two experimental conditions was calculated. These differences were then correlated with 3 other measures:

- score on the Apathy scale (as a measure of clinical motivation)
- score on Ravens Coloured Progressive Matrices (as a measure of general intellectual functioning)
- score on the Fagerstrom Test of Nicotine Dependence (as a measure of nicotine dependence)

The Pearson correlation method was employed, except where one of the variables did not show a normal distribution (i.e. Ravens Matrices), where the Spearman method was used. Results are shown in Table 3.8. It should be acknowledged that this analysis was highly exploratory, and should be regarded as tentative because of the instability of correlation coefficients with a sample of such small size.

A Bonferroni correction was applied in order to adjust for multiple analyses, meaning that for statistical significance at the 95% confidence level, a correlation needed to have a p

value of less than 0.017. None of the measures showed a significant correlation with the difference in reward responsivity.

Table 3.8 Results of correlational analyses between selected variables and measures shown to be significantly affected by nicotine intake. Spearman calculations shown in italics.

	Apathy scale	Ravens CPM	FTND
Difference in reward responsivity [1]	0.29 (ns)	*0.25 (ns)*	0.20 (ns)

[1] (rewarded speed.CIG - nonrewarded speed.CIG) - (rewarded speed.ABS - nonrewarded speed.ABS)

Summary of results

The only significant differences in performance across the experimental conditions were on the CARROT. There was the predicted CONDITION x REWARD interaction. Additionally, there were two-way interactions of CONDITION x ORDER (found to be highly significant) and REWARD x ORDER. There was also a main effect of CONDITION. There was also some evidence of a within-session increase in sorting speed, and that participants who were abstinent on the first occasion sorted cards considerably slower in this condition.

There were also three other measures showing near-significant differences across conditions. There was a trend for participants to score better under the CIG condition on the Digit Span Backwards task, and also to show greater hedonic tone (Snaith-Hamilton Pleasure Scale scores) under this condition. There was a near-significant order effect

related to the latter finding, in that this trend appeared to be predominantly explained by those who were abstinent for the second administration (CIG/ABS) having lower hedonic tone under this condition.

On the VOSP Cube analysis task, there was a near-significant difference between the numbers of participants that achieved a perfect score between conditions, with four participants achieving maximum scores in the ABS condition, but less than maximum in the CIG condition. It should be noted that three of these had already completed the task previously in the CIG condition.

None of the three measures used in a post-hoc analysis were significantly correlated with a measure of degree of enhancement of reward responsivity after smoking (compared to when abstinent)

DISCUSSION

The main hypothesis that the current study aimed to investigate was that on tasks specifically involving 'willed action', or executive functioning, brain-injured smokers would show enhanced performance after smoking a cigarette compared to when they had been abstinent for at least 2 hours. This hypothesis was partially confirmed by the results, with reward responsivity being the only measure showing significant improvement after smoking. The findings corresponding to each measure are discussed in turn below.

CARROT

Reward responsivity

It was predicted that reward responsivity in the current sample would be enhanced after smoking a cigarette compared to when abstinent, as this effect has been seen in a neurologically intact sample (Al-Adawi and Powell, 1997). The reward responsivity measure from the CARROT has also been associated with a number of tasks thought to involve willed action / executive functioning (e.g. Powell *et al,* 1996).

The specifically predicted two way interaction signifying enhanced reward responsivity (CONDITION x REWARD) was confirmed. There was no interaction with the order in which the participants were tested, meaning that this did not influence the result.

The interaction suggests that the findings of Al-Adawi and Powell (1997) and Powell *et al* (in press), who found enhanced reward responsivity after a cigarette in neurologically intact participants, can be generalised to include brain-injured participants. It also indicates that brain-injured individuals show increased reward responsivity in response to different dopamine agonists, since Powell *et al* (1996) showed such an increase after administration of bromocriptine.

As this study involved multiple tasks, and therefore multiple statistical analyses, there is a risk that this finding (where p was only slightly less than .05) is in fact a Type I error, as the likelihood that one of the apparently significant differences (at the $p<0.05$ level) is in fact due to random variation increases. However. as this finding is in accordance with previous studies that have used the CARROT with both brain-injured and neurologically intact populations, one can conclude with more confidence that the difference in means is associated with the dependent variable of acute smoking status.

It is interesting to note that, compared with previous studies, there was a relatively small effect of reward on sorting rate (2.5% increase under reward after a cigarette, 1% decrease when abstinent). The percentage increased sorting rate (under rewarded compared with non-rewarded conditions) from previous studies with non brain-injured individuals ranges from 2.5% (Powell *et al,* in press) to 21% (after smoking a cigarette; Al-Adawi and Powell, 1997). In brain-injured participants, Al-Adawi *et al* (1998)

reported an increase in sorting rate of 11% under reward, and Powell *et al* (1996) found increases of 1.5% (before administration of bromocriptine) and 16.5% (after bromocriptine) in a sample of individuals with clinically significant problems with apathy. The magnitude of the reward (10p for every 5 cards) was constant across these studies, so the apparently small effect of incentive in the present study cannot be attributed to what some might consider a meagre reward (usually around £1.30). Significant effects on sorting speed have consistently been shown in the past, suggesting that even this small amount of money is rewarding, especially if defined in behavioural terms. i.e. it effects positive behavioural change.

Other aspects of performance on the CARROT

Apart from the predicted two-way interaction, the results raised several other issues pertinent to theories of 'willed action' and executive functioning.

A notable observation was that there appeared to be a 'within session' practice effect. This refers to the increase in mean sorting rates across the 4 trials in both smoking and abstinent conditions. This generally included an increase in rate from T3 (rewarded trial) to T4 (the second non-rewarded trial), something not seen in at least two of the previous CARROT studies, including one involving brain-injured participants (Al-Adawi, 1998). Many of the studies with neurologically intact participants discarded trial T4, as its

inclusion did not make a significant difference to the final reward responsivity index (Powell, personal communication).

There was also a general improvement in sorting rates between first and second testing sessions, which was more marked in those who had been abstinent first. There is no relevant available data from previous studies to confirm whether or not sorting rates increased with practice across test occasions, although one might expect some improvement between sessions as a result of familiarity with the test.

By definition, the fact that the current sample were still generally increasing their mean sorting rate even on the final trial of 8 (in total) suggests that they had not yet reached (or they had only just reached) their optimal speed. It therefore seems reasonable to conclude that brain-injured people may take significantly longer than non-injured people to reach 'full speed' on this task. There is contradictory evidence from a previous CARROT study (Al-Adawi *et al*, 1998), where there was a decrease in mean sorting rate from T3 to T4. However, the mean rate for the sample from that study was around half that of the present sample, and there may be some interaction between information processing speed and acquired deficits in motor speed that is salient here.

What may be more important to note here is the highly significant two-way CONDITION x ORDER interaction (with the main effect of CONDITION subsumed by this two-way interaction). Further analysis of the CONDITION x ORDER interaction suggests that

sorting rates were relatively similar if either a) the participants had smoked a cigarette, or b) they were abstinent but had done the task before having just smoked a cigarette. On the other hand, if participants were abstinent, and had never done the task before, they sorted considerably slower (see Fig. 3.2).

It would be inaccurate to conclude that motivation to sort as fast as possible (independent of reward status) only occurs when acutely under the influence of nicotine, as those participants who were abstinent on the second testing occasion showed the fastest mean sorting rate of all. What seems more likely is that it is the novelty of the task that is important, and it could be concluded that, when abstinent, participants generally sort at a slower rate when the task is novel.

It could be that nicotine aids either motivation to attempt a novel task (independent of financial incentive), or ability to learn a new skill (e.g. sorting faster), or a combination of the two factors. Further research would be needed to clarify this; however, the results suggest that the acceleration of sorting rates across individual trials (i.e. rate of learning to sort fast) was only marginally quicker (if at all) under the influence of nicotine, but that the initial sorting rate on the first trial (and therefore subsequent trials) was considerably higher if a cigarette had recently been smoked. Although this would provide only a very preliminary hypothesis for any future studies, it seems possible that nicotine facilitates initial attempts at the CARROT, and that increased motivation, as opposed to increased ability to learn, may more accurately characterise the nature of this facilitation.

How these findings concur with, or extend, current theories of 'willed action' and/or executive functioning

The predicted finding that reward responsivity is significantly higher after smoking a cigarette (compared to when abstinent) supports the idea that nicotine intake (and the concurrent hypothesized increase in dopaminergic activation to the frontostriatal circuits) is related to an increase in the ability to respond to normally motivating events, i.e. available rewards in the environment (in this case, financial incentive). The finding supports a generalisation of this idea to encompass brain-injured as well as non-injured people.

It is noteworthy that the effect of financial incentive appeared to be of smaller magnitude than previous CARROT studies (see Al-Adawi, 1998), with the exception of its effect in an apathetic, brain-injured sample (Powell *et al*, 1996), and in a non-injured sample with low nicotine dependency (Powell *et al*, in press). It would be inappropriate to reach firm conclusions from direct comparisons with previous studies, and any contrast with a non-injured population would require a healthy control group to be matched on potentially critical factors such as age and severity of nicotine dependence, and for the task to be titrated for level of 'task difficulty'. The present study did not attempt to do this, focusing instead on whether brain-injured individuals would show any effect of acute smoking status, rather than the relative size of such an effect.

However, if an assumption was made that the smaller effect of financial incentive in the current sample was a valid observation, one could speculate more about possible factors that might explain this smaller effect, including hypotheses relating to acquired brain injury. Firstly, the current sample was, in general, apathetic, as suggested by the apparent low reward responsivity and the high scores on the revised Apathy scale (although neither measure has been standardised against a normal population). It has previously been shown that low reward responsivity, as measured by the CARROT, and clinical indices of motivation are significantly correlated in this way (Al-Adawi *et al,* 1998). Together, these two observations suggest that many of the sample had some acquired motivational difficulties (as is common in people with neurological insult); this would be predicted by the frequency of frontal lobe damage reported by either the participants or their medical records (at least 10 of the 15 available reports include damage to frontostriatal areas). One might conclude that if there was damage to the frontostriatal circuits, this may to some extent impede the potentially beneficial effects of a dopamine agonist, e.g. it would be less able to increase dopaminergic activation of the frontal areas (associated with motivation / reward responsivity) because of the acquired damage.

Secondly, the current sample were not heavily dependent smokers, and it is possible that lighter smokers are less affected by financial incentive after smoking a cigarette than heavier smokers. Al-Adawi and Powell's (1997) sample showed a 21% increase in sorting rate under financial incentive in the smoking condition, and had a nicotine

dependence score of 7.9 (heavier smokers), whereas the current study and Powell *et al's* (in press) sample both showed 2.5% increases in sorting rate in the smoking condition, and had comparable nicotine dependence scores, of 3.5 and 3.7 respectively (lighter smokers). The mechanisms for this depend on the theoretical assumption made about the effect of smoking upon reward responsivity. If one assumes that there is a simple enhancement of reward responsivity after acute smoking, then it could be concluded that heavier smokers experience greater enhancement than lighter smokers (suggesting a possible rationale for their higher intake). If one assumes that abstinence from chronic smoking manifests as a motivational deficit due to previous neural adaptations to smoking, then it could be concluded that lighter smokers have undergone less of these neural adaptations, and are therefore less affected by acute smoking status.

It is also worth noting that although reward responsivity was significantly increased after a cigarette compared to when abstinent, the difference was very small compared to the results of Powell *et al* (1996), who measured reward responsivity before and after administering doses of bromocriptine to a sample of neurological patients with clinically significant problems with apathy. Again, although direct comparisons are inappropriate, it seems likely the amount of nicotine in a cigarette had a smaller effect on dopaminergic activation (and therefore reward responsivity) than the daily doses of bromocriptine administered over a period of several weeks to the participants in Powell *et al's* (1996) study.

However, there is an alternative interpretation of why the effect was smaller in this study that is less related to the concept of reward responsivity, namely that this sample did not reach their potential optimum sorting speed. This could have the consequence that many of the participants were still showing psychomotor learning between T3 and T4, thus reducing the relative magnitude of the reward responsivity effect.

Jahanshahi and Frith (1998) have argued that willed action systems, which probably involve dopaminergic activation to some extent, function more when a task is novel. In terms of executive functioning, novelty requires supervisory attentional system (SAS) involvement. Once the task becomes routine or automatic, willed action systems (or SAS involvement) are required to a much lesser extent, and action falls more under the control of other neurological systems.

The results suggested that the novelty of the task interacted with smoking status, in that those who first attempted the CARROT within the abstinent condition sorted considerably slower. It seems plausible that brain-injured individuals could take longer to accelerate to maximal speed if they have damage to frontostriatal (willed action) circuits. With such acquired impairment, it may take longer to become skilled at certain novel tasks, as there would be a decreased ability to facilitate the shift to automatic control of behaviour. If there is further decreased dopaminergic activation of the frontostriatal circuits due to abstinence from a smoking habit, it may take even longer for the shift to automatic control to occur. Abstinence *per se* would not cause slower sorting rates, as if

the task has been practiced before, it may already have come under automatic control to a certain extent, and frontostriatal areas (i.e. those affected by levels of dopamine activation) would no longer be as involved. The observations from the current study would be consistent with this speculative interpretation.

In summary, nicotine significantly increased reward responsivity in smokers with brain injury. There was also evidence that nicotine enabled the participants to sort cards faster when the task was novel. Both of these findings are in accordance with existing theories of willed action and executive functioning. However, for these theories to be seen as useful frameworks for understanding and describing the nature of the neuropsychological effects of nicotine, other tasks involving willed action / executive functioning would have to show enhanced performance after nicotine consumption compared to when abstinent. In addition, tasks which supposedly do not involve willed action / the SAS (the control tasks) would have to show no difference in performance across conditions.

Interpretation of other results

Hedonic tone (the Snaith-Hamilton Pleasure Scale)

Firstly, it should be noted that caution should be exercised in interpreting this particular scale, as an unvalidated variant on the original scoring system was used in order to detect

subtle changes in hedonic tone due to smoking that may have been missed by the original, coarse scoring system.

It was hypothesized that hedonic tone (the ability to experience pleasure) is a subjective correlate of reward responsivity. Intuitively, it would follow that whilst in a state of high reward responsivity, it should seem more worth expending energy to obtain available rewards, either due to increased motivation, or because the subjectively perceived value of the potential reward is enhanced in some way. It was therefore predicted that participants would rate their expectations for normally rewarding events as higher after smoking when compared to abstinence.

The evidence from the current study is inconclusive. After applying a Bonferonni correction, the difference falls short of significance, though shows a trend towards higher hedonic tone after nicotine intake compared to when abstinent.

There is also anecdotal evidence from the open-ended enquiries as to why the participants smoked. One of the most common answers was that they smoked out of boredom. It was also informally noted that a number of the participants who were in a rehabilitation centre stated during or after testing that they especially needed to smoke now they were in rehabilitation, which was a very boring experience. It seems possible that statements about boredom are equivalent to stating that there does not seem to be anything in their immediate environment worth making an effort for (i.e. being responsive to), with the

goal of obtaining positive reinforcement (reward). It might then follow that chronic self-administration of a drug that increases reward responsivity in such situations would be an adaptive response in countering boredom.

Digit Span

There was a non-significant trend in the direction of enhanced performance on Digit Span Backwards after nicotine consumption, compared to abstinence. This is commonly seen as a test of working memory / executive functioning. There was no difference in performance on Digit Span Forwards across conditions.

There are two conclusions that could be drawn here. It may be that nicotine intake has no effect on executive functioning, and that the trend with Digit Span Backwards is due to a spurious effect of measurement error. In this case, one might be tempted to further conclude that the neurological pathways associated with reward responsivity are separate to those utilised when attempting a Digit Span task.

However, there are a number of studies that have identified an enhancing effect of nicotine on performance on Digit Span (often measured as a total score, adding forwards and backwards spans; e.g. Levin and Rose, 1995; Al-Adawi and Powell, 1997). Again, it may be appropriate to note the low levels of smoking dependence in the current study, and to contrast the results from Al-Adawi and Powell (1997), who found a significant

enhancement in Digit Span performance in heavy smokers, and Powell *et al* (in press), who did not find a significant difference in performance with a sample of smokers comparable to the current sample in terms of dependency. It could be that nicotine does indeed affect executive functioning (as associated with performance on Digit Span Backwards), but that unless the individual is a heavy smoker, this neurobiological enhancement will not be enough to significantly increase their backwards span (i.e. the task is not sensitive enough to the smaller changes in neurobiology that occur when a lighter smoker smokes).

Verbal fluency (the COWAT)

One considerable barrier to concluding that the 'willed action' framework is useful in describing which functional systems are enhanced by smoking is that there was no enhancing effect of smoking on performance on verbal fluency. This task, which requires participants to generate words not prompted by external stimuli, has been consistently shown by neuroimaging studies to require activation of frontostriatal circuits, which overlap with the mesocorticolimbic dopamine pathways implicated here.

There are a number of possible interpretations. As before, the lack of enhancing effect of nicotine could be due to the fact that the current sample are light smokers. If the same studies that reported a differential enhancement of smoking between light and heavy smokers on the Digit Span task (Al-Adawi and Powell, 1997; Powell *et al*, in press) are

compared, a similar pattern emerges regarding the verbal fluency task, in that verbal fluency was only significantly affected in heavier smokers. It could be that dopamine is involved in the same neurological pathways that mediate both verbal fluency and reward responsivity, but that a greater difference in activation levels across conditions than that experienced by lighter smokers is needed to bridge a threshold where performance on verbal fluency would improve.

It could also be noted that the mean score for the sample was very impaired, suggesting that for many of the participants, there was acquired damage in the frontostriatal circuits associated with performance on this task. As with possible lowered reward responsivity in a brain-injured sample, one could conclude that such damage may to some extent preclude the potentially beneficial effects of nicotine as a dopamine agonist, perhaps because increased dopaminergic activation is partly irrelevant if structural damage to pathways hinders adequate neurotransmission. However, it would have to follow that verbal fluency and reward responsivity were mediated by different pathways, as reward responsivity was enhanced in this sample.

Mood and Physical Symptoms Questionnaire

There was no difference in subjectively reported withdrawal symptoms across experimental conditions. This could again partly be because the sample were relatively

light smokers, and it could be assumed that they did not experience withdrawal symptoms to a large degree.

The main implication of this finding is that the lower reward responsivity (and, debatably, hedonic tone) during abstinence cannot be attributed to a general malaise following nicotine withdrawal, and supports the idea that lowered reward responsivity is, in its own right, a symptom of nicotine abstinence.

Control tasks

The VOSP Object Decision task and the stem completion task showed no difference in performance across conditions, confirming the prediction that these tasks, with little or no involvement of willed action / SAS, were not affected by nicotine intake and putatively increased dopaminergic activation.

The VOSP Cube Analysis task in fact showed (after application of a Bonferonni correction) a trend towards enhanced performance in the abstinent condition. It is difficult to come to any strong conclusions about this finding, because there was a marked ceiling effect (participants scored very highly in both experimental conditions). Methodologically, it was difficult to identify an 'effortless' control task which was not too easy, and would therefore result in a ceiling effect (N.B. there was such an effect for

the Object Decision task as well). However, it was not anticipated that the sample would score as highly as they did, given that they were brain-injured.

There was no complication of a ceiling effect on the stem completion task, providing some clearer evidence that non-willed action tasks are not affected by acute smoking status. The lack of effect of nicotine on this task concurs with the conclusions of Warburton *et al* (2001), who found that nicotine only improves memory for word lists via the associative attentional process of rehearsal. In the case of the current study, the participants were not instructed to remember the word, and the task explicitly presented to them arguably did not involve semantic orientation.

Is there any aspect of functioning / acquired impairment that predicts the magnitude of the effects of smoking / abstinence?

It is important to reaffirm that this attempt to establish whether certain aspects of functioning predict the magnitude of effect of smoking status, is highly exploratory. There are no a priori predictions, as the literature in this area is unresolved on a number of key issues, and there have been no previous studies looking at the relationship between acquired neuropsychological impairment and the effects of smoking.

These post-hoc analyses were restricted to the one variable, reward responsivity, on which the study had illustrated a significant effect of smoking status. It was postulated

that the size of the reward responsivity effect might be modulated by severity of nicotine dependence, general intellectual processing (as indicated by performance on Ravens Matrices), and severity of apathy. The results showed that none of the measures were significantly correlated with reward responsivity after smoking a cigarette compared to when abstinent.

It should be acknowledged that adminstration of the Raven's Matrices was conducted under random smoking conditions, with half of the sample having smoked and half abstinent. This measure was included in the battery partly to simply describe the sample, but there remains the possibility that nicotine (compared to abstinence) facilitated performance on the task, especially as it intuitively appears effortful. However, if considering that smoking status had only a modest effect at best on performance on the other measures, and that there was considerable variability of scores on the Ravens, it seems likely that this variability mostly reflected pre-morbid functioning minus acquired intellectual impairment.

It is perhaps surprising that level of nicotine dependence did not correlate with the degree of enhancement in reward responsivity, as there are a number of indications that the level of dependence is an important factor here, as has been stated above. It may be that a sample with a wider range of nicotine dependency would have been more enlightening in this respect, as the large majority of the current sample (15 of 18) scored 5 or below on

the Fagerstrom Test of Nicotine Dependence. One cannot make a useful comparison between 'light' and 'heavy' smokers when there are so few 'heavy' smokers.

In summary, there is no conclusive evidence to suggest that any particular aspect of a brain-injured individual's functioning or smoking status predicts that he/she has more to 'gain' from nicotine (in terms of reward responsivity) than any other individual.

Methodological problems

Some of the methodological difficulties involved with the study have been outlined above. There are other additional areas of difficulty. Firstly, there is debatable validity in using a generic brain-injured sample, as any conclusions drawn from the results will inevitably miss taking into account the considerable heterogeneity of the sample, in terms of pre-morbid functioning, localisation of injury, extent of injury, extent of verbal and motor deficits and cause of injury (e.g. RTA, stroke, etc.) to name but a few. With a small sample, the power was too low to subdivide the sample by aetiology, even if there had been any a priori reasons for doing so.

Secondly, although the study focuses on frontostriatal functioning in many ways, poor performance on tasks tapping the functioning of these particular circuits can be influenced by other deficits (such as expressive aphasia) related to damage in separate areas.

Although a group effect can still be observed, it might be 'diluted', resulting in a reduction in statistical power.

Thirdly, the fact that this was a small scale study is also relevant here. When a sample is heterogeneous (i.e. its standard deviation is large), there is a consequent loss of statistical power, which is further exacerbated by having a low number of participants. However, Al-Adawi and Powell (1997), in a study with a very similar design, achieved a significant effect size on several measures with around 12 non-injured participants in each group. If one increases the size of the sample to compensate for heterogeneity in brain injury, it was envisaged that 18 participants would be sufficient for the current study in order to achieve a significant effect size. This judgement could not be informed by previous studies into smoking in a brain-injured population (as they do not exist), so can only be described as speculative.

Nevertheless, the power of the current study was sufficient to achieve significant effects on one of the experimental measures. It is possible that increased statistical power (via a greater number of participants) may have revealed significant differences between experimental conditions on a number of the measures, and that the current non-significant differences actually reflect a Type II error (not finding a genuine significant difference where one exists). One might suspect that the measures where non-significant trends were found between conditions (e.g. Digit Span Backwards, Snaith Hamilton Pleasure

Scale), or those where previous studies have shown an effect (verbal fluency) are those where the existence of a Type II error is most likely.

Fourthly, there are difficulties in ascertaining the extent of executive involvement in performing each task, which is especially relevant when selecting 'control' tasks. Norman and Shallice stated that the SAS is needed to a certain extent for every task, so the selection of tests could not possibly be totally dichotomous, where performance on tests of purely executive function / willed action were compared with tests where there was no involvement of these systems at all. There are also further problems in selecting an 'automatic' (non-willed) task that is difficult enough to avoid ceiling effects (which would significantly decrease the explanatory power of any observed difference across conditions). One method was to utilise the implicit / explicit distinction covered in great detail by numerous studies (especially with regard to memory processes), where implicit processes are non-conscious and automatic, contrasting with explicit processes that are conscious and effortful (see Crabb and Dark, 1999). This distinction has many parallels with a willed / non-willed action or executive / non-executive distinction. By definition, non-conscious implicit tasks are neither 'willed' nor require SAS involvement to any great extent as they do not require attention to action, meaning that an implicit memory test is an appropriate choice as a control task. The current study also attempted to use perceptual tasks as control tasks, but this decision may in retrospect have been based on the intuitive premise that perception is a fairly effortless process, and not due to any empirical data showing that these tasks involve little frontostriatal functioning. It may be

that any future similar studies might look to empirical data more closely before selecting tests.

There is also the issue of using multiple tests, and its effect of increasing the probability of Type I errors (or alternatively, reducing the p value necessary for a significant result, and therefore reducing statistical power). Other similar studies in this field have all used multiple measures (e.g. Al-Adawi and Powell, 1997; Tracey *et al*, 2000, McDowell *et al*, 1998), and it was felt that this was necessary given the exploratory nature of the current study.

A Bonferroni correction was applied to all of the statistical tests bar one, reducing the risk of Type I error. The only test where this was not applied was with the CARROT, where observations from previous studies, and a cohesive theoretical background, predicted the two-way interaction corresponding to reward responsivity. However, there was no a priori reason to predict the (just) significant REWARD x ORDER interaction on the CARROT, and therefore this may represent a Type I error (i.e. a finding of significance which is in fact due to non-systematic variation).

There were also methodological problems with the modified version of the Apathy scale used. Firstly, the use of proxy ratings had never been validated; however, self-report in a brain-injured sample may not be valid anyway, due to the possibility of poor insight. Secondly, as the sample came from numerous different centres, the scale was completed

by 6 different raters, with the participants in a range of situations (from independence in the community to an acute hospital setting). These factors were unavoidable, and it is to be hoped that future research will develop appropriate and valid techniques for assessing apathy in a brain-injured population.

The limitations of the CO meter should also be acknowledged, in that it does not give information on how much nicotine has been delivered to the individual, and that little is known about the relationship between exhaled CO levels and smoking variables. However, it is non-intrusive, convenient and gives rapid feedback, meaning that abstinence from smoking could be immediately confirmed before testing commenced.

Conclusions and Implications

In summary, it was found that only aspects of performance on the CARROT were affected by acute smoking status, with the increase in reward responsivity after smoking occurring as predicted. This confirms the findings of previous studies, and suggests that reward responsivity is more readily modulated by acute smoking status than many other variables. This leaves the possibility that nicotine intake, and the consequent increased dopaminergic activation, has a specific effect upon aspects of motivation sampled by the reward responsivity measure.

The finding is generalisable across settings, and for a range of periods elapsed since injury, as participants were taken from an acute rehabilitation ward, a longer-term rehabilitation centre, and also those living in the community (some for many years). Participants did not change their smoking habits past abstaining for a few hours, so the finding could be seen as reflecting 'everyday' modulations in reward responsivity.

There is not much evidence from the present study that Jahanshahi and Frith's (1998) 'willed action' framework is relevant for helping understand the effects of smoking and dopaminergic activation in brain injured individuals; certainly with lighter smokers it seems that only certain indices of willed action are affected. Further research with a more heavily dependent sample would be necessary to ascertain whether this assertion holds for all brain injured smokers, as it is possible that heavier smokers may indeed show greater enhancement after smoking of most, if not all, tasks tapping willed action or executive functioning.

However, the willed action framework does provide an explanation as to why the novelty of the CARROT task appeared to interact with smoking status. It is interesting that attempting the other tasks under the CIG condition on the first occasion did not appear to aid performance for that and the subsequent trial, although there was some hint from the data that smoking may have aided the ability or motivation to learn how to do the VOSP Cube Analysis task. It is unclear why smoking aids only initial performance on the CARROT and not the other measures used here; this may be due to task demands (e.g.

more effortful attentional demands, or an extra degree of repetition that allows for practice effects), or the sensitivity of the measure.

It is also possible that the framework is not yet developed and refined enough to accurately delineate what willed action is, in terms of its subcomponents, the degree to which it relates to the 5 frontostriatal loops, the precise role of dopamine activity, or its equivalence to other constructs such as the SAS. This early stage of development may limit the extent to which precise predictions can be made about how indices of willed action are likely to be affected by nicotine intake.

The present study also provides more clarity about the processes involved in performance on the CARROT, especially when administered to people with brain injury. For example, it seems that there is a practice effect involved, and that brain-injured individuals may take a long time to reach 'full speed', even under the reward condition. The present analyses also suggest that nicotine may enhance initial improvement of the card sorting rate. Information such as this could aid refinement of the CARROT as a research tool for future studies with brain injured people.

Although it is not the main focus of the current study, there are potentially important clinical implications of the hypothesis that reduced reward responsivity is a consequence of withdrawal from nicotine. If this hypothesis is valid, then smokers who abstain might experience reduced responsiveness to at least some environmental sources of pleasure or

incentive, i.e. the world will seem a less rewarding place. Intuitively, it seems that this will heighten the probability of relapse. In terms of whether people with brain injury are more prone to relapse if trying to give up, this may be complex. On the one hand, there is a suggestion that reward responsivity in brain-injured individuals is less affected by their acute smoking status, and therefore one could infer that they will experience less impairment when abstaining than their non-injured counterparts (at least in terms of reward responsivity), indicating one reason why quitting might be slightly easier. However, one might assume that there are other factors unrelated to reward responsivity that make it more difficult for brain-injured individuals to give up (e.g. increase in stereotyped, habitual behaviour due to impaired SAS; more likely to act on impulses, increased anxiety after brain injury). These factors are beyond the scope of this report.

What may be concluded from the current study is that a brain-injured person with lowered dopaminergic activation in prefrontal areas will only be able to experience modest enhancements in reward responsivity through smoking, at least if they are light smokers. The fact that this sample of predominantly frontal-lobe damaged individuals remained light smokers, many of them several years post-injury, suggests that substantial increases in smoking frequency does not tend to spontaneously occur. This would contradict a self-medication hypothesis, suggesting that individuals with brain injury are not attempting to medicate for their acquired impairments.

In terms of the interpretation of routine neuropsychological assessments with brain injured patients, it seems that their acute smoking status does not have a great influence, at least with lighter smokers. For example, the mean performance on Digit Span Backwards decreased by only half a point during abstinence. However, some tasks may be more affected than others. In particular, as reward responsivity appears to be fairly specifically modulated by smoking status, the possible impact of nicotine deprivation on effortful tasks should be borne in mind when designing and interpreting neuropsychological and observational assessments, and in devising appropriate treatment and rehabilitation plans, particularly with heavy smokers.

There are also implications for a possible role of nicotine (although not in cigarette form) as a therapeutic agent in a brain-injured population. The current study shows beneficial effects for at least some aspects of motivation, and in attempting novel tasks. One could speculate that these are just the two benefits identified by the measures employed by the current study, and that a wider range of functioning (e.g. other aspects of motivation) could benefit from some type of nicotine therapy.

On this point, it might be important for future research to address the question of whether nicotine enhances cognitive performance, or abstinence from nicotine impairs performance, as only the former finding would indicate nicotine therapy. This is a difficult question to address, especially with brain-injured individuals, as one cannot know on what basis to match a non-smoking brain-injured control group with an equivalent

group of smokers in a repeated measures design such as the one currently reported. For example, if matching participants during abstinence, it is not known to what extent their poorer performance is due to neurological damage, and how much is due to the abstinence. If matching a non-smoking group with smokers who have just smoked, one cannot be sure that those smokers are not enhanced, and therefore incorrectly matched. An alternative and potentially useful design might be to use non-smoking brain-injured participants, and utilise an alternative, harmless method of nicotine delivery, such as transdermal patches. If performance was enhanced when wearing an active nicotine patch compared to a placebo patch, this might suggest enhancement. This would raise further pertinent questions, such as whether nicotine would lose its efficacy over time due to possible neuroadaptation.

It would be interesting to attempt to replicate the current study, either with heavier smokers only, or with two groups that varied on measures of smoking dependence. This would test the hypothesis that levels of dependence affect the degree of change in performance between smoking and abstinent conditions. Other further research in this area could focus on a more in-depth analysis of what aspects of functioning, or types of impairment, might be related to a greater enhancement effect after smoking in a brain-injured population. This would extend the cursory post-hoc investigation that was attempted within the design of the present study. Such exploration might suggest what types of impairment would benefit most from therapy with nicotine, or another dopamine agonist, and may enlighten discussion regarding the validity of a self-medication

hypothesis within this patient group. Another possible follow-up study might wish to investigate the relationship between hedonic tone and reward responsivity, perhaps in a larger sample of heavier smokers, with a validated, more sensitive measure of hedonic tone.

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APPENDICES

Appendix 1

Fagerstrom Test For Nicotine Dependence

Please answer each question by ticking the response with which you agree most

1. How soon after you wake up do you smoke your first cigarette?

   Within 5 minutes
   6-30 minutes
   31-60 minutes
   After 60 minutes

2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g. in church, at the library, in cinema etc.?

   Yes
   No

3. Which cigarette would you hate most to give up?

   The first one in the morning
   All others

4. How many cigarettes a day do you smoke?

   10 or less
   11 - 20
   21 - 30
   31 or more

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?

   Yes
   No

6. Do you smoke if you are so ill that you are in bed most of the day?

   Yes
   No

Appendix 2

Hospital Anxiety and Depression Scale (HADS)

Name: Date:

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D			A	D
		I feel tense or 'wound up'	**I feel as if I am slowed down**		
[3]		Most of the time	Nearly all the time		[3]
[2]		A lot of the time	Very often		[2]
[1]		From time to time, occasionally	Sometimes		[1]
[0]		Not at all	Not at all		[0]
		I still enjoy the things I used to enjoy	**I get a sort of frightened feeling like 'butterflies' in the stomach**		
	[0]	Definitely as much	Not at all	[0]	
	[1]	Not quite so much	Occasionally	[1]	
	[2]	Only a little	Quite often	[2]	
	[3]	Hardly at all	Very often	[3]	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
[3]		Very definitely and quite badly	Definitely		[3]
[2]		Yes, but not too badly	I don't take as much care as I should		[2]
[1]		A little, but it doesn't worry me	I may not take quite as much care		[1]
[0]		Not at all	I take just as much care as ever		[0]
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	[0]	As much as I always could	Very much indeed	[3]	
	[1]	Not quite as much now	Quite a lot	[2]	
	[2]	Definitely not so much now	Not very much	[1]	
	[3]	Not at all	Not at all	[0]	
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**		
[3]		A great deal of the time	As much as I ever did		[0]
[2]		A lot of the time	Rather less than I used to		[1]
[1]		Not too often	Definitely less than I used to		[2]
[0]		Very little	Hardly at all		[3]
		I feel cheerful	**I get sudden feelings of panic**		
	[3]	Never	Very often indeed	[3]	
	[2]	Not often	Quite often	[2]	
	[1]	Sometimes	Not very often	[1]	
	[0]	Most of the time	Not at all	[0]	
		I can sit at ease and feel relaxed	**I can enjoy a good book or radio or television programme**		
[0]		Definitely	Often		[0]
[1]		Usually	Sometimes		[1]
[2]		Not often	Not often		[2]
[3]		Not at all	Very seldom		[3]

Now check that you have answered all the questions.

A D

TOTAL [ ][ ]

Appendix 3

Apathy Evaluation Scale (abridged)

Please rate the client on the following questions, with respect to how they present currently. If you are not sure of an answer, please take your best guess, but indicate with a question mark where you feel you are guessing.

	A lot	Some	Slightly	Not at all
Is the client interested in learning new things?				
Does anything interest them?				
Are they concerned about their condition?				
Do they put much effort into things?				
Are they always looking for something to do?				
Do they have plans and goals for the future?				
Do they have motivation?				
Do they have energy for daily activities?				
Does someone have to tell them what to do each day?				
Are they indifferent to things?				
Are they unconcerned with many things?				
Do they need a push to get started on things?				
Are they neither happy nor sad, just in-between?				
Would they consider themselves apathetic?				

TOTAL SCORE:

RATED BY:

Scoring: For items above the bold line, 'a lot' = 0, 'some' = 1, 'slightly' = 2, and 'not at all' = 3. For items below the bold line, 'a lot' = 3, 'some' = 2, 'slightly' = 1, and 'not at all' = 0.

Appendix 4

Mood and Physical Symptoms Questionnaire (adapted)

Please show on each of the scales below how you feel *at this minute*.

	Extremely	Very	Moderately	Slightly	Not at all
Depressed					
Irritable					
Anxious					
Drowsy					
Restless					
Hungry					
Poor concentration					
Exhausted					
Worthless					
Active					
Hopeless					
Energetic					

Appendix 5

The Snaith-Hamilton Pleasure Scale

This questionnaire is designed to measure your ability to experience pleasure at the moment.
It is important to read each statement *very carefully*.
Tick *one* of the boxes (□) to indicate how much you agree or disagree with each statement.

1. I would enjoy my favourite television or radio programme:
Strongly disagree □
Disagree □
Agree □
Strongly agree □

2. I would enjoy being with my family or close friends:
Strongly disagree □
Disagree □
Agree □
Strongly agree □

3. I would find pleasure in my hobbies or pastimes:
Strongly disagree □
Disagree □
Agree □
Strongly agree □

4. I would enjoy be able to enjoy my favourite meal:
Strongly disagree □
Disagree □
Agree □
Strongly agree □

5. I would enjoy a warm bath or refreshing shower:
Strongly disagree □
Disagree □
Agree □
Strongly agree □

6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread:
Strongly disagree □
Disagree □
Agree □
Strongly agree □

7. I would enjoy seeing other people's smiling faces:
Strongly disagree □
Disagree □

Agree ☐
Strongly agree ☐

8. I would enjoy looking smart when I have made an effort with my appearance:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

9. I would enjoy reading a book, magazine or newspaper:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

10. I would enjoy a cup of tea or coffee or my favourite drink:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

11. I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

12. I would be able to enjoy a beautiful landscape or view:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

13. I would get pleasure from helping others:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

14. I would feel pleasure when I receive praise from other people:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

Thank you for your time and participation

Appendix 6

Stem completion task

Word list 1

disarm, blond, peruse, basin, gravity, frock, behold, patron, truncheon, harness, infect, scandal, tractor, penguin, drama, reputation, champ, math, solemn, trout.

Word list 2

shark, destiny, magnet, growl, garage, plank, rough, salmon, assess, breeze, quail, decade, barley valid, colt, invent, porous, supper, musket, resort.

East London and The City **HEALTH AUTHORITY**

Appendix 7

Mr M Richardson
Sub-Department of Clinical Health Psychology
University College London
Gower Street
London WC1E 6BT

Our Ref: ED/SG/N00031

11th July 2000

Dear Mr Richardson

Re: N/00/031 - Investigating the influence of smoking on 'willed action' and cognitive function in individuals with brain injury

Thank you for your letter of 2nd July 2000 addressing the points of the Committee's earlier letter. I am happy to tell you that I am now able to approve this study on Chairman's action to be noted at future meeting of the Committee.

Please note the following conditions to the approval:

1. The Committee's approval is for the length of time specified in your application. If you expect your project to take longer to complete (i.e. collection of data), a letter from the principal investigator to the Chairman will be required to further extend the research. This will help the Committee to maintain comprehensive records.

2. Any changes to the protocol must be notified to the Committee. Such changes may not be implemented without the Committee or Chairman's approval.

3. The Committee should be notified immediately of any serious adverse events or if the study is terminated prematurely.

4. You are responsible for consulting with colleagues and/or other groups who may be involved or affected by the research, such as extra work for laboratories.

5. You must ensure that, where appropriate, nursing and other staff are made aware that research in progress on patients with whom they are concerned has been approved by the Committee.

6. The Committee should be sent one copy of any publication arising from your study, or a summary if there is to be no publication.

I should be grateful if you would inform all concerned with the study of the above decision.

Your application has been approved on the understanding that you comply with Good Clinical Practice and that all raw data is retained and available for inspection for 15 years.

Please quote the above study number in any future related correspondence.

Yours sincerely

S. Swash

PROFESSOR M SWASH MD FRCP FRCPath
Chairman
ELCHA Research Ethics Committee

East London and The City NHS
Health Authority

Appendix 8

Aneurin Bevan House, 81 Commercial Road, London E1 1RD
Telephone Number: 020 7 655 6622
Fax Number: 020 7 655 6621
Email Address: Sandra.Burke@elcha.nhs.uk

Mr M Richardson
3 Watermint Quay
London N16 6DN

Our Ref: SB/N00031

22nd February 2001

Dear Mr Richardson

Re: N/00/031 - Investigating the influence of smoking on 'willed action' and cognitive function in individuals with brain injury

Further to your recent letter I am happy to confirm that the following request has been approved under Chair's Action on behalf of the Sub-Committee.

- Additional subjects to be recruited from East London Headway House, Alfred Health Centre, 186 Homerton High Street, London E9 6AG.

In order to keep an accurate record of this study a copy of the centre manager's letter agreeing to clients being approached and access to the site is requested.

Please note the conditions as stated in the Sub-Committee's letter of 11th July 2000 apply.

Yours sincerely

SANDRA BURKE
Acting Chairman
ELCHA Research Ethics Sub-Committee

EAST SURREY LOCAL RESEARCH ETHICS COMMITTEE

Santhams,
West Park Hospital,
Horton Lane,
Epsom, Surrey,
KT19 8PB.

Appendix 9

SH/AJR
Date: 21st August 2000.

To: Matt Richardson,
Clinical Psychologist in Training,
University College London,
Gower Street,
London, WC1E 6BT.

Dear Mr Richardson,

RE: INVESTIGATING THE INFLUENCE OF SMOKING ON 'WILLED ACTION' & COGNITIVE FUNCTION IN INDIVIDUALS WITH BRAIN INJURY
REF: 06MRWA(254) - to be quoted on all future correspondence please

Thank you for your recent letter (undated) in response to our letter of concerns dated 24th July 2000, which has now been reviewed and I confirm that Chairman's Approval has been given to go ahead with this trial.

In future, the Committee would like to follow up all new trials. Therefore, we would be grateful if you could send us an update after a period of a year from the commencement of the study with the following details:-

1. Is the research still continuing?
2. If it is, which stage has it reached:-
2.1. Data being collected
2.2. Data being analysed
2.3. Research being written up
2.4. Research published.

N.B. If you are sending any Protocol Amendments to us, please ensure that you highlight the areas of change.

Thank you for your trouble.

Yours sincerely,

Selina Harris,
Manager - ESLREC

c.c. JT
c.c. MO

Appendix 10

The participants gave the following responses to the question "What are your personal reasons for smoking?"

Participant no.	Verbatim response
1	"a habit, nothing special, it's relaxing sometimes"
2	"always enjoyed it, more than it being a habit, never wanted to give up"
3	"I enjoy smoking after a meal; it's not sociable but I like it; it relaxes me, especially if you feel a bit anxious; I concentrate better"
4	"because I get bored, especially now I get bored quicker. I smoked before my accident, but I smoked less. I started when I was younger"
5	"it calms my temper, it relaxes me"
6	"it's a habit I've got, I need it otherwise I've got nothing to do, I'd get so bored. I smoke when I socialise"
7	"don't know really, I just like it"
8	"out of boredom. Nicotine gives me something, a small buzz"
9	"calming effect, feeling of relaxation"
10	"calms me down, takes the edge off agitation"
11	"out of boredom, also because everyone else does, I want to join in"
12	"no reason not to, boredom, and the first drag gives a moment of serenity"
13	"stupidity, it kills you, I don't really know"
14	"I smoke to think, to increase pleasure of another chemical like caffeine or chocolate. It goes with food. To cope with stress, and to impress, but that's a generational thing"
15	"coz I like it"
16	"it's a habit, I started when I was young, I used to smoke cannabis. I feel like I need one"
17	"it's a bad habit, I used to enjoy it after a meal, but not any more"
18	"boredom, it's become a habit. All my friends smoked when I was 17 / 18"

Appendix 11 - Participant information sheet

'Investigating the influence of smoking on 'willed action' and cognitive function in individuals with brain injury'.

Regional Neurological Rehabilitation Unit, Homerton Hospital
Invitation to Participate in a Research Project

We invite you to take part in a research study which we think may be important. The information which follows tells you about it. It is important that you understand it. It says what will happen if you take part and what the risks might be. Try to make sure you know what will happen to you if you decide to take part. Whether or not you do take part is entirely your choice. Please ask any questions you want to about the research and we will try our best to answer them.

The research is trying to find out if smoking helps or hinders motivation and responsiveness in people with brain injury. You have been invited to take part in this study as you are in contact with the Outreach team. You have also been identified as a smoker.

If you agree to take part, you will be doing some straightforward tests for about 40 minutes, on two separate occasions. At one of these times, you will be asked to not smoke at least 2 hours beforehand. This can be arranged for early in the morning before your first cigarette of the day, if that is more convenient. You will be asked to breathe into a hand-held meter to check that you have not smoked in that 2 hours. In one of the tests, there will be a small financial reward available, up to about £3.00 over the two testing times.

Taking part in the study won't affect your treatment in any way, and there are no risks involved. The study will not help to make you any better, but will help us to understand some of the reasons people with brain injuries smoke.

Testing can take place at a place that is most convenient for you, e.g. at home, if you wish.

All records and results of the tests will be completely confidential, and will not be kept in your medical files.

You don't have to join the study. You are free to decide not to take part or to drop out at any time. If you decide not to be in the study, or drop out, this will not affect your ordinary medical care.

If you are worried, you will always be able to contact the person below to discuss your concerns:

Jane Powell
Department of Psychology,
Goldsmiths College,
Lewisham Way,
London SE14 6NW
0171 - 919 7199

What happens if something goes wrong?

We will take every care in the course of this trial. If through our negligence any harm to you results, you will be compensated. However, a claim may have to be pursued through legal action. Even if the harm is not our fault, the Trust will consider any claim sympathetically. If you are not happy with any proposed compensation you may have to pursue your claim through legal action.

Appendix 12

WRITTEN CONSENT FORM:
Title of research proposal: 'Investigating the influence of smoking on 'willed action' and cognitive function in individuals with brain injury'. REC Number:

Name of Patient/Volunteer (Block Capitals):
Address:

- The study organisers have invited me to take part in this research. ☐
- I understand what is in the letter about the research. I have a copy of the letter to keep. ☐
- I have had the chance to talk and ask questions about the study. ☐
- I know what my part will be in the study and I know how long it will take. ☐
- I have been told about any tests or questionnaires I might be given. ☐
- I know how the study may affect me. ☐
- I understand that I should not **actively** take part in more than 1 research study at a time. ☐
- I know that the local East London and The City Health Authority Research Ethics Committee has seen and agreed to this study. ☐
- I understand that personal information is strictly confidential: I know the only people who may see information about my part in the study are the research team. ☐
- I freely consent to be a subject in the study. No-one has put pressure on me. ☐
- I know that I can stop taking part in the study at any time. ☐
- I know if I do not take part I will still be able to have my normal treatment. ☐
- I know that if there are any problems, I can contact:

  Dr. Jane Powell on
  0171 - 919 7199

Patient's/Volunteer's: Signature .....

Witness's Name .....

Witness's Signature: .....

Date .....

As the Investigator responsible for this research or a designated deputy, I confirm that I have explained to the patient/volunteer named above the nature and purpose of the research to be undertaken.

Clinician's Name: .....
Clinician's Signature: ..... Date: .....