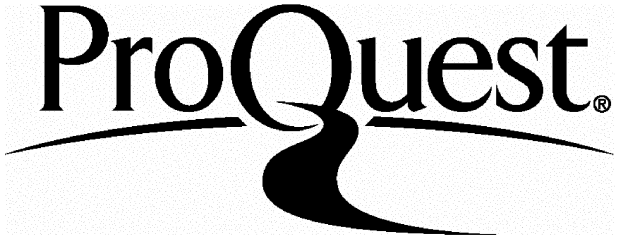
Neuropsychological Aspects of Apathy in Parkinson's Disease

Graham Christopher Pluck

Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

The Institute of Neurology

University College London



Abstract

Patients with Parkinson's disease (PD) are often described as failing to show a normal range of goal directed behaviours. Among explanations that have been proposed for this apathy are effects of personality, depression and disability. This thesis investigated the phenomena from a neuropsychological perspective. It was found that PD patients are significantly more apathetic than equally disabled osteoarthritis patients, indicating that their apathy is a primary symptom of the disease. No evidence was found relating apathy in PD to personality, depression, anxiety or anhedonia. It was found that the PD patients with high levels of apathy were impaired on cognitive tests, but only those that required executive control. Using visual-search tasks it was shown that this association could not be accounted for by a reduction in effort applied. It was also shown that attention to novelty or curiosity arousing stimuli were not reduced in PD patients with apathy. However, it was shown that they persevered on task for longer than patients with low apathy in conditions in which there was no prompt to stop. This may be due to a willed action deficit that retards actions in situations that lack formal guidance. To test this hypothesis further, a task was developed to record response times for stimuli and will driven actions and was validated in a single case study of an akinetic patient. Although PD patients with high apathy appeared to show a willed action deficit, it was also found that other executive impairments might confound interpretation. It is concluded that apathy in PD may be an expression of executive impairment, but further research is needed to assess the relative contributions of cognitive and motivational dysfunction. There are significant implications to the findings, including the conceptualisation of apathy as a symptom and the potential for therapeutic interventions with apathetic patients.

Contents

List of Tables

CHAPTER 7

CHAPTER 8

List of Figures

CHAPTER 7

CHAPTER 8

Acknowledgements

I would like to thank Dr Richard Brown for his support and guidance over the last few years. I can not imagine a more appropriate person to have supervised my doctoral training. His patience, imagination and awesome knowledge of neuroscience made the work, though difficult at times, always enjoyable. If I were mad enough to attempt another PhD, I would again choose Richard to supervise it. I would also like to thank Professor Niall Quinn for allowing me to attend teaching clinics and for suggesting appropriate patients under his care. I learnt much about both the science and human aspects of disease from Niall.

A special mention must also be made of the numerous subjects who donated their time to this research, particularly the patients. Invaluable help in preparation of this thesis was provided by my wife Helen, by Sandy, Duncan, Jody, Mandy and Big Al by their excellent proof-reading skills.

I would like to dedicate this thesis to the memory of my father Chris, and my sister Joanne.

The Extent of My Personal Contribution

In accordance with the requirements of the University of London, the extent of my personal contribution to the work in this thesis is specified as follows:

During the time that this research was conducted, I was funded by a MRC studentship at the MRC Human Movement and Balance Unit. My primary supervisor was Dr Richard Brown and my secondary supervisor was Professor John Rothwell. I made major contributions to the design of the studies reported in this thesis, all computer programming, data collection and analysis was performed by myself.

This thesis is entirely my own original work and no other person should be held accountable for its contents.

Graham Christopher Pluck

Chapter 1: Parkinson's Disease

Basic Features of Parkinson's Disease

Clinical Features

Parkinson's disease (PD) is a progressive neurodegenerative disorder, primarily affecting aspects of movement. James Parkinson first described the disease in 1817 after he observed sufferers on the streets of London (Parkinson, 1817). Despite the fact that three of the six cases reported were never formally examined, as they were people he met in public, his descriptions of the main symptoms could hardly be faulted today. In his essay, Parkinson emphasised tremor, stooping posture, balance problems and weakness.

First signs of the disease are most common in people aged over 50, with prevalence increasing exponentially above this age. Although incidence varies slightly between races, overall about one in 1000 of the population are affected (Marsden, 1994a). The disease progresses slowly, but with the aid of modern medicine life expectancy is not significantly reduced. However, in the later stages of this disease moderate to severe disability is inevitable.

Symptoms in PD typically have a unilateral onset, affecting only one side of the body. With disease progression, both sides invariably begin to show symptoms (Gelb, Oliver, & Gilman, 1999). The main motor symptoms of PD are tremor, rigidity and akinesia. For a diagnosis of PD, patients must show two or more of these symptoms as well as evidence of postural abnormality.

Tremor is often the most visible symptom of PD, occurring in at least 70% of cases (Marsden, 1994a). The magnitude of the tremor can vary from a minor problem in the early stages of the disease to a major disability that prevents the sufferer from even being able to feed themselves in advanced stages. A resting tremor typically occurs first in one hand and involves opposite movements of the thumb and the other digits (pill-rolling tremor). With disease progression, this becomes bilateral. In addition, over time the rest tremor in PD advances to include postural and action tremors (Deuschl & Krack, 1998).

Rigidity is defined as "*increased resistance to stretch and the inability to achieve complete muscle relaxation*" (Wichmann & DeLong, 1993 p 58). Extensor and flexor muscles are equally affected and rigidity is not confined to distal, proximal or axial muscles, though it is unclear whether some muscles are more affected than others (Delwaide & Gonce, 1998). A notable feature of rigidity in PD is the phenomena of cog wheeling, an oscillatory loss of rigidity under passive movement at a rate of 5-8 Hz. However, cog wheeling is by no means confined to PD as even essential tremor patients may show this (Gelb et al., 1999).

Akinesia is a general poverty of movement evidenced by slowness in the initiation and execution and a reduction in the amplitude of movements. It is considered to be the most direct clinical feature of the nigrostriatal dopamine depletion (discussed below). Estimates of the occurrence of akinesia as a symptom in PD vary between 77% and 98% depending on its definition (Gelb et al., 1999). One of the earliest signs is reduced size of writing (micrographia, Oliveira, Gurd, Nixon, Marshall, & Passingham, 1997) and this may often precede a formal diagnosis of PD. Another example that is often used to diagnose PD is loss of arm swing whilst walking. Perhaps the most striking

example of akinesia is in locomotion. Patients, particularly in late stages of their disease, may find that their feet feel 'frozen' to the ground. This is often more likely to occur in confined spaces such as passing through a doorway, paradoxically walking up and down stairs may be relatively well preserved (Nutt, 1998).

Akinesia also refers to slowness in the actual initiation and execution of movements (Aziz, Davies, Stein, & France, 1998). Single movements are often performed after a longer delay than normal and when sequential movements are involved individual parts are performed less accurately than when performed alone (Weiss, Stelmach, & Hefter, 1997).

As a symptom of PD, akinesia is of particular interest, as it appears to involve cognitive components. Micrographia is a good example of this. Olivera et al. (1995) have shown that providing visual cues improved writing style and they suggest that this was due to forcing an attentional element and preventing automaticity in the task. Focusing attention is also thought to override 'freezing'. By performing a novel act, such as stepping over the base of a cane or deliberately kicking the cane, patients can resume locomotion. However the task must have some deliberate intentional aspect, with routine use the strategies can lose their novelty and fail (Nutt, 1998). It appears that by switching to a more deliberate, cognitive mode of execution, akinesia can often be reduced. This phenomenon has been called 'paradoxical gait' (Hanakawa, Fukuyama, Katsumi, Honda, & Shibasaki, 1999).

Apart from the facilitation effects of attention, some aspects of akinesia can also be viewed as a cognitive adaptation to a motor impairment. It has been shown that PD patients typically undershoot when making simple ballistic movements. However when

the distance to be moved is reduced, the patients still undershoot (Beradellia, Dick, Rothwell, Day, & Marsden, 1986). This indicates that it is not motor weakness that causes the hypometric reaching. Brown and Jahanshahai (1996) have suggested that this may be due to the motor system adapting to its own reduced accuracy. By making hypometric movements, later adjustments can be made to complete the movement, but hypermetric movements would be more problematic as the target would strike the hand. They therefore consider akinesia not as a pure motor deficit, but as an action deficit, that includes cognitive and motor elements.

The final feature of akinesia is an actual loss of spontaneous actions. Patients often show a mask-like face, verbalise less and generally make fewer intentional movements. This was described above as a general poverty of movement. Experimentally this aspect of akinesia has been neglected, possibly due to the difficulties involved in measuring movements that have no manipulable cues. However, these problems are not insurmountable and recent methods such as PET imaging have allowed the development of paradigms in which spontaneous actions can be examined (Ingvar, 1994). Brown and Jahanshahai (1996) discussing akinesia in PD concluded that *"The way is open to ask fundamental questions about action in man, its control and neuronal substrate, and to expand the enquiry to address issues of emotion and motivation"* (p 30).

Pathophysiology

The most striking alteration visible in the brains of PD patients is the loss of cells in the substantia nigra. This small brain stem nucleus is named as such due to the cells within it that contain the pigment melanin, which causes the tissue to appear dark brown or black in colour. It has been observed that in the brains of PD patients most of these cells are absent (Tretiakoff, 1919).

Physiologically, the importance of the substantia nigra is in its dopaminergic projections to the striatum (caudate and putamen). This nigrostriatal projection is one of the three main dopamine systems in the brain (Nolte, 1988). In PD patients dopamine levels in this area are approximately only 10% of the normal level (Ehringer & Hornykiewicz, 1998, originally published in German in 1960). Without dopaminergic innervation, the striatum itself can not function normally. The substantia nigra and striatum are involved with multiple cortical-subcortical loops (Alexander, DeLong, & Strick, 1986) and so physiological processes are disturbed even at sites distant from the primary cell loss.

At post-mortem the substantia nigra of PD patients is shown to have substantial cell loss. It is often claimed that around 70% of nigral cells have to be lost before symptoms appear, however recent evidence does not support this. An ^{18}F dopa scan of 32 PD patients estimated that the reduction of putimal dopamine at symptom onset was around only 25% (Morrish, Rakshi, Bailey, Sawle, & Brooks, 1998). As putimal dopamine is dependent on nigral input, the level of cell loss in the substantia nigra itself that is required to produce symptoms of PD may be less than originally thought.

The substantia nigra also shows other changes, apart from gross cell loss many of the surviving cells display Lewy bodies and Lewy neurites. Such cells eventually die for reasons that are still unclear (Braak et al., 1995). Aside from the substantia nigra, the other main dopaminergic system originates in the ventral tegmental area (VTA). Dopaminergic cells project via the medial forebrain bundle to multiple cortical areas (the mesocortical system) and limbic areas including the nucleus accumbens (mesolimbic system) (Nolte, 1988). Furthermore, Lewy bodies and Lewy neurites are present in several other PD brain areas that are not closely associated with dopamine. For example the locus coeruleus (noradrenergic) and oral raphe nuclei (serotonergic) are

known to be affected (Braak et al., 1995). These changes therefore lead to a widespread decrease in brain monoamines in subcortical and cortical regions.

Causes

Despite extensive research, the cause of PD is still unknown, though multiple risk factors have been identified. Interpretations are hindered by difficulties in achieving correct differential diagnoses of PD and similar parkinsonian syndromes such as progressive supranuclear palsy, Lewy body dementia and multiple systems atrophy (Litvan et al., 1997). It is likely that the majority of investigations into risk factors for PD have included patients who have other disorders. Autopsy studies of supposedly PD patients fail to confirm the diagnosis in as many as 25% of the cases.

Despite this, some progress has been made. There is increasing support for the role of genetic factors. Both family studies and studies of twin pair concordances have indicated increased risk of development of PD if another family member is a sufferer (Wood, 1997). However, in many cases of PD a genetic link can not be established.

Exposure to toxins is also a possible factor (Schapira, 1997). On the pacific island of Guam a parkinsonism dementia complex and amytrophic sclerosis are far more common than would be expected. No familial link or contagion has been identified but a neurotoxin has been found in cycad seeds, a main food source (Kurland, 1988). This neurotoxin, BMAA, produces parkinsonian features when administered to cynomolgus monkeys and is the likely cause of most cases of parkinsonism dementia complex and amytrophic sclerosis on the island. BMAA is highly unlikely to be the cause of idiopathic PD but it does illuminate the fact that environmental chemicals are capable of producing parkinsonism.

Another important discovery occurred when MPTP, a pro-toxin of MPP+, was accidentally injected by a group of heroin addicts in California in the early 1980's, resulting in a condition almost identical to PD (Langston, Ballard, Tetrud, & Irwin, 1983). Although this is not the cause of the idiopathic form of the disease, it is feasible that an MPP+ like chemical in the environment could be. In fact, several such chemicals are known. One example is paraquat, a widely used herbicide that is structurally similar to MPTP. In cases of poisoning in humans, it has been shown to produce parkinsonian signs such as tremor. Additionally, at autopsy damage to the substantia nigra, a site also damaged in PD, is prominent (Grcevic, Jadron-Santel, & Jukic, 1977). Despite these associations, there is no direct evidence that MPP+ like chemicals are the cause of PD.

The possibility of a contagious agent has also been considered. This theory became particularly popular following the encephalitis lethargic epidemic that began in Austria and France in 1917 and soon spread across the world. Many people who were infected initially recovered but developed parkinsonism over the next ten years (Cheyette & Cummings, 1995). More recent support for the theory of infectious transmission has come from observations that activated microglia are seen post-mortem in the brains of PD patients. This implies that an immune response was active, though suspicious viral particles have not yet been detected (Schapira, 1997). In addition, the lack of significant geographical clusters of cases and lack of temporal variation in incidence makes a viral infection seem unlikely.

Treatment

There is no known cure for PD and so most treatments are aimed at reducing or controlling the symptoms (Marsden, 1994a). The most widely used treatment involves pharmacological attempts to counter the loss of dopamine. This can be done in a

number of ways. Dopamine can not cross the blood-brain barrier and so dopamine agonists are often taken, which can reduce motor symptoms in many patients (Lieberman, Ranhosky, & Korts, 1997). An alternative strategy is to take L-dopa, the precursor chemical of dopamine that can then increase dopamine levels indirectly (Birkmayer & Hornykiewicz, 1998, originally published in German in 1961). L-dopa is taken orally and so has a systemic effect, a consequence of this is that much of the dose is broken down peripherally. In order to prevent this and leave more L-dopa to circulate into neural tissue, a drug that blocks the action of DDC, an enzyme that breaks down L-dopa, may also be taken. As this also can not cross the blood-brain barrier, it prevents loss of L-dopa by DDC in the liver and gut, allowing a greater proportion to enter the neural tissue. The most common preparation combining these two chemicals is marketed as Sinemet. L-dopa usually produces better results than agonists but can result in complications with disease progression (Shannon, Bennett, & Friedman, 1997).

Recently two new drugs, Tolcapone and Entacopone, have become available that can prolong the action of L-dopa by blocking the action of COMT, another enzyme involved in the metabolism of L-dopa (Schwarz & Storch, 1999). By prolonging the action of L-dopa, on-off phenomena (sudden changes in mobility) are reduced. Furthermore, they reduce plasma levels of the L-dopa metabolite 3-OMD which competes with L-dopa for transport across the blood brain barrier. The shift in metabolism towards COMT by the use of DDC inhibitors may therefore reduce the clinical efficacy of L-dopa. COMT inhibitors can therefore potentially increase the half life and bioavailability of L-dopa (Oechsner, Buhmann, Strauss, & Stuerenburg, 1999). However, concerns over liver damage have lead to one of these drugs, Tolcapone, being withdrawn from use in the U.K.

Neuroprotection may be possible. The anti-depressant drug Selegeline has been shown to block MPTP toxicity in primates and has been associated with slower disease progression in PD patients (Tetrud & Langston, 1989). However, it has since been suggested that Selegeline itself has a mild antiparkinsonian effect, so it is unclear whether this offers neuroprotection or simply treatment (Marsden, 1994a). Dopamine agonists may offer the best option for neuroprotection in PD. Paradoxically dopamine is toxic to dopamine cells (Schwarz & Storch, 1999) and so the use of agonists rather than L-dopa may slow disease progression.

Surgical treatment for PD is available, but is usually only used in advanced stages of the disease when pharmacotherapy is insufficient or producing excessive side effects. Surgical lesions for the treatment of PD have been used intermittently since the 1930's but the first hint that this may be feasible was actually provided by Parkinson himself. He noted that one of his patients (case IV) improved bilaterally following hemiparesis and that this was probably caused by a stroke (Parkinson, 1817). However, medical attention was focused on the controlled ablation of basal ganglia nuclei when a surgical accident in 1952 involved the rupturing of the anterior choridal artery. This damaged the globus pallidus but produced a reduction in tremor and rigidity in the PD patient involved (Redfern, 1989). Pallidotomy is now a relatively common procedure that improves motor performance in PD (Samuel et al., 1997).

However, the recent increased usage of surgical therapy has been made possible due to enhanced understanding of the anatomy of the basal ganglia and of the pathophysiology of PD. For example it is now also known that lesions of the thalamus (Marsden & Obeso, 1994b), and subthalamic nucleus (Bergman, Wichmann, & DeLong, 1990) can also be of use. A current advance has been the use of high frequency stimulation in

place of ablations. This involves the permanent surgical insertion of a probe, the tip of which terminates in the target nuclei. The application of high frequency electrical stimulation produces a functional lesion that can be reversed if necessary, unlike a conventional ablation. This has fewer risks and can improve motor performance in PD (Deiber et al., 1993).

A more controversial surgical approach has been the implantation of dopamine secreting cells directly into the brain. Studies in MPTP treated primates have shown that implantation of foetal tissue reduces parkinsonian signs (Ridley & Baker, 1991). Attempts to extend this approach to humans with PD are controversial as the tissue is extracted from aborted human foetuses. Despite this, the method has been used with some success (Lindvall et al., 1990). One problem is the difficulty with poor survival rates of grafted tissue but this may be reduced by the use of neurotrophic factors to minimise the chance of the cells dying following implantation (Lindvall & Odin, 1994). In order to reduce both ethical objections and risks from the extensive use of imunosuppresents, it may be possible to genetically alter cells from the patient's own body so that they produce dopamine and use these for the intracerebral implant (Gage, Kawaja, & Fisher, 1991).

Anatomy and Connections of the Basal Ganglia

Although the most critical anatomical feature of PD is loss of dopaminergic cells in the substantia nigra, this affects the function of multiple subcortical nuclei that are heavily interconnected. These nuclei, the basal ganglia, themselves form loops with several cortical areas, in particular the frontal cortex (Alexander et al., 1986). The term basal ganglia was originally used to describe all of the subcortical grey matter within the cerebrum, including the amygdala and thalamus (Nolte, 1988). However, modern

terminology tends to limit this to include only the caudate, putamen, subthalamic nucleus and substantia nigra. The nucleus accumbens is also sometimes included as part of the basal ganglia (Heimer et al., 1997), others consider it a part of the limbic system (Mega, Cummings, Salloway, & Malloy, 1997).

Despite the differences in terminology, the interconnections of these nuclei and their connections with the cerebral cortex are relatively well documented. These interconnections are vital to a neurobiological understanding of the deficits seen in PD. Early theories of the organisation of the basal ganglia gave them a role in the communication of information from widespread cortical areas via the thalamus to the motor cortex. Thus they were thought to 'funnel' diffuse information such that it could be used in guiding movements (e.g. see Passingham, 1993). Recently 'loop' theories that emphasise a processing role for subcortical structures have become more popular.

Alexander et al. (1986) suggested a partially funnelling architecture in which particular areas of the frontal cortex loop through certain subcortical nuclei and back to the original area of output. The five proposed loops have gross similarities in that each project to the same four main sites (cortex, striatum, pallidum/substantia nigra and thalamus), but each loop involves different sub-regions of these main sites. Other cortical areas also contribute to these loops as open afferents but are not efferently involved. Alexander et al. proposed a list of five such loops, motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate. These loops are displayed schematically in Figure 1.

The loop specified in the greatest detail by Alexander et al. (1986), is the frontal-subcortical motor loop. The entry from the cortex is via the supplementary motor

cortex (SMA) and somatosensory cortex. The area of the striatum innervated is the putamen. The mappings of the two cortical areas are preserved (e.g. motor cortex 'leg' and somatosensory 'leg' cortex both project to the same part of the putamen). Further innervation comes from the premotor cortex and area 5 (medial parietal). From here projections go to the ventrolateral globus pallidus interna (vl-GPi) and caudolateral substantia nigra pars reticulata (cl-SNr) and these in turn project to the ventralis lateralis pars oralis (VLo) and ventralis lateralist pars medialis (VLm) of the thalamus. The loop is closed by projections from these thalamic regions back to the SMA.

Alexander et al. (1986) suggests that the second motor loop deals primarily with eye movements. The corticosubcortical projections are from the frontal eye field (area 8), dorsolateral prefrontal cortex (DLC) and posterior parietal cortex (PPC). Each of these areas has been shown in single cell recordings studies to be sensitive to eye movements. The first destination is not the putamen, as in the motor circuit, but the body of the caudate nucleus. From here projections descend to the caudal dorsomedial globus pallidus interna (cdm-GPi) and the ventrolateral substantia nigra pars reticulata (vl-SNr). From here projections are sent to the lateral ventralis anterior pars magnocellularis (l-VAmc) and medialis dorsalis pars parvocellularis (MDpl) of the thalamus. The loop is closed by projections from these thalamic regions back to the frontal eye field.

However, the designation of this route as the oculomotor loop is complicated by a recent review of blood flow studies during eye movements in humans that suggest that Brodman's area 6 not 8, should be considered the human frontal eye field (Paus, 1996). Indeed, the concept of this loop has changed since it was first proposed by Alexander et al. (1986). Some authors prefer to envisage this loop as a 'visual' loop, rather than a

'motor' loop (Lawrence, Sahakian, & Robbins, 1998). In support of this, Lawrence et al. point out that patients with Huntington's disease perform poorly on visual discrimination learning and they attribute this to damage to their visual loop which is equivalent to Alexander et al.'s oculomotor loop. If correct, this would imply that this loop has a more executive function than originally proposed.

Whereas the motor and oculomotor loops were initially suggested as being primarily involved with movement, the other loops are thought to be more involved with cognitive, emotional and motivational processing (Mega & Cummings, 1994). Cognitive processing is particularly thought to involve the DLC loop through the basal ganglia. The cortical areas involved are the DLC, PPC and arcuate premotor area. The subcortical projection is to the dorsolateral aspect of the head of the caudate nucleus. From here projections descend to the lateral dorsomedial globus pallidus interna (ldm-GPi) and the rostromedial substantia nigra pars reticulata (rm-SNr). These feed into the ventralis anterior pars parvocellularis (VApc) and medialis dorsalis pars parvocellularis (MDpc) of the thalamus, which close the loop by projecting back to the DLC.

Impairment of the DLC loop is thought to compromise executive functions. This is characterised by memory problems, reduced verbal fluency, difficulty shifting set, poor abstraction skills and difficulties with response inhibition (Cummings, 1995).

A further 'cognitive' loop originates in the lateral orbitofrontal cortex. Although this loop is poorly defined functionally, Alexander et al. (1986) suggests that impairments of the loop, by lesions either of the orbitofrontal cortex or the particular area of the caudate it innervates, produce perseveration. It may therefore be linked with behavioural regulation in terms of the switching of behavioural set. However Cummings (1995),

hypothesised that impairment of this loop would produce disinhibited, tactless and impulsive behaviour, stressing personality more than cognition as a primary function.

The orbitofrontal loop is particularly involved with the association cortex. Hence the cortical involvement comes from the lateral orbitofrontal cortex (LOF), the superior temporal gyrus (STG) and the inferior temporal gyri and anterior cingulate area (ACA). The cortex projects to the ventromedial head of the caudate (vm-Cau (h)), which projects to the medial dorsomedial globus pallidus interna (mdm-GPi) and to the rostromedial substantia nigra pars reticularta (rm-SNr). These innervate the medial aspects of the ventralis anterior pars magnocellularis and medialis dorsalis pars magnocellularis (MDpm) of the thalamus which closes the loop by projection back to the LOF.

The final loop proposed by Alexander et al. (1986) involves some areas that have been described as being part the limbic system. Indeed some authors prefer to call this 'the limbic circuit', (Darvesh & Freedman, 1996). Alexander et al. realise that this is the least well specified loop in terms of its behavioural associations and decline to comment on its function, preferring to name it the anterior cingulate loop, a purely anatomical title. This loop is unusual in that the cortical projections arrive in the ventral striatum, all the other loops enter subcortically via the caudate or putamen. The ventral striatum consists of two main structures, the nucleus accumbens and the olfactory tubercle. The cortical input to this area is widespread including the hippocampal cortex (HC), entorhinal cortex (EC) superior and inferior temporal gyri. The ventral striatum communicates with the rostrodorsal substantia nigra pars reticulata (rd-SNr) and both the rostrolateral globus pallidus interna (rl-GPi) and the ventral pallidum (VP). These

then project to the whole of the posteromedial aspect of the medialis dorsalis of the thalamus. The circuit is closed by thalamic feedback from this region to the ACA.

The role of the anterior cingulate circuit is unclear. However, the two brain areas that clearly distinguish the loop from the others described by Alexander et al. (1986), the anterior cingulate cortex and the ventral striatum have both been implicated in motivational functions. The anterior cingulate if damaged in man can lead to "*akinetic mutism, diminished self awareness and depression, motor neglect and impaired motor initiation, reduced responses to pain and aberrant social behaviour*" (Devinsky, Morrell, & Vogt, 1995 p 118). Clearly, many of these deficits can be interpreted as related to motivation. Similarly the nucleus accumbens, a major part of the ventral striatum, is implicated in behavioural responses to novelty both in pharmacological studies in animal (Hooks & Kalivas, 1995) and in imaging studies in man (Berns, Cohen, & Mintun, 1997). Mega and Cummings (1994) have expressly labelled this as dealing with motivation, pointing out that anterior cingulate lesions produce akinetic mutism (discussed in Chapter 2); they further point to descriptions of apathy in PD as support.

Although it seems likely then that the anterior cingulate loop contributes in some way to motivation, it would be too simplistic to describe the anterior cingulate loop as the actual neurological substrate of motivation. All of the other loops are probably involved in certain aspects of motivated behaviour, for example the DLC loop, which is assumed to be involved in executive function, could be envisaged as having a pivotal role as could the motor loop, damage to which is often thought to produce akinesia.

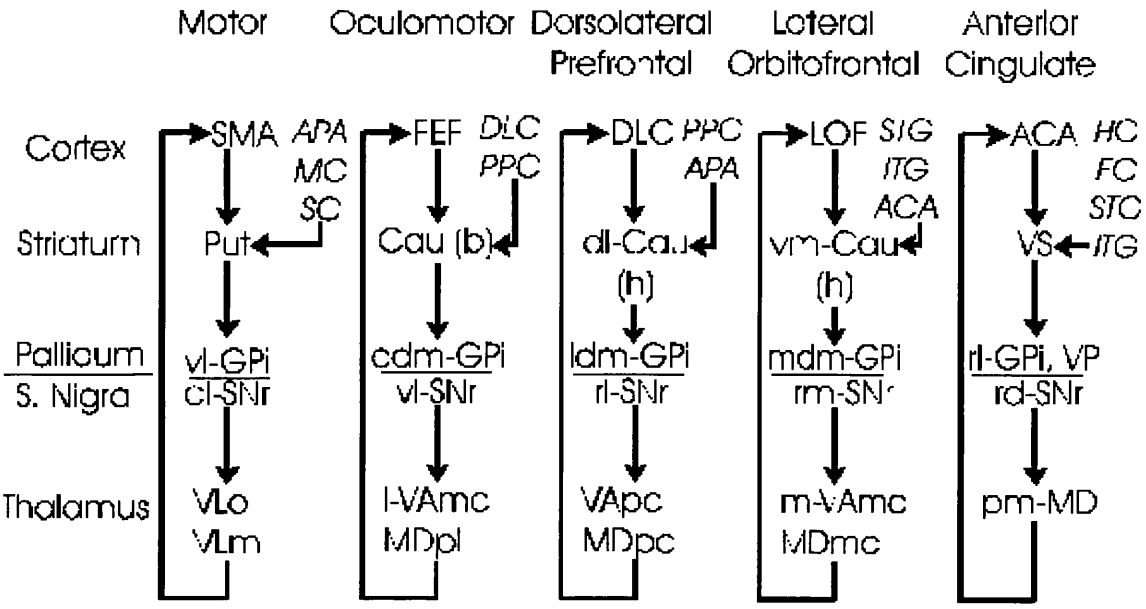


Figure 1: The five proposed cortical-basal ganglia-thalamic-cortical loops from Alexander et al. (1986).

Abbreviations are as follows: ACA: anterior cingulate; APA: arcuate premotor area; Cau: caudate, (b) body, (h) head; DLC: dorsolateral prefrontal cortex; EC: entorhinal cortex; FEF: frontal eye field; GPi: internal segment of the globus pallidus; HC: hippocampal cortex; ITG: inferior temporal gyrus; LOF: lateral orbitofrontal cortex; MC: motor cortex; MDpl: medialis dorsalis pars paralamellaris of the thalamus; MDmc: medialis dorsalis pars magnocellularis of the thalamus; MDpc: medialis dorsalis pars parvocellularis: of the thalamus; PPC: posterior parietal cortex; PUT: putamen; SC: somatosensory cortex; SMA: supplementary motor area; SNr: substantia nigra pars reticulata; STG: superior temporal gyrus; VAmc: ventralis anterior pars magnocellularis of the thalamus; VApc: ventralis anterior pars parvocellularis of the thalamus; VLm: ventralis lateralist pars medialis of the thalamus; VLo: ventralis lateralis pars oralis of the thalamus; VP: ventral pallidum; VS: ventral striatum; cl-:caudolateral; cdm-:caudal dorsomedial; dl-:dorsolateral; l-:lateral; ldm-: lateral dorsomdedial; m-:medial; mdm-:medial dorsomedial; pm-: posteromedial; rd-:rostrodorsal; rl-:rostrolateral; rm-rostromedialv; m-:ventromedial; vl-:ventrolateral. Open loop cortical inputs are shown in Italics.

The loops from the frontal cortex through subcortical regions and back, detailed above, can be seen as 'direct' routes. However, indirect routes involving the same loops have also been identified (Cummings, 1995). In each case projections arising from the striatum also project to the globus pallidus externa and then onto the subthalamic

nucleus. The subthalamic nucleus then projects to the globus pallidus interna and substantia nigra that project to the mediarlis dorsarlis of the thalamus. The indirect loops are completed by projections from the mediarlis dorsarlis of the thalamus to the area of frontal cortex that originally innervated the loop. Thus, in addition to the five direct routes there are five indirect routes, which if impaired could alter processing in ways other than impairment of the direct routes.

Frontal-Subcortical Loops in Relation to Parkinson's Disease

The known pathology in PD is sufficient to cause disruption in all five of the loops described above and so mappings between structure and function based on performance of PD patients is difficult. However, it is known that of the striatum in PD patients, the putamen, rather than the caudate shows the greatest reduction of ^{18}F Dopa in PET studies (Brooks, 1997). This may be why during early PD, motor symptoms are observed but cognitive performance is in the normal range, as putimal dysfunction would selectively impair the motor loop.

Studies of the effects of dopaminergic medication can also be of use in PD. Greatest cognitive impairment in PD patients is found in some tasks when off medication and in others when on medication (Gotham, Brown, & Marsden, 1988). This may be due to disease progression related differences between the patients in the dopamine depletion in the caudate and DLC. As the drug dosage is dictated by the motor symptoms, which probably reflect putimal dopamine levels some may have over stimulation and some understimulation in the caudate and DLC (Brown & Marsden, 1990). If so, this further indicates that the loops involving the caudate are less impaired than the motor loop that involves the putamen. If this were not so, all loops involving the caudate would be impaired more when on medication than off, due to overstimulation.

The situation is further complicated by the anterior cingulate loop that enters the ventral striatum, rather than either the putamen or caudate. The nucleus accumbens is often considered to be the critical area in the ventral striatum and it is unclear how affected this area is by PD relative to the other areas. However, a major dopaminergic input to the accumbens comes via the mesolimbic projection from the ventral tegmental area (Wu, Hrycyshyn, & Brudzynski, 1996), an area known to suffer dopamine depletion in PD. Furthermore, the ventral tegmental area is also the source of the mesocortical dopamine system and so widespread hypoperfusion of cortical dopamine, particularly in the frontal lobes, occurs.

Non-Motor Aspects of Parkinson's Disease

Cognition

In his original definition of the disease James Parkinson included the phrase "*the senses and intellects being uninjured*" (Parkinson, 1817 p 1). However, it is now understood that a wide range of cognitive impairments can be seen in non-demented patients with PD (Brown & Marsden, 1990). Furthermore, dementia is thought to be a risk in PD, particularly in the later stages of the disease (Hobson & Meara, 1999). Several studies have been performed with very little agreement concerning estimates of prevalence in PD, depending partly on the assessments used and patient selection. One review pointed out that such estimates of dementia occurrence have varied between 10% and 45% of patients (Mayeux, 1987).

In an ageing population such as PD patients, a significant level of dementia would be expected anyway. However, it is thought that the cognitive problems in dementia associated with PD are different to those seen in the most common form of dementia,

Alzheimer's disease (Mahieux et al., 1995). This implies that a distinct dementia syndrome may be a symptom in PD. This proposal has been put forward most strongly by those who argue for a distinction between cortical and subcortical dementia. Cortical dementia is said to involve such neuropsychological syndromes as agnosia, aphasia and apraxia while subcortical dementia involves bradyphrenia (slowed thought), apathy, depression and memory impairments (Darvesh & Freedman, 1996). This dichotomy is often refuted by studies in which patient groups perform in ways counter to their diagnosis, for example apraxia can be seen in subcortical disease (Leiguarda et al., 1997) and apathy in cortical disease, (Ott, Notto, & Fogel, 1996).

However, much of the research has focused on cognitive deficits in patients who are seemingly not demented. Initial attempts at studying cognitive function in PD used a "*look and see*" (Brown & Marsden, 1990 p 21) approach in which tests were administered without any theoretical reason to suspect a deficit. However the cognitive aspects of PD are now better understood and theories that include the known pathology are being developed.

It is clear that non-demented PD patients show deficits in a range of cognitive neuropsychological tests. The most commonly reported neuropsychological profile in PD is the 'frontal-type' deficit. On a range of tests initially designed for use in patients with frontal lobe damage, PD patients also perform worse than normal controls (Taylor & Saint-Cyr, 1995). Such tests include; the spatial short term memory task, stockings of Cambridge task and attentional set shifting task of the CANTAB battery, (Robbins et al., 1994), the Wisconsin Card Sorting Test and verbal fluency test, (Gotham et al., 1988), and random letter generation, (Robertson, Hazlewood, & Rawson, 1996).

A particular skill that is needed to perform many executive tasks is 'working memory'. This has been described as the ability to "*hold briefly in your mind and manipulate the information... essential for comprehension, reasoning and planning*" (Wickelgren, 1997a p 580). Although this involves a range of skills, it is thought to be closely associated with the frontal lobes (Owen, Evans, & Petrides, 1996). On tests of working memory PD patients have been found to perform poorly on recall (Hugdahl, Asbornsen, & Wester, 1993) but normally on recognition tests (Ivory, Knight, Longmore, & CaradocDavies, 1999).

It has been suggested that this dissociation arises due to the reliance of recall on strategic operations that are not needed for recognition performance. PD patients show this pattern due to difficulties in strategy application (Stebbins, Gabrieli, Masciari, Monti, & Goetz, 1999). Support for this interpretation comes from findings that other forms of non-strategic memory performance such as eyeblink conditioning (Sommer, Grafman, Clark, & Hallett, 1999) and word completion priming (Ivory et al., 1999) are not impaired in PD. Furthermore, delayed recognition of semantically related verbal material, but not immediate recognition, involves strategic semantic reorganisation of the items and consequently facilitates performance. If PD patients have an impairment of strategy application then they should perform normally on immediate recognition but not delayed recognition. Research has confirmed this (Stebbins et al., 1999).

Executive task performance is thought to rely heavily on frontal lobe areas and so PD patients have been described as having a 'frontal-type' deficit. This description fits well with the anatomical theories given above that the subcortical areas involved in PD are elements of larger loops involving the frontal cortex. However, the frontal-type deficit is a wide term describing a range of skills and some tasks which are supposedly

'frontal' are performed normally by patients with PD, for this reason attempts have been made to offer a functional, rather than associative, description of the impairments seen in PD. Brown and Marsden (1990) have reviewed the evidence for the frontal-type deficit and suggest that performance is impaired only in tasks that require internal cues, on tasks where this reliance is removed, PD patients tend to perform normally. This theory can explain poor performance on set shifting tasks such as the Wisconsin Card Sorting Test in addition to the working memory impairments.

However, other researchers have proposed alternative functional explanations. One explanation is that cognitive problems are not due to reliance on attentional cues produced by reduced central resources but a specific attentional shifting impairment (Downes, Sahakian, Evenden, Morris, & Robbins, 1989). They found evidence that attentional shifts were selectively impaired when this involved learning a discrimination rule that was interdimensional but not when it was intradimensional. They suggested that the cognitive deficit in PD reflects an instability of response set that produces an enhanced tendency to ignore a previously irrelevant dimension.

It has further been shown using verbal fluency tasks that PD patients are selectively impaired on alternating between different domains compared to within domain alternations (Downes, Sharpe, Costall, Sagar, & Howe, 1993). Comparing the findings from this and their earlier study, Downes et al. suggest that a deficit in the growth and release of inhibitory processes that control attentional sets produces slow and inaccurate selection of responses when previously inhibited cognitive strategies are appropriate. However, in one condition patients were cued as to when to switch by being shown coloured cards. As this would have effectively prompted faster switching, the total number of words produced should have increased but it did not. Downes et al. proposed

a second impairment in terms of algorithm application to explain this finding. Although this theory explains the observed performance, the presumption of two combined deficits lacks parsimony. Conversely, the single deficit theory of Brown and Marsden (1990) can not explain why the 'switching' prompts failed to restore performance.

Despite the confusion concerning the role of strategic attentional processes, research has also focused on visuospatial performance in PD. Early studies used simple perceptual judgements and often failed to find support for impairment in patients with PD. More recently, methodologies for studying visual attention developed in normal experimental psychology have been applied to patients with PD. The two methodologies favoured have been the visual search technique, (Treisman & Gelade, 1980) and the orientation of attention technique, (Posner, 1980). Both have identified impairments in aspects of visual attention in PD.

Visual search involves participants being presented with an array of stimuli that they must scan as quickly as possible in order to decide whether a particular target stimulus is present. The main finding from such studies is that there are two main types of search, parallel and serial (Treisman, 1996). A parallel search can be performed if the target stimulus differs from the distractor stimuli by a single feature. The target is said to 'pop-out' of the display and increasing the number of distractors has very little effect on the time taken to detect it. Alternatively, if the target differs from the distractors by a conjunction of features, i.e. no single feature distinguishes it from all of the others, then pop-out does not occur and increasing the number of distractors has a detrimental linear effect on how fast the task can be completed.

It has been shown that in tasks where controls show parallel search patients with PD do not (Troscianko & Calvert, 1993). Conversely, the serial form of search has been shown to be normal in PD (Weinstein, Troscianko, & Calvert, 1997). This dissociation has been confirmed using a signal detection variation that avoided any confounds of patients with PD having generally slower motor response times (Lieb et al., 1999). One researcher has suggested that problems with orientation pop-out may have implications for gait hesitation and door way blocking (Moore & Murphy, 1992).

The attentional orienting paradigm involves participants responding to a simple stimulus presented either to the left or right of fixation. Cues are given as to which side the target will appear and the subject has to make a single response whenever the stimulus is detected. The results using this orientating of attention method (Posner, 1980), have been less conclusive. In one study PD patients showed a reduced effect of invalid cueing, that would imply that the attentional engagement was weaker in this group (Wright, Burns, Geffen, & Geffen, 1990). However, a later study failed to replicate this which casts doubts on the result (Bennett, Waterman, Scarpa, & Castiello, 1995). This is further complicated by a study in which PD patients were found to be impaired only at certain stimulus onset asynchronies and not in the way described by Wright et al. (1990). Using both endogenous (a directional marker) and exogenous (the location flashed) cues, it was found that the only difference was in the effect of cueing, not in disengagement (Filoteo et al., 1997a).

Comparing the two methodologies used, there appears to be greater agreement that parallel searching is impaired in PD than there is that covert orienting of attention is. The role of covert orientation of attention in PD remains unclear. Despite this, it has been shown that overt shifts of attention (spontaneous eye movements) do show

impairments. When presented with a texture and told to search for a novel item, normal controls tend to search the left of the visual field first. Patients with hemi-spatial neglect will tend to search the right of the field first. It has also been found that patients with PD show this effect, hinting at the possibility of sub-clinical spatial neglect of the left hemifield in PD (Ebersbach et al., 1996). However, this is a controversial issue. For example, evoked potentials do not differ depending on which side of the body is stimulated in PD, as they do in classical parietal neglect. This has been cited as evidence against 'parkinsonian neglect' (Garcia-Larrea, Brousolle, Gravejat, Chazot, & Mauguiere, 1996).

Personality

It has often been noted by clinicians that there appears to be a particular personality type associated with PD. Common descriptions include, "*an emotional and attitudinal inflexibility, a lack of affect and a predisposition to depressive illness*" (Todes & Lees, 1985 p 97). However, it can be seen that such a behavioural pattern could feasibly be a result of the disabling effects of the illness. In one study, patients with PD were described as showing premature social ageing. The disease may force early retirement and this is reflected by a drop in income, PD patients have fewer friends and spend more time in solitary tasks, they show less involvement in household chores (Singer, 1973). Furthermore, Singer suggests this premature social ageing is a consequence not of PD directly, but of having a chronic illness. It therefore becomes difficult to separate aspects of the disease process from their consequences.

One way of separating these two hypotheses is to look at premorbid aspects of the patients. If the patients showed these behavioural characteristics even before disease onset, then it can not be a reaction to disability. However, there are inherent limitations

to such studies in that they have to be performed retrospectively. Despite this, there is some support for a premorbid personality style in PD. One study involved patients and a close relative completing the GIESSEN-TEST personality inventory in the way they would have completed it before disease onset. Both the patients themselves and the relatives rated the premorbid personality as being more self controlled and depressive compared to standard norm data (Poewe, Gerstenbrand, Ransmayr, & Plorer, 1983).

A second line of theory has looked at particular premorbid behaviours, in particular smoking. PD patients are more likely to be non-smokers than the general population (Poewe, Karamat, Kemmler, & Gerstenbrand, 1990). From this, it has been suggested that PD patients are less hedonistic or more self controlled than the average person. However, it has recently been suggested that there is an inverse dose-response relationship between smoking and PD. Rather than supporting a premorbid personality in PD, this implies that smoking has a neuroprotective effect against developing PD, which causes the association.

Despite this, there is still mounting evidence for a particular personality style in PD. A recently developed personality scale, the Tridimensional Personality Questionnaire is based around a neurochemical model of personality (Cloninger, 1987). Of particular interest in this scale is the trait of 'novelty seeking', which is suggested as being related to dopaminergic tone. Novelty seeking is defined as "*a heritable bias in the activation or initiation of behaviours such as frequent exploratory activity in response to novelty, impulsive decision making, extravagance in approach to cues of reward and quick loss of temper and active avoidance of frustration*" (Cloninger, Svrakic, & Przybeck, 1993 p 977).

The relationship between novelty seeking and dopamine has been supported by genetic studies in humans that have found that novelty seeking scores correlate with the level of polymorphism of dopamine receptor genes (Ebstein et al., 1996). The description of novelty seeking given above seems to match the opposite of the parkinsonian personality and so it could be hypothesised that PD patients would tend to score low on this trait. This has been observed. In one study PD patients were shown to have significantly lower novelty seeking scores than disability matched arthritis patients (Menza, Golbe, Cody, & Forman, 1993). In a follow up study, the role of dopamine in the parkinsonian personality was confirmed by the finding that ^{18}F Dopa striatal uptake in PET scans correlated with novelty seeking scores in PD patients.

It therefore seems that there is a particular personality style associated with PD and that the trait of novelty seeking is a useful measure of this. There is less support for the premorbid nature of the disease and for a causal relationship between smoking and personality in PD.

Psychiatric

A range of psychiatric disturbances have been reported in PD, such as psychosis (Parsa & Bastani, 1998), delirium (Factor, Molho, & Brown, 1998) and agitation (Aarsland et al., 1999). In some cases these may be related to side effects of medication (Lieberman, 1998). In other cases they may relate to other pathology or misdiagnosis, for example dementia with Lewy bodies is associated with hallucinations but has a similar initial presentation to PD (Gelb et al., 1999). However, other psychiatric symptoms are thought to exist independently and be related to non-pharmacological aspects of the disease. Three main psychopathologies have been identified, anxiety, depression and apathy.

Anxiety has been shown to be more prominent in PD than in normal samples (Berrios, Campbell, & Politynska, 1995a). However, it is unclear whether this is a response to, or a symptom of, the disease itself. For example, it has been shown that anxiety varies with motor fluctuations and correlates with disease progression (Siemers, Shekhar, Quaid, & Dickson, 1993). These relationships could be viewed as either indicating a neurobiological or a reactive mechanism of anxiety in PD. In support of a neurobiological cause is the observation that anxiety is usually lower in elderly groups compared to younger groups. The prevalence of anxiety in PD has been estimated at 40% and so this is a very high proportion of PD patients (Richard, Schiffer, & Kurlan, 1996).

The exact physiological reason for the high prevalence of anxiety is unclear. Anxiety is known to be related to autonomic function in PD indicating a possible link in which objective but pathological sympathetic activity produces a subjective feeling of anxiety (Berrios et al., 1995a). Other researchers have focused on neurochemical changes in PD as being the substrate of increased proneness to anxiety. However, this area is also unclear. Multiple neurotransmitters have been hypothesised as being involved in anxiety including dopamine, norephenehrine, serotonin and GABA (Richard et al., 1996).

The relationship between depression and PD is also poorly understood. Different studies have produced different estimates of its prevalence and a variety of theories are available to explain its occurrence. Prevalence estimates have varied between 4% and 70% (Cole et al., 1996). This may partly reflect patient selection. Patients with the non-classical form of PD, with akinesia and rigidity but not tremor, are more likely to develop depression than those patients with the classical form that includes tremor

(Starkstein et al., 1998). However, perhaps the most important issue is the nature of depression in PD. If the depression is reactive, a natural response to the disability, then prevalence will vary depending on the level of disability, tolerability of drug side effects, social support available etc. However, if the depression is endogenous, an actual symptom of the disease, then it may be expected to vary among patients, in a similar way to the prevalence of specific motor symptoms. Although disability is likely to contribute to endogenous depression, it will not be as closely linked as when the depression is reactive.

One way of separating the potential contributions of reactive and endogenous varieties is to examine the specific contribution of disability to depression, (e.g. see Mayeux, 1983). However even then, different proposals have been made to explain the relationship. A simple prediction that has been made is that depression is raised as a result of chronic disability (Gotham, Brown, & Marsden, 1986). They found that the level and type of depressive symptoms were the same in PD as in arthritis patients. This clearly supports a reactive basis for the role of depression in PD in that it implies that aspects of the disability exacerbate negative mood. The contrary position, that depression is a symptom of the disease and that it exacerbates disability has been proposed (Cole et al., 1996). In support of their suggestion, Cole et al. showed that depression impacted on social, role and physical functioning of PD patients independent of their clinical disease severity rating. However, the small sample size in their study (N=31), the lack of sophistication in the severity rating employed (Hoehn and Yahr, 1967) and the fact that the effect was only shown in a subset of the patients (male) indicates a cautious interpretation is required.

It seems likely that there are both endogenous and reactive aspects to depression in PD and a strict theoretical dichotomy between the two fails to capture the source of the psychopathology. It has been shown that depression in PD is related to the occurrence of autonomic symptoms, indicating that the experience of depression may be due to the subjective interpretation of these physiological aspects (Berrios et al., 1995a). A more overtly cognitive model has been proposed in which physiological changes predispose PD patients to develop reactive depression (Serra-Mestres & Ring, 1999). In support of this theory Serra-Mestres et al. found that non-clinically depressed PD patients showed a correlation between depression scores and the interference found in the emotional Stroop task, which measures the extent to which people are distracted by negative stimuli. This implies that there is an intimate link between cognitive impairments and later development of clinical depression in PD. This approach is consistent with depression research in other patients. Depressed patients without known neurological deficits show impaired performance on a range of tasks, particularly those with an executive component (Elliott, 1998).

The role of cognition in depression has also been reinforced by functional-anatomical studies of mood in PD. For example, it has been shown that PD patients with major depression show reduced blood flow in cingulate and medial frontal regions relative to both PD patients without depression and healthy controls. Furthermore, this medial frontal hypometabolism is also seen in major depression without PD (Ring et al., 1994). Other researchers have attempted to relate depression in PD to impaired mesolimbic and mesocortical dopamine systems that project to the medial frontal cortex (Fibiger, 1984). Despite this support for a dopaminergic system impairment, other neurotransmitter systems are probably also involved in depression. For example, it has been shown using transcranial sonography that there are morphological changes to the serotonergic dorsal

raphe in depressed but not non-depressed PD patients, even when motor impairment is controlled for (Becker et al., 1997).

A potential problem in comparing PD patients with and without depression is the possible confound of patients with predominantly more negative symptoms related to motivation rather than to mood. For example, Fibiger (1984) emphasises research in animals that has shown the importance of mesolimbic projections in reward and motivation. Consequently, Fibiger's interpretation is based more on the anhedonic/motivational aspects than the dysphoric aspects of depression. Therefore, it is unclear whether impairments in these systems are actually associated with depression as opposed to apathy in PD.

This problem arises because there is a theoretical overlap between apathy and depression (Marin, 1990). Both DSM-IV and the Hamilton rating scale for depression, two of the most widely used criteria for defining depression, include aspects related to apathy (Levy et al., 1998). In order to distinguish the two it is necessary to make new definitions of apathy and depression. This has been attempted. Apathy has been defined as "*lack of motivation that is not attributable to diminished level of consciousness, cognitive impairment or emotional distress*" (Marin, 1990 p 143). Depression has been defined as "*considerable emotional distress, evidenced by tearfulness, sadness, anxiety, agitation, insomnia, anorexia, feelings of worthlessness and hopelessness, and recurrent thoughts of death*" (Levy et al., 1998 p 314). The key difference between the two definitions being the presence of emotional distress. Incorporating this distinction, scales have been developed in order to diagnose apathy independently of emotional distress. The two main scales developed are the Neuropsychiatric Inventory (NPI, Cummings et al., 1994), and the Apathy Evaluation

Scale (AES, Marin, Biedrzycki, & Firinciogullari, 1991). The first of these, the NPI, is not designed specifically for the assesment of apathy and contains sections that screen for a range of neuropsychiatric disorders in patients with Alzheimer's disease and other dementias. The symptoms assessed by the NPI are delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, nighttime behaviours and appetite and eating disorders. For each symptom, a screening question is asked to a caregiver in order to assess whether the psychopathology is present. If the caregiver responds 'no' then a zero is recorded. If the caregiver responds 'yes' then sub-questions are asked dealing with specific aspects of the problem behaviour. On the basis of responses to the sub-questions estimates are made of the frequency (scores range between one and four), and severity (scores range between one and three). A total score is calculated for each neuropsychiatric symptom by multiplying the frequency score by the severity score.

The AES is only designed to assess the symptom of apathy and the full set of 18 items is completed using a Likert scale. Items probe motivation, initiative, interests and social involvement. Each item is scored between one and four, giving a total range of scores between 18 and 72. In addition, the AES has three forms that can be administered as a questionnaire to either the patient or a caregiver or as a semi-structured interview by a researcher with the patient. The benefit of the NPI is that it is quick to administer and provides information on a wide range of symptoms. It has been used successfully to identify neuropsychiatric symptoms in several neurodegenerative disorders (see for e.g. Kaufer, Cummings, & Christine, 1996; Litvan, Cummings, & Mega, 1998; Litvan, Mega, Cummings, & Fairbanks, 1996). However, the AES, unlike the NPI apathy score, has been more fully assessed for validity. It has been found that self report and researcher rated versions are highly correlated, for example in myotonic dystrophy

(Rubinsztein, Rubinsztein, Goodburn, & Holland, 1998) and that ratings made by different researchers are highly correlated for example in patients with depression, Alzheimer's disease or stroke (Marin et al., 1991). It has been shown that AES scores can distinguish between patients (left or right hemisphere stroke or Alzheimer's disease) and healthy controls and that scores predicate behaviour when exposed to novelty toys or playing video games. In addition the researcher rated AES has been shown to predict involvement by older adults in a geriatric rehabilitation programme, further emphasising its predictive validity as a measure of apathy (Resnick, Zimmerman, Magaziner, & Adelman, 1998). The structure of the AES is described in more detail in Appendix B.

Despite these recent advances in the detection and measurement of apathy as a symptom, the existence of apathy in PD is still unclear. As early as 1880 Charcot had noticed low motivation in PD patients and used the now outdated term 'Aboulia', meaning disease of the will, to describe it (Sacks, 1973 p 9). Recently, clinical descriptions of PD have also mentioned low motivation (Marsden, 1994a). Despite this, it has yet to be shown empirically using either of the above scales that patients with PD are apathetic. In one study that used the NPI, PD patients were shown to have low levels of apathy compared to patients with other neurodegenerative diseases (Levy et al., 1998). An earlier study had suggested the existence of apathy in PD when using a shortened version of the AES. However, this was based on the bimodal distribution of scores not on comparison to a control group (Starkstein et al., 1992). The indirect evidence therefore points to the existence of apathy in at least some PD patients. However, controlled studies have yet to be performed to verify this.

The Significance of Apathy in Parkinson's Disease

The Occurrence of Apathy in PD

The study by Starkstein et al. (1992) of a consecutive series of 50 patients attending a movement disorders clinic suggested that 12% of the patients studied had apathy alone and a further 30% had both apathy and depression. Thus, nearly half of the sample showed signs of apathy. Starkstein further showed that the apathy scores were related to cognitive performance, indicating that the occurrence of apathy may be linked to cognitive impairments. Conversely, of 40 preoperative pallidotomy patients studied by Levy et al. (1998), only 5% had apathy alone and a further 28% had both apathy and depression. The lower figures described by Levy et al. are potentially biased by the sample of preoperative patients, as they may have been preselected for relatively preserved mental status. A more recent survey with the NPI of 139 PD patients selected from the community found that apathy was reported in only 16.5% of the cases regardless of depression status (Aarsland et al., 1999). However, although apathy was not the most commonly reported neuropsychiatric disorder, it was the most severe. Therefore, apathy can be seen in at least a subset of PD patients, and often in patients who are not depressed.

Implications of Apathy for Clinical Care

Apathy may have implications for the clinical care of patients. Though not studied in PD, the occurrence of apathy has been shown to produce distinctive problems for patients with other clinical disorders, their carers and medical professionals. For example, it has been shown that in a geriatric rehabilitation setting, apathy scores on the AES predicted both the degree of participation in rehabilitation and level of functioning at discharge (Resnick et al., 1998). This clearly relates motivation levels to the benefits

to the patient of some forms of therapy. Low motivation has also been identified as a significant caregiver burden in brain trauma patients, indicating that patient apathy also impinges negatively on support systems (Marsh, Kersel, Havill, & Sleigh, 1998).

Furthermore, there is a complex link between support systems, handicap and depression. Reduction in aspects of social functioning are related to handicap as they impact negatively on an individual's ability to perform premorbid roles. This is of relevance because it has been shown in a community sample of older adults that handicap is a significant risk factor for depression, but this is modified by social connections (Prince, Harwood, Thomas, & Mann, 1998). Social connections are known to be reduced in PD (Singer, 1973), a clear indication of reduced motivation. Therefore, apathy in PD is likely to have negative impacts on the presence and severity of both handicap and depression. Finally, decisions about care and treatment made by clinicians may be more difficult when dealing with apathetic patients. Ethical problems may arise when clinicians must make decisions concerning the prevention of neglectful behaviour, in some cases apathy may paradoxically be associated with dangerous behaviour or deliberate avoidance of treatment, under such circumstances involuntary treatment may be necessary (Krupp, 1997).

Implications of Apathy for Understanding Brain-Behaviour Relationships

Psychology was once viewed as the study of three elements, conation (will), cognition and emotion. Of these conation has been neglected within modern psychology whilst the other two have been intensively researched (Baars, 1993). Similarly, over the last century within neurology and psychiatry, disorders of the will, which were once thought to be central issues, have received scant attention (Berrios & Gili, 1995b). Various reasons for this change have been proposed but it seems likely that the emphasis in

experimental psychology for clear stimulus-response relationships may be responsible. Intentional concepts such as the will can not easily be expressed in terms of stimuli and response.

Over the last decade there has been increasing interest in studying willed action within neuroscience. In the comparative field, methods have been developed to study voluntary actions in primates with surgical ablations (Passingham, 1993). Such paradigms can not easily be developed for use in human research, and so brain imaging is often used in conjunction with tasks assumed to involve willed components, such as making random movements (Frith, Friston, Liddle, & Frackowiak, 1991).

Purely behavioural studies of willed actions, such as the recording of reaction times, are difficult to perform in human subjects. For example, in the case of a reaction time, the critical data is the latency between the go signal and subjects' response. However such responses have a large reactive component and may not reflect will driven actions well. The study of apathy has recently been suggested as being a method for gaining an understanding of willed actions (Jahanshahi & Frith, 1998). Disorders such as apathy in PD may therefore serve as useful models, or what have been described as 'natural experiments', for studying the psychological and physiological processes of the will and motivation in man.

Chapter 2: The Concepts of Motivation, the Will and Goal Directed Behaviour

Until the early 20th century the 'will' was an important concept within psychology and clinical brain sciences. Mental life was commonly described as based upon conation (will), thought and emotion (see for example Urban, 1919). So strong was the emphasis on disorders of the will in clinical practice that it even had an impact on main stream literature, which used the same concepts to describe cultural behaviour (Jurkevich, 1992). However, interest in the will began to decline after the turn of the 20th century (Berrios & Gili, 1995b). A variety of psychiatric and neurological syndromes were considered disorders of the will, reductions in activity were described as abulia and excesses as impulsive behaviour. Impulses have since defied explanation and the term abulia is now rarely used (Berrios & Gili, 1995c).

One reason for this was probably the rise of psychoanalysis as an alternative explanation for human behaviour. Although motivated processes were central to psychoanalytic theory, they were conceptualised as being mostly unconscious. For example, a modern psychoanalyst has stated that *"Much of human behaviour is in fact simultaneously motivated by multiple goals, which would disrupt goal-directed behaviour if they all had to be represented in consciousness"* (Westen, 1998 p 343). This emphasis on unconscious motivation was unreconcilable with earlier views of the will.

A further reason for the decline of interest in the will was the advent of behaviourism. Volitional behaviour was still researched, but as with psychoanalysis behaviourism

denied the importance of attentive or conscious aspects. A consequence of this was that a less value-laden term was introduced to emphasise the actual observable behaviour of the individual, the word 'motivation' replaced 'will'. Despite the more recent decline of behaviourism in favour of cognitivism in many areas of psychology, research into motivation has continued (using behaviourist principles) in comparative neuroscience. Since the 1920's the behaviour of different animals has been studied in order to identify rules that can be generalised to all species and the associated physiological basis of these abilities (Hull, 1943).

With the growth of cognitivism, motivation has received less attention within psychology. In a recent review of motivation research focusing on neuroscience, it was commented that *"we were disappointed not to have seen a greater input from human cognitive neuropsychology"*, (Robbins & Everitt, 1996 p 233). Although mechanisms of motivation are still hotly debated within the comparative neurosciences, research in human motivation (either clinical brain sciences or psychology) is scarce. Despite this, concepts such as action are still used, but these tend to focus on the relationship between intention and performance errors (see e.g. Baars, 1993). These have little in common with earlier concepts of motivation or the will to perform an action, but focus on the action itself.

One probable reason for this is that vague concepts such as motivation and the will are difficult to operationalise in human experimental terms. Motivation as studied by psychologists has been defined as *"the control of behaviour; that is, the process by which behaviour is activated and directed toward some definable goal"*, (Buck, 1988 p 5). This definition seemingly covers a wide a range of processes. Similarly, a recent definition of the will is *"the inner experience that one can produce inner concrete or*

abstract goals for one's future behaviour and/or cognition. Then with the aid of one's will, one tries to achieve the goal conceived of" (Ingvar, 1999 pp 1-2). There are many similarities between these two terms. Perhaps the crucial difference is that the will can dictate a goal, but motivation enables the direction and intensity of particular behaviours towards a goal.

In other words, the will was proposed as a need to achieve a goal and motivation the force behind the implementation of this need. This distinction has reappeared through attempts to define these broad concepts. For example, a definition from the field of phrenology in 1873 defines the will as *"a peculiar mode of action of the intellectual faculties, different from perception and judgement. It results from the decision and resolution of the understanding or intellect to follow a certain course of action prompted by the propensities, by the sentiments, by both acting together, or by external compulsion"* (Coombe, 1873 p 141). Compare this definition with a modern description of motivation, *"motivation encompasses a range of interlocking processes, including biologically defined urges and desires, acquired affinities and aversions, and the implementation of conscious intentions"*, (Parkinson & Colman, 1995 p xii). The crucial difference between the definitions is the role of the initial conception of a goal and a need to achieve it. The 1873 definition of the will is equivalent to a contemporary definition of intention. The 1995 definition of motivation is equivalent to a description of the processes that provide the strength of the need to achieve the goal of the intention.

It is clear therefore, that multiple definitions have been utilised at different times and in different disciplines to describe overlapping concepts observed in human behaviour. Furthermore, although the definitions of the phenomena in question have their own

idiosyncrasies, in practice they are generally interchangeable, leading to confusion concerning which aspects of behaviour are actually being referred to.

Cognitive Models of Motivation, the Will and Goal Directed Behaviour

Perhaps driven by such ambiguity, more recently attempts have been made to fuse many of the previous observations into a more coherent model. Recently it has become popular to consider the vast array of actions performed by humans and other animals in terms of the concept of Goal Directed Behaviour (GDB). The approaches have ranged from the purely philosophical through social and psychological studies to basic science. For example the nature of intention and choice has been examined in philosophy (Hodgson, 1995) while the corresponding psychological topic, response selection has been considered in cognitive neuroscience (Baker et al., 1996). In the basic sciences, interest has focused mainly on the modulation of GDB and the corresponding physiological changes by reward factors (Schultz, 1999).

Within cognitive psychology, Norman and Shallice (1986) have based a theory of action on the assumption that the processes involved in routine acts are qualitatively different from those used in non-routine acts. To account for this distinction, the model is comprised of two main components, action schemata and a Supervisory Attentional System (SAS). Norman and Shallice developed the concept of action schemata as hierarchical units that link actions to co-ordinate behaviour. A commonly cited example is driving a car. This would involve a large number of schemata, some would enhance each other's activity, for example depressing the brake pedal would enhance depression of the clutch pedal but inhibit other actions such as depressing the accelerator pedal. In the performance of routine acts the action schemata can be

modulated from perceptual input and require little attention. This process is known as 'contention scheduling'.

However, in some instances the task demands are such that action schemata can not be driven by perceptual input alone. This would occur for example in the performance of novel tasks, when attention is required. This influence is provided by the SAS, a general-purpose processor that can modulate the activity of the schemata and has access to 'intentions' (Shallice, 1988). In the driving example given above, the SAS would be required for example in negotiating a new route or dealing with an unexpected event such as a puncture.

This theory has been partially supported by neuropsychological cases. Shallice (1988) suggests that a case described by Damasio and Van Hoesen (1983) exemplifies what would be expected from disconnection of the SAS from the schemata system. This patient made no spontaneous actions, but could answer questions and perform complex actions to verbal command. This case is considered in more detail below. In addition, utilisation behaviour, the compulsive use of objects seen in some frontal damaged patients, (Lhermitte, Pillon, & Serdaru, 1986) has been cited in support of the model. It is suggested that this behaviour occurs when the SAS is impaired and so the schemata are triggered by sensory stimuli without higher level modulation (Shallice, Burgess, Schon, & Baxter, 1989). However, it is unclear why the akinetic mute patient did not also show utilisation behaviour, as presumably damage to the SAS would have the same effect as its disconnection as both would leave the schemata system uncontrolled.

A similar approach has been taken by Frith and Done (1988). On the basis of results from reaction time experiments (Frith & Done, 1986), every-day action slips (Reason,

1979), and neuropsychiatric studies (Frith & Done, 1983) a model was proposed that distinguished willed from stimulus driven actions (Frith & Done, 1988). Willed actions are driven initially by planning and goal formation and closely resemble actions driven by the SAS in the Norman and Shallice (1986) model. Similarly, stimulus driven actions have much in common with the schemata driven actions. However, the willed-stimulus driven theory has been used with some success to account for negative and positive symptoms of schizophrenia and certain motor abnormalities in PD.

A common feature of both of these models is that action is considered entirely within cognitive terms. This reductionist approach has been beneficial in that it allowed the function of a poorly understood system to be operationalised, particularly for use in cognitive neuropsychology. However, as described above, findings in other areas have emphasised a range of non-cognitive factors. A fuller interpretation of GDB could be achieved if, for example, the roles of motivation, reward and goal representation in action were considered.

A Framework for Understanding Goal Directed Behaviour

In order for the concept of GDB to be useful it is necessary to collate diverse approaches into a single framework such that different factors can be considered when interpreting the reduction in GDB seen clinically. One such attempt is given by Brown and Pluck (2000) and is shown below in Figure 2.

The framework attempts to capture the key features of the diverse contemporary models in descriptive factors such as intention, emotion, motivation, learning and cognition. They can then be considered as parts of a functional system underlying GDB. In this way individual aspects can be delineated as well as describing the interactions of these

same aspects. The framework does not replace older concepts such as intention, the will and motivation but seeks to examine the differences as well as the overlap in these often confused concepts.

Most voluntary behaviour is initially driven by an intention to act (Schultz, 1999). This intention (**A**) is the least well-defined aspect of the framework but one in which everyday experience suggests to us is the crux of our behaviour. It is proposed that intention is modulated by internal determinants such as urges, perhaps stemming from previous cognitive events and from external determinants such as perceptual cues to act.

Internal and external influences have much in common and in many instances of GDB both have been responsible for the activation of intentions. In some situations, certain stimuli are 'flagged' as being linked to an intention. This is, for example, what occurs in a reaction time experiment when a subject is told to press a key when a particular stimulus appears. Although the imminent stimulus is an external determinant, internal determinants have set a 'trigger' for when the stimulus is encountered. This process has been described as 'marker activation' and its impairment said to underlie some aspects of the disorganisation of behaviour of patients with frontal lobe damage (Shallice & Burgess, 1991). Such triggers are also likely to be involved in prospective memory, the ability to remember to perform an action at a future time (Ellis, 1996).

External determinants are also involved in modulating intention directly, for example when salient non-flagged stimuli are encountered, such as novelty or deviations from expectations. The detection of such unexpected but salient stimuli is unlikely to be a single modular function and a variety of different processes and functions probably

underlie this proposed ability. However, the right frontal cortex has been suggested as being particularly important (Goldberg, Podell, & Lovell, 1994).

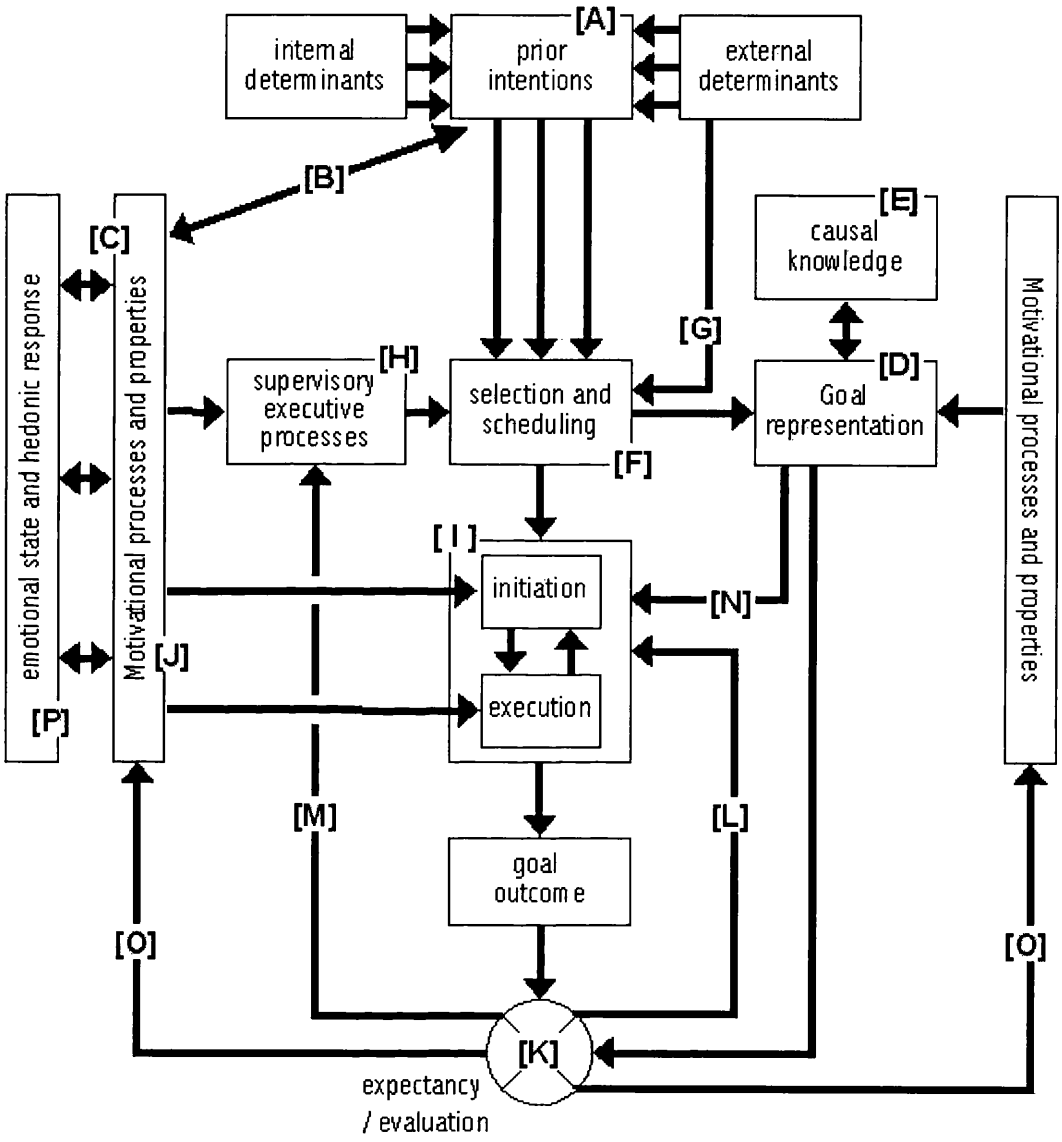


Figure 2: A Framework for interpreting goal directed behaviour.

Intentional states are also influenced by motivational factors (**B**). These may be learned influences involving reinforced associations between actions and rewards/punishments or innate motivators such as desire for food or sex that have primary reinforcing properties. Motivational factors, by definition, alter the probabilities of behaviours being performed dependent on the value placed on the expected outcome (Shizgal,

1997). Those actions with expected pleasant outcomes are more likely to occur while those that are expected to produce unpleasant outcomes are less likely to (Olds, 1966). For this reason, motivational factors are closely associated with emotional and hedonic status (**C**).

A logical prerequisite for GDB is that there is an identifiable expected outcome or goal (**D**) (Schultz, 1999). This could operate over very short periods or as long as several years (Ingvar, 1999). A goal has motivational properties, perhaps achieved through pavlovian conditiong. Imaging studies have suggested that the most anterior regions of frontal cortex may be the substrate of goal representation (Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999). In addition, for a goal representation to be utilised it is necessary that the organism has causal knowledge (**E**) of the relationship between directed behaviours and goals (Ingvar, 1999). Such knowledge may often be available to consciousness, for example, in planning tasks, but such awareness may not be necessary. It has been shown that people are capable of displaying adaptive behaviour in terms of decision making without knowing the reasons for their successful responses (Bechara, Damasio, Tranel, & Damasio, 1997). Such experiments demonstrate that the causal relationships between actions and goals can operate without conscious awareness.

The action selection itself involves producing an appropriate serially ordered programme to achieve the goal (**F**). This process labelled 'selection and scheduling' may involve comparison of multiple possible routines to select the most appropriate. These routines can be considered intentional despite not necessarily being preceded by an urge or desire to achieve the goal. This may occur for example in a highly habitual

task in which attentional demand is at a minimum and selection and scheduling can be adequately controlled by external determinants (**G**).

In many instances, appropriate GDB will not be achieved by external determinants alone modulating action selection and scheduling. When there is no pre-learned situation-action link then higher level selection must be used to select an action schema. This is represented in the framework by supervisory executive processes (**H**). This influence would be required for example when perceptual input alone can not achieve the wanted goal. In the driving example, this would be needed to negotiate a novel environment. Supervisory executive processes are generally effort demanding, and are, therefore, in part influenced by motivational and associated hedonic properties.

This may be why depressed patients show cognitive impairments, particularly on effortful compared to routine tasks (Elliott, 1998) as the influence of hedonic responses on the executive processes is reduced. Patients with depression have also been described as showing 'subnormal volition' a description based on observations of low initiative and ambition plus general inactivity (Ingvar, 1999). This may represent the hypofunctioning of the GDB system at the level of executive processes. Behavioural support for this association is highlighted by the relationship between reduced GDB and depression in many neurological conditions such as PD (Starkstein et al., 1992).

The distinction between external determinants (**G**) linking directly to, and supervisory executive processes (**H**) intervening in action selection (**F**) is consistent with the model of GDB proposed by Frith et al. (1992) in terms of stimulus driven and willed action systems. This highlights the considerable overlap between the concepts of executive function and willed action. Indeed clinically, much of the support for willed action

deficits in schizophrenia is based on performance of tests such as verbal fluency and two choice guessing that are often considered as executive function tests (Frith & Done, 1988).

When an action programme is selected it must be initiated and executed (**I**) with sufficient effort consistent with the motivational factors associated with the goal (**J**). The success of the executed actions needs to be evaluated in respect to the goal outcome by a comparator (**K**). Maintenance of the actions may be needed to persevere to achieve the goal, or the actions may need to be halted when the goal is achieved to prevent perseveration (**L**). If the action programme is failing to achieve the goal the comparator may need to signal that reselection is needed (**M**) reactivating supervisory executive processes.

When the goal can only be achieved over an extended time period the initiation and execution activation can be maintained by the goal representation and its associated motivational properties (**N**). If the comparator signals that the goal has been achieved then there will be a state change in the motivational properties (**O**) and emotional and hedonic responses (**P**) via incentive learning. This change will increase the probability of the action sequence being repeated in the future. If the action sequence fails to achieve the goal then this will lead to a negative response in hedonic and motivational aspects. The overall effect will be to reduce the probability of the behaviour being repeated in the future.

Patterns of Disturbance of Goal Directed Behaviour

Human motivation and the will are again becoming popular after nearly a century of neglect. In particular the processes underlying GDB are being investigated from a

neuropsychological perspective (Jahanshahi & Frith, 1998). Neurological or psychiatric patients can show a range of disturbances of GDB ranging from excessive and disorganised behaviour to a marked lack of behaviour. Traditionally a clinical distinction has been made between positive or 'florid' symptoms and negative or 'defect' symptoms (Jackson, 1931). Examples of positive or agitated symptoms include such things as hyperactivity, restlessness, talkativeness, irrational fear, delirium and paranoia (Fisher, 1983). In addition, the term positive symptoms has been extensively used to describe features of schizophrenia such as hallucinations, delusions and thought disorder (Crow, 1980). These are linked because they display a pathological exaggeration or increase in behaviours and experiences above those in the healthy individual.

Damage to the frontal lobes has long been associated with excessive or positive influence on GDB. Patients often display disorganised behaviour (Burgess & Shallice, 1996a) impulsivity (Miller, 1992), a lack of response inhibition (Verfaellie & Heilman, 1987), restlessness (Brazzelli, Colombo, Della Salla, & Spinnler, 1994) and unnecessary actions (Lhermitte et al., 1986). However, more recently it has been recognised that reductions in GDB or negative symptoms are also common following frontal lobe damage (Duffy & Campbell, 1994). Patients may seem apathetic (Wheatley & McGrath, 1997), hypokinetic (Fuster, 1989) or inattentive (Mesulam, 1981).

The positive symptoms on GDB are often linked to executive control, and indeed models such as that proposed by Norman and Shallice (1986) were designed to account for the disorganised behaviour of frontal lobe damage patients. However, the negative aspects can not necessarily be adequately explained by such models. This is because

the range of systems that if impaired could potentially reduce GDB is much wider. For example, motivational and hedonic response systems need to be considered.

Studies of clinical groups in which GDB is reduced may give wider ranging insights as to the function of normal action control systems. For example, this has been attempted in schizophrenic patients showing negative signs (Fuller & Jahanshahi, 1999a). However, there is consequently also a broad range of clinical conditions in which reduced GDB is observed. Investigations of such patients may also have significant therapeutic implications, as well as enhancing psychological and neuroscientific knowledge.

Clinical Syndromes Related to Reduced Goal Directed Behaviour

Akinetic Mutism

In 1941, Cairns et al. described the case of a 14 year old girl who showed a profound action impairment. The patient seemed awake and would follow people in the room with her eyes but did not make any other spontaneous movements. She seemed unaffected by painful stimuli and would swallow bitter, as well as sweet solutions that were placed in her mouth. Speech was absent except for quiet, monosyllabic responses to questioning, limb movements could be made to command. Cairns et al. named the syndrome 'akinetic mutism'. The crucial difference between this and other similar disorders was the apparent consciousness of the patient and the ability to produce meaningful actions in some circumstances. These factors distinguish akinetic mutism from superficially similar conditions such as the persistent vegetative state, in which there may appear to be wakefulness, but GDB can not be elicited (Plum, Schiff, Ribary, & Llinas, 1998).

Investigations of the patient reported by Cairns et al. (1941) revealed a cyst in the 3rd ventricle that affected surrounding structures, in particular the medial thalamus bilaterally. Surgical intervention produced a remarkable recovery: *"Aspiration of the 3rd ventricle cyst was followed by prompt return of vocalisation, speech, interest in her surroundings, emotional feeling and voluntary movement"* (Cairns, Oldfield, Pennybacker, & Whitteridge, 1941 p 280).

Since this first description, several other authors have described similar states. A patient with lesions to the mesencaphalic tegmentum showed a total lack of spontaneous movement but could grasp with his hands or protrude his tongue on command (Daly & Love, 1958). A review of eight patients with similar clinical conditions found that seven had lesions in the pons, whilst the other had prominent damage in the globus pallidus (Cravioto, Silberman, & Feigin, 1960). Akinetic mutism has been interpreted as being indicative of severe loss of motivation (Marin, 1990). This interpretation rests on the assumption that the patients were fully awake. However, it is unclear to what extent the patients really were conscious. It has been suggested that the loss of GDB in akinetic mutism is simply a consequence of the complete absence of consciousness (Damasio, 2000).

Therefore, akinetic mutism needs to be considered in some depth to establish whether this really is a relatively selective GDB impairment. This is important because such a profound lack of GDB would not be surprising if the patient were in a stuporous state. A patient described as being *"mute, akinetic and indifferent to painful stimuli"* (Barris & Schuman, 1953 p 44), showed a progression of symptoms that went from apathy, through stupor and eventually coma. However, on hospital admission, the patient would not respond to questions and eye movements were random. Therefore, during

the akinetic stage, consciousness was questionable. Furthermore, eye movements that track objects in the environment are not strictly indicative of consciousness, as even patients in chronic vegetative states have been known to do this (Banich, 1997).

Verbal reports following recovery are also problematic. The patients of Cairns et al. (1941) and Daly and Love (1958) were amnesic for the period of akinetic mutism. The patients of Cravioto et al. (1960) and Barris and Schuman (1953) failed to recover and in none of the above cases were neuropsychological tests performed. It is therefore unclear, whether these cases represent impaired GDB or impaired consciousness. Early reports of akinetic mutism tended to be of patients with lesions to the brainstem. This area includes the reticular activating system, a region that has been closely associated with arousal and vigilance (Mesulam, 1981). Therefore, impaired arousal, in at least some of these patients, is an alternative explanation.

More recent clinical reports of akinetic mutism have described patients with lesions directly affecting frontal-subcortical circuits. In addition some have included neuropsychological tests to clarify the mental state of patients. Mega et al. (1997) reported a patient with bilateral damage to the globus pallidus interna and ventral striatum. This would have been sufficient to disrupt all five of the frontal subcortical loops proposed by Alexander et al. (1986), but it would have particularly affected the anterior cingulate loop due to the ventral striatal lesions. The patient showed a classical akinetic mute state, she could open and close her eyes on request and repeat five word phrases but made no spontaneous actions. Mental state testing revealed disorientation for place and time but intact recognition of family members. The patient could answer some questions correctly but only with 'yes or no' responses. She failed to recover and

died eight weeks after admission, as such, no meaningful verbal reports of the state are available (Mega & Cohenour, 1997).

More informative is the case study of a patient who developed a state that probably conformed to the clinical picture of akinetic mutism, though the authors did not describe her in this way (Damasio & Van Hoesen, 1983). This patient suffered a unilateral lesion that included the left anterior cingulate cortex and supplementary motor area (SMA). In the acute stage the patient lay motionless but would track people with her eyes. She could not answer questions verbally but could nod her head to signal comprehension. There was no evidence of bucofacial apraxia and sentence repetition was intact. At the third day, comprehension was formally assessed and seemed to be preserved, she performed the token test normally and was capable of comprehending written material. Recovery was remarkable, after three weeks the patient was able to converse using sentences with no evidence of agrammatism.

This case is of particular interest partly because of the demonstration of intact comprehension, but also because after recovery she was able to describe her experiences during the acute period. She claimed that her mind was *"empty"*, that *"nothing mattered"*, she had *"nothing to say"*, and that her will to move or communicate was *"neutralised"* (Damasio & Van Hoesen, 1983 pp 98-100). If these verbal reports can be believed then this indicates that a profound GDB impairment was present that could not be accounted for by being in a state of reduced alertness or consciousness. In addition, the ability to perform complex actions such as demanded by the token test indicates a preserved motor system.

Abulia and Apathy

Akinetic mutism has often been cited as the extreme, but rare, clinical presentation of a GDB impairment that is more often seen in less severe cases described as apathy or abulia (Marin, 1997). Abulia is an old medico-psychological term defined as "*loss, lack or impairment of the power to will what is in mind*" (Baldwin, 1901, p 816). Severe abulics may spend much of their time awake in bed and rarely speak spontaneously (Yamanaka, Fukuyama, & Kimura, 1996). Apathy, a related term is more commonly used. Apathy is defined as "*primary absence of motivation, that is, lack of motivation not attributable to disturbances of intellect, emotion, or level of consciousness*" (Marin, 1991 p 244). It is often stated that apathy is the least severe impairment, akinetic mutism the most severe with abulia falling between these extremes and that all three represent motivational impairment (Marin, 1990).

However, it is unclear whether the three syndromes really are related in terms of a gradient of motivation. By definition a patient with abulia should be able to adequately will an action but lack the ability to carry it out, in apathy it appears that it is the will to act that is lacking. In some aspects abulia may lead to a less extreme impact on the individual because with help, many goals could still be achieved. Additionally, the term abulia is sometimes used to describe patients that other researchers would have described as apathetic (Marsden, 1994a) or akinetic-mute (Fisher, 1983).

In light of this confusion, some researchers have used the umbrella term of 'Apathy and Related Disorders of Diminished Motivation (or ADDM)' (Marin, 1997). However, this is no more informative than the umbrella term of 'abulia'. In addition, it is not fully established that the cause of the phenomena is a loss of motivation. When the framework presented above is considered, it is clear that apathy and other disorders of

GDB could result for a variety of reasons other than impaired motivation. In this thesis the term apathy is used to describe patients as this term has been specified in greatest detail and is currently the most widely used term used in neurology to describe mild to moderate reductions in GDB.

Although apathy is currently the most widely used term to describe reduced GDB impairment in brain diseased patients, a variety of other expressions have been used to describe patients that conform to the definition of apathy given above. These include 'prefrontal syndrome' (Duffy & Campbell, 1994), 'executive impairment' (Wheatley & McGrath, 1997), 'psychic akinesia' (Lugaresi, Montagna, Morreale, & Gallassi, 1990), 'psychic loss of self activation' (Laplane, 1994), 'negative symptoms' (Galynker, Levinson, Miner, & Rosenthal, 1995), 'athymhormia' (De La Sayette et al., 1992), 'disorder of motility' (Fuster, 1989) or simply 'motivational deficits' (Powell, Al-Adawi, Morgan, & Greenwood, 1996). In addition, the primate Kluver-Bucy syndrome allegedly has apathy as one of its main features, and so the human form is considered briefly below, as this may constitute a distinct action impairment syndrome. In addition, psychic akinesia is discussed in order to assess its relationship to the terms apathy and abulia.

Psychic Akinesia

In the 1980's, several reports described a remarkable clinical state in patients following globus pallidus damage, usually from carbon monoxide poisoning. The patients were described as having no, or only minor, motor impairments and normal 'intellectual capacities'. However, they showed reduced spontaneous behaviour. This manifested in the patients spending much of their time sitting quietly or lying awake in bed. This was named 'psychic akinesia', (Laplane, Baulac, Widlocher, & Dubois, 1984). A key

feature was that normal behaviour could be produced in these patients in response to external stimulation. This was suggested as showing dissociation between 'hetero-activation' and 'self-activation' (Laplane, 1990). The patients were thought to be impaired in self-activation but could be roused by elements in the environment, revealing intact hetero-activation. This aspect of the condition was also widely described as 'psychic loss of self-activation', (Bogousslavsky, Regli, Delaloye, & Delaloye Bischof, 1991).

Another feature of psychic akinesia was only apparent from verbal reports of the patients themselves. This revealed a 'mental emptiness' that was disclosed by the patients describing their inner psychological life as a 'void' (Laplane, 1994). Furthermore, they claimed never to get bored despite their lack of activity. These two negative features paired with normal motor and intellectual functions were assumed to be characteristic of a newly recognised clinical entity. Indeed, one paper discussed the *"recently delineated syndrome of 'psychic akinesia', i.e. blunting of affect and loss of internal motivational drives without motor disturbances or intellectual deterioration"* (Lugaresi et al., 1990 p 168).

There is reason to question the novelty of psychic akinesia. The reversibility of the condition during external stimulation (hetero-activation) is not unique to these patients. It has already been stated that a key feature of akinetic mutism is total lack of spontaneous movement but with some preserved responding. Although patients with psychic akinesia are not suffering akinetic mutism, similar effects have been noted in more able cases. Some frontal lobe damaged patients may be capable of performing complex actions but will not do so without instructions or environmental prompts (Lezak, 1982). Furthermore, the cases described above all showed neuropsychological

impairments resembling frontal lobe syndrome. Neuropsychological testing was limited, but of the eight psychic akinesia cases most often described in the clinical literature, all showed reduced verbal fluency and all but one performed poorly on the Wisconsin Card Sort Test (Laplane, 1994).

The other key feature highlighted as a symptom of psychic akinesia is the mental void reported by most patients. Again, this is not a unique observation. In abulia following frontal lobe damage, similar behaviour has been reported. For example: *"Abulics generally deny nervousness, worry, tenseness, or depression. They lack awareness of their condition and express little in the way of needs or satisfaction. They do not have temper outbursts or show anger. As far as can be learned by later questioning, patients have no flow of thoughts"* (Fisher, 1995 p 183).

It appears therefore, that psychic loss of self-activation and psychic akinesia, rather than being new concepts, are consistent with frontal lobe deficits with consequent abulia. This interpretation is consistent with the patient's lesions predominantly being in the basal ganglia. As described in Chapter 1, the basal ganglia are closely associated with frontal lobe function. Indeed, in a recent description of 'psychic akinesia' following bilateral thalamic damage CT scanning was reported. This revealed hypoperfusion in the medial frontal lobes (Engelborghs, Marien, Pickut, Verstaeten, & De Deyn, 2000).

However, it will require further research before the validity of psychic akinesia as a distinct syndrome can be fully assessed. Although superficially similar to the syndrome of abulia, there may be some differences. For example, it is not clear whether the positive response to external stimulation (hetero-activation) is seen to a significantly greater extent in psychic akinesia, when contrasted with abulia.

Kluver-Bucy Syndrome

Although the most common brain areas associated with apathy are the frontal lobes and basal ganglia (discussed below), the temporal cortex has also been implicated. Bilateral removal of the temporal lobes including the uncus and hippocampus produces a striking behavioural change in rhesus monkeys. This syndrome includes visual agnosia (psychic blindness), altered and increased sexual behaviour, distractibility and enhanced orality (Kluver & Bucy, 1937). However, also of note was a placidity and loss of emotional responses such as fear. This has often been interpreted as apathy (see e.g. Duffy, 1997). Indeed, bilateral temporal lobotomies have been performed in the belief that they would offer relief to agitated schizophrenic patients. In a report of two cases, the first patient initially became apathetic but this was short lived and she was then given a bilateral frontal lobotomy three weeks later. The second patient had already failed to improve following a bilateral frontal lobotomy and was given a bilateral temporal lobotomy. This produced a range of neuropsychological complications but, according to the surgeon "*he was calm*" and "*without any interest in the outside world*" (Obrador, 1947 p 191). Although this seems to show that the human Kluver-Bucy syndrome includes apathy, the patient already had frontal brain lesions and chronic schizophrenia, it is therefore difficult to draw conclusions from such a complex pathological case.

Other examples of the human Kluver-Bucy syndrome have been reported. In one case bilateral temporal lobe removal was performed to control epilepsy (Terzian & Ore, 1955). This patient also developed a complex neuropsychological profile that approximated the rhesus Kluver-Bucy syndrome (e.g. change in sexuality, agnosia, and distractibility). He also initially developed a "*reduction of spontaneous activity*" (p 375), and a placid nature (he had previously been prone to violent outbursts). However, the reduction in spontaneous behaviour more closely resembled catatonia than apathy,

as during these periods he would not respond to any instructions at all. The placidity could be explained by the curing of his epilepsy, which was the likely cause of his rage attacks. Therefore, this case does not support the notion of apathy as a symptom of the Kluver-Bucy syndrome in humans.

Patients described as developing the Kluver-Bucy syndrome as a consequence of disease such as encephalitis have also been reported. To some extent these are a better model, as they do not have an underlying long-term illness, unlike the surgical patients described above. Again, apathy is not a clear feature of the wider clinical picture. Of 12 cases reviewed, all were said to be placid, however their neuropsychological status was extremely poor. Most developed dementia, aphasia and amnesia as well as the Kluver-Bucy features such as visual agnosia (Lilly, Cummings, Benson, & Frankel, 1983). Therefore, interpretation of the apathetic status would be unreliable. Similarly, of a group of seven children who developed Kluver Bucy syndrome following herpes simplex encephalitis, all showed placidity but this was not associated with reduction in GDB (Pradhan, Singh, & Pandley, 1998). Therefore, despite some claims to the contrary, there is actually little support for a reduction in GDB in the human Kluver-Bucy syndrome.

Diseases Associated with Symptoms of Reduced Goal Directed Behaviour

Behavioural deficits such as apathy and abulia are commonly reported as part of the frontal lobe syndrome (Lezak, 1982). Indeed, 'motivational' impairment is one of the behavioural disorders synonymous with frontal lobe dysfunction. Duffy and Campbell (1994) have suggested three regional prefrontal syndromes. The 'dysexecutive type' caused by damage to the dorsolateral prefrontal cortex, the 'disinhibited type' caused by damage to the orbitofrontal cortex and the 'apathetic type' caused by damage to the

medial frontal cortex. These theoretical distinctions have similarities to the loop theory discussed in Chapter 1. Executive function is suggested as being mediated by the dorsolateral frontal circuit, empathy and personality by the orbitofrontal circuit and motivation by the anterior cingulate circuit (Cummings, 1995). Indeed, there is a great deal of clinical data associating the anterior cingulate region with GDB. For example, damage to this area commonly produces akinetic mutism (Devinsky et al., 1995).

Therefore, diseases that affect the frontal lobes, particularly medial frontal regions, are commonly associated with reduced GDB. Similarly, negative signs are common in schizophrenia such as 'avolition' and 'poverty of speech' (Schmand et al., 1994). These may also reflect the frontal lobe dysfunction that is often reported in schizophrenia (Andreasen, 1997). It is of interest that dysfunction of the anterior cingulate region of the frontal lobes has been particularly associated with negative signs in schizophrenia (Dolan et al., 1995).

However, the role of subcortical regions in GDB has been suggested by many authors, who have emphasised the importance of the basal ganglia. In particular, the subcortical aspect of the anterior cingulate circuit has been suggested as being responsible for dealing primarily with motivation (Mega & Cummings, 1994). Indeed, diseases that mainly affect subcortical structures have also been shown to be associated with reduced GDB. Basal ganglia strokes have been associated with 'negative symptoms' (Galynker et al., 1995). In another report, meta-analysis of 240 cases with focal basal ganglia lesions revealed that 'abulia' was reported in 13% of all cases and 28% of those with caudate lesions (Bhatia & Marsden, 1994). However, in this report the criteria for abulia necessarily referred to a wide range of clinical phenomena.

The entry point to subcortical structures in the anterior cingulate loop is the ventral striatum. Documented damage to this brain area is rare. Mega and Cohenour (1997) presented one new case and reviewed four known previously published cases of pallidal damage with ventral extension that would have involved the ventral striatum. Four of the five patients had akinetic mutism; the one that did not was described as apathetic. Clearly, the globus pallidus and ventral striatum are important regions for the expression of GDB. The nucleus accumbens, one of the main structures of the ventral striatum, is affected in schizophrenia (Pakkenberg, 1991), a disease associated with GDB impairment (i.e. negative signs).

The anterior cingulate circuit, like the other circuits, 'close loop' by projecting back to their original cortical innervation area via the thalamus. Damage to the thalamus often produces symptoms of reduced GDB (Scheibel, 1997). This is particularly so for the medialis dorsalis (MD) nucleus. All of the circuits suggested by Alexander et al. (1986) involve the MD, however the anterior cingulate loop is unique in that all of its output is channelled through this nucleus via its posteromedial portion. Other circuits also send projections via the ventralis anterior (VA) nucleus or the ventralis lateralis (VL) nucleus of the thalamus and so may be less at risk from disruption following MD lesions. This may be why one of the most striking behavioural disturbances following MD damage is reduced GDB (Stuss, Guberman, Nelson, & Larochelle, 1988). It is also of interest that in schizophrenic brains the MD nucleus is known to show lower cell densities (Pakkenberg, 1991); this may partly explain the negative signs of the disease. It therefore appears that any disease process that impairs the function of the anterior cingulate circuit or its open afferents has the potential to impair GDB. In addition, due to the common structures, such as the MD nucleus, involved in all five known circuits,

GDB may be affected following dysfunction in circuits other than the one originating in the anterior cingulate cortex.

There is a wide range of degenerative diseases that have been associated with various levels of GDB impairment, examples are shown in Table 1. There is a commonality in that all involve the frontal subcortical loops to some extent. Alzheimer's disease (AD) is often considered to be a posterior cortical disorder, though frontal cortical involvement is also present (Cummings, 2000). Damage to the nucleus basalis of Meynert, in the basal forebrain is particularly important in AD (Richardson & DeLong, 1988). This subcortical region is the primary source of cortical acetylcholine. Cholinergic projections from this region are widespread but one of the main destinations is the anterior cingulate region (Banich, 1997). In addition, apathy has been reported in AD (Levy, Miller, Cummings, Fairbanks, & Craig, 1996) and correlates with executive task performance commonly thought to rely heavily on frontal lobe function (Kuzis, Sabe, Tiberti, Dorrego, & Starkstein, 1999). This appears to fit well with the theory that the anterior cingulate loop deals primarily with GDB.

Progressive Supranuclear Palsy (PSP) also shows a pattern of impairment in brain regions associated with the anterior cingulate loop, including the thalamic MD nucleus (Salmon, Van der Linden, & Franck, 1997). This atypical parkinsonian syndrome results from multiple lesions including the caudate, putamen, globus pallidus and brain stem (Daniel, de Bruin, & Lees, 1995). Cognitive dysfunction (Robbins et al., 1994) and apathy (Litvan et al., 1996; Litvan, Paulsen, Mega, & Cummings, 1998) are both common features in addition to the motor, gaze and balance abnormalities that are the clinical features of the disease (Litvan et al., 1997). Of particular relevance in the pathology of PSP is damage to the cholinergic pedunculopontine tegmental nucleus of

the brain stem (Jellinger, 1988). This region is thought to project mainly to the thalamus and so has a wide influence on frontal-subcortical circuits (Rye, Saper, Lee, & Wainer, 1987). The pedunculopontine tegmental nucleus has also been implicated in cognitive function (Steckler, Inglis, Winn, & Sahgal, 1994) and experimental lesions in primates produce an akinetic state (Aziz et al., 1998). It may therefore be an important neurological component controlling GDB, possibly by its cholinergic influence on the basal ganglia.

PD is a classic example of a disease affecting the basal ganglia. Dopamine is closely associated with these structures and any systemic reduction in dopamine will have a negative impact on the frontal and subcortical regions, including those associated with GDB. In PD both the nigrostriatal and mesocortical dopamine system levels are reduced. GDB deficits were first described in PD over a century ago (Charcot, 1880). However, as was noted above, descriptions of the will in neurology were neglected during most of the 20th century.

Charcot used the term abulia to describe the PD patients he saw and this term has also been used more recently by Marsden et al., (Bhatia & Marsden, 1994; Brown & Marsden, 1998; Marsden, 1994a). However, the more common description of patients with PD is apathy (Brown & Pluck, 2000; Levy et al., 1998; Pluck & Brown, 1999; e.g. Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1993). This may reflect the nature of the disease producing progressive levels of GDB impairment, and the overlapping nature of the terms abulia and apathy. Impairments of GDB in PD are often evident to the patients themselves. For example, a sufferer of PD who wrote about his condition stated that *"I feel I could move faster if I really wished to do so, but some kind of mental blockage robs me of the will. If I force myself to try to complete some task quickly, my*

limbs seem to freeze up and my hands shake violently. But I still have the feeling that the difficulty is mental, not physical- all I need is the will" (Thompson, 1989 p 176).

Table 1: Neurological diseases associated with GDB impairment.

Disease	Effect on GDB	Reference
Postencephalitic parkinsonism	Apathy	Sacks (1973)
Parkinson's disease	Apathy	Starkstein et al. (1992)
Progressive supranuclear palsy	Apathy	Litvan et al. (1998)
Alzheimer's disease	Apathy	Levy et al. (1996)
HIV (with or without AIDS)	Apathy	Castellon et al. (1998)
Creutzfeldt-Jakob disease	Akinetic mutism	Otto et al. (1998)
Myotonic dystrophy	Apathy	Rubinsztein et al. (1998)
Huntington's disease	Apathy	Litvan et al. (1998)
Corticobasal degeneration	Apathy	Litvan et al. (1998)
Frontotemporal dementia	Apathy	Levy et al. (1998)
Sydenham chorea	Apathy	Mayeux (1983)
White matter dementia	Abulia	Filley et al. (1999)

Approaches to the Study of Goal Directed Behaviour

Comparative Neuroscience

Research into GDB within comparative neuroscience has focused mainly on behaviourist principles of motivation and consequently the concept of reward has been crucial. The idea that actions are dependent on consequences was first proposed by Thorndike who suggested the 'law of effect'. This states that actions that are followed by satisfaction are likely to be repeated (Thorndike, 1911). This formed the basis for behaviourist psychology, but was still non-biological. The adaptation of this principle to biology was made by Hull in the 1940's who formulated the concept of 'drive'. Perturbations in the homeostatic status in an animal (such as hunger) produce an energisation of behaviour (such as exploration). This increases the chance of an adaptive response (such as the finding of food) occurring. According to the law of effect, this behaviour will then be repeated and learning has occurred. Motivation, or drive in Hull's terminology, is therefore dependent on a specific homeostatic imbalance (Hull, 1943).

However, it has been found that electrical brain stimulation (EBS) of the rat septal area produces a strong positive reinforcement (Olds & Milner, 1954). This is inconsistent with the homeostatic drive theory as the rats have no biological deprivation that could be restored by EBS. Therefore, reinforcement is not merely the reduction of a homeostatic drive. Since Olds' and Milner's pioneering work it has been found that one the most effective areas for producing reinforcement with EBS is the medial forebrain bundle (Shizgal, 1997). This is involved in the dopaminergic innervation from the ventral tegmental area to the nucleus accumbens (Nolte, 1988). In addition, the nucleus accumbens itself has been found to be very sensitive to the reinforcing effects of EBS.

Dopamine release in the nucleus accumbens is associated with a range of reinforcers, particularly abused drugs (Wise, 1996).

The association between dopamine in the nucleus accumbens and reinforcement formed the basis for what became know as the 'hedonia' hypothesis (Wise, 1996). Dopamine was seen as signalling pleasure and as such was a crucial link between learning and motivation. This can been seen most clearly in a study in which rats stopped pressing a lever in order to receive an intravenous infusion of amphetamine when treated with Pimozide, a dopamine antagonist (Yokel & Wise, 1975). Thus, reduction in dopamine activity produced a reduction in the normal behaviour, as if the animals had been rendered abulic. However, it has been found that dopamine cells do not merely fire in response to the presence of a primary reward such as a piece of food, as suggested by the hedonia hypothesis.

Dopamine cells in the basal ganglia also respond to signals that predict the arrival of the reward (Schultz, 1999). For example, in primates, striatal dopamine cells do not normally respond to an auditory stimulus such as a click. If the click is paired with a reward (i.e. Pavlovian conditioning), the clicks soon begin to elicit responses in the striatum (Kimura, Aosaki, & Graybiel, 1996). Furthermore, the primary reward will lose its ability to elicit responses. This implies that dopamine cells have a more direct role in learning than signalling pleasure. They are effectively learning the appropriate response via the changes in the conditions that induce firing. Furthermore, if the primary reward is not given when on the basis of conditioning the animal is expecting it, there is a reduction in firing rate at the expected arrival time of the reward (Redgrave, Prescott, & Gurney, 1999).

In addition to responding to conditioned stimuli, dopamine neurone responses can also be reliably elicited by unexpected reward (Schultz et al., 1993). Yet, as described above, a totally expected reward will not elicit responses. This has led to a revised hypothesis that dopamine neurones indicate errors between expected and actual rewards and could therefore offer a signal for associative learning (Schultz, Dayan, & Montague, 1997). This suggestion stresses the role of dopamine neurones in a purely learning system, therefore implying that they have less involvement in motivation than first thought.

However, there are discrepant findings that are not well accounted for by the 'error signal' hypothesis. Sensory events that are neither conditioned stimuli nor rewarding can also produce cellular responses (Horvitz, Stewart, & Jacobs, 1997). If the dopamine cells merely respond to novelty then this could be reinforcing, punishing or neutral upon later investigation. Therefore, a potentially noxious or neutral stimulus could elicit a rewarding response that would not aid learning (Redgrave et al., 1999). The responses of dopamine neurones are typically of short latency, between 50 and 110 milliseconds. This is faster than the time taken for the pre-saccadic response in the superior colliculus that begins the process of orienting the eyes to the stimulus. The pre-saccadic burst usually occurs after about 150 msecs. Therefore, the dopamine responses, which are supposedly error signals, occur before the stimulus has been fully evaluated.

Conditioning experiments involve the production of a behavioural response and so interruption of ongoing behaviour is inevitable. However, considering the time course of dopamine cell responses and the nature of the stimuli that elicit them, a plausible alternative explanation for the findings is that dopamine neurones act as an 'attention-getting device' (Wickelgren, 1997b). This suggestion is also consistent with findings

that unilateral dopamine dysfunction in the basal ganglia produces lateralised attentional deficits in humans (Craft, Gourovitch, Dowton, Swanson, & Bonforte, 1992). Therefore, dopamine cells in the basal ganglia may contribute to GDB by diverting attention and consequently action, to significant aspects of the environment. Thus, they may be able to operate as novelty detectors as hypothesised in the framework of GDB described above in Figure 2.

In other fields of research, the focus has been on the brain structures involved in actions generated with or without sensory cues. This type of research corresponds quite closely to the distinction raised between willed and stimulus driven actions (Jahanshahi & Frith, 1998). For example, in monkeys, temporary lesions caused by rapid cooling of the globus pallidus impaired repetitive movements in the absence of visual prompts but not when visual guidance was available (Hore, Meyer-Lohmann, & Brooks, 1977). During visual guidance, there is less reliance on internal representations and attention to the goals of the action. In the absence of visual guidance, the animal must rely on its own representations to achieve the goal of the action.

Researchers using ablation methods have followed a similar line of research. Passingham (1993) describes experiments performed by himself and colleagues in which monkeys are trained to perform specific motor tasks followed by surgical ablation of specific cortical regions. He trained monkeys in a simple task of manipulating a handle by either pulling it or twisting it, depending on visual cues. After bilateral removal of the lateral premotor cortex the monkeys could no longer do this. They could distinguish the difference between the visual cues, but could not select movements based upon them. This shows that the lateral premotor cortex is involved in externally driven aspects of GDB. However, in terms of internal aspects and GDB it is

of interest to know which brain areas are necessary for responding in the absence of cues.

It has been found that certain frontal brain areas are essential for this type of behaviour. Monkeys were trained to lift their arm in a totally dark room, if they did so their hand would break an infrared beam and they would automatically be rewarded with a peanut. Note that this type of task has no external prompt to initiate the action. Following removal of either the SMA or anterior cingulate cortex, the monkeys were incapable of performing this task. This deficit was selective for actions with no external guidance. The SMA lesioned animals were tested with a tone to signal when a reward was available and this restored performance, presumably because the tone provided an external cue to act. This distinction between internally and externally driven actions may partially explain the clinical deficits described above. For example, the akinetic mute patient described by Damasio and Van Hoesen (1983), who had lesions to both the SMA and anterior cingulate cortex, could respond to a command but made no internally generated actions. It is worth repeating, that after recovery she described herself during the akinetic period as having her will 'neutralised'.

Human Neuroscience

The research in humans has focused on similar issues to those described in the SMA and anterior cingulate cortex lesioned animals described above (Passingham, 1993). Indeed, PET studies in normal controls have been used to extend his findings to human behaviour. PET imaging has shown that actions that are not fully specified by the instructions given to the subjects activate different brain areas compared to actions in which the instructions are fully provided or well learned tasks (Spence & Frith, 1999). Such tasks are comparable to those devised by Passingham (1993) in which the monkey

lifts its arm either at will or routinely in response to a tone. In humans this can be achieved for example, by asking subjects to lift either of two fingers when either of them is touched (internally driven) or to only lift the finger that is touched (externally driven). This procedure produces bilateral activation in the dorsolateral prefrontal cortex for the internally driven task relative to the externally driven task (Frith et al., 1991).

It is apparent that much of the research in the human neuroscience of GDB has focused on attentionally mediated actions compared with other less cognitive factors. A major conceptual paradigm responsible for this approach is the SAS (described above).

Researchers using EEG recordings have taken a slightly different approach to the study of voluntary actions. When a person makes a simple finger movement, without a stimulus to tell them when to respond, electrical potential changes can be detected approximately 800 msecs prior to detectable muscle movement. This is thought to correspond to activity in the frontal lobes, particularly the supplementary motor area (Deecke & Kornhuber, 1978). This task conforms to what has been described above as an internally driven action and so can be used to gain insights into internally driven actions both in normal and clinical samples. For example, it has been shown that this movement-related potential (MRP) may be reduced in schizophrenia. Patients with negative signs but not positive symptoms showed reduced amplitudes and slopes for self-triggered but not externally triggered movements (Fuller & Jahanshahi, 1999c). This was interpreted by the authors to reflect a deficit in willed driven action as the underlying cause of negative signs in schizophrenia, a current neurocognitive theory of symptom expression (Frith, 1992).

However, more controversial use of MRPs has been into research that suggests that the volitional process is initiated unconsciously (Libet, 1999). As the MRP occurs up to a second before the actual movement, this is counter to introspective evidence that movement is performed very soon after the intention is formed. In order to record awareness of intention in relation to the MRP a clock face can be used. The subject is instructed to report the time at which the decision to move is made. Using this technique, it has been found that the MRPs can be detected around 550 msecs prior to the movement beginning. However, subjects report the intention to move at around 200 msecs before the movement (Gomes, 1999). Therefore, it appears that there is a 350 msec period in which the subject is preparing the action but is not yet aware that they are intending to act (Libet, 1985). It has been suggested on the basis of single cell recordings in primates that the intention builds up in basal ganglia loops between half and five seconds in advance of the actual movement with between 20 and 150 cycles of the circuits (Schultz, 1999).

Furthermore, in the human studies, the perceived time of the actual movement occurs before the actual movement. This means that subjects think they have moved about 100 msecs before they actually do. The implication of this is that people must have conscious access to their own motor processes and do not simply infer them from peripheral sensory events (Haggard, Newman, & Magno, 1999). Although the results from these experiments are still controversial, they do show that voluntary actions, in particular those that are internally driven, can be studied behaviourally under certain circumstances.

It is also of note that internally driven actions are in essence, a particular form of executive skill by definition (see below). Indeed, the model of attentive and routine

actions suggested by Norman and Shallice (1986) is in more general terms a model of executive function. However, executive performance involves other abilities not just self-generated movements. As such the relationship between GDB and executive performance is discussed in more detail below.

It can be seen comparing the comparative and human research into GDB that the concept of reward and reinforcement has been relatively neglected in favour of cognitive perspectives. However, as suggested in the framework described in Figure 2 the concept of reward has important influences, particularly on the motivational and hedonic aspects of GDB. Reward has been shown to influence simple psychomotor tasks. In the Card Arranging Reward Responsivity Objective Test (CARROT) it was reported that normal subjects sort cards in to piles faster when offered a financial reward (Pickering et al., 1997) and that motivation impaired brain damaged patients showed enhanced responsivity when treated with bromocriptine, a dopamine agonist (Powell et al., 1996). It has further been shown that reward responsivity on the CARROT is reduced in abstaining smokers but increases after smoking a single cigarette, a result attributed to the boosting of dopamine levels by nicotine in smokers (Al-Adawi & Powell, 1997).

The association between reward responsivity and dopamine suggests that this may be impaired in PD due to the dopamine depletion in this disease. It has been found using PET scanning, that reward responsivity shows activation in the nucleus accumbens, but that this activation is reduced in PD patients (Goerent, Lawrence, & Brooks, 1999). At the behavioural level it has been demonstrated that in late stage PD, responsivity on the CARROT is reduced (L. Dawkins, personal communication).

Curiosity and Novelty

A great deal of research has been conducted on rats using naturalistic observations, such as amount of exploratory movement when placed in a novel environment (see e.g. Floresco, Seamans, & Phillips, 1997). Consequently, such behaviours are relatively well understood in the rat, for example it has been shown that exploratory behaviour is dependent on the integrity of the ventral tegmental area, ventral pallidum and nucleus accumbens (Hooks & Kalivas, 1995).

In rats, exploratory behaviour diminishes with age. However, it is unclear whether this results from increased fear of the testing environment or from apathy (Lalonde & Badescu, 1995). In humans, the alternative terminology to 'exploratory drive' would be 'curiosity'. In stark contrast to the work with rats, little is known about human curiosity. The research that has been performed, has tended to focus on educational issues (see e.g. Maw & Maw, 1962). However, there is a small body of neuropsychological work pioneered by Daffner et al. that demonstrates that unlike rats, successful human ageing seems to have no systematic effect on curiosity, as measured by responses to novel visual stimuli (Daffner, Scinto, Weintraub, Guinessey, & Mesulam, 1994a; Daffner, Scinto, Weintraub, & Mesulam, 1994b). Curiosity is closely linked to motivational constructs (Spielberger & Starr, 1994). It may therefore be a possible explanation for GDB impairments seen in brain damaged individuals.

This hypothesis has been tested in patients with AD. In one study it was found that AD patients spent less time than controls examining novel incongruous images, a test that was assumed to measure curiosity (Daffner, Scinto, Weintraub, Guinessey, & Mesulam, 1992). It was also found that those patients who showed little interest in the novel items were rated as higher in apathy by their carers. This seems to show that reduced

curiosity is related to apathy in AD. However, theoretically, curiosity to novel items as measured above can be distinguished from curiosity to 'information gaps' such as exemplified in crosswords (Loewenstein, 1994). In the framework of GDB shown in Figure 2, curiosity-arousing stimuli would come under the process of external determinants.

It is of interest, but as yet unknown, whether loss of curiosity is inevitable in disorders, other than AD, that result in reduced GDB. Furthermore, it is unclear whether responses produced by novelty and responses produced by information gaps can equally be processed as salient stimuli in apathetic patients.

Information Processing Speed

As a longer term consequence of the encephalitis lethargica pandemic in the 1920's many patients went on to develop a parkinsonism syndrome (Cheyette & Cummings, 1995). As part of this syndrome a range of non-motor symptoms were noted such as apathy, depression, slowed thought process and mild memory disturbance; these came to be grouped together as 'subcortical dementia'. However, it was not until the 1970's that the concept of subcortical dementia was applied to other diseases such as PD, progressive supranuclear palsy and Huntington's disease (Darvesh & Freedman, 1996). The neuropsychological profile in subcortical dementia is contrasted with that of Alzheimer's disease as discussed in Chapter 1.

A related concept to subcortical dementia is 'bradyphrenia'. This was first used to describe patients with postencephalitic parkinsonism and had a remarkably similar clinical description to subcortical dementia, i.e. reductions in voluntary attention, initiative and slight diminution of memory (Naville, 1922). However, the term

bradyphrenia has in recent years taken on a more specific definition. Spicer et al. (1994) have defined bradyphrenia as *"slowing of cognition or mentation"* (p 457).

The relationship of bradyphrenia to GDB is unclear. Some authors consider apathy to be a crucial component of bradyphrenia (Rogers, Lees, Smith, Trimble, & Stern, 1987), but in their study motivation was not formally assessed and so definite conclusions can not be drawn. Starkstein et al. (1992) used an abridged version of the apathy evaluation scale devised by Marin et al. (1991). It was found that apathy in patients with PD was associated with poor performance on verbal fluency and Trails B of the Reitan trail making test, this was explained as a consequence of bradyphrenia. Starkstein et al. conclude that *"the cognitive slowing so frequent in patients with PD may be related to the presence of apathy"* (p 138). However, in order to demonstrate bradyphrenia it is necessary to show a non-specific slowing, not just deficits on particular tasks.

In addition, the evidence for bradyphrenia existing at all in PD is controversial and many researchers have failed to demonstrate the phenomena. For example no slowing was detected using lexical decisions (Spicer, Brown, & Gorell, 1994), similarly no effect was found using a mental rotation task (Duncombe, Bradshaw, Iansek, & Phillips, 1994). The evidence of a relationship between apathy and bradyphrenia presented by Starkstein et al. (1992) rests on the poor performance of high apathy compared with low apathy PD patients on verbal fluency and trail making tasks. Both of these tasks involve executive skills and it is feasible that PD patients with apathy show poor executive performance but without generalised cognitive slowing when measured by other non-executive tasks. Indeed, there is evidence that deficits in executive task performance are particularly associated with motivational impairment, even on tasks such as two choice guessing, which do not have a timed component (Al-Adawi, Powell, &

Greenwood, 1998). This implies that the cognitive dysfunctions in apathetic PD patients are related to executive skills and not necessarily generalised cognitive slowing.

Executive Function

Executive function is a term used to describe a range of cognitive skills. It can be defined such that *"executive control is necessary to deal with novel tasks that require us to formulate a goal, to plan and to choose between alternative sequences of behaviour to reach this goal, to compare these plans in respect of their chosen goal, to initiate the plan selected and to carry it through, amending it as necessary"* (Rabbitt, 1997 p 3). Such a description is strikingly similar to the concept of willed actions that are performed in situations where a response has to be chosen from competing alternatives (Spence & Frith, 1999). In the framework of GDB described above supervisory executive processes are included to account for GDB in these situations. It is therefore clear that executive dysfunction could be a cause of reduced GDB.

As stated above, Starkstein et al. (1992) found that performance on two executive tasks was impaired in PD patients with apathy. He related this to bradyphrenia as both of these tasks involve level of performance in a given time period. However, many researchers have found that cognitive skills traditionally considered as executive, but not those considered as non-executive are negatively associated with GDB levels in neurological patients. For example, working memory scores are correlated with apathy in patients with HIV-1 dementia but serial or choice reaction times are not (Castellon, Hinkin, Wood, & Yarema, 1998) and with the Stroop task and dual task performance but not single task performance (Castellon, Hinkin, & Myers, 2000). Similarly, in the cases described as showing psychic akinesia the only reliable cognitive impairments

were in set shifting and verbal fluency, both of which are considered executive skills (Laplane, 1994).

However, in some cases of GDB impairment amnesia is prevalent. This is most common for patients with thalamic damage (Catsman Berrevoets & von Harskamp, 1988; Pasquier, Lebert, & Petit, 1995). This may simply represent the co-involvement of the thalamus in mnesic and GDB processing. Also of note, is that memory performance is related to apathy in AD (Kuzis et al., 1999). However, as memory performance is a very good indicator of disease progression in AD, it would be more surprising if this were not so. A reported drug trial of bromocriptine on motivation impaired patients is also relevant here. Powell et al. (1996) found that not only did dopaminergic therapy improve motivation, it also improved memory performance as measured by digit span and the Buschke Selective Reminding Test (BSRT). Therefore, it appears that mnemonic functions may also be associated with apathy.

The importance of this finding is unclear. Powell et al. (1996) suggests that the BSRT may be sensitive to strategy application during both encoding and recall, and so poor performance would indicate executive dysfunction. Alternatively, memory ability may be essentially normal, but performance is impaired due to the overall level of effort applied, which may be reduced as a consequence of a broader GDB deficit. The deficit on digit span is also difficult to interpret. Although this task is often considered to assess attention, it also has a working memory component. It is noteworthy that the patients reported by Powell et al. also improved on a task known to be highly executive in nature (verbal fluency). Consequently, improvement in executive function in these patients is a possible explanation for the improved memory performance.

Therefore, despite some evidence for memory dysfunction on some tests in motivational impaired patients, this may be a manifestation of an underlying executive dysfunction. There are no reported cases of motivational impairment in neurological patients whose executive performance has been shown to be normal. However, motivational impairment has been demonstrated in those with seemingly normal memory ability. In two cases of severe motivational impairment resulting in abulia, both patients had perfect scores on the mini mental state examination, a measure that is weighted towards memory performance (Yamanaka et al., 1996).

Perhaps the strongest position on the association between executive skills and motivation has been presented by Al-Adawi et al. (1998). They performed a comprehensive range of neuropsychological tests on 54 brain-injured patients (either traumatic brain injury or subarachnoid haemorrhage) as well as estimating their motivation levels. Of three general intelligence tests, none were related to motivation. Of four executive tasks, impairments were associated with three (towers of London, two choice guessing and verbal fluency but not the Wisconsin Card Sorting Test). Of two memory tests both were related to motivation (digit span, BSRT).

Their interpretation was that motivational impairment is a manifestation of disrupted executive function. Although they showed that both current and premorbid I.Q. estimates (Ravens Progressive Matrices and the National Adult Reading Test) were unrelated to motivation, they found, as in the bromocriptine trial described above, that memory performance was. Al-Adawi et al. (1998) attributed the correlation between the BSRT and motivation to the amount of effort applied by subjects rather than a memory or executive dysfunction per se.

If the results are considered in terms of the framework of GDB presented above, three possible explanations are available. Firstly, that there is dysfunction at the level of the supervisory executive processes which has the combined effect of impairing memory test performance and reducing GDB levels. Alternatively, dysfunction at the level of the supervisory executive processes could disconnect much of the influence of motivation on the GDB system. Finally, if the deficit was at the level of motivation it could lead to reduced effort being applied to memory and executive tasks.

There is therefore at present insufficient evidence to distinguish between deficits at different levels of the framework in terms of cognitive test scores. There is however, no doubt that cognitive function, and in particular executive and mnemonic skills, are closely associated with impairments in GDB.

Chapter 3: Disability, Cognition, Mood and Personality in Relation to Apathy in Parkinson's Disease

Introduction

Reduced Goal Directed Behaviour (GDB) is increasingly being recognised as an important feature of PD. Although older descriptions of a GDB impairment in this disease are available (see e.g. Charcot, 1880) only recently have systematic investigations been performed into the aspects of the disease described as apathy. The first, by Starkstein et al. (1992) used a customised version of the Apathy Evaluation Scale (AES) of Marin et al. (1991). This 14-point questionnaire was completed by 50 PD patients visiting a neurology clinic. The frequencies of individual apathy scores indicated a bimodal distribution. It was estimated that 42% of the sample had apathy based on this distribution. A later report used the Neuropsychiatric Inventory (NPI) of Cummings et al. (1994). This was administered to the carers of 40 PD patients during pre-operative assessment for pallidotomy surgery. It was found that 33% of the sample could be described as apathetic (Levy et al., 1998). The only other research to date, also using the NPI, was conducted on a community sample of 139 PD patients. This produced a much smaller estimate of the prevalence of apathy in PD at 16.5% (Aarsland et al., 1999).

The discrepancy in estimates of prevalence probably reflects sampling effects. For example, it is highly likely that the pre-pallidotomy patients were, on average, more advanced cases than those reported in the community or outpatient samples. However, a major flaw in each of these studies is the lack of a baseline of apathy scores in a non-neurological population. Starkstein et al. (1992), using the modified AES, assumed that

bimodality of the distribution indicated those with and those without apathy. In the two studies that used the NPI, it was implicitly assumed that apathy is a pathological response not present in patients without neurological dysfunction. Therefore, in none of the above reports was the distribution of scores in normal samples considered. This has two negative implications. First, it is impossible to estimate accurately how the PD patients differ from normal populations in terms of apathy. Second, it is impossible to say whether apathy is a secondary social consequence of the chronic disease process, a distinct symptom reflecting the underlying pathology, or a non-specific physiological response to chronic illness. This latter possibility is raised by the observation that, in animals, illness reliably produces a range of behavioural changes including a loss of interest for daily activities (Aubert, 1999). This is likely to be a physiological rather than a behavioural adaptation, a key factor that produces a GDB change in sick animals is the level of cytokines in the body (Anisman, Kokkinidis, Borowski, & Merali, 1998). Therefore, specific physiological changes can cause reduced GDB. In PD patients, this may be an alternative explanation to apathy being a psychological reaction to physical impairment.

A further question is 'what factors are associated with apathy in PD'? Many of these issues were discussed in Chapters 1 and 2 and so will only briefly be recapitulated here. The relationship between depression and apathy is important. Apathy is often not distinguished from depression in PD as a separate clinical entity (see e.g. Lieberman, 1998). In one review depression without sadness (sometimes called 'masked depression'), has been described in older adults (Gallo & Rabins, 1999). It is controversial whether depression should be diagnosed in the absence of negative mood, indeed emotional distress is crucial to many definitions of depression (see e.g. Parkinson & Colman, 1995). If lack of interest is apparent in the absence of emotional

distress then the state more readily resembles apathy as defined in Chapter 1. The problem arises due to symptoms of depression that overlap with the construct of apathy. Intuitively there are common aspects to each, and indeed depression has been described as showing signs of 'sick-will' (Ingvar, 1994). Clearly, the relationship between depression and apathy is worthy of study.

The conclusions from what little research has been performed into the relationship between apathy and depression in PD are unclear. Starkstein et al. (1992) found that the majority of patients they described as apathetic were also depressed. While 42% of PD patients were described as apathetic, only 12% showed no signs of depression. This seems to indicate that there is a close co-morbidity of apathy and depression in PD. Levy et al. (1998) compared 154 patients with neurodegenerative disease, composed of patients with Alzheimer's disease, fronto-temporal dementia, progressive supranuclear palsy, Huntington's disease and PD. They failed to find a correlation between apathy and depression in this combined group. When only the scores of the 40 PD patients were compared a significant but small ($r=.34$) association between apathy and depression was found. The most recent study by Aarsland et al. (1999) also found a significant relationship between apathy and depression. Of the 23 PD patients in the sample identified as having apathy, only six showed no signs of depression.

It is already well known that anxiety is a common symptom in PD patients (Siemers et al., 1993). However, it is not usually associated with apathy. Disinterest, a feature of apathy, seems to be opposite to many common descriptions of anxiety that emphasise increased attention to stimuli or 'hypervigilance' (Wenzel & Holt, 1999). Empirical work has also tended to support the independence of anxiety and apathy. For example, Starkstein et al. (1992) failed to find a relationship between apathy and anxiety in their

PD sample. However, Arsland et al. (1999) used a factor analysis approach and found that in PD patients apathy and anxiety scores on the NPI were correlated and clustered into one factor. Furthermore, it has been shown that in normal samples low anxiety is linked to 'behavioural activation' (see e.g. Pickering et al., 1997). Therefore, raised anxiety may be related to apathy in PD patients. This hypothesis is tested below.

Other mood variables are also worthy of consideration. Anhedonia, the inability to experience pleasure, is a concept closely related to apathy. It has been stated that *"anhedonia borders upon a number of other constructs; these include diminution of interest, reactivity of mood, flattening of affect, apathy and anergia"* (Snaith, 1993 p 957).

In comparative research, the dopamine system, particularly projections between the ventral tegmental area and the nucleus accumbens, has been identified as being closely associated with reward (Meredith & Totterdell, 1999). As discussed in Chapter 1, the dopamine system is also impaired in PD and so it could be hypothesised that the processing of reward is hindered in patients with PD. There is some evidence for this from PET studies. For example, it has been found that in a search task in which financial rewards were manipulated, normal controls showed activation in the substantia nigra, nucleus accumbens and prefrontal cortex. This activation was absent in PD patients (Goerent et al., 1999). However, there are no direct observations of anhedonia in PD. The only minor exceptions being a psychophysics study of taste preferences that found PD patients preferred higher sucrose concentrations than lower concentrations in a way that differed from the control subjects. The authors suggested that this might reflect impairment of the 'hedonic' value of the sensation (Travers et al., 1993). The other is a description of the reduced ability of a psychostimulant (methylphenidate) to

improve positive mood in PD patients compared to controls (Persico, Reich, Henningfield, Kuhar, & Uhl, 1998). Consequently, although reward processing seems susceptible to the physiological changes seen in PD, the presence of anhedonia has not been confirmed. It is therefore of interest to assess whether anhedonia is present in PD patients and its possible relationship to apathy.

A related issue is the question of personality in PD patients. A particular 'parkinsonian personality', characterised by inflexibility, moral rigidity and introversion has often been reported (Poewe et al., 1990). This is considered to be directly related to the dopaminergic abnormalities in PD brains (Menza, Mark, Burn, & Brooks, 1995). Indeed, dopamine is considered an important substrate of extraversion, a trait that is defined in terms of motivation, impulsivity and agency (Depue & Collins, 1999). Therefore both the specific personality and apathy described independently in PD may be different aspects of the same phenomenon. Alternatively, the occurrence of apathy and the parkinsonian personality may be relatively independent manifestations of physiological alterations in PD patients. At present, there is no clear way of distinguishing between these two hypotheses.

Cognition has been studied extensively in PD. Although the most commonly observed cognitive profile in PD patients is an executive disorder (Brown & Marsden, 1990), a range of other cognitive impairments has also been described. These include abnormalities in memory (Hugdahl et al., 1993), visuo-spatial abilities (Cronin-Golomb & Braun, 1997), visual attention (Lieb et al., 1999) and semantic processing (Spicer et al., 1994). In several studies, executive skills have been shown to be impaired in apathetic patients with non-parkinsonian disorders such as Alzheimer's disease (Kuzis et al., 1999) and HIV infection (Castellon et al., 1998). The only study that has looked

at cognition and apathy specifically in PD has also found that apathy is associated with executive dysfunction, but non-executive skills were not fully assessed (Starkstein et al., 1992). Therefore, it is unclear to what extent executive rather than non-executive cognitive skills are associated with apathy.

There are several questions that need to be answered, regarding apathy in PD. These include: 1) Is apathy a reaction to disability or a direct symptom of PD? 2) Are PD patients with apathy cognitively impaired? If so, what broad domains of function are implicated? 3) What is the relationship between apathy and other psychopathologies such as depression, anxiety and anhedonia in PD? 4) Are the parkinsonian personality and apathy in PD descriptions of the same phenomenon?

Method

In order to answer the questions stated above, 66 patients with either PD or osteoarthritis (OA) were visited in their homes and given a wide range of assessments of disease characteristics, cognitive skills, psychiatric status and personality. OA patients were included as they were considered a suitable control group for the patients with PD. OA, like PD is a chronic, progressive, presently incurable illness that results in difficulty or inability to perform day-to-day tasks with usual diagnosis in later life (Felson et al., 2000). Furthermore, PD and OA are similar in that once diagnosed, sufferers know that the disease will be part of the rest of their lives. There is therefore, no expected 'length of illness'. The use of a medical control group such as this is employed when it is necessary to have groups who differ only in the disease type, not experience of chronic disease. This approach has been used successfully in previous reports to examine factors in PD such as depression (Gotham et al., 1986) and personality (Leiva, Galvan, & Matius-Guia, 1996; Menza et al., 1993; Poewe et al.,

1983). All assessments were administered by the author of this thesis. Ethical approval was granted for each patient group from the appropriate hospital ethics committees.

Subjects

Subjects were initially contacted by telephone and an appointment made for the full assessment. All of the patients in the PD sample were current or past patients of the National Hospital for Neurology and Neurosurgery in London. Forty-seven PD patients were initially assessed, but data on two were rejected due to changes in diagnoses discovered later (one progressive supranuclear palsy and the other Lewy body dementia). Twenty-three of the patients were female, the mean age of the sample was 66.36 years (range 48-79 years). The sample included a wide range of disease progression; the mean Hoehn and Yahr stage (described in Appendix C) was 2.6 (range 1-5). The OA patients were all current or past patients of the Department of Rheumatology, Kings College Hospital in London. Nineteen patients were initially assessed, but data on two were rejected due to possible neurological involvement (one showed signs of undiagnosed parkinsonism, the other was at high risk of having ischemic white matter lesions). Twelve of the OA patients were female. The mean age of the sample was 67.29 years (range 49-84 years). There was no significant difference between the two groups for age ($t(60)=.37$, $p=.712$) but the OA patients had significantly fewer years of education (OA=11.18, SD=2.54; PD=13.00, SD=2.85; $t(58)=-2.30$, $p=.025$).

Assessments

The assessment of the two groups was identical with the exception that Hoehn and Yahr and Schwab and England (Schwab & England, 1969) disease progression stagings were

only appropriate for the PD sample. Activities of daily living (ADL) scores were recorded with a scale previously developed for use in comparing PD and arthritis patients. This 24 point self-report Likert scale assesses aspects of day-to-day life that the patients are physically capable of but not what they actually choose to do. Patients are asked to rate their ability to perform a range of common manual dexterity and mobility tasks such as 'Get out of bed' or 'Open tins' without special aids. This scale is described in more detail in Appendix D. Cognitive function was assessed with the Cambridge Examination of Cognition in the Elderly (CAMCOG, Roth, Huppert, Tym, & Mountjoy, 1988) and the Mini-Mental State Examination (MMSE, Folstein & Folstein, 1975). Both tools have previously been used successfully in evaluating global cognitive function in PD (Hobson & Meara, 1999). In addition, three tests of executive function were included, the Stroop task (Stroop, 1935), verbal fluency (FAS, Benton, 1986) and the Wisconsin Card Sort Test-short version (WCST, Nelson, 1976). Further details of the cognitive assessments used including scoring methods are given in Appendix E.

In order to assess current psychiatric status the Beck Depression Inventory (BDI, Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983) and the Snaith-Hamilton Pleasure Scale (SHPS, Snaith et al., 1995) were included to give estimates of depression, anxiety and anhedonia respectively.

For the assesment of personality the Tridimensional Personality Questionnaire (TPQ) was used (Cloninger, 1987). This measures three personality dimensions, Novelty Seeking (NS), Harm Avoidance (HA) and Reward Dependence (RD). However, more recent factor analysis has indicated that a previous sub-factor of RD should be

considered separately (Stallings, Hewitt, Cloninger, Heath, & Eaves, 1996). This fourth factor is called Persistence (P).

Additionally, to assess apathy all patients completed the Self-report version of the Apathy Evaluation Scale (AES-S) and were questioned to obtain scores on the Researcher rated Apathy Evaluation Scale (AES-R, Marin et al., 1991). The AES-R is administered as a semi-structured interview. Additionally, if a caregiver was available they were asked to complete the Informant version (AES-I). Details of the items and structure of the AES-S, AES-R and AES-I are given in Appendix B.

Administration

A few days before the date of the appointment, all patients were sent copies of the TPQ, BDI and SHPS and were asked to complete these before the researcher arrived, this was performed to minimise the time spent in a single session and reduce the risk of assessments being aborted due to fatigue. At the beginning of the actual session individual details such as date of birth and gender were collected first, followed by the ADL assesment, and where appropriate, the Hoehn and Yahr and Schwab and England assessments. Following this all patients completed the verbal fluency (FAS) task followed by the CAMCOG examination, which includes the MMSE and category fluency assessments. Next, all patients were asked to complete the HADS and AES-S. If a caregiver was available and the patient consented, the caregiver was asked if they would complete the AES-I. The patients were not allowed to see the caregivers responses. Following this, the AES-R interview was completed followed by the Stroop task and the WCST. Due to fatigue, time constraints and occasional objections, some assessments were not completed by all patients. The lowest completion rates by the patients were for the HADS and WCST which were only completed by 52 (84%) of the

patients. A full list of completion rates is given in Appendix F. Caregiver apathy ratings (AES-I) were only obtained for 30 (66.7%) of the PD patients and five (29%) of the OA patients. The time to complete the full session took approximately two hours per patient.

The AES-R is the most in-depth tool currently available for the assessment of apathy of subjects 'in the field' and has proven reliability and validity (discussed in Chapter 2). In addition to this measure, a large amount of data on disability, cognitive and psychiatric status and personality were also collected. This gave the opportunity to examine the contribution of multiple factors to the presence of apathy in PD patients. These factors are considered individually below.

Results of Disability and Apathy

In order to check for a difference in the functional ability of the two patient groups, a t-test was performed on the ADL data. This revealed that there was a small difference between the PD group and the OA group on the ADL scale, with the PD group being slightly more disabled, but this did not reach significance (PD mean=53.45, SD=21.35; OA mean=43.71, SD=16.5; $t(59)=-1.69$, $p=.096$). In terms of apathy, the OA group scored an average of 23.29 (SD=3.82) on the AES-R. This is significantly lower than the PD group who scored 35.29 (SD=11.37), $t(60)=-4.24$, $p<.001$. Similar significant group differences were also found using the self-report AES-S version. The PD patients scored 32.95 (SD=9.03) and the OA patients scored 26.88 (SD=5.01), $t(59)=-2.61$, $p=.011$. Between group comparisons were not attempted using the informant version (AES-I) given to caregivers. This was because although data was available on 30 PD patients, it was only available on five OA patients. It was considered that the sample size in the latter group was too small to be representative.

In order to assess the consistency of the three measures of apathy, their level of agreement was compared using pairwise parametric correlations. It was found that all pairs were significantly correlated at the level of $p<.001$. The self-report AES-S was positively correlated with the AES-R (.717) and with the AES-I (.766). The highest correlation was between the AES-I and AES-R (.777). To check reliability, 20 PD patients completed the AES-S at a second session three to six months after the initial assessment. The correlation between the two administrations was high, $r=.848$, $p<.001$. Both the researcher rated and self-rated apathy scores significantly identified the differences between the two groups in apathy and are highly correlated. As Marin et al. (1991) have previously shown that the AES-R has greater predictive validity, further analysis was limited to this more in-depth measure.

The distribution of AES-R scores by the OA and PD groups are shown in Figure 3. In the PD sample, It can be seen that there was a bimodal distribution. A cut-point of below 38 identified one peak and a score of 38 or higher the other. This criterion was used to divide the PD patients into two groups. The high apathy PD group (PD-HA) contained 15 patients (33.3%) and the low apathy PD group (PD-LA) contained 30 patients (66.7%).

Using this grouping, none of the OA patients was within the range of scores in the PD-HA group (38-62). Twenty-five (83.3%) of the PD-LA sample were within the range of scores in the OA group (18-33). If the OA group are compared with the results found using the AES-R with an American sample of healthy individuals of a comparable age, all OA patients were within two standard deviations of the American group mean (Marin et al., 1991).

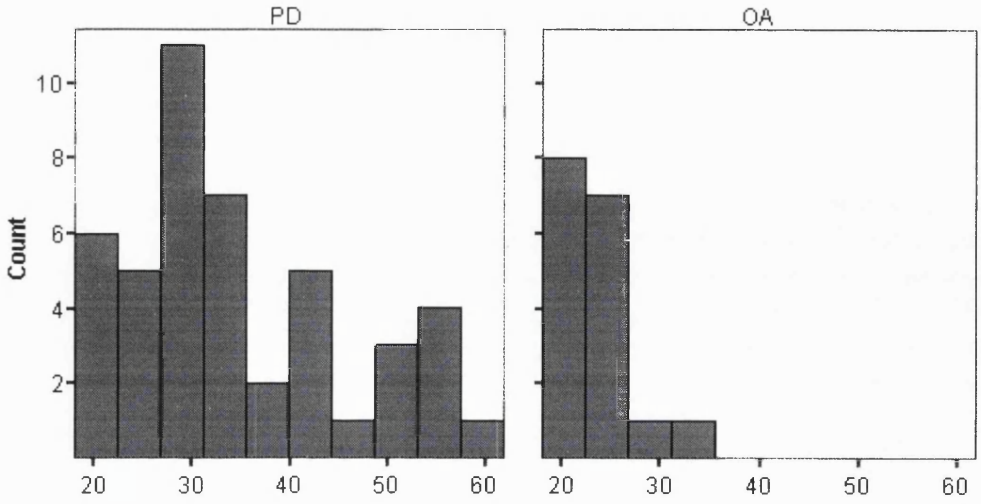


Figure 3: The distribution of AES-R scores in the PD and OA groups.

The PD-LA patients had a mean apathy score of 28.4 (SD=4.77) and the OA patients a mean score of 23.29 (SD=3.82). This difference is significant, $t(45)=3.78$, $p<.001$. Therefore, although the bimodality indicates the highest apathy PD patients, the remaining PD patients also have higher scores than the OA patients. If the cut-off point is recalculated as the OA mean plus two standard deviations, 25 PD patients (55.6%) fulfil the criteria for apathy. For this reason, the PD patients represented in the curve within the low scores of the distribution are described as Low Apathy (LA) rather than no apathy.

Data were available for disease progression in the PD groups. The mean Schwab and England score for the PD-HA group was 66 (SD=15.49), which implied more advanced disease progression than the PD-LA group who scored a mean of 76.67 (SD=15.16). This difference was found to be significant, $t(43)=2.21$, $p=.033$. Hoehn and Yahr stages also varied between the groups. The PD-HA patients tended to be at a later disease stage (mean = 2.9, SD=1.37) than the PD-LA patients (mean =2.48, SD=1.05). However, a t-test revealed that this difference was not significant ($t(43)=1.14$, $p=.117$).

The percentages of group members at each stage of the Hoehn and Yahr scale are shown in Table 2.

Table 2: Percentage of the PD-HA and PD-LA group members at each Hoehn and Yahr stage.

Hoehn and Yahr Stage	PD-HA	PD-LA
1	6.7	20
1.5	6.7	6.7
2	40	13.3
2.5	0	16.7
3	13.3	23.3
4	13.3	20
5	20	0

Further comparisons were made between the 30 PD-LA patients, the 15 PD-HA patients and the 17 OA patients using one way ANOVAs with planned contrasts wherever necessary. As there was a small (but non-significant) difference between PD and OA patients on ADL scores this is considered as a covariate were appropriate. In addition due to the significant difference between OA and PD groups in years of education this was also considered as a covariate where appropriate. The contrasts were 1) the PD-HA group compared to the PD-LA group and 2) the PD-HA group compared to the OA group. This in practice allows the comparison of the high apathy patients with two control groups, low apathy PD and OA. Of these, the comparison with the PD-LA

group is the most relevant as the only essential difference between these groups is the level of apathy.

A one way ANOVA was performed on the ADL scores of the three groups with years of education as a covariate. The PD-HA group scored a mean of 57.86 (SD=22.26) on the ADL assessment. This indicates a slightly higher level of impairment than the PD-LA group who scored a mean of 51.40 (SD=20.98) or the OA group who scored a mean of 43.71 (SD=16.5). However, differences between the groups were found to be non-significant ($F(3,55)=1.70$, $p=.178$). A correlation was performed to examine the relationship between apathy and ADL scores in the PD sample directly. There was found to be no relationship, ($r=.087$, $p=.576$).

Discussion of Disability and Apathy

Two groups of patients were compared, one with PD and the other with OA. Although there was a trend for the PD patients, particularly those with high apathy, to be more disabled than the OA group, the differences were not significant, and all patients showed mild to moderate levels of disability. The scale used to assess physical abilities has previously been used to compare PD and OA patients. OA patients have similar day to day problems as PD patients. In addition, both are chronic progressive diseases. Therefore, a crucial difference between the groups is the disease type.

If the consequences of the diseases in terms of reduced mobility and opportunity for normal activities are a significant source of apathy in patients, then there should be comparable levels of apathy in the two groups, and at least increased levels of apathy in the OA group compared to normal age matched controls. Conversely, if it is the presence of PD pathology that is crucial then it would be expected that the PD patients

would be more affected. The latter result was clearly found. The PD patients showed higher levels of apathy than the OA patients did. Even when high apathy PD were compared with low apathy PD and OA patients, there was still no significant difference between them on ADL scores. Furthermore, within the PD sample, there was no significant correlation between ADL scores and apathy.

When comparing just the high apathy PD with low apathy PD, a difference was found for disease progression in the two groups. On the Schwab and England scale, the high apathy PD patients indicated further disease progression. However, using an alternative estimation, the Hoehn and Yahr scale, no significant difference was found. A possible reason for this may be the nature of the two scales. Scores on the Hoehn and Yahr disease progression scale are dependent on the presence of specific motor abnormalities and it is therefore a primarily objective assesment (the scale is described in Appendix C).

The Schwab and England scale, although also based partly on symptom presence (e.g. slowness), reflects the patient's interpretation of their abilities. Scores on this scale are allocated dependent on the patient's ability to cope with household chores and the level to which this is slowed or prevented by the presence of PD. This information is gathered by verbal report from the patients. The Schwab and England scale is therefore more subjective than the Hoehn and Yahr scale. It is possible that irrespective of motor difficulties, the presence of apathy tends to inflate Schwab and England scale scores. The Hoehn and Yahr scale is not susceptible to this lack of specificity between actual and potential ability. It can therefore be concluded that there may be some relationship between disease progression and the development of apathy in PD, but that this relationship is quite weak.

Based on these results, the conclusion is that apathy in PD is a primary symptom of the disease process, not a psychological response to physical impairment and associated disability. Although a weak association was found between disease progression and apathy, it is probably not strong enough to explain the current results. Furthermore, if apathy is a direct symptom of the disease process it will, to some extent, be related to disease progression. Conversely, if apathy is viewed as a reaction to disability, then no difference would be expected between the PD and OA groups. It can therefore be concluded that apathy is a primary symptom of PD.

Although this position has been assumed by previous researchers (e.g. Starkstein et al., 1992; Aarsland et al., 1999) the current findings are the first to demonstrate empirically that it is not caused by a simple reaction to physical impairment. In addition, it has not been universally accepted that apathy is a direct symptom of PD. Singer (1973) used the term 'premature social ageing' to explain her findings that patients with PD, compared to normal controls, spend more time in solitary activities such as watching television, are less likely to engage in household chores and are less likely to have a close circle of friends. She attributed this to the general effect of having a chronic disabling illness. However, in view of the current findings it is likely that PD patients develop reduced social circles etc., at least in part, as a direct result of specific disease related physiological changes.

On the evidence presented above it can not be stated that physical impairment does not contribute to the development of apathy. A second control group with no chronic illness would have been needed to fully investigate this hypothesis. However, the OA patients scored a mean apathy score of only 23.29. The scale used, the AES-R, can produce a range of scores between 18 and 72. Thus, the OA group was close to the

bottom of this scale. It could be stated therefore, that even if a second completely healthy control group were included, the OA patients would not have scored much worse. In fact, Marin et al. (1992) using the same scale found mean apathy scores of around 25.9 in a comparably aged American sample, that was not selected for physical impairment (although it is likely that some did). Thus, it is unlikely that the current OA group would have scored higher on apathy than a healthy control group. This implies that motivation is relatively unaffected by physical impairment.

Results of Cognition and Apathy

In order to test for differences in cognitive skills associated with apathy, results on all cognitive assessments were compared using the same statistical approach described above. That is, one way ANOVAs with group membership as a between subjects factor and ADL scores and years of education considered as covariates. Planned contrasts when necessary were made between the PD-HA patients and the other groups.

The MMSE and CAMCOG tests are widely used for dementia screening and so are considered sensitive to global cognitive decline. MMSE scores were similar in all three groups, although the PD-HA group had the lowest mean score. The PD-HA group scored a mean of 26.93 (SD=3.22), the PD-LA group scored a mean of 28.21 (SD=1.87) and the OA group scored a mean of 27.63 (SD=2.94). Statistical analysis with ANOVA revealed no significant differences between groups ($F(4,51)=2.07$, $p=.099$). The PD-HA group also scored lower than either of the other groups on the CAMCOG. The PD-HA mean of 88.79 (SD=7.94) was lower than the PD-LA group mean of 95.04 (SD=4.22) and the OA group mean of 92.69 (SD=9.91). A one way ANOVA revealed that this difference was significantly different, $F(4,51)=3.81$, $p=.009$. In the planned

contrasts a significant difference was found between the PD-HA group and the PD-LA group (p=.021), but not the OA group (p=.317).

The global score of the CAMCOG assessment can be broken down into eight broad domains of cognition. These are; orientation, language, memory, attention, praxis, calculation, abstract reasoning and perception. Further details of the CAMCOG sub-scales are given in Appendix E, where the constituent tasks and marking schemes are described. Mean scores for each group on each of the CAMCOG sub-scales are shown graphically in Figure 4.

ANOVA calculations revealed significantly different scores between groups on the sub-scales of language ($F(4,51)=3.03$, $p=.026$) memory ($F(4,51)=3.71$, $p=.01$) and abstract reasoning ($F(4,51)=3.79$, $p=.009$). Contrasts showed that the PD-HA group scored significantly lower than the PD-LA group (p=.007) but not lower than the OA group (p=.14) on the language sub-scale. The contrasts on the memory sub-scale showed that the PD-HA group scored significantly lower than the PD-LA group (p=.002). The contrast between the PD-HA and OA groups for memory narrowly missed significance (p=.051). For abstract reasoning neither of the contrasts were significant, (PD-HA:PD-LA, p=.812; PD-HA:OA, p=.226). There were no significant differences on any of the other CAMCOG sub-scales.

As the language sub-scale includes a test of category fluency, this is potentially influenced by executive function, irrespective of more central language skills (the association between apathy and category fluency is considered below). In order to test this the language sub-score was recalculated without the category fluency component.

When this was performed, language scores were no longer significantly different between groups ($F(4,51)=1.97$, $p=.114$).

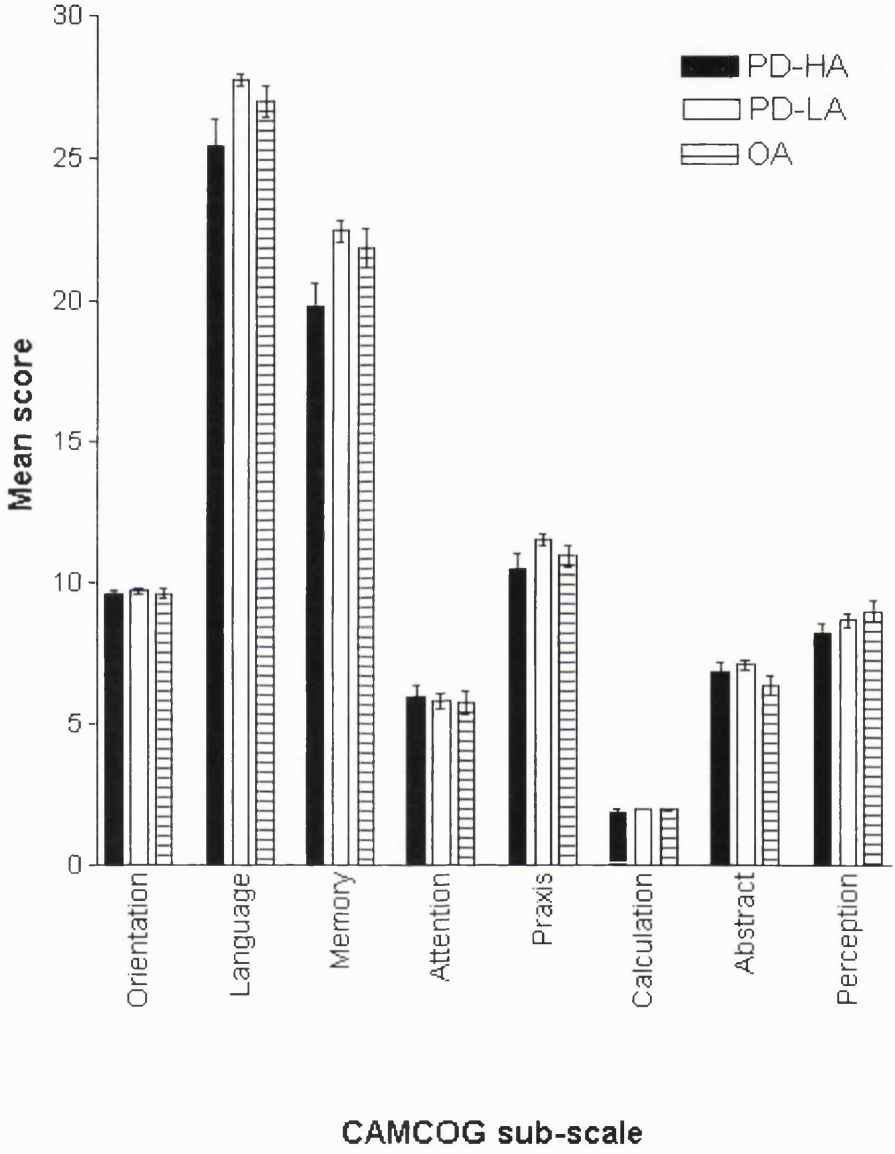


Figure 4: Mean scores (and SEMs) on the sub-scales of the CAMCOG examination for the PD-HA, PD-LA and OA patients.

To examine the relationship between cognitive performance (on the MMSE and CAMCOG) and apathy in the PD group directly, correlational methods were employed. Statistical values from the parametric correlations are shown in Table 3. Significant

relationships were found between apathy and MMSE and apathy and the total CAMCOG score (lower performance associated with higher apathy). The significant relationship with MMSE performance was not detected previously in the ANOVA calculations.

Table 3: Correlational statistics for the relationship between apathy and MMSE and CAMCOG derived measures in the PD patients.

Measure	Sub-scale	r Value	p Value
MMSE	Total Score	-.348	.024
CAMCOG	Total Score	-.511	.001
	Orientation	-.148	.348
	Language	-.471	.002
	Language (-fluency)	-.420	.006
	Memory	-.504	.001
	Attention	-.038	.814
	Praxis	-.352	.022
	Calculation	-.293	.060
	Abstract Reasoning	-.291	.062
	Perception	-.118	.458

As in the ANOVA calculations, memory scores were related to apathy in the expected direction. Similarly, language sub-scale scores, either in their initial form or recalculated to remove the verbal fluency component, were correlated with apathy, again in the expected direction of worse performance with increased apathy. The correlation approach revealed a relationship that was not detected in the ANOVA

calculations. This was a significant negative correlation between apathy and praxis scores. The PD patients with the highest levels of apathy achieved the lowest praxis scores.

Three tests of executive performance were performed by the patients; the WCST, verbal fluency for letters (FAS) and the Stroop task. In addition, the language sub-scale of the CAMCOG examination includes a task of category fluency that is also considered an executive task (Gurd & Oliveira, 1996). The mean scores for each group on each measure of executive function are shown in Table 4.

The findings above using the MMSE and CAMCOG imply that there is some group difference in level of cognitive decline. In order to control for this and minimise its confounding effects on the interpretation of executive skill performance, MMSE scores were considered as a covariate in the ANOVA calculations of the executive skill tasks. This is in addition to the use of ADL and years of education scores being covaried, as described above.

A one way ANOVA revealed a significant group difference for the number of categories achieved on the WCST, ($F(5,41)=2.51$, $p=.045$). As shown by the contrasts, the PD-HA group achieved significantly less categories than the PD-LA patients ($p=.011$) but not the OA patients ($p=.058$), though this was approaching significance. There was also a significant group difference for the total number of errors made ($F(5,39)=3.58$, $p=.009$). The contrasts revealed that the PD-HA group made more errors than the PD-LA group ($p=.049$) but not the OA group ($p=.064$), but again, this was approaching significance. There was also a significant between-group difference for the number of non-perseverative errors ($F(5,39)=4.11$, $p=.004$), but contrasts revealed that

this was not directly related to the presence of apathy as the PD-HA group did not differ significantly from either of the other groups. There was no significant group difference for the number of perseverative errors ($F(5,39)=1.94$, $p=.109$).

In the Stroop task, individual data points represent the number of items named/read in 45 seconds, in addition, as described in Appendix E, it is useful to provide a statistic representing interference performance that controls for the rate of verbal output. This can either be achieved by subtracting the complex condition (interference) from the simple condition (colour naming) or by calculating the ratio of the complex/simple conditions. Both methods are reported here (the merits of the two statistics are discussed in Appendix E). Significant group differences were found on the word reading ($F(5,47)=3.60$, $p=.008$) but not the colour naming conditions ($F(5,47)=1.62$, $p=.174$). Contrasts in the word reading condition revealed significant differences between the PD-HA and PD-LA groups ($p=.017$) and the PD-HA and OA groups ($p=.003$). There was also a significant group difference between groups on the interference condition ($F(5,47)=3.3$, $p=.012$). Contrasts revealed that PD-HA performed below the level of PD-LA patients ($p=.001$) and OA patients ($p=.011$) on the interference condition.

When rate of verbal output is controlled for it was found that there was no significant difference using the subtraction method ($F(5,47)= 1.60$, $p=.180$). However, as there was some indication of different speech rates from the significant difference on the word reading condition between groups, the ratio statistic for the Stroop task is relevant. Using this method of calculating the effect of interference on output, it was found that there were significant group differences ($F(5,47)=3.09$, $p=.017$). The contrasts

indicated that the PD-HA patients were more affected by interference than the PD-LA patients (p=.008) but not the OA patients (p=.179).

Table 4: Means (and SDs) for the PD-HA, PD-LA and OA groups on tests of executive skills.

Test	Measure	PD-HA	PD-LA	OA
WCST	Categories achieved $_{1,2}$	2.91 (2.63)	5.11 (1.4)	5 (1.68)
	Total errors $_{1,2}$	18.11 (14.54)	9.64 (7.86)	7.42 (7.68)
	Non- perseverative errors$_1$	10.56 (8.22)	6 (4.7)	4.08 (5.6)
	Perseverative errors	7.56 (8.02)	3.64 (4.18)	3.33 (3.08)
Stroop	Reading $_{1,2}$	69.92 (14.21)	87.26 (14.09)	93.38 (19.61)
	Colour naming	52 (8.31)	60.22 (12.37)	67.75 (17.17)
	Interference $_{1,2,3}$	21.23 (8.56)	33.3 (8.09)	31.94 (8.77)
	Subtraction (colour-interference)	30.67 (7.66)	27.36 (9.45)	35.81 (13.65)
	Ratio (interference/colour) $_{1,2}$	.40 (.14)	.56 (.10)	.49 (.16)
Verbal	FAS $_{1,2,}$	9.71 (3.56)	13.16 (3.62)	10.76 (4.89)
Fluency	Category $_{1,2,3}$	14.2 (4.3)	18.39 (4.58)	19.35 (4.26)

$_1$ = Main effect for group, $_2$ =PD-HA significantly worse than PD-LA, $_3$ = PD-HA significantly worse than OA.

Scores on the letter fluency task (FAS) differed significantly between groups, $F(5,49)=5.44$, $p<.001$. Planned contrasts revealed that the PD-HA group performed significantly less well than the PD-LA group ($p=.036$) but not the OA group ($p=.194$).

There was a significant group difference for category fluency, $F(5,50)=8.47$, $p<.001$. The planned contrasts indicated that the PD-HA group produced significantly fewer words than both the PD-LA patients ($p=.049$) and the OA patients ($p=.005$).

As there was a significant difference in the word reading condition of the Stroop task, it remains possible that the differences in verbal fluency were not due to an executive deficit per se, but to limited verbal output skills in the PD-HA patients. To assess this, the calculations between the PD-HA and PD-LA groups were repeated for the verbal fluency tasks but with the word reading scores on the Stroop considered as a covariate. It was found that the PD-HA group still performed significantly less well than the PD-LA group on both the letter fluency ($F(2,37)=4.64$, $p=.016$) and category fluency tasks ($F(2,37)=4.80$, $p=.014$).

To investigate further the relationship between apathy and executive function in PD, parametric correlations were performed between apathy scores on the AES-R and the measures of executive function displayed in Table 4. The results are shown in Table 5. Apathy scores correlated with all measures on the executive tasks except colour naming and the subtraction statistic (colour naming condition minus interference condition) in the Stroop task. All significant correlations were in the direction of performance decreasing with increases in apathy score.

Table 5: Correlational statistics for the relationship between apathy and executive function in the PD patients.

Test	Measure	r Value	p Value
WCST	Categories achieved	-.489	.002
	Total errors	.465	.004
	Non- perseverative errors	.404	.013
	Perseverative errors	.443	.006
Stroop	Reading	-.458	.003
	Colour naming	-.259	.106
	Interference	-.533	<.001
	Subtraction	.050	.712
	Ratio (interference/colour)	-.320	.016
Verbal Fluency	FAS	-.439	.003
	Category	-.421	.005

Discussion of Cognition and Apathy

On the two assessments of global cognitive performance, apathy in PD was associated with lower performance on both the CAMCOG and the MMSE. However, the result for lower scores associated with higher apathy on the MMSE was only apparent in the correlational analysis restricted to the PD patients alone. CAMCOG scores were shown to be lower in high apathy PD patients than the low apathy PD patients in both the ANOVA and correlational analyses. There is therefore evidence of reduced scores on dementia ratings in patients with higher levels of apathy, though the correlation values suggest the effect is stronger when examined with the CAMCOG than the MMSE. This

maybe because the MMSE, although widely used, is thought to be insensitive to the types of cognitive impairments often seen in non-demented PD patients (Mahieux et al., 1995). Furthermore, the MMSE is thought to be insensitive to all but gross cognitive impairment. The CAMCOG is considered more sensitive and it has been concluded by one group that the *"Camcog can discriminate between individuals even at the high end of the ability range"* (Roth et al., 1988 p 68). Furthermore, the CAMCOG has been found to be sensitive to cognitive changes in non-demented elderly subjects indicating it's ability to identify cognitive impairments in individuals who are not grossly impaired (Cullum et al., 2000).

The CAMCOG may be more sensitive than the MMSE due to the greater emphasis placed by it on executive skills. Such skills are often impaired in PD (Elias & Treland, 1999) and have previously been related to apathy in PD (Starkstein et al., 1992). The current results therefore partially support previous findings. However, a more precise assessment of the relationship of executive and non-executive skills to apathy is available from analysis of the sub-scale scores of the CAMCOG.

It was found that the only cognitive domains impaired in the high apathy PD patients were memory, language and praxis. Apraxia is commonly thought of as a cortical disorder (Darvesh & Freedman, 1996) but is sometimes seen after lesions to the basal ganglia (Della Salla, Basso, Laiacona, & Papagno, 1992) and has been described in PD and other subcortical degenerative diseases (Leiguarda et al., 1997).

Scores on the language sub-scale of the CAMCOG were found to be significantly different between groups in the main analysis, only when the category fluency component was included. When the language sub-scale score was recalculated without

this executive aspect, the group difference was found to be non-significant. This implies that the language sub-scale was only related to apathy due to the influence of the category fluency component. However, the correlation analysis restricted to the PD patients found that there were significant negative correlations between apathy scores and the language sub-scale scores, whether the category fluency component was removed or not. It must therefore be concluded that there is some association between apathy in PD and language use ability.

Language use is of particular interest in this context as spontaneous use of language is often used to diagnose apathy both clinically and in research. The Percentage Participation Index (PPI) of Powell et al. (1996) is a measure of motivation that involves an index of the patient's amount of time actively participating in therapy sessions. Similarly the AES-R used in this thesis involves the use of open-ended questions, responses to which are used to assess intensity and emotion, these are thought to indicate the level of apathy. There is therefore the possibility that the method of apathy assesment has confounded the interpretation of the relationship between apathy and language sub-scale scores. This is because language use itself was partly responsible for the allocation of apathy scores, and this may be why they are related to the language sub-scale of the CAMCOG.

Although the result should be treated with caution, it may be worth considering possible interactions between apathy and language on theoretical grounds. Certain deficits of spontaneous language use are known in the cognitive neuropsychology literature as dynamic aphasia (Costello & Warrington, 1989). Patients described as such produce sparse spontaneous utterances in normal life but on formal testing show few signs of aphasia. Although dynamic aphasia patients are not usually described as being

apathetic, tools such as the PPI and AES-R would probably rate dynamic aphasic patients as having some level of motivational impairment. Conceptually it is unclear whether such cases should be considered as having primarily linguistic or GDB impairments. Although dynamic aphasia has not been described in PD, it has in another parkinsonian syndrome, progressive supranuclear palsy (Esmonde, Giles, Xuereb, & Hodges, 1996), in which apathy is almost universally found (Levy et al., 1998). Interestingly, in the Esmonde et al. study, two of the three patients reported also showed personality change. In one this was described as a loss of 'sense of humour' and in the other 'anergia', descriptions consistent with apathy and a more global GDB impairment.

The memory sub-scale of the CAMCOG was also found to be related to the apathy levels of the patients, in both the group comparisons and the correlation within the PD group. Memory impairment has been associated with GDB reductions in other groups. It has been found to be correlated with levels of negative symptoms in schizophrenia, and this was vaguely interpreted as either a loss of motivation or a willed action impairment (Brebion et al., 2000).

Al-adawi et al. (1998) found that memory performance was related to level of motivation in their group of traumatic brain injury and subarachnoid haemorrhage patients. They attributed this to the amount of effort applied to the task. However, it is unclear how this explanation could explain the current findings. If effort was a crucial factor then reduced scores by the apathetic patients would have been expected on other sub-scales of the CAMCOG such as 'attention' that include 'serial sevens', a task many people find effort demanding. If reduced level of effort applied is the cause of cognitive deficits in apathetic PD patients, then a more general cognitive impairment would be expected. A possible alternative explanation for the reduced memory scores is that the

strategies, rather than the effort applied, are important contributions to reduced memory function in relation to apathy.

Strategic processes have previously been associated with apathy in a range of disorders including PD. The current findings strengthen these results. The high apathy PD patients in this study were impaired on all four of the executive tasks administered. Three of the tasks involved measuring rate of speech (the Stroop task and the two verbal fluency tasks) and so it is important to consider whether the deficit in the PD-HA group is simply one related to ease of vocalisation. In the case of the Stroop task this interpretation can be rejected because when the ratio of the interference to colour naming was used the significant difference remained. If both had been equally affected by difficulties with vocalisation in the PD-HA group, then the ratio statistic would not have been different between the two PD groups. However, a significant difference was found indicating that the interference condition performance was particularly impaired relative to the colour naming condition by the high apathy PD patients. Similarly, the ease of output interpretation can be ruled out as an explanation of the difference between high and low apathy PD patients on the verbal fluency tasks. When word reading scores (from the Stroop task) were used as a covariate in the difference calculations, the high apathy PD patients were still significantly below the level of the low apathy PD patients.

The result concerning the impaired performance on the WCST being linked to apathy is of particular interest. High apathy PD patients achieved fewer categories and made more errors than PD patients with low levels of apathy. Starkstein et al. (1992) found impaired performance in their high apathy PD patients on executive tasks but attributed this to bradyphrenia, as all of the tests associated with apathy in their battery had time

constraints. However the WCST is not performed under time restrictions and so bradyphrenia is not a convincing explanation for the current finding. This adds to the finding of Al-adawi et al. (1998) that performance on two choice guessing, another untimed executive function test, was correlated with motivation levels in their brain injured patients.

Results of Mood and Apathy

The scale used for the assessment of anhedonia, the SHPS, uses a binary marking system for each item (though there are four possible responses). A total score of greater than two is considered abnormal. The distribution of scores on this binary marking method for all the patients by group is shown below in Figure 5. There is marked negative skewing of the distributions in each group due to floor effects. Only one of the 30 PD-LA patients scored abnormally, and only two of the 12 PD-HA patients who completed the questionnaire scored abnormally. Of the 15 OA patients who completed the questionnaire, all scored zero. Due to the extreme skewing and large variance differences, statistical analysis was not attempted on these data. In order to correct for these problems and allow statistical analysis, individual questionnaires were re-marked on a Likert scale of one to four; this produced data with a range of possible scores between 14 and 56. The distribution of the re-marked SHPS data is shown in Figure 6 where it can be seen that the distribution is considerably less skewed. Mean scores from each patient group are shown in Table 6. On the re-marked data the PD-HA group scored higher levels of anhedonia than either of the other groups. However, a one way ANOVA failed to find significant group differences ($F(4,46)=.97$, $p=.432$).

Scores for depression were available from the BDI and the depression sub-scale of the HADS. Scores for anxiety were available from the anxiety sub-scale of the HADS. Scores for each group on these three measures are also shown in Table 6.

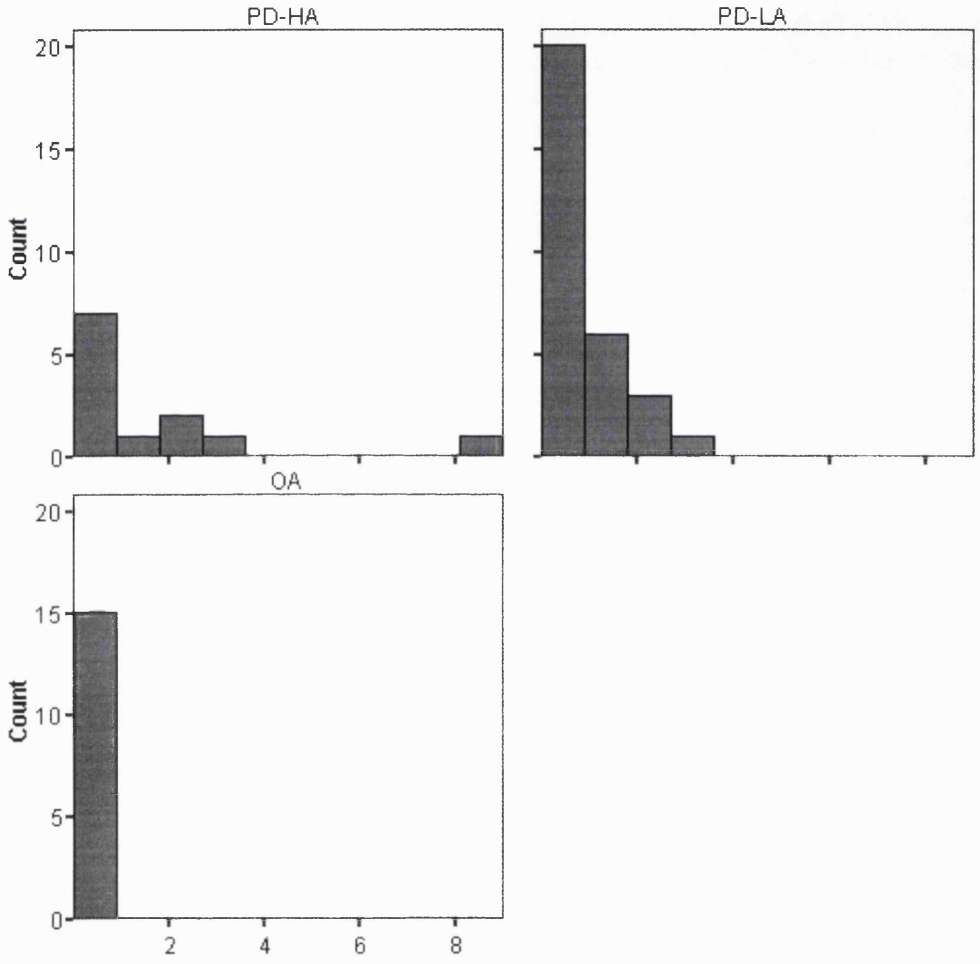


Figure 5: The distribution of binary SHPS scores for the PD-HA, PD-LA and OA groups.

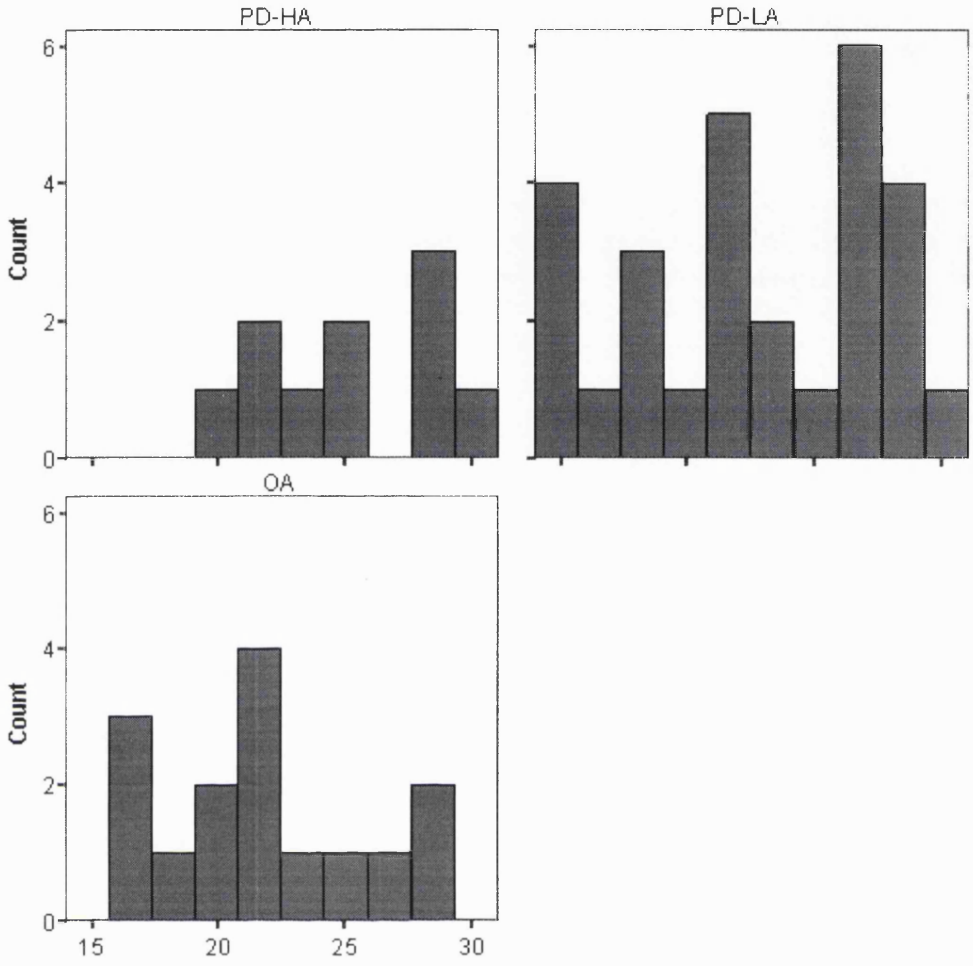


Figure 6: The distribution of Likert scale SHPS scores for the PD-HA, PD-LA and OA groups.

Table 6: Mean (and SD) scores on anhedonia (Likert scale), depression and anxiety for the PD-HA, PD-LA and OA groups.

	PD-HA	PD-LA	OA
SHPS (Anhedonia)	25.1 (3.60)	22.46 (4.98)	21.67 (4.01)
BDI (Depression)	15.43 (9.08)	12.87 (5.90)	8.46 (4.63)
HADS (Depression)	7.17 (4.22)	4.62 (2.62)	3.93 (3.22)
HADS (Anxiety)	9.17 (5.36)	8.27 (4.14)	6.71 (5.11)

The PD-HA group scored higher than both of the other groups on depression as measured by the BDI. A one way ANOVA confirmed a significant group difference ($F(4,49)=4.20$, $p=.005$). However, planned contrasts revealed that the PD-HA group differed from the OA group ($p=.011$) but not the PD-LA group ($p=.196$). Using the HADS measure depression also showed a significant group difference, $F(4,45)=3.26$, $p=.020$, however the planned contrasts revealed that this was not related to apathy. The PD-HA group were significantly different to neither the PD-LA group ($p=.057$) nor the OA group ($p=.084$).

As the PD-HA group scored significantly higher than OA patients did on the total BDI, further calculations were performed on the three factors that can be extracted from the BDI as described by Brown et al. (1988). These correspond to items examining guilt and self-blame, dysphoria and somatic aspects of depression. When these factors were used instead of the total BDI, it was found that both dysphoric ($F(4,49)=2.66$, $p=.043$) and somatic ($F(4,49)=4.55$, $p=.003$) component scores differed between groups, but the guilt component did not ($F(4,49)=1.40$, $p=.247$). Contrast analysis indicated that for neither the dysphoric nor somatic components did the PD-HA patients differ significantly from the PD-LA patients. For dysphoria the PD-HA group scored

significantly higher than the OA group (p=.032), but not the PD-LA group (p=.339). Similarly for the somatic component, the PD-HA group scored significantly higher than the OA group (p=.006) but not the PD-LA group (p=.142).

Anxiety scores as derived from the HADS differed slightly between groups. The PD-HA showed the highest levels of anxiety and the OA patients the lowest levels. The PD-LA reported levels of anxiety intermediate between the other groups. However, the group differences were not found to be significant ($F(4,45)=1.99$, $p=.113$).

To examine the relationship between mood variables and apathy in PD directly, parametric correlations were performed. The mood variables considered were total BDI and the three sub-scales described above, depression and anxiety scales of the HADS and the Likert marked SHPS data. The results are shown in Table 7 where it can be seen that there was no significant correlation between total BDI depression scores and apathy. However, there was a small but significant correlation between the somatic complaints sub-scale of the BDI and apathy, in the direction of higher depression accompanying higher apathy.

A significant positive correlation was also found between depression on the HADS and apathy, but not anxiety on the HADS. There was also a small but significant positive correlation between apathy and anhedonia, the more apathetic PD patients were found to be more anhedonic.

Table 7: Correlational statistics for the relationship between apathy and mood variables in the PD patients.

Scale	Sub-scale	r Value	p Value
BDI	Total	.268	.078
	Guilt	.094	.543
	Dysphoria	.210	.171
	Somatic	.309	.041
HADS	Depression	.490	.002
	Anxiety	.195	.240
SHPS	Total (Likert)	.351	.031

Discussion of Mood and Apathy

Of the three mood variables assessed, none showed a strong relationship with apathy in PD. On some measures, group differences were detected, but these were not between the high and low apathy patients. The correlational analysis found support for the comorbidity of mood disorders and apathy, but the lack of effect in the main analysis means that the results should be interpreted cautiously.

Although significant between-group effects were observed with different measures of depression, in all cases planned contrasts failed to show significant differences between PD patients with either high or low apathy. The significant differences that were found were all between high apathy PD patients and OA controls. The risk of depression in PD is thought to be elevated (Cole et al., 1996), and so the findings of higher depression in the PD patients when compared with the OA controls supports this. But this does not

provide any evidence that apathy is related to depression in the PD patients. The crucial statistics for this were the contrasts between the high and low apathy patients, all of which failed to reach significance.

There were, however, significant positive correlations between apathy scores and depression scores when only the PD patients were considered. Although the total BDI score did not correlate with apathy, the somatic aspects sub-scale did. The somatic items of the BDI include statements intended to probe information such as 'interest in other people' and 'interest in sex'. Such items may be more sensitive to the presence of apathy than the presence of depression. The depression sub-scale of the HADS also correlated with apathy in the combined PD sample. The HADS depression sub-scale also contains items that show significant overlap with the concepts of apathy. Items on the HADS require a response to the level of agreement with statements such as 'I feel as if I am slowed down' and 'I have lost interest in my appearance'. The total depression score on the HADS may, like the somatic component of the BDI, partly assess apathy. Therefore, it is unlikely that the PD patients identified in this chapter as having high apathy were more depressed than the other PD patients were. A more likely explanation is that depression inventories such as the BDI assess both apathy and depression, this can lead to apathetic patients with no emotional distress endorsing statements that artificially elevate depression scores.

Anhedonia was postulated as being related to apathy on the theoretical grounds that there is, as with depression, some similarity between the symptoms (Snaith, 1993). Furthermore, the dopamine systems impaired in PD are also thought to be involved in reward processing (Al-Adawi & Powell, 1997). Some evidence was found for a relationship between apathy and anhedonia. Although on the assesment administered, a

binary classification is normally used (Snaith et al., 1995), this was thought inappropriate in the current samples due to the floor effects observed in the distribution of scores. The developers of the scale suggest a score of greater than two can identify anhedonic individuals (Snaith et al., 1995). Only three of the PD patients (16.67% of the PD-HA group and 3.3% of the PD-LA group) fulfilled this criterion. When re-marked on a Likert scale, no association with apathy was found comparing PD groups with high or low apathy and control OA patients. However, there was a small but significant correlation between apathy scores and re-marked anhedonia scores in the full PD sample. There is therefore, some weak support for a relationship between apathy and anhedonia in PD. This would be consistent with the theory that motivational impairment in neurologically impaired patients is accompanied by a reward responsivity deficit (Al-Adawi et al., 1998).

In terms of anxiety, no relationship was detected with apathy. Either in the group comparisons that included high and low apathy PD patients and the OA control group, or the correlation confined to the PD group, no significant relationship was found. Although anxiety levels are often thought to be raised in PD patients (Richard et al., 1996), there is no evidence that apathy is related to this.

Results of Personality and Apathy

The TPQ scale was used in this analysis. This can be used to derive four personality traits, Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD) and Persistence (P). The latter of these was initially considered a sub-scale of RD and so both the original and modified measures of RD are considered in the analysis. The mean TPQ scores by trait for each group are shown in Table 8. One way ANOVAs were performed on the personality scale data with group membership as a between

subjects factor. The three groups were PD-HA, PD-LA and OA as described above. There were no significant differences on any of the personality dimensions (F and p values are shown in the table). To assess relationships between apathy and personality in PD directly, parametric correlations were performed using the TPQ and AES-R data. The results are shown in Table 9. It can be seen that the only personality trait as measured by the TPQ that was significantly correlated with apathy was P. Although RD was approaching significance (p=.069), when the P sub-scale is removed the significance is weakened (p=.290).

Table 8: Mean (and SD) scores on the TPQ for the PD-HA, PD-LA and OA patients.

	PD-HA	PD-LA	OA	F and p Values
NS	13.38 (6.09)	12.39 (5.04)	12.08 (4.17)	F(4,46)=.37, p=.832
HA	20.31 (8.05)	18.71 (6.69)	16.46 (7.1)	F(4,46)=1.65, p=.178
RD	16.85 (3.39)	17.43 (5.3)	17.77 (3.72)	F(4,46)=.76, p=.560
RD-P	13.54 (2.3)	12.89 (4.03)	13.46 (3.36)	F(4,46)=.82, p=.521
P	3.31 (1.93)	4.54 (2.2)	4.54 (1.9)	F(4,46)=1.51, p=.216

Personality, as assessed by the TPQ, is assumed to measure behavioural control systems and also specific neurotransmitter 'tone'. Because of this it is of interest to check for correlations with cognitive processes. This is of particular relevance in the PD sample, as PD patients are known to have both abnormal personality and cognitive profiles. To do this, scores on the TPQ were compared with the scores on the CAMCOG, MMSE, Stroop interference, WCST categories, letter and category fluency for the PD patients as

a whole group. No significant correlations between personality and cognitive variables were found. The results are shown in Table 10.

Table 9: Correlational statistics for the relationship between apathy and personality variables in the PD patients.

Trait	r Value	p Value
NS	-.092	.567
HA	.219	.170
RD	-.287	.069
RD-P	-.169	.290
P	-.348	.026

Table 10: Correlation values for personality scores and cognitive measures in the full PD sample.

Trait	CAMCOG	MMSE	Stroop	WCST	FAS	Cat
NS	r=-.072	r=.025	r=.202	r=.022	r=-.052	r=.157
	p=.669	p=.881	p=.230	p=.900	p=.751	p=.339
HA	r=-.148	r=-.157	r=.006	r=-.011	r=-.188	r=-.293
	p=.376	p=.347	p=.973	p=.951	p=.245	p=.071
RD	r=.034	r=.098	r=.024	r=-.091	r=.259	r=.060
	p=.838	p=.558	p=.887	p=.598	p=.107	p=.718
RD-P	r=.011	r=.086	r=-.037	r=-.197	r=.208	r=.057
	p=.947	p=.609	p=.830	p=.250	p=.197	p=.731
P	r=.056	r=.073	r=.107	r=.104	r=.221	r=.036
	p=.736	p=.663	p=.528	p=.545	p=.170	p=.827

Discussion of Personality and Apathy

The concept of a parkinsonian personality has been given considerable credibility. Furthermore, the TPQ has previously been used to demonstrate that PD patients tend to score differently on certain aspects of personality than disability matched controls (Menza et al., 1993).

Personality characteristics in PD have long been debated, but many believe that there is a particular style that identifies patients. This has been postulated as being related to dopamine depletion (Lawrence, Koepp, Gunn, Cunningham, & Grasby, 1999). An inventory based on a neurochemical model of personality was used in the current study (Cloninger, 1987). The trait of particular relevance is 'Novelty Seeking' (NS) as it has been argued that this is based on dopaminergic tone. Validation of the dopamine relationship has come from several sources. A study of a normal population has shown that NS scores correlate with genetic expression of dopamine D4 receptor levels (Ebstein et al., 1996). Clinical studies have shown that NS scores are lower in PD patients (Menza et al., 1993) and that scores correlate with striatal ^{18}F Dopa binding in PD patients (Menza et al., 1995).

There is therefore reasonable support for the suggestion that PD patients have lower NS scores than comparable normal populations. The current findings failed to detect this, as there was no significant difference between the PD and OA patients. It is unclear why previous findings were not replicated. Normative data are available for NS scores of over 1000 US adults (Cloninger, Przybeck, & Svrakic, 1991). The mean ages of the sub-groups described (black or white, male or female) ranged from 43.2-45.3 and so are approximately 20 years younger than the current sample. If age differences were used to extrapolate scores, this would predict average NS scores in the US sample ranging

from 10-11.7. These scores are similar to, but slightly lower than those observed in the current study.

One possible reason for this is that, although NS has a large heritable basis (Stallings et al., 1996), it may be subject to environmental circumstances. Education levels varied between groups; the control OA patients may have lower novelty seeking scores due to this. However, in the main group comparison education level was considered as a covariate. If an environmental factor that varied between the groups is masking the effect, it can not be simply attributed to years of education.

The main hypothesis relating to personality in this thesis was that NS scores would be lower in PD patients with high apathy. This hypothesis can be rejected, as there were no significant differences between PD patients with different apathy levels (either in split-group comparisons or correlational). The other main traits of the TPQ are harm avoidance and reward dependence, but neither of these was significantly related to apathy either. However, although not significant in the group analysis, it was found that a minor trait of the TPQ, persistence, was significantly correlated with apathy scores in the PD patients.

The trait of persistence is described as *"perseverance despite frustration and fatigue"* (Cloninger et al., 1993 p 978). Items in the TPQ are scored as true or false and example items from the persistence scale are 'Other people think I am too independent because I won't do what they want' and 'I am usually so determined that I continue to work long after other people have given up'. Such items have a lot in common with apathy and there is significant overlap in the concepts. Patients who score high on persistence could a priori be expected to receive low scores in the apathy assesment.

Although a significant relationship was found between apathy and a single personality trait, this does not imply that the parkinsonian personality and apathy are synonymous. The trait of persistence itself is not directly related to the concept of a parkinsonian personality. This is usually described in terms of behavioural rigidity (Booth, 1940), introversion (Poewe et al., 1990) and low novelty seeking (Menza et al., 1995). Persistence as a trait is probably best considered as a closely related description of apathy.

If there is a particular personality of PD patients that is related to NS, it is relatively independent of the symptom of apathy. This could be explained tentatively by differential involvement of dopamine receptor systems in PD. NS has been associated with D4 receptor polymorphism as described above. The dopaminergic involvement in motivation has been more associated with D3 receptor systems. For example, D3 receptors are thought to be denser in the nucleus accumbens than the dorsal striatum (Levesque et al., 1995). The nucleus accumbens is an area critically involved in the frontal-subcortical circuit posited as dealing with motivation (Mega & Cummings, 1994). Furthermore, there are suggestions that motivation in PD is improved as a side effect of treatment with Pramipexole, a dopamine agonist with high affinity for the D3 receptor (Lieberman et al., 1997).

Additionally it has been shown that apathy in PD is closely related with cognitive function, in particular executive skills. If the personality of the patients is related to apathy then it would be expected that personality scores would to some extent correlate with executive performance too. However, no evidence for this was found.

A further reason to suspect that apathy is unrelated to conventional personality descriptions is that diseases such as progressive supranuclear palsy and Huntington's disease commonly result in apathy (Rosenblatt & Leroi, 2000) but sufferers are not described as having a particular personality type. Furthermore, there is evidence to believe that the personality type is evident in PD patients even five years before motor symptom onset (Hubble, Venkatesh, Hassanein, Gray, & Koller, 1993). Apathy has not been reported as being present before PD diagnosis.

General Discussion

Although the PD patients and OA patients did not differ significantly in terms of ADL scores, they did differ significantly on measures of apathy. This indicates that apathy is not simply a response to physical difficulties in everyday life, but is related to the neurophysiological changes associated with PD.

However, two potential criticisms of the current research should be considered. Firstly, although a large sample of 45 patients with PD was assessed, only 17 OA patients were included. While the number of control subjects is small, the level of significance achieved ($p<.001$) seems to indicate that a type one error is unlikely and that the testing of a larger sample would not have increased the accuracy of the results. Indeed, a similar level of significance was found for apathy scores in myotonic dystrophy compared with Charcot-Marie-Tooth disease controls (Rubinsztein et al., 1998). In that study only 13 control subjects were studied. A second criticism is the possibility of unconscious bias by the researcher in the evaluation of apathy levels. This arises because the researcher knew of the hypothesised direction of the results and could not practically be blind to the diagnosis of the patients. However this can not be a confound as even the self-report questionnaire identified significantly higher apathy levels in the

PD patients relative to controls. Furthermore, the researcher rated apathy scores were highly correlated with carer rated apathy scores in the PD sample, indicating the accuracy of the researcher ratings.

Based on the bimodality of the distribution of apathy scores, it is suggested that 33% of the PD patients showed unusually high levels of apathy. If it is assumed that apathetic patients would be less likely to participate in a research project, the present figure may even be an underestimate. There is very little previous work on prevalence estimations of apathy in PD, and what work has been performed has used different assessment tools. These have produced estimates of between 16.5% and 42%. However even the PD patients described as low apathy in this study had a mean apathy score significantly higher than the OA mean. If an arbitrary cut-point of the OA mean plus two standard deviations is taken as indicating high apathy in the PD sample this would produce an even higher estimate of prevalence at 55.6%. Previous research has not included a control group for the PD patients and so the slightly higher estimate of prevalence in the current findings needs to be considered seriously.

Apathy in patients can pose difficulties for their care. It is considered a considerable carer burden (Marsh et al., 1998) and has negative implications for responses to rehabilitation (Resnick et al., 1998). Therefore, further investigations of apathy are likely to have wide-ranging practical implications.

Apathy in the PD patients appears to be relatively unrelated to other psychopathologies. Anxiety was not associated with apathy in PD. The results from depression seem to imply that when there is co-morbidity of depression and apathy this is coincidental. Previous findings of a relationship are probably an artefact of the measures used to

assess depression that often contain activity/motivation-related items. Some support for the presence of anhedonia in PD patients with high apathy was though found, this was only detected in a correlational analysis and not a split-group comparison. Furthermore, the incidence of anhedonia in the PD sample as a whole was quite low. Using the criteria suggested by the developers of the scale only 7.1% of the PD sample would have been classified as anhedonic.

The concept of a parkinsonian personality, at least as measured by novelty seeking, also failed to explain the presence of apathy in PD patients. However, the minor trait in the TPQ, persistence, was associated with apathy.

The most salient results in this study concerned domains of cognitive processing. It has previously been shown that executive skill performance tends to be reduced in PD patients displaying apathy (Starkstein et al., 1992). This finding was replicated. On four different measures of executive performance the high apathy PD patients performed below the levels of low apathy PD patients and often also non-neurological controls. Considering the PD patients alone, apathy correlated with poor performance on all four tasks.

The possibility that the observed executive impairments are due to a general disease progression related cognitive decline can be ruled out. This is because in all of the between group comparisons of the high and low apathy PD patients and OA patients, scores on the MMSE assesment were used as a covariate. The MMSE is designed specifically to assess widespread cognitive impairment and so should act as a good measure of this (Folstein & Folstein, 1975). If there was a general cognitive decline that was simply more prominent in the high apathy PD patients, controlling for MMSE

performance should have removed the significant element from the executive task differences, but it did not.

This result is of particular interest as these are the very tests that define the predominant cognitive profile of PD patients (Brown & Marsden, 1990). It could be speculated, and is certainly worthy of further study, that impaired performance of PD patients on such tests is confined to the sub-set of PD patients who are apathetic.

The role of non-executive performance as a cognitive deficit associated with apathy has not previously been reported sufficiently. Although it was found that overall scores on the CAMCOG were lower in high apathy PD patients, many of the sub-tests would have involved some degree of executive skill. Analysis of the sub-scale scores found that three domains were linked to apathy; memory, praxis, and language. However, when the executive component is removed from the language sub-scale, the groups no longer differ significantly. This seems to imply the independence of apathy and language scores, though a negative correlation was found in calculations limited to the PD sample, even with the category fluency component of the language sub-scale removed.

Links between motivation and language were described above in the neuropsychological phenomenon of dynamic aphasia. It was suggested that as language use is itself a form of GDB that impairment of linguistic skills might be a direct consequence of apathy. However, another possibility can be considered, that the language system is impeded as a secondary consequence to apathy. This is suggested, for example, by the iconic gesture theory of lexical retrieval. This states that gestures during spontaneous speech are not simple by-products of language use, but that they aid lexical retrieval (Hadar & Butterworth, 1997). In support of this, it has been shown in

healthy subjects that preventing hand gestures reduces the fluency of spontaneous speech (Rauscher, Krauss, & Chen, 1996). Although it has not been confirmed, it is certainly reasonable that apathy in PD is related to a reduction in spontaneous gesturing. If so, this could have as a secondary consequence difficulties with lexical access. However this remains theoretical, further research is needed to understand the complex relationship between apathy, gesture and language skills in PD.

A further possible non-executive measure impaired in association with apathy was the memory sub-scale of the CAMCOG. However, it is unclear to what extent the memory deficit represents a non-executive impairment, in most circumstances involving learning and retrieval of information there are executive components, particularly working memory (Owen et al., 1996). Short term working memory is known to be impaired to some extent in PD (Downes, Phillips, & Sagar, 1991) and there is some evidence of long term memory impairment (Hugdahl et al., 1993).

Furthermore, it is known that PD patients tend to perform normally on recognition tests but poorly on tests involving recall (Ivory et al., 1999). It has been argued that this dissociation arises because PD patients are impaired at applying strategies at recall which are not normally needed for recognition, but that this can also affect recognition performance when the working memory demand is high (Stebbins et al., 1999). This suggests that a wide range of memory skills would be impaired in PD patients with executive impairments. Indeed, it has been shown that performance on a range of memory tests correlate with executive dysfunction in PD (Le Bras, Pillon, Damier, & Dubois, 1999). Therefore, the association between apathy and memory performance found in this chapter is consistent with the findings of executive dysfunction being closely related to apathy in PD.

The final sub-scale of the CAMCOG examination that was found to be related to apathy was praxis. This sub-scale includes items such as folding a piece of paper and sealing it in an envelope. Multiple step actions such as this are well known to be disorganised after frontal lobe damage (Schwartz, Reed, Montgomery, Palmer, & Mayer, 1991) and are closely related to the planing aspects of executive function. Reduced praxis scores in high apathy PD patients is therefore also broadly consistent with a dysexecutive interpretation.

However, the dysexecutive interpretation of apathy would predict that other sub-scales of the CAMCOG would be similarly affected if they have executive processing components, in particular abstract reasoning and calculation. These scores were not found to differ significantly dependent on the presence of apathy and so the negative results should be considered. One possible explanation is that executive functions tend to show some degree of selective impairment in that patients can be impaired on one executive task but perform normally on another (the case study reported in Chapter 7 is an example of this).

Alternatively, it may be that calculation and abstract reasoning are moderately impaired in PD patients with apathy but that the current methodology lacked sufficient sesnsitivity to detect this, that is, a 'type two error' may have occurred. This could have resulted from the lower executive demands of tasks such as calculation relative to the more direct tests such as verbal fluency and the Stroop task. Larger sample sizes may have allowed these weaker cognitive effects to be confirmed. Indeed, the high apathy PD patients did score slightly lower on both of these sub-scales than the low apathy PD patients, though not significantly so. Also, there was some indication of moderate negative correlations between apathy scores and calculation (-.293) or abstract

reasoning scores (-.291), that were approaching, but failed to reach statistical significance. Further research is needed to clarify the relationship between apathy and cognitive function and in particular executive skills.

It therefore appears that apathy in PD is closely related to cognitive disorder. This is highlighted particularly well if only those analyses in which the high apathy PD group differed significantly from the low apathy PD group are considered. From this perspective, worse performance by the high apathy patients was detected in two different verbal fluency tasks, the Stroop task, the WCST and the praxis and memory sub-scales of the CAMCOG. Conversely, no difference was found on four different personality traits, five measures of depression, and one each of anxiety and anhedonia.

The best indication of apathy in patients is the presence of executive difficulties, not particular mood states or personality. It is feasible that apathy in PD is a consequence of frontal-striatal dysfunction that produces impairments of the types of skills considered executive. The manifestation of this dysexecutive syndrome, at the behavioural level, is a reduction of GDB that is manifest clinically as apathy. The current conclusion is therefore that apathy is a correlate of cognitive disorder.

Chapter 4: Effort Applied and Information Processing Speed in Parkinson's Disease Patients with Apathy

Introduction

In Chapter 3 evidence was presented to link apathy in PD with executive function. Apathy is defined as a reduction in motivation (Marin, 1991). It could, therefore, be assumed that low motivation interferes with executive processing, as this would be an explanation for the current results. However, this is not a sufficient explanation as it does not indicate in enough detail how executive skills are impaired. Executive tasks are often poorly defined and it is rarely obvious what aspects of a task a particular patient finds difficult (Duncan, 1986). The patient in question may not be able to perform on executive tasks because they do not have sufficient cognitive flexibility to do so. This is the conventional explanation for poor performance of PD patients on executive tasks (Brown & Marsden, 1990; Downes et al., 1993). However, when dealing with patients who are known to have motivation deficits, there may be alternative explanations.

The most obvious suggestion is that, with conventional tests, a patient could potentially fail despite being able to perform at a higher level if they simply didn't allocate adequate resources to the task or misapplied motivational 'effort'. If sufficiently motivated to attend to the task, performance may have been normal. The simple way to test this would be to look at performance of apathy patients on non-executive tasks to observe whether performance on these tasks is correspondingly depressed. However, non-executive tasks are typically easier then executive tasks. It is therefore still often not

conclusive to distinguish between cognitive differences that are due to a general motivational problem as opposed to specific computational aspects.

Despite this, such explanations have been attempted. As in this thesis, Al-Adawi et al. (1998), found poor memory performance in their unmotivated patients. They interpreted this as a reduction in effort applied to the task, rather than a computational deficit per se, thus suggesting that motivation affects performance on all effortful tasks, regardless of the type of cognitive processing required. Such explanations are based upon the assumption that the effort applied is independent of the computations necessary to complete a particular task. Such a position has been argued strongly on neurophysiological grounds (Pribram & McGuinness, 1975). They attempted to describe an 'attentional' system that was independent of cognitive processes.

The theory of Pribram and McGuinness (1975) has been further developed by Sanders (1983) to provide a model of how 'energy' can impinge on the cognitive processes underlying a simple task such as choice reaction time. An assumption made in this model is that energetic factors are required very little or not at all for automatic tasks such as stimulus processing and feature extraction. When less automatic processes are needed, such as response choice, the effect of energetic factors is much higher (Sanders, 1983).

This could potentially explain why some tasks are generally performed poorly by unmotivated patients. In psychotic patients, for example, Sanders' (1983) model has been used to argue that poor performance on choice RT is a motivational deficit. However, it is further argued that this is a consequence of reduced energetic processing and that *"many cognitive disorders of psychosis are caused by energetical, rather than*

computational factors" (Schmand et al., 1994 p 881). If extrapolated to other patient groups considered to have motivation deficits, such as PD, this suggests that many of the cognitive deficits observed are really a result of reduced effort. This has been argued, though in a less extreme form concerning PD patients. Based on studies of event-related potentials and physical response force it has been suggested that in addition to cognitive deficits, patients with PD have a deficit in energetical factors (Wascher et al., 1997).

There is also anatomical reason to suspect that patients with motivational deficits may have difficulties with all effortful tasks irrespective of the cognitive nature of the processes assumed to be involved. The anterior cingulate cortex has been linked to motivation on the basis of numerous cases of reduced GDB after damage to this brain area in man (Devinsky et al., 1995). However, functional imaging studies have consistently found the anterior cingulate cortex active in a wide range of tasks. Although the area is often considered crucial for executive processing (Badgaiyan, 2000), many of the tasks that seem to produce neural activity in this area are non-executive in nature, for example production of precision grip (Kinoshita, Oku, Hashikawa, & Nishimura, 2000). The reason for this may be that the anterior cingulate is involved with 'task difficulty', this was the finding of a meta-analysis of 107 blood flow studies that found the area to be active primarily on effortful tasks (Paus, Koski, Zografos, & Westbury, 1998).

A generalised loss of effort constitutes a possible opposite explanation for the poor performance of PD patients with apathy on executive tasks. Such tasks are generally difficult and non-automatic and would therefore be susceptible to reductions in energetical or motivational factors. Conversely, tasks that are more automatic would be

performed normally or close to normal, as they are less energy dependent; this would explain why non-executive performance seems relatively unimpaired in PD patients with apathy.

In the framework of GDB provided in Chapter 2, motivational (or energetic) properties have a powerful influence on the overall GDB system, including the cognitive aspects. The influence is at multiple levels and therefore could be impaired at multiple levels. It therefore remains unclear whether the apathy in PD reflects primarily a specific motivational-executive disturbance or a more widespread motivational-cognitive disturbance.

The motivational-cognitive explanation is similar to that expressed by Starkstein et al. (1992) that bradyphrenia is the core deficit in PD patients with apathy. They suggested that bradyphrenia has the dual effects of producing apathy in PD patients and degrading performance on timed cognitive tests. This would explain why tasks that have large cognitive demands, such as executive tasks, are performed poorly by patients with apathy. However, it becomes circular to define a reduction in GDB in terms of apathy, bradyphrenia and effort. This is unfortunately the case to some extent with all explanations in terms of effort/drive/energy/motivation as descriptions of apathy. However, if clear frameworks such as that proposed in Chapter 2 are used, this problem can be limited.

The motivational-executive explanation is also consistent with the published data. However, this approach limits the impairment to tasks that have major executive components. These will in most cases be 'effortful' and therefore in most situations the motivational-executive explanation will make the same predictions concerning task

performance of apathetic patients as the motivational cognitive explanation. The main difference would be that if there is an impairment confined to motivational-executive processing, performance on difficult tasks that lack executive components would not be impaired.

Therefore, different predictions can be made for the performance of apathetic patients on non-executive tasks that require either high or low levels of effort. If there is a generalised cognitive impairment or slowing caused by low motivation/effort then performance on all tasks will be impaired, though this may be only apparent on the more difficult or effort demanding tasks. If the effect of low motivation on cognition acts mainly on executive processes, then performance should be normal on any task that lacks executive components, regardless of the amount of subjective effort needed to complete the task.

A methodology capable of testing these hypotheses is the visual search paradigm (Treisman & Gelade, 1980). This has the advantage that PD patients are known to have problems with this type of skill (Weinstein et al., 1997). Considering the high level of apathy in PD patients it is possible that poor performance is particularly linked to the co-occurrence of apathy.

The visual search paradigm can be used to distinguish automatic, parallel processing, of a display from attentive, serial processing (Treisman, 1996). By varying the target type in a visual search task, it is possible to manipulate whether processing will be parallel or serial. For example, a target that differs from all of the distractors on a single dimension (for example a green letter amongst blue and red letters) will 'pop-out' of the display (Treisman, 1988). Increasing the number of distractor items has very little effect on

pop-out, indicating parallelism. If the target differs by a conjunction of features (e.g. a blue O amongst red O's and blue T's), the target does not pop-out and has to be searched for consciously. In this situation, increasing the number of distractors has a detrimental effect on the time taken to detect the target. Feature search has been described as 'automatic' and conjunctive search as 'voluntary' emphasising the different involvement of effort in these tasks (Palmer, Ames, & Lindsey, 1993). Subjectively, participants report the parallel search task easy and the serial search task considerably more effort demanding.

In addition, search tasks such as these are not considered executive in nature. Performance is associated with posterior, not anterior processing (Ashbridge, Walsh, & Cowey, 1997; Corbetta, Shulman, Miezin, & Petersen, 1995). Additionally, it has been shown that PD patients, either with or without executive impairment, show identical effects of display size on response times (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999).

Therefore, parallel searching involves processes that according to Sanders (1983) will not be subject to large reliance on effort. Serial searching however, will involve reliance on effort. This form of theory would predict that serial search performance would be particularly impaired in patients with apathy. Parallel search performance would be less affected, or not at all. However, if the negative influence of low motivation is limited to executive skills, then a detriment in performance on neither of the tasks would be expected, because they are not executive in nature.

Method

Materials and apparatus

Experiments were performed on a Dell laptop computer with a colour 12.1" LCD monitor. Responses were made via a button pad linked to a digital timing card in the computer (Computer Boards inc., PCM-D24CTR3). Input from the keys was sampled at the rate of 1000 Hz. The tasks used in this investigation were based on an existing visual search paradigm that was implemented via a tachistoscope (Treisman & Gelade, 1980). However, for the current investigation a computerised version was developed using the Visual Basic programming language. The tasks are described below.

The experimental tasks

Two experiments were performed by each subject in counterbalanced order. In the parallel search task, the target was either any green letter (O's and T's were used) or a letter 'X', while in the serial search task it was a blue 'O'. A target was present on half of the trials. For each trial, the subject pressed one button for 'target present' and another for 'target absent'. The total number of distractors was varied pseudo-randomly such that the total number of elements on the screen was 1, 5, 15 or 30. The distractors were made up of roughly equal numbers of blue 'T's and Red 'O's. The elements were displayed semi-randomly across the central area of the screen, and not in a regular grid. Elements never overlapped. For each experiment there were 20 practice trials followed by 160 data trials. These were comprised of 20 trials of each of the four display sizes and the two display types (target-present or target-absent). Errors were recorded but not used for response time analysis. Such trials were replaced randomly later in the experiment so that the total number of data points was not reduced. Any trial that

followed an error trial was excluded from the data set in order to control for post-error slowing.

Subjects

A total of 23 PD patients were tested in this experiment, nine of these were female. However, due to fatigue by the subjects and occasional technical problems, data was not always available on each task. Twenty-two PD patients completed the parallel search task and 20 completed the serial search task (20 completed both tasks). Sixteen healthy control subjects also participated. Of these, only 13 completed the parallel search task and all completed the serial search task. The PD patients were drawn from the sample described in Chapter 3. The current research was conducted three to six months later. The control subjects were all volunteers who responded to advertisements or were non-academic friends of the author. Twelve of the control subjects were female. There was no significant difference between the patients and controls for age. The mean age of the PD patients was 67.20 (SD=9.32) and the controls was 68.08 (SD=9.99).

For the 23 PD patients the median score on the AES-R derived in Chapter 3 was 35. This was used to allocate patients to either a high apathy group (PD-HA) or a low apathy group (PD-LA). For the two tasks, parallel and serial search, there were slightly different patient numbers. However, the median AES-R score in each sub-group was also 35. Data for the PD-HA and PD-LA groups on mean age, years of education, Hoehn and Yahr stage, ADL score, MMSE score, CAMCOG score, BDI score, AES-R score and handedness are shown in Table 11. There were no significant differences between the groups on these factors, except that as expected the PD-HA group had significantly higher AES-R scores ($t(21)=6.60$, $p<.001$). These data were collected during the initial assessment three to six months previously.

PD patients were tested off medication. In practice, this meant that they had not taken any drugs for control of their PD since the previous evening. Test sessions were performed approximately 11 hours since the last dose of medication was consumed.

Table 11: Means (and SDs) for the characteristics of the PD-HA and PD-LA patients.

	PD-HA (N=10)	PD-LA (N=13)
Age	67.83 (10.6)	66.45 (8.14)
Education	12.91 (2.39)	13 (2.46)
Hoehn & Yahr	2.25 (.89)	2.09 (1.16)
ADL	43.67 (12.63)	45.45 (20.93)
MMSE	28.33 (1.23)	28.18 (1.94)
CAMCOG	94.5 (4.15)	93.45 (4.78)
BDI	13.5 (10.18)	13.09 (5.45)
AES-R	45.0 (7.15)	29.31 (4.19)
Handedness (L:R)	2:8	0:13

Procedure

Subjects sat directly facing and approximately two feet from the laptop monitor. All test sessions were performed in the subjects' own homes. In each location dim lighting was employed to enhance the visibility of the display. Subjects were instructed to search for any green letter or any 'X' in the parallel search task and for a blue 'O' in the serial search task. Two fingers of the preferred hand were used to respond via the

response keys; one for target present and the other for target absent. Subjects were instructed to respond as quickly as possible, but without making a large number of errors. They received auditory feedback whenever an error was made. The entire test session lasted approximately 40 minutes.

Hypothesis

PD patients with either high or low apathy will perform in a similar manner on both parallel and serial search tasks.

Results

Median reaction times were calculated for individual response times in each condition and for each task (parallel or serial search). Two separate two factor repeated measures ANOVA calculations were made on the reaction time data, one on the parallel and the other serial search task. This was performed, rather than use task type as a factor due to the slightly different compositions of the subjects in each task. In each calculation, analysis was restricted to the reaction times in the target present trials as these are the most direct measure of processing speed. The underlying processes for target absent responses are less well understood and likely to be influenced by factors such as re-checking (Zacks & Zacks, 1993). In addition, simple regressions were performed on individual subjects' median response times so that slope and intercept values could be derived. These data were also analysed.

Errors were analysed in separate ANOVA calculations. However, target presence/absence was considered as a factor as this information is important for assessing the possibility of speed/accuracy trade-offs on target present trials.

Parallel search

For the parallel search task there was a significant main effect on response time for display size ($F(3,96)=42.74$, $p<.001$). Response times significantly increased with display size. However, there was no main effect for group ($F(2,32)=1.48$, $p=.244$) and no interactions between group and display size ($F(6,96)=2.03$, $p=.975$). Response times of the three groups in the target present trials in the parallel search task are shown in Figure 7. From this it can be seen that the major effect of set size on RT was in the difference between set size of one and set sizes of greater than one.

In the analysis of visual search data, it is common to perform regression analysis on response times in order to estimate the effect of display size increases and calculate the linearity of the relationship. This is of interest so that comparisons can be made between slope values for target present and target absent responses. Such analyses are displayed in Table 12. The target absent slopes, relative to the target present slopes were approximately 7.21 times larger in the PD-HA group, 8.41 times larger in the PD-LA group and 5.82 times larger in the control group. The slope value in these regression equations relate to the cost of increased display size and so provide a relatively pure measure of processing speed. The intercept value represents the extrapolated response time searching in an array of zero elements and so is a relatively good measure of overall motor speed.

The individual slope and intercept values for the target present trials were entered into a one way ANOVA, with group as a between-subjects factor. There was no significant difference between either the parallel search slopes ($F(2,32)=.37$, $p=.692$) or the intercept values ($F(2,32)=1.90$, $p=.167$).

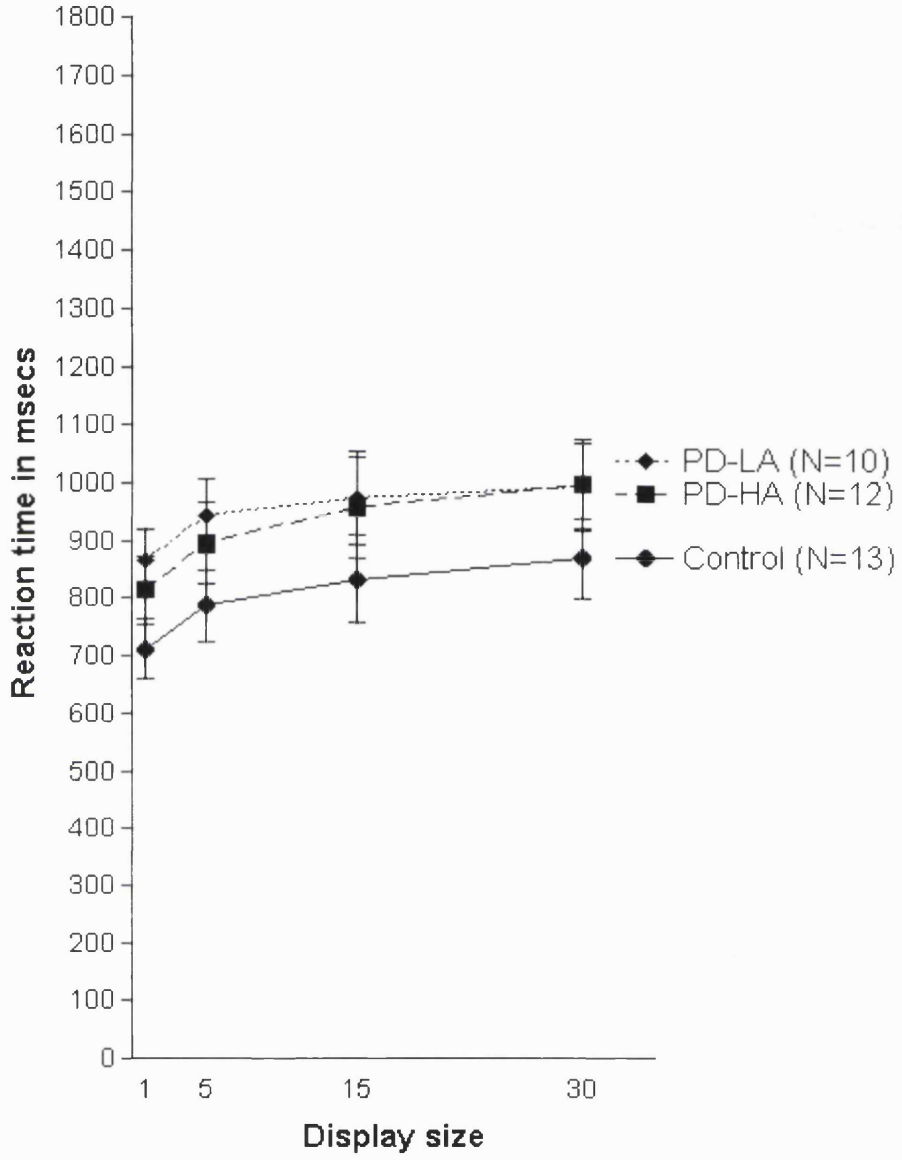


Figure 7: Response times on the parallel search task for the PD-HA, PD-LA and control subjects for target present trials.

Table 12: Linear regressions of response times on display size for the parallel search task.

Group	Display Type	Slope	Intercept	% of Variance With Display Size That is Due to Linearity
PD-HA	Target Present	5.62	843.3	84.2
	Target Absent	40.51	1022.6	99.9
PD-LA	Target Present	3.66	897.2	71.5
	Target Absent	30.79	1036.7	97.8
Control	Target Present	4.76	738.9	82.9
	Target Absent	27.7	940.6	98.0

Error rates for the parallel search task were analysed with a mixed model ANOVA with display type (target present/absent) and display size as within subjects factors and group membership as a between subjects factor. There was a significant main effect for display size ($F(3,96)=4.50$, $p=.005$). Error rates increased with display size. However for display type, errors were more likely in the target present trials (false negative) than in the target absent trials (false positive), ($F(1,32)=16.74$, $p<.001$). The interaction between display size and display type for total errors was also significant ($F(3,96)=10.79$, $p<.001$). For target present trials errors were more likely in larger display sizes, in target absent trials errors were more likely in smaller display sizes. There was no main effect for group ($F(2,32)=.34$, $p=.716$), and no interactions with either display type ($F(2,96)=.1.79$, $p=.837$), or display size ($F(6,96)=.5$, $p=.810$). Error rates for the parallel search task are shown in Table 13.

Table 13: Mean number (and SE) of errors made in the parallel search task.

Display Type	Display Size	PD-HA	PD-LA	Control
Target Present	**1**	.90 (.44)	.917 (.4)	.85 (.36)
	5	2.3 (.87)	1.58 (.79)	2.08 (.76)
	15	2.2 (.59)	1.33 (.54)	1.69 (.52)
	30	3.4 (1.05)	2.92 (.96)	2.23 (.92)
Target Absent	**1**	1.3 (.30)	.58 (.27)	.46 (.26)
	5	.4 (.38)	1 (.35)	.69 (.34)
	15	1.1 (.49)	1 (.45)	.31 (.43)
	30	.4 (.14)	.25 (.13)	.15 (.12)

Serial search

For the serial search task the results differed from the parallel search task. As expected there was a significant main effect on response time for display size ($F(3,99)=104.68$, $p<.001$). Response times significantly increased with display size. There was a main effect for group ($F(2,33)=4.28$, $p=.022$) and an interaction with display size ($F(6,99)=.3.11$, $p=.008$). The reaction times in the serial search task are shown in Figure 8. It appears that the significant group effect is due to the controls having a shallower search slope than either of the PD groups. To investigate this further, regression analyses were performed and the individual slope and intercept values entered into a one-way ANOVA to examine between-group differences. There was a significant difference between groups in the slope values for target detection ($F(2,32)=4.19$, $p=.024$) but not the intercept values ($F(2,32)=1.60$, $p=.217$). A post-hoc

t-test on the slope values confirmed that the control subjects serial search slopes were significantly lower than the combined PD groups, $t(34)=-2.79$, $p=.009$.

Regression analyses of mean response times in each group are shown in Table 14. The target absent slopes, relative to the target present slopes were approximately 1.87 times larger in the PD-HA group, 1.53 times larger in the PD-LA group and 2.53 times larger in the control group.

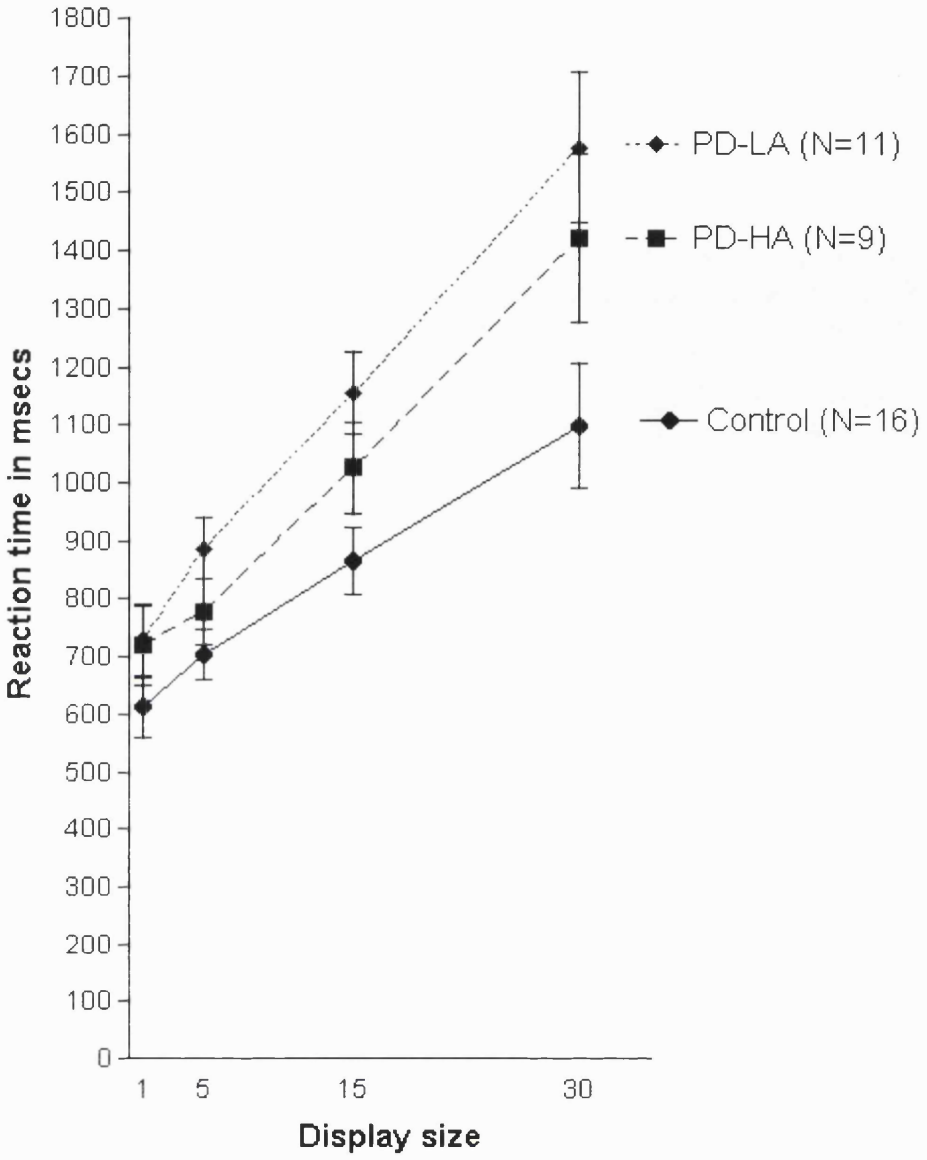


Figure 8: Response times on the serial search task for the PD-HA, PD-LA and control subjects for target present trials.

Table 14: Linear regression of response times on display size in the serial search task.

Group	Display Type	Slope	Intercept	% of variance with display size that is due to linearity
PD-HA	Target Present	24.63	671.9	99.6
	Target Absent	46	967.6	99.9
PD-LA	Target Present	28.67	721.4	99.8
	Target Absent	43.94	1024.6	98.8
All PD	Target Present	26.85	699.1	>99.9
	Target Absent	44.87	999.0	99.6
Control	Target Present	16.44	609.8	99.7
	Target Absent	41.61	858.2	99.1

For the total number of errors produced, the results were much the same as for the parallel search task. There was a significant main effect for display size due to errors being more common in higher display sizes ($F(3,99)=19.50$, $p<.001$). For display type, errors were more likely in the target present trials (false negative) than in the target absent trials (false positive), ($F(1,33)=24.90$, $p<.001$). As with the parallel search, the interaction between display size and display type for total errors was also significant ($F(3,99)=21.58$, $p<.001$). Errors were more common in higher display sizes in the target present trials, but in target absent trials, errors were more likely in smaller display sizes. There was no main effect for group ($F(2,32)=.1.65$, $p=.207$), and no interactions

with either display type (F(2,96)=.55, p=.584), or display size (F(6,96)=.89, p=.507). Error rates for the parallel search task are shown in Table 15.

Table 15: Mean number (and SE) of errors made in the serial search task.

Display Type	Display Size	PD-HA	PD-LA	Control
Target Present	**1**	.33 (.25)	.27 (.22)	.38 (.18)
	5	.89 (.54)	1.55 (.49)	.75 (.41)
	15	2.44 (1.20)	5.90 (1.09)	2.06 (.9)
	30	5.78 (2.42)	7.64 (2.19)	6.56 (1.82)
Target Absent	**1**	1.00 (.4)	.82 (.36)	.31 (.3)
	5	.67 (.31)	.73 (.28)	.19 (.23)
	15	.56 (.22)	.55 (.2)	.06 (.16)
	30	.22 (.37)	1.28 (.34)	.25 (.28)

Discussion

Before the performance of the apathetic PD patients is discussed, it is crucial to evaluate whether the above experiments really were tapping parallel and serial processes. The crucial data for this analysis comes from the regression slope values. The slopes in the single feature search task for target detection were generally quite small. The slope for the control subjects was 4.76 msecs/item. Parallel searching is generally assumed when slopes are low. The current findings were of slopes slightly larger than found in earlier work. For example, Treisman and Gelade (1980) based their original theory of parallelism in this type of task on slopes achieved by their subjects of between 2.5 and 3.8 msecs/item. However, later work has often found values that are slightly larger than

this, slope values have been reported in 'parallel' search tasks up to 7.4 msecs/item (Quinlan & Humphreys, 1987). Of more relevance is the relationship of the single feature search to the feature conjunction search task slopes. Slopes for a conjunction of features were 16.44 msecs/item for the control subjects, indicating that this task was being performed qualitatively differently from the single feature search.

A further criterion for distinguishing parallel from serial search is the relationship between target positive and target negative slopes. If a serial search strategy is being used, it is assumed that the subject will, on average, detect the target after searching half of the items. If no target is present, all items must be searched before a response can be made. Therefore, the slope of target absent responses should be approximately twice that of target present responses. In the control subjects this was found. The actual difference was that target absent responses for the feature conjunction task were about 2.5 times target present responses. However, it is accepted that due to occasional re-checking by subjects the ratio is often slightly larger than 2:1 (Zacks & Zacks, 1993). This can be contrasted with the ratio of the slopes in the single feature search. The target absent response slope was approximately 5.8 times steeper than the target present slope indicating that different search strategies were in use for making present or absent responses. It can therefore be assumed that the two tasks employed in this chapter did differentially access parallel and serial search abilities.

The role of errors should be considered as a possible confound. Significant differences were found for error frequencies between display sizes. The target present trials are the most relevant in this study and in these errors were more likely for all groups in higher display sizes. Thus, a trade-off relationship could have occurred to increase the speed of responses when there were large numbers of distractors on the screen. This would

have had the effect of reducing the slopes of response times. However, any influence would not have a confounding effect on the main hypotheses being tested. This is because the trend in the error scores was nearly identical in each group and so one group could not have performed more trading off than another.

In terms of apathy, there were no significant differences found between the high and low apathy PD groups. In the parallel search task all groups performed at the same level, there was no group effect for either the actual response times, slope values or intercept values. For the serial search task there was a significant difference found between groups, but a post-hoc analysis indicated that this was between the control subjects and both PD groups. Analysis of intercept values failed to show any group difference in this task.

These results indicate that the presence of apathy in the PD patients produces neither slower responses nor slower processing of the display. This null result seems to indicate that the suggestion of a generalised reduction in effort is not a good explanation for the cognitive impairments associated with apathy in PD. As suggested by Sanders (1983) in terms of effort applied, it would have been expected that the serial search task would have been performed particularly slowly by high apathy PD patients, a result that was not found. Similarly, the bradyphrenia theory of Starkstein et al. (1992) is not supported because this would have predicted that high apathy patients would be particularly affected by timed cognitive tasks such as those employed here. The increased slope values of the PD patients in general offers some support for a bradyphrenia model, but one independent of apathy.

The current findings can be explained in terms of the GDB framework proposed in Chapter 2. Although motivational factors can have an effect on many of the processes underlying GDB, there is a specific input to executive processes. Impairment to the motivation-executive aspects could explain why PD patients with apathy consistently show impairments on executive tasks such as verbal fluency but did not show an impairment on the current tasks. It is suggested that the motivational impairment does not influence attentional processing per se, only tasks that require non-routine processes.

However, it should be acknowledged that this is a null result, and only tentative conclusions can be drawn. It is possible for example, that if more difficult tasks or larger subject numbers were employed differences would have been detected. The point concerning difficulty is particularly relevant to interpretation of the parallel search result, a task that most people find easy. However, it can be stated that the serial search task is by definition effort demanding and if a generalised reduction in effort were crucial to the expression of apathy then a difference would have been expected.

Although there were no significant differences between the two PD groups, it was found that the PD group as a whole were more affected by display size in the serial search task than were the controls. This was revealed in both an ANOVA calculations using the response times as data and an ANOVA on the individual regression slope values. Furthermore, this difference can not be due to generally slower movement times in the PD group. Regression slope values are independent of the intercept of the slope. That is, overall slower responding will not influence the slope value.

This result differs qualitatively from previous findings. The most commonly reported pattern is for PD patients to be impaired relative to controls on parallel searching (Troscianko & Calvert, 1993), but to have preserved serial searching abilities (Weinstein et al., 1997). This basic finding has also been replicated using a signal detection paradigm (Lieb et al., 1999). The explanation for this is based on the known depletion of dopamine in the primary visual cortex in PD. This is suggested as impairing basic feature extraction (Weinstein et al., 1997). However, in one published report both parallel and serial search skills were found to be normal in PD patients (Berry et al., 1999).

The current finding of preserved parallel searching with impaired serial searching was therefore unexpected. An explanation for the current findings can only be tentatively suggested. The exact nature of visual search in PD may be more complex than has been found in the studies described above. For example in at least one study it has been found that parallel processing, rather than being impaired, could be more efficient in PD patients compared to controls (Moore & Murphy, 1992). However this was found only with some types of visual stimuli, when alternative stimuli where used, performance was worse than expected.

Possibly, PD patients have search difficulties that are only evident for specific stimuli. In the parallel search task, the stimuli were sufficient to allow normal searching, but the stimuli in the serial search task were not. There is some minor evidence to support a stimuli-dependent explanation. In one visual search experiment it was found that PD patients showed an unusual pattern of errors dependent on stimuli types relative to normal control subjects (Filoteo, Williams, Rilling, & Roberts, 1997b).

Therefore at present, it is unclear how visual search skills are affected in PD patients. However, the current findings indicate that the presence of apathy in the patients has no or very little contribution to deficits. It is possible that other attentional skills are involved in apathy in PD. However, the fact that a single effortful task is performed normally contradicts suggestions that low motivation is inevitably associated with a generalised cognitive impairment, at least in PD patients.

Chapter 5: Attention to Novel Stimuli and its Relationship to Apathy in Parkinson's Disease

Introduction

In Chapter 4 it was found that visual attention, at least in terms of visual search tasks, appears not to be influenced by the expression of apathy in PD. This finding implied that visual attentional processes are independent of motivational components of apathy. It was tentatively suggested that this is because motivation primarily affects the cognitive system where flexibility is crucial, i.e. executive skills. The visual search tasks used were non-executive. However, some aspects of visual attention are more closely related to abilities thought to be related to GDB.

In an important theoretical paper on attention, Mesulam stressed the role of the cingulate cortex in attention to motivational valence. This emphasises the importance that has been attributed to the attentive detection of salient environmental stimuli (Mesulam, 1981). In particular, responses to novelty have traditionally been considered as crucial to adaptation and action within a changing environment (Berlyne, 1960). Indeed, novelty in the environment is often considered a pre-requisite for exploratory behaviour (Birke & Archer, 1983).

In the framework of GDB described in Chapter 2 the role of 'external determinants' is suggested as being a primary influence on the formation of an intention. Although the notion of 'external determinants' covers a wide range of situations, a change in the environment, i.e. novelty would be a common example. The model of attentional control originally posited by Norman and Shallice (1986) (this was discussed in Chapter

2) also emphasises the role of novelty. Central to the theory is the concept of a supervisory attentional system that is needed to deal with unexpected events (Shallice, 1988). When routine actions are not going to be sufficient to achieve a goal, it is first necessary to detect a novel event in the environment that may be relevant. Although the role of novelty detection is not seen as being within the domain of the supervisory system, it is considered essential (Shallice & Burgess, 1996). Theoretically, a reduction in the ability to react to novelty may produce a reduction in GDB by preventing the formation of intentions/activation of the supervisory system (Goldberg et al., 1994).

Studies of the effect of novelty have rarely been performed in a neuropsychological context. Patients with schizophrenia have been shown to alter routes less often when negotiating pencil and paper mazes (Howard, 1961). This was interpreted by the author in terms of stimulus-seeking behaviour, but could equally be explained simply by perseveration. A single case study of bilateral frontal lobe damage seems to show the disruption of attention to novelty. The patient was shown to be unreactive to unexpected events (such as a doctor entering the room wearing a lion mask). However, her overall appearance did not imply any reduction in behaviour, and in fact, she displayed akathisia (Brazzelli et al., 1994). Studies in patients with Alzheimer's disease (AD) have shown that a reduction in responses to novelty is a common phenomenon (Daffner et al., 1992) and is associated with the presence of apathy (Daffner, Mesulam, Cohen, & Scinto, 1999). There is therefore some evidence to link a lack of normal responses to novelty to reduced GDB.

The widespread pathology in AD makes it difficult to make predictions of the anatomical focus of the reduced novelty response. However, the role of novelty detection has also been closely related with frontal lobe function. Patients with frontal

lobe lesions are often described as showing poor responses to novelty (Goldberg et al., 1994). In addition, event related potential studies have linked the processing of the P300 wave to the frontal lobes (Knight & Grabowecky, 1996). This electro-physiological response is reliably elicited by unexpected events (Yamaguchi & Knight, 1991). It therefore seems reasonable to hypothesise that a possible source of apathy observed in frontal lobe patients is related to an alteration in the tendency to attend to novel events.

There is good reason to suspect that, at least in frontal lobe damage patients, reduction in the detection of novelty does contribute to apathy. For example, it has been shown that the P300 wave is related to the viewing of incongruous images in normal subjects (Daffner et al., 1998). Furthermore, patients with lesions to the frontal lobes fail to attend to the stimuli in the same way as controls (Daffner et al., 2000a). Finally, apathy is closely related with viewing times of incongruous figures by frontal damaged patients and this is linked to P300 amplitude. The amplitude of the P300 wave has been shown to account for most of the difference in viewing times between frontal lobe patients and controls (Daffner et al., 2000b).

The P300 wave is delayed in PD (Hansch et al., 1982) and is thought to involve a dopaminergic substrate (Sohn, Kim, Huh, & Kim, 1998). Cells in the nucleus accumbens have been shown to respond to novelty in rats. When placed in a novel environment catecholamine activity is increased in the accumbens but not the rest of the striatum (Rebec, Grabner, Johnson, Pierce, & Bardo, 1997). In particular the D4 dopamine receptor is implicated. Knock-out mice that do not express the D4 receptor display less exploration in novel environments (Dulwa, Grandy, Low, Paulus, & Geyer,

1999) and the personality trait of novelty seeking is correlated with D4 polymorphism in humans (Ebstein et al., 1996).

Despite the amount of evidence from event related potentials in PD patients and animal research on the role of dopamine in novelty processing, there are few behavioural reports of impaired novelty processing in PD. This could possibly be due to the lack of paradigms for behavioural recordings of responses to novelty. Alternatively, research that has been performed could have produced null results because novelty processing is normal in PD. However, this seems unlikely considering the strong association between dopamine and novelty responses. A third possibility is that novelty processing has not been detected in groups of PD patients, because only a sub-sample expresses the effect. If this is correct, then we may hypothesise that only those PD patients with high levels of apathy will show alterations in the processing of novel stimuli.

A methodology capable of testing the impact of novelty on attention is an adaptation of the attentional cueing paradigm (Posner, 1980). In the common version, arrowheads presented at the centre of a display can facilitate response times to stimuli that later appear at the cued location. It has been shown that novel visual elements in a display can attract covert shifts of attention (Johnston, Hawley, Elliot, & DeWitt, 1990; Johnston & Schwarting, 1996). In a Posner paradigm if either novel or repetitive background stimuli are manipulated instead of arrowheads, these could act as attention grabbing elements and attract covert shifts in attention. Response times to target stimuli in the attended location would then give a measure of unconscious novelty processing.

Method

Materials and apparatus

Experiments were performed on a Dell laptop computer with a colour 12.1" LCD monitor. Subjects sat approximately two feet from the display. All test sessions were performed in the subjects' own homes. In each location, dim lighting was employed to enhance the visibility of the display. Responses were made via a button pad linked to a digital timing card in the computer (Computer Boards inc., PCM-D24CTR3). Input from the key was sampled at the rate of 1000 Hz. For the actual stimuli in the task 80 novel computer graphics were produced. For this investigation, a novel computerised task was developed using the Visual Basic programming language. This task is described below.

The experimental task

The subjects were required to make a simple response to a white dot appearing at fixed locations either to the left or right of a central cross on the monitor of the lap top computer. When the dot appeared on the left, it was always in the same location and when it appeared to the right, it was always in the same location. Whether it appeared to the left or right was unpredictable and occurred with equal frequency. A pair of coloured stimuli always appeared 200 msecs before the target stimulus (the white dot). These appeared simultaneously to both the left and right of the central cross in every trial and always at the same locations. Therefore, the appearance of the coloured shapes was irrelevant to the actual response required as they appeared on every single trial and in the same locations. One of the shapes was always a khaki square.

The other shape was varied such that a totally novel, different coloured shape, would often be substituted for the previous shape. The substitutions occurred randomly every four to seven trials. Therefore, the same two shapes would be presented several times in successive trials but randomly alternating in their relative left-right locations. Because the substitution of a novel shape occurred randomly every four to seven trials the same pair may be present sequentially across trials for example four times in some instances, five times in others, etc. Therefore the subject would see the same shapes for a few trials, but unpredictably a novel shape would be introduced and then this would be seen for a few trials .

These coloured shapes always occurred as background to the target stimulus (appearing 200 msecs in advance and remaining visible throughout the trial). On 14% of the trials the target stimuli were withheld and a three second delay inserted before the next trial began. This was used to prevent stereotypical responding. However, the target stimulus was never withheld on a trial that immediately preceded the introduction of a novel shape. If the response key was pressed on trials where no target stimulus was present, then the computer emitted a tone and the word 'error' was displayed on the screen. The number of errors was recorded by the computer. The substitution of a novel shape occurred more often after 7 trials (probability =.4) than after 4, 5 or 6 trials (the probability for each was .2). This was manipulated to partially counter the effect of there being fewer data points available for reaction times with large intervals between shape changes.

The location of the shape stimuli alternated randomly left to right, independently of the side that the target stimulus would appear on. It was therefore unpredictable whether the khaki square would appear to the left and the novel shape to the right or vice versa.

The shapes therefore were irrelevant to task performance, as shifting attention to either would confer no advantage in predicting the location of the target stimulus. However, if orientation of attention is influenced spontaneously then this may be reflected in the subjects' reaction times. After each trial the shape stimuli and target stimulus (if present) disappeared and there was a one second delay before the start of the next trial. Reaction times and number of errors were automatically recorded to a computer file. A visual representation of the temporal sequence of events in a typical trial is shown in Figure 9.

Subjects

A total of 20 PD patients were tested in this experiment, 11 of these were female. All patients were drawn from the sample described in Chapter 3. The current research was conducted three-six months later. Thirteen healthy control subjects also participated, all were volunteers who responded to advertisements or were non-academic friends of the author. Ten of the control subjects were female and all bar one were right handed. The mean age of the PD patients was 68.45 (SD=9.44) and for the controls it was 69.69 (SD=9.08). There was no significant difference between the patients and controls for age, $t(31)=.38$, $p=.710$.

PD patients were tested off medication. In practice, this meant that they had not taken any drugs for control of their PD since the previous evening. Test sessions were performed approximately 11 hours since the last dose of medication was consumed. For the 20 PD patients the median score on the AES-R derived in Chapter 3 was 34. This was used to allocate patients to either a high apathy group (PD-HA) or a low apathy group (PD-LA).

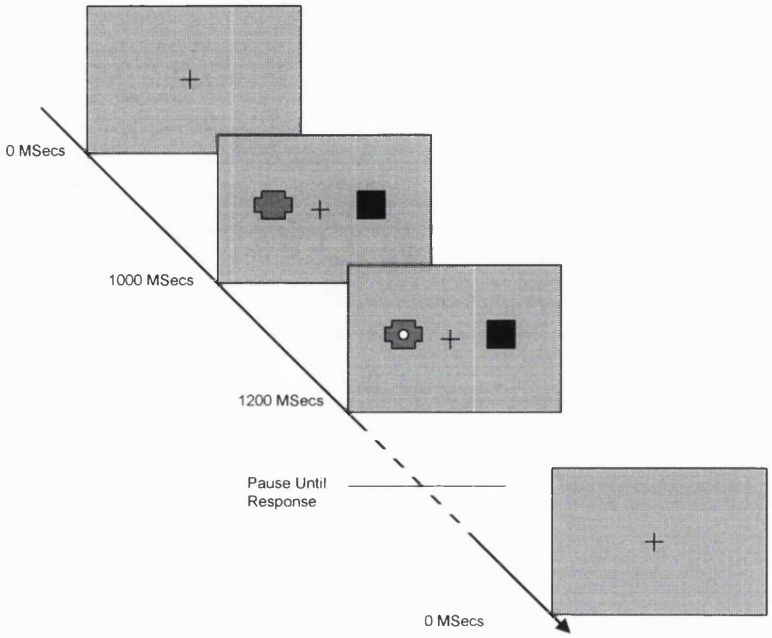


Figure 9: The temporal order of events in a single trial of the novelty attention task.

At the beginning of a block of trials, only the fixation cross is visible. After 1000 msecs two shapes are presented, one to either side of the fixation cross. One of these is a khaki square and the other could be one of several different novel shapes in a non-khaki colour. The location of each is random between left and right. In the example above, the novel shape is presented to the left. After a 200 msec delay, the target stimulus is displayed. This white dot can appear randomly either to the right or left of fixation, in the example above it has appeared to the left. After the subject has responded the sequence repeats with the same stimuli, but the shapes may appear in the opposite locations (e.g. the novel stimulus to the right) and the target may appear to either the left or right of fixation. This pattern repeats several times until after 4-7 repeats a totally novel shape substitutes the previous novel shape. Note the khaki square remains unchanged and the target stimulus is also unchanged. Therefore, response times can be recorded for targets that appear either in conjunction with the novel shape or the repetitive shape (khaki square). Furthermore, the 'level of novelty' has seven levels due to the repeating nature of the trials before a novel shape is substituted. For example, the trial shown above has a level of novelty of one because this is the first time that the novel shape has been presented. On the following trial the same shapes are used and so the level of novelty is two, etc, until after maybe five trials a novel shape is substituted and this trial would then have level of novelty one.

Data for the PD-HA and PD-LA groups on mean age, years of education, Hoehn and Yahr stage, ADL score, MMSE score, CAMCOG score, BDI score, AES-R score and handedness are shown in Table 16. T-tests, where appropriate, confirmed that there were no significant differences between the groups on these measures except as would be expected, the PD-HA group had significantly higher AES-R scores ($t(18)=4.98$, $p<.001$). These data were collected during the initial assessment three-six months previously.

Table 16: Means (and SDs) for the characteristics of the PD-HA and PD-LA patients.

	PD-HA (N=10)	**PD-LA (N=10)**
Age	69.0 (10.83)	67.9 (8.39)
Education	13.11 (2.61)	14.06 (2.54)
Hoehn & Yahr	2.0 (.71)	1.85 (.97)
ADL	44.1 (12.68)	39.4 (15.23)
MMSE	28.7 (1.16)	28.5 (2.12)
CAMCOG	94.7 (4.55)	93.9 (5.13)
BDI	13.1 (10.95)	12.5 (4.77)
AES-R	42.6 (7.9)	28.5 (4.2)
Handedness (R:L)	9:1	8:2

Procedure

Each subject was tested individually in his or her own home. They were sat in front of the lap top computer so that the screen was maximally clear. One finger of the

dominant hand was held over a microswitch and the subject was told to press the button as quickly as possible whenever they saw a white dot appear either to the left or right of the central cross. They were told to try and keep their fixation on this cross but that coloured shapes would appear in the background and that these would change occasionally. They were further instructed that they did not need to pay any attention to the coloured shapes, just the white dot.

Two blocks of trials were performed. Each block involved 40 novel stimuli. There were 200 trials in each block. Each block took about 8 minutes to complete.

Results

Main Analyses

Data from the first seven trials in each block were excluded, as they did not involve a novel change of stimulus. In addition, trials that occurred immediately after a withheld response were excluded. To control for pre-emptive responding or lapses of attention, RTs of less than 100 msecs or more than 1000 msecs were excluded. From the remaining data sets, averages were calculated for the location of the target (either in conjunction with the repetitive or novel stimuli) and for the level of novelty. Level of novelty was defined as the number of times that the subject had seen the shape, including the current trial. Therefore, level of novelty ranged from 1-7, with 1 being a shape that was displayed for the first time. For each subject there were more data points for level of novelty 1-4 than for 5, 6 or 7. For this reason, mean rather than median averages were used to summarise the raw data as these are considered more appropriate for un-equal data sets (Miller, 1988).

Prior to the main analysis including the PD patients, the data from the control subjects were examined to check that the task is sensitive to responses to novelty. Response times for the 1st, 3rd and 7th presentation of the novel stimuli when it appeared in conjunction with the target were compared in a one way ANOVA. It was found that there was a significant effect of novelty on response times ($F(2,24)=4.33$, $p=.025$). Response times were fastest at the 3rd presentation of the novel stimuli (361.31 msecs) and slowest the first time it was presented (377.38 msecs) with intermediate times (366.46 msecs) for the 7th presentation. It is therefore clear that the novel stimuli had a detectable impact on response times, in a manner that implies a distraction from task effect.

Response times for all subjects, including the two PD groups are shown in Table 17. To analyse the effect of apathy in the PD sample in responses to novelty, data were entered into a factorial ANOVA. The within subject factors were the location of the target (repetitive or novel) and level of novelty (1-7). Group membership (PD-HA, PD-LA and control) was a between subjects factor. The analysis revealed a significant main effect for location. Response times were significantly faster for targets appearing in conjunction with the novel stimuli compared with the repetitive stimuli, ($F(1,30)=7.00$, $p=.013$).

Table 17: Response times (and SEMs) for the PD-HA, PD-LA and control subjects in the novelty attention task.

Group	PD-HA			PD-LA			Control		
Repeats (Level of Novelty)	**Novel**	**Rep**	**Diff**	**Novel**	**Rep**	**Diff**	**Novel**	**Rep**	**Diff**
1	404.90	411.80	6.9	430.20	438.20	8	377.39	382.85	5.5
(Hi)	(24.38)	(24.59)		(24.38)	(24.59)		(21.84)	(21.57)	
2	399.20	404.70	5.5	419.10	428.10	9	369.85	380.15	10.3
	(24.87)	(23.98)		(24.87)	(23.98)		(21.82)	(21.03)	
3	391.40	392.70	1.3	431.40	436.40	5	361.31	371.39	10.1
	(25.15)	(24.79)		(25.15)	(24.79)		(22.06)	(21.74)	
4	402.60	407.50	4.9	437.50	424.40	-13.1	372.08	379.85	7.8
	(25.57)	(24.82)		(25.57)	(24.82)		(22.25)	(21.77)	
5	388.00	401.50	13.5	429.90	430.70	.8	367.85	386.08	18.2
	(26.10)	(27.50)		(26.10)	(27.50)		(22.89)	(24.12)	
6	407.50	403.80	-3.7	388.50	432.70	44.2	375.62	382.39	6.8
	(27.76)	(26.31)		(27.76)	(26.31)		(24.35)	(23.08)	
7	403.40	395.20	-8.2	408.00	440.70	32.7	366.46	371.31	4.9
(Low)	(27.50)	(24.96)		(27.50)	(24.96)		(24.19)	(21.89)	
Overall Means	**399.57**	**402.46**	**2.9**	**420.66**	**433.03**	**12.37**	**370.08**	**379.14**	**9.06**

Notes: Novel indicates when the target appeared in conjunction with the novel stimuli and Rep when it appeared in conjunction with the repetitive stimuli. Diff is the difference between these two average response times, giving an estimate of the effect on response times of the novel compared with the repetitive stimuli. The level of novelty ranges from when a novel shape was shown for the very first time (1) to when it had been shown 7 times.

Response times for targets appearing in conjunction with either the novel or repetitive location are shown bygroup in Figure 10. There was no main effect of the level of novelty, i.e. response times did not vary significantly depending on whether it was the 1^{st}, 2^{nd} 3^{rd}, 4^{th}, 5^{th}, 6^{th} or 7^{th} presentation of the novel stimuli ($F(6,180)=1.35$, $p=.238$). There was also no main effect for group membership ($F(1,30)=1.30$, $p=.287$). The two-way interaction between location of the target and level of novelty was not significant ($F(1,30)=.65$, $p=.426$). The three-way interaction including group membership approached but was found not to be significant ($F(12,180)=1.77$, $p=.056$).

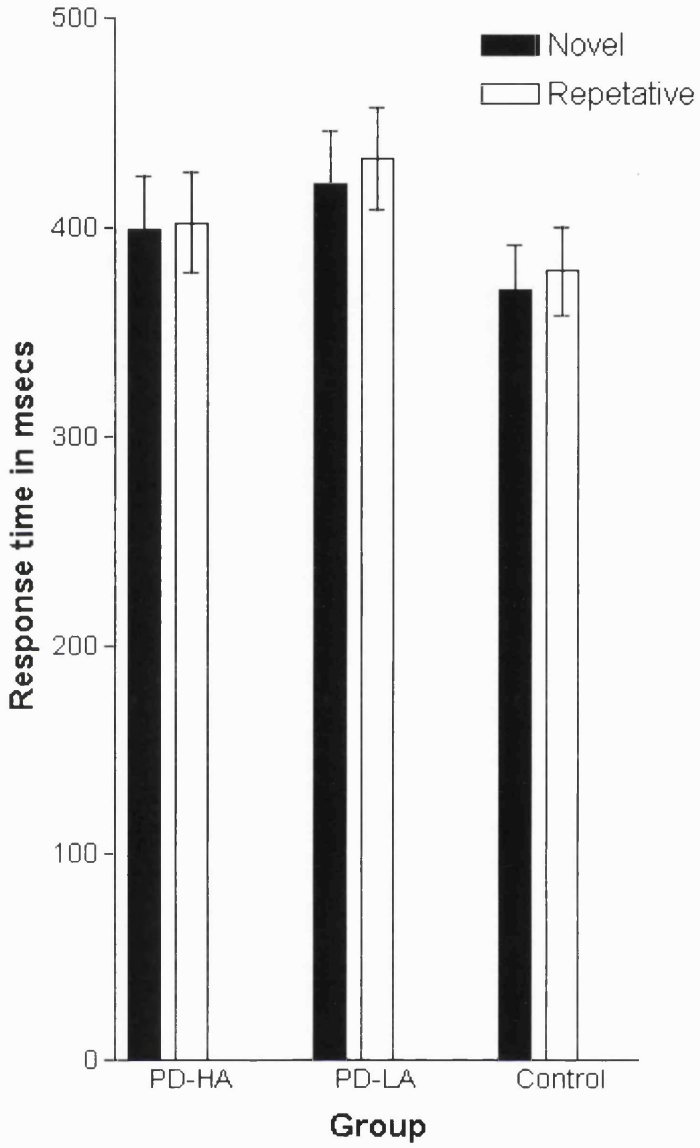


Figure 10: Response times to targets in either the novel or repetitive location for the PD-HA, PD-LA and control groups.

In order to compare more directly the effect of novelty, rather than exact level of novelty the data points were averaged to provide three main groups of novelty level, when the novel shape first appeared, the mean of the responses for the 2nd and 3rd time, and the mean of the 4th, 5th, 6th, and 7th presentations. This effectively reduced the novelty factor from seven to three levels.

These data points were again entered into a factorial ANOVA as described above. The results were broadly similar. There was a main effect of location ($F(1,30)=10.08$, $p=.003$) but not of group ($F(1,30)=1.35$, $p=.274$) and the interactions involving group membership remained non-significant. However, this analysis did reveal an effect of novelty overall ($F(3,90)=3.81$, $p=.013$). The first presentation resulted in response times approximately 8 msecs slower than either the 2nd set (novelty level 2 and 3) and the 3rd set (novelty level 4, 5, 6 and 7). The exact values in msecs were 407.56, 398.81 and 398.87 respectively. The group reaction time data for these responses are shown in Figure 11 (when the targets appeared in conjunction with the novel stimuli) and Figure 12 (when the targets appeared in conjunction with the repetitive stimuli).

Data on incorrect responses in the experimental task were also collected. In this task, there was only one type of response available and so the only errors that could occur were the execution of responses in the absence of an appropriate stimulus. The absolute number of such responses was recorded for each subject and are displayed in Table 18. From the table it can be observed that the PD-HA group made more errors than either of the other groups, however, this difference was found to be non-significant ($F(2,30)=.41$, $p=.666$).

Table 18: Mean and SEM number of errors made by each group and the percentage of blank trials that were affected.

Group	Mean	SEM	% of Trials
PD-HA	5.30	2.27	9.46
PD-LA	3.70	1.14	6.61
Control	3.54	0.81	6.32

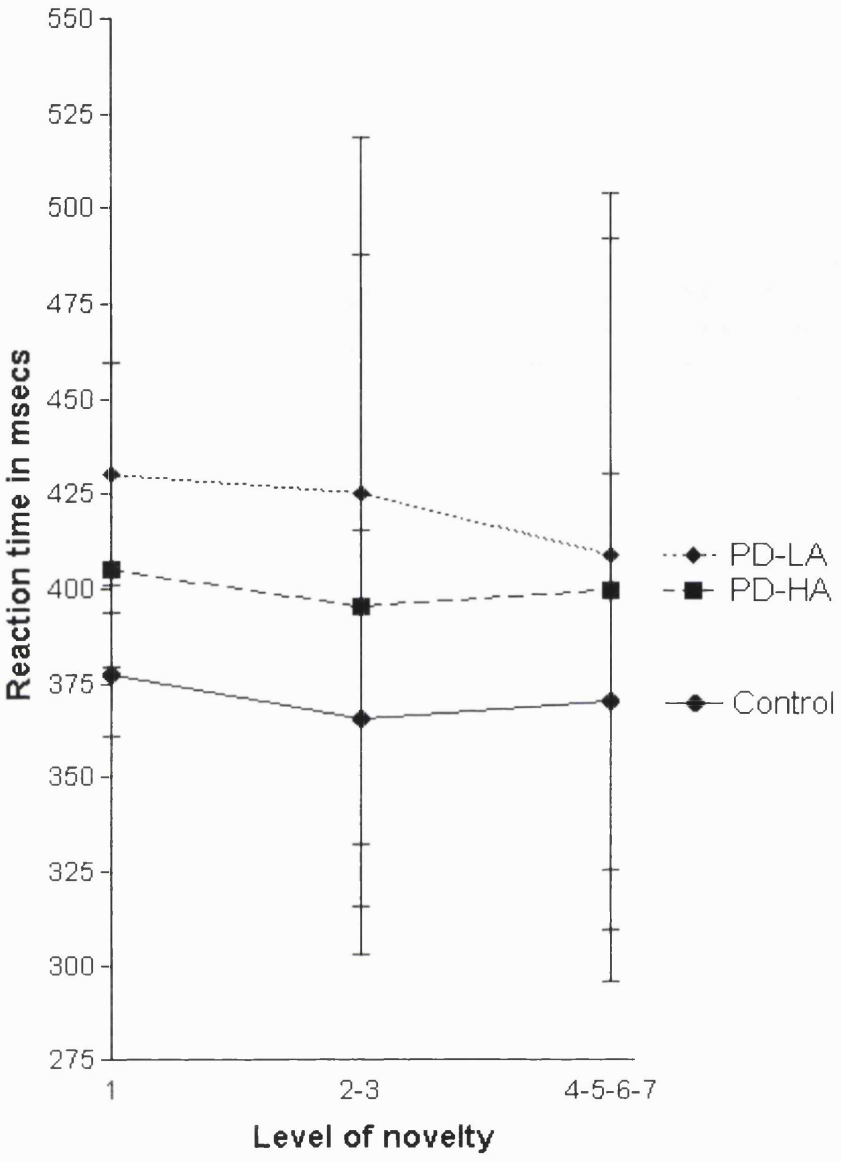


Figure 11: Response times (and SEMs) for the three groups (PD-HA, PD-LA and control) on the trials in which the target appeared in conjunction with the novel shape.

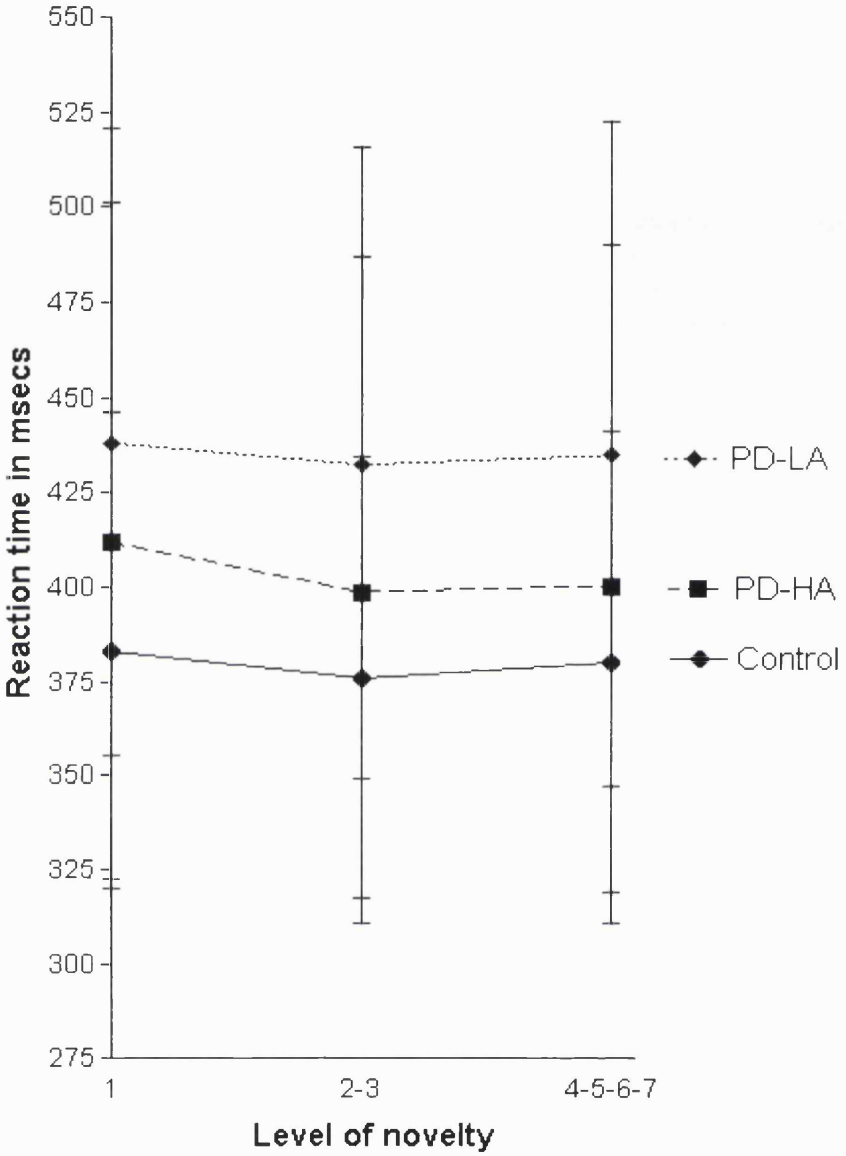


Figure 12: Response times (and SEMs) for the three groups (PD-HA, PD-LA and control) on the trials in which the target appeared in conjunction with the repetitive shape.

Correlation Analyses

From examination of Figure 11 it can be seen that in each group there was a decrease in response times for the combined 2nd and 3rd presentation of the novel stimuli relative to its 1st presentation. This implies that detection of the novel stimuli produces a distractory influence on responding. The difference between these two could therefore indicate an overall effect of novel stimuli on responding. As the trait of novelty seeking has been defined in terms of responses to novelty it is of interest whether novelty seeking is related to this behavioural measure of cognitive processing in PD patients. To test this, the difference between 1st presentation and combined 2nd and 3rd presentation response times when the target appeared in conjunction with the novel stimuli were compared with scores derived on the TPQ (data from the study reported in Chapter 3).

In addition, as a final check concerning the influence of apathy on novelty responses raw apathy scores from the AES-R were compared with this response time difference. The correlation values are shown in Table 19 where it can be seen that there was a significant negative correlation between the distracting effect of the novel stimuli and novelty seeking scores ($r=-.518$, $p=.023$). Scores from other traits and apathy scores where not significantly correlated.

Table 19: Correlations between the distracting effect of the novel stimuli and psychometrically derived scores of personality and apathy.

Personality Trait / AES-R	r value	p value
Novelty Seeking	-.518	.023
Harm Avoidance	-.242	.318
Reward Dependence	.004	.987
Reward Dependence (-Persistence)	-.088	.721
Persistence	.113	.644
AES-R	-.071	.767

Discussion

Before the influence of apathy on novelty processing is considered it is important to discuss the effectiveness of the methodology in detecting the impact of visual novelty on responding. As this was a new procedure which had not been previously reported its validity should be assessed. It was found that in the control subjects alone there was a significant effect of level of novelty when only targets appearing in conjunction with the novel stimuli were compared. This indicates that the task was sufficiently sensitive to detect alterations in responding contingent on the occurrence of novel events. Furthermore, there was a significant location effect in both comparisons that involved all three groups. That is, responses were generally faster when the target appeared in conjunction with the novel stimuli. The procedure therefore is capable of measuring the influence of the novel visual events on response times.

It was also found in the second main comparison in which level of novelty was reduced to three from seven levels, that there was a significant level of novelty effect. Responses tended to be relatively faster on 2nd and 3rd (combined) and 4th, 5th, 6th, 7th (combined) presentations of the novel stimulus relative to 1st presentation. This effect occurred whether the target appeared in conjunction with the novel or repetitive stimulus. It is not possible to definitely say whether this effect occurred because the novel stimuli slowed or enhanced responses. For example, faster responses at level of novelty X than at level of novelty Y could indicate that response times were reduced at level of novelty X.

Alternatively, response times at level of novelty Y may have been increased, producing the same overall pattern or results. Although these two hypotheses can not be tested fully in this procedure, there is some indication that the general effect of novelty on response times was to slow them down. Response times were slower when the novel stimulus was seen for the first time relative to when it was less novel having been seen one to six times previously. This could have occurred due to a distraction from task effect. Such effects have been observed when novel elements 'pop-out' and familiar items 'sink-in' to the display (Johnston & Schwarting, 1996).

However, this interpretation must be considered cautiously and it is still possible that novelty had an enhancing rather than distracting effect. This could have occurred if the processing of the novelty of the stimulus was sufficiently slow to not allow it to enhance response times on its first presentation. Despite the ambiguity of the interpretation, the aim was to investigate whether PD patients with apathy showed less impact of novelty. This aim is irrespective of the interpretation of the way that novelty may have impacted on the results.

There was also a main effect of target location. Response times in general were significantly faster when the target appeared in conjunction with the novel, relative to the repetitive stimuli. In the paradigm of attentional cueing developed by Posner (1980), faster response times at a cued location are taken to assume that attention is orientated to the location prior to the presentation of the target, hence faster response times. The current findings show that novelty can act to unconsciously cue attention to a spatial location.

This supports the theory of novel 'pop-out' which suggests that novel visual elements attract rapid covert shifts in attention (Johnston et al., 1990; Johnston & Schwarting, 1996). A possible confound to this interpretation is that target detection may simply have been easier against the backgrounds of the novel shapes relative to the repetitive shape. This alternative interpretation can not be ruled out at present, however, the most salient difference between the shapes was the novelty of them and so this seems the most likely explanation.

It appears therefore that the presence of the novel shape had two effects on response times. Firstly, there was a general impact on response times irrespective of target location, interpreted tentatively as a distraction from task effect for totally novel shapes. There was also an endogenous orienting effect, attention was cued towards the location of the novel shape. These suggestions at first seem contradictory, however, the pattern of results could occur if there was a general distraction effect for high novelty (e.g. first exposure) but a covert orientating effect for less novel items (e.g. 2^{nd}, 3^{rd}, 4^{th} exposure).

In respect of group membership, it was found that the patients with high apathy performed normally on this task relative to patients with low apathy and normal

controls. There were no significant differences between groups for either the number of error responses or the effect of novelty or location on response times. In fact, it can be seen that the high apathy patients performed the task with generally faster response times than the low apathy patients. The reason for this is unclear and only a tentative explanation can be offered. Although there were no differences between groups considering the level of novelty, the high apathy patients did tend to show less impact in general of the novel shape (see e.g. Figure 10). Although this effect was not found to be significant, it may indicate that novelty had less of a distracting effect on response times in the high apathy patients. Consequently, they showed faster response times than PD patients with low apathy.

However, it must also be considered that by chance, patients with slightly faster response time abilities were allocated to the high apathy group. This is an unfortunate consequence of the quasi-experimental design used, however it probably does not confound the results. The crucial aspects of the data are the differences between different levels of novelty and the location of the novel stimuli, between-group differences in general response time abilities will not affect this. However, it is of note that faster response times in the high apathy sample adds further to the findings reported in Chapter 4 that there is little evidence for cognitive slowing being responsible for apathy in PD.

In order to obtain a single measure of the effect of the novel stimulus on responding, the difference between response times from the 1st presentation and combined 2nd-3rd presentations for targets appearing in conjunction with the novel event were calculated. This gives a simple measure of the impact of novelty on individual subjects. For the PD sample, personality scores were available from the Tridimensional Personality

Questionnaire that were reported in Chapter 3. This includes the trait of 'novelty seeking' and so it is of interest whether this trait, rather than apathy is linked to performance on the current task. It was found that there was a significant negative correlation between the task-derived score and novelty seeking. Those patients with low novelty seeking scores showed the highest impact of novelty on the responses.

Novelty seeking is described as "*a heritable bias in the activation or initiation of behaviours such as frequent exploratory activity in response to novelty*" (Cloninger et al., 1993 p 977). Novelty seeking is considered to be a trait dependent on dopaminergic tone (Cloninger, 1987) and has been found to be lower in PD patients (Menza et al., 1993), although this result was not replicated in Chapter 3. The negative correlation therefore seems to be paradoxical in that it may have been hypothesised that high novelty seeking individuals would show the highest impact of the novel stimuli. However, it may be that as low novelty seeking predisposes to lower behavioural responses to novelty, the initial presentation of the novel stimulus produced inhibited responding. When the level of novelty was reduced (2^{nd}-3^{rd}) presentation responding was returning to normal therefore giving a larger difference on the impact of novelty. In this interpretation low novelty seekers are not less able to detect novel events, but may inhibit responses to them.

Regardless of the direction of the correlation, this result further indicates that apathy and low novelty seeking in PD patients are not related. This was argued in Chapter 3 on the basis of a lack of correlation between the two phenomena. The current finding that apathy is not associated with experimentally induced novelty responses but the trait of novelty seeking is, is strong evidence that apathy is not a reflection of the premorbid personality of the PD patients, but a distinct clinical symptom.

Returning to the effect of apathy on attention, further observations can be made. In the current investigation, it was shown that spontaneous shifts in attention could be attracted by novel visual stimuli. However, this ability appears to be independent of the expression of apathy in patients with PD. Therefore, spontaneous attentional shifts do not appear to differ between PD patients with and without apathy. This partially explains why the findings differ qualitatively to previous neuropsychological studies of responses to novelty. In the introduction to this Chapter, studies of the responses of patients with apathy to novelty were described. These found differences in the voluntary viewing of novel images relative to less novel images. In those studies, there was an obvious involvement of goal directed attention. The subjects were given the opportunity to visually inspect novel stimuli. The responses were covert attentional shifts, often indexed by eye movements and self paced trial-by-trial inspection time (Daffner et al., 1999; Daffner et al., 2000a; Daffner et al., 2000b).

Furthermore, the patients reported by Daffner et al. were capable of identifying the novel or incongruous items if asked to do so (Daffner et al., 1994b). Therefore, previous neuropsychological findings may have been measuring dysfunction of voluntary interest in novelty, not the detection of and orienting to novelty itself. The phenomenon of voluntary attention to stimuli has been described as 'epistemic curiosity' (Berlyne, 1960). The current methodology involved attempting to automatically 'hijack' visual attention and this may be a crucial difference between methodologies.

If neurological patients with high apathy have normal capabilities for detecting novel events but are less curious concerning them this would reconcile the current findings with previous research. It may therefore be of interest as the next step to examine

curiosity' in apathetic patients, rather than basic attentional components that seem to be uninvolved in the expression of apathy. This is the approach taken in Chapter 6.

Chapter 6: Curiosity and its Relationship to Apathy in Parkinson's Disease

Introduction

Descriptions of the behaviour of patients with PD often include descriptions of behavioural rigidity (Booth, 1940), introversion (Poewe et al., 1990) and low Novelty Seeking (NS, Menza et al., 1993). The three traits are related, behavioural rigidity would not be expected for example in individuals who where extroverted and keen on seeking novelty in their lives. In Chapter 3, it was reported that no association was found between the personality trait of NS and apathy in PD. However, the role of curiosity is worthy of further investigation.

NS and curiosity are related concepts. NS is considered a tendency in some people to seek out novel or risky situations for their own sake (McCourt, Gurrera, & Cutter, 1993). It is often suggested that NS is the human equivalent of exploration in other animals (Cloninger et al., 1993). However, exploration of the environment is a widespread phenomenon, shown by a wide range of species, and does not necessarily involve novel environments. For example, it is well know that rats will 'patrol' their usual settings, even locations that have never been rewarding in the past (Birke & Archer, 1983). This is a form of unconditioned behaviour that involves exploration, but not a novel environment.

Curiosity is similar to NS in that it stresses the desire to encounter the unknown, but can not be considered as a singular personality trait. In fact patrolling is a good example of what has been described as 'intrinsic exploration' as opposed to 'extrinsic exploration'.

In the former curiosity is the driving force and in the latter some other need such as hunger (Berlyne, 1960). Therefore, intrinsic exploration and curiosity are almost synonymous, the only difference being that intrinsic exploration is the behaviour and curiosity the explanation. Distinctions such as this have been criticised as adding nothing to explanation, just adding a new term (Spielberger & Starr, 1994). Therefore, the term 'curiosity' will be used in this thesis in its loose sense referring both to the motivation to explore and the expression of this motivation (exploration).

Despite the confusion concerning words such as curiosity and exploration, the distinction between intrinsic and extrinsic curiosity remains useful. It is this intrinsic curiosity that is of interest in respect to apathy in PD. Apathy has been described as involving a reduction in GDB, expressed partly by a 'lack of interest in learning new things', (Marin, 1996). This could therefore be interpreted as a reduction in curiosity.

In fact, there is good reason to suspect that as a group there may be a tendency for reduced curiosity in PD patients. Areas known to be involved in the pathology of PD have been shown to be active in tasks involving intrinsic exploration. The frontal lobes, particularly the lateral and medial premotor cortices have been implicated in exploration of visual scenes using blood flow PET imaging (Mellet, Tzourio, Denis, & Mazoyer, 1995). An exploration task performed without vision found activity in the right medial premotor cortex, but also the right anterior cingulate and right caudate nucleus (Gitelman et al., 1996).

The involvement of the caudate nucleus and anterior cingulate cortex are of particular interest in relation to PD, as they are known to be affected by the disease, particularly in patients with cognitive dysfunction (Lichter et al., 1988). However, it is also of interest

that other basal ganglia systems have been implicated. In a nucleotide binding study it was estimated that dopamine activity was greatly increased in the ventral striatum while subjects navigated a virtual environment searching for rewards (Koepp et al., 1998).

If it is hypothesised that curiosity is reduced in PD, it immediately raises the question of why no effect of apathy on attention to novelty was found in Chapter 5. The paradigm reported in Chapter 5 appears to be in a sense a curiosity test in that its aim was to detect spontaneous behaviour in response to novel stimuli. However, a distinction is often made when describing human curiosity between two distinct forms. 'Perceptual curiosity' occurs when a stimulus has some contextual property such as novelty and invokes attention or approach by raising arousal. The alternate form 'epistemic curiosity', which applies mainly to human behaviour, is a desire for knowledge (Berlyne, 1960). Although the terms perceptual and epistemic curiosity were first used in the sixties, the concepts can be dated back much further. William James in his classic 'Principles of Psychology' discussed essentially the same phenomena when he distinguished between curiosity elicited by the novelty of the environment and 'scientific curiosity' (James, 1890).

Returning to Berlyn's terminology, we can propose that perceptual curiosity was the phenomenon measured in Chapter 5, as novelty was central to the paradigm. Interestingly, perceptual curiosity also seems to correspond to some extent with NS. In one factor analysis study of trait measures of curiosity, it was found that a scale of perceptual curiosity seemed to load on the same factor as sensation seeking (Olson & Camp, 1984), a trait often considered identical to NS (McCourt et al., 1993). Perhaps, perceptual curiosity is related to NS and epistemic curiosity to GDB, and in its pathology, apathy.

The concept of epistemic curiosity has recently been elaborated, such that it is defined sufficiently to be testable experimentally. It has been suggested that epistemic curiosity is produced when gaps in information are presented to people, a prime example being crossword puzzles (Loewenstein, 1994). Loewenstein based his interpretation partly on the Gestalt principle of closure. This asserts that there is a cognitive motivation to complete items that appear to be missing a part (Koffka, 1935). This can be extended to knowledge, such that being presented with a question will identify an incomplete whole. The cognitive system is then motivated to complete the domain by looking for an answer. It is argued that epistemic curiosity only occurs when we become aware that there is a lack of knowledge about something, what Loewenstein calls 'information gaps'. If we are not aware there is an information gap, then there is no curiosity. Similarly, if we already know the information, there is no need to become curious. This theory has been used to explain a range of findings in the psychology of curiosity over the last 50 years.

A simple test of epistemic curiosity would therefore involve informing subjects that a piece of information was missing from a set and giving them the opportunity to find the missing information. The control condition would involve a similar task, but in which the meaning of the information was not related to any information gap. Despite this, there are as yet no empirical tests reported that have attempted to measure epistemic curiosity. The only paper that I know of remains unpublished (Loewenstein, G., personal communication).

It is hypothesised in this chapter that PD patients high on apathy will show less epistemic curiosity than patients low on apathy or normal controls, and furthermore, they will spend less time on the task in general. In order to test these hypotheses the use

of word search puzzles were employed. It was considered that giving a clue to the words meaning in advance would produce an information gap. This can be compared with equivalent task where no clue was given. Therefore we would expect curiosity to be aroused when a clue is present and this would motivate subjects to persevere on tasks that they may otherwise have stopped doing sooner. This suggestion was tested in a pilot study, reported below.

Pilot Study: Method and Results

The experimental task

Subjects were required to perform a large number of word search tasks from grids of letters. The trials were similar to the word search tasks in popular puzzle magazines. However, the four x four grids of letters to search were relatively small compared to those often seen in magazines and puzzle books. In addition, only half of the trials contained a word. This was arranged partly so that simple 'word present' and 'word absent' responses could be used and also so that termination of trials in which words were not present could be examined.

Of both the word absent and word present trials, the availability of clues to the word meaning were available on half of the trials. In this way 'information gaps' could be manipulated without any clue as to the correct response on any given trial. In total, there were 60 trials covering four conditions based on word presence (yes/no) and clue presence (yes/no). There were, therefore, 15 trials in each condition. Because clues were available on some trials even when a word was absent, the presence of a clue did not indicate the appropriate response to make. However, in the word present trials it could potentially speed responses by aiding detection. In the word absent trials this

could not happen and therefore the pure effect of clue presence could be assessed without the confound of its effect on detection. To administer the experiment a novel computerised task was developed using the Visual Basic programming language.

As this was a very novel investigation with no precedent, it was important to establish using the test that information gaps actually do affect performance. To do this 14 healthy subjects, mainly academic staff at the Institute of Neurology participated in a pilot study. The mean age of the pilot sample was 25.9 (SD=4.9), nine were male. The task was as described above. It was administered on a desktop PC in a hospital office; responses were made via either the left or right buttons of the PC mouse.

The effect of clues on response time in conditions with no words present is of primary interest and is the only pilot data reported here. When a clue was present, the pilot subjects spent approximately 8 percent longer than when a clue was not present. This difference was significant (for a one tailed test), $t(13)=2.118$, $p=.027$. Thus, there was sufficient reason to continue the investigation with patients and aged controls.

Main Study: Method

Subjects

A total of 20 PD patients were tested in this experiment, 17 of these were female. All patients were drawn from the sample described in Chapter 3. The current research was conducted three-six months later. Fifteen healthy control subjects also participated, all were volunteers who responded to advertisements or were non-academic friends of the author. Twelve of the control subjects were female and all but two were right handed. The mean age of the PD patients was 66.7 (SD=10.29) and for the controls it was 61.0

(SD=10.27). There was no significant difference between the patients and controls for age ($t(33)=-1.62$, $p=.11$).

PD patients were tested off medication. In practice, this meant that they had not taken any drugs for control of their PD since the previous evening. Test sessions were performed approximately 11 hours since the last dose of medication was consumed.

For the 20 PD patients the median score on the AES-R derived in Chapter 3 was 34.5. This was used to allocate patients to either the high apathy group (PD-HA) or low apathy group (PD-LA). Data for the PD-HA and PD-LA groups on mean age, years of education, Hoehn and Yahr stage, ADL score, MMSE score, CAMCOG score, BDI score, AES-R score and handedness are shown in Table 20. T-tests, where appropriate, confirmed that there were no significant differences between the groups on these measures, other than the PD-HA group having significantly higher apathy scores on the AES-R ($t(18)=5.42$, $p<.001$). These data were collected during the initial assessment three-six months previously.

Table 20: Means (and SDs) for the characteristics of the PD-HA and PD-LA patients.

	PD-HA (N=10)	PD-LA (N=10)
Age	68.2 (11.67)	65.2 (9.08)
Education	13.22 (2.54)	13.17 (2.37)
Hoehn & Yahr	2.05 (.685)	1.95 (1.01)
ADL	42.3 (13.47)	44.8 (18.1)
MMSE	28.9 (.99)	28.0 (1.58)
CAMCOG	94.90 (4.51)	94.89 (2.62)
BDI	11.3 (7.26)	13.4 (4.14)
AES-R	42.0 (6.85)	28.2 (4.24)
Handedness (R:L)	8:2	9:1

Apparatus

Administration of this experiment involved the use of a Dell laptop computer with a colour 12.1" LCD monitor. This was used to display stimuli and record response times and accuracy. Subjects sat approximately two feet from the display. During each test session dim lighting was employed to enhance the visibility of the computer display. Responses were made via mouse buttons situated within the casing of the computer. Unlike the previously reported experimental investigations, precise millisecond recordings were not required and so the standard PC clock was used for recording response times. As the task involved responses taking several seconds this was thought to be acceptable. The task was the same as used in the pilot study, described above.

Stimulus materials

Forty-five common four-letter words were selected from a published corpus of English word usage (Johansson & Hofland, 1989). All words had estimated occurrences in English of between 40 and 100 times per million. For each word, four different clues were produced. Multiple clues were produced for trials that had to be repeated due to incorrect responses (described below). The clues were deliberately vague to prevent subjects from purposefully searching for particular words, for example the clue 'It's heavy' was used with the word 'Safe'. For 15 of the 45 word-clue pairs, both were used, i.e. trials that had both a word and clue. For 15 of the remaining 30 word-clue pairs, only the clue was used, i.e. trials that had a clue but not a word. The remaining 15 pairs were used in trials in which there was a word but not a clue. Word-clue pairs were randomly allocated to each of these three conditions. This procedure was followed to prevent unconscious bias by the experimenter in the construction of clues for word present and word absent trials. The final condition used neither clues nor words and so word-clue pairs were not needed.

In the word present trials the words were located within the letter grid in the ten locations possible for words that read either left to right, top to bottom or both (i.e. four horizontal, four vertical and two diagonal). As there were 15 trials but only 10 locations, some locations were used more than once, but this was kept constant across conditions. The non-word letters in each grid were controlled so that they had the exact same frequency as the letters in the target words. The result of this was that non-word and word trials were practically identical in terms of their individual elements. Therefore, strategies such as simply spotting an odd letter or too many consonants would be ineffective.

After initial composition of the letter grids each was subjected to a custom written programme that generated all legal and pseudo-legal (i.e. spelt backwards) three and four letter strings and compared these with a computerised dictionary. If any extraneous three or four letter words were found, the distractor letters were rearranged and the procedure repeated until only the intended words were present. This procedure eliminated all extraneous four-letter words and the vast majority of three letter words. A small number of words such as 'moo' were practically unavoidable due to the constraints on location and letter frequency. However, this was not a problem as subjects were explicitly told to only search for four-letter words.

Procedure

Each subject was tested individually in his or her own home. They were told that the task involved searching grids of letters in order to find a single English word. It was explained to them the locations that the word could be in and that it would always be English and four letters long if present. Special care was taken to make sure that each subject realised that clues were present just as often when a word was present as when it was absent. In explaining the procedure, it was stressed that accuracy was very important and that they could take as long as they wished on each trial. They were not told that response times were to be recorded. At the beginning of each trial either a clue or the words 'no clue' were presented in a box near the top of the screen. Three seconds after this the letter grid was displayed clearly in large letters in the middle of the screen. An example of the visual display is shown in Figure 13, in this example a clue is present but not a word.

Two buttons on the mouse-pad of the laptop were used to respond. The left button was used for 'Yes' and the right button for 'No'. Subjects were allowed to press the buttons

with either hand. After each response, feedback was given by way of a tick or cross. The clue and letter grid remained visible during this one second interval. Following this, the next trial began. If an incorrect response was given, the letter grid was automatically repeated at the end of the experiment. If this were a trial in which a clue was given, a new clue would be used (as described above). The experiment continued until each trial had been completed or was abandoned by the programme. Trials were abandoned after four incorrect responses. The procedure was performed in 2 blocks. Total testing time varied greatly as this was a self-paced task. The range of test completion times ranged from 15 to 60 minutes.

Hypotheses

1) The effect of clue availability in the conditions in which a word is absent will be reduced in patients high on apathy compared with patients low on apathy or control subjects.
2) Patients high on apathy will spend less time searching in the conditions in which a word is absent than patients low on apathy or control subjects.

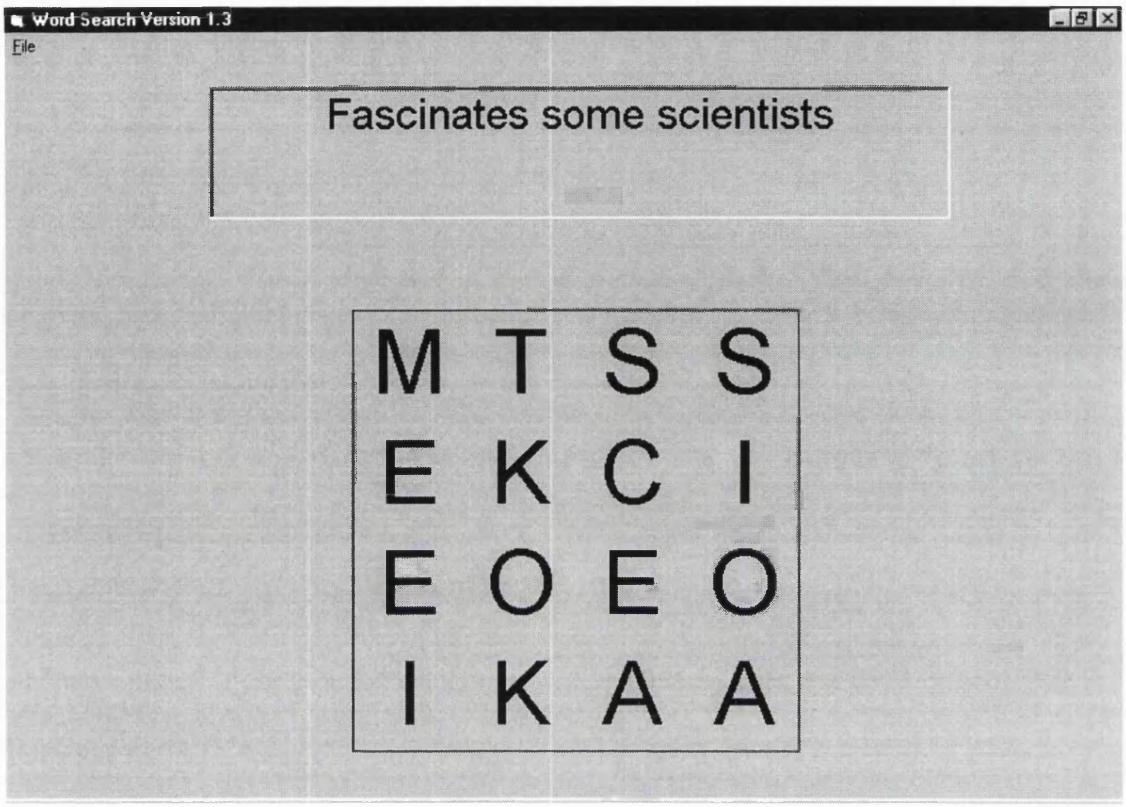


Figure 13: A sample trial of the display in the word search task (word absent condition).

Results

Main Analysis

Prior to examination of the response times, the error rates are considered. The mean number of errors was calculated for each subject and group means are displayed in Table 21. These data were compared in a repeated measures ANOVA with clue presence (yes/no) and word presence (yes/no) as within subjects factors and group membership as a between subjects factor. There was a main effect of word presence, significantly more errors were made of omission than commission ($F(1,32)=41.23$, $p=<.001$). However, there was no main effect of clue presence ($F(1,32)=.44$, $p=.511$) and no interaction between word and clue presence ($F(1,32)=.21$, $p=.648$). There was a main effect of group ($F(2,32)=3.55$, $p=.041$). The PD-HA group made overall more

errors than the PD-LA or control group (3.6, 2.58 and 1.73 errors respectively). Planned contrasts revealed that there was a significant difference between the PD-HA group and controls (p=.012) but not between the two PD groups (p=.192).

Table 21: Mean (and SD) of the total errors made in each condition of the word search task by the PD-HA, PD-LA and control subjects.

Word Present	Clue Present	PD-HA	PD-LA	Control
Yes	Yes	5.8 (4.76)	4.4 (3.41)	3.2 (3.19)
	No	6.8 (5.77)	4.8 (2.78)	2.73 (2.28)
No	Yes	1 (1.15)	.3 (.48)	.53 (1.06)
	No	.8 (1.32)	.8 (.92)	.47 (.64)

The interactions involving group were all non-significant, (word*group F(2,32)=2.06, p=.145, clue*group F(2,32)=.71, p=.499, word*clue*group F(2,32)=.94, p=.402). This indicates that the error rate did not vary systematically, the PD-HA group simply tended to make more errors.

For the main analysis median response times were calculated for each subject in each condition, these are displayed for the word present trials in Figure 14 and for the word absent trials in Figure 15. A repeated measures ANOVA was performed to detect any significant differences within the data. Word presence (yes/no) and clue presence (yes/no) were within subjects factors and group membership (PD-HA, PD-LA, control) was a between subjects factor. It was found that there was a main effect of word presence. Not suprisingly, there was a tendency towards longer response times to decide that a word was not present than to decide that one was (F(1,32)=46.29, p<.001).

The group main effect was not significant ($F(2,32)=.22$, $p=.808$), indicating that overall response times were similar for each group. Indeed, the effect of clue availability overall did not vary significantly by group ($F(2,32)=.47$, $p=.627$).

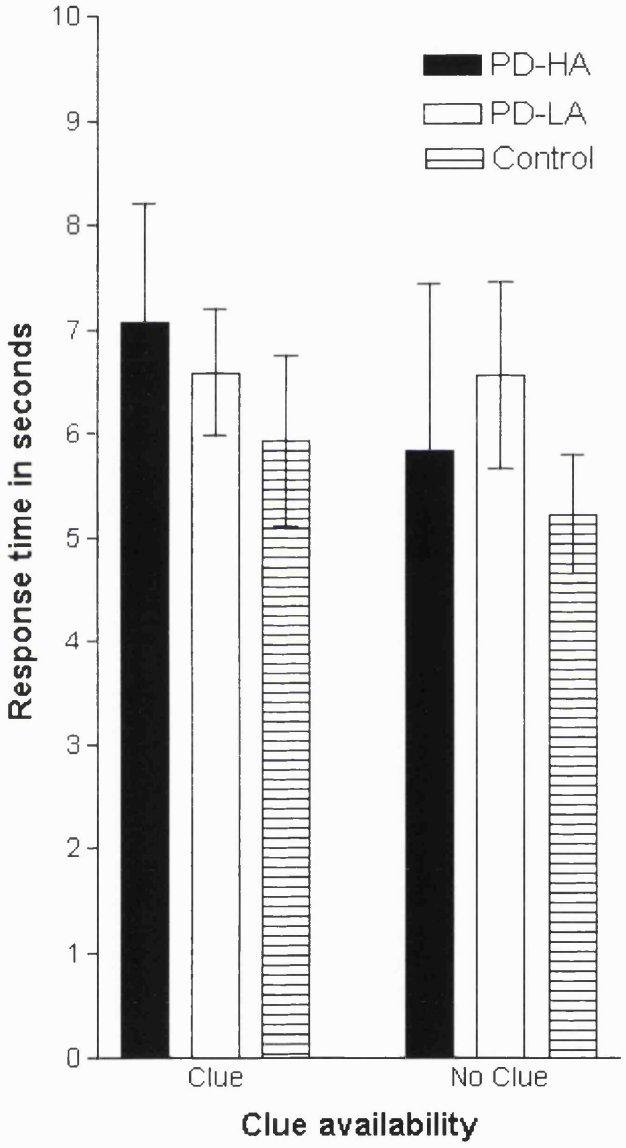


Figure 14: Response times in seconds (and SEMs) of the three groups for the word present conditions in the word search task.

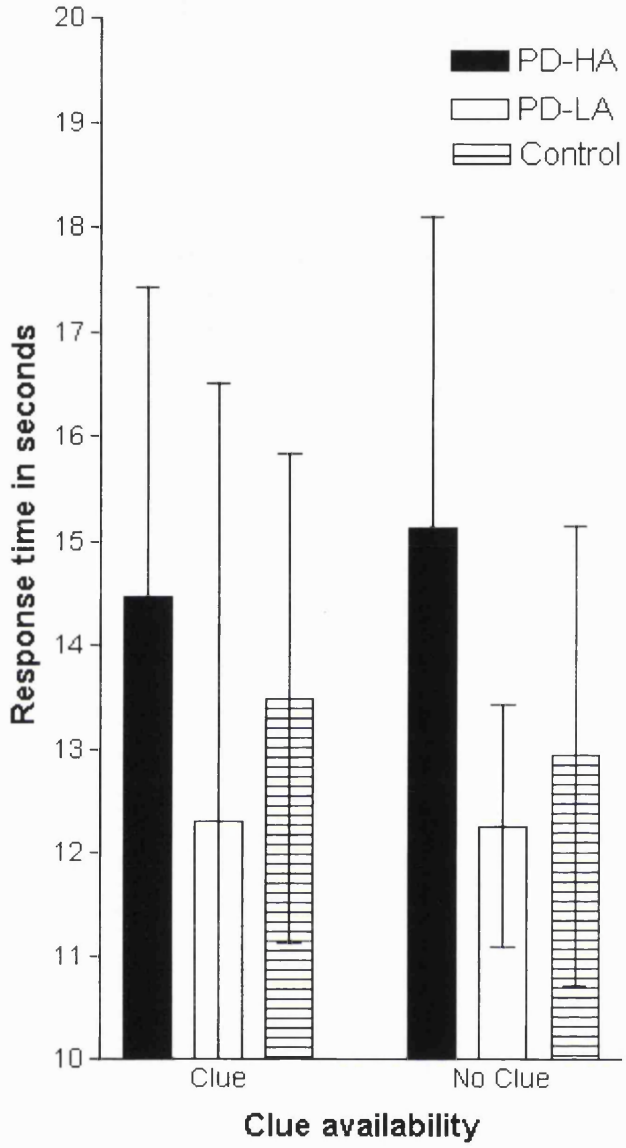


Figure 15: Response times in seconds (and SEMs) of the three groups for the word absent conditions in the word search task.

There was no main effect for clue presence ($F(1,32)=3.40$, $p=.231$). Comparing Figure 14 and Figure 15 it can be seen that there was a tendency for clues to extend response times in the word present trials and to reduce response times in the word absent conditions. This implies that there was a differential effect of clue availability dependent on word presence. However, the crucial statistical test of this is the clue-presence*word-presence interaction which was found to be non-significant

(F(1,32)=1.39, p=.246). The interaction between group and word presence was also not significant (F(2,32)=.50, p=.609). Furthermore, the three-way interaction of clue presence, word presence and group membership was found to be non-significant (F(2,32)=1.06, p=.357) indicating that subjects in different groups tended to perform in similar ways in response to clues in both the word absent and word present conditions.

The first hypothesis was that patients high on apathy would respond less to the clue in the word absent conditions than the low apathy patients and control subjects would. This prediction was tested partly in the main ANOVA calculation. However, it is appropriate to examine it directly. Just the word absent conditions were compared in a repeated measures ANOVA with clue present or absent as a between subjects factor and group membership as a within subjects factor. The main effect of clue availability was not significant (F(1,32)<.01, p=.957) nor was the group main effect (F(2,32)=.26, p=.771). Crucially, the interaction between clue availability and group was also found to be non-significant (F(2,32)=.91, p=.415) indicating that the PD-HA group did not perform significantly differently than the other groups.

The second hypothesis concerning apathy was that high apathy patients would spend less time on the word absent conditions than the other groups. However, the interaction between group and word presence reported above was not significant. To test this prediction more directly the mean of the two word absent conditions was calculated and compared by group membership in a one-way ANOVA. This was found to be non-significant (F(2,32)=.26, p=.771). Examination of the means revealed that the PD-HA group actually spent longer in seconds (14.79) on word absent conditions than the PD-LA group (12.27) or control group (13.21).

Correlation Analysis

Although the group comparison of word absent trials was not significant, the trend was in the opposite direction than initially hypothesised. It is appropriate to examine further the relationship between apathy and response times. In order to assess this, apathy scores (on the AES-R) were compared with response times using parametric correlation statistics. The response times in each condition, as well as the averaged response times for word present and word absent trials were compared. The results are shown in Table 22.

It can be seen that response times in word present trials were not correlated with apathy levels. However, significant correlations were found between apathy and the average response times in word absent conditions (clue and no clue combined, r=.465, p=.039) and word absent (no clue) conditions (r=.506, p=.023). The correlation for word absent (clue) conditions was approaching significance (r=.409, p=.073). The direction of the correlations indicates that increases in apathy were accompanied by longer response times.

In Chapter 5, the personality trait of NS was found to be related to responses to novel visual stimuli. As apathy has been shown to correlate with response times in the current study, it is of interest to examine whether other individual differences such as NS are similarly associated with response times. To test this, scores derived for the PD patients from the Tridimensional Personality Questionnaire (data collected initially for use in Chapter 3) were compared with response times in a correlational design. As described in Chapter 3, Persistence, the sub-scale of Reward Dependence is considered separately. Only combined word present conditions and word absent conditions were used in this comparison to reduce the number of analyses and limit the risk of type one errors. The results of the correlations with personality traits are shown in Table 23 where it can be

seen that none reached significance. However, it is notable that NS scores were approaching significance in the correlation with word absent response times (r=.39, p=.089).

Table 22: Correlations between apathy scores and response times in the word search task.

Response Time Measure	r Value	p Value
Word and Clue	.246	.295
Word and No Clue	.062	.795
Word (Both)	.191	.421
No Word Clue	.409	.073
No Word No Clue	.506	.023
No Word (Both)	.465	.039

Finally, as a further test of the validity of the procedure (it was shown in the pilot study that clues extended response time in the word absent conditions) the median response times for the controls were compared. It was found that in the word absent conditions, the presence of a clue slowed responses by approximately 4.2% (clue mean =13.48 seconds, SD=9.10; clue absent mean =12.93 seconds, SD=8.58). A t-test comparison revealed that there was no significant difference between response times when a clue was present and when it was absent for the controls in the word absent trials (t(14)=1.41, p=.181).

Table 23: Correlations between personality trait scores and response times in the word search task.

Personality Trait	Word Present Response Times	Word Absent Response Times
Novelty Seeking	r=.342, p=.140	r=.390, p=.089
Harm Avoidance	r=.285, p=.223	r=.158, p=.505
Reward Dependence	r=.142, p=.550	r=.223, p=.344
Reward Dependence - Persistence	r=.062, p=.794	r=.284, p=.225
Persistence	r=.209, p=.376	r=.000, p=998

Discussion

The aim of this study was to examine the ways in which PD patients with either high or low apathy, or normal aged controls, responded to curiosity arousing stimuli. Word search tasks were used that varied depending on whether there was a word present or absent. The conditions in which a word was absent were of primary interest. In a pilot study it was found that clues had the expected effect of extending response times in these conditions, and it is assumed that this is because the clues made the subjects more curious about the solution to the task so that they spent longer searching before responding. The primary aim of this study was to examine whether this effect would be reduced in PD patients with high levels of apathy. However, before these results are considered, the results on trials in which a word was present will be discussed.

The conditions in which a word was present should not be capable of detecting the effects of clues on curiosity. This is because the response times will be mainly a function of how long it takes to detect a word, not how long is spent checking. The effect of clues themselves could either facilitate response times by aiding detection or slow responses by providing a distraction. There seemed to be a distraction effect rather than a facilitation effect, across groups response times were longer when a clue was present than when it was absent in the word present trials, however this was a weak trend and was not statistically significant.

The most likely explanation for this is that when a word was found in the no clue condition, the next step was to respond. When a clue was present in the clue condition, the subjects could have responded immediately if they wished, but may have waited to compare the word with the clue prior to responding. Regardless of why this occurred, there were no significant group differences. This is what would have been anticipated. Semantic processing is not usually thought to be implicated in the cognitive profile of PD.

The null result for the word present trials is also important because it demonstrates that the apathetic patients were willing to co-operate in completing the task to the same level as the other groups. For example, if the apathetic patients had spent less time searching in general, this would have resulted in a group difference on the word present trials. This was not found, so it can be concluded that apathy did not affect the general amount of effort applied to the task. This allows a clearer interpretation of the results in the word absent trials.

Analysis of errors in the word present trials showed that although errors were relatively common, they are unlikely to have interfered with the response time results. The high apathy PD patients did make significantly more errors than the control subjects did overall, but not more than the low apathy PD patients. There were also no interactions between group membership and conditions. Therefore it is unlikely that a trade off between speed and accuracy could mask a between groups effect on response times. Returning to the word absent conditions, it was suggested that providing a clue to the word's meaning (even though no word was present) would normally invoke curiosity and induce subjects to spend slightly longer searching before terminating the trial by making a 'No' response. This is what was found in the pilot study. Furthermore, it was hypothesised that PD patients with high apathy would not show this effect to the same extent.

The data showed a tendency in this direction. Relative to the condition with no clue, the response times when a clue was present were extended most in the controls and least in the high apathy patients. Despite the trend being in the expected direction, the analysis of response times comparing the different groups failed to reach statistical significance.

Analysis of errors in these no-word conditions showed that errors were relatively rare and did not vary significantly between conditions or groups. This is as expected because in the no-word present conditions, errors could only occur if a) the subject just got the response buttons mixed up or b) they thought they had found a word when none was present. The low frequency and lack of group differences for errors imply that a trading-off of response times for accuracy is unlikely.

It must therefore be concluded that clues do not differentially affect response times between the groups. The most probable explanation for the results is therefore that the null hypothesis is correct, patients with high apathy are as curious as those with low apathy or healthy control subjects. Correlational analyses of response times and personality data were also insignificant, though it was noted the trait of NS was approaching significance.

The results did show a tendency in the expected direction of less clue responsivity in the word absent trials for the high apathy patients. It is possible that if more trials were used to minimise the overall effect of individual variation in response times and a larger sample were tested, a significant effect may have been found.

One important alternative explanation for the result must also be considered. This is also probably a major fault in the study. When only the aged control subjects are considered, the effect of the clue was quite small, even in this group, and was found to be non-significant. Therefore, although the high apathy patients failed to react to the clue, the control subjects showed only a small effect. This was a novel task and there were no comparable methods available in the psychology literature. Therefore, when the test was developed it was piloted on a small number of younger subjects. The initial results seemed to suggest that the test was effective in measuring curiosity, response times were significantly longer when a clue was present than when it was absent in trials were no word was available.

The question that remains therefore, is why the control subjects failed to show the anticipated effect. It is certainly possible that there was an age-related effect involved. Ageing is associated with a reduction in exploratory behaviour in a range of animals

(Lalonde & Badescu, 1995). It could be postulated that ageing in humans is associated with a similar reduction in curiosity. Certainly, trait scores of NS tend to reduce with age when large samples are examined (Cloninger et al., 1991). One study that examined viewing preferences for novel stimuli in young and old subjects found no differences, indicating curiosity may be age-independent (Daffner et al., 1994a). The picture is further complicated by a study that found that lack of curiosity as a personality trait is a significant mortality risk factor in the elderly (Swan & Carmelli, 1996). The surviving elderly, would presumably be non-representative of the population as a whole due to their above average levels of curiosity.

A further explanation of why the pilot study subjects appeared more curious may simply have been due to sampling effects. In the main study, the control subjects were recruited from a variety of backgrounds, but the pilot study subjects were predominantly scientists. It is certainly feasible that the scientist group were particularly more curious in general than the aged group because of situational or personality differences.

Although no difference could be detected for the first hypothesis concerning the effect of clues, significant correlations were found between apathy and response times. As apathy increased, there were corresponding increases in response times in word absent trials. There was no correlation between apathy scores and word present trials, and no association with personality trait measures such as NS, though this was approaching significance. The only individual difference measure that significantly predicted increased response times was high apathy. This is probably because word present trials have a predefined stopping point (word detection). However, in word absent conditions there is not an obvious point at which a response should be made, because it is

essentially deciding to give up searching. It is therefore not too surprising that the point at which the decision is made (reflected by response time) is related to motivation.

What is surprising is the direction of the association. Patients with high levels of apathy spent longer on the tasks before deciding to terminate the search than patients with low apathy. This indicates that the performance difference can not be simply attributed to laziness or lack of effort. If apathy caused subjects to simply take their time while searching, this would have been reflected in word present trials too, but it was not. The only reasonable explanations are that a) patients with high apathy searched normally, but continued to search for longer before abandoning the task, b) patients with apathy searched normally for most of the task (long enough to detect a word if present) but then stopped searching briefly before responding. If the first suggestion is correct, this may reflect a lack of confidence in success of search strategies. For example if subjects searched methodically through all possibilities, a 'confident searcher' would be able to respond at the end of the search. A 'less confident searcher' may repeat the search or parts of it. If PD patients with high apathy followed this strategy, then the current results could be explained. It would be of interest to test this hypothesis with larger grids in which exhaustive search strategies would be impractical and approaches that are more heuristical had to be used. This would allow distinctions between confidence and curiosity to be drawn.

Whichever interpretation is correct, this may have resulted because there was no cue to prompt the 'absent' response. If the high apathy patients were impaired on generating a response in the absence of a prompt then this result would be expected.
In summary, there is no evidence to implicate a generalised reduction in curiosity in PD patients, even those who display apathy. This at first appears contrary to descriptions of

PD patients, and in particular those with apathy. The lack of interest almost seems synonymous with a lack of curiosity. However, by looking comparatively at other disorders of GDB such as psychic akinesia and abulia, a possible reconciliation can be found. Patients with abulia are often said to require external stimulation to act (Fisher, 1995). Similarly, it has been reported that patients with psychic akinesia following globus pallidus damage can perform at normal levels with sufficient prompting (Laplane, 1994). Perhaps the lack of interest is present in unclearly structured situations in which there are insufficient prompts to guide behaviour.

It was found in the current experiment that overall response times were higher for patients with apathy in the conditions in which there was no prompt to respond (word absent). Perhaps, the focus of the cognitive impairment associated with reduced GDB is in response production in the absence of prompts to act. This suggestion is explored in the next two chapters of this thesis.

Chapter 7: Willed and Stimulus driven Action: A Single Case Study of an Akinetic Patient

Introduction

Findings in the previous chapters have provided little support for deficits in attention and curiosity as components of apathy in PD. However, it has been shown that apathy was associated with delayed response termination in one task (Chapter 6). Thus, the patients appeared to be performing the task normally when there was a prompt to act, but continuing when there was no such prompt. This pattern resembles anecdotal descriptions of single case studies of patients with psychic akinesia.

Such patients have been repeatedly reported by Laplane et al., who have identified several cases, usually resulting from damage to the globus pallidus (Laplane et al., 1984). One feature of the syndrome is described as a loss of mental content. Based on verbal report, it is claimed that patients with psychic akinesia have a lack of ideas, statements include such things as *"my mind just seems to be blank"* (Laplane, 1994 p 570). However, of particular focus is what has been described as 'loss of psychic self-activation' (Bogousslavsky et al., 1991). This term is used to explain the observation that the patients with psychic akinesia tend to perform normally when given guidance or instruction, but will not do so if this structure is absent. An explanation has been attempted for this phenomena in terms of 'hetero-activation', the guidance of action by external stimuli and 'self-activation', the guidance of action by intention. The former is suggested as being controlled cortically, and the later via cortical and sub-cortical systems (Laplane, 1994).

This division between hetero-activation and self-activation, is very similar to other concepts developed in experimental psychology that have proposed separate routes to action based on action slips (Reason, 1979) and reaction times (Frith & Done, 1986). Furthermore, studies of animals with experimental brain lesions have confirmed the behavioural distinction and partially supported the distinction between cortical and cortical-subcortical control (Passingham, 1993). The emerging consensus has been between 'willed action' and 'stimulus driven action'. These concepts are also implicit in the supervisory system theory of attention, which was developed to explain the 'willed and automatic control of behaviour' (Norman & Shallice, 1986). Indeed, disconnection of the supervisory system has been proposed as an explanation for the symptoms of a patient (described in more detail in Chapter 2) who displayed a profound reduction in willed behaviour (Shallice, 1988). This patient made no spontaneous actions other than eye movements, but was capable of performing many tasks, such as the token test, when asked (Damasio & Van Hoesen, 1983).

This distinction between willed and stimulus driven actions has been used to interpret a range of neurological and psychiatric symptoms (for a comprehensive review see Jahanshahi & Frith, 1998). But, emphasis has focused primarily on the negative signs of schizophrenia patients (Frith, 1992; Fuller & Jahanshahi, 1999a; Fuller & Jahanshahi, 1999b; Fuller & Jahanshahi, 1999c). It is hypothesised that a selective deficit in the willed action route causes a reduction in GDB in negative sign schizophrenic patients. The manifestation of negative signs such as poverty of speech, flattened affect and psychomotor retardation (Krawiecka, Goldberg, & Vaughan, 1977) are viewed as resulting from a global reduction in willed action.

It has further been suggested that impairment of the will driven route to action can occur at two levels. Plan formation can be disconnected from willed intention processes, or willed intention processes can be disconnected from action processes. However, either disconnection will have the overall effect of reducing the efficiency of willed actions, and in both cases GDB will be reduced (Frith, 1992; Jahanshahi & Frith, 1998).
The explanation of negative signs in schizophrenia as a willed action impairment could equally account for the reduction in behaviour observed in psychic akinesia patients as well as PD patients with apathy. However, willed action has never been tested directly in clinical groups. The willed action theory in schizophrenia is based mainly on clinical description and of impairments in executive skills such as excessive perseveration (Frith & Done, 1983) and reduced verbal fluency (Frith, 1992).

Patients with psychic akinesia show impairments in executive skills such as verbal fluency (Laplane et al., 1989), as do patients with PD and apathy (see e.g. Chapter 3). However, this does not necessarily imply a deficit in willed action as reflected by a reduction in GDB. Poor performance on executive tasks is also associated with excessive and impulsive behaviour, not reduced GDB, such as seen in some patients with frontal lobe damage (Lezak, 1982) or children diagnosed as showing attention deficit hyperactivity disorder (Barkley, 1997). This is not to say that executive and intentional processes are independent. Willed actions are essentially manifestations of executive processing. Executive skills have been defined as being *"involved in planning and allocation of attentional resources to ensure that goal-directed behaviour is initiated, maintained and monitored adequately to achieve goals"* (Jahanshahi et al., 2000 p 1144). This definition emphasises the role of executive skills in GDB in general, it is the planning and attentional conditions that distinguish willed from stimulus driven actions.

A common way of viewing willed actions is that they are most apparent when selection for action occurs in the absence of cues or prompts (Jahanshahi et al., 2000; Passingham, 1993; Spence & Frith, 1999). This is also consistent with the framework of GDB described in Chapter 2 and the Norman and Shallice (1986) model of attentional control. Both propose that actions that cannot be driven by perceptual input must rely on executive control.

Despite the significant overlap, it seems premature to base conclusions concerning the source of negative signs or apathy on willed action, when the assesment tools used are standard executive skill tests. Indeed, the strongest case for a willed action deficit contributing to a GDB deficit has been argued for schizophrenic patients with negative signs (Frith & Done, 1988). However, impaired performance on tasks thought to indirectly indicate willed action deficits are present in both negative and positive symptom schizophrenia patients (Mignone et al., 1995). Furthermore, Laplane, who described many of the patients with 'loss of psychic self-activation' (LPSA), did not consider the executive impairment in his patients as reflecting their GDB impairment and commented *"it would be interesting to see whether there are tests which correlate with LPSA"* (Laplane, 1990 p 34). Although Laplane expresses a need for associations, theoretically more powerful and of more interest would be patterns of dissociations in patients with reduced GDB.

There is therefore confusion concerning which aspects of GDB are predicted by executive function tests. This is primarily because they are not specifically designed to detect willed action impairments. It is imperative to develop tests that minimise processes that are not directly related to GDB such as set-shifting but still assess willed response generation. Only when these conditions are satisfied will it be appropriate to

assert that particular patients have willed action deficits, as opposed to a general dysexecutive syndrome.

A method of comparing willed and stimulus driven actions would need to use identical motor responses, but in the stimulus driven condition have a sensory trigger that was absent in the will driven condition. This is a seemingly impossible restriction, but there are in fact events that do not have a corresponding sensory trigger. One such event is a duration. Durations *"have no specific sensory impact, but are relativized by the perceiving subject"* (Fraisse, 1984 p 4). For example if a subject was asked to watch a stream of visual items, each separated by one second intervals, and to respond to either a green target circle or to no stimuli being presented, then two separate types of responses could be recorded. Responding to the green circle would be a simple stimulus driven action, responding to a lack of stimulus would involve a willed action, as there is no prompt to act other than a perceived duration after which time an event is judged not to have happened.

If, as claimed, patients with psychic akinesia have a deficit in self-activation (willed action), but unimpaired hetero-activation (stimulus driven action), then using this task, responses to the green circle should be normal, but responses to a lack of a stimulus would be impaired. A similar pattern would be predicted for schizophrenia patients with negative signs according to the willed action theory of schizophrenia. Indeed, such a test should in principle be able to distinguish willed from stimulus driven actions in any patients with reduced GDB.

To pre-empt the rest of this chapter slightly, it was decided to implement such a task and administer it to a patient who is profoundly akinetic following basal ganglia

damage. This type of patient should be a suitable model to compare routes to action. It is hypothesised that the damage will cause a disruption to willed actions, leaving stimulus driven actions relatively intact.

Case history

TYR is a right-handed English speaking white male who had previously worked as a roof tiler. In September 1994, aged 27, he injected heroin, that had been purchased from a new source. Approximately two hours later he fell and hit his head. When he came to, he had poor balance and difficulty speaking. Over the next three weeks he developed a severe akinetic rigid syndrome that left him wheelchair bound and anarthric. The strike to the head was considered to be minor and it was assumed that his neurological symptoms were related to the heroin dose he had taken.

A MRI scan in March 1994 revealed symmetrical extensive high signals in the basal ganglia. A sample image from this scan is shown in Figure 16. Over the next three years there was no improvement in his mobility and he was admitted as an in-patient to the National Hospital for Neurology and Neurosurgery in London for further tests.

On examination, he was alert and orientated, with a mini-mental state examination score of 28-29/30. Speech was slow and hypophonic, though he communicated readily with a typing device. There was no evidence of dysphasia. Eye movements were normal and there were no signs of visual field defects or inattention. Axial and limb rigidity was present, though power was normal. His writing was micrographic. There is no family history of parkinsonism and the patient was HIV negative. He has not taken heroin since the incident. For symptomatic treatment of his motor problems he is prescribed dopamine agonists and L-dopa drugs, that have a small beneficial effect.

Neuropsychological examination

TYR was followed up for this investigation between May and June 1999 at which time he was age 32. All test sessions were conducted at his parents' home, who now care for him. Medication was not withdrawn due to the negative effect this would have on his mobility.

Due to his speech and writing difficulties, only non-spoken tests and those with a minimal amount of writing were administered. A self-assesment scale of physical ability normally used for patients with PD revealed a score of 65, this is relatively high and would be expected in advanced stage PD (Brown, MacCarthy, Gotham, Der, & Marsden, 1988). Motivation was assessed with the short form of the Apathy Evaluation Scale, he scored 5 out of 42, a score which is well below the cut-off point of 14 indicative of apathy (Starkstein et al., 1992). On the Beck depression inventory he scored 13, indicative of mild depression (Beck et al., 1961).

To assess current non-verbal intelligence Raven's Progressive Matrices (Raven, 1965) were used. TYR scored 8 out of 12, which has a National Adult Reading Test (NART) IQ equivalent of 117. This is in the normal range. Premorbid verbal intelligence was assessed with the Spot-The-Word test (Baddeley, Emslie, & Nimmo Smith, 1992), a non-spoken analogue of the NART. TYR scored 45 out of 60, which placed him at the 25^{th} percentile for his age. This score is slightly lower than expected based on the Ravens progressive matrices, but within normal limits.

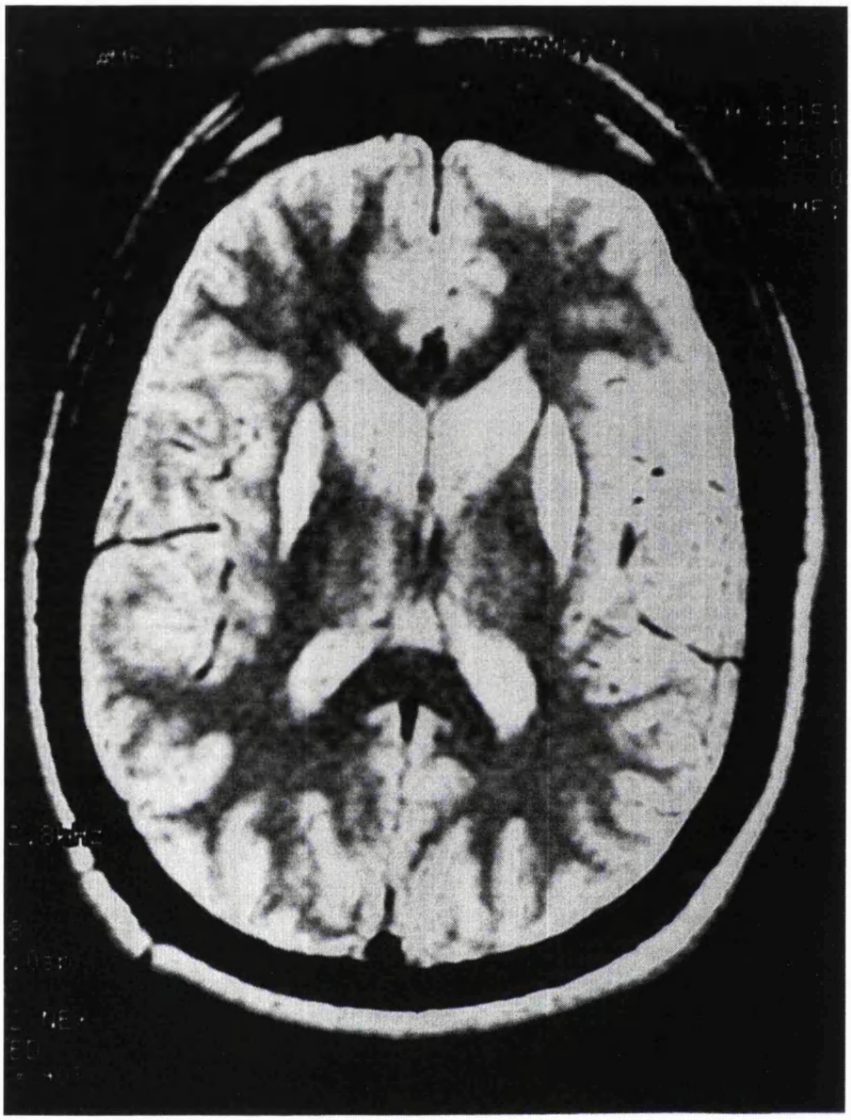


Figure 16: Axial T1 weighted MR image of patient TYR dated 10/3/95, showing high signals in the basal ganglia bilaterally.

Although his clinical notes recorded that there was no evidence of dyspraxia, TYR's mother commented that his walking was improved by verbal instruction, a statement that the patient agreed with. In order to assess praxis a test was used that assessed buccofacial, transitive limb and intransitive limb (tool use), this was based on an assessment described previously for non-language assessment in aphasia (Goodglass & Kaplan, 1972). Comparisons were made of ability to perform actions to verbal

command, if this was failed to imitation, and if this was failed, and where appropriate, with tools provided.

The buccofacial actions assessed were cough, sniff, blow out a match, suck through a straw and puff out cheeks. Of these 3/5 were failed to command but could be performed to imitation. This indicates a degree of buccofacial apraxia.

The intransitive limb actions assessed were; wave 'goodbye', beckon 'come here', place finger on lip for 'shhh', salute and use the palm to signal 'stop'. Using his right hand TYR failed two actions to command but was able to perform normally to imitation. The results were identical when the left hand was used.

For transitive actions the following tasks were used; brush teeth, stir coffee with a spoon, hammer, saw wood and use a screwdriver. To imitation TYR tended to perform 'body part as object' actions, a phenomena common in apraxia (Mozaz, Marti, Carrera, & De la Puente, 1990). Using his right hand he failed 3/5 actions to command but performed these normally when imitating. Using his left hand he failed only 1/5 actions, but this one difficult action, 'stir a cup of coffee', was also failed to imitation. The provision of a cup and spoon allowed the normal action to be demonstrated.

The results are consistent with moderate levels of both bilateral limb and buccofacial apraxia. This is shown by the large improvement in action production when imitating or with actual tool use relative to oral command. This is a very common pattern in patients with apraxia (Belanger, Duffy, & Coelho, 1996).

'Frontal' cognitive performance was assessed with several established tests. These were the Reitan Trail Making Test (Reitan, 1958), Wisconsin Card Sorting Test (Nelson, 1976), Visual-visual Conditional Learning (Petrides, 1985), and the Self-ordered Pointing Test (Petrides & Milner, 1982). The results of these are shown in Table 24 and are compared with control data available from other reports. The criteria for normality used is whether the score is within two standard deviations of the mean of the control group.

Using this method of analysis it is shown that TYR performed within normal limits on all tests apart from the Wisconsin Card Sorting Test. In the Reitan Trail Making Test, performance was not considered for the individual times to completion of forms A and B, as TYR's motor impairment would confound this. However, the crucial B-A statistic was used, as this is independent of movement time. TYR performed within the normal range on this measure. TYR's performance on frontal tests is therefore inconsistent, but the available evidence suggests that there is at worst, only minor, relatively specific, executive impairment.

Table 24: Performance by TYR on standard tests of executive performance.

Task	Measure	TYR	Control Mean (SD)	Control Characteristics	Source
Trail Making	B-A (in secs)	15	56.03 (25.9)	24 Controls, Mean Age = 29.5, SD = 6	Smith et al. (1998)
Wisconsin Card Sorting	Categories Achieved	1	5 (1.7)	46 Controls (32 non-CNS patients and 11 healthy), Mean Age = 45, SD = 14	Nelson, (1976)
	% Perseverative Errors	31	23 (14)		
Visual-visual Conditional Learning	Trials to Criterion	52	42.7 (17.4)	12 Controls, Mean Age = 55.1, SD = 10.9	R.G. Brown, personal communication
	Total Errors	22	15.7 (9.5)		
Self-ordered Pointing	Total Errors	7	6.4 (3.1)	16 Controls, Mean Age = 39.5, SD = 12.4	R. Fuller, personal communication

Experiment 1

Subjects

This task was completed by TYR (age 32) and 10 right handed, healthy control subjects with a mean age of 31.7 (SD=5.56). Eight were male and two female. Control subjects were selected to be similar to TYR in terms of socio-economic status and education level. All subjects were tested in their own homes. The task was administered in two blocks, each taking approximately 10 minutes.

Apparatus

For this study the same laptop computer used to control experiments reported in previous chapters was used. This was fitted with a digital timing card (Computer Boards inc., PCM-D24CTR3) that allowed connection of a microswitch and millisecond accuracy recording of responses. For display of stimuli and recording of data, a programme was written in the Visual Basic programming language.

Experimental task and procedure

To compare willed and stimulus driven actions a task was devised in which a stream of coloured distractor stimuli shapes were presented in the centre of a laptop computer screen. Each was present for one second and there was a one second delay before presentation of the next stimulus. Occasionally there would be either a green circle displayed or the sequence would be halted (a blank screen). A response to a green circle would be specified by the target and would therefore require a stimulus driven response. A response to acknowledge that the sequence had stopped has no sensory cue to specify it and so will require a willed action.

Either event was equally likely to be presented and overall each event occurred 21 times during the experiment. An event occurred at the time the 3rd, 6th or 9th distractor stimuli could have been expected. There were equal numbers of 3rd, 6th and 9th location events. Therefore, an event would occur on average every 11 seconds (5 seconds of distractors being displayed and six seconds of inter-distractor interval). However, events could also occur as early as five seconds since the previous event or as late as 17 seconds since the previous event. The intervening time would be filled by distractor stimuli appearing one every two seconds.

The subjects' task was to hold down a micro-switch with the index finger of the right hand until either a green circle appeared or the sequence stopped. If a green circle was to appear it would do so after a one second interval since the preceding stimuli was removed. If the sequence was halted, this could not be detected before one second had elapsed since the preceding stimulus was removed. Therefore both events had pre-determined onset times. Reaction times from this onset time to when the switch was released were recorded.

A schematic representation of the procedure is shown in Figure 17. This shows a typical sequence of visual displays starting at the previous response and showing how, first a delay event is presented (willed action trial), and second a target stimulus event is presented (stimulus driven trial). In this example, both events occurred five seconds after the preceding event. However, in the actual test the arrival of events could be not be anticipated because they arrived unpredictably every 5, 11 or 17 seconds. Each subject responded by lifting his or her index finger off the microswitch. The laptop began recording the reaction time at event onset and continued until the microswitch was released. The target event remained present until a response was made.

Immediately after responding, the subjects returned their finger to the switch and the experiment continued.

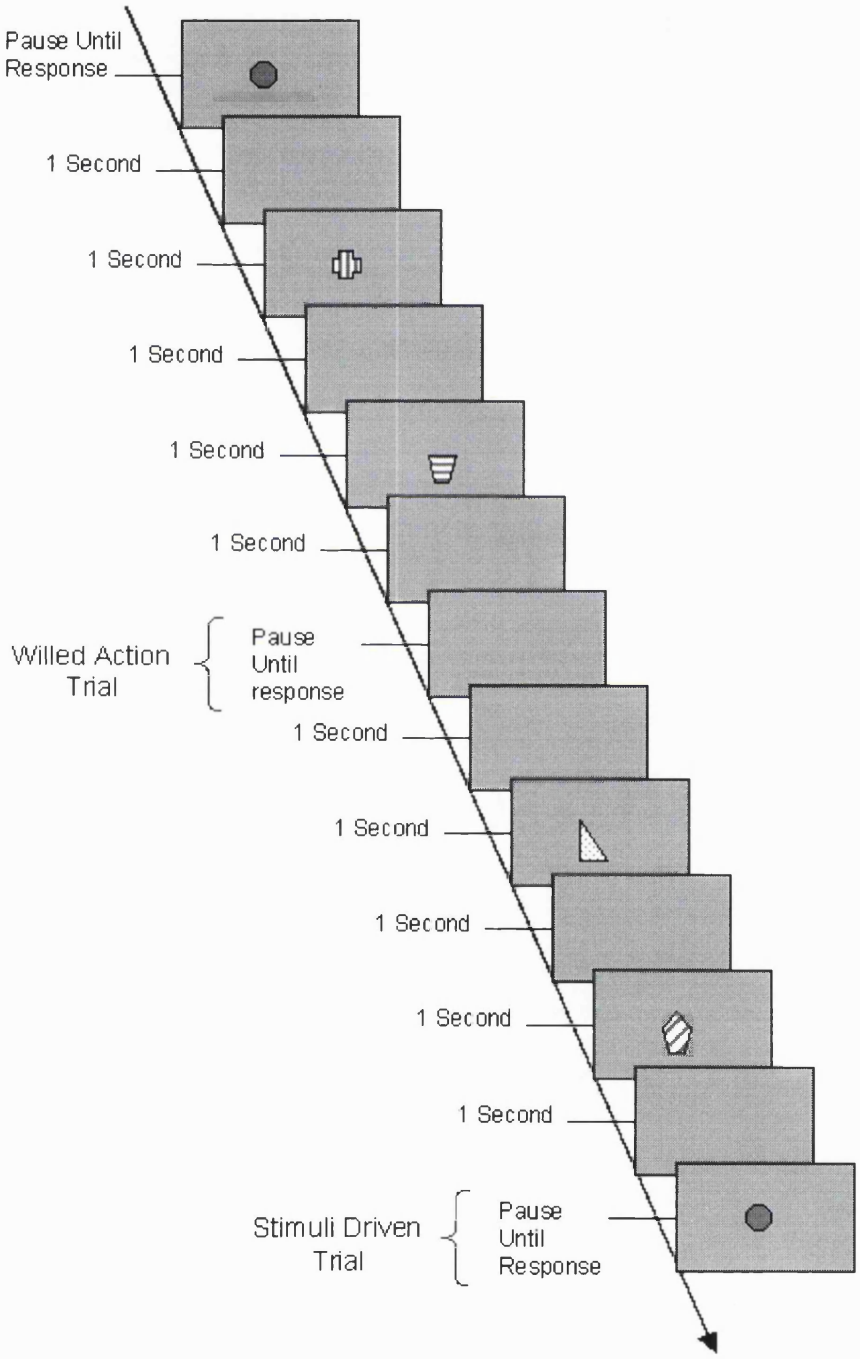


Figure 17: Schematic representation of the presentation sequences in the will/stimulus driven action task.

Hypothesis

It is hypothesised that TYR will show impairments on the willed action components of the task and relatively preserved performance on the stimulus driven components.

Results of Experiment 1

Median response times were calculated for TYR and the 10 control subjects and are displayed in Figure 18. It can be clearly seen that TYR was slower to respond in general. This difference between TYR's and the control performance was compared in a t-test analysis modified for use with single case research (Crawford & Howell, 1998a). The difference in overall response times was found to be highly significant, $t(9)=22.93$, $p<.001$. However, he was particularly impaired on the willed action condition, his median response time was more than three seconds longer than the control mean. To examine this difference the same modified t-test procedure was used. The difference was found to be highly significant, $t(9)=-23.5$, $p<.001$. TYR was also slower to respond in the stimulus driven condition, responding 429.9 msecs later than the control group. This difference was found to be significant ($t(9)=7.8$, $p<.001$). As both conditions were performed significantly more slowly by TYR than the controls, it is necessary to examine differential impairments. In this case, whether the willed performance is significantly more impaired than the stimulus driven performance. This was achieved using a modified paired sample t-test for comparing effects in single case research (Crawford, Howell, & Garthwaite, 1998b). It was found that TYR's performance in the willed action condition was significantly more impaired than his performance in the stimulus driven condition, $t(9)=12.8$, $p<.001$.

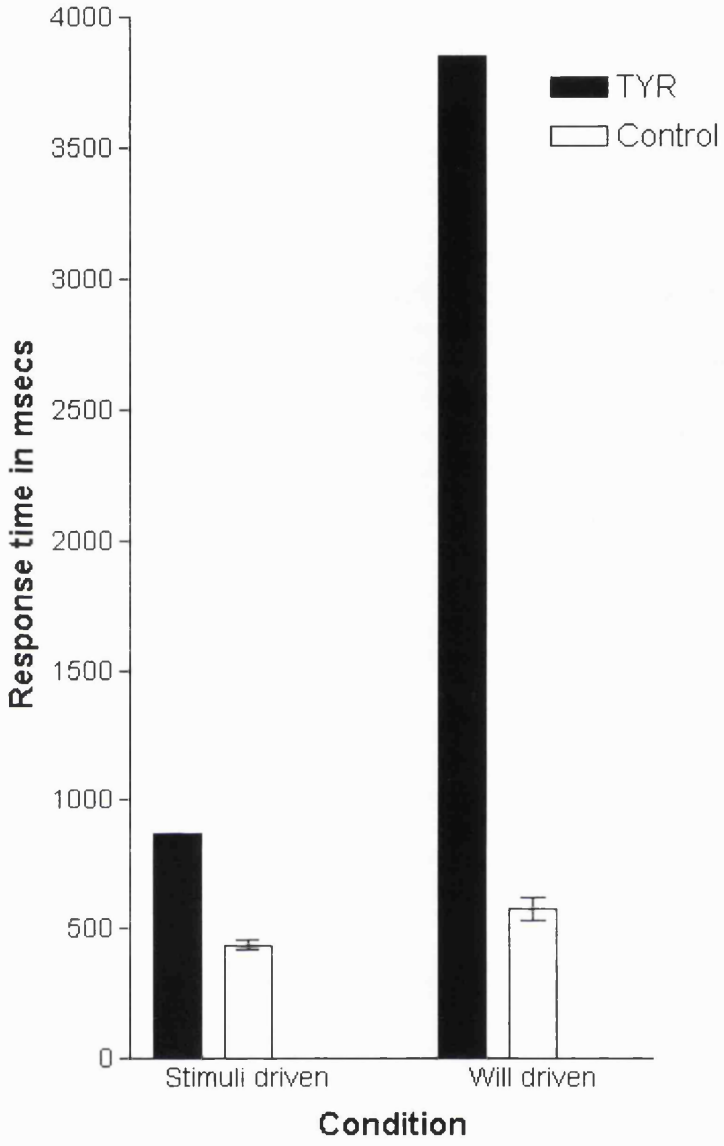


Figure 18: Median response times for TYR and controls (and SEM) on the will/stimulus driven action task.

The individual responses by TYR were subject to large variance for both the willed and stimulus driven trials. The actual mean (and SEM) for response times in the willed condition for TYR were 5,645 (1,245) msecs, and in the stimulus driven condition 2,580 (1,151) msecs. Individual response times for TYR are shown in Figure 19 and for comparison a typical control subject in Figure 20. It can be seen from Figure 19 that TYR made two unusually long responses, one in each condition. The median score was

used in all calculations and so these outliers should not have had a substantial impact on the results. If the calculations are repeated with these two outliers removed from the data set then the differences reported above remain significant.

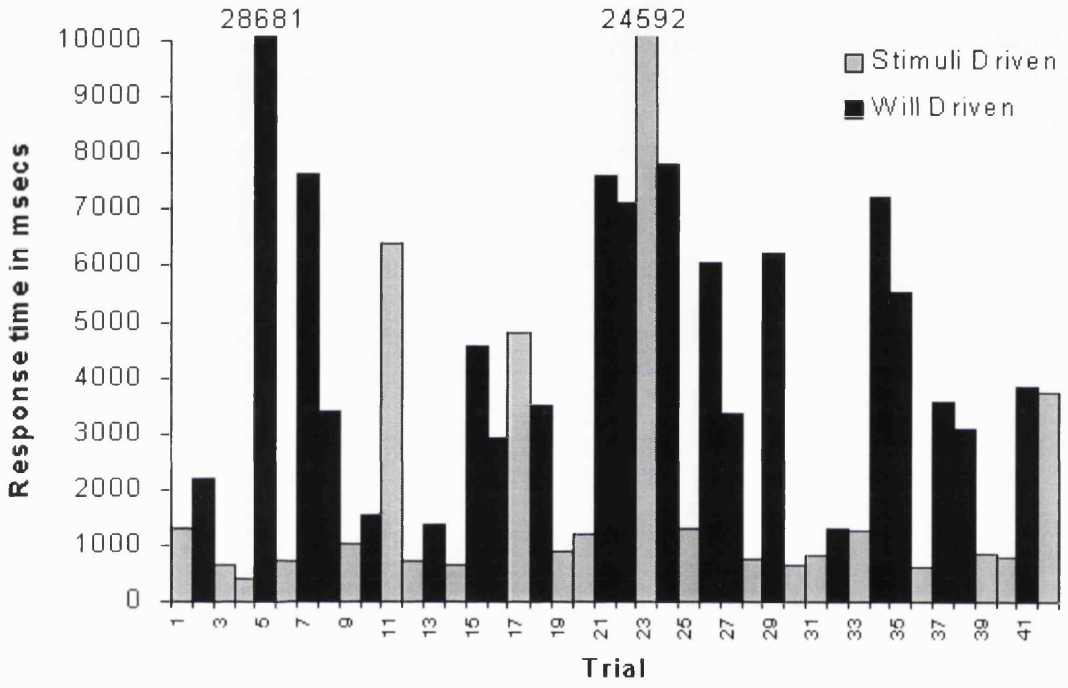


Figure 19: Individual responses by TYR in the will/stimulus driven action task.

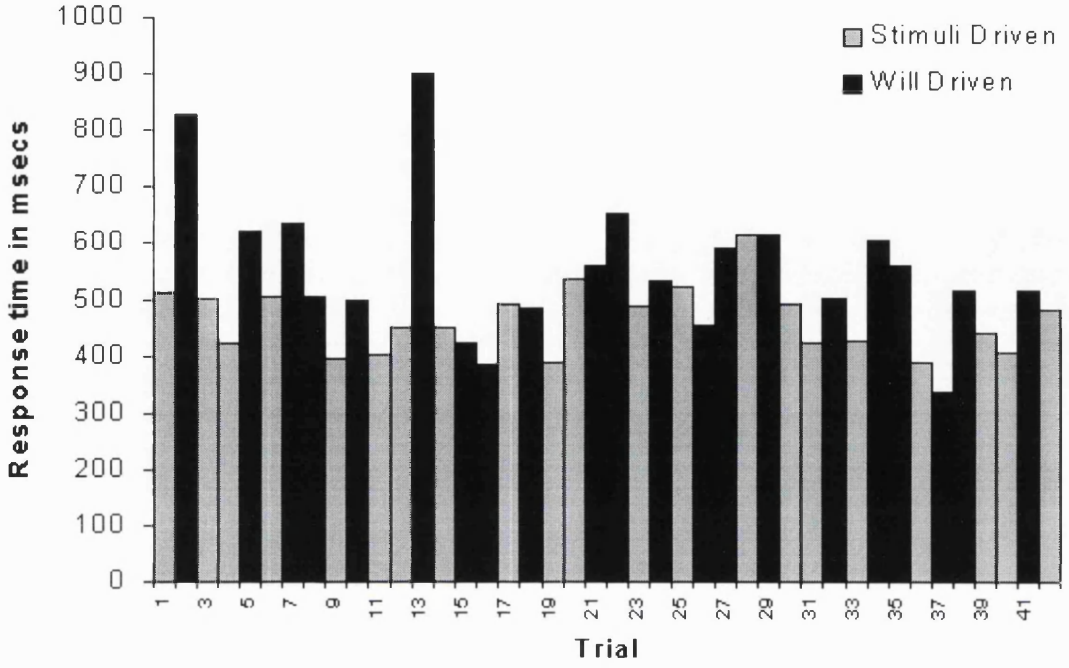


Figure 20: Individual responses by a typical control subject in the will/stimulus driven action task.

Discussion of Experiment 1

A simple task was performed in which the only response was to raise the index finger when either a green circle was presented or no shape stimulus was presented. Responding to the green circle is clearly a stimulus driven response. Responding to the lack of stimuli requires processes that cannot so simply be triggered by a sensory event. It is asserted that in the latter case more involvement is required of willed action resources to initiate a response.

TYR was found to be significantly slower to respond in both stimulus driven and willed conditions. However, considering his chronic motor impairments this result could have been expected. His performance on the willed action condition was particularly slow, taking over three seconds longer to respond than the controls. The response time difference in the stimulus driven condition was less than half a second. It was found

that the performance in the will driven condition was significantly more impaired than in the stimulus driven condition. Therefore, the hypothesis that TYR has a particular difficulty with willed actions is supported.

However, an alternative explanation could be that TYR is impaired at perceiving time durations. As there was no unique visual stimulus to prompt a response in the willed action condition, performance has to be guided by the subject appreciating that more than the expected one second inter-stimulus interval (ISI) has elapsed. This is appropriate considering TYR's lesions being mainly in the basal ganglia, a region that has been associated with time perception (Harrington, Haaland, & Hermanowitz, 1998; Ivry & Keele, 1989). If TYR could not appreciate small time differences then his performance would be slower in the 'willed' condition, but not necessarily because of a willed action impairment. This alternative interpretation is considered in the next experiment.

Experiment 2

Subjects

The patient TYR and the same 10 control subjects participated in this experiment.

Experimental task and procedure

In order to test for time duration appreciation, a task was developed in which subjects had to examine a temporal series of visual events and judge whether one event was delayed. As Experiment 1 involved appreciating that more than one second had elapsed

since the previous stimulus was presented, this procedure is mimicked in a yes/no judgement task for whether more than one second has elapsed.

The task involved the same visual elements as in Experiment 1. However, in this task two distractor shapes appeared as previously, each being visible for one second with a one second ISI. Then a third element would be presented, this was always the same green circle as used in Experiment 1. There were 90 trials in total completed by each subject. In half of the trials the green circle was presented one second after the previous stimuli had been removed, it therefore conformed almost identically to the stimulus driven condition of Experiment 1. The correct response in this task though was to press a button for 'Yes' as the previous delay had been one second (i.e. the triplet sequence was a consistent .5 Hz). In the remainder of the trials, the final stimulus (the green circle) would be presented after an additional delay to the expected one second ISI. The correct response in this instance would be to press a button for 'No' as the previous delay had been more than one second (i.e. the triplet sequence was temporally irregular).

The trials in which the final stimulus was delayed were controlled so that there were 15 trials of three different additional durations. These additional durations were 250, 500 and 1000 msecs. A summary of the temporal events in each condition is given in Table 25. Trials from each of the four conditions were presented in a random sequence that was kept constant for all subjects.

Table 25: Order and temporal sequence of events in the delay detection task.

Time in msecs	Condition 1 (45 Trials)	Condition 2 (15 Trials)	Condition 3 (15 Trials)	Condition 4 (15 Trials)
0-999	Blank	Blank	Blank	Blank
1000-1999	Distractor	Distractor	Distractor	Distractor
2000-2999	Blank	Blank	Blank	Blank
3000-3999	Distractor	Distractor	Distractor	Distractor
4000-4999	Blank	Blank	Blank	Blank
5000+	Target	Blank	Blank	Blank
5250+		Target	Blank	Blank
5500+			Target	Blank
6000+				Target

This experiment was performed using the same laptop computer as in Experiment 1. The buttons used to respond 'Yes' or 'No' were the control buttons of the mouse pad, which are built into the casing of the computer. Feedback on accuracy was given on a trial by trial basis by a tone that indicated when an error had been made. Subjects were told to concentrate on accuracy and take as much time as they wished to decide before responding. The experiment was performed in two blocks that took approximately 12 minutes each to complete.

Hypothesis

It is hypothesised that TYR will not be able to make judgements of duration presence to the same level as the control subjects.

Results of Experiment 2

The accuracy score in each condition was converted to a percentage to allow direct comparison of the conditions composed of different numbers of trials. TYR's scores and the mean scores for the control group are shown in Figure 21. It can be seen that TYR was less accurate at detecting each of the extended durations (250, 500 and 1000 msecs) but slightly more accurate at detecting the absence of a delay (0 msecs). Modified t-tests as described above were used to compare TYR with the controls for the 0, 250 and 500 msec durations. At the zero duration, accuracy represents correctly identifying that there was no delay. There was no significant difference between TYR and the controls on this measure, $t(9)=-.19$, $p=.195$. For the 250, 500 and 1000 msec durations, accuracy represents successfully recognising that there had been a delay. At 250 msecs there was no significant difference between TYR and controls, $t(9)=-.91$, $p=.908$. However, TYR was significantly worse than controls at the duration of 500 msecs, $t(9)=-3.01$, $p=.015$.

At the duration of 1000 msecs all controls scored 100% (15/15) and TYR scored 93.33% (14/15). Due to the complete ceiling effect in the controls at this duration, parametric statistics can not be used. However, due to the extremely high scores in both the controls and TYR it is clear that the task was performed well. That is, the ability to notice the duration was demonstrated sufficiently by both TYR and the controls.

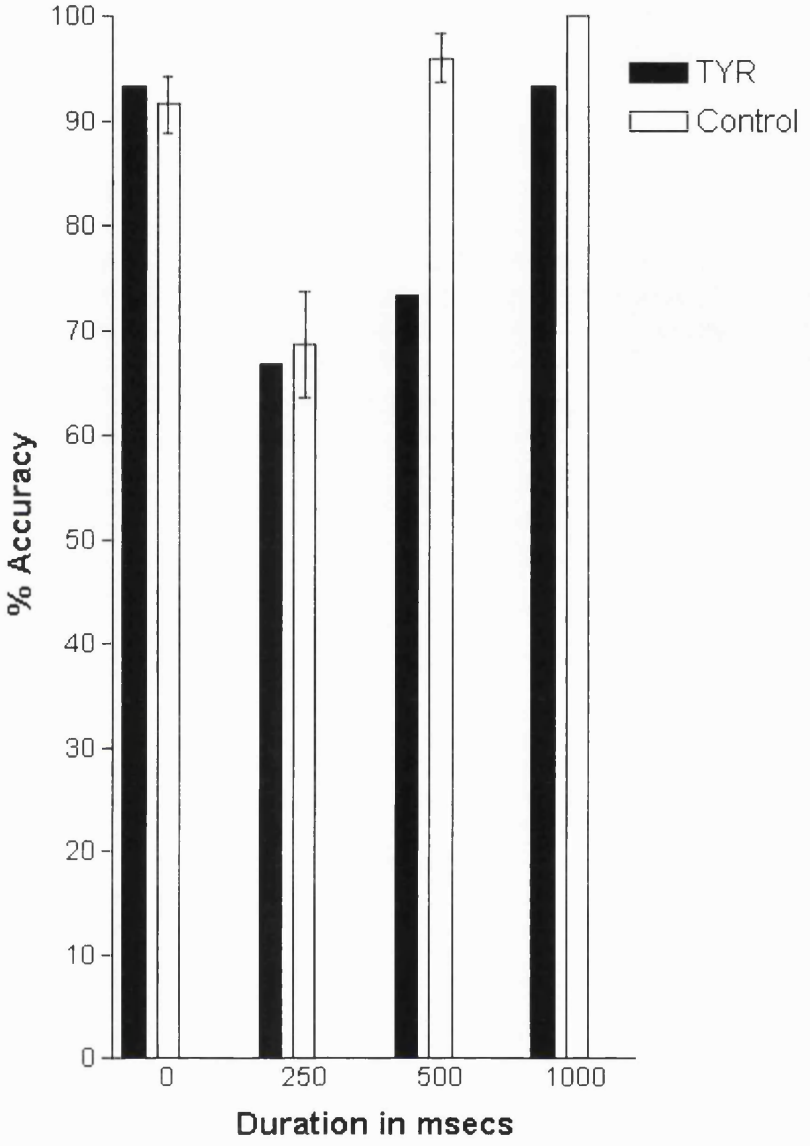


Figure 21: Percentage accuracy scores for TYR and controls (including SEM) in the delay detection task.

Discussion of Experiment 2

This experiment was performed to assess the ability of TYR to perceive time durations. The most stringent distinction in this task was the detection of a 250-msec delay. TYR was able to do this at the same level as the control subjects. However, he was significantly worse at the seemingly easier task of detecting a delay that lasted 500 msecs. At 1000 msecs, although he made a single error and the controls were at ceiling, he clearly showed that he was able to recognise that there had been a delay. Statistical

analysis of this small difference would have been inappropriate. In responding to trials in which there was not a delay, TYR was as accurate as the controls. Accuracy based on responding 'No delay' represents the ability to recognise the normal repeating pattern as opposed to patterns that include one of the three of the actual delays. The pattern that the response is distinguishing from is therefore the average of the three (583.3 msecs).

The results are therefore slightly mixed. On three out of four conditions, TYR performed at the level of the controls and this included the most stringent test, the 250-msec delay. Only at detecting the 500 msec delay was TYR impaired. Why this should be so is not clear. As described above the accurate response to a zero delay is distinguishing it from delays that have an average duration of 583 msecs. TYR was able to do this on 84 out of 90 trials, and at a level slightly higher than the control average. It therefore appears that he is capable of distinguishing delays of around 500 msecs. The single significant difference can not therefore be easily explained.

However, the results provide sufficient evidence that TYR does not have profound duration recognition impairment. It is certainly not impaired sufficiently to account for the greater than three-second difference between TYR and controls in the willed action condition of Experiment 1. Therefore, the hypothesis that TYR would show impaired appreciation of time durations can be rejected.

A final alternative hypothesis concerning TYR's performance on the tasks reported above involves sustained attention over time. Vigilance has been shown to be effected by basal ganglia disease (Stern, Mayeux, & Cote, 1984) and so maybe an issue in TYR's overall neuropsychological profile. If TYR was less capable of sustained attention than controls then this may account for the results. It was often necessary to wait several

seconds between responses and a loss of vigilance could impair performance. This hypothesis was tested in Experiment 3.

Experiment 3

Subjects

The patient TYR and the same 10 control subjects performed in this experiment.

Experimental task and procedure

In order to assess vigilance a similar procedure to that used in Experiment 1 was utilised. The only differences were that a) there were no distractor stimuli and b) all the events were green circle targets. Therefore, the laptop computer screen remained blank until a green circle appeared at intervals of 5, 11 and 17 seconds. The subjects' task was to hold down a microswitch with the index finger of the right hand until an event occurred and then to release it and immediately replace it. The computer recorded the response times between stimulus onset and response to the nearest msec. There were 21 trials at each ISI. The task was performed in two blocks, each taking approximately 10 minutes. As in Experiments 1 and 2, the current experiment was administered in the subjects' own homes.

Hypothesis

Patient TYR will show a decrease in vigilance over extended durations relative to controls.

Results of Experiment 3

Median response times were calculated for individual subjects at each ISI and are shown in Figure 22. TYR spent significantly longer overall responding than the controls when the data from the different ISIs are combined, modified $t(9)=6.50$, $p<.001$. Overall TYR took 672.5 msecs and the controls took a mean of 286.63 msecs (SD=56.56).

The overall response time by TYR in this task is slightly faster than he achieved in the stimulus driven condition of experiment 1 (868 msecs). In order to assess whether TYR showed a different pattern over time (i.e. at different ISIs) compared with the controls, the percentage difference between response times at each ISI was calculated (percentage change from 5 to 11 seconds, 5 to 17 seconds, and 11 to 17 seconds). Modified t-tests were performed to compare TYR's performance with the controls at each of these ISI differences, none reached significance (5-11 seconds, $t(9)=.15$, $p=.89$; 5-17 seconds, $t(9)=.72$, $p=.49$; 11-17, $t(9)=2.05$, $p=.07$).

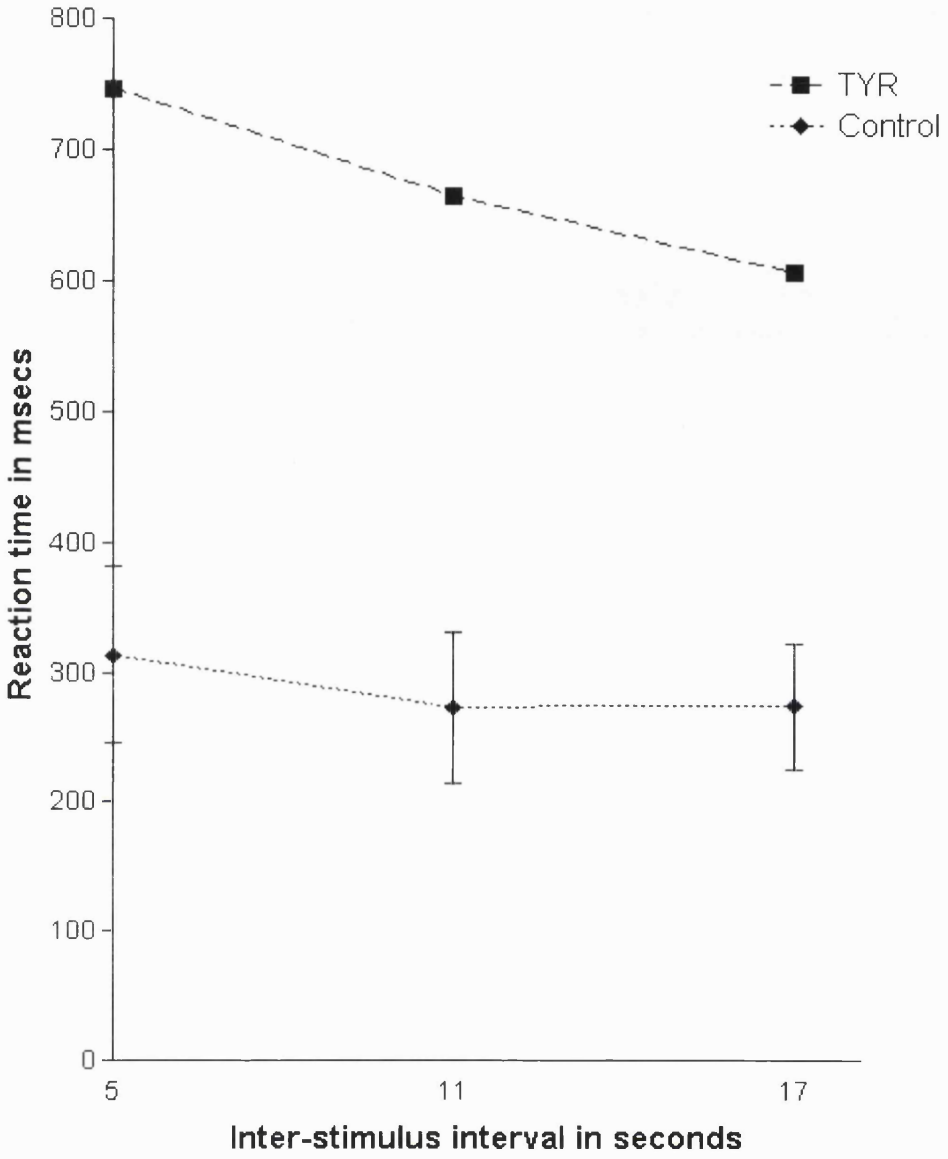


Figure 22: Response times for TYR and control subjects (including SEMs) in the vigilance task.

Discussion of Experiment 3

In Experiment 1, it was suggested that there was a willed action impairment that could account for the difference found in TYR's response time performance. However, an alternative interpretation could be that TYR has reduced vigilance. For example, if TYR was prone to rapid drops in vigilance then he may have performed particularly

poorly on the willed action aspect of the task because responses tended to be slower after prolonged delays prior to responding.

In the current experiment, it was shown that TYR does not show a significant effect of delay on response times relative to control subjects. The delays between responding and the total numbers of responses were identical in Experiments 1 and 3 and so any performance detriment related to vigilance should have been apparent. In fact, TYR showed a non-significant tendency to improve response times with larger ISIs relative to the controls.

Furthermore, in this task at each ISI, TYR's responses were faster than he achieved in the stimulus driven condition of experiment 1. This demonstrates that TYR is not prone to slowed response times after extended intervals. Therefore, the hypothesis that TYR would show reduced vigilance over longer inter-response delays can be rejected.

General Discussion

The patient TYR has a profound movement disorder, which leaves him unable to walk, speak or care for himself. The movements he does make are abnormally slow as demonstrated by the response times in Experiments 1 and 3. However, in general his intellectual abilities seem unimpaired as revealed by normal performance on the mini-mental state examination and two different assessments of intelligence.

The neural damage that lead to his akinetic rigid state probably resulted from an unidentified toxin accidentally administered as a contaminant of recreational heroin use. The available imaging information suggests that damage is mainly in the basal ganglia, which would be consistent with the resultant movement disorder. It is tempting to

suggest parallels between this case and a group of Californian heroin addicts who developed parkinsonian symptoms in the 1980's via heroin contaminated with the neurotoxin, MPTP (Langston et al., 1983). However, TYR does not show a full parkinsonian disorder, for example tremor is almost absent. Furthermore, MPTP neurotoxicity is known to be highly selective for the substantia nigra (DeLong, 1990). The MRI scan of TYR revealed damage to other subcortical regions. Therefore, it is unlikely that the neurotoxin consumed was MPTP, but the actual substance remains unknown.

Despite normal intellectual functions, it was found that TYR is mildly apraxic. Although apraxia is often associated with parietal damage (Rapcsak, Ochipa, Anderson, & Poizner, 1995), it is not uncommon following damage to the basal ganglia (Pramstaller & Marsden, 1996), and can be demonstrated in patients with PD (Leiguarda et al., 1997). In TYR limb actions to command were slightly impaired and improved to imitation or actual tool use. This is the most common pattern observed in ideomotor apraxia (Rothi, Ochipa, & Heilman, 1991). However, the opposite pattern has also been demonstrated, i.e. better performance to verbal command than to vision (Pilgrim & Humphreys, 1991). This double dissociation has been interpreted as indicating different routes to action (Riddoch, Humphreys, & Price, 1989).

In the Riddoch et al. (1989) model, it is suggested that there are three routes to action. Directly computed affordances allow the competitive selection of actions based on purely visual information such as size and slant. Visual affordances may also be useful in the attentive top-down selection of items that can fulfil current goals (Humphreys & Riddoch, 2001). There is also a separate visual route that involves structural descriptions of known objects and a conceptual route linking audition to action via

semantic representations. It is suggested that the directly computed visual route is dominant during visually guided movements, but that this can be modulated by the visual structural and conceptual routes. The visual affordance and structural description routes therefore have many similarities with the stimuli-driven route discussed in Chapter 6. An equivalent of the willed action route is less obvious but has some similarity to the semantic route of Riddoch et al. (1989).

This action model has been developed primarily to account for normal performance based on the results from apraxic patients, emphasis has been on impairments of the visual affordance route as *"visual routes to action modulate apraxia"* (Pilgrim & Humphreys, 1991 p 473). Although TYR was mildly apraxic, the focus of the current investigation was not just visual routes to action but also willed action.

In previous reports willed action deficits have been assumed to be based on, or strongly associated with, poor executive performance and reduced GDB such as negative signs in schizophrenia. The current patient, TYR, does have reduced GDB behaviour but it is not clear to what extent this represents global motoric impairment. Conversely, his executive performance seems generally intact. Of the four frontal/executive tasks administered, he failed only one. Therefore, it might be presumed that based on standard executive task performance, his willed action performance is preserved. However, as will be described, the presumption would be wrong.

In order to examine whether his extreme motor impairment is a general motor deficit, or a more cognitive action based deficit, a novel task that has both willed and stimulus driven conditions was administered. The task involved TYR raising his finger from a microswitch whenever he experienced either a green circle (stimuli driven) or an

absence of a new visual display (will driven). It was found that TYR was particularly slow to respond in the will driven compared with the stimulus driven task. However, his stimulus driven responses were still significantly slower than those of the controls.

This strongly suggests that TYR's motor impairment involves higher level cognitive aspects. It is not simply that his motor output systems are impaired with preserved action planning. If this were the case his performance on both tasks would have been similarly slower than the controls, but it was found that there was a large difference in the efficiency of willed and stimulus driven routes.

It appears that TYR's reduced GDB can in part be attributed to impaired action systems, stimulus driven actions may be involved, but particularly relevant is a willed action deficit. It could be hypothesised that TYR has a disconnection between the willed intention systems and action production systems as suggested by Frith (1992). This would be consistent with his relatively normal performance on standard executive tasks. However, the current task does not distinguish between planning and action based aspects of movement and, it is suggested, measures the overall efficiency of the willed action route. The distinction between executive and initiation aspects of the willed action route are considered in more detail in Chapter 8.

The dissociation between willed and stimulus driven action systems in TYR's performance is reminiscent of the distinction made in cases of psychic akinesia between hetero-activation and self-activation (Laplane, 1990). Under this scheme, TYR could be considered particularly poor at self-activation. On the neuroanatomical level, TYR had predominantly subcortical damage and so the current results are consistent with the

suggestion that self-activation involves cortical-subcortical processing and hetero-activation cortical only processing (Laplane, 1994).

The task used to reveal this apparent dissociation involved a crucial element of implicit appreciation of time durations. Impaired performance in this domain could therefore produce the same pattern of results (i.e. apparent impaired willed action). It was therefore important to examine TYR's ability to perceive temporal durations. A task was used that had many similarities to the willed action task. It was found that in general TYR was capable of fine temporal distinctions, and at the same level as matched controls. He did perform significantly worse on part of the test, recognising a 500 msec delay. This result was at odds with his normal performance on parts of the experiment, such as recognising a 250 msec delay. Although his results were not perfect, he did demonstrate sufficient temporal judgement ability to rule this out as a source of the dissociation in Experiment 1. For example he responded over three seconds later than control subjects in the willed action condition, but was correct on 93.3 percent of trials in distinguishing a one second delay from those that were extended by 250, 500 or 1000 msecs. This was slightly better (though not significantly so) than the control group.

A time perception impairment can therefore be ruled out in this case. This is of interest in itself as strong claims have been made concerning the dependence of time perception on basal ganglia function (see for e.g. Rammsayer & Classen, 1997). This conclusion is based on the findings that PD patients are less accurate than healthy controls at temporal perception over a wide range of time scales (Artieda, Pastor, Lacruz, & Obeso, 1992; Harrington et al., 1998; Pastor, Artieda, Jahanshahi, & Obeso, 1992). The current findings suggest that the basal ganglia are not essential for accurate time perception. It

could be hypothesised that the findings of impaired temporal perception in PD patients may be due to cortical involvement, rather than basal ganglia damage.

Returning to TYR's apparent willed action deficit, a second alternative hypothesis was considered. This was that a loss of vigilance in TYR could have particularly delayed attention to the willed action condition. No evidence was found for this. A task was used in which TYR and the controls made movements of the same type, to stimuli that were dispersed over time in the same way as in the will/stimulus driven task of Experiment 1. No significant differences were found other than generally slower responses by TYR than controls. TYR's response times even over the longest time delays were equivalent, and generally slightly faster than his performance in the stimulus driven condition of Experiment 1. There is no evidence that TYR shows a time-related drop in vigilance.

It is therefore asserted that TYR has a willed action impairment. This no doubt contributes significantly to his disability and can be seen as a key aspect of his overall reduced GDB. A willed action impairment will contribute to disability because it will leave sufferers dependent on others to provide environmental structure and instruction for the guidance of behaviour. TYR may also have impairment to the stimulus driven route, but if so, this is less affected than the will driven route.

TYR's performance shows a dissociation between willed action and stimulus driven action and so supports theories based on this distinction (e.g. Frith & Done, 1986). It is of interest whether the opposite pattern could be observed, i.e. efficient willed action and impaired stimulus driven action. If such a patient was observed this would provide a double dissociation. In fact, such a patient may have already been reported in another

context. A patient described by Riddoch et al. (1989) had a visual apraxia of his right hand. CD was able to gesture the use of objects if given their names, but was much poorer when they were visually presented to him. Of his errors in visual presentation, he never made incorrect actions, but was unable to initiate the appropriate actions at all. Agnosia or a naming impairment could be ruled out because in some instances, despite being unable to initiate the gesture, he could still name the tool. This was interpreted by Riddoch et al. as demonstrating an impairment of a direct route from perception to action. In the terminology employed in this thesis this could be translated as a stimulus driven route impairment with presumed normal willed action (no mention was made of reduced GDB symptoms such as apathy). When CD and TYR are compared, it appears to show a double dissociation between willed and stimulus driven action.

Willed action deficits are therefore demonstrable empirically, without need to infer the impairment from existing executive function tests. Furthermore, the impairment can be more obviously linked to the observed loss of GDB in the patient in question. It is clear why difficulty in the task reported in Experiment 1 may translate to real-life impairment, but not why, for example, perseveration in a guessing task might. Although driven executively, willed actions can be impaired in patients who appear to have intact executive processing as measured by conventional cognitive assessments.

TYR had a GDB impairment, in that he made few spontaneous actions and those that he did were slow and inaccurate. However, he scored well below the cut off score for apathy. Although the scale used is not infallible, TYR did demonstrate that he had interests and hobbies that tend to support the notion that TYR was not apathetic. He was for example very keen on playing video games such as car racing and snowboarding. This is somewhat surprising considering his action impairments.

However, one explanation may be that the high levels of optic-flow helped maximise use of his relatively preserved stimulus driven route to action. TYR may be avoiding pastimes that involve a large dependence on willed action systems.

Patients with PD typically have a less severe loss of GDB and this is accompanied by self-reports of increased apathy. These patients seem quite different to TYR in that their impairment is subtler. Although there are mobility issues, the loss of GDB in PD is linked to a loss of interest, rather than an inability to physically perform. Therefore, it is unclear whether a willed action deficit could also account for the reduction of GDB in PD patients. This issue is considered in the final experimental chapter of this thesis, Chapter 8.

Chapter 8: Willed Action, Executive Function and Apathy in Parkinson's Disease

Introduction

In Chapter 6, it was shown that apathy scores correlated with time taken on a word search task that had no obvious termination point. It was suggested that this may have reflected impairment in PD patients with apathy in generating responses in the absence of environmental guidance. This concept was elaborated in the introduction to Chapter 7 in terms of a willed action disorder. Furthermore, a task capable of examining willed actions was validated in a single case study of a patient with bilateral basal ganglia damage and extreme GDB impairment.

Therefore, the question is raised whether apathy in PD is associated with a willed action impairment. The single case described in Chapter 7 had a movement disorder that was described as akinetic. Akinesia is a term that subsumes a range of movement impairments including delayed initiation, slowness of execution and a general poverty of movement, in that, patients make less spontaneous movements (Wichmann & DeLong, 1993). Akinesia is also a common symptom in PD (Rifkin, Quitkin, & Klein, 1975), in fact, akinesia along with tremor and rigidity, is a key aspect in the clinical presentation. For a diagnosis of PD to be made, a common criterion is that patients must show two or more of these symptoms as well as evidence of postural abnormality. The occurrence of akinesia as a symptom in PD has been estimated as between 77% and 98% depending on its definition (Gelb et al., 1999). An early sign of akinesia is micrographia, a reduction in the size of writing (Oliveira et al., 1997) and this was also observed in the patient described in Chapter 7. Perhaps the most striking example of

akinesia in PD is in locomotion. Particularly in late stages of their disease, patients may report that their feet feel 'frozen' to the floor. Confined spaces such as walking through doorways seem to exacerbate this phenomenon, but the reasons for this are not known (Nutt, 1998).

Frith and Done (1988) have presented a model of routes to action and suggested that in schizophrenia with negative signs willed actions are impaired and stimulus driven actions relatively preserved. This has further been extended to account for a willed action impairment in PD (Frith, 1992). However, the suggested functional impairment is different in the disorders. Schizophrenic patients are said to have a disconnection of plan formation from willed intention processes, whereas in PD the disconnection is said to be between willed intentions and the actual movement/action processes. Therefore, PD patients are said to *"know what they want to do, but cannot do it"* (Jahanshahi & Frith, 1998 p 502). This is in contrast to schizophrenia patients with negative signs, whom it is said fail to generate the willed intention at all.

The planning stage in the Frith and Done (1988) model represents a type of executive skill (Frith & Dolan, 1996). Planning ability has been examined mainly using the Towers of London task and performance on this has been linked to the prefrontal cortex in both brain damaged patients (Goel & Grafman, 1995) and imaging studies (Baker et al., 1996). In this model, therefore reduced GDB can result from impaired executive function, or a disconnection between executive ability and processes involved in willed intention. In the framework of GDB described in Chapter 2 therefore, the impairment that is theorised as producing negative signs in schizophrenia is between 'supervisory executive processes' (**H**) and 'selection and scheduling' (**F**). The theorised impairment

that produces akinesia in PD is between 'selection and scheduling' (**F**) and 'initiation and execution' (**I**).

However, executive dysfunction is known to be strongly associated with apathy in PD. In Chapter 3 evidence was found linking apathy to impaired performance on verbal fluency, the Wisconsin Card Sorting Test and Stroop test. Other research has found apathy in PD to be associated with impaired performance on the Trail Making Test and a test of verbal memory (Starkstein et al., 1992). Similar observations in other pathologies have led to the formation of a model in which low motivation and apathy are a manifestation of disrupted executive function (Al-Adawi et al., 1998; Powell, Al-Adawi, & Greenwood, 1996). Furthermore using principal component analysis Al-Adawi et al. (1998) found that a factor of initiation-motivation accounted for a large proportion of the variance in a clinically derived motivation assesment. Several indices of executive function, including planning time on the Tower of London task, were loaded on this factor.

There is evidence from functional imaging to support a willed action impairment in PD. Tasks used typically involve random generation of actions such as finger movements compared with identical movements that have been fully specified for the subject. Using such methods willed actions have been found to particularly involve the prefrontal cortex (Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000). Patients with PD have been shown to have reduced activity in this region during performance of similar self-organised actions but have normal brain activations when performing externally triggered actions (Jahanshahi et al., 2000). In addition, in the willed task, the PD patients showed less activation in the SMA (relative to controls). This region has been implicated in the expression of akinesia (Wichmann & DeLong,

1993). The EEG recorded readiness potential precedes self-paced movements and is thought to originate in the SMA (Deecke & Kornhuber, 1978). In PD patients, this potential is reduced (Dick et al., 1989). The SMA has also been implicated in willed movements as opposed to stimulus driven movements, that involve the adjacent lateral premotor cortex in ablation studies of primates (Passingham, 1993).

Can the apathy in PD therefore be explained in terms of this willed action model? The answer is 'probably not'. There may well be a willed action impairment involved in akinesia, but this can not necessarily be extended to explain symptoms of apathy. For example, apathy has been shown to be equally prevalent in PD patients with symptoms of akinesia as similar patients in which the primary symptom is tremor (Starkstein et al., 1998). When a wider range of neuropsychiatric symptoms are considered, hallucinations, delusions and agitation all correlate with akinesia scores in PD, but apathy does not (Aarsland et al., 1999).

It remains a theoretical possibility that apathy in PD is a manifestation of a willed action impairment. This would be consistent for example with the findings in Chapter 3 of poor performance by PD patients with apathy on standard tests of executive function. This is because willed action, by definition, is the behavioural consequence of executive processing. However, this leads to the untenable conclusion that executive dysfunction has, as its behavioural consequence, apathy. This suggestion is contrary to the numerous reports of the impulsive and disorganised (but certainly not apathetic) behaviour of many patients with frontal lobe damage and dysexecutive syndromes (see for e.g. Duncan, 1986).

The source of this apparent contradiction is the use of the term 'executive' to explain a wide range of processes. If it is assumed that executive processing can dissociate then there may be specific categories of dysexecutive syndrome. It has been suggested for example that the breakdown of executive skills after prefrontal cortical damage can be classified as fitting one of three patterns. These are the dysexecutive type, disinhibited type and apathetic type (Duffy & Campbell, 1994). PD patients with reduced GDB would obviously be comparable to the apathetic type, however for progress to be made it is necessary to show different patterns of cognitive performance in different sub-categories, otherwise all that has been gained is a new term with the same theoretical problems.

There is some evidence for such fractionation of executive systems. In one study, patients with frontal lobe lesions were asked to complete sentences in which the final word was missing, with either an appropriate or inappropriate word. It was thought that appropriate completion time is a measure of action initiation, and errors of inappropriate completion, an example of response inhibition. It was found that frontal lobe patients were worse at both tasks than patients with posterior brain lesions. However, of particular interest was the lack of correlation between the two tasks. This implies that response initiation and response inhibition are dissociable processes within executive function (Burgess & Shallice, 1996b).

A distinction between disorders of initiation and inhibition may be useful in interpreting impaired performance on standard executive tasks. It has been suggested that reduced verbal fluency is an example of loss of verbal initiation (Costello & Warrington, 1989). Indeed, it could be argued that verbal fluency is a good example of a test that invokes willed actions. This is because other than basic information such as letter or category

fluency there is no guidance as to how to select from the thousands of potentially appropriate responses. Response inhibition is demonstrated in the Stroop task as successful performance primarily involves the active avoidance of word reading. A further example of response inhibition is in the go/no-go paradigm. This involves responding to one or more stimuli whilst withholding responses to other stimuli (Jackson, Jackson, & Roberts, 2000).

It therefore seems that separate components of executive processes can be identified. After brain damage, the loss of inhibitory control can be seen in the classic frontal lobe disorder e.g. in impulsivity (Burgess & Shallice, 1996a; Miller & Milner, 1985b) and utilisation behaviour (Lhermitte et al., 1986; Shallice et al., 1989). For the current purpose it would be of significant interest to identify executive disorders in which the primary impairment appears to involve a loss of initiation as this would show impaired willed action. The disorder of dynamic aphasia appears to be an example of an executive disorder primarily affecting initiation, in this case in the verbal domain. Dynamic aphasics present with very little spontaneous verbal output but show no signs of impairment on standard aphasia assessments (Robinson, Blair, & Cipolotti, 1998). Although only reported in the verbal domain, it is possible that some patients described as dynamic aphasics have a more general reduction of GDB that affects non-verbal behaviour. In several case reports in which the empirical focus was on dynamic aphasia, some general loss of 'motivation' or 'drive' was also noted (De La Sayette et al., 1992; Didic, Ceccaldi, & Poncet, 1998; Esmonde et al., 1996).

A more generalised disruption of executive function that primarily affected initiation was reported in a study of patients who had received bilateral cingulotomies as treatment for intractable pain. After surgery patients performed less well on tests of

design fluency and object construction (for details of these tests see Lezak, 1982), but were not impaired on tests involving set shifting such as Trail Making and the Wisconsin Card Sorting Test (Cohen et al., 1999).

It appears that disorders of willed intention and initiation are not uncommon consequences of brain damage. Shallice and Burgess (1996) have suggested that fractionation of the supervisory system may be possible and that a sub-process of 'delayed intention marker realisation' may be dissociable from sub-processes explicitly involved with monitoring and problem solving. Intention realisation is said to involve the preparation of a temporal strategy (schema) and its storage in working memory. This consists of 'if-then' rule pairs that can be applied when non-routine control of action is needed. Marker formation involves setting triggers such that the temporary strategy is applied at the appropriate time. These markers signal the significance of events (either mental or perceptual) so that when they occur current behaviour is interrupted and the new strategy acted upon.

Impairment of marker formation and triggering is thought to explain the performance of three patients with frontal lobe damage who showed a marked lack of spontaneity in their lives (Shallice & Burgess, 1991). All three rarely planned social events or performed domestic chores such as cleaning or shopping. Experimental investigations revealed that each patient was impaired at organising strategies for effective performance of simple tasks. This phenomena was interpreted as a distinct form of executive impairment and named 'strategy application disorder'. Interestingly, a key feature of the patients' poor performance was perseveration on task, as if they lacked 'markers' to tell them when to stop performing. This closely resembles the findings in

Chapter 6 that PD patients with high apathy spent longer on task than patients with low apathy.

An executive disorder within the domain of strategy generation or marker formation and triggering may be most appropriate for considering patients with reduced GDB. It is hypothesised that apathy in PD is related to the strategy application disorder in that the patients fail to activate strategies that would normally be triggered by internal representations. A particular disturbance of internal as opposed to external control has long been associated with the broad concept of executive impairment (see for e.g. Duncan, 1986). The distinction has been particularly associated with PD as it captures the pattern of impaired and preserved cognitive processes found in patients with the disease (Brown & Marsden, 1990).

Of particular relevance to the current hypothesis is an experimental test of marker formation and triggering performed on patients with prefrontal lesions. The task involved binary choice reaction time measures, with either well practised or novel stimulus-response associations. It was found that prefrontal damage impaired processing of novel but not well learned decisions, the authors concluded that *"the frontal lobes are involved in non-routine operations at the stage of creation of internal referents"* (Godefroy & Rousseaux, 1997 p 699). Thus, the patients were said to have similar impairments to those described as strategy application disorder by Shallice and Burgess (1991). However, of significant interest was that Godefroy and Rousseaux showed that the impairment in novel decision making was highly correlated with the patients' apathy levels.

The consequence of an inability to realise strategies marked by internal representations would be expressed as a willed action deficit. On-going routine behaviour would be unaffected but spontaneous behaviour would be diminished. This therefore gives a theoretical basis for how an executive impairment could reduce the efficacy of will driven actions, which may well be expressed behaviourally as apathy. This has the further benefit of accounting for different effects of impaired executive systems. Damage to the executive system elsewhere may lead to the classic frontal behaviour pattern of inappropriate strategy use, but damage to processes involved in strategy generation and marker formation, and intention realisation would lead to an inability to apply strategies sufficiently (Shallice & Burgess, 1996).

It has been suggested that one method of assessing whether clinically observed behaviour patterns are examples of executive dysfunction is to design tests that intuitively require aspects of supervisory control and then see if task performance is impaired in the patients (Shallice & Burgess, 1997). In Chapter 7 it was argued that a task in which subjects had to respond to either a green circle or a delay was sensitive to stimulus driven and will driven actions respectively. The task is essentially a modified go/no-go procedure, in that subjects have to withhold responses to distractor stimuli and only respond to either of two predefined events. Overall, performance is therefore likely to be associated with executive systems. However, according to the model described above, only willed actions will involve strategy application that is triggered by internal representations. This is because the preceding process to action initiation has to be an internal representation of temporal events (i.e. the delay) that can act as a trigger. This is in contrast to action initiation in which the preceding process (the trigger) is the recognition of the green circle.

It is therefore hypothesised that if there is an executive impairment particularly associated with apathy in PD that impairs initiation triggered by internal representations, it will be detected by longer response times in the will driven condition of the task described in Chapter 7. It is further hypothesised that verbal fluency impairments, as described above as being sensitive to response initiation, will be correlated with willed response times. This correlation would support the hypothesis that a feature of apathy is a tendency for reduced responding when the antecedent of the initiation is a mental representation. A final minor hypothesis is that response times for stimulus driven actions will correlate with Stroop task performance due to the general response inhibition aspects of each task.

As the will/stimulus driven task involves the use of durations as response initiation events, it is of relevance to interpretation of findings to know to what extent apathy is associated with time processing impairments. Although this may seem unlikely, duration processing is thought to involve working memory systems (Gruber, Kleinschmidt, Blinkofski, Steinmetz, & von Cramon, 2000). In PD it is known that both time perception (Artieda et al., 1992; Pastor et al., 1992) and working memory impairments (Stebbins et al., 1999) are prominent cognitive features. It is therefore a distinct possibility that time perception performance will be associated with apathy in patients with PD.

Experiment 1

Subjects

A total of 20 PD patients were tested in this experiment, 12 of these were female. All patients were drawn from the sample described in Chapter 3. The current research was

conducted 3-6 months later. Eleven healthy control subjects also participated, all were volunteers who responded to advertisements or were non-academic friends of the author. Nine of the control subjects were female and all but two were right handed. The mean age of the PD patients was 66.8 (SD=8.5) and for the controls it was 67.9 (SD=9.1). There was no significant difference between the patients and controls for age ($t(29)=.34$, $p=.74$).

PD patients were tested off medication. In practice, this meant that they had not taken any drugs for control of their PD since the previous evening. Test sessions were performed approximately 11 hours since the last dose of medication was consumed.

For the 20 PD patients the median score on the AES-R derived in Chapter 3 was 34.5. This was used to allocate patients to either the high apathy group (PD-HA) or low apathy group (PD-LA). Data for the PD-HA and PD-LA groups on mean age, years of education, Hoehn and Yahr stage, ADL score, MMSE score, CAMCOG score, BDI score and handedness are shown in Table 26. Also included is a measure of whether their most obvious symptom was tremor or akinesia, this was judged by observation and verbal report of the patients themselves. T-tests (and where appropriate Chi2) confirmed that there were no significant differences between the groups on these measures, other than the expected significant difference between AES-R scores ($t(18)=7.41$, $p<.001$). These data were collected during the initial assessment three to six months previously.

Apparatus

The same equipment and control programme that were reported in Experiment 1 of Chapter 7 were employed in this experiment.

Table 26: Means (and SDs) for the characteristics of the PD-HA and PD-LA patients.

	PD-HA (N=10)	PD-LA (N=10)
Age	68.6 (10.7)	65.0 (5.8)
Education	12.2 (1.9)	13.4 (2.5)
Hoehn & Yahr	2.7 (.9)	2.4 (1.1)
ADL	49.8 (10.7)	47.5 (19.6)
MMSE	28.4 (1.5)	28.2 (1.8)
CAMCOG	92.2 (3.6)	94.9 (2.9)
Tremor:Akinesia	8:2	6:4
BDI	15.3 (9.8)	15.8 (4.5)
AES-R	46.2 (7.18)	26.7 (4.22)
Handedness (R:L)	8:2	9:1

Experimental task and procedure

The experimental task has been described in Chapter 7 and will only be briefly recapitulated here. All testing was performed in the subjects' own homes in a dimly lit room. The subjects' task was to hold down a microswitch with the index finger of the dominant hand while observing a stream of visual stimuli on the laptop monitor. They were instructed to respond whenever they saw either a green circle or when the sequence of stimuli stopped. A response simply involved lifting the finger from the microswitch and then replacing it.

The events, green circles or absence of stimuli, were relatively infrequent (on 1/3rd of trials the event would occur after two distractor stimuli, on 1/3rd after five and 1/3rd after eight). Response times were recorded by the computer. It is assumed that response times to the green circle involve stimulus driven actions and responses to the absence of stimuli involve willed actions. The task was administered in two blocks. Each block took approximately 10 minutes to complete.

Hypotheses

1) Patients high on apathy will show slower response times in the will driven action condition relative to patients low on apathy and the normal controls, and that stimulus driven actions will be relatively preserved.
2) Within the PD sample, slower response times for will driven actions will be associated with reduced verbal fluency and slower stimulus driven actions will be associated with worse performance on the Stroop task. This final hypothesis involves data collected for the study reported in Chapter 3.

Results of Experiment 1

Median response times were calculated for each subject in each condition (stimulus driven or will driven). These are shown in Figure 23 where it can be seen that the PD-HA group was slower to respond in the willed action condition than either the PD-LA group or controls. The same pattern, though to a lesser extent, was found in the stimulus driven condition. These differences were compared in a repeated measures ANOVA with condition as a within subjects factor and group as a between subjects factor. It was found that there was a significant main effect of condition ($F(1,28)=26.66$, $p<.001$). The willed action condition produced slower responses

overall compared with the stimulus driven condition. There was also a significant main effect of group membership ($F(2,28)=16.54$, $p<.001$). From Figure 23 it can be seen that the PD-HA group were slowest overall and that the controls were fastest overall. The interaction between group and condition was also significant ($F(2,28)=5.74$, $p=.008$), indicating that there was a differential effect of condition across the three groups.

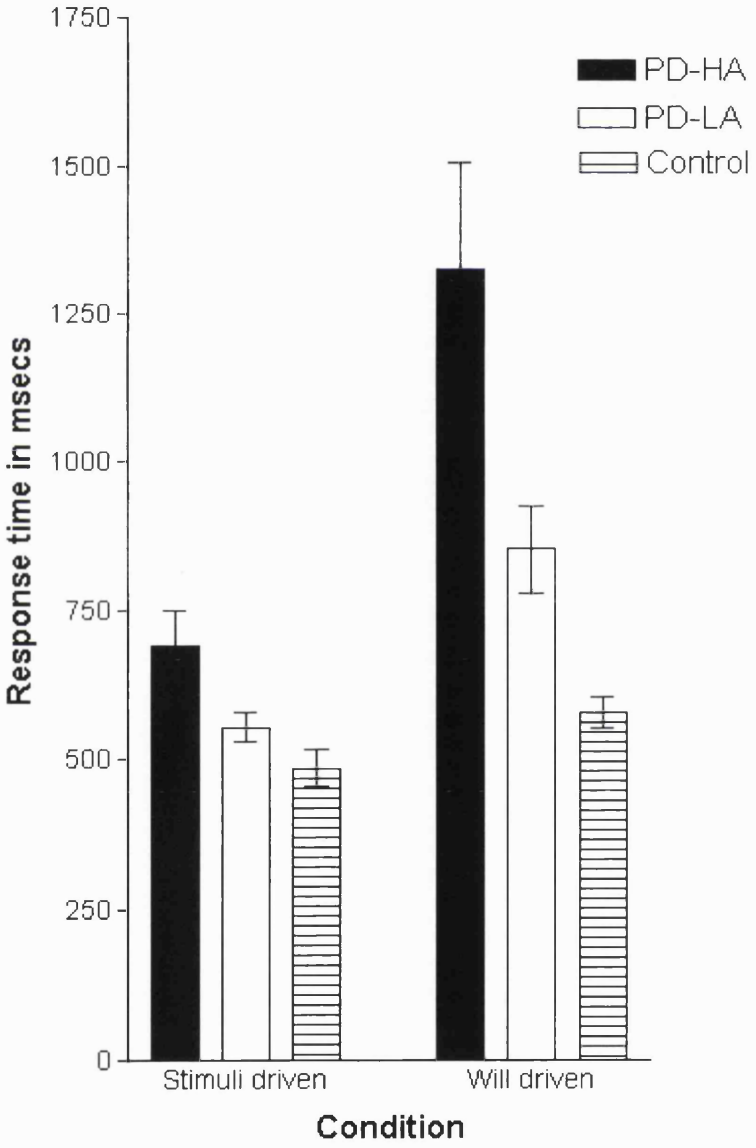


Figure 23: Response times (and SEMs) in the stimulus driven and will driven conditions of Experiment 1 for the PD-HA, PD-LA and control groups.

To analyse this effect further, two separate repeated measures ANOVAs were performed on the stimulus driven and will driven conditions. In each, group membership was a between subjects factor. Planned contrasts were performed to compare the PD-HA group with the PD-LA group and the PD-HA with the control group.

When only the stimulus driven condition was considered it was found that there was a significant between groups effect ($F(2,28)=6.83$, $p=.004$). The planned contrasts revealed that the PD-HA group made significantly slower responses than the control group ($p=.001$). However, the contrast between the PD-HA and PD-LA group was not significant ($p=.25$). In the will driven action condition there was a also a significant between groups effect ($F(2,28)=11.91$, $p<.001$). Significant contrasts were found between the PD-HA and control group ($p<.001$) and between the PD-HA and PD-LA group ($p=.006$). As a visual aid to comparison, the entire data sets are presented for a typical subject from each group. Figure 24 shows the data set from a member of the control group, Figure 25 shows a set from a member of the PD-LA group and Figure 26 shows a set from a member of the PD-HA group. The general pattern of slower will driven response times in PD-HA patients compared to controls, with PD-LA patients performing at an intermediate level, can be clearly seen in these figures.

To examine the association between apathy and action directly in the PD sample, parametric correlations were performed between apathy scores and the median response times in the stimulus driven and will driven conditions. Also included was the difference between the willed and stimulus driven response times for each patient. This was included as it represents the extra time spent on preparing the willed action, relatively independent of the movement time. It was found that there was no significant

correlation between apathy scores and stimulus driven action response times (r=.241, p=.306). However, there was a significant correlation between apathy scores and will driven action response times (r=.503, p=.024), indicating that high apathy in PD was associated with slower will driven responses. The correlation between apathy scores and the difference statistic (will-stimuli) narrowly missed significance (r=.439, p=.053). A second hypothesis was that will driven response times will correlate with verbal fluency scores due to the common initiation component. Furthermore, stimulus driven response times will correlate with Stroop task performance due to the common response suppression component.

One tailed correlation statistics to test for associations between executive function test scores and response time data are shown in Table 27. In addition to the actual median response times, individual difference scores between will and stimulus driven responses are included. It was found that stimulus driven response times were, as predicted, significantly correlated with impaired performance on the interference condition of the Stroop task, but not with other measures of executive impairment. Will driven response times were also significantly correlated with performance on the Stroop task, but additionally, as predicted, with reduced verbal fluency for both letter and category versions of the test. There was some indication that Wisconsin Card Sorting Test impairment may have been related to will driven response times, but these correlations did not reach significance. The individual differences between will and stimulus driven response times were thought to provide a relatively pure measure of willed initiation pre-response processing. However, when this statistic was used to derive the correlations, all relationships failed to reach significance.

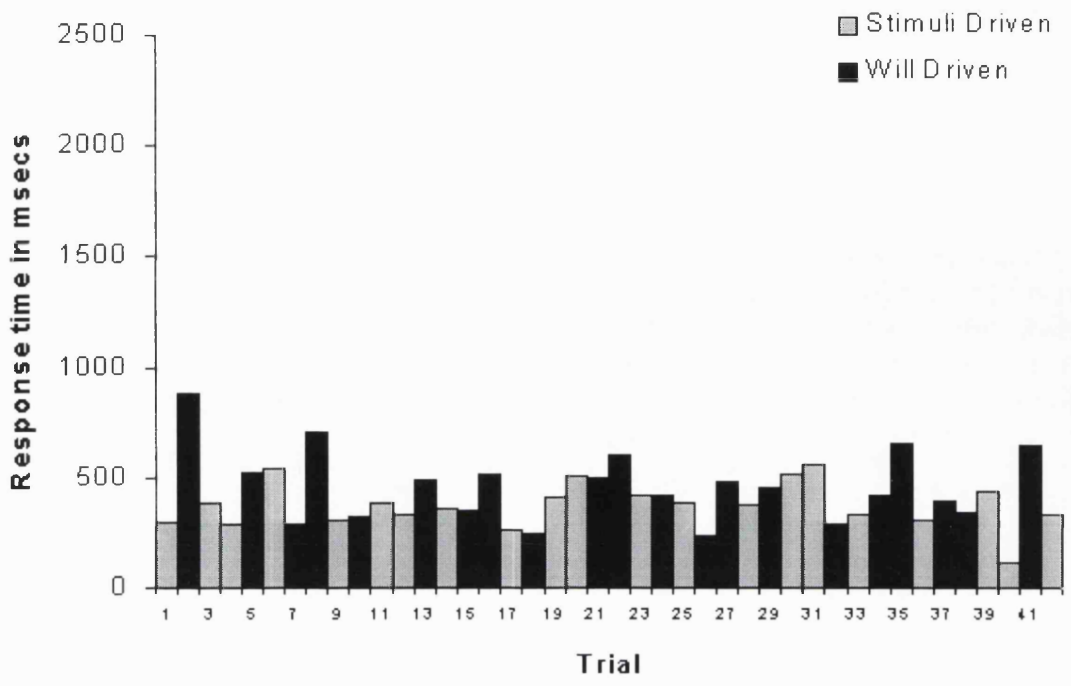


Figure 24: Response times in individual trials for a typical subject from the control group. This was a 65 year old right-handed female subject.

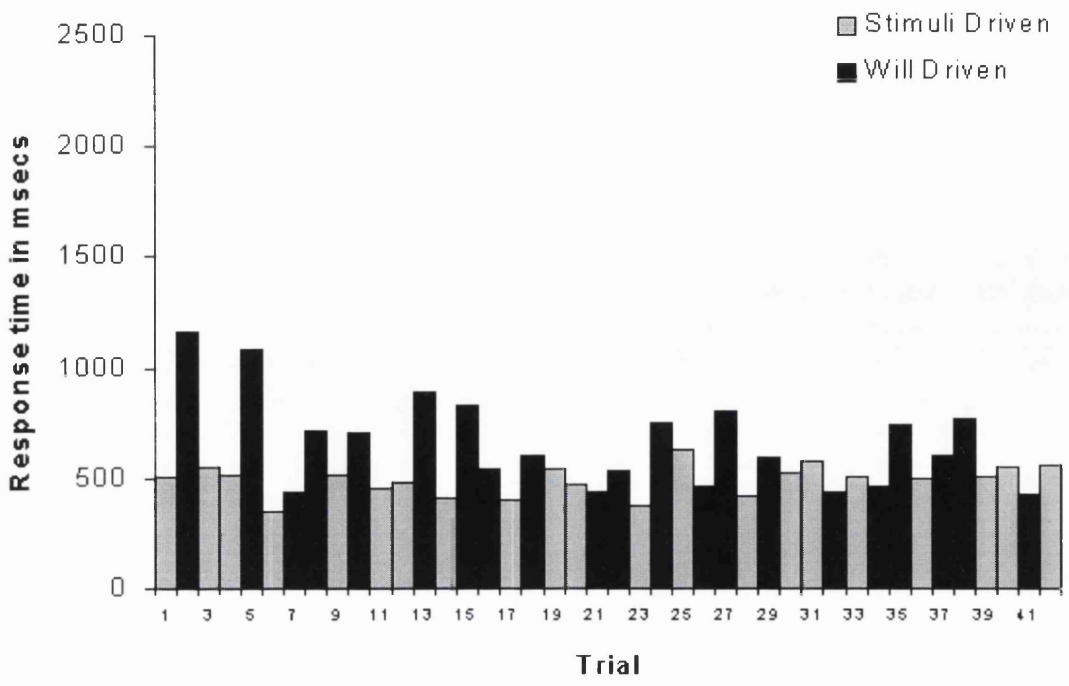


Figure 25: Response times in individual trials for a typical subject from the PD-LA group. This was a 64 year old right-handed female patient, apathy score = 22, CAMCOG score = 94.

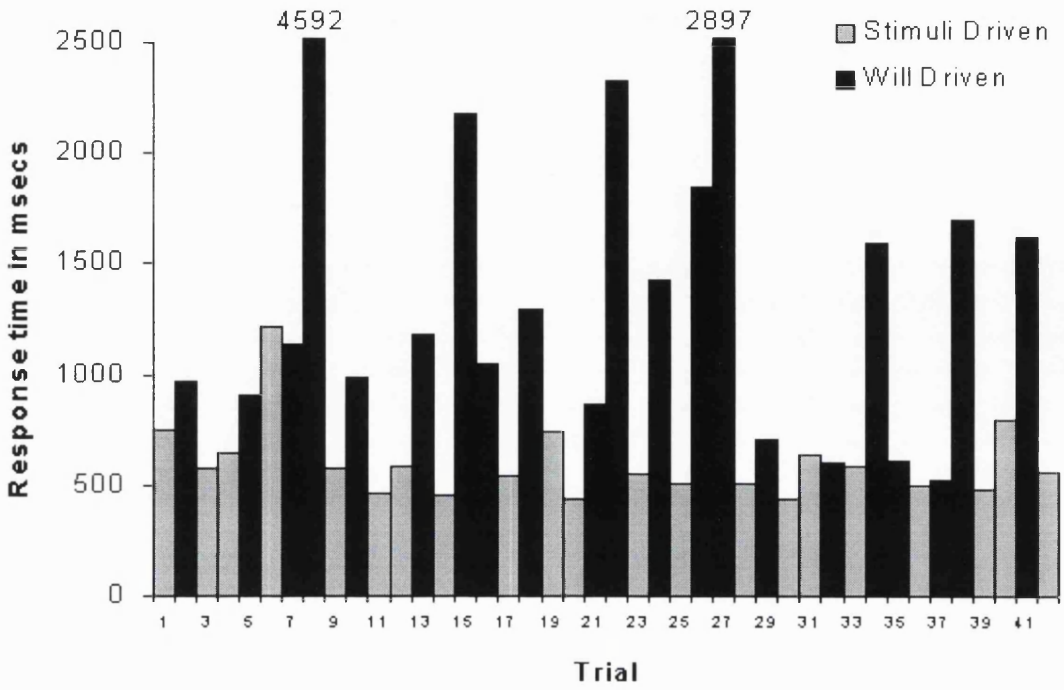


Figure 26: Response times in individual trials for a typical subject from the PD-HA group. This was a 62 year old right-handed male patient, apathy score = 57, CAMCOG score = 93.

In Chapters 4, 5 and 6, calculations were performed on the correlation between personality scores derived from the Tridimensional Personality Questionnaire (TPQ) and experimentally derived measures of cognitive performance. In the current chapter this was repeated with the response times for will and stimulus driven responses. Of particular interest is the association between the trait of Novelty Seeking (NS) and responses times as this aspect of personality has been associated with behavioural activation systems (Cloninger, 1987). The results of the correlational analysis are shown in Table 28. For this analysis, as in previous chapters, the sub-scale of Reward Dependence (RD), Persistence (P), was considered separately. It was found that none of the four traits on the TPQ were associated with stimulus driven or will driven response times.

Table 27: Correlational r (and p) values for the analysis between response times on the will driven, stimulus driven and the difference between the two with executive function test scores.

Task	Measure	Stimulus driven Responses	Will Driven Responses	Will-Stimuli Difference
Verbal Fluency	FAS	-.081 (.371)	-.453 (.026)	-.441 (.059)
	Category	-.257 (.144)	-.426 (.035)	-.354 (.138)
Stroop	Interference	-.449 (.027)	-.428 (.034)	-.292 (.225)
WCST	Categories	.084 (.371)	-.342 (.082)	-.358 (.145)
	Errors	.059 (.411)	.332 (.097)	.314 (.220)

Table 28: Correlational r (and p) values for the analysis between response times on the will driven, stimulus driven and the difference between the two with personality scores.

Trait	Stimulus driven Responses	Will Driven Responses	Will-Stimuli Difference
Novelty Seeking	-.099 (.677)	-.127 (.593)	-.098 (.681)
Harm Avoidance	-.070 (.768)	.339 (.143)	.374 (.104)
Reward Dependence	.280 (.232)	-.207 (.380)	-.308 (.186)
Reward Dependence - P	.282 (.229)	-.032 (.893)	-.128 (.591)
Persistence	.158 (.507)	-.369 (.110)	-.434 (.056)

Discussion of Experiment 1

It was found that stimulus driven actions were slower in the patients with high apathy when compared to controls. However, stimulus driven actions did not differ significantly between patients with either high or low apathy. This implies that apathy in PD is not associated with a stimulus driven action impairment. Although the high apathy PD patients were slower than controls, this can be accounted for by the motor slowing seen in general in PD. It is sufficient in the current experiment that a stimulus driven impairment was not more apparent in patients with high apathy.

In contrast, willed actions were found to be significantly slower in the PD patients with high apathy when contrasted with either low apathy PD patients or control subjects. This implies that there is a willed action impairment associated with apathy in PD.

Taken together, these results suggest that apathy in PD involves a willed action impairment with relatively preserved stimulus driven action ability. This is essentially the same argument that has been made to explain the poverty of action observed clinically in schizophrenia patients who show negative signs (Frith, 1992).

It was also found that slow will driven responses were associated with impaired performance on letter and category fluency and Stroop task performance but not with WCST performance. It was specifically hypothesised that reduced verbal fluency would be associated with willed responding due to the overlap between the tasks in the extent to which they assess response initiation. The significant correlation between will driven response times and impaired interference on the Stroop task was not specifically hypothesised but is consistent with the highly executive nature of willed responding. It was also found that slow stimulus driven actions were associated with interference on the Stroop task. This confirmed the second part of the hypothesis concerning correlations between response times and executive task performance. It is suggested that responding in both will and stimulus driven conditions involves overcoming response inhibition that has built up during the no-go aspects of the task. This will have the largest impact on the stimulus driven trials because the effect is not masked by the slowing induced by the willed aspects of the response.

It was found that the difference statistic between the two response times did not correlate with executive task performance. It was thought that this may have provided a more pure measure of time engaged in the willed aspects of responding, but the lack of correlation suggests it actually has less predictive validity. A possible explanation for this is that will driven and stimulus driven responses do not have equivalent motor components that allow simple subtraction to derive the non-motor component. For

example, it has been found that the two types of response tend to involve different motor parameters such as force applied (S. Obhi, personal communication). Novelty seeking has previously been associated with behavioural activation systems and so it may be expected that such scores would correlate with response times. However, no significant correlation was found between any of the personality traits measured by the TPQ and response time measures.

In can be concluded from Experiment 1 therefore, that apathy in PD is associated with slower will driven responses. However, an important consideration is the ability of patients to accurately perceive brief time durations. As responding in the willed action condition was dependent on the ability to appreciate that more than one second had elapsed since the previous stimuli, a deficit in this ability may extend response times without necessarily indicating a willed action impairment. This is a particularly important consideration because it has been shown that in PD, time perception judgements are often impaired (Harrington et al., 1998). Furthermore, time perception is often considered to involve working memory. A working memory impairment could therefore potentially confound the results of this experiment. It is currently unknown whether this ability is particularly impaired in PD patients with apathy, though its close association with executive skill may indicate that it is a distinct possibility. For this reason, time perception was assessed in the same patient group. This experiment is reported below.

Experiment 2

Subjects

The same subjects were used in this experiment as in Experiment 1. However, one

control subject failed to complete the test session due to fatigue, leaving 10 controls. The control subject who is not included was a 73 year old left handed women. The non-significant difference between ages in the PD and control sample remained.

Experimental task and procedure

In order to assess time duration perception the same task as used in Experiment 2 of Chapter 7 was used. To briefly repeat the details, the task was to decide whether the final visual stimulus in a train of three was delayed relative to the preceding two. This final stimulus was delayed on half of the trials. In the half in which it was delayed, the delays were one of 250, 500 or 1000 msecs.

The subjects' task was to respond via two keys in the casing of the laptop to indicate either a delay or not. Testing took place in the same session as Experiment 1, in the patients' own homes in a dimly lit room. The experiment was performed in two blocks that took approximately 12 minutes each.

Hypothesis

It is hypothesised that PD patients with high apathy will be as accurate as patients with low apathy or normal controls on judgements of time duration.

Results of Experiment 2

The accuracy score in each condition was converted to a percentage to allow direct comparison of the conditions composed of different numbers of trials. The mean percentage accuracy scores by each group and in each duration are shown in Figure 27.

It can be clearly seen that the PD-HA group performed less accurately at each duration than both the PD-LA and control groups.

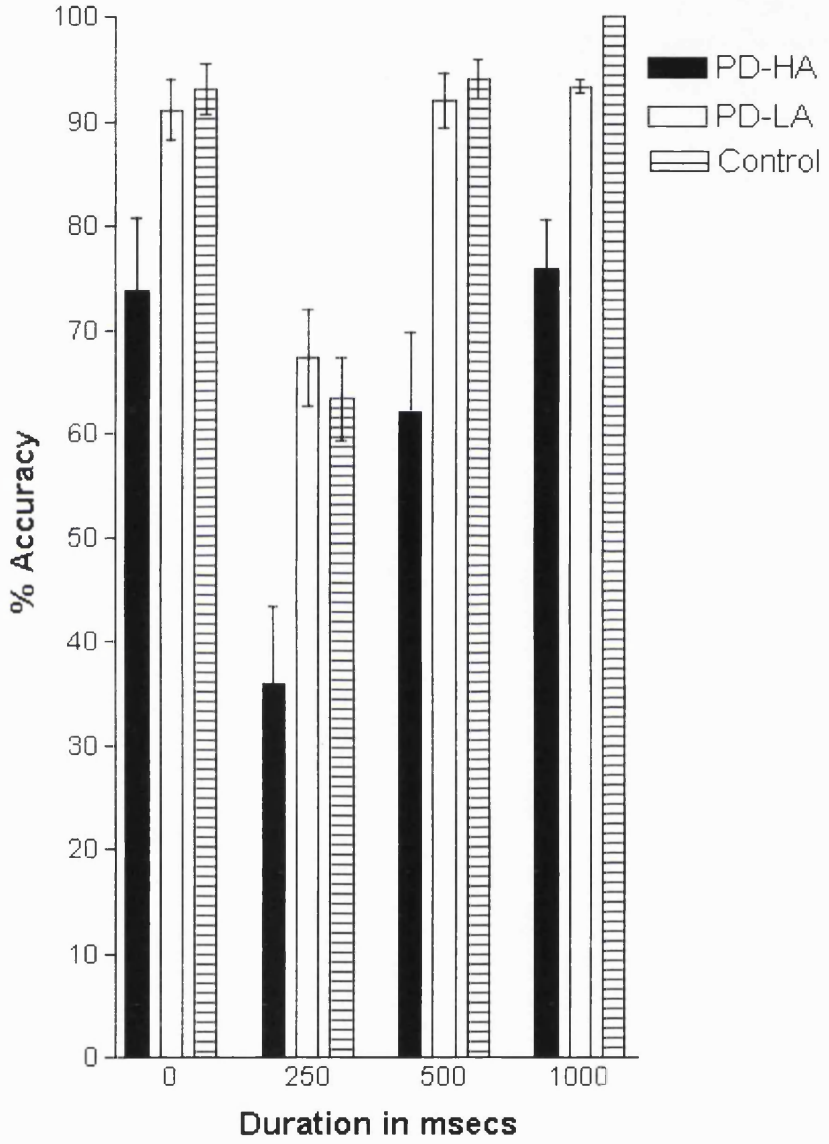


Figure 27: Mean percentage accuracy scores (including SEMs) for PD-HA, PD-LA and control groups on the delay detection task in Experiment 2.

To compare the groups statistically, percentage accuracy scores were entered into a repeated measures ANOVA with duration as a within subjects factor and group

membership as a between subjects factor. For this analysis, durations of 1000 msecs were not considered due to the ceiling effect on scores by the control subjects (mean = 100, SD = 0). Such abnormally distributed data are not appropriate for parametric tests. There were significant main effects for duration ($F(2,54)=39.30$, $p<.001$) and group ($F(2,27)=20.56$, $p<.001$). The interaction between group and duration was not significant indicating that error patterns were similar in each group ($F(2,27)=1.34$, $p=.279$). Planned contrasts comparing the different groups revealed that the PD-HA group was significantly less accurate overall than either the PD-LA ($p<.001$) or control ($p<.001$) groups.

To examine the relationship further in the PD sample a correlation analysis was performed between the individual overall error scores and apathy scores on the AES-R. It was found that there was a significant positive correlation between apathy and errors made ($r=.747$, $p<.001$). This indicates that higher apathy in the PD patients was associated with higher error rates in the duration judgement task.

As there was a question of the role of executive processes in the task used in Experiment 2, correlational analysis was used to examine the relationship between errors and scores on executive task performance of the PD patients for the tests reported in Chapter 3. The executive function measures examined were verbal fluency (FAS and category), interference on the Stroop task and total categories achieved and total errors in the WCST. The correlation statistics are shown in Table 29 where it can be seen that high error rates were associated with poor executive skill performance on all measures except the total number of errors in the WCST.

Table 29: Correlation statistics for the relationship between errors made in the duration judgement experiment and executive task performance.

Task	Measure	r Value	p Value
Verbal Fluency	FAS	-.475	.040
	Category	-.468	.043
WCST	Categories Achieved	-.489	.039
	Total Errors	.337	.186
Stroop	Interference	-.615	.005

Discussion of Experiment 2

It was found that the PD patients with high apathy were impaired on making judgements of durations between visual stimuli. Their performance was significantly below that of either the PD patients with low apathy or the normal controls. Indeed, their performance at delays of 250 msecs was below chance. Therefore, the hypothesis that they would show normal duration perception performance should be rejected.

It was also found that in the full PD sample higher error rates were associated with a range of executive task impairments. Therefore, it must be concluded that time duration perception as measured in Experiment 2 is closely related to executive performance.

The time perception experiment was performed in order to test for impairments that would alter the interpretation of Experiment 1. As a significant impairment in duration perception was demonstrated it was decided to re-analyse the key result from Experiment 1. This is reported below.

Re-analysis of results from Experiment 1

The high level of errors made in duration perception in Experiment 2 has implications for the interpretation of the willed response times in Experiment 1. A one-way ANOVA was performed on the will driven response time data with group membership as a between subjects factor as performed previously, but in the current analysis the number of errors made in Experiment 2 was entered as a covariate. The same planned contrasts were used, PD-HA compared to each of the other two groups. Using this modified procedure it was found that the main effect of group remained ($F(3,26)=9.15$, $p<.001$). The corrected group means (and SDs) were 682.82 (122.65) for the control group, 946.41 (120.28) for the PD-LA group and 1129.77 (152.75) for the PD-HA group. The between group differences are therefore similar to the uncorrected data, but to a lesser magnitude. However, the contrast between the PD-HA and PD-LA groups is no longer significant ($p=.413$). The contrast between the PD-HA and control groups was approaching significance ($p=.057$).

General Discussion

The primary aim of this study was to examine the ability of PD patients with apathy to generate will driven actions. A procedure was used that was shown in Chapter 7 to be capable of detecting impairments in will driven actions when compared to stimulus driven actions. It was hypothesised that PD patients with high apathy would show slower will driven actions and relatively preserved stimulus driven actions.

This hypothesis was partially supported. It was found that PD patients with high apathy took significantly longer to respond to the absence of a sensory cue than to a sensory cue itself. It is argued that actions generated without a cue to guide the behaviour make

more demands on specific executive systems than simple stimulus driven responses. This is consistent with previous work on action initiation (Jahanshahi et al., 2000; Jenkins et al., 2000; Passingham, 1993).

As willed actions are a relatively pure measure of executive processes underlying action initiation, it was hypothesised that response times would correlate with reduced verbal fluency, which it is argued is also a relatively pure measure of executive-initiation processes. This was found, the PD patients who were slowest to perform willed actions were also less productive in verbal fluency tasks. This therefore provides some support for the validity of the experimental procedure.

It was also found that slower stimulus driven responses were correlated with greater interference in the Stroop task. The reason for the correlation may be due to the response inhibition aspects of the procedure. When neither a stimuli nor will driven 'event' was provided, correct performance was to withhold a response. Such a task resembles go/no-go paradigms that are used to examine executive control of response suppression (Jackson et al., 2000). Performance on go/no-go tasks has been associated with frontal brain regions thought to be involved in executive processing in imaging studies (Konishi et al., 1999) and response suppression is known to be impaired after frontal lobe damage in man (Burgess & Shallice, 1996b; Miller, 1985a; Miller & Milner, 1985b).

Although stimulus driven response times were found to be associated with interference on the Stroop task, they were not correlated with verbal fluency scores and WCST performance. There is therefore some executive involvement in stimulus driven responses in the current task, but this may be limited to response suppression aspects of

performance. Will driven responses were associated with a wider range of executive skills illuminating the theoretical similarity between the concepts. The strongest correlations were with the tasks that a priori were considered measures of action initiation. Furthermore, imaging studies have shown that the prefrontal cortex is active in both willed responding (Frith et al., 1991) and traditional executive task performance (Baker et al., 1996; Bechara, Damasio, Tranel, & Anderson, 1998; Konishi et al., 1998). The current finding adds behavioural support to this anatomical association.

It was found in Chapter 3, and has previously been reported (see e.g. Starkstein et al., 1992), that executive impairment is associated with apathy in PD. If so, it raises the question why were stimulus driven response times (that correlate with Stroop performance) not slower in the high apathy PD patients? There was some indication of this. Although not significantly so, the high apathy PD patients were slower to make stimulus driven responses than the low apathy PD patients (see e.g. Figure 23). Considering the similarity between the stimulus driven condition of the current task and go/no-go procedures, if a larger PD sample was used a significant difference may have been found. However, it is suggested that although there may be a general impairment to executive systems in PD, the most prominent aspect is in willed initiation, rather than response suppression.

It can be concluded overall from Experiment 1 that PD patients with apathy have a particular difficulty with initiating actions for which the antecedent has a purely mental reference, in this case a duration. This was hypothesised based partly on theories of executive function that suggest that strategy generation and marker formation processes are identifiable and potentially dissociable from other aspects of the executive system (Shallice & Burgess, 1997; Shallice & Burgess, 1991; Shallice & Burgess, 1996).

Theories of the breakdown of executive function that have emphasised the distinction between internal and external control were also influential (Brown & Marsden, 1990; Duncan, 1986). The results of Experiment 1 provide support for this hypothesis concerning the breakdown of GDB and executive impairment expressing as a willed action disorder.

However, the task used in Experiment 1 exploited the fact that time durations have definable onsets but not direct sensory impact (Fraisse, 1984). Therefore, in the will driven condition, responses had to be generated in conjunction with an internal representation of the brief time durations. This feature was used to record response times based on the onset of the durations. However, in order for the results from the task to be interpreted for comparing groups or individuals, it is essential to show that they have equivalent abilities to detect the durations.

This was the purpose of Experiment 2. The durations used varied between zero and one second and were additional to a constant one second interval. This range of durations was appropriate because it adequately covered aspects that normal controls had difficulty with at one extreme (250 msecs, accuracy 63%) and found easy at the other extreme (one second, accuracy 100%). On this task it was found that the PD patients with apathy were significantly more impaired overall than similar patients with low apathy and normal controls. Consequently, this complicates interpretation of the results of Experiment 1. Although there may be a willed action impairment producing the extended response times, a perfectly reasonable alternative explanation is that they only resulted because the high apathy patients failed to realise that a duration had begun. In support of this alternative explanation, it was found that when the number of errors made was considered as a covariate, the key result from Experiment 1 was no longer

significant (high apathy patients did not take longer to respond than low apathy patients).

It cannot be argued that the task used in Experiment 1 is incapable of detecting willed action impairments due to this. The patient reported in Chapter 7 showed extended response times in the willed action condition of the task, but was found to have sufficiently preserved ability to perceive time durations. This indicates that the two abilities can dissociate after brain damage. The problem only arises when they are associated.

Timing production and perception are known to be impaired in PD. For example it has been shown that PD patients tend to tap at a faster rate than instructed (rates of between three and nine seconds) and underestimate visually presented durations of the same lengths (Pastor et al., 1992). This implies that PD patients' internal clocks are running at a slower pace than objective time. Time perception in PD has also been found to be 'running slowly' for much shorter durations (msec differences). It has been found that the threshold to distinguish two stimuli as separate percepts is higher in PD patients for auditory, somatosensory and visual modalities (Artieda et al., 1992). The threshold for distinguishing between a single or pair of auditory stimuli appears to be about 70 msecs longer in PD patients compared to controls (Rammsayer & Classen, 1997). The most appropriate study for comparing the current results also found a 'slow clock' in PD. It was found that PD patients tended to overestimate, more than healthy controls, durations of 300 msecs and particularly 600 msecs (Harrington et al., 1998). It therefore appears that there is sufficient evidence to assert that in PD, time perception is slowed (however, for evidence of normal time perception in PD see Ivry & Keele, 1989). The current findings support a time perception impairment in at least some PD

patients, though it can not be concluded whether or not this is due to a slow running central clock.

A time perception impairment in PD could account for slower performance in the 'will driven' condition of Experiment 1 and for poor performance of PD patients in Experiment 2. However, a significant difference in time perception was found between groups of PD patients with either high or low apathy. It is therefore necessary to clarify why a time perception impairment should be particularly associated with apathy in PD.

It is suggested that a time perception impairment in PD patients with apathy is related to an executive function/working memory impairment. It has been theorised that the central neurological time keeper is in the cerebellum but that planning aspects of time estimation and production are carried out by the prefrontal cortex (Lalonde & Hannequin, 1999). In support of this, an fMRI study of working memory for durations found activations in the right prefrontal cortex (Gruber et al., 2000).

In addition, time estimation has been shown to be impaired in frontal lobe damage patients and errors correlate with difficulties on the Wisconsin Card Sorting Test (Mimura, Kinsbourne, & O'Connor, 2000). This may be attributable to the close functional interplay between attentional/selection processes and working memory (Frith & Dolan, 1996). It is thought that working memory is needed to hold representations that can be acted on by attentional allocation systems, involving executive processing (Koechlin et al., 1999). Both executive processes (Badgaiyan, 2000) and visual or visuo-spatial working memory (Owen et al., 1996) have been found in imaging studies to involve the lateral prefrontal cortex. However, within this region, working memory representations have been shown to be associated with slightly different regions to the

strategic aspects of cognition. Both response selection (Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000) and decision making (Bechara et al., 1998) have been shown to activate close but anatomically distinct regions of the lateral prefrontal cortex to regions involved in working memory representations related to the tasks.

The lateral prefrontal cortex is affected by the physiological subcortical impairments in PD (Alexander et al., 1986). It is therefore not surprising that in addition to the well documented executive impairment in PD (for a review see Brown & Marsden, 1990), there is also a working memory impairment (Le Bras et al., 1999; Stebbins et al., 1999). It is likely that a deficit in working memory would itself interfere with the planning and response selection skills, and in a sense, working memory therefore represents an aspect of executive skill.

In Chapter 3 it was found that memory scores on the CAMCOG examination were lower in PD patients with high apathy. This was attributed to the executive aspects of memory processes. In addition, HIV dementia, like PD, is associated with subcortical dopamine dysfunction (Berger & Arendt, 2000). Sufferers display apathy and this is correlated with working memory impairment (Castellon et al., 2000).

It therefore seems likely that the time perception impairment in PD patients with high apathy found in Experiment 2, can be attributed to a difficulty with executive aspects of the internal representation of time. This could either be a difficulty with accurate representation or a strategic difficulty in utilising the information for decision making, but would have the consequence of impairing performance on the task reported in Experiment 2. In support of this executive interpretation, in the PD sample, it was found that impairments in duration perception were correlated with executive

dysfunction as measured by verbal fluency, Stroop interference and the Wisconsin Card Sorting Task.

Despite the link between time perception, working memory and executive skill, it is certainly not intuitive that this would be linked to a disorder defined by apathy. It is possible that this duration processing difficulty in the high apathy patients is related to the hypothesis made in the introduction to this chapter; that the executive disorder in apathy is an inability to utilise internal representations for triggering new action strategies. It is tentatively suggested that PD patients with high apathy will be impaired on any tasks in which responses are defined by the contents of internal representations (e.g. working memory). It is hypothesised that if an analogue of the task was used in which the relationship between elements was represented externally, for example the visual stimuli are separated spatially, but not temporally, then performance would be equivalent in the high and low apathy patients. Future research may be able to address these issues.

Although it is unclear whether there is impaired representation or impaired strategic use of an otherwise intact duration representation, it can be argued that this is consistent with a specific form of executive disorder. This apathetic form of the dysexecutive syndrome results in reduced GDB and contrasts sharply with the traditional frontal impairment of unrestrained or impulsive GDB. The latter is likely to be associated with misapplication of strategies, rather than an inability to generate or realise them.

The conclusion must therefore be that apathy in PD is associated with executive system impairment. This resulted in slower response times to duration events in Experiment 1 and poor time perception in Experiment 2. It seems likely that PD patients with apathy

have difficulties in using internal representations of relevant information for the generation of intentional actions. The crucial test of this was the extended responses in the will driven condition of Experiment 1 shown by the PD patients with high apathy. However, it is not clear whether this was due to the difficulty with response selection per se, or an impairment relating to the internal representation of the temporal aspects of the stimuli. However, it is clear that executive processes are impaired in PD patients with high levels of apathy.

Chapter 9: General Discussion

The aim of this thesis was to investigate psychological factors that may underlie apathy in PD. In the preceding chapters, several such factors were considered. In this chapter, the findings will only briefly be described as they have been discussed at length in the individual chapters. The focus will be on reviewing the extent to which this approach has been successful and on reaching more general conclusions. These include implications for therapeutic interventions and the definition and concept of apathy.

Summary of Findings

The purpose of Chapter 3 was to answer basic questions regarding apathy in PD that would guide research issues dealt with later in the thesis. Perhaps the most crucial finding was that apathy is a primary symptom of PD. This conclusion was reached because evidence was not found for the main alternative interpretation that apathy is a secondary response to disability. If disability is the most important factor in the development of apathy then it would have been equally expressed by patients with osteoarthritis, but this was not found. The PD patients were clearly more apathetic. This single finding indicated that apathy in PD is an effect of the neurological aspects of the disease, and implied that other neuropsychological phenomena may also be impaired. Indeed, it was found that the typical cognitive profile of patients with apathy included difficulties with executive function tests, but seemingly preserved cognitive abilities on non-executive assessments.

The possibility remains that apathy in PD is associated with a more widespread cognitive decline, and probably also linked to disease progression. This caveat is

particularly pertinent because there was some indication of greater disease progression in the high apathy PD patients compared to those with low levels of apathy. Although on one measure the groups did not differ significantly, on an alternative measure they did, with the high apathy patients indicating more advanced disease. This could in turn imply further generalised cognitive decline. It is therefore worth considering global cognitive disorder as an alternative functional pathology to the selective executive disorder suggested above and in Chapter 3.

Are there therefore grounds to suspect that PD patients with high apathy levels have a form of sub-clinical global dementia? Theoretically, this appears less likely than an interpretation in terms of a more localised frontal-subcortical processing impairment. The known cognitive profile in PD is most closely related to executive skills (Brown & Marsden, 1990; Elias & Treland, 1999), even when dementia is evident in patients with PD, executive impairment is the most prominent feature (Goldman, Baty, Buckles, Sahrmann, & Morris, 1998). It is therefore reasonable on theoretical grounds to assume that executive impairment would at least be the most severe cognitive disturbance related to disease progression. Furthermore, apathy as a loss of GDB seems to correspond most closely to executive dysfunction due to the similarity between the concepts in terms of behavioural adaptation and control. It is less clear why a more generalised cognitive decline would be associated. It appears that even if there were more widespread cognitive disturbance, there would be a dissociation due to more severely affected executive processing.

Nevertheless, this is an empirical issue that was addressed to some extent in Chapter 3. As an attempt to control for the possibility of a disease progression related, non-specific cognitive decline, statistical between group comparisons were used that covaried scores

on the MMSE. This was performed because, despite some limitations, the MMSE gives a reliable estimate of global cognitive impairment. If the apparent impairments on executive tasks such as verbal fluency simply reflected global cognitive impairment then covariance with the MMSE should have controlled for this. However, in all four executive tasks employed the high apathy patients were found to have performed significantly less well than similar low apathy patients. Therefore, the results of cognitive testing in Chapter 3 suggest that executive processing is implicated in the development of apathy. Furthermore, on assessments that were low weighted on executive aspects, impairments were generally not observed. Together, these support the suggestion that non-executive skills are relatively unaffected in patients with high levels of apathy. But it must be emphasised that more sensitive measures and larger sample sizes may show this to be incorrect if subtle non-executive cognitive disturbances can be identified in future research.

Clear associations between apathy and mood variables (i.e. depression, anhedonia and anxiety) were not found. Modest correlations were found between apathy and depression and apathy and anhedonia scores, but these were not demonstrated in the more rigorous main statistical comparisons. The possible involvement of a disease-specific personality was also investigated, but this was found to be unrelated to the presence of apathy symptoms in the PD sample.

The finding of impaired executive task performance has also been observed in the only other published report on the neuropsychology of apathy in PD (Starkstein et al., 1992). In this report, the association was hypothesised to reflect the presence of a third factor, bradyphrenia. Thus, it was suggested that slowed information processing was responsible for the apparent executive impairment. This hypothesis was tested and

rejected in Chapter 4. Using visual search methods, it was shown that PD patients who scored high on apathy were capable of equally fast information processing as PD patients with low levels of apathy.

The potential contribution of visual attention was investigated further in Chapter 5. It has been suggested that apathy in patients with frontal lobe lesions or Alzheimer's disease is associated with impaired attentional responses to novel stimuli (Daffner et al., 2000b; Daffner et al., 1992). However, using a custom designed task to detect involuntary attention shifts to novel visual stimuli, no difference was found in the performance of patients with either high or low apathy. The possibility that the attentional impairment is only evident in voluntary aspects of task performance was investigated using word search tasks in Chapter 6. However, although the main analysis failed to find any difference, a correlational analysis revealed the opposite pattern to that anticipated. PD patients with high apathy spent more time on the task, not less time, relative to patients with low apathy. It was suggested that this might reflect a tendency in patients with high apathy to fail to generate responses in the absence of clear environmental cues. Such an interpretation is consistent with the willed action theory of Frith (1988,1992) and would partially explain the behaviour reported anecdotally in patients with psychic akinesia (Laplane et al., 1984) and abulia (Fisher, 1995).

In Chapter 7 the concept of willed action was elaborated and evidence that will driven actions can dissociate from stimulus driven actions was presented. This was revealed by analysis of the performance of a single patient (TYR) who developed an akinetic state following basal ganglia damage. A task was employed that indicated that when responding to a delay that had no direct sensory impact, TYR was particularly impaired

in performing a simple action. It was further shown that this impairment was due to neither time perception difficulties nor a drop in vigilance.

As it is known that apathy is associated with executive impairment, it was hypothesised that this might be expressed as a difficulty with willed action generation. This would therefore provide an obvious link to why failure on abstract executive function tasks reflects a reduction in activity in real life (i.e. apathy). In Chapter 8 it was indeed found that PD patients with high apathy showed the same pattern of results as TYR when responding to a delay, hinting at a willed action impairment. However, it was also found that there was a robust relationship between apathy and time perception that complicates the interpretation of the willed action deficit. This chapter was therefore inconclusive in terms of whether there is a willed action impairment associated with apathy in PD. However, both tasks used had considerable executive components and in both instances, PD patients with high apathy were impaired relative to patients with low levels of apathy. These findings therefore add further support to the association between executive dysfunction and apathy in PD.

The key findings therefore are that apathy is a primary symptom of PD and is closely related to cognitive dysfunction, in particular, impairments in executive abilities. The executive dysfunction may be most prominent in those aspects related to response initiation such as strategy formation and use. However, it becomes circular to overtly define apathy and GDB in terms of executive function and willed action due to the overlap within the concepts. It is therefore not asserted that apathy is caused by cognitive disturbance. It is simpler to consider the different aspects of the phenomena in terms of the level of analysis required, e.g. symptomatic (apathy), behavioural (reduced GDB) or cognitive (executive impairment).

Potential Limitations of the Studies

The most obvious domain of impairment found in relation to apathy in PD was in executive processing. However, such processes are unlikely to be a functionally modular system and appear to fractionate after brain damage (Shallice & Burgess, 1996). It is too simplistic to simply consider apathy an expression of executive dysfunction. It may be that only certain aspects of higher cognitive function are associated with apathy in PD. In this thesis some progress was made in defining which aspects of executive processes may be most relevant. Further research will be needed to define precisely the pattern of impaired and preserved cognitive functions in PD patients with apathy.

Furthermore, although no differences were found concerning other aspects of cognition such as visual attention, using different paradigms or more sensitive measures, associations may be revealed. This restriction on the interpretation of negative results extends to other non-cognitive issues such as the contribution of anhedonia to apathy. However, there are sufficient grounds to argue that even if there are subtle effects that were missed in this thesis, the most pertinent observation is still the executive impairment. A related issue is the number of statistical comparisons performed. An exploratory approach was taken in general and this involved the examination of multiple factors, such as personality and cognition. Corrections were not performed to control for multiple comparisons, as this would have increased the possibility of relevant associations being missed. It was considered that due to the nature of the thesis as identifying phenomena for further investigation, false positives were more acceptable than false negatives.

This thesis drew on a wide range of psychological issues. For example, the influence of disability, mood, visual attention, curiosity and willed action were all investigated to some extent, rather than in-depth studies of a single area. This approach was chosen deliberately as so little is known about the neuropsychology of apathy that the there was a need to identify broad domains of impairment. This is the first comprehensive attempt at defining the neuropsychology of apathy in PD and future research may be able to refine the observations.

There may also be limitations to the findings due to methodological issues. Fundamental to most of the observations in this thesis are the apathy scores of the individual PD patients. These were used to allocate patients to groups and in the correlational analyses. It could be argued that the apathy assesment is too inexact to allow such fine-grained classification of patients. To limit this potential problem, the most in-depth tool that could practically be used was employed. The Apathy Evaluation Scale-researcher rated (AES-R) involved a clinical interview that drew on both the subjects' declarations and the researcher's interpretation of their behaviour (Marin et al., 1991). This is considerably more in-depth than the questionnaire approach that often does not involve the patient's own responses at all, but is completed by a relative or carer of the patient (Cummings et al., 1994; Kertesz, Nadkarni, Davidson, & Thomas, 2000; Kuzis et al., 1999). In addition, Marin et al. have validated the AES-R by demonstrating its ability to predict how much time brain damaged subjects spent in an experimental situation examining novel toys and playing video games. The alternative methodologies lack this validation. Furthermore, it could be argued that the validity of the AES-R is further demonstrated by the consistent and robust correlations with cognitive variables found in this thesis.

Based on data from the AES-R, the predominant strategy used in this thesis was the comparison of patients with either high or low levels of apathy. Group studies such as this have been criticised on the grounds that emphasis on group averages neglects potentially relevant individual patient behaviour (Shallice, 1979). Although this may often be true when the ultimate aim of the research is defining the function of the normal cognitive system, in the current thesis the ultimate aim was the description of deficits in a specific population (PD). The findings are likely to be of most interest to those with specific interests in PD and related disorders and those interested in the phenomenon of apathy as a clinical symptom. It is argued therefore that the use of group studies was justified. Additionally, in the one chapter that was not specifically focused on PD but on the normal cognitive system (willed and stimulus driven action) a single case methodology was utilised.

A further potential problem with the group approach used is that the principle of random allocation of subjects to conditions is violated. Patients were allocated to groups on the basis of their symptoms, in this case apathy scores. However, attempts were made to control for, and assess for, the presence of potentially confounding group differences. For example, it was shown that PD patients in high or low apathy groups did not differ significantly in terms of age, depression, disease progression etc. Furthermore, it has been argued that the division of patient groups on the basis of symptoms is superior to simple patient-control comparisons, that often include heterogeneous samples who may have little in common in terms of specific symptomology (Frith, 1992).

Implications for Cognitive Neuroscience

As a primary symptom of PD, apathy reflects the dysfunction of intentional systems in the human brain. Apathy as a symptom, therefore, may be a good model of an

avolitional state in neuroscience. Consciousness has recently become a popular research topic within the cognitive neurosciences, this is in part due to cognitive neuropsychological reports of patients who appear to show dissociations within conscious processing (De Haan, Young, & Newcombe, 1991; Giacino, 1997; Weiskrantz, 1997). It is argued that intention as a research topic could receive a similar boost if neuropsychological cases such as patients with apathy are considered. Furthermore, it has recently been (tentatively) suggested that a new field of 'cognitive neuropsychiatry', drawing on neurology, psychiatry and cognitive psychology may be a successful route to understanding the mind and brain (Baddeley, 1996). It is argued that the cognitive studies of apathy reported in this thesis are representative of the potential of this new approach within the neurosciences, in providing cognitive explanations for neuropsychiatric symptoms.

A good example of the 'neuropsychology of intention' is the research reported on the single case study of Chapter 7. TYR displayed an impairment in will driven actions with relatively preserved stimulus driven actions. The validity of this theoretical distinction is based mainly on imaging studies (Badgaiyan, 2000) and from experimental psychology (Frith & Done, 1986). However, this thesis is the first to report cognitive neuropsychological evidence supporting the theory. It is acknowledged that there has been neuropsychological work in this field (for e.g. Brebion et al., 2000; Fuller & Jahanshahi, 1999a; Fuller & Jahanshahi, 1999b). However, previous research has attempted to interpret impairments on cognitive tests in terms of willed action deficits, rather than to directly demonstrate a willed action impairment.

It is possible that patients with PD also have impairments in willed action generation. However, the task used to assess this had a working memory component that may have

confounded their performance on the task. Although it is not possible to conclude that PD patients with high levels of apathy have problems with willed actions in general, it was clearly found that they do have impairments in executive skills (including working memory). It is hypothesised that this may be due to an inability to utilise internal representations to guide behaviour. The overall pattern of executive impairment is similar to that which has been described in frontal lobe patients as 'strategy application disorder' (Shallice & Burgess, 1991).

A possible inconsistency with the 'internal representation' conclusion is that the PD patients with high apathy were not significantly impaired on two sub-tasks of the CAMCOG, abstract reasoning and calculation. As both of these are non-routine and require abstract representations (semantic classes in the case of abstract reasoning and numerosity in the case of calculation) it would be predicted that these tasks would be performed relatively poorly by PD patients with high apathy.

In the case of abstract reasoning there is further evidence that this ability is indeed less efficient in patients with apathy, based on the findings of fewer categories being achieved on the WCST reported in Chapter 3. This assesment is thought to rely heavily on abstract thought and number of categories achieved may be a marker of this (Nelson, 1976). Why, therefore, did the high apathy PD patients perform significantly less well on this measure of abstract reasoning but not on the abstract reasoning sub-task of the CAMCOG? The most likely explanation may simply be that abstract reasoning is impaired to some extent in PD patients with apathy, but that the sub-task of the CAMCOG was not sufficiently sensitive to this in the current sample. There was some indication of impaired performance in the high apathy patients, amongst the PD sample there was a modest negative correlation between abstract reasoning scores and apathy,

which was approaching but failed to reach significance. It may therefore be that abstract reasoning is impaired in patients with apathy due to a difficulty with responses based on internal representations, but that more challenging tasks are needed to reveal this. Further research is clearly needed to resolve this issue.

The same difficulty with interpretation applies to the calculation sub-task of the CAMCOG. On the theory outlined above, it could be expected that high apathy patients would perform poorly on tasks of calculation. Again, a moderate but not quite significant negative correlation was detected between cognitive and apathy scores in the PD sample. In this sub-task, there is further difficulty with interpretation due to the ceiling affect on scores; many subjects scored maximum on this sub-task. This was probably due to the simple nature of the task (only addition and subtraction) and the small number of items. A better test of the theory would use multi-step calculations, as these would rely more heavily on mental representations of numerical values. The current assesment requires this only to a minor extent. As with abstract reasoning, further work is required to resolve this issue. If a more difficult calculation task was shown to be performed normally by PD patients with high apathy, that would be sufficient to challenge the internal representation theory. The lack of significant difference in the current findings can not be used as evidence for or against the internal representation theory described above, due to the difficulties with interpretation and the 'hint' of an impairment in the correlation statistics.

Impaired executive performance is associated with PD (Downes et al., 1991; Downes et al., 1989; Gotham et al., 1988) and other basal ganglia disorders such as Huntington's disease (Lawrence et al., 1998). This is one of the reasons that sub-cortical structures have been reconceptualised in recent years and are now thought to be involved in a wide

range of cognitive processes (Brown, Schneider, & Lidsky, 1997). The findings in this thesis of apathy being particularly associated with poor executive task performance implies that significant differences between PD patients and controls in previous studies, may have been particularly related to the apathy levels of the PD sample. It is of significant interest that poor executive performance in PD may be limited to pre-identifiable sub-groups of patients. This does not imply that previous studies have been misinterpreted, but indicates that executive impairment may not be an inevitable consequence of basal ganglia disease. Executive function may be most at risk in sub-groups of patients for whom there are particular physiological changes that are not present in all patients. At the behavioural level, these physiological changes may be the source of apathy. In future assessments of cognition in groups of PD patients, it would be advisable to include an assesment of apathy. In this way the characteristics of the apathetic sub-group can be more adequately defined and this will in turn shed further light on the role of the basal ganglia in cognitive processing.

In Chapter 2 a framework was presented that may be useful for interpretation of findings of research into GDB. This is a comprehensive framework and covers a wide range of factors that are thought to influence overall behaviour. Consequently, in the current thesis, it was not possible to fully evaluate the framework experimentally. However, certain aspects were considered in terms of how they relate to apathy in PD. For example, 'external determinants' (G) were suggested as having a role in GDB behaviour by both driving routine 'selection and scheduling' and signalling salient stimuli such as novelty. No evidence was found for an attentional deficit in PD with apathy using three different measures of visual attentional function. It is therefore suggested that impaired processing of external determinants is unlikely to be the source of reduced GDB in PD.

It is also unlikely that an emotional disorder underlies apathy in PD. There was not a clear relationship between depression and apathy and it was suggested that when scores do correlate, this will usually reflect the non-specificity of the assesment tools used. Previous findings have reported an association but this has typically been quite weak. Starkstein et al. (1992) found that while 42% of PD patients in their sample were described as apathetic, 12% showed no signs of depression. Although this indicates a relatively close association, it is of note that several patients showed a lack of co-morbidity between apathy and depression symptoms. Levy et al. (1998) compared apathy and depression scores in a group of 154 patients with various neurodegenerative diseases, including PD. They failed to find a correlation between apathy and depression in this group. When only the scores of the PD patients were compared a significant but small (r=.34) association between apathy and depression was found. The lack of association found in this thesis indicates that 'emotional state' is not a cause of apathy in PD.

Anhedonia was also investigated in this thesis. The pathophysiology in PD suggests that anhedonia may be a symptom of the disease. This is because the brain regions affected are considered to be involved in reward processing in the intact brain (Fibiger, 1984). However, no support was found for the presence of anhedonia in PD patients compared with controls, and only a weak relationship with apathy symptoms was detected. It is therefore argued that 'emotional state and hedonic response' ('G' in the GDB framework) are not aspects of the model that are a source of apathy in PD.

The most pertinent finding was that performance of executive tasks is impaired in PD patients with apathy. This was found in Chapters 3 and 8. The framework of GDB presented in Chapter 2 suggests that 'supervisory executive processes' are subject to

motivational input. Therefore, as apathy has been described as a 'loss of motivation' (Marin, 1991), it could be suggested that low motivation is hampering the function of the executive systems. There is evidence from experimental psychology that motivational variables such as reward enhance executive skills in normal populations (Poulsen & Segalowitz, 2000). It has been suggested that rewards tend to enhance cognitive processing of tasks that involve the anterior cingulate and dorsolateral prefrontal cortex via stimulating dopamine release (Ashby, Isen, & Turken, 1999). Furthermore, it has been argued that nicotine use modulates executive skill performance and reward responsivity via dopaminergic mechanisms (Powell et al., 1996). This would therefore explain why executive performance in PD is particularly affected by low motivation.

Is this therefore the source of the association between cognitive function and apathy in PD? Unfortunately, there is insufficient evidence to reach this conclusion. The results in this thesis only show that there is an association between executive impairment and apathy, not a causal relationship. Furthermore, it is suggested that causal attribution between different levels of explanation is not appropriate. It may be conceptually simpler to consider apathy as the symptomatic level and cognitive or motivational dysfunction the psychological level of the same phenomenon. However, it is still appropriate to consider attribution of cause within individual levels of explanation, for example, whether low motivation causes executive processing problems.

Although it may be that low motivation reduces the efficiency of the executive system, there is an alternative explanation. 'Low motivation' has not actually been shown in PD patients, although they may be described as showing apathy, what is really meant is that they show a reduction in GDB. Is this reduction in GDB due to low motivation, or is

the impression of low motivation due to a GDB impairment that is executive in origin? This is essentially the same problem that was encountered by Duncan (1986) in his analysis of the frontal lobe syndrome. On acknowledging that his own theory could not distinguish between motivational and cognitive components he commented that *"Disentangling the absence of motivation from an inability to translate motivation into action will provide one of the most important challenges to future work in the area"* (Duncan, 1986 p 288). It could be hypothesised that motivation is essentially the same thing as efficient, executive controlled GDB. When specific executive abilities are compromised at the psychological level, such as in PD, the consequence is a behavioural level reduction in GDB that is described at the symptom level as apathy. Such a position would also be consistent with the current findings of this thesis.

The purely executive explanation is attractive in its simplicity, but there is insufficient evidence to rule out the possibility of a primary impairment in motivational systems with consequent secondary executive dysfunction. It is clear that executive dysfunction is closely linked to apathy in PD and this may been seen as either a motivation-executive impairment or simply as an executive impairment. The lack of clear evidence for significant levels of anhedonia in PD may imply that the central deficit is in strategy, not reward processing. This would be consistent with a purely executive description of apathy in PD. The executive explanation would also be consistent with the neuropsychological model of motivation proposed by Powell et al. (1997). They postulated that apathy and poor motivation were one manifestation of disrupted executive processing.

A Note on Neurophilosophy

It has become increasingly popular for neuroscientists and psychologists to write on philosophical topics and for philosophers to write on neuroscientific topics (see for e.g. Davies & Humphreys, 1993). The reason for this maybe that, although abstract issues such as consciousness and intention have long been considered in philosophy, it is only relatively recently that psychologists and neuroscientists have seriously considered them. This field has been dubbed 'neurophilosophy' (Churchland, 1986; Hatfield, 1988). A particular source of common interest has been the range of neuropsychological disorders that have revealed dissociations between awareness and action. For example it has been shown that some cortically blind patients can respond at above chance levels to visual stimuli that they report no conscious awareness of (Weiskrantz, 1997). From such cases of 'blindsight', it has been argued that they show that access to visual information and visual consciousness can dissociate (Kentridge & Heywood, 1999). This has been an argument of great interest in the philosophy of mind (Holt, 1999).

Patients with GDB impairment, in a loose sense, represent the opposite to blindsight. Whereas blindsight is action without awareness, apathy is awareness without action. Investigations of patients with GDB impairment may raise interesting issues regarding the relationship between intention and consciousness. For example, a distinction that has been made within philosophy is between volitional consciousness and perceptual consciousness (Searle, 2000). Patients displaying apathy are clearly relevant to the understanding of this dichotomy, as they may have impaired volitional but normal perceptual consciousness. Although philosophy was not any part of the aims of this thesis, it is of interest to note that findings may have philosophical relevance.

Implications for Therapeutic Interventions

The finding that apathy in PD is a primary symptom of the disease has implications for its treatment. There may be some potential for social adaptations such as education of family members to the needs of the patient (Campbell & Duffy, 1997). However, as a symptom of the disease process itself, pharmacological interventions may be particularly appropriate.

It has been shown in numerous reports, that in non-parkinsonian brain injured patients, dopamine agonists, such as bromocriptine or methylphenidate, are capable of improving motivation (Barrett, 1991; Catsman Berrevoets & von Harskamp, 1988; Powell et al., 1996; Van Reekum et al., 1995; Watanabe et al., 1995; Whyte et al., 1997). This is consistent with the observation that symptoms of reduced GDB are most common after frontal-subcortical damage (Brown & Pluck, 2000). Dopamine is an important neurotransmitter associated with frontal and subcortical structures (Nolte, 1988). It is a common finding that reduced GDB is associated with hypofunction in the frontal cortex, and this is often assumed to be due to subcortical dopamine system impairments (Okada, Kobayashi, Yamagata, Takahashi, & Yumaguchi, 1997; Sultzer, 1996; Yamanaka et al., 1996). Consequently, there are strong theoretical grounds supporting the action of dopamine agonists in the treatment of apathy.

Dopamine agonists maybe a potential treatment for apathy in PD. However, the situation is more complicated in PD patients because of the motor impairment and the effect on dementia. Dosage of dopamine agonists and L-dopa drugs are often carefully maintained in PD patients as there is only a small 'therapeutic window' (Marsden, 1994a). Increasing doses even slightly can often induce unpleasant side effects such as dyskinesias. Furthermore, in PD patients with existing cognitive impairment, dopamine

agonists can produce delirium and therefore have to be carefully monitored and often discontinued when cognitive impairment is suspected (Lieberman, 1998).

In addition, PD patients are already taking dopamine-enhancing drugs and still display apathy. There is also evidence that dopamine agonists are ineffective in improving mood in PD and may therefore have poor motivating effects too (Persico et al., 1998). In PD, dopamine replacement is clearly not a simple route to treatment of apathy. However, there are still some possibilities. The dopamine agonist Pramipexole can be used for treatment of the motor symptoms in PD, but is unusual in that it has a particular affinity for the dopamine D3 receptor (Shannon et al., 1997). The D3 receptor is more common in the ventral than the dorsal striatum (Levesque et al., 1995) and is therefore closely related to the anterior cingulate-subcortical circuit (Alexander et al., 1986). This circuit is thought to be involved primarily with motivation (Cummings, 1995). It may be hypothesised therefore, that Pramipexole could reduce apathy in PD patients. There is an anecdotal observation to this effect (Lieberman et al., 1997) but as yet this has not been confirmed in controlled trials.

A further possibility is the use of acetylcholine promoting drugs such as the cholinesterase inhibitors. These include Tacrine, Rivastigmine and Donepezil. Such drugs were initially developed as treatments for the cognitive disorder in Alzheimer's disease (AD) and have shown some clinical effect (Cummings, 2000). Furthermore, it has been suggested that they may be appropriate for the treatment of cognitive impairments in PD patients (Lieberman, 1998). Fully controlled trials have not yet been reported in PD, but there is some suggestion that Tacrine can greatly improve cognitive performance in PD without having a negative impact on motor ability (Hutchinson & Fazzini, 1996).

Due to the close relationship between cognitive function and apathy, improvement in cognitive skills may also reduce apathy. Although this has not been demonstrated in PD, it has been found that Tacrine reduces apathy in AD patients (Kaufer et al., 1996) and Rivastigmine reduces apathy in Lewy body dementia patients (McKeith et al., 2000). It is therefore possible that cholinesterase inhibitors such as Tacrine will prove to be effective treatments for both cognitive impairment and apathy in PD patients.

However, PD patients often already use a wide range of drugs for treatment of the motor aspects of the disease. To avoid further medication, there may also be possibilities for neuropsychological rehabilitation techniques. One major problem with this approach is gaining sufficient co-operation from patients who are poorly motivated and may not view their behaviour as a problem (Campbell & Duffy, 1997). It has been shown for example, that high apathy scores indicate those patients who fail to participate in rehabilitation sessions (Resnick et al., 1998). Despite this, there are some reports of successful rehabilitation of patients with reduced GDB. Behaviourist principles and behaviour modification methods have been used successfully in a case described as 'clinical abulia' (Rosenthal & Meyer, 1971). However, of more appeal in the light of the findings in this thesis are cognitive rehabilitation techniques. The close association between executive impairment and apathy suggests that methods that target executive skills may be particularly appropriate.

One such approach is based on Duncan's (1986) 'goal list' model of frontal lobe function. Briefly, this suggests that disorganised behaviour after frontal lobe damage can be understood as the failure of goals to assume and retain control of GDB. The theory has been operationalised as Goal Management Training (GMT) and may be useful in training planning behaviour in brain injured patients (Robertson, 1996).

Indeed, with patients in whom the primary problem is in not focusing attention on task, GMT has been shown to improve specific abilities such as food preparation (Levine et al., 2000). However, other aspects of GMT are theoretically applicable to deficits of reduced GDB. For example, GMT involves five steps that the patient is trained to perform. These are 1. Stop (evaluate goals) 2. Define (plan what needs to be done) 3. List (think of the sub-goals) 4. Learn (the steps) 5. Check (I am doing what I planned). Clearly, the later steps (3,4 and 5) would be particularly relevant to patients with disorganised behaviour, but the initial steps (1 and 2) may be particularly applicable to PD patients with apathy as these promote plan formation.

A further cognitive intervention, which could possibly be integrated with GMT, is prospective memory training. Prospective memory is remembering to do things (Ellis, 1996). Although it is not known whether there is a prospective memory problem in PD, particularly in patients with apathy, this is quite likely. Irrespective of this, it is suggested that prospective memory methods could be used to promote planning of GDB in PD patients. For example, it has been shown that Alzheimer's disease patients show improvements in day-to-day functioning by being trained to check a calendar every day for appointments or urgent tasks (Camp, Foss, Stevens, & O'Hanlon, 1996). Similar training in PD patients with apathy may increase the probability of adequate goal planning and execution.

Interventions such as GMT or prospective memory training have the potential to enhance the lives of PD patients with apathy without recourse to further drug treatments. Reducing the effects of apathy would not only be of benefit to the patients, but also their carers who often report the patient's apathy as being particularly stressful (Marsh et al., 1998).

Implications for the Concept of Apathy

The most commonly cited definition of apathy is *"diminished goal-directed activity due to lack of motivation"* (Marin, 1997 p 19). In this system, motivational impairment is considered crucial. However, at the psychological level, it is unclear whether the source of apathy in PD necessarily is motivational in nature, it is suggested that an executive impairment is a feasible alternative explanation.

The problem arises because although apathy can be recognised by observing reduced GDB, there is at present no way of assessing whether the reduced GDB is due to loss of motivation. The concept of apathy is further complicated when differential diagnosis is defined. Marin (1990) has suggested that *"apathy describes only those patients whose lack of motivation is not attributable to a diminished level of consciousness, an intellectual deficit, or emotional distress"* (Marin, 1990 p 22). It has been shown that an 'intellectual deficit' is closely associated with apathy, i.e. the consistent association between apathy and executive impairment. Such a correlation was observed in this thesis amongst PD patients but has been described previously in patients with HIV infection (Castellon et al., 2000), Alzheimer's disease (Kuzis et al., 1999) and progressive supranuclear palsy (Litvan et al., 1996) to list but a few.

It seems likely that the definition of apathy as being caused by motivational loss and not associated with cognitive dysfunction is too theoretically restrictive. At present, there is insufficient evidence to decide whether the reduced GDB seen in PD and other frontal-subcortical disorders is motivational or cognitive in nature. It may be more prudent to define apathy in purely observable terms. In practice, this was performed in this thesis, patients with high apathy were those who were classified as showing reduced GDB. It is further suggested that the term apathy itself is too value laden and suggests that the

disorder is primarily due to attitudes. The term 'negative' signs or symptoms is also often used but this has its own problems. As they are observed rather than reported they should be considered signs of the disease not symptoms of it (Frith, 1992). Such a classification system is appropriate in schizophrenia because the reduced GDB is part of the diagnosis. This is not the case for many other diseases such as PD that are diagnosed on other features, but that may also show reduced GDB. Therefore, in these conditions, reduced GDB is not strictly a sign of the disease.

Perhaps a better term to describe general observations of reduced GDB would be 'hypoactivity'. This has the benefit of not implying underlying causes to the deficit described and more accurately describes the observable features. Furthermore, it is applicable to behavioural descriptions independent of diagnostic considerations. Hypoactivity, as a clinical description, has considerably more appeal than the current often confused use of terms such as; apathy, abulia and amotivational syndrome.

Suggestions for Future Research

In order for progress to be made in respect of the neuropsychology of apathy, it is imperative that research is performed to elucidate the relative contributions of executive and motivational impairments. At present, it is unclear whether there is impairment to a motivational system, an executive function system or both. Furthermore, non-neuropsychological work in normal groups may also be beneficial in this regard. Although there is some work on the role of motivation in executive performance (Derryberry, 1993; Poulsen & Segalowitz, 2000), the precise relationship remains elusive. As described above, there may be possibilities for cognitive rehabilitation of apathy in PD. This is worthy of further research because of its potential clinical benefits. However, if cognitive neuropsychological rehabilitation was shown to be

effective, this would also provide evidence that the central deficit in apathy in PD is cognitive, not motivational.

The exact nature of the executive function deficit in apathy also needs to be described in greater detail. At present it is unclear why executive dysfunction should be linked to apathy in some patients (e.g. in this thesis) but is linked to excessive or impulsive GDB in other patient groups (Barkley, 1997; Bechara et al., 1997; Miller, 1985a). It may be that some aspects of executive function manifest as apathy and some as impulsivity when impaired. Some progress in this direction has been made in this thesis, but until more research is carried out examining cognitive skills in patients with action disorders, such explanations will remain hypothetical.

Of particular theoretical interest is the role of executive skills in memory function. Low scores on memory assessments have been described in a range of patients with GDB impairment including those in this thesis. The role of executive processes in memory is well established but difficult to define in detail (Burgess, 1992). Further work is needed to establish whether PD patients with apathy have memory impairments in tasks in which executive demands are low. It would certainly be of interest to compare recall and recognition performance in PD patients with either high or low apathy. Recall is thought to involve considerably more strategy application than recognition. If executive dysfunction is crucial to the cognitive profile of apathy, then it would be expected that recall, but not recognition performance, would be impaired.

In the final experimental chapter of this thesis, an attempt was made to demonstrate a willed action impairment in PD patients with apathy. The findings were inconclusive. Although a relatively simple distinction, the willed and stimulus driven action theory is an early step toward a neuropsychology of intention. The role of willed action systems

should be investigated in PD patients with apathy and other GDB impaired patients. Future neuropsychological studies have the potential to dramatically enhance both clinical understanding of the disorders and our academic understanding of the brain.

Conclusions

Apathy is a very real and common symptom of PD. Although the exact cause is unknown, it has been found that the best indicator of apathy in patients, at the psychological level, is the presence of cognitive impairment. The lack of a strong relationship between apathy and anhedonia or depression indicates that cognitive dysfunction may have a crucial role in the expression of apathy. However, no evidence was found for cognitive impairment in patients with apathy when the domains were non-executive in nature, such as in visual attentional tasks. Only impairments in cognitive tasks with executive components are associated with apathy in PD. At the psychological level, this could be due to either executive impairment producing apathy or a motivational deficit producing executive impairment. It therefore remains to be elucidated whether the core deficit is motivational or cognitive in nature. However, the findings have academic implications for the understanding of intention and applied implications for the treatment of patients with apathy.

References

Aarsland, D., Larsen, J.P., Goek Lim, N., Janvin, C., Karlsen, K., Tandberg, E., & Cummings, J.L. (1999). Range of neuropsychiatric disturbances in patients with Parkinson's disease. Journal of Neurology Neurosurgery and Psychiatry, 67, 492-496.

Al-Adawi, S., & Powell, J. (1997). The influence of smoking on reward responsiveness and cognitive functions: a natural experiment. Addiction, 92(12), 1773-1782.

Al-Adawi, S., Powell, J.H., & Greenwood, R.J. (1998). Motivational deficits after brain injury: A neuropsychological approach using new assessment techniques. Neuropsychology, 12(1), 115-124.

Alexander, G.E., DeLong, M.R., & Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neuroscience, 9, 357-381.

Andreasen, N.C. (1997). Linking mind and brain in the study of mental illnesses: A project for a scientific psychopathology. Science, 275, 1586-1592.

Anisman, H., Kokkinidis, L., Borowski, T., & Merali, Z. (1998). Differential effects of interleukin (Il)1b, IL2 and IL6 on responding for rewarding lateral hypothalamic stimulation. Brain Research, 779, 177-187.

Artieda, M.A., Pastor, M.A., Lacruz, F., & Obeso, J.A. (1992). Temporal discrimination is abnormal in Parkinson's disease. Brain, 115, 199-210.

Ashbridge, E., Walsh, V., & Cowey, A. (1997). Temporal aspects of visual search studied by transcranial magnetic stimulation. Neuropsychologia, 35(8), 1121-1131.

Ashby, F.G., Isen, A.M., & Turken, U. (1999). A neuropsychological theory of positive affect and its influence on cognition. Psychological Review, 106(3), 529-550.

Aubert, A. (1999). Sickness and behaviour in animals: a motivational perspective. Neuroscience and Biobehavioral Reviews, 23, 1029-1036.

Aziz, T.Z., Davies, L., Stein, J., & France, S. (1998). The role of descending basal ganglia connections to the brain stem in parkinsonian akinesia. British Journal of Neurosurgery, 12(3), 245-249.

Baars, B.J. (1993). Why volition is a foundation problem for psychology. Consciousness and Cognition, 2, 281-309.

Baddeley, A., Emslie, H., & Nimmo Smith, I. (1992). The speed and capacity of language-processing test. Bury St Edmunds: Thames Valley Test Company.

Baddeley, A.D. (1996). Cognition, neurology, psychiatry: golden triangle or Bermuda triangle? Cognitive Neuropsychiatry, 1(3), 185-189.

Badgaiyan, R.D. (2000). Executive control, willed action, and nonconscious processing. Human Brain Mapping, 9, 38-41.

Baker, S.C., Rogers, R.D., Owen, A.M., Frith, C.D., Dolan, R.J., Frackowiak, R.S.J., & Robbins, T.W. (1996). Neural systems engaged in planning: A PET study of the Tower of London task. Neuropsychologia, 34(6), 515-526.

Baldwin, J.M. (1901). Dictonary of philosophy and psychology. London: MacMillan.

Banich, M.T. (1997). Neuropsychology: The neural basis of mental function. Boston: Houghton Mifflin Company.

Barkley, R. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. Psychological Bulletin, 121(1), 65-94.

Barrett, K. (1991). Treating organic abulia with bromocriptine and lisuride: four case studies. Journal of Neurology Neurosurgery and Psychiatry, 54(8), 718-721.

Barris, R.W., & Schuman, H.R. (1953). Bilateral anterior cingulate lesions. Neurology, 3, 44-52.

Bechara, A., Damasio, H., Tranel, D., & Anderson, S.W. (1998). Dissociation of working memory from descision making within the human prefontal cortex. The Journal of Neuroscience, 18(1), 428-437.

Bechara, A., Damasio, H., Tranel, D., & Damasio, A.R. (1997). Deciding advantageously before knowing the advantageous stratagy. Science, 275, 1293-1295.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J.E., & Erbaugh, J.K. (1961). An inventory for measuring depression. Archives of General Psychiatry, 4, 561-571.

Becker, T., Becker, G., Seufert, J., Hoffman, E., Lange, K.W., Naumann, M., Lindner, A., Reichmann, H., Riederer, P., Beckmann, H., & Reiners, K. (1997).

Parkinson's disease and depression: Evidence for an alteration of the basal limbic system detected by transcranial sonography. Journal of Neurology Neurosurgery and Psychiatry, 63(5), 590-596.

Belanger, S.A., Duffy, R.J., & Coelho, C.A. (1996). The assesment of limb apraxia: An investigation of task effects and their cause. Brain and Cognition, 32, 384-404.

Bennett, K.M.B., Waterman, C., Scarpa, M., & Castiello, U. (1995). Covert visuospatial attentional mechanisms in Parkinson's disease. Brain, 118, 153-166.

Benton, A.L. (1986). Differential behavioural effects in frontal lobe disease. Neuropsychologia, 6, 63-80.

Beradellia, A., Dick, J.P.R., Rothwell, J.C., Day, B.L., & Marsden, C.D. (1986). Scaling the size of the first agonist EMG burst during rapid wrist movements in patients with Parkinson's disease. Journal of Neurology Neurosurgery and Psychiatry, 49, 1273-1279.

Berger, J.R., & Arendt, G. (2000). HIV dementia: The role of the basal ganglia and dopaminergic systems. Journal of Psychopharmacology, 14, 214-221.

Bergman, H., Wichmann, T., & DeLong, M.R. (1990). Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science, 249, 1436-1438.

Berlyne, D.E. (1960). Conclift, arousal and curiosity. London: McGraw-Hill.

Berns, G.S., Cohen, J.D., & Mintun, M.A. (1997). Brain regions responsive to novelty in the absence of awerness. Science, 276, 1272-1275.

Berrios, G.E., Campbell, C., & Politynska, B.E. (1995a). Autonomic failure, depression and anxiety in Parkinson's disease. British Journal of Psychiatry, 166(6), 789-792.

Berrios, G.E., & Gili, M. (1995b). Abulia and impulsiveness revisited: a conceptual history. Acta Psychiatrica Scandinavica, 92(3), 161-167.

Berrios, G.E., & Gili, M. (1995c). Will and its disorders: a conceptual history. History of Psychiatry, vi, 87-104.

Berry, E.L., Nicolson, R.I., Foster, J.K., Behrmann, M., & Sagar, H.J. (1999). Slowing of reaction time in Parkinson's disease: the involvement of the frontal lobes. Neuropsychologia, 37, 787-795.

Bhatia, K.P., & Marsden, C.D. (1994). The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain, 117, 859-876.

Birke, L.I.A., & Archer, J. (1983). Some issues and problems in the study of animal exploration. In J. Archer & L. I. A. Birke (Eds.), Exploration in animals and humans. (pp. 1-21). Wokingham: Van Nostrand Reinhold (UK).

Birkmayer, W., & Hornykiewicz, O. (1998). The effect of L-3,4-dihydroxyphenylalanine (=Dopa) on akinesia in parkinsonism. Parkinsonism and Related Disorders, 4, 59-60.

Bogousslavsky, J., Regli, F., Delaloye, B., & Delaloye Bischof, A. (1991). Loss of psychic self-activation with bithalamic infarction: neurobehavioural, CT, MRI, and SPECT correlates. Acta Neurologica Scandinavica, 83(5), 309-316.

Booth, G. (1940). Psychodynamics in parkinsonism. Psychosomatic Medicine, 10(1), 10-25.

Braak, H., Braak, E., Yilmazer, D., Schultz, C., de Vos, R.A., & Jansen, E.N. (1995). Nigral and extranigral pathology in Parkinson's disease. Journal of Neural Transmission Supplement, 46, 15-31.

Brazzelli, M., Colombo, N., Della Salla, S., & Spinnler, H. (1994). Spared and impaired cognitive-abilities after bilateral frontal damage. Cortex, 30, 27-51.

Brebion, G., Amador, X., Smith, M., Malaspina, D., Sharif, Z., & Gorman, J.M. (2000). Depression, psychomotor retardation, negative symptoms and memory in schizophrenia. Neuropsychiatry Neuropsychology and Behavioral Neurology, 13(3), 177-183.

Brooks, D.J. (1997). PET and SPECT studies in Parkinson's disease. Bailliere's Clinical Neurology, 6(1), 69-87.

Brown, L.L., Schneider, J.S., & Lidsky, T.I. (1997). Sensory and cognitive functions of the basal ganglia. Current Opinion in Neurobiology, 7, 157-163.

Brown, P., & Marsden, C.D. (1998). What do the basal ganglia do? Lancet, 351, 1801-1804.

Brown, R.G., MacCarthy, B., Gotham, A.M., Der, G.J., & Marsden, C.D. (1988). Depression and disability in Parkinson's disease: A follow-up of 132 cases. Psychological Medicine, 18, 49-55.

Brown, R.G., & Marsden, C.D. (1990). Cognitive function in Parkinson's disease: from description to theory. Trends in Neurosciences, 13(1), 21-29.

Brown, R.G., & Pluck, G. (2000). Negative symptoms: the 'pathology' of motivation and goal-directed behaviour. Trends in Neurosciences, 23(9), 412-417.

Buck, R. (1988). Human motivation and emotion. New York: John Wiley and Sons.

Burgess, P.W. (1992). The role of the frontal lobes in human memory. Unpublished PhD thesis. University of London;

Burgess, P.W., & Shallice, T. (1996a). Bizarre responses, rule detection and frontal lobe lesions. Cortex, 32, 241-259.

Burgess, P.W., & Shallice, T. (1996b). Response suppression, initiation and stratagy use following frontal lobe lesions. Neuropsychologia, 34(4), 263-273.

Cairns, H., Oldfield, R.C., Pennybacker, J.B., & Whitteridge, D. (1941). Akinetic mutism with an epidermoid cyst of the 3rd ventricle. Brain, 64, 273-290.

Camp, C.J., Foss, J.W., Stevens, A.B., & O'Hanlon, A.M. (1996). Improving prospective memory task performance in persons with Alzheimer's disease. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), Prospective memory: theory and applications. (pp. 351-367). Mahwah: LEA.

Campbell, J.J., & Duffy, J.D. (1997). Treatment strategies in amotivated patients. Psychiatric Annals, 27, 44-49.

Castellon, S.A., Hinkin, C.H., & Myers, H.F. (2000). Neuropsychiatric disturbance associated with executive dysfunction in HIV-1 infection. Journal of the International Neuropsychological Society, 6, 336-347.

Castellon, S.A., Hinkin, C.H., Wood, S., & Yarema, K.T. (1998). Apathy, depression, and cognitive performance in HIV-1 infection. The Journal of Neuropsychiatry and Clinical Neurosciences, 10, 320-329.

Catsman Berrevoets, C.E., & von Harskamp, F. (1988). Compulsive pre-sleep behavior and apathy due to bilateral thalamic stroke: response to bromocriptine. Neurology, 38(4), 647-649.

Charcot, J. (1880). De la paralysie agitante: Lecons sur les maladies du systeme nerveux. Paris: Adrien Delahaye.

Cheyette, S.R., & Cummings, J.L. (1995). Encephalitis lethargica - lessons for contemporary neuropsychiatry. The Journal of Neuropsychiatry and Clinical Neurosciences, 7, 125-134.

Churchland, P.S. (1986). Neurophilosophy: Toward a unified science of the mind/brain. London: MIT Press.

Cloninger, C.R. (1987). A systematic method for clinical description and classification of personality variants. Archives of General Psychiatry, 44, 573-588.

Cloninger, C.R., Przybeck, T.R., & Svrakic, D.M. (1991). The Tridimensional Personality Questionnaire: U.S. normative data. Psychological Reports, 69, 1047-1057.

Cloninger, C.R., Svrakic, D.M., & Przybeck, T.R. (1993). A psychobiological model of temperament and character. Archives of General Psychiatry, 50, 975-990.

Cohen, R.A., Kaplan, R.F., Zuffante, P., Moser, D.J., Jenkins, M.A., Salloway, S., & Wilkinson, H. (1999). Alteration of intention and self-initiated action associated with blilateral anterior cingulotomy. The Journal of Neuropsychiatry and Clinical Neurosciences, 11(4), 444-453.

Cole, S.A., Woddard, J.L., Juncos, J.L., Kogos, J.L., Youngstrom, E.A., & Watts, R.L. (1996). Depression and disability in Parkinson's disease. The Journal of Neuropsychiatry and Clinical Neurosciences, 8, 20-25.

Coombe, G. (1873). Elements of phrenology. (10th ed.). Edinburgh: McLachlan.

Corbetta, M., Shulman, G.S., Miezin, F.M., & Petersen, S.E. (1995). Superior parietal cortex activation during spatial attention and visual feature conjunction. Science, 270, 802-805.

Costello, A.L., & Warrington, E.K. (1989). Dynamic aphasia: The selective impairment of verbal planning. Cortex, 25 (1), 103-114.

Craft, S., Gourovitch, M.L., Dowton, S.B., Swanson, J.M., & Bonforte, S. (1992). Lateralized deficits in visual attention in males with developmental dopamine depletion. Neuropsychologia, 30(4), 341-351.

Cravioto, H., Silberman, J., & Feigin, I. (1960). A clinical and pathological study of akinetic mutism. Neurology, 10, 10-21.

Crawford, J.R., & Howell, D.C. (1998a). Comparing an individual's test score against norms derived from small samples. The Clinical Psychologist, 12, 482-486.

Crawford, J.R., Howell, D.C., & Garthwaite, P.H. (1998b). Payne and Jones revisited: Estimating the abnormality of test score differences using a modified paired samples t-test. Journal of Clinical and Experimental Neuropsychology, 20, 898-905.

Cronin-Golomb, A., & Braun, A.E. (1997). Visuospatial dysfunction and problem solving in Parkinsons's disease. Neuropsychology, 11(1), 44-52.

Crow, T.J. (1980). Molecular pathology of schizophrenia: More than one disease process. British Medical Journal, 280, 66-68.

Cullum, S., Huppert, F.A., McGee, M., Dening, T., Ahmed, A., Paykel, E.S., & Brayne, C. (2000). Decline across different domains of cognitive function in normal ageing: results of a longitudinal population-based study using CAMCOG. International Journal of Geriatric Psychiatry, 15(9), 853-862.

Cummings, J.L. (1995). Anatomic and behavioral aspects of frontal-subcortical circuits. Annals of the New York Academy of Sciences, 769, 1-13.

Cummings, J.L. (2000). Cholinesterase inhibitors: a new class of psychotrophic compounds. American Journal of Psychiatry, 157(1), 4-15.

Cummings, J.L., Mega, M., Gray, K., Rosenberg, T.S., Carusi, D.A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. Neurology, 44(12), 2308-2314.

Daffner, K., Mesulam, M.M., Cohen, L.G., & Scinto, L.F.M. (1999). Mechanisms underlying diminished novelty-seeking behavior in patients with probable Alzheimer's disease. Neuropsychiatry Neuropsychology and Behavioral Neurology, 12(1), 58-66.

Daffner, K.R., Mesulam, M.M., Holcomb, P.J., Calvo, V., Acar, D., & Chabrerie, A. (2000a). Disruption of attention to novel events after frontal lobe injury in humans. Journal of Neurology Neurosurgery and Psychiatry, 68(18), 24

Daffner, K.R., Mesulam, M.M., Scinto, L., Acar, D., Calvo, V., Faust, R., Chabrerie, A., Kennedy, B.P., & Holcomb, P.J. (2000b). The central role of the prefrontal cortex in directing attention to novel events. Brain, 123, 927-939.

Daffner, K.R., Mesulam, M.M., Scinto, L.F.M., Cohen, L.G., Kennedy, B.P., West, W.C., & Holcomb, P.J. (1998). Regulation of attention to novel stimuli by frontal lobes: An event related potential study. Neuroreport, 9(5), 787-791.

Daffner, K.R., Scinto, L.F.M., Weintraub, S., Guinessey, J.E., & Mesulam, M.M. (1992). Diminished curiosity in patients with probable Alzheimer's disease as measured by exploratory eye movements. Neurology, 42, 320-328.

Daffner, K.R., Scinto, L.F.M., Weintraub, S., Guinessey, J.E., & Mesulam, M.M. (1994a). The impact of aging on curiosity as measured by exploratory eye movements. Archives of Neurology, 51(4), 368-376.

Daffner, K.R., Scinto, L.F.M., Weintraub, S., & Mesulam, M.M. (1994b). Mechanisms underlying diminished curiosity in Alzheimers disease [Abstract]. Neurology, 44, 239-239.

Daly, D.D., & Love, J.G. (1958). Akinetic mutism. Neurology, 8, 238-242.

Damasio, A. (2000). The Feeling of what happens. London: Vintage.

Damasio, A.R., & Van Hoesen, G.W. (1983). Emotional disturbances associated with focal lesions of the limbic frobtal lobe. In K. M. Heilman & P. Satz (Eds.), Neuropsychology of human emotion. (pp. 85-110). London: Guilford Press.

Daniel, S.E., de Bruin, V.M., & Lees, A.J. (1995). The clinical and pathological spectrum of Steele-Richardson- Olszewski syndrome (progressive supranuclear palsy): a reappraisal. Brain, 118, 759-770.

Darvesh, S., & Freedman, M. (1996). Subcortical dementia: a neurobehavioural approach. Brain and Cognition, 31, 230-249.

Davies, M., & Humphreys, G.W. (1993). Consciousness: psychological and philosophical essays. Oxford: Blackwell.

De Haan, E.H., Young, A.W., & Newcombe, F. (1991). Covert and overt recognition in prosopagnosia. Brain, 114(6), 2575-2591.

De La Sayette, V., Le Doze, F., Bouvard, G., Morin, I., Eustache, F., Fiorelli, M., Viader, F., & Morin, P. (1992). Right motor neglect associated with dynamic aphasia, loss of drive and amnesia: A case report and cerebral blood flow study. Neuropsychologia, 30(2), 109-121.

Deecke, L., & Kornhuber, H.H. (1978). An electrical sign of participation of the mesial 'supplementary' motor cortex in human voluntary finger movement. Brain Research, 159, 473-476.

Deiber, M.P., Pollak, P., Passingham, R., Landais, P., Gervason, C., Cinotti, L., Friston, K., Frackowiak, R., Mauguiere, F., & Benabid, A.L. (1993). Thalamic stimulation and suppression of parkinsonian tremor. Evidence of a cerebellar deactivation using positron emission tomography. Brain, 116(1), 267-279.

Della Salla, S., Basso, A., Laiacona, M., & Papagno, C. (1992). Subcortical localization of ideomotor apraxia: a review and an experimental study. In G. Vallar, S. F. Cappa, & C. W. Wallesch (Eds.), Neuropsychological disorders associated with subcortical lesions. (pp. 357-380). Oxford: Oxford University Press.

DeLong, M.R. (1990). Primate models of movement disorders of basal ganglia origin. Trends in Neurosciences, 13(7), 281-285.

Delwaide, P.J., & Gonce, M. (1998). Pathophysiology of Parkinson's signs. In J. Jankovic & E. Tolosa (Eds.), Parkinson's disease and movement disorders. (pp. 159-175). Baltimore: Williams & Wilkins.

Depue, R.A., & Collins, P.F. (1999). Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behavioral and Brain Sciences, 22(3), 491-517.

Derryberry, D. (1993). Attentional consequences of outcome-related motivational states: congruent, incongruent, and focusing effects. Motivation and Emotion, 17(2), 65-89.

Deuschl, G., & Krack, P. (1998). Tremors: differential diagnosis, neurophysiology, and pharmacology. In J. Jankovic & E. Tolosa (Eds.), Parkinson's disease and movement disorders. (pp. 401-418). Baltimore: Williams & Wilkins.

Devinsky, O., Morrell, M.J., & Vogt, B.A. (1995). Contributions of anterior cingulate cortex to behaviour. Brain, 118, 279-306.

Dick, J.P.R., Rothwell, J.C., Day, B.L., Cantello, R., Buruma, O., Gioux, M., Benecke, R., Berardelli, A., Thompson, P.D., & Marsden, C.D. (1989). The bereitschaftpotential is abnormal in Parkinson's disease. Brain, 112, 233-244.

Didic, M., Ceccaldi, M., & Poncet, M. (1998). Progressive loss of speach: A neuropsychological profile of premotor dysfunction. European Neurology, 39, 90-96.

Dolan, R.J., Fletcher, P., Frith, C.D., Friston, K.J., Frackowiak, R.S.J., & Grasby, P.M. (1995). Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. Nature, 378, 180-182.

Downes, J.J., Phillips, R.E., & Sagar, H.J. (1991). Short-term memory for order information in Parkinson's disease (PD). Journal of Clinical and Experimental Neuropsychology, 13, 32

Downes, J.J., Sahakian, B.J., Evenden, J.L., Morris, R.G., & Robbins, T.W. (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: Evidence for a specific attentional dysfunction. Neuropsychologia, 27, 1329-1343.

Downes, J.J., Sharpe, M.H., Costall, B.M., Sagar, H.J., & Howe, J. (1993). Alternating fluency in Parkinson's disease. Brain, 116, 887-902.

Duffy, J.D. (1997). The neural substrates of motivation. Psychiatric Annals, 27, 24-29.

Duffy, J.D., & Campbell, J.J. (1994). The regional prefrontal syndromes: a theoretical and clinical overview. The Journal of Neuropsychiatry and Clinical Neurosciences, 6(4), 379-387.

Dulwa, S.C., Grandy, D.K., Low, M.J., Paulus, M.P., & Geyer, M.A. (1999). Dopamine D4 receptor-knock-out mice exhibit reduced exploration of novel stimuli. Journal of Neuroscience, 19(21), 9550-9556.

Duncan, J. (1986). Disorganisation of behaviour after frontal lobe damage. Cognitive Neuropsychology, 3(3), 271-290.

Duncombe, M.E., Bradshaw, J.L., Iansek, R., & Phillips, J.G. (1994). Parkinsonian patients without dementia or depression do not suffer from bradyphrenia as indexed by performance in mental rotation tasks with and without advance information. Neuropsychologia, 32(11), 1383-1396.

Ebersbach, G., Trottenberg, T., Hattig, H., Schelosky, L., Schrag, A., & Poewe, W. (1996). Directional bias of initial visual exploration: A symptom of neglect in Parkinson's disease. Brain, 119, 79-87.

Ebstein, R.P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., Bennett, E.R., Nemanov, L., Katz, M., & Belmaker, R.H. (1996). Dopamine D4 receptor (D4DR) exon iii polymorphism associated with the human personality trait of novelty seeking. Nature Genetics, 12(1), 78-80.

Ehringer, H., & Hornykiewicz, O. (1998). Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. Parkinsonism and Related Disorders, 4, 53-57.

Elias, J.W., & Treland, J.E. (1999). Executive function in Parkinson's disease and subcortical disorders. Seminars in Clinical Neuropsychiatry, 4(1), 34-40.

Elliott, R. (1998). The neuropsychological profile of unipolar depression. Trends in Cognitive Sciences, 2(11), 447-454.

Ellis, J. (1996). Prospective memory or the realization of delayed intentions: a conceptual framework for research. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), Prospective memory: theory and applications. (pp. 1-22). Mahwah, New Jersey: Lawrence Erlbaum Associates.

Engelborghs, S., Marien, P., Pickut, B.A., Verstaeten, S., & De Deyn, P.P. (2000). Loss of psychic self-activation after paramedian bithalamic infarction. Stroke, 31, 1762-1765.

Esmonde, T., Giles, E., Xuereb, J., & Hodges, J. (1996). Progressive supranuclear palsy presenting with dynamic aphasia. Journal of Neurology Neurosurgery and Psychiatry, 60(4), 403-410.

Factor, S.A., Molho, E.S., & Brown, D.L. (1998). Acute delirium after withdrawal of amantadine in Parkinson's disease. Neurology, 50(5), 1456-1458.

Fahn, S., Elton, R.L., & Members of the UPDRS Development Committee. (1987). Unified Parkinson's disease rating scale. In S. Fahn, C. D. Marsden, M. oldstein, & D. B. Calne (Eds.), Recent developments in Parkinson's disease. (pp. 153-163). New York: Macmillan.

Felson, D.T., Lawrence, R.C., Dieppe, P.A., Hirsch, R., Helmick, C.G., Jordan, J.M., Kington, R.S., Lane, N.E., Nevitt, M.C., Zhang, Y., & Sowers, M. (2000). Osteoarthritis: new insights. Part 1: the disease and its risk factors. Annals of Internal Medicine, 133, 635-646.

Fibiger, H.C. (1984). The neurobiological substrates of depression in Parkinson's disease. Le Journal Canadien des Sciences Neurologiques, 11(1), 105-107.

Filley, C.M., Thompson, L.L., Sze, C.I., Simon, J.A., Prakavitz, J.F., & Kleinscmidt-DeMasters, B.K. (1999). White matter dementia in CADSIL. Journal of the Neurological Sciences, 163(2), 163-167.

Filoteo, J.V., Delis, D.C., Salmon, D.P., Demadura, T., Roman, M.J., & Shults, C.W. (1997a). An examination of the nature of attentional deficits in patients with Parkinson's disease: evidence from a spatial orienting task. Journal of the International Neuropsychological Society, 3, 337-347.

Filoteo, J.V., Williams, B.J., Rilling, L.M., & Roberts, J.W. (1997b). Performance of Parkinson's disease patients on the visual search and attention test: impairment in single-feature but not dual-feature visual search. Archives of Clinical Neuropsychology, 12(7), 621-634.

Fisher, C.M. (1983). Honored guest presentation: abulia minor vs. agitated behavior. Clinical Neurosurgery, 31, 8-31.

Fisher, C.M. (1995). Abulia. In J. Bogousslavsky & L. Caplan (Eds.), Stroke syndromes. (pp. 182-187). New York: Cambridge University Press.

Floresco, S.B., Seamans, J.K., & Phillips, A.G. (1997). Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. The Journal of Neuroscience, 17(5), 1880-1890.

Folstein, S.E., & Folstein, M.F. (1975). "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189-198.

Fraisse, P. (1984). Perception and estimation of time. Annual Review of Psychology, 35, 1-36.

Frith, C., & Dolan, R. (1996). The role of the prefrontal cortex in higher cognitive functions. Cognitive Brain Research, 5, 175-181.

Frith, C.D. (1992). The cognitive neuropsychology of schizophrenia. Hove: Lawrence Erlbaum Asssociates.

Frith, C.D., & Done, D.J. (1983). Stereotyped responding by schizophrenic patients on a two-choice guessing task. Psychological Medicine, 13, 779-786.

Frith, C.D., & Done, D.J. (1986). Routes to action in reaction time tasks. Psychological Research, 48, 169-177.

Frith, C.D., & Done, D.J. (1988). Towards a neuropsychology of schizophrenia. British Journal of Psychiatry, 153, 437-443.

Frith, C.D., Friston, K., Liddle, P.F., & Frackowiak, R.S.J. (1991). Willed action and the prefrontal cortex in man: a study with PET. Proceedings of the Royal Society of London.Series B, 244, 241-246.

Fuller, R., & Jahanshahi, M. (1999a). Concurrent performance of motor tasks and processing capacity in patients with schizophrenia. Journal of Neurology Neurosurgery and Psychiatry, 66, 668-671.

Fuller, R., & Jahanshahi, M. (1999b). Impairment of willed actions and use of advance information for movement preparation in schizophrenia. Journal of Neurology Neurosurgery and Psychiatry, 66, 502-509.

Fuller, R., & Jahanshahi, M. (1999c). Movement-related potentials prior to self-initiated movements are impaired in patients with schizophrenia and negative signs. Experimental Brain Research, 126(4), 545-555.

Fuster, J.M. (1989). The prefrontal cortex: Anatomy, physiology and neuropsychology of the frontal lobe. (2nd ed.). New York: Raven Press.

Gage, F.H., Kawaja, M.D., & Fisher, L.J. (1991). Genetically modified cells: applications for intracerebral grafting. Trends in Neurosciences, 14(8), 328-333.

Gallo, J.P., & Rabins, P.V. (1999). Depression without sadness: Alternative presentations of depression in later life. American Family Physician, 60(3), 820-826.

Galynker, I.I., Levinson, I., Miner, C., & Rosenthal, R.N. (1995). Negative symptoms in patients with basal ganglia strokes. Neuropsychiatry Neuropsychology and Behavioral Neurology, 8(2), 113-117.

Garcia-Larrea, L., Brousolle, E., Gravejat, M.F., Chazot, G., & Mauguiere, F. (1996). Brain responses to detection of right or left somatic targets are symetrical in unilateral Parkinson's disease: A case against the concept of 'Parkinsonian neglect'. Cortex, 32, 679-691.

Gelb, D.J., Oliver, E., & Gilman, S. (1999). Diagnostic criteria for Parkinson's disease. Archives of Neurology, 56 , 33-39.

Giacino, J.T. (1997). Disorders of consciousness: differential diagnosis and neuropathologic features. Seminars In Neurology, 17, 105-111.

Gitelman, D.R., Alpert, N.M., Kosslyn, S., Daffner, K., Scinto, L., Thompson, W., & Mesulam, M.M. (1996). Functional imaging of human right hemispheric activation for exploratory movements. Annals of Neurology, 39(2), 174-179.

Godefroy, O., & Rousseaux, M. (1997). Novel decision making in patients with prefrontal or posterior brain damage. Neurology, 49(3), 695-701.

Goel, V., & Grafman, J. (1995). Are the frontal lobes implicated in "planning" functions? Interpreting data from the Tower of Hanoi. Neuropsychologia, 33(5), 623-642.

Goerent, I.K., Lawrence, A.D., & Brooks, D.J. (1999). Reward processing in the parkinsonian brain: an activation study using PET. Parkinsonism and Related Disorders, 5, 58-58.

Goldberg, E., Podell, K., & Lovell, M. (1994). Lateralization of frontal lobe functions and cognitive novelty. The Journal of Neuropsychiatry and Clinical Neurosciences, 6(4), 371-378.

Golden, C.J. (1978). Stroop Color and Word Test. Chicago: Stoelling.

Goldman, W.P., Baty, J.D., Buckles, V.D., Sahrmann, S., & Morris, J.C. (1998). Cognitive and motor functioning in Parkinson's disease. Archives of Neurology, 55, 674-680.

Gomes, G. (1999). Volition and the readiness potential. Journal of Consciousness Studies, 6, 59-76.

Goodglass, H., & Kaplan, E. (1972). The assessment of aphasia and related disorders. Philadelphia: Lea & Febiger.

Gotham, A.M., Brown, R.G., & Marsden, C.D. (1986). Depression in Parkinson's disease: a quantitative and qualitative analysis. Journal of Neurology Neurosurgery and Psychiatry, 49, 381-389.

Gotham, A.M., Brown, R.G., & Marsden, C.D. (1988). 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain, 111, 299-321.

Grant, D.A., & Berg, E.A. (1948). A behavioural analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card sorting problem. Journal of Experimental Psychology, 38, 404-411.

Grcevic, N., Jadron-Santel, D., & Jukic, S. (1977). Cerebral changes in paraquat poisoning. In L. Roizin, H. Shiraki, & N. Grcevic (Eds.), Neurotoxicology. (pp. 469-484). New York: Raven Press.

Gruber, O., Kleinschmidt, A., Blinkofski, F., Steinmetz, H., & von Cramon, D.Y. (2000). Cerebral correlates of working memory for temporal information. Neuroreport, 11, 1689-1693.

Gurd, J.M., & Oliveira, R.M. (1996). Competitive inhibition models of lexical-semantic processing: experimental evidence. Brain and Language, 54, 414-433.

Hadar, U., & Butterworth, B. (1997). Iconic gestures, imagery and word retrieval in speech. Semiotica, 115, 147-172.

Haggard, P., Newman, C., & Magno, E. (1999). On the perceived time of voluntary actions. British Journal of Psychology, 90, 291-303.

Hanakawa, T., Fukuyama, H., Katsumi, Y., Honda, M., & Shibasaki, H. (1999). Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Annals of Neurology, 45(3), 329-336.

Hansch, E.C., Syndulko, K., Cohen, S.N., Goldberg, Z.I., Totvin, A.R., & Tourtellote, W.W. (1982). Cognition in Parkinson's disease: an event-related potential perspective. Annals of Neurology, 6 , 599-607.

Harrington, D.L., Haaland, K.Y., & Hermanowitz, N. (1998). Temporal processing in the basal ganglia. Neuropsychology, 12(1), 3-12.

Hatfield, G. (1988). Neuro-philosophy meets psychology: reduction, autonomy, and physiological constraints. Cognitive Neuropsychology, 5(6), 723-746.

Heimer, L., Alheid, G.F., de, O.J., Groenewegen, H.J., Haber, S.N., Harlan, R.E., & Zahm, D.S. (1997). The accumbens: beyond the core-shell dichotomy. The Journal of Neuropsychiatry and Clinical Neurosciences, 9(3), 354-381.

Hobson, P., & Meara, J. (1999). The detection of dementia and cognitive impairment in a community population of elderly people with Parkinson's disease by use of the CAMCOG neuropsychological test. Age and Ageing, 28, 39-43.

Hodgson, D.H. (1995). What zombies can't do. Journal of Consciousness Studies, 2(4), 360-361.

Hoehn, M.M., & Yahr, M.D. (1967). Parkinsonism: onset, progression, and mortality. Neurology, 17, 427-442.

Holt, J. (1999). Blindsight in debates about qualia. Journal of Consciousness Studies, 6(5), 54-71.

Hooks, M.S., & Kalivas, P.W. (1995). The role of mesoaccumbens-pallidal circuitry in novelty-induced behavioral activation. Neuroscience, 64(3), 587-597.

Hore, J., Meyer-Lohmann, J., & Brooks, V.B. (1977). Basal ganglia cooling disables learned arm movements of monkeys in the absence of visual guidance. Science, 195, 584-586.

Horvitz, J.C., Stewart, T., & Jacobs, B.L. (1997). Burst activity of ventral tegmental neurons is elicited by sensory stimuli in the awake cat. Brain Research, 759(2), 251-258.

Howard, K.I. (1961). A test of stimulus-seeking behavior. Perceptual and Motor Skills, 13, 416-416.

Hubble, J.P., Venkatesh, R., Hassanein, R.E.S., Gray, C., & Koller, W.C. (1993). Personality and depression in Parkinson's disease. The Journal of Nervous and Mental Disease, 181(11), 657-662.

Hugdahl, K., Asbornsen, A., & Wester, K. (1993). Memory performance in Parkinson's disease. Neuropsychiatry Neuropsychology and Behavioral Neurology, 6(3), 170-176.

Hull, C.L. (1943). Principles of behavior. New York: Appleton-Century-Crofts.

Humphreys, G.W., & Riddoch, M.J. (2001). Detection by action: Neuropsychological evidence for action-defined templates in search. Nature Neuroscience, 4(1), 84-88.

Huntington Study Group. (1996). Core Assessment Program for Intracerebral Transplantation in Huntington's Disease (CAPIT-HD). Movement Disorders, 11(2), 143-150.

Hutchinson, M., & Fazzini, E. (1996). Cholinesterase inhibition in Parkinson's disease. Journal of Neurology Neurosurgery and Psychiatry, 61, 324-325.

Ingvar, D.H. (1994). The will of the brain: cerebral correlates of willful acts. Journal of Theoretical Biology, 171, 7-12.

Ingvar, D.H. (1999). On volition: a neurophysiologically oriented essay. Journal of Consciousness Studies, 6(8-9), 1-10.

Ivory, S.J., Knight, R.G., Longmore, B.E., & CaradocDavies, T. (1999). Verbal memory in non-demented patients with idiopathic Parkinson's disease. Neuropsychologia, 37, 817-828.

Ivry, R.B., & Keele, S.W. (1989). Timing functions of the cerebellum. Journal of Cognitive Neuroscience, 1, 136-152.

Jackson, H. (1931). Selected writings . London: Hodder and Stoughton.

Jackson, S.R., Jackson, G.M., & Roberts, M. (2000). The selection and suppression of action: ERP correlates of executive control in humans. Neuroreport, 10, 861-865.

Jahanshahi, M., Ardouin, C.M.A., Brown, R.G., Rothwell, J.C., Obeso, J.A., Albanese, A., Rodriguez, M.C., Moro, E., Benabid, A.L., Pollak, P., & Limousin-Dowsey, P. (2000). The impact of deep brain stimulation on executive function in Parkinson's disease. Brain, 123, 1142-1154.

Jahanshahi, M., & Frith, C.D. (1998). Willed action and its impairments. Cognitive Neuropsychology, 15(6/7/8), 483-533.

Jahanshahi, M., Jenkins, I.H., Brown, R.G., Marsden, C.D., Brooks, D.J., & Passingham, R.E. (2000). Self-initiated verses externally triggered movements. i. An investigation useing measurment of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain, 118, 913-933.

James, W. (1890). Principles of psychology. New York: Dover.

Jellinger, K. (1988). The pedunculopontine nucleus in Parkinson's disease, progressive supranuclear palsy and Alzheimer's disease. Journal of Neurology Neurosurgery and Psychiatry, 51, 540-543.

Jenkins, H., Jahanshahi, M., Jueptner, M., Passingham, R., & Brooks, D.J. (2000). Self-initiated verses externally triggered movements ii. The effect of movement predictabillity on regional cerebral blood flow. Brain, 123, 1216-1228.

Johansson, S., & Hofland, K. (1989). Frequency analysis of English vocabulary and grammer. Volume 1, tag frequencies and word frequencies. New York: Oxford University Press.

Johnston, W.A., Hawley, K.J.P.S.H., Elliot, J.M.G., & DeWitt, M.J. (1990). Attention capture by novel stimuli. Journal of Experimental Psychology: General, 119(4), 397-411.

Johnston, W.A., & Schwarting, I.S. (1996). Reassessing the evidence for novel popout. Journal of Experimental Psychology: General, 125(2), 208-212.

Jurkevich, G. (1992). Abulia, nineteenth-century psychology and the generation of 1898. Hispanic Review, 60, 181-194.

Kaufer, D.I., Cummings, J.L., & Christine, D. (1996). Effect of tacrine on behavioral symptoms in Alzheimer's disease: an open-label study. Journal of Geriatric Psychiatry and Neurology, 9, 1-6.

Kentridge, R.W., & Heywood, C.A. (1999). The status of blindsight. Journal of Consciousness Studies, 6(5), 3-11.

Kertesz, A., Nadkarni, N., Davidson, W., & Thomas, A.W. (2000). The frontal behavioral inventory in the differential diagnosis of frontotemporal dementia. Journal of the International Neuropsychological Society, 6, 460-468.

Kimura, M., Aosaki, T., & Graybiel, A. (1996). Role of basal ganglia in the acquisition and initiation of learned movement. In N. Mano, I. Hamada, & M. R.

DeLong (Eds.), Role of the cerebellum and basal ganglia in voluntry movement. (pp. 83-87). Amsterdam: Elsevier Science.

Kinoshita, H., Oku, N., Hashikawa, K., & Nishimura, T. (2000). Functional brain areas used for the lifting of objects using a precision grip: a PET study. Brain Research, 857, 119-130.

Kluver, H., & Bucy, P.C. (1937). "Psychic blindness" and other symptoms following bilateral temporal lobectomy in rhesus monkeys. American Journal of Physiology, 119, 352-353.

Knight, R.T., & Grabowecky, M. (1996). Escape from linear time: prefrontal cortex and conscious experience. In M. Gazzinga (Ed.), The cognitive neurosciences. (pp. 1357-1371). Cambridge, MA: MIT Press.

Koechlin, E., Basso, G., Pietrini, P., Panzer, S., & Grafman, J. (1999). The role of the anterior prefrontal cortex in human cognition. Nature, 399, 148-151.

Koepp, M.J., Gunn, R.N., Lawrence, A.D., Cunningham, V.J., Dagher, A., Jones, T., Brooks, D.J., Bench, C.J., & Grattan, L.M. (1998). Evidence for striatal dopamine release during a video game. Nature, 393, 266-268.

Koffka, K. (1935). Principles of Gestalt psychology. New York: Harcourt Brace.

Konishi, S., Nakajima, K., Uchida, I., Kameyama, M., Nakahara, K., Sekihara, K., & Miyashita, Y. (1998). Transient activation of inferior prefrontal cortex during cognitive set shifting. Nature Neuroscience, 1, 80-84.

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. Brain, 122, 981-991.

Krawiecka, M., Goldberg, D., & Vaughan, M. (1977). A standardized psychiatric assessment scale for rating chronic psychotic patients. Acta Psychiatrica Scandinavia, 55, 299-308.

Krupp, B.H. (1997). Ethical considerations in apathy syndromes. Psychiatric Annals, 27, 50-54.

Kurland, L.T. (1988). Amyotrophic lateral sclerosis and Parkinson's disease complex on Guam linked to an environmental neurotoxin. Trends in Neurosciences, 11(2), 51-54.

Kuzis, G., Sabe, L., Tiberti, C., Dorrego, F., & Starkstein, S.E. (1999). Neuropsychological correlates of apathy and depression in patients with dementia. Neurology, 52, 1403-1407.

Lalonde, R., & Badescu, R. (1995). Exploratory drive, frontal lobe function and adipsia in aging. Gerontology, 41(1), 134-144.

Lalonde, R., & Hannequin, D. (1999). The neurobiological basis of time estimation and temporal order. Reviews in the Neurosciences, 10, 151-173.

Langston, J.W., Ballard, P., Tetrud, J.W., & Irwin, I. (1983). Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. Science, 219, 979-980.

Laplane, D. (1990). Is 'loss of psychic self-activation' a heuristic concept? Behavioural Neurology, 3, 27-38.

Laplane, D. (1994). Function of the basal ganglia in mental activity. In G. Percheron, J. S. McKenzie, & J. Feger (Eds.), The basal ganglia IV. (pp. 569-576). New York: Plenum Press.

Laplane, D., Baulac, M., Widlocher, D., & Dubois, B. (1984). Pure psychic akinesia with bilateral lesions of basal ganglia. Journal of Neurology Neurosurgery and Psychiatry, 47, 377-385.

Laplane, D., Levasseur, M., Pillon, B., Dubois, B., Baulac, M., Mazoyer, B., Tran, D.S., Sette, G., Danze, F., & Baron, J.C. (1989). Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions. A neuropsychological, magnetic resonance imaging and positron tomography study. Brain, 112, 699-725.

Lawrence, A.D., Koepp, M.J., Gunn, R.N., Cunningham, V.J., & Grasby, P.M. (1999). Steps to a neurochemistry of personality. Behavioral and Brain Sciences, 22(3), 528-529.

Lawrence, A.D., Sahakian, B.J., & Robbins, T.W. (1998). Cognitive functions and corticostriatal circuits: insights from Huntington's disease. Trends in Cognitive Sciences, 2(10), 379-388.

Le Bras, C., Pillon, B., Damier, P., & Dubois, B. (1999). At which steps of spatial working memory processing do striatofrontal circuits intervene in humans? Neuropsychologia, 37, 83-90.

Leiguarda, R.C., Pramstaller, P.P., Merello, M., Starkstein, S., Lees, A.J., & Marsden, C.D. (1997). Apraxia in Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, and neuroleptic-induced parkinsonism. Brain, 120, 75-90.

Leiva, C., Galvan, B., & Matius-Guia, J. (1996). Personality in Parkinson's disease. Movement Disorders, 11(Suppl 1), 142

Levesque, D., Martres, M.P., Diaz, J., Griffon, N., Lammers, C.H., Sokoloff, P., & Schwartz, J.C. (1995). A paradoxical regulation of the dopamine D3 receptor expression suggests the involvement of an anterograde factor from dopamine neurones. Proceedings of the National Acadamy of Science, 92, 1719-1723.

Levine, B., Robertson, I.H., Clare, L., Carter, G., Hong, J., Wilson, B.A., Duncan, J., & Stuss, D.T. (2000). Rehabilitation of executive functioning: An experimental-clinical validation of goal management training. Journal of the International Neuropsychological Society, 6, 299-312.

Levy, M.L., Cummings, J.L., Fairbanks, L.A., Masterman, D., Miller, B.L., Craig, A.H., Paulsen, J.S., & Litvan, I. (1998). Apathy is not depression. The Journal of Neuropsychiatry and Clinical Neurosciences, 10, 314-319.

Levy, M.L., Miller, B.L., Cummings, J.L., Fairbanks, L.A., & Craig, A.H. (1996). Alzheimer disease and frontotemporal dementias: behavioral distinctions. Archives of Neurology, 53, 687-690.

Lezak, M.D. (1982). The problem of assessing executive functions. International Journal of Psychology, 17(2-3), 281-297.

Lhermitte, F., Pillon, B., & Serdaru, M. (1986). Human autonomy and the frontal lobes. Part 1: Imitation and utilization behavior: a neuropsychological study of 75 patients. Annals of Neurology, 19, 326-334.

Libet, B. (1985). Unconscious cerebral initiative and the role of conscious will in voluntary action. Behavioral and Brain Sciences, 8, 529-566.

Libet, B. (1999). Do we have free will? Journal of Consciousness Studies, 6, 47-57.

Lichter, D.G., Corbett, A.J., Fitzgibbon, G.M., Davidso, O.R., Hope, J.K., Goddard, G.V., Sharples, K.J., & Pollock, M. (1988). Cognitive and motor dysfunction in Parkinson's disease. clinical, performance, and computerised tomographic correlations. Archives of Neurology, 8, 854-860.

Lieb, K., Brucker, S., Bach, M., Els, T., Lucking, C.H., & Greenlee, M.W. (1999). Imparment in preattentive visual processing in patients with Parkinson's disease. Brain, 122, 303-313.

Lieberman, A. (1998). Managing the neuropsychiatric symptoms of Parkinson's disase. Neurology, 50(s6), 33-38.

Lieberman, A., Ranhosky, A., & Korts, D. (1997). Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double blind, placebo controlled, parallel-group study. Neurology, 49, 162-168.

Lilly, R., Cummings, J.L., Benson, F., & Frankel, M. (1983). The human Kluver Bucy syndrome. Neurology, 33, 1141-1145.

Lindvall, O., Brundin, P., Widner, H., Rehncrona, S., Gustavii, B., Frackowiak, R., Leenders, K.L., Sawle, G., Rothwell, J.C., Marsden, C.D., & Bjorklund, A. (1990). Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science, 247, 574-577.

Lindvall, O., & Odin, P. (1994). Clinical application of cell transplantation and neurotrophic factors in CNS disorders. Current Opinion in Neurobiology, 4(5), 752-757.

Litvan, I., Campbell, G., Mangone, C.A., Verny, M., McKee, A., Chaudhuri, K.R., Jellinger, K., Pearce, R.K., & D'Olhaberriague, L. (1997). Which clinical

features differentiate progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) from related disorders? A clinicopathological study. Brain, 120, 65-74.

Litvan, I., Cummings, J.L., & Mega, M. (1998). Neuropsychiatric features of corticobasal degeneration. Journal of Neurology Neurosurgery and Psychiatry, 65, 717-721.

Litvan, I., Mega, M.S., Cummings, J.L., & Fairbanks, L. (1996). Neuropsychiatric aspects of progressive supranuclear palsy. Neurology, 47(5), 1184-1189.

Litvan, I., Paulsen, J.S., Mega, M.S., & Cummings, J.L. (1998). Neuropsychiatric assessment of patients with hyperkinetic and hypokinetic movement disorders. Archives of Neurology, 55, 1313-1319.

Loewenstein, G. (1994). The psychology of curiosity: a review and reinterpretation. Psychological Bulletin, 116(1), 75-98.

Lugaresi, A., Montagna, P., Morreale, A., & Gallassi, R. (1990). 'Psychic akinesia' following carbon monoxide poisoning. European Neurology, 30(3), 167-169.

Macleod, D., & Prior, M. (1996). Attention deficits in adolescents with ADHD and other clinical groups. Child Neuropsychiatry, 2, 1-10.

Mahieux, F., Michelet, D., Manifacier, M.J., Boller, F., Fermanian, J., & Guillard, A. (1995). Mini-mental Parkinson: First validation study of a new bedside test for Parkinson's disease. Behavioural Neurology, 8, 15-22.

Marin, R.S. (1990). Differential diagnosis and classification of apathy. American Journal of Psychiatry, 147(1), 22-30.

Marin, R.S. (1991). Apathy: a neuropsychiatric syndrome. The Journal of Neuropsychiatry and Clinical Neurosciences, 3(3), 243-254.

Marin, R.S. (1996). Apathy: concept, syndrome, neural mechanisms and treatment. Seminars in Clinical Neuropsychiatry, 1(4), 304-314.

Marin, R.S. (1997). Apathy - who cares? An introduction to apathy and related disorders of diminished motivation. Psychiatric Annals, 27(1), 18-23.

Marin, R.S., Biedrzycki, R.C., & Firinciogullari, S. (1991). Reliability and validity of the apathy evaluation scale. Psychiatric Research, 38, 143-162.

Marsden, C.D. (1994a). Parkinson's disease. Journal of Neurology Neurosurgery and Psychiatry, 57, 672-681.

Marsden, C.D., & Obeso, J.A. (1994b). The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. Brain, 117, 877-897.

Marsh, N.V., Kersel, D.A., Havill, J.H., & Sleigh, J.W. (1998). Caregiver burden at 1 year following severe traumatic brain injury. Brain Injury, 12(12), 1045-1059.

Maw, W.H., & Maw, E.W. (1962). Selection of unbalanced and unusual designs by children high in curiosity. Child Development, 33, 917-922.

Mayeux, R. (1983). Emotinal changes associated with basal ganglia disorders. In K. M. Heilman & P. Satz (Eds.), Neuropsychology of human emotion. (pp. 141-164). London: Guilford Press.

Mayeux, R. (1987). Mental state. In W. C. Koller (Ed.), Handbook of Parkinson's disease. New York: Marcel Dekker.

McCourt, W.F., Gurrera, R.J., & Cutter, H.S.G. (1993). Sensation seeking and novelty seeking are they the same? Journal of Nervous and Mental Disease, 181(5), 309-312.

McKeith, I.G., Grace, J.B., Walker, Z., Byrne, E.J., Wilkinson, D., Stevens, T., & Perry, E.K. (2000). Rivastigmine in the treatment of dementia with Lewy bodies: preliminary findings from an open trial. International Journal of Geriatric Psychiatry, 15(5), 387-392.

Mega, M.S., & Cohenour, R.C. (1997). Akinetic mutism: disconnection of frontal-subcortical circuits. Neuropsychiatry Neuropsychology and Behavioral Neurology, 10(4), 254-259.

Mega, M.S., & Cummings, J.L. (1994). Frontal-subcortical circuits and neuropsychiatric disorders. The Journal of Neuropsychiatry and Clinical Neurosciences, 6(4), 358-370.

Mega, M.S., Cummings, J.L., Salloway, S., & Malloy, P. (1997). The limbic system: an anatomic, phylogenetic, and clinical perspective. The Journal of Neuropsychiatry and Clinical Neurosciences, 9, 315-330.

Mellet, E., Tzourio, N., Denis, M., & Mazoyer, B. (1995). A positron emission tomography study of visual and mental spatial exploration. Journal of Cognitive Neuroscience, 7(4), 433-445.

Menza, M.A., Golbe, L.I., Cody, R.A., & Forman, N.E. (1993). Dopamine-related personality traits in Parkinson's disease. Neurology, 43, 505-508.

Menza, M.A., Mark, M.H., Burn, D.J., & Brooks, D.J. (1995). Personality correlates of [18F]dopa striatal uptake: Results of positron-emission tomography in

Parkinson's disease. The Journal of Neuropsychiatry and Clinical Neurosciences, 7(2), 176-179.

Meredith, G.E., & Totterdell, S. (1999). Microcircuits in nucleus accumbens shell and core involved in cognition and reward. Psychobiology, 27(2), 165-186.

Mesulam, M.M. (1981). A cortical network for directed attention and unilateral neglect. Annals of Neurology, 10, 309-325.

Mignone, M.L., D'Amato, A.C., Saviano, P., Mucci, A., Galderisi, S., & Maj, M. (1995). Impaired performance on tests sensitive to fronto-subcortical dysfunction is related to both the positive and negative dimensions of schizophrenia. Neuropsychopharmacology, 5(3), 320-320.

Miller, J.O. (1988). A warning about median reaction times. Journal of Experimental Psychology: Human Perception and Performance, 14, 539-543.

Miller, L. (1985a). Cognitive risk-taking after frontal or temporal lobectomy-1. The synthesis of fragmented visual information. Neuropsychologia, 23(3), 359-369.

Miller, L., & Milner, B. (1985b). Cognitive risk-taking after frontal or temporal lobectomy-2. The synthesis of phonemic and semantic information. Neuropsychologia, 23(3), 371-379.

Miller, L.A. (1992). Implulsivity, risk-taking, and the ability to synthesize fragmented information after frontal lobectomy. Neuropsychologia, 30(1), 69-79.

Mimura, M., Kinsbourne, M., & O'Connor, M. (2000). Time estimation by patients with frontal lesions and by Korsakoff amnesics. Journal of the International Neuropsychological Society, 5(517), 528

Moore, A.P., & Murphy, P. (1992). Serial and parallel visual processing in Parkinson's Disease (PD). Movement Disorders, 7(Supplement 1), 89-89.

Morrish, P.K., Rakshi, J.S., Bailey, D.L., Sawle, G.V., & Brooks, D.J. (1998). Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [18F]dopa PET. Journal of Neurology Neurosurgery and Psychiatry, 64, 314-319.

Mozaz, M., Marti, J.F., Carrera, E., & De la Puente, E. (1990). Apraxia in a patient with lesion located in right sub-cortical area. Analysis of errors. Cortex, 26(4), 651-655.

Naville, F. (1922). Etudes sur les complications et les sequelles mentales de l'encephaite epidemiqe la bradyphrenie. L'encephale, 17, 369-375.

Nelson, H.E. (1976). A modified card sorting test sensitive to frontal lobe defects. Cortex, 12, 313-324.

Nolte, J. (1988). The human brain an introduction to its functional anatomy. (3rd ed.). St. Louis: Mosby Year Book.

Norman, D.A., & Shallice, T. (1986). Attention to action: Willed and automatic control of behavior. In R. J. Davidson, G. E. Schwartz, & D. Shapiro (Eds.), Consciousness and self regulation. New York: Plenum Press.

Nutt, J.G. (1998). Gait and balance disorders: a syndrome approach. In J. Jankovic & E. Tolosa (Eds.), Parkinson's disease and movement disorders. (pp. 687-699). Baltimore: Williams & Wilkins.

Obrador, S. (1947). Temporal lobotomy. Journal of Neuropathology and Experimental Neurology, 6, 185-193.

Oechsner, M., Buhmann, C., Strauss, J., & Stuerenburg, H.J. (1999). Long term follow up of levodopa metabolism during COMT-inhibition with Tolcapone. Parkinsonism and Related Disorders, 5(Suppl.), 81-81.

Okada, K., Kobayashi, S., Yamagata, S., Takahashi, K., & Yumaguchi, S. (1997). Poststroke apathy and regional cerebral blood flow. Stroke, 28(12), 2437-2441.

Olds, J. (1966). Self-stimulation and differentiated reward systems. In D. Bindra & J. Stewart (Eds.), Motivation. (pp. 297-317). Harmondsworth: Penguin.

Olds, J., & Milner, P. (1954). Positive reiforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of Comparative and Physiological Psychology, 47, 419-427.

Oliveira, R.M., Gurd, J.M., Nixon, P., Marshall, J.C., & Passingham, R.E. (1997). Micrographia in Parkinson's disease: the effect of providing external cues. Journal of Neurology Neurosurgery and Psychiatry, 63, 429-433.

Olson, K.R., & Camp, C.J. (1984). Analysis of curiosity measures in adults. Psychological Reports, 54, 491-497.

Ott, B.R., Notto, R.B., & Fogel, B.S. (1996). Apathy and loss of insight in Alzheimer's disease: a SPECT imaging study. Journal of Neuropsychiatry, 8, 41-46.

Otto, A., Zerr, I., Lantsch, M., Weidehaas, K., Riedemann, C., & Poser, S. (1998). Akinetic mutism as a classification criterion for the diagnosis of Creutzfeldt-Jakob disease. Journal of Neurology Neurosurgery and Psychiatry, 64, 524-528.

Owen, A.M., Evans, A.C., & Petrides, M. (1996). Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. Cerebral Cortex, 6, 31-38.

Pakkenberg, B. (1991). Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenia. Archives of General Psychiatry, 47, 1023-1025.

Palmer, J., Ames, C.T., & Lindsey, D.T. (1993). Measuring the effect of attention on simple visual search. Journal of Experimental Psychology: Human Perception and Performance, 19, 108-130.

Parkinson, B., & Colman, A.M. (1995). Introduction. In B. Parkinson & A. M. Colman (Eds.), Emotion and motivation. London: Longman.

Parkinson, J. (1817). An essay on the shaking palsy. London: Sherwood, Neely, and Jones.

Parsa, M.A., & Bastani, B. (1998). Quetiapine (Seroquel) in the treatment of psychosis in patients with Parkinson's disease. Journal of Neuropsychiatry, 10(2), 216-219.

Pasquier, F., Lebert, F., & Petit, H. (1995). Dementia, apathy, and thalamic infarcts. Neuropsychiatry Neuropsychology and Behavioral Neurology, 8(3), 208-214.

Passingham, R. (1993). The frontal lobes and voluntary action. Oxford: Oxford University Press.

Pastor, M.A., Artieda, M., Jahanshahi, M., & Obeso, J.A. (1992). Time estimation and reproduction is abnormal in Parkinson's disease. Brain, 115, 211-225.

Paus, T. (1996). Location and function of the human frontal eye feild: a selective review. Neuropsychologia, 34(6), 475-483.

Paus, T., Koski, L., Zografos, C., & Westbury, C. (1998). Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: A reveiw of 107 PET activation studies. Neuroreport, 9(9), R37-R47

Persico, A.M., Reich, S., Henningfield, J.E., Kuhar, M.J., & Uhl, G.R. (1998). Parkinsonian patients report blunted subjective effects of methylphenidate. Experimental and Clinical Psychopharmacology, 6(1), 54-63.

Petrides, M. (1985). Deficits on conditional associative-learning tasks after frontal- and temporal-lobe lesions in man. Neuropsychologia, 23, 601-614.

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal and temporal lobe lesions in man. Neuropsychologia, 20(3), 249-262.

Pickering, A.D., Corr, P.J., Powell, J.H., Kumari, V., Thornton, J.C., & Gray, J.A. (1997). Individual differences in reactions to reinforcing stimuli are neither black nor white: To what extent are they gray? In H. Nyborg (Ed.), The scientific study of human nature: Tribute to Hans J. Eysenck at eighty. (pp. 37-67). New York: Elsevier Science.

Pilgrim, E., & Humphreys, G.W. (1991). Impairment of action to visual objects in a case of ideomotor apraxia. Cognitive Neuropsychology, 8(6), 459-473.

Pluck, G.C., & Brown, R.G. (1999). Neuropsychological aspects of apathy in Parkinson's disease [Abstract]. Parkinsonism and Related Disorders, 5, S90-S91

Plum, F., Schiff, N., Ribary, U., & Llinas, R. (1998). Coordinated expression in chronically unconscious persons. Philisophical Transactions of The Royal Society of London.Series B, 353, 1929-1933.

Poewe, W., Gerstenbrand, F., Ransmayr, G., & Plorer, S. (1983). Premorbid personality of Parkinson patients. Journal of Neural Transmission, 19(Suppl.), 215-224.

Poewe, W., Karamat, E., Kemmler, G.W., & Gerstenbrand, F. (1990). The premorbid personality of patients with Parkinson's disease: a comparative study with healthy controls and patients with essential tremor. In M. B. Streifler, A. D. Korezyn, E. Melamed, & M. B. H. Youdim (Eds.), Advances in neurology: Parkinson's disease: anatomy, pathology, and therapy . (pp. 339-342). New York: Raven Press.

Posner, M.I. (1980). Orienting of attention. Quarterly Journal of Experimental Psychology, 32, 3-25.

Poulsen, C., & Segalowitz, N. (2000). Selective effects of prior motivational experience on current on-line control of attention. Brain and Cognition, 43, 365-370.

Powell, J., Al-Adawi, S., & Greenwood, R. (1996). A neuropsychological and psychopharmacological model of poor motivation after brain injury. Journal of Neurology Neurosurgery and Psychiatry, 60, 117

Powell, J.H., Al-Adawi, S., Morgan, J., & Greenwood, R.J. (1996). Motivational deficits after brain injury: effects of bromocriptine in 11 patients. Journal of Neurology Neurosurgery and Psychiatry, 60(4), 416-421.

Pradhan, S., Singh, M.N., & Pandley, N. (1998). Kluver Bucy syndrome in young children. Clinical Neurology and Neurosurgery, 100, 254-258.

Pramstaller, P.P., & Marsden, C.D. (1996). The basal ganglia and apraxia. Brain, 119, 319-340.

Pribram, K.H., & McGuinness, D. (1975). Arousal, activation, and effort in the control of attention. Psychological Review, 82(2), 116-149.

Prince, M.J., Harwood, R.H., Thomas, A., & Mann, A.H. (1998). A prospective population-based cohort study of the effects of disablement and social milieu on the onset and maintenance of late-life depression. The Gospel Oak Project VII. Psychological Medicine, 28, 337-350.

Quinlan, P.T., & Humphreys, G.W. (1987). Visual search for targets defined by combinations of color, shape, and size: An examination of the task constraints on feature and conjunction searches. Perception and Psychophysics, 41(5), 455-472.

Rabbitt, P. (1997). Introduction: Methodologies and models in the study of executive function. In P. Rabbitt (Ed.), Methodology of frontal and executive function. (pp. 1-38). Hove: Psychology Press.

Rammsayer, T., & Classen, W. (1997). Impaired temporal discrimination in Parkinson's disease: Temporal processing of brief durations as an indicator of degeneration of dopaminergic neurons in the basal ganglia. International Journal of Neuroscience, 91(1-2), 45-55.

Rapcsak, S.Z., Ochipa, C., Anderson, K.C., & Poizner, H. (1995). Progressive ideomotor apraxia: Evidence for a selective impairment of the action production system. Brain and Cognition, 27(2), 213-236.

Rauscher, F.H., Krauss, R.M., & Chen, Y. (1996). Gesture, speech and lexical access: The role of lexical movements in speech production. Psychological Science, 7, 226-231.

Raven, J.C. (1965). Guide to using the coloured progressive matrices. London: H.K. Lewis.

Reason, J.T. (1979). Actions not as planned: the price of automisation. In G. Underwood & R. Stevens (Eds.), Aspects of consciousness, vol 1. psychological issues. London: Academic Press.

Rebec, G.V., Grabner, C.P., Johnson, M., Pierce, R.C., & Bardo, M.T. (1997). Transient increases in catecholaminergic activity in medial prefrontal cortex and nucleus accumbens shell during novelty. Neuroscience, 76(3), 707-714.

Redfern, R.M. (1989). History of stereotactic surgery for Parkinson's disease. British Journal of Neurosurgery, 3(3), 271-304.

Redgrave, P., Prescott, T.J., & Gurney, K. (1999). Is the short-latency dopamine response too short to signal reward error? Trends in Neurosciences, 22, 146-151.

Reitan, R.M. (1958). Validity of the trail making test as an indicator of organic brain damage. Perceptual and Motor Skills, 8, 271-276.

Resnick, B., Zimmerman, S.I., Magaziner, J., & Adelman, A. (1998). Use of the apathy evaluation scale as a measure of motivation in elderly people. Rehabilitation Nursing, 23(3), 141-147.

Richard, I.H., Schiffer, R.B., & Kurlan, R. (1996). Anxiety and Parkinson's disease. The Journal of Neuropsychiatry and Clinical Neurosciences, 8, 383-392.

Richardson, R.T., & DeLong, M.R. (1988). A reappraisal of the functions of the nucleus basalis of Meynert. Trends in Neurosciences, 11(6), 264-267.

Riddoch, M.J., Humphreys, G.W., & Price, C.J. (1989). Routes to action: evidence from apraxia. Cognitive Neuropsychology, 6(5), 437-454.

Ridley, R.M., & Baker, H.F. (1991). Can fetal neural transplants restore function in monkeys with lesion-induced behavioural deficits? Trends in Neurosciences, 14(8), 366-370.

Rifkin, A., Quitkin, F., & Klein, D. (1975). Akinesia: A poorly recognised drug induced extrapyramidal behavioral disorder. Archives of General Psychiatry, 32, 672-674.

Ring, H.A., Bench, C.J., Trimble, M.R., Brooks, D.J., Frackowiak, R.S.J., & Dolan, R.J. (1994). Depression in Parkinson's disease. British Journal of Psychiatry, 165, 333-339.

Robbins, T.W., & Everitt, B.J. (1996). Neurobehavioural mechanisms of reward and motivation. Current Opinion in Neurobiology, 6, 228-236.

Robbins, T.W., James, M., Owen, A.M., Lange, K.W., Lees, A.J., Leigh, P.N., Marsden, C.D., Quinn, N.P., & Summers, B.A. (1994). Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy

in tests sensitive to frontal lobe dysfunction. Journal of Neurology Neurosurgery and Psychiatry, 57(1), 79-88.

Robertson, C., Hazlewood, R., & Rawson, M.D. (1996). The effects of Parkinson's disease on the capacity to generate information randomly. Neuropsychologia, 34(11), 1069-1078.

Robertson, I.H. (1996). Goal Management Training: a clinical manual. Cambridge: PsyConsult.

Robinson, G., Blair, J., & Cipolotti, L. (1998). Dynamic aphasia: An inability to select between competing verbal responses? Brain, 121, 77-89.

Rogers, D., Lees, A.J., Smith, E., Trimble, M., & Stern, G.M. (1987). Bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness: an experimental study. Brain, 110(3), 761-776.

Rosenblatt, A., & Leroi, I. (2000). Neuropsychiatry of Huntington's disease and other basal ganglia disorders. Psychosomatics, 41, 24-30.

Rosenthal, T.L., & Meyer, V. (1971). Case report: Behavioral treatment of clinical abulia. Conditional Reflex, 6(1), 22-29.

Roth, M., Huppert, F.A., Tym, E., & Mountjoy, C.Q. (1988). CAMDEX: The Cambridge examination for mental disorders of the elderly. Cambridge: Cambridge University Press.

Rothi, L.J.G., Ochipa, C., & Heilman, K.M. (1991). A cognitive neuropsychological model of limb praxis. Cognitive Neuropsychology, 8(6), 443-458.

Rowe, J.B., Toni, I., Josephs, O., Frackowiak, R.S.J., & Passingham, R. (2000). The prefrontal cortex: Response selection or mainenance within working memory? Science, 288, 1656-1660.

Rubinsztein, J.S., Rubinsztein, D.C., Goodburn, S., & Holland, A.J. (1998). Apathy and hypersomnia are common features of myotonic dystrophy. Journal of Neurology Neurosurgery and Psychiatry, 64, 510-515.

Rye, D.B., Saper, C.B., Lee, H.J., & Wainer, B.H. (1987). Pedunculopontine tegmental nucleus of the rat: Cytoarchitecture, cytochemistry and some extrapyramidial connections of the mesopontine tegmentum. Journal of Comparitive Neurology, 259, 483-528.

Sacks, O. (1973). Awakenings. London: Gerald Duckworth.

Salmon, E., Van der Linden, M., & Franck, G. (1997). Anterior cingulate and motor network metaboloic impairment in progressive supranuclear palsy. Neuroimage, 5, 173-178.

Samuel, M., Ceballos, B.A., Turjanski, N., Boecker, H., Gorospe, A., Linazasoro, G., Holmes, A.P., DeLong, M.R., Vitek, J.L., Thomas, D.G., Quinn, N.P., Obeso, J.A., & Brooks, D.J. (1997). Pallidotomy in Parkinson's disease increases supplementary motor area and prefrontal activation during performance of volitional movements an H2(15)O PET study. Brain, 120, 1301-1313.

Sanders, A.F. (1983). Towards a model of stress and human performance. Acta Psychologica, 53, 61-97.

Schapira, A.H.V. (1997). Pathogenesis of Parkinson's disease. Bailliere's Clinical Neurology, 6(1), 15-36.

Scheibel, A.B. (1997). The thalamus and neuropsychiatric illness. The Journal of Neuropsychiatry and Clinical Neurosciences, 9, 342-353.

Schmand, B., Kuipers, T., Van-der-Gaag, M., Bosveld, J., Bulthuis, F., & Jellema, M. (1994). Cognitive disorders and negative symptoms as correlates of motivational deficits in psychotic patients. Psychological Medicine, 24(4), 869-884.

Schultz, W. (1999). The primate basal ganglia and the voluntary control of behaviour. Journal of Consciousness Studies, 6, 31-45.

Schultz, W., Dayan, P., & Montague, P.R. (1997). A neural substrate of prediction and reward. Science, 275, 1593-1599.

Schultz, W., Ljungberg, T., Apicella, P., Romo, R., Mirenowicz, J., & Hollerman, J.R. (1993). Primate dopamine neurons: From movement to motivation and back. In N. Mano, I. Hamada, & M. R. DeLong (Eds.), Role of the cerebellum and basal ganglia in voluntary movement. (pp. 89-97). Amsterdam: Elsevier Science Publishers.

Schwab, R.S., & England, A.C. (1969). Projection technique for evaluating surgery in Parkinson's disease. In F. J. Gillingham & M. C. Donaldson (Eds.), Third symposium on Parkinson's disease. Edinburgh: Livingstone.

Schwartz, M.F., Reed, E.S., Montgomery, M., Palmer, C., & Mayer, N.H. (1991). The quantitative description of action disorganisation after brain damage: a case study. Cognitive Neuropsychology, 381-414.

Schwarz, J.,& Storch, A. Effects of COMT-inhibition on dopaminergic neurons in vitro. In T. Chase & P. Bedard (Eds.), Focus on Medicine: Vol. 14. Oxford: Blackwell Science.

Searle, J.R. (2000). Consciousness, free action, and the brain. Journal of Consciousness Studies, 7(10), 3-22.

Serra-Mestres, J., & Ring, H.A. (1999). Vulnerability to emotionally negative stimuli in Parkinson's disease: an investigation using the emotional stroop task. Neuropsychiatry Neuropsychology and Behavioral Neurology, 12(1), 52-57.

Shallice, T. (1979). Case-study approach in neuropsychological research. Journal of Clinical Neuropsychology, 1, 183-111.

Shallice, T. (1988). From neuropsychology to mental structure. Cambridge: Cambridge University Press.

Shallice, T., & Burgess, P. (1997). Higher-order cognitive imparments and frontal lobe lesions in man. In P. Rabbitt (Ed.), Methodology of frontal and executive function. (pp. 125-138). Hove: Psychology Press.

Shallice, T., & Burgess, P.W. (1991). Deficits in stratagy application following frontal lobe damage in man. Brain, 114, 727-741.

Shallice, T., & Burgess, P.W. (1996). The domain of supervisory processes and temporal organisation of behaviour. Philisophical Transactions of The Royal Society of London.Series B, 351, 1405-1412.

Shallice, T., Burgess, P.W., Schon, F., & Baxter, D.M. (1989). The origins of utilization behaviour. Brain, 112, 1587-1598.

Shannon, K.M., Bennett, J.P., & Friedman, J.H. (1997). Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. Neurology, 49, 724-728.

Shizgal, P. (1997). Neural basis of utility estimation. Current Opinion in Neurobiology, 7, 198-208.

Siemers, E.R., Shekhar, A., Quaid, K., & Dickson, H. (1993). Anxiety and motor performance in Parkinson's disease. Movement Disorders, 8(4), 501-506.

Singer, E. (1973). Social costs of Parkinson's disease. Journal of Chronic Disease, 26, 243-254.

Smith, G.L., Large, M.M., Kavanagah, D.J., Karayanidis, F., Barrett, N.A., Michie, P.T., & O'Sullivan, B.T. (1998). Further evidence for a deficit in switching attention in schizophrenia. Journal of Abnormal Psychology, 107(3), 390-398.

Snaith, P. (1993). Anhedonia: a neglected symptom of psychopathology. Psychological Medicine, 23(4), 957-966.

Snaith, R.P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. British Journal of Psychiatry, 167(1), 99-103.

Sohn, Y.H., Kim, G.W., Huh, K., & Kim, J.S. (1998). Dopaminergic influences on the P300 abnormality in Parkinson's disease. Journal of Neurological Sciences, 158, 83-87.

Sommer, M., Grafman, J., Clark, K., & Hallett, M. (1999). Learning in Parkinson's disease: eyeblink conditioning, declarative learning, and procedural learning. Journal of Neurology Neurosurgery and Psychiatry, 67, 27-34.

Spence, S.A., & Frith, C.D. (1999). Towards a functional anatomy of volition. Journal of Consciousness Studies, 6, 11-29.

Spicer, K.B., Brown, G.G., & Gorell, J.M. (1994). Lexical decision in Parkinson's disease: lack of evidence for generalized bradyphrenia. Journal of Clinical and Experimental Neuropsychology, 16(3), 457-471.

Spielberger, C.D., & Starr, L.M. (1994). Curiosity and exploratory behavior. In H. F. O'Neil Jr. & M. Drillings (Eds.), Motivation: theory and research. (pp. 221-243). Hillsdale: Lawrence Erlbaum Associates.

Stallings, M.C., Hewitt, J.K., Cloninger, C.R., Heath, A.C., & Eaves, L.J. (1996). Genetic and environmental structure of the Tridimensional Personality Questionnaire: three or four temperament dimensions? Journal of Personality and Social Psychology, 70(1), 127-140.

Starkstein, S.E., Fedoroff, J.P., Price, T.R., Leiguarda, R., & Robinson, R.G. (1993). Apathy following cerebrovascular lesions. Stroke, 24(11), 1625-1630.

Starkstein, S.E., Mayberg, S.E., Preziosi, T.J., Andrezejewski, P., Leiguarda, R., & Robinson, R.G. (1992). Reliability, validity and clinical correlates of apathy in Parkinson's disease. Journal of Neuropsychiatry, 4(2), 134-139.

Starkstein, S.E., Petraca, G., Chemerinski, E., Teson, A., Sabe, L., Merello, M., & Leiguarda, R. (1998). Depression in classic versus akinetic-rigid Parkinson's disease. Movement Disorders, 13(1), 29-33.

Stebbins, G.T., Gabrieli, J.D.E., Masciari, F., Monti, L., & Goetz, C.G. (1999). Delayed recognition memory in Parkinson's disease: a role for working memory? Neuropsychologia, 37, 503-510.

Steckler, T., Inglis, W., Winn, P., & Sahgal, A. (1994). The pedunculopontine tegmental nucleus: a role in cognitive processes? Brain Research Reviews, 19(3), 298-318.

Stern, Y., Mayeux, R., & Cote, L. (1984). Reaction time and vigilance in Parkinson's disease. Possible role of altered norepinephrine metabolism. Archives of Neurology, 41(10), 1086-1089.

Stroop, J.R. (1935). Studies of interference in spatial and verbal reactions. Journal of Experimental Psychology, 18, 643-662.

Stuss, D.T., Guberman, A., Nelson, R., & Larochelle, S. (1988). The neuropsychology of paramedian thalamic infarction. Brain and Cognition, 8(3), 348-378.

Sultzer, D.L. (1996). Behavioral syndromes in dementia: neuroimaging insights. Seminars in Clinical Neuropsychiatry, 1(4), 261-271.

Swan, D.E., & Carmelli, D. (1996). Curiosity and mortality in aging adults: A 5-year follow-up of the Western Collaborative Group Study. Psychology and Aging, 11(3), 449-453.

Taylor, A.E., & Saint-Cyr, J.A. (1995). The neuropsychology of Parkinson's disease. Brain and Cognition, 28, 281-296.

Terzian, H., & Ore, G.D. (1955). Syndrome of Kluver and Bucy reproduced in man by bilateral removal of the temporal lobes. Neurology, 5(6), 373-380.

Tetrud, J.W., & Langston, J.W. (1989). The effect of deprenyl (selegeline) on the natural history of Parkinson's disease. Science, 245, 519-522.

Thompson, A.W.S. (1989). On being a parkinsonian. Rhode Island: Rumford.

Thorndike, E. (1911). Animal intelligence. New York: Macmillan.

Todes, C.J., & Lees, A.J. (1985). The pre-morbid personality of patients with Parkinson's disease. Journal of Neurology Neurosurgery and Psychiatry, 48, 97-100.

Travers, J.B., Akey, L.R., Chen, S.C., Rosen, S., Paulson, G., & Travers, S.P. (1993). Taste preferences in Parkinson's disease patients. Chemical Senses, 18(1), 47-55.

Treisman, A. (1988). Features and objects: the fourteenth Bartlett memorial lecture. Quarterly Journal of Experimental Psychology, 40A(2), 201-237.

Treisman, A.M. (1996). Selection for perception for selection for action. Commentry on "Two stages in visual information processing and visual perception" by A.H.C. van der Heijden. Visual Cognition, 3(4), 353-357.

Treisman, A.M., & Gelade, G. (1980). A feature-integration theory of attention. Cognitive Psychology, 12, 97-136.

Trenerry, M.R., Crosson, B., DeBoe, J., & Leber, W.R. (1989). Stroop Neuropsychological Screening Test Manual. Odessa, FL: Psychological Assesment Resources.

Tretiakoff, C. (1919). Contribution a l'etude de l'anatomia pathologique du locus niger. Doctoral Thesis. University of Paris;

Troscianko, T., & Calvert, J. (1993). Impaired parallel visual search mechanism in Parkinson's disease: implications for the role of dopamine in visual attention. Clinical Vision Science, 8, 281-287.

Urban, W.M. (1919). Definition and analysis of the consciousness of value. Psychological Review, 14(1), 1-36.

Van Reekum, R., Bayley, M., Garner, S., Burke, I.M., Fawcett, S., Hart, A., & Thompson, W. (1995). N of 1 study: Amantadine for the amotivational syndrome in a patient with traumatic brain injury. Brain Injury, 9(1), 49-53.

Verfaellie, M., & Heilman, K.M. (1987). Response preparation and response inhibition after lesions of the medial frontal lobe. Archives of Neurology, 44(12), 1265-1271.

Wascher, E., Verleger, R., Vieregge, P., Jaskowski, P., Koch, S., & Kompf, D. (1997). Responses to cued signals in Parkinson's disease. Distinguishing between disorders of cognition and of activation. Brain, 120, 1355-1375.

Watanabe, M.D., Martin, E.M., DeLeon, O.A., Gaviria, M., Pavel, D.G., & Trepashko, D.W. (1995). Successful methylphenidate treatment of apathy after subcortical infarcts. The Journal of Neuropsychiatry and Clinical Neurosciences, 7(4), 502-504.

Weinstein, A., Troscianko, T., & Calvert, J. (1997). Impaired visual search mechanisms in Parkinson's disease (PD): a psychophysical and event-related potentials study. Journal of Psychophysiology, 11, 33-47.

Weiskrantz, L. (1997). Consciousness lost and found. New York: Oxford University Press.

Weiss, P., Stelmach, G.E., & Hefter, H. (1997). Programming of a movement sequence in Parkinson's disease. Brain, 120(1), 91-102.

Wenzel, A., & Holt, C.S. (1999). Dot probe performance in two specific phobias. British Journal of Clinical Psychology, 38(4), 407-410.

Westen, D. (1998). The scientific legacy of Sigmund Freud: Toward a psychodynamically informed psychological science. Psychological Bulletin, 124(3), 333-371.

Wheatley, J., & McGrath, J. (1997). Co-occurrence of executive impairment and amnesic syndrome following subarachnoid haemorrage: a case study. Cortex, 33, 711-721.

Whyte, J., Hart, T., Schuster, K., Fleming, M., Polansky, M., & Coslett, H.B. (1997). Effects of methylphenidate on attentional function after traumatic brain injury: A randomized, placebo-controlled trial. American Journal of Physiotherapy and Medical Rehabilitation, 76, 440-450.

Wichmann, T., & DeLong, M.R. (1993). Pathophysiology of parkinsonian motor abnormalities. In H. Narabayashi, T. Nagatsu, N. Yanagisawa, & Y. Mizuno (Eds.), Advances in neurology. (pp. 53-61). New York: Raven Press.

Wickelgren, I. (1997a). Getting a grasp on working memory. Science, 275, 1580-1582.

Wickelgren, I. (1997b). Getting the brain's attention. Science, 278, 35-37.

Wise, R.A. (1996). Neurobiology of addiction. Current Opinion in Neurobiology, 6, 243-251.

Wood, N. (1997). Genetic aspects of parkinsonism. Bailliere's Clinical Neurology, 6(1), 37-50.

Wright, M.J., Burns, R.J., Geffen, G.M., & Geffen, L.B. (1990). Covert orientation of visual attention in Parkinson's disease: an impairment in the maintenance of attention. Neuropsychologia, 28(2), 151-159.

Wu, M., Hrycyshyn, A.W., & Brudzynski, S.M. (1996). Subpallidal outputs to the nucleus accumbens and the ventral tegmental area: anatomical and electrophysiological studies. Brain Research, 740(1-2), 151-161.

Yamaguchi, S., & Knight, R.T. (1991). P300 generation by novel somatosensory stimuli. Electroencephalography and Clinical Neurophysiology, 78(1), 50-55.

Yamanaka, K., Fukuyama, H., & Kimura, J. (1996). Abulia from unilateral capsular genu infarction: report of two cases. Journal of the Neurological Sciences, 143, 181-184.

Yokel, R.A., & Wise, R.A. (1975). Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. Science, 187, 547-549.

Zacks, J.L., & Zacks, R.T. (1993). Visual search assessed without reaction times: a new method and an application to aging. Journal of Experimental Psychology: Human Perception and Performance, 19(4), 798-813.

Zigmond, A.S., & Snaith, R.P. (1983). The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica, 67 , 361-370.

Appendix A: Guide to Abbreviations Used in this Thesis

Listed below are many of the abbreviations used within this thesis and the full meaning. Anatomical abbreviations are listed separately below Figure 1. Abbreviations that have been used in the thesis but are not listed below include chemical abbreviations that are rarely presented in their full form (e.g. L-Dopa) and standard abbreviations used in psychology, (e.g. PET, SD).

AD: Alzheimer's Disease

ADL: Activities of Daily Living

AES-R: Apathy Evaluation Scale - Researcher rated

AES-S: Apathy Evaluation Scale - Self rated

BDI: Beck Depression Inventory

BSRT: Buschke Selective Reminding Test

CAMCOG: Cambridge examination of Cognition in the elderly

CARROT: Card Arranging Reward Responsivity Objective Test

EBS: Electrical Brain Stimulation

FAS: verbal fluency for the letters F,A and S

GDB: Goal Directed Behaviour

GMT: Goal Management Training

HA: Harm Avoidance

HADS: Hospital Anxiety and Depression Scale

LPSA: Loss of Psychic Self-Activation

MMSE: Mini-Mental State Examination

MRP: Movement Related Potential

NART: National Adult Reading Test

NPI: NeuroPsychiatric Inventory

NS: Novelty Seeking

P: Persistence

PD: Parkinson's Disease

PD-HA: Parkinson's Disease with High Apathy

PD-LA: Parkinson's Disease with Low Apathy

PPI: Percentage Participation Index

PSP: Progressive Supranuclear Palsy

RD: Reward Dependence

RD-P: Reward Dependence calculated without the Persistence sub-scale

SAS: Supervisory Attentional System

SHPS: Snaith-Hamilton Pleasure Scale

TPQ: Tridimensional Personality Questionnaire

TYR: the patient reported in Chapter 7

WCST: Wisconsin Card Sorting Test

Appendix B: Structure and Administration of the Apathy Evaluation Scale

The AES can be administered either as a self-report questionnaire given to the subject for completion (AES-S) or as part of a semi-structured clinical interview (AES-R). In both situations, the same 18 closed-response statements are presented and the subject indicates their level of agreement. Responses are scored on a 4 point Likert scale (1-4) with higher scores indicating higher apathy. In addition, when administering the researcher rated version two additional open-ended instructions are given. These are not scored but are used to gain information on interests, expression and enthusiasm that can guide decisions by the researcher on how to interpret the 18 main responses.

The first open-ended instruction is:

"To begin, tell me about your current interests. Tell me about anything that is of interest to you. For example, hobbies or work; activities you are involved in or would like to do; interests within the home or outside; with other people or alone; interests that you may be unable to pursue, but which are of interest to you".

The second open-ended instruction is:

"Now I'd like you to tell me about your average day. Start from the time you wake up to when you go to bed in the evening".

The researcher notes the number of activities, the detail offered, the intensity and emotion of the descriptions, etc.

The 18 closed-response statements are:

1. *"You are interested in things"*
2. *"You get things done during the day"*
3. *"Getting things started on your own is important for you"*
4. *"You are interested in having new experiences"*
5. *"You are interested in learning new things"*
6. *"You put little effort into anything"*
7. *"You approach life with intensity"*
8. *"Seeing a job through to the end is important to you"*
9. *"You spend time doing things that interest you"*
10. *"Someone has to tell you what to do each day"*
11. *"You are less concerned about your problems than you should be"*
12. *"You have friends"*
13. *"Getting together with friends is important to you"*
14. *"When something good happens you get excited"*
15. *"You have an accurate understanding of your problems"*
16. *"Getting things done during the day is important to you"*
17. *"You have initiative"*
18. *"You have motivation"*

Subjects are encouraged to give descriptive answers including examples or explanations, as well as a response on the Likert scale. For questions 3, 8, 13 and 16 the subjects' response is recorded. For the remaining items the researchers opinion is recorded, this is based on the response of the subject to the specific statement, but also

observations made of the answers given to the open-ended instructions. Further details on administration of the AES-R are given in Marin et al. (1991).

Appendix C: Details of the Hoehn and Yahr Parkinson's Disease Progression Scale

The Hoehn and Yahr scale is the most widely used method for the description of severity and presence of symptoms in PD. Stages do not represent the length of time that the disease has progressed but describe the presence of PD specific symptoms that are know to develop sequentially. In its initial form five clinical stages were identified and described accordingly on a five-point scale (Hoehn & Yahr, 1967). However, it has become more common to include two further stages (1.5 and 2.5) within the scale. This seven level equivalent is still described on a scale between one and five and represents a refinement and not a change in description. The seven level version has become standard within PD research as it is included in the Unified Parkinson's Disease Rating Scale (Fahn, Elton, & Members of the UPDRS Development Committee, 1987), the system used in the majority of PD drug trials.

The Hoehn and Yahr scale was designed for use in the clinic and is therefore based on observations of the presence of certain symptoms and signs. Stage 1 indicates only minor, unilateral, signs of disease. Typically, this would involve tremor of one hand but not the other and loss of arm swing in the same limb. If limb symptoms are unilateral but there is evidence of axial involvement (e.g. stooped posture) then this would indicate stage 1.5 is appropriate.

Stage 2 is indicated by the bilateral presence of symptoms but without any impairment of balance. Balance impairment can be noted by patient reports of recent falls or observing the patient walk a short distance and then turn 180 degrees. If the patient indicates difficulties with balance ability, the 'pull test' is performed in which the patient

is gently pulled quickly with warning from behind by pressure to the shoulders. If the patient is able to recover then they are considered to be in Stage 2.5.

Failure to recover on the pull test and reports of falls indicate more advanced disease. If the patient is still physically independent, they are considered at Stage 3 disease. If the level of impairment has significantly affected independence but the patient is still able to stand or walk unassisted they are considered to be at Stage 4 disease. Stage 5 disease is appropriate when symptoms are severe enough to render the patient wheelchair or bed bound.

Appendix D: Details of the ADL Assesment Used in Chapter 3

The ADL assesment used was originally developed to match arthritis and PD patients on day to day physical difficulties in studies of depression (Brown et al., 1988; Gotham et al., 1986). This is a 24 item self-rated scale, covering various aspects of everyday life that are likely to be influenced by a chronic illness such as PD or OA. Items cover activities involving manual dexterity for example 'cut food with a knife and fork' to mobility for example, 'get up from a chair'. Subjects are asked to rate their own ability to perform each activity on a Likert scale from 1-'alone without difficulty' to 5-'unable to do at all'. Scores therefore can potentially range between 24 and 120.

In order to take into account fluctuations in functional ability patients are asked to rate according to how they would expect to perform in general. They are further instructed to consider how they would perform each activity without any special aids such as an electric toothbrush or walking frame. The emphasis within the scale is on what the patients are capable of, not what they actually choose to do. Gotham et al. (1986) provide median averages for healthy controls and patients with arthritis and PD. These are shown below.

Group	Sample Size	Mean Age in years (SD)	Median ADL Score
Control	100	64 (9.5)	25.6
Arthritis	57	57 (13)	53.0
PD	187	64 (9.6)	46.8

The actual questionnaire is shown below.

Using the scale opposite, place a number between 1 & 5 next to each activity below to indicate how difficult you find it. If you are more able at some times of the day, indicate how you are in general at the times when you would normally perform the activity. If you use a frame or walking stick or any other special aids (including electric tin openers and toothbrushes etc.), please answer according to how you would manage without the aid. Please answer all questions.

Scale

1. Able to do alone without difficulty
2. Able to do alone with a little effort
3. Able to do alone with a lot of effort or with a little help
4. Able to do but only with a lot of help
5. Unable to do at all

Get out of bed	
Get up from an armchair	
Walk outside (eg to local shops)	
Travel by public transport	
Walk up stairs	
Walk down stairs	
Wash face and hands	
Get into a bath	
Get out of a bath	
Get dressed	
Get undressed	
Brush your teeth	
Open tins	
Pour milk from a carton or bottle	
Make a cup of tea or coffee	
Hold a cup and saucer	
Wash and dry dishes	
Cut food with a knife and fork	
Pick up an object from the floor	
Insert and remove an electric plug	
Dial a telephone	
Hold and read a newspaper	
Write a letter by hand (not type)	
Turn over in bed	

Appendix E: Description and Scoring Methods of Cognitive Assessments Used in Chapter 3

Given below are details of the executive tasks employed and also the structure of the CAMCOG assesment including the methods used for deriving sub-scale scores.

Verbal Fluency (FAS)

This is an assesment of the subjects ability to produce English words beginning with particular letters and is considered to be a test sensitive to frontal lobe impairment (Benton, 1986). The subject is asked to say as many English words as they can think of beginning with the letter 'F', they are further instructed that names of people or places do not count. They are given one minute to perform this task and the experimenter writes down each word spoken. This procedure is then repeated with the letter 'A' and finally the letter 'S'. The final score is the total number of different appropriate words produced divided by 3 (to give an average production performance for a single trial).

Category Fluency

Category fluency is similar to the FAS task described above but requires words to be produced from a specified category with no constriction on initial letter. In this thesis only one category was used, 'Animals'. The subject is asked to say as many animals as they can think of. They are given one minute to perform this task and the experimenter writes down each word spoken. The score derived as an executive function measure is the total number of appropriate different words produced. The category of 'Animals' is interpreted broadly and names of types of bird, fish etc are considered appropriate. This test also makes up part of the language sub-scale of the CAMCOG examination

described below. However, for the CAMCOG total and sub-scale score a different scoring system is employed as shown below:

Number of Words Produced	Score
0	0
1-4	1
5-9	2
10-14	3
15-19	4
20-24	5
25 or more	6

Stroop Task

Multiple versions of the Stroop task are currently in use (see e.g. Golden, 1978; Trenerry, Crosson, DeBoe, & Leber, 1989). The method used in this thesis is equivalent to that described by Golden (1976, 1978) but the actual implementation involved materials produced for studies of cognitive function in Huntington's disease patients who had received intracerebral tissue grafts (Huntington Study Group, 1996). Norm data is available in the test manual (Golden, 1978). This version consists of three conditions. In the first the subject is presented with a sheet of 100 colour bars (red, blue or green) in a 10 by 10 matrix on a white sheet of A4 paper and asked to say as quickly as possible the colour of each bar as if reading as text (i.e. from left to right on each line). In the next condition, the colour words are presented written in black ink and the subject is asked to read the words as quickly as possible. In the final condition the subject is asked to name the colour of the ink that the word is written in, however, the word meaning is always incongruent to the colour of the ink (e.g. the word 'BLUE' written in red ink).

In each condition, the subject is only given 45 seconds to attempt to complete the task. If errors are made that are not self-corrected by the subject, this is pointed out to them and then they continue. The raw data consists of the total number of items correctly articulated by the subjects. The performance on the final condition gives a measure of executive control as this involves inhibiting the prepotent response of simply reading the word. However, in addition it is possible to derive measures that control for rate of production by either subtracting the interference condition score from the simple colour naming score or by calculating a ratio by dividing the interference condition score by the colour naming score. The first of these, the subtraction method is recommended in the Stroop manual (Golden, 1978). However, for neuropsychological research or research in which there are age differences this method can be misleading. For example a subject who completes 10 items in one condition and 20 in the other has performed quite differently to a subject who completes 40 items in one condition and 50 in the other, though both would score '10' on the subtraction method. For this reason the ratio method is the preferred statistic for research in which there is a possibility that one group may be generally slower than others, as this provides a better method of controlling for the rate of verbal output (Macleod & Prior, 1996). In this thesis, results using both methods are reported.

Wisconsin Card Sorting Test (WCST)

The WCST is probably the most often used neuropsychological test of frontal lobe function, and as with other commonly used assessments, there are several implementations. The version used in this thesis is the widely used 'short version' (Nelson, 1976). The standard WCST involves subjects being presented with four abstract key cards that differ from each other in terms of the shapes on them, the number of shapes and the colour of the shapes. The subject is then given further cards

that they have to sort into piles below the key cards in terms of rules that they have to discover themselves. Feedback is given by the administrator, but without warning the rule is changed and so previously correct responses become incorrect responses, the rules are; shape, colour and number (Grant & Berg, 1948). The Nelson (1976) version of the test uses the same set of stimuli materials but attempts to avoid some of the difficulties with the initial Grant and Berg version. For example, only cards that can unambiguously be matched to one key card are used. In the original many cards matched the key cards by more than one category such as being both the same shape and colour.

The Nelson version has the advantage that it is clearer what the subject's intention was and the test is shorter. This second point is important as failure on the WCST can be stressful to subjects and a shorter administration is desirable. Furthermore, in the Nelson version of the test, less emphasis is placed on potentially stressful negative feedback. Unlike in the original version, the subject is told in advance that a rule is about to be changed. The first category chosen (i.e. colour, shape or number) is always considered correct and this defines the first rule. After six successive correct responses with this rule the subject is told that rule is changed and the next category chosen is considered correct and this defines the second rule etc. Further information and norm data is provided by Nelson (1976).

CAMCOG and MMSE

The CAMCOG is the cognitive section of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX, Roth et al., 1988). This assesment battery was designed to detect different aspects of cognitive and psychiatric disorder associated with ageing, including various forms of dementia. The CAMCOG section contains all 19

items of the Mini-Mental State Examination (MMSE, Folstein & Folstein, 1975) plus other items that it was considered were not fully evaluated by the MMSE. However, it follows the general style of administration of the MMSE in that multiple questions and simple tasks are employed that are marked by a simple category such as correct yes/no or number of errors. The MMSE contains items that assess cognitive skills often impaired in patients with dementia such as orientation (What year is it?) and memory (recall of items named previously). The range of potential scores on the MMSE is 0-30.

The additional items in the CAMCOG allow a more in-depth assesment of memory skill such that both remote and recent memory and recall and recognition are tested. Furthermore, there is greater emphasis placed on skills not closely related to memory or orientation, such as praxis and perception. The full CAMCOG examination contains 60 items, 14 of these are common to the MMSE, while five are included in the full MMSE score but not the CAMCOG score. In the study reported in Chapter 3, one item was missed out from the full CAMCOG as it was not relevant in the setting (identify a person near by, such as a nurse or cleaner). The range of scores obtainable on the CAMCOG as employed in this thesis is 0-107.

The larger number of items in the CAMCOG allows the derivation of sub-scale scores so that an estimate of different types of cognitive impairment can be made rather than a 'global' cognitive estimate as is the case with the MMSE. The different sub-scales are described below. The full CAMCOG score is the sum of the sub-scale scores.

CAMCOG Sub-Scale	Range of Scores	Description	Sample Items
Orientation	0-10	Tests orientation for present time and location	"What is the date today" "Can you name two main streets nearby"
Language	0-30	Tests ability to express and use language effectively (see also 'Category Fluency' above)	"Can you touch your right ear with your left hand" "Can you tell me what an opinion is"
Memory	0-27	Assess the recall of remote and recent information and the ability to store and retrieve given information	"Who was the famous flyer who's son was kidnapped" "What was the address I asked you to write down earlier"
Attention	0-7	The ability to focus on task	"Can you take away seven from 100" (then repeated several times). "Can you count backwards from 20 for me"

This table continues on the following page.

CAMCOG Sub-Scale	Range of Scores	Description	Sample Items
Praxis	0-12	The ability to copy drawings and draw from memory and to perform actions without tools to hand	"Can you copy this picture for me" (a picture of a house). "Show me how you would brush your teeth"
Calculation	0-2	The ability to perform simple addition and subtraction	"What do these two coins add up to" "If you got this much change in a shop and you had paid with a pound, how much would you have spent"
Abstract Reasoning	0-8	The ability to see conceptual similarities between exemplars from broad categories	"Can you tell me how a plant and an animal are similar" "Can you tell me how a dress and a shirt are similar"
Perception	0-11	The ability to recognise objects (coins) by touch, and famous people or unusual view objects from vision	"I'm going to put a coin in your hand, without looking, can you tell me what it is" "Who is this" (shown photo, for e.g. of the Pope).

Appendix F: Completion Rates of Assessments Described in Chapter 3

The table below lists the completion rates for each assesment in described in Chapter 3. This shows the total number of subjects and the percentage who completed each assesment in each group.

	Group				
Assesment	**All Patients (N=62)**	**All PD (N=45)**	**OA (N=17)**	**PD-HA (N=15)**	**PD-LA (N=30)**
ADL	61 (98.4%)	44 (97.8%)	17 (100%)	14 (93.3%)	30 (100%)
MMSE	58 (93.5%)	42 (93.3%)	16 (94.1%)	14 (93.3%)	28 (93.3%)
CAMCOG	58 (93.5%)	42 (93.3%)	16 (94.1%)	14 (93.3%)	28 (93.3%)
Letter Fluency	60 (96.8%)	43 (95.6%)	17 (100%)	14 (93.3%)	29 (96.7%)
Category Fluency	60 (96.8%)	43 (95.6%)	17 (100%)	15 (100%)	28 (93.3%)
Stroop Task	56 (90.3%)	40 (88.9%)	16 (94.1%)	13 (86.7%)	27 (90%)
WCST	52 (83.9%)	39 (86.7%)	13 (76.5%)	11 (73.3%)	28 (93.3%)
BDI	57 (91.9%)	44 (97.8%)	13 (76.5%)	14 (93.3%)	30 (100%)
HADS	52 (83.9%)	38 (84.4%)	14 (82.4%)	12 (80%)	26 (86.7%)
SHPS	57 (91.9%)	42 (93.3%)	15 (88.2%)	12 (80%)	30 (100%)
TPQ	54 (87.1%)	41 (91.1%)	13 (76.5%)	13 (86.7%)	28 (93.3%)