Attention and novelty processing in stroke and Parkinson's disease

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Declaration

I, Victoria Singh-Curry, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that it has been indicated in the thesis.

Acknowledgements

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Abstract

The ventral fronto-parietal network has been considered to play a crucial role in reorienting attention towards significant environmental events, while the dorsal system is thought to be dominant in controlling goal-directed behaviour (Corbetta and Shulman 2002). I begin by reviewing literature which suggests this distinction may not be so clear cut and suggest my own scheme which takes into account this evidence (Singh-Curry and Husain 2009). Specifically, ventral areas, particularly the right inferior parietal lobe (IPL), appear to be activated by tasks involving sustained attention, responding to salient task-relevant events, detecting novel stimuli and switching between tasks. Accordingly, I hypothesise that the right IPL may play a crucial role in reconfiguring behaviour between a task-engaged state and a more exploratory mode of functioning, which permits the identification of potentially important novel events.

The first few chapters of my thesis aimed to test this hypothesis by examining attention deficits in stroke patients with hemispatial neglect, the syndrome which frequently occurs following damage to the right IPL. These patients were shown to have difficulty sustaining attention over time, even when no spatial shifts of attention were required. This deficit in sustained attention was particularly evident for stimuli of lower perceptual salience. More importantly, however, these deficits were found to interact with each other, as well as the direction of spatial attention, suggesting that these functions may be dependent on an interrelated brain network. Consistent with this notion, the results of lesion-symptom analysis indicated that the Right IPL and ventral attention network

appears to be crucial in the mediation of all of these processes, including the processing of novel stimuli, supporting my hypothesis.

The detection of novel events has also been found to activate the midbrain dopaminergic system (Bunzeck and Duzel 2006), while the principal pathological feature of Parkinson's disease (PD) is degeneration of these neurons (Hornykiewicz 1998). Although PD is traditionally considered a disorder of movement, more recently it has been recognised that there may be associated cognitive deficits, including disorders of impulse control (Weintraub 2008). At present, however, the factors which predispose some individuals with PD to develop such problems are unclear.

Accordingly, in the second part of my thesis, I examined novelty processing and risk-taking behaviour in PD in order to identify subgroups which may be particularly vulnerable to developing impulse control problems. In addition to PD patients with impulse control disorders (ICD), those who were classified as akinetic-rigid, as opposed to tremor dominant – without ICD – were found to process novelty more quickly than non-novel perceptually salient stimuli, unlike tremor dominant PD patients. Novelty seeking was found to be associated with relative preservation of the mesolimbic dopaminergic system in patients without ICD, while increased risk-taking was associated with preservation of the mesolimbic system in ICD patients. Mesolimbic sparing, in addition to the akinetic-rigid motor phenotype of PD may therefore increase susceptibility to impulse control problems in PD.

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Chapter 1

The principal aim of this thesis will be to explore some of the functions attributable to the right inferior parietal lobe (IPL). Ever since the time of the early lesion studies (Brain 1941; Paterson and Zangwill 1944), the right IPL has been considered vital in the mediation of visuospatial processes, with lesions here leading to '… a complex disorder affecting perception, appreciation and reproduction of spatial relationships …' page 337 (Paterson and Zangwill 1944) and a tendency to neglect the contralesional side of space. However, as will be seen in the first part of this introductory chapter, the right IPL also appears to play an important role in *non-spatial* attentional processes, such as the ability to sustain attention, detect salient stimuli and reorient attention to novel events.

Two influential theories of *cortical visual processing* (Ungerleider and Mishkin 1982; Milner and Goodale 1995), which have segregated cortical pathways into dorsal and ventral streams, have attempted to incorporate the visuospatial aspect of IPL function. These dichotomies, however, do not address the non-spatial components of IPL functionality, while more recent formulations of the cortical *control of visual attention* (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008) fail to capture the full extent of the role played by this region.

I will therefore begin this chapter by discussing the limitations of some of these existing proposals, with particular regard to the right IPL, before reviewing the literature on the non-spatial processes which may be attributed to this region. I will then proceed to

develop my own scheme of IPL function which I hope takes into account more of the extant experimental findings than do these previous theories.

The disorder that frequently occurs following damage to the right IPL is that of hemispatial neglect (Vallar and Perani 1986; Mort, Malhotra et al. 2003). The most characteristic deficit of patients with this condition is an inability to orient to stimuli and events that occur to the contralesional side of space (Heilman 1992; Heilman, Valenstein et al. 2000; Kerkhoff 2001; Buxbaum, Ferraro et al. 2004; Milner and McIntosh 2005). Neglect, however, is not a unitary disorder, but rather a syndrome. Patients may neglect the contralesional side of their own body (personal neglect), near space (peripersonal neglect) or distant space (extrapersonal neglect) (Buxbaum, Ferraro et al. 2004). Some are primarily deficient at attending to and perceiving objects in contralesional space, despite not having any primary sensory disorder, while others may show little spontaneous use of their contralesional limb (motor neglect), even though that limb may be reasonably strong (Fink and Marshall 2005). Furthermore, individual patients may show different combinations of neglect behaviour and different patterns of deficit on cognitive tests (Buxbaum, Ferraro et al. 2004). Importantly, more recently it has also become apparent that non-spatial deficits, such as the ability to sustain attention, may also be involved in neglect (Hjaltason, Tegner et al. 1996; Samuelsson, Hjelmquist et al. 1998; Robertson 2001; Husain and Rorden 2003).

Such variation may be based on the known heterogeneity of the brain lesions involved in producing the syndrome (see Figure 1.1). Although the right IPL is the region most

consistently implicated in the pathogenesis of neglect (Vallar and Perani 1986; Mort, Malhotra et al. 2003), damage to the inferior frontal lobe is also common (Husain and Kennard 1996). However, subcortical strokes too may lead to neglect due to remote effects, for example by causing hypoperfusion of overlying cortical regions or because of disconnection of parieto-frontal circuits (Karnath, Himmelbach et al. 2002; Hillis, Newhart et al. 2005). Other studies have also suggested a role for lateral (Karnath, Ferber et al. 2001) or medial temporal lesions in the right hemisphere (Mort, Malhotra et al. 2003; Bird, Malhotra et al. 2006). Even within the classically implicated inferior parietal and inferior frontal regions, the extent of lesions can vary considerably, and because these regions have multiple functions, the exact combinations of deficits observed is likely to vary according to the distribution of the lesion and its distant effects.

Nevertheless, the use of lesion-symptom analysis techniques to probe for voxels that are significantly associated with particular deficits can surmount the inherent difficulty of using individuals with large lesions and provide important information regarding the essential nature of brain regions in the mediation of cognitive processes (Rorden, Karnath et al. 2007). In this thesis I employ such techniques in groups of right hemisphere stroke patients, with and without neglect, to examine the role of the right IPL in several non-spatial functions: sustaining attention and encoding stimulus salience (Chapters 2 and 3), as well as the processing of stimulus novelty (Chapter 5). The first half of this introduction discusses the motivation for these studies.

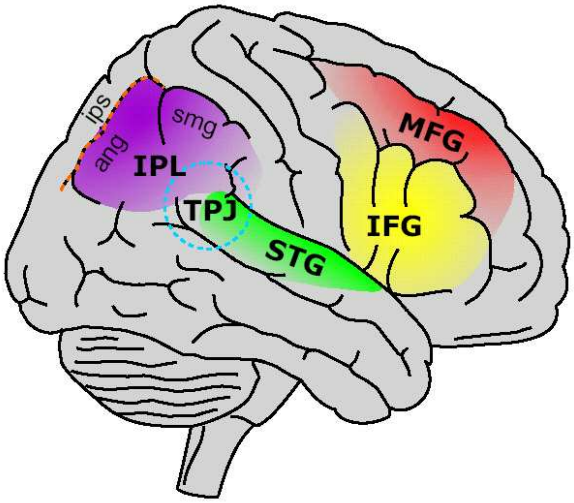


Figure 1.1. The anatomy of hemispatial neglect.

A variety of cortical lesions can lead to the syndrome of neglect, particularly lesions of the right IPL and IFG.

ang: angular gyrus, IFG: inferior frontal gyrus, IPL: inferior parietal lobe,
ips: intraparietal sulcus, MFG: middle frontal gyrus, smg: supramarginal gyrus, STG: superior temporal gyrus

In the latter half of this introductory chapter, I discuss how the ability to reorient attention to potentially important novel stimuli is also associated with activation of the mesolimbic dopaminergic system (Bunzeck, Schutze et al. 2007). Parkinson's disease is a neurodegenerative condition which is characterised by loss of dopaminergic neurons in the midbrain (Hornykiewicz 1998). Although Parkinson's disease is primarily a disorder of movement control, cognitive problems in this population have more recently been recognised; including the development of impulse control disorders, such as pathological gambling and compulsive medication overuse (Potenza, Voon et al. 2007; Aarsland, Bronnick et al. 2009). This has frequently been attributed to the use of particular dopamine agonists in the literature to date (Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007), but this argument fails to explain why some patients develop such problems, while others do not. I will argue in this chapter that there may be differences in susceptibility to impulse control disorders in different subgroups of Parkinson's disease and later in the thesis will investigate how disorders of impulse control may relate to risk-taking behaviour and alterations in novelty processing (Chapters 6 and 7).

Of course, in addition to involving degeneration of the midbrain dopaminergic system, Parkinson's disease may also be associated with cortical changes, particularly affecting frontal and parietal regions (Beyer, Janvin et al. 2007). Alterations in novelty processing in Parkinson's disease may therefore also result from these changes. To begin with however, I will now discuss existing models of visuo-attentional processing, in order to provide a background for my own proposal regarding IPL functionality.

1.1. The position of the inferior parietal lobe within visual processing streams

There have been numerous influential attempts to segregate the cortical visual system into dorsal and ventral streams of processing. Ungerleider and Mishkin originally proposed that the dorsal stream, connecting visual cortex with the posterior parietal cortex (PPC), is dedicated to the processing of *spatial* information and termed this the *'where'* pathway (Ungerleider and Mishkin 1982; Mishkin, Ungerleider et al. 1983). This was in contrast to the ventral stream, extending from occipital to inferotemporal cortex, which they considered to mediate object identification: the *'what'* pathway. However, subsequent evidence suggested that both streams manipulate information about the nature of objects and their location in space and the dichotomy was revised by Milner and Goodale. According to their model, the dorsal stream is responsible for the visual control of action, while the ventral pathway is concerned with producing enduring perceptual representations of the surrounding world (Milner and Goodale 1995).

In Milner and Goodale's view, the dorsal *vision-for-action* system operates in real time, computing the absolute metrics of a target and its position in egocentric coordinates to allow accurate eye and limb movements (Milner and Goodale 1995; Goodale, Westwood et al. 2004). This dorsal system delivers information directly to the motor system for immediate reaching, grasping or eye movements. In contrast, the ventral stream is specialised for *vision-for-perception* and may also have a role in movement planning based on memory of an object and its relationship to other items. While aspects of this model capture important features of the functional architecture of the cortical visual

system, there remains a sense of unease about how well the model accommodates all findings; a point recently acknowledged by Milner and Goodale themselves (Milner and Goodale 2008).

A crucial area of controversy is the proposed function of the human IPL and whether this region fits easily into either of the dorsal-ventral dichotomies. This may in part be because the studies on which this functional segregation was based were performed in the monkey, in which there is no clear homologue of the human IPL (Orban, Van Essen et al. 2004; Husain and Nachev 2006). There appears to be an asymmetry of function between the cerebral hemispheres in the human, which is not evident in the monkey, a point that is pertinently made by consideration of two very different syndromes which occur following IPL damage: limb apraxia after left-sided lesions (De Renzi, Motti et al. 1980; Haaland, Harrington et al. 2000) and hemispatial neglect secondary to right IPL damage (Vallar and Perani 1986; Mort, Malhotra et al. 2003). Neither of these human syndromes have a clear equivalent, in terms of severity or functional impact, in the monkey.

I will begin by considering some aspects of the Milner and Goodale model, focussing on those which deal with IPL function. This will be followed by an examination of other recent formulations, which have dealt more specifically with IPL functionality. In all of these discussions, the focus will be on the proposed function of the right IPL, because my interest in this thesis is to consider the cognitive deficits that follow damage to this area. I will then go on to consider data, not dealt with well by any of the existing schemes of cortical visual processing, which suggests that the right IPL is involved in the detection of

salient new events in the environment, as well as in sustaining attention on task goals, even in situations that do not require visual guidance of action or spatial shifts of attention.

On the basis of this evidence, I propose a novel hypothesis (Singh-Curry and Husain 2009): that a primary function of the right IPL is in both *maintaining* attention on current task goals, and encoding *salient* events in the environment so that task-sets can be quickly *reconfigured* to deal with new challenges. These aspects of attentional control, traditionally considered to be solely the remit of frontal structures, are crucial for maintaining focus on a task in the face of distraction, and conversely also for flexibly switching to new external demands should that be necessary for optimal guidance of behaviour.

I will argue that the right IPL is a crucial node in a fronto-parietal system, which has often been associated independently by various authors with *sustaining attention* (Pardo, Fox et al. 1991; Johannsen, Jakobsen et al. 1997; Hager, Volz et al. 1998; Sturm, de Simone et al. 1999; Adler, Sax et al. 2001; Vandenberghe, Gitelman et al. 2001; Sturm, Longoni et al. 2004), *detecting salient or novel events* (Linden, Prvulovic et al. 1999; Clark, Fannon et al. 2000; Marois, Leung et al. 2000; Kiehl, Laurens et al. 2001; Huang, Lee et al. 2005; Kiehl, Stevens et al. 2005; Lagopoulos, Gordon et al. 2006; Gur, Turetsky et al. 2007; Williams, Felmingham et al. 2007), *phasic alerting* (Fan, McCandliss et al. 2005; Thiel and Fink 2007) and *switching between task-sets* (Buchsbaum, Greer et al. 2005). It is my view that these behaviours are all different aspects of a cognitive system dedicated to allocating resources optimally, to either current behavioural goals, or reconfiguring goals

to novel, salient challenges presented in the environment. I will attempt to integrate available evidence with these ideas in order to form a coherent proposal, which will be tested in later chapters of this thesis.

1.1.1. The IPL in Milner and Goodale's dorsal-ventral dichotomy

Much of the supporting evidence for Milner and Goodale's perception-action model comes from double dissociations between two pathological deficits of visual function: optic ataxia and visual agnosia. Optic ataxia refers to the condition in which patients experience difficulty in the *on-line control* of reaching movements to visual targets (Jeannerod 1986; Perenin and Vighetto 1988), but suffer no problems in correctly identifying such objects, and actually perform reaching movements more accurately when they can use information from memory (instead of on-line visual input) to guide their actions (Milner, Dijkerman et al. 2003). In contrast, visual agnosia is characterised by a deficit in object perception and recognition, with intact visual control of actions (Milner, Perrett et al. 1991; Milner 1997). Optic ataxia usually occurs following lesions of superior parietal areas (within the dorsal stream) (Auerbach and Alexander 1981; Perenin and Vighetto 1988; Jeannerod, Decety et al. 1994; Buxbaum and Coslett 1998), while visual agnosia is associated with temporal lesions (in the ventral stream) (Farah 1995; Milner 1995). This evidence has not gone without criticism, with some authors even going as far as to suggest that these double dissociations do not exist at all (Pisella, Binkofski et al. 2006), although Milner and Goodale have recently countered some of these arguments (Milner and Goodale 2008). My prime area of dispute however, relates to the IPL, which is all I shall be concerned with here.

The original anatomical studies leading to the exposition of the two segregated cortical pathways were all performed on the monkey brain (Ungerleider and Mishkin 1982; Mishkin, Ungerleider et al. 1983; Ungerleider and Desimone 1986; Distler, Boussaoud et al. 1993). The ventral pathway projects from the striate cortex to the inferior temporal lobe, while the dorsal pathway terminates in the PPC, which is divided into the SPL and IPL, respectively by the intraparietal sulcus (IPS). In the monkey, the dorsal pathway is considered to extend into the IPL. However, Milner and Goodale proposed that in humans, the dorsal stream terminates in the SPL and IPS, and does not project as far as the IPL. Such a view would be consistent with Brodmann's scheme (based on cytoarchitechtonic observations) that the human superior parietal region contains the homologue of the monkey IPL (Brodmann 1909). However, this leaves the human IPL unaccounted for in terms of the original dorsal-ventral dichotomy (Husain and Nachev 2006) – see Figure 1.2.

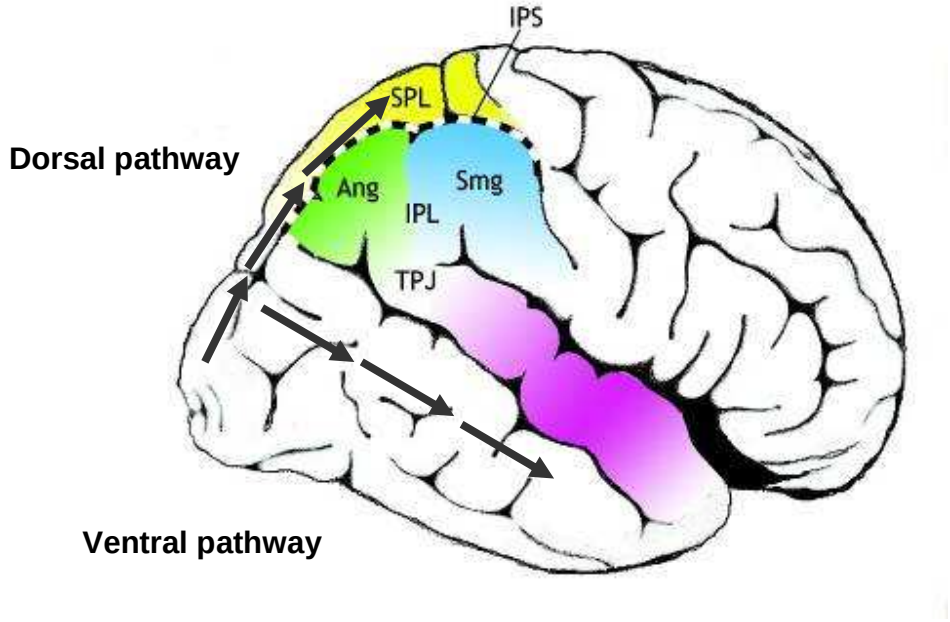
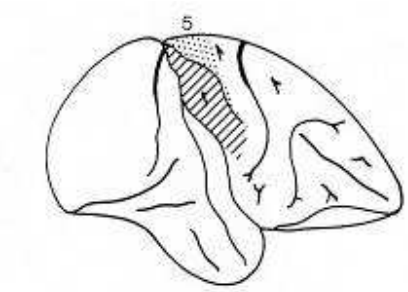


Figure 1.2. The human IPL does not fit into either the dorsal or ventral stream (from Husain & Nachev, 2006).

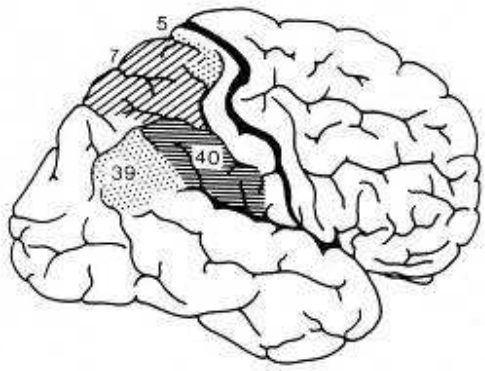
In humans, it has been suggested that the dorsal pathway extends from primary visual cortex to terminate in the SPL and IPS. On the other hand, the ventral stream projects to the inferotemporal cortex. This leaves the IPL unaccounted for in terms of this dichotomy.

The black arrows indicate the proposed pathways of the dorsal and ventral streams. Ang: angular gyrus, IPL: inferior parietal lobe, IPS: intraparietal sulcus, Smg: supramarginal gyrus, SPL: superior parietal lobe, TPJ: temporoparietal junction.

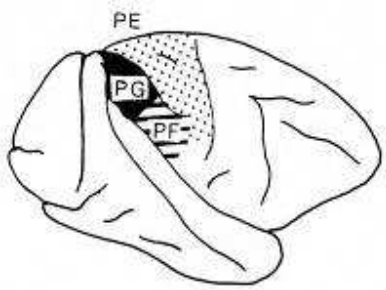
Homology between the human and monkey PPC has been a controversial issue. Von Bonin and Bailey (Von Bonin and Bailey 1947) drew parallels between the SPL and IPL in both species (see Figure 1.3). Their parcellation of the monkey PPC closely corresponds to that of the human, according to von Economo's analysis (Von Economo 1929). This has led more recent investigators, such as Rizzolatti and Matelli to suggest that homology between the monkey *IPL* and human *SPL* would imply a jump of the IPL across the IPS during the course of evolution, which they consider to be highly unlikely (Rizzolatti and Matelli 2003). Instead, they draw parallels between the SPL in humans and monkeys, and the IPL across both species. In their view, these regions are largely homologous. The issue of homology of parietal sub-regions will be discussed more thoroughly later on, when an alternate scheme of visual processing, advanced by Rizzolatti and Matelli, is examined.



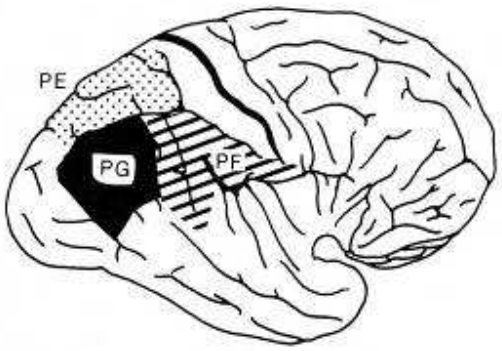
Brodmann – monkey



Brodmann – man



von Bonin and Bailey – monkey



von Economo – man

Figure 1.3. Anatomy of monkey and human posterior parietal cortex

According to Brodmann's examination of the monkey and human posterior parietal cortex, there is no monkey homologue of the human IPL. In contrast, von Bonin and Bailey's parcellation of the monkey posterior parietal cortex corresponds closely to that of the human as outlined by von Economo – here the monkey SPL and IPL are homologous to the human SPL and IPL.

Milner and Goodale speculated that the *human* IPL may be a high-level spatial representation system which subserves perceptual awareness by transforming information derived from both streams, but *predominantly* the ventral stream (Milner and Goodale 1995). This hypothesis is consistent with some of the object-related phenomenology that has been associated with hemispatial neglect (McIntosh, McClements et al. 2004; McIntosh, McClements et al. 2004), the syndrome that often follows lesions of the IPL and temporoparietal junction (TPJ), particularly in the right hemisphere (Vallar and Perani 1986; Heilman and Watson 2001; Mort, Malhotra et al. 2003).

Although most investigators consider hemispatial neglect to be a multi-faceted disorder, with several potential components (Samuelsson, Hjelmquist et al. 1998; Robertson 2001; Husain and Rorden 2003; Buxbaum, Ferraro et al. 2004), the most obvious problem in many patients with the syndrome consists of an inability to attend to events occurring in the contralesional side of space. Milner and Goodale's theory of IPL function (Milner and Goodale 1995) gives a good account of 'object-centred' neglect, where patients may fail to attend to the left *side of objects*, regardless of their location in space. This phenomenon is relatively rare, however. In contrast, Milner and Goodale do not offer explanations for potentially more common spatial deficits in neglect: often conceptualised as impairments in egocentric spatial representation, directing attention or planning movements (Heilman 1992; Bisiach 1993; Mesulam 1999; Heilman, Valenstein et al. 2000; Kerkhoff 2001).

It has previously been suggested on the basis of patient studies, that right IPL damage may be associated with directing movements into the contralesional side of space – *directional*

hypokinesia (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000). However, lesions in those studies involved white matter as well as cortical regions. Thus, although maximal lesion overlap may have been in the IPL, fibres of passage from, for example, neighbouring structures such as the IPS (that are known to hold motor representations (Culham and Valyear 2006)) might also have been involved.

Additionally, it is becoming increasingly apparent that *non-spatial* cognitive processes may also contribute to the neglect syndrome, for example the ability to sustain attention or encode stimulus salience (Robertson 2001; Husain and Rorden 2003; Nachev and Husain 2006). I will consider these processes in more detail later on in a reformulation of the functions of this region; the key point here is that these processes have no manifestation in the Milner and Goodale scheme. The only attentional components they discuss in relation to their model are selective mechanisms: '…operating in the ventral stream to facilitate perceptual analysis of objects … alongside those in the dorsal stream which facilitate particular actions directed at those objects' (Milner and Goodale 1995).

In summary, the deficits which follow right IPL lesions in humans – spatial and non-spatial – make it difficult to place within the Milner and Goodale dorsal-ventral model (Husain and Nachev 2006). Similarly, damage to the left IPL in humans is associated with limb apraxia (a syndrome associated with difficulty copying or producing gestures and movements to command), which is also not dealt with easily in their scheme (Ietswaart, Carey et al. 2001). These concerns about IPL function have played a key role in the

development of alternative proposals, including the model developed by Rizzolatti and Matelli (Rizzolatti and Matelli 2003).

1.1.2. Rizzolatti and Matelli's two dorsal stream model

Rizzolatti and Matelli propose, on the basis of anatomical and functional evidence, that the dorsal visual stream is in fact formed by two subsystems (Rizzolatti and Matelli 2003). They argue that a *dorsal-dorsal* stream has the basic characteristics of Milner and Goodale's dorsal stream and includes the SPL. Thus they interpret the data on optic ataxia and imaging studies on visually guided reaching as being broadly consistent with an on-line system for action. Their major departure concerns the IPL, which they envisage as a part of a separate *ventro-dorsal* stream. In their view, this pathway plays a fundamental role in *both* perception and action. Specifically they consider the right IPL in humans to play a role in both spatial perception and action, with damage to this region causing hemispatial neglect. The left IPL, on the other hand, is thought to play a role in action recognition, grasping and manipulation, with lesions here leading to limb apraxia.

Like the original anatomical studies leading to the segregation of the cortical visual system into separate pathways (Ungerleider and Mishkin 1982; Mishkin, Ungerleider et al. 1983), Rizzolatti and Matelli's model developed from studies of the macaque visual system. As alluded to earlier, their analysis suggests to them that the IPS is functionally homologous in both macaques and humans, so it can be considered to divide the parietal cortex of both species into functionally similar SPL and IPL regions. One problem with considering that there are direct homologies between *all* areas of the macaque and human parietal cortex is

the hemispheric asymmetry that is so clear in humans and is an important part of the Rizzolatti and Matelli model. A similar difference between left and right IPL regions has never been demonstrated in macaques. This would also explain why there is no good monkey model of neglect that encompasses the severity, duration and impact on everyday functions of the syndrome observed in humans (Husain and Nachev 2006). Furthermore, there does not appear to be any report of the syndrome of limb apraxia, as observed in humans, after lesions of the macaque IPL.

A second issue is that there may be differences between how the monkey and human PPC is organised, quite apart from hemispheric asymmetries. Comparative studies show that the IPS and IPL are markedly expanded in humans compared to the macaque monkey – at a ratio at least twice that of the overall increase in the rest of the cortical surface – particularly the angular gyrus and TPJ (Orban, Van Essen et al. 2004). Functionally, there also seem to be differences in this region between the two species (Orban, Van Essen et al. 2004; Orban, Claeys et al. 2006), for example regarding analysis of 3D-structure-from-motion (Vanduffel, Fize et al. 2002). In fact, on the basis of functional magnetic resonance imaging (fMRI) studies performed in both humans and monkeys, the human IPS has been shown to contain more functional regions than the monkey IPS (Vanduffel, Fize et al. 2002; Orban, Fize et al. 2003; Orban, Claeys et al. 2006). The human IPS has been reported to have at least four motion-sensitive areas: ventral IPS, parieto-occipital IPS, dorsal IPS medial and dorsal IPS anterior; whilst the (rhesus) monkey IPS contains only one motion sensitive region (VIP) (Orban, Claeys et al. 2006). The expansion of the IPS and IPL in humans may represent the cortical correlate of characteristically human

attributes, such as tool use, which would rely on a more detailed analysis of visual information (Rushworth, Behrens et al. 2006).

A third problem with the Rizzolatti and Matelli scheme is that it has recently been claimed that the monkey IPL is not formed by just two areas (as previously thought) but by four: Opt, PG, PFG and PF (Rozzi, Calzavara et al. 2006). Each of these regions was found to display distinct sets of connections with visual, somatosensory, auditory and limbic areas; in addition to robust interconnections between themselves. This newer data suggests that Rizzolatti and Matelli's formulation may be too simplistic.

Nevertheless Rizzolatti and Matelli do attempt to address some of the issues regarding the IPL which are not really dealt with very well by the earlier models. For example they discuss the syndrome of limb apraxia in the context of the known responses of neurons in the IPL and IPS to action perception and control in the macaque. They also briefly address the spatial aspects of the neglect syndrome occurring after right IPL damage in humans. However, their account does not offer an explanation as to why individuals with neglect frequently have impairments of cognitive processes which do not have spatial perceptual or action-oriented components (Robertson 2001; Husain and Rorden 2003; Nachev and Husain 2006).

1.1.3. Glover's planning-control model

Another model attempting to explain the function of the IPL is Glover's planning-control model (Glover 2004); which bears some resemblance to Milner and Goodale's perception-

action scheme. Anatomically, the planning-control model incorporates the dorsal and ventral streams of visual processing. Where it diverges however, is in the functions it attributes to the two processing streams, and in particular to the IPL and SPL. Glover considers the IPL to form a third stream, with bidirectional input from both the dorsal and ventral pathways, responsible for the planning of movements. Planning in this proposal is quite a broad term, referring to the integration of spatial and non-spatial information about potential targets for actions, as well as the 'kinetic parametrisation' of movements, including their timing and velocity. In other words, the IPL is seen as being responsible for everything from initial goal or target selection down to the programming of the constituent phases of action. The SPL is viewed as being responsible for the on-line control of movements, comparing visual and propioceptive feedback during the course of a movement, to the action plan generated by the IPL. Milner and Goodale's model attributes action selection to visual processing in the ventral stream and IPL, but the programming of the initial parameters of movement to processing in the dorsal stream and SPL (Goodale and Milner 2004).

Glover relies heavily on studies using illusions in normal individuals to support his planning-control model. These investigations show that illusions exert a larger effect in the early phases of a movement compared to the later stages. He argues that this is because illusions primarily affect planning, rather than the on-line control of actions. It has, however, been suggested that these effects can be explained without invoking the existence of different visual representations for planning and control (Brouwer, Brenner et al. 2004) and that this evidence in itself is weak and difficult to replicate (Franz 2004;

Gaveau and Desmurget 2004). The rationale for this model is also based on neuroimaging studies. However, the investigations cited are exclusively confined to positron emission tomography (PET), which does not have the spatial resolution of fMRI. In fact there are fMRI studies which suggest that it is the dorsal stream that is responsible for the transformation of visual information into motor coordinates, and not the IPL (Connolly, Goodale et al. 2002; Culham, Danckert et al. 2003).

Although the planning-control model seems to offer a better explanation for ideomotor apraxia, caused by *left* IPL lesions, it encounters difficulty explaining the full range of deficits associated with damage to the IPL in the *right* hemisphere. Glover admits that it is difficult to show a relationship between right IPL damage and motor deficits, but that it has been shown, for example, that patients with neglect can have a motor component to their impairment in the form of directional hypokinesia (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000). However, as mentioned earlier, lesions in these studies involved white matter as well as cortical regions, and although maximal lesion overlap may have been in the IPL, fibres of passage from neighbouring structures such as the IPS might also have been involved. Moreover, this model does not consider perceptual or attentional deficits in neglect. Therefore, for all these reasons, it is my opinion that this model cannot account for the phenomenology of hemispatial neglect and hence is unable to provide an adequate account of right IPL function.

In summary, the planning-control model proposed by Glover can be heavily criticised, on the basis of the evidence used to support it, but also for being vague in terms of how it

defines the planning component. Some aspects of it may be useful in terms of defining what may be happening in the left IPL. However, regarding right IPL function it, like the Rizzolatti and Matelli model, completely fails to address non-spatial cognitive processes, (which are not action oriented – such as a non-lateralised reduction in attentional capacity) that have been found to be involved in hemispatial neglect (Samuelsson, Hjelmquist et al. 1998; Robertson 2001; Husain and Rorden 2003; Husain and Nachev 2006). These components of the neglect syndrome also need to be addressed if accounts of right IPL function are to be credible. One important move in this direction comes from a model articulated by Corbetta and Shulman for attention systems in the human brain (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008), which will be discussed next.

1.1.4. Corbetta and Shulman's goal-directed and stimulus driven streams

In their proposal, Corbetta and Shulman focused on segregating pathways from parietal to frontal cortex for different aspects of directed attention (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). Their scheme therefore does not directly assess the functional architecture from primary visual cortex to the parietal or temporal lobes. In this respect it is not concerned with the all issues dealt with by some of the proposals already discussed here. Nevertheless, it is an important model which challenges the way in which both SPL and IPL functions are viewed from a visual system perspective. Perhaps confusingly though, Corbetta and Shulman also used a dorsal and ventral distinction in their terminology, which does not map on to the traditional anatomical divisions for the visual system. Their *dorsal fronto-parietal* network incorporates the SPL, IPS and dorsal frontal cortex including the frontal eye fields (FEF), while the *ventral fronto-parietal* network,

lateralised to the right hemisphere, involves the TPJ, IPL and ventral frontal cortex including the middle frontal gyrus and inferior frontal gyrus or IFG (see Figure 1.4). They are not specific about which regions provide afferents to these networks.

According to this model, the dorsal fronto-parietal network is involved in the goal-directed or 'top-down' selection of stimuli and responses: while the ventral fronto-parietal network detects salient, behaviourally significant events occurring in the environment (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). In this scheme, top-down control of attention refers to prior knowledge about where in space to attend to or what object features (such as shape, colour or motion) to search for in relation to current task or goal demands – *perceptual set*. It can also refer to advance information regarding what response needs to be produced – *motor set*.

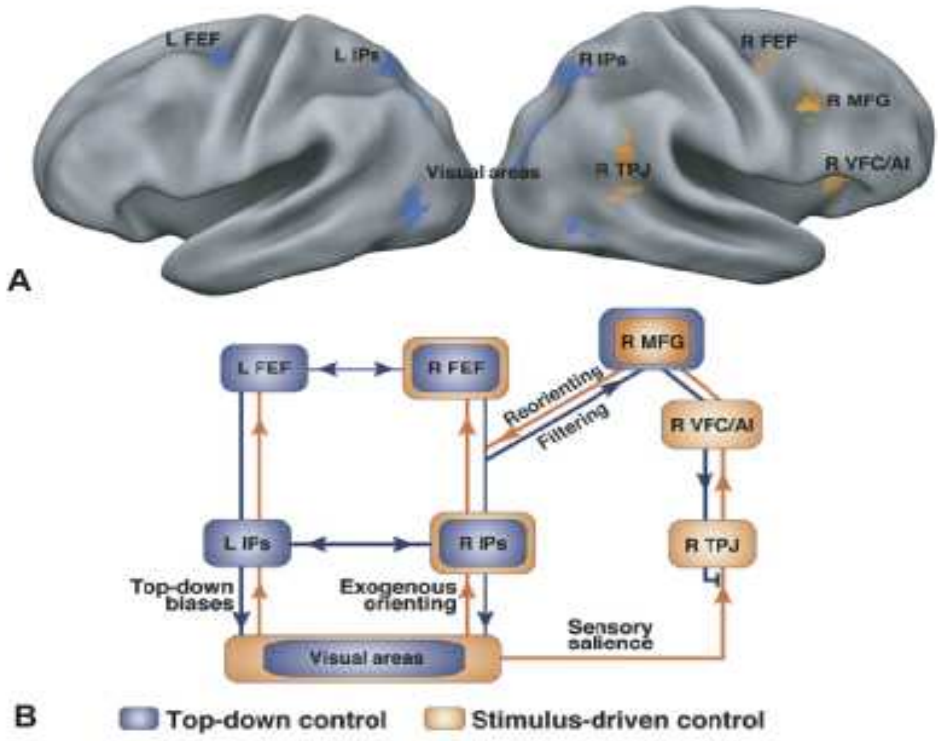


Figure 1.4. Corbetta and colleagues dorsal and ventral networks (from Corbetta *et al*, 2008).

A. Regions in purple are consistently activated by central (endogenous) cues that indicate the location or feature of a subsequent target. Areas in orange are consistently activated when attention is reoriented to an unexpected but behaviourally relevant object.

B. Corbetta and colleagues' model of dorsal (purple) and ventral (orange) networks. Regions where interactions between the two networks may occur are shown in purple and orange. Dorsal network regions FEF and IPS send top-down biases to visual areas and via the MFG to the ventral network, restricting ventral activation to behaviourally important stimuli (possible filtering mechanism). Overall, the dorsal network coordinates stimulus-response selection. Conversely, when a salient stimulus occurs during stimulus driven reorienting, the ventral network sends a reorienting signal to the dorsal network. They consider this to occur through the MFG.

FEF: frontal eye fields, IPs: intraparietal sulcus, MFG: middle frontal gyrus, TPJ: temporoparietal junction, VFC/AI: ventral frontal cortex.

Such goal-directed signals for the allocation of spatial attention are usually assessed by tasks which provide a directional, *endogenous* cue regarding the subsequent location of a target. fMRI experiments have shown that, unlike occipital regions, which respond only transiently to such cues, sustained activation is observed in the IPS and FEF in response to endogenous cues (Corbetta, Kincade et al. 2000). Thus dorsal fronto-parietal regions are activated when subjects direct spatial attention endogenously. Other studies have also separated *preparatory* signals for attending to stimuli from simple visual analysis, detection or response to such stimuli, consistently observing activity in the SPL, IPS and FEF (Kastner, Pinsk et al. 1999; Hopfinger, Buonocore et al. 2000; Sylvester, Shulman et al. 2007), which possibly reflects the top-down modulation of sensory representations. Accordingly, anticipatory activity may predict performance to subsequent targets (Sapir, d'Avossa et al. 2005; Giesbrecht, Weissman et al. 2006; Sylvester, Shulman et al. 2007). These same areas are also active during action selection, e.g. both eye movement and arm related activity have been reported in the FEF and IPS (Connolly, Goodale et al. 2000; Connolly, Goodale et al. 2002; Astafiev, Shulman et al. 2003).

What about the proposed *ventral* fronto-parietal network? Corbetta and Shulman consider the TPJ, which lies at the border of the IPL and superior temporal gyrus (STG), to be a crucial node in 'stimulus-driven reorientation of attention', encoding and directing attention to salient, behaviourally significant events. Stimulus salience refers to the properties of a stimulus which make it stand out from the surrounding background. For example, a red flower in a field of green grass stands out and hence rapidly draws attention because of its difference in shape and colour in relation to the green blades of

grass. Similarly, abrupt visual onsets or unexpected stimuli may also capture attention 'bottom-up'. The effects of such sudden, distinctive events may be examined by tasks incorporating an *exogenous* cue – a flashed stimulus – which facilitates responses to a target at the cued location. Such effects can occur across different stimulus sensory modalities (Santangelo, Van der Lubbe et al. 2006).

In their most recent formulation (Corbetta, Patel et al. 2008), Corbetta and Shulman argue that exogenous cues only seem to activate the TPJ if they are task-relevant. Salient peripheral cues of no informational or behavioural value have been found not to be associated with activation of the ventral network (Kincade, Abrams et al. 2005) – at least not in the context of engagement in an ongoing task. However, in this study, the exogenous cues were of no informational value because they were *equally* likely to be helpful as *un*helpful – hence using them could damage performance as often as it might aid it – and in terms of overall perceptual salience, it could be argued that they were no more salient than the neutral cues which occurred on all other trials, and that they were therefore not very salient at all. In contrast, other studies have found that novel stimuli, of no task-relevance, do activate the right TPJ (Downar, Crawley et al. 2002), indicating that at least in some circumstances, the TPJ does respond to salient stimuli of no immediate behavioural relevance. Furthermore, other investigations have demonstrated activity in the IPL and IFG in response to task-irrelevant novel stimuli *in the context of an ongoing task*. These areas are outside of the TPJ, but nevertheless key regions of Corbetta and Shulmans's ventral network (Kiehl, Laurens et al. 2001; Kiehl, Stevens et al. 2005).

Corbetta and Shulman argue that the ventral fronto-parietal network, including TPJ and ventral frontal cortex, performs a 'circuit-breaking' or 'reset' function, reorienting attention to sudden, behaviourally salient events. This network is strongly right lateralised and therefore may have direct implications for the pathophysiology of hemispatial neglect (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). Unlike the dorsal fronto-parietal network, the ventral fronto-parietal network is not activated by generating or maintaining an attentional set, but is strongly engaged by target detection (Corbetta, Kincade et al. 2000; Perry and Zeki 2000). Furthermore, when targets occur at an unexpected location – and are therefore very salient – activation is further enhanced in this network and shows even more lateralisation to the right hemisphere (Arrington, Carr et al. 2000; Corbetta, Kincade et al. 2000; Shulman, Astafiev et al. 2009). Importantly, activation in this network is also observed when infrequently occurring stimuli occur at locations not requiring a spatial shift of attention, for example at gaze fixation (Marois, Leung et al. 2000). Right TPJ and ventral frontal cortex are also activated regardless of the stimulus modality of change (Downar, Crawley et al. 2000).

Corbetta and Shulman have argued that the poor response of their ventral network to distinctive, but behaviourally unimportant, stimuli when an individual focuses on a task prevents shifts of attention that could interfere with its performance. In a demanding task, in which subjects had to search for the occasional occurrence of a target digit, regions of the ventral network demonstrated a sustained *deactivation* during search of distractor stimuli, whilst the appearance of targets still triggered a robust positive response (Shulman, McAvoy et al. 2003). They suggest that this may have been due to gating or

filtering of activity in the ventral network by task relevance, with only targets passing the filter. In fact, stronger filtering seems to correlate with better performance, with the average deactivation in the TPJ being greater on trials in which the target was subsequently detected rather than missed (Shulman, Astafiev et al. 2007).

During this experiment, regions of the dorsal network were some the few areas that showed sustained *activation* to distractors prior to target detection, suggesting that these sustained signals may have been responsible for filtering input to the ventral network (Shulman, McAvoy et al. 2003). Sustained increases in activation were also observed in the anterior cingulate and anterior insula – which have been postulated to form the core of a network for cognitive control (Dosenbach, Visscher et al. 2006) – making these other candidate areas responsible for the filtering mechanism. The influence from these cortical regions on the ventral network may be direct, through cortico-cortical interactions, or indirect via subcortical loops, which are likely to involve the locus coeruleus, a noradrenergic nucleus in the midbrain (Corbetta, Patel et al. 2008), which seems to show similar responses as the TPJ and IPL in response to significant environmental events (Aston-Jones and Cohen 2005).

A significant problem with Corbetta and Shulman's scheme is that recent studies have clouded the apparent distinction between dorsal and ventral networks, particularly regarding the process of *stimulus-driven reorienting*. For example one study conducted by their group has shown that parts of the FEF and SPL show responses to task-relevant exogenous stimuli which appear similar to those found in the TPJ, in addition to the

previously described spatially selective sustained responses (Shulman, Astafiev et al. 2009). They have also found that the dorsal stream responds to task-irrelevant exogenous stimuli (Kincade, Abrams et al. 2005) – as discussed above, a feature previously attributed solely to ventral regions.

As a result of such findings, their most recent formulation (Corbetta, Patel et al. 2008) reads somewhat confusingly when they try to identify the precise roles of these 'opposing' networks and discuss the way in which they interact. However, there are aspects of their scheme which, I believe, provide some valuable insights into the possible functions of the IPL and TPJ. In particular, the role of these regions in protecting task-focused activity from the influence of distractors, while also playing an important part in reorienting attention to stimuli of task-related importance, has some similarities to the proposal that will be developed later on in this chapter. However, Corbetta and colleagues attribute quite a restricted set of roles to the TPJ and IPL, although, as discussed, these are no longer quite as distinct as they originally suggested. In contrast, I will argue that the right IPL plays an important part in both 'top-down' and 'bottom-up' attentional functions. Additionally, their suggestion that input from the locus coeruleus may be important in 'resetting' or reorienting processes are also a crucial factor in my own scheme (Singh-Curry and Husain 2009).

Another important aspect of this model is that it can be argued that the anatomy of the neglect syndrome corresponds closely to Corbetta and Shulman's ventral system (Corbetta and Shulman 2002). They also propose that because the process of stimulus-driven

reorienting in the TPJ is right lateralised, their model would be consistent with neglect being far more frequent following right hemisphere lesions. Damage to the TPJ is associated with impaired orienting to invalidly cued stimuli in contralesional space (Friedrich, Egly et al. 1998), a function originally attributed to the SPL (Posner, Walker et al. 1984) but since revised by many of the original investigators. Furthermore, studies which show that neglect may follow focal lesions of the right ventral frontal cortex (Damasio, Damasio et al. 1980; Husain and Kennard 1996) would also be consistent with this proposal.

Corbetta and Shulman argue that neglect patients with IPL or TPJ lesions may, as a result, experience a disruption of the 'reset' or 'circuit-breaking' signal, which would impair shifting of attention between objects or events in the environment, wherever they occur in space. This may therefore underlie some of the non-lateralised deficits that these patients incur (Samuelsson, Hjelmquist et al. 1998; Robertson 2001; Husain and Rorden 2003). However, deficits in the ability to sustain attention are also prominent in many patients with hemispatial neglect (Samuelsson, Hjelmquist et al. 1998; Robertson 2001; Husain and Rorden 2003; Wilson and Manly 2003; Buxbaum, Ferraro et al. 2004), a process which is not dealt with in their scheme.

It might be argued that the ability to sustain attention on a task is primarily a goal-driven ('top-down') or endogenous cognitive process, dependent on the subject holding the task or goal 'set' in mind for the duration of the task – a process that Corbetta and Shulman would actually consider to be a component of dorsal network functionality (Corbetta and

Shulman 2002; Corbetta, Patel et al. 2008). As will be discussed next, numerous functional imaging studies in normal human subjects have identified activity in the IPL during experiments incorporating sustained attention. These findings, I believe, raise questions about the validity of a simple distinction between a dorsal fronto-parietal system primarily specialised for the goal-related or 'top-down' control of behaviour and a ventral system dedicated to the stimulus-driven ('bottom-up') reorientation of attention.

1.2. The role of the inferior parietal lobe in vigilance and sustaining attention

According to traditional theories, attention can be broadly divided into two domains: a *selectivity* aspect and an *intensity* aspect (Posner and Boies 1971). Some authors have distinguished between vigilance and sustained attention as two extremes of a continuum within the intensity domain. Thus *vigilance* has been considered as 'a state of readiness to detect and respond to *small* changes occurring at random time intervals in the environment' (Mackworth 1957) and is studied primarily through long, tedious tasks – vigils – requiring individuals to continuously monitor the environment for rare events. Detection of an infrequent blip on a radar screen would be an example of where vigilant attention is considered to be deployed. *Sustained attention* on the other hand has been invoked in situations where the flow of information is more rapid, requiring continuous active processing and monitoring (Leclerq 2002). For example, an interpreter giving an on-line translation of a speech would be considered to be actively sustaining attention to the words of the speaker. In my opinion, both ends of this intensity spectrum require holding goals or task instructions in mind in order to monitor incoming information from

the environment and produce (motor) outputs which satisfy the goal/task demands. In this sense, both vigilance and sustained attention require processes which are often termed as being 'top-down' in nature.

There is now ample evidence for a right hemisphere bias in the control of these intensity aspects of attention, even in terms of simple reaction time measures, from both patient studies (Howes and Boller 1975) and investigations in normal control subjects (Sturm, Reul et al. 1989). Within the right hemisphere, lesion studies have specifically identified the IPL and ventral frontal cortex as crucial regions either for sustaining attention or vigilance, for example in patients with tumour excisions (Wilkins, Shallice et al. 1987; Rueckert and Grafman 1996; Rueckart and Grafman 1998). Remarkably, the results of functional imaging studies have also been extremely consistent with these findings.

Thus while the SPL has been associated with spatial shifts of attention and the visual guidance of actions (Vandenberghe, Gitelman et al. 2001; Connolly, Andersen et al. 2003; Culham, Cavina-Pratesi et al. 2006), the IPL and ventral frontal cortex have been implicated repeatedly in tasks assessing sustained attention or vigilance in healthy subjects (Pardo, Fox et al. 1991; Johannsen, Jakobsen et al. 1997; Paus, Zatorre et al. 1997; Coull, Frackowiak et al. 1998; Coull and Frith 1998; Hager, Volz et al. 1998; Sturm, de Simone et al. 1999; Adler, Sax et al. 2001; Vandenberghe, Gitelman et al. 2001; Foucher, Otzenberger et al. 2004; Sturm, Longoni et al. 2004). Figure 1.5 depicts the results of a meta-analysis I conducted using MRIcro software (www.sph.sc.edu/comd/rorden,mricro), of activations obtained in studies which used either PET or fMRI (also see Table 1 for full

details). Investigations were included in this meta-analysis only if they employed a task in which subjects had to detect the occurrence of rare events at single locations (in various sensory modalities), or a version of the continuous performance task (CPT). The CPT typically involves the presentation of a relatively rapid, pseudorandom series of letters or digits at a rapid, fixed rate, with the instruction to respond to a particular stimulus letter or digit. Figure 1.5 demonstrates that both vigilant and sustained attention protocols consistently activate the right IPL and ventral frontal cortex (Singh-Curry and Husain 2009).

Table 1.1. Meta-analysis of studies assessing sustained attention

Study	Task used	Modality of imaging	No of subjects	Regions activated	Talairach Coordinates (x,y,z)	Z/t score of activation*
Pardo *et al*, 1991	Visual and somatosensory vigilance tasks	PET	23	Parietal lobe	29, -51,34 35,-35,48 39,-27,46 49,-25,46	>2.1 >2.1 >2.1 >2.1
				Frontal lobe	45,21,34 31,17,44	>2.1 >2.1
Johannsen *et al,* 1997	Visual and vibration vigilance tasks	PET	17	IFG MFG IPL	44,20,-8 40,34,23 43,-61,44	3.1 2.9 3.5
Paus *et al,* 1997	Auditory CPT	PET	8	VLPFC ILP	36,27,12 36,22,-11 38,20,-5 59,-37,35	3.6 4.9 3.7 3.4
Coull & Frith, 1998**	Visual CPT variant	PET	4	IFG IPS	36,20,10 36,-56,44	4.59 4.72
Coull *et al*, 1998	Visual vigilance task	PET	6	IPL DLPFC	48,-52,36 36,10,40	4.42 5.22
Hager *et al*, 1998	Visual CPT	fMRI	12	DLPFC	30,43,44 41,38,41 37,27,33	5.44 4.05 2.71
Sturm *et al,* 1999	Visual vigilance task	PET	15	MFG IPL	36,36,32 30,46,4 54,-52,24	4.74 4.73 4.29
Adler *et al,* 2001	Visual CPT	fMRI	14	DLPFC Anterior insula IPL	38,43,15.5 34,15,11.5 38,-49,39.5	
Vandenberge *et al,* 2001	Visual vigilance task	fMRI	12	Angular gyrus PMC MFG Anterior insula	54,-60,33 57,-51,30 60,-45,42 48,12,42 39,48,21 51,33,21 39,30,-9	6.44 6.15 5.26 5.75 5.27 5.24 4.94
Foucher *et al,* 2004	Visual vigilance task	fMRI	7	IFS IPL SPL	47.5,41.1,7.2 39.6,46,-10.7 53.5,-40.1,51.8 33.7,-68.8,49.5	7.51 4.95 6.39 6.36
Sturm *et al,* 2004	Auditory vigilance task	PET	10	IFG IPL	32,26,-15 40,23,3 51,-49,36	4.81 4.63 3.7

Table 1.1. Meta-analysis of studies assessing sustained attention (legend)

The studies included in this meta-analysis (performed via a literature search), employed tasks assessing vigilance/sustained attention, in any sensory modality, at *a single location* only in healthy control subjects. Only right hemisphere fronto-parietal activations are shown in this table and plotted in MRICro (Figure 1.4).

* Z/t scores given where available

** This study employed the same stimuli but different instructions in 2 tasks. In the sustained attention task subjects had to respond to all stimuli, in the selective attention task they had to respond to target stimuli only. The coordinates given here refer to areas activated by both tasks.

CPT: continuous performance task, IFG: inferior frontal gyrus, MFG: middle frontal gyrus, IPL: inferior parietal lobe, VLPFC: ventroleteral prefrontal cortex, DLPFC: dorsolateral prefrontal cortex, PMC: premotor cortex, IFS: inferior frontal sulcus

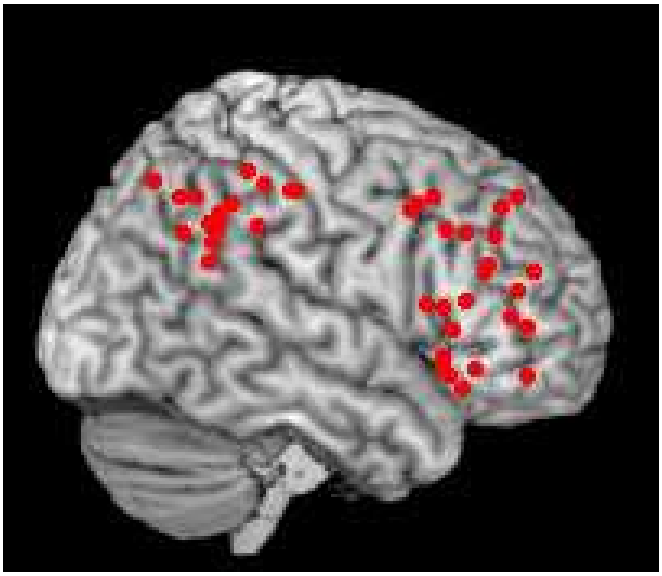


Figure 1.5. Activation sites associated with sustaining attention.

Meta-analysis (performed in MRIcro – www.sph.sc.edu/comd/rorden/mricro) of sites of activation obtained during tasks assessing sustained attention in normal control subjects. Only areas within the right frontal and parietal lobes are shown here.

The role of the IPL and ventral frontal regions in sustaining attention is also supported by studies of patients with hemispatial neglect. For example, it has been reported in a study of 44 right hemisphere stroke patients that individuals exhibiting neglect performed far worse on a non-spatial task of auditory sustained attention than control right hemisphere patients without neglect (Robertson, Manly et al. 1997). In fact performance on this task was found to be a better discriminatory test than line bisection, a more conventional measure of neglect. *Persistent* neglect has also been found in other studies to be related to an impairment in sustained attention (Hjaltason, Tegner et al. 1996; Samuelsson, Hjelmquist et al. 1998). Furthermore, it has been demonstrated that improving vigilance can ameliorate aspects of neglect (Wilson and Manly 2003). The use of computerised training tasks designed to increase endogenous maintenance of attention has been found to lead not only to improvement in tasks assessing neglect, but to greater activation in right hemisphere areas, including preserved parts of the IPL (Sturm, Thimm et al. 2006; Thimm, Fink et al. 2006). Finally, it has also been shown that use of the noradrenergic agonist guanfacine can produce benefits in these patients, most likely by improving performance in maintaining attention (Malhotra, Parton et al. 2006).

All of these findings provide a strong evidence base for the role of the right IPL in maintaining attention, one of the intensity-based aspects of attention, which is not discussed in any of the models I have reviewed here. The right IPL also has a role in responding to salient events, as Corbetta and colleagues propose (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). However, as discussed in the next section, their model may not fully capture the contributions of this region to this process.

1.3. The role of the inferior parietal lobe in salience detection and phasic alerting

Salience refers to the properties of a stimulus which make it stand out from the background. This may be because it represents something which we have not encountered recently (*novelty*), or because its properties have behavioural significance to our current goal set (*behavioural* or *target-related salience*). Here, I also propose that a stimulus may be salient because it acts as a warning of an event of behavioural significance (*phasic alerting*), for example the ringing of an emergency alarm in a public building. Clearly these different types of salience may have many similarities, but they also differ, for example in the extent to which they involve 'goal-directed' versus 'stimulus-driven' processes. In other words, brain mechanisms involved in responding to salient stimuli are likely to depend upon a combination of these 'opposing' processes. Each of these categories of stimulus salience, and the role of the IPL in their mediation, will now be discussed in turn.

1.3.1. Target-related salience

Target-related salience refers to the process where the characteristics of a target stimulus must be held in mind to direct subsequent actions appropriately, depending on what is perceived in the environment or during the task. It is most frequently assessed using the *'oddball paradigm'*, which consists of infrequently occurring target stimuli (to which the subject must respond) embedded in a stream of frequently occurring standard non-target stimuli, to which responses must be withheld. In healthy subjects, event related potentials (ERPs) have often been used to study the neurophysiological correlates of orienting to

target stimuli in the oddball paradigm. Detection of such salient events leads to a characteristic positive response centred over the parietal lobe (Vaughan and Ritter 1970) occurring approximately 300-500ms after target presentation, but not following familiar non-targets. This wave is known as the P3 (Ritter, Vaughan et al. 1968) or P300 response (Smith, Donchin et al. 1970). Lesions of the TPJ lead to elimination of the P3 (Knight, Scabini et al. 1989), whereas patients with prefrontal lesions have alterations of the P3 over posterior areas (Barcelo, Suwazono et al. 2000). Moreover, patients with hemispatial neglect also show a reduction of P3 amplitude (Lhermitte, Turell et al. 1985).

In healthy control subjects, during target detection using this paradigm, the cortical areas most consistently activated on functional imaging are the right sided IPL, IPS, TPJ and frontal regions (Linden, Prvulovic et al. 1999; Clark, Fannon et al. 2000; Marois, Leung et al. 2000; Kiehl, Laurens et al. 2001; Foucher, Otzenberger et al. 2004; Huang, Lee et al. 2005; Kiehl, Stevens et al. 2005; Bunzeck and Duzel 2006; Lagopoulos, Gordon et al. 2006; Gur, Turetsky et al. 2007; Williams, Felmingham et al. 2007; Strobel, Debener et al. 2008; Friedman, Goldman et al. 2009). This is illustrated in Figure 1.6, which plots right hemisphere activation foci obtained in a meta-analysis I performed of these studies (also listed in Table 2). The investigations included in this analysis employed the oddball paradigm using stimuli of any sensory modality, but presented at a single location only (Singh-Curry and Husain 2009).

Performance on the oddball task clearly may involve ‘bottom-up’ or ‘stimulus-driven’ capture of attention by virtue of targets being rare, as has previously been argued

(Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). However, in current terminology, keeping the target in mind during the oddball task might also be considered to be a ‘top-down’ or ‘goal-directed’ activity. The right IPL therefore appears to play a key role in responding to salient task-relevant events, which requires *both* the task goal to be maintained – so targets can be discriminated from non-targets – as well as detection of successive stimuli in the task.

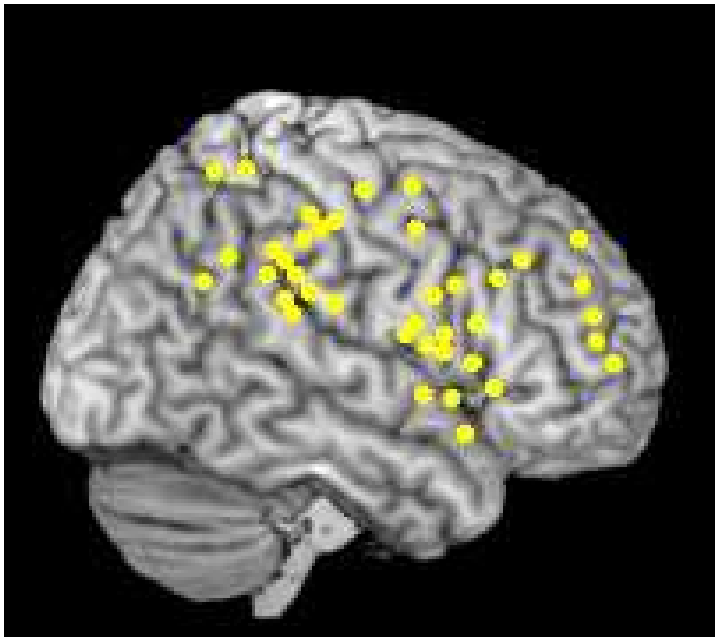


Figure 1.6. Activation sites associated with target-related salience detection. Meta-analysis (performed in MRIcro – www.sph.sc.edu/comd/rorden/mricro) of brain activation sites associated with target detection during the oddball paradigm in healthy control subjects. Only right hemisphere frontal and parietal regions are shown.

Table 1.2. Meta-analysis of studies assessing target-related salience detection.

Study	Modality of task	No of subjects	Regions activated	Talairach coordinates (x,y,z)	Z/t score of activation*
Linden *et al*, 1999	Visual and auditory	5	IPL IFL	52, -31, 41 55, -36, 35 41, -29, 48 55, -33, 31 55, -29, 26 48, 4, 11 44, 9, 9 42, 2, -3 43, 11, -4 45, 1, 44	
Clark *et al*, 2000	Visual	6	IPL MFG IFL	48, -39, 38 32, 0, 56 44, 17, 6	>3.09 >3.09 >3.09
Kiehl *et al,* 2001	Visual and auditory	10	MFG IFG SPL IPL	28, 48, 28 52, 12, 28 28, -56, 60 60, -36, 24	7.2 6.67 7.16 9.42
Foucher *et al,* 2004	Visual	7	MFG IPL	27.7, 56.7, 6.4 55.4, -58.8, 28.7	4 3.37
Huang *et al*, 2005	Somatosensory	9	IPL dPMA DLPFC VPMA	46.1, 46.6, 41.3 36.6, -14, 54.8 37.5, 23.8, 30.4 48.9, 6.1, 24.7	
Kiehl *et al*, 2005	Auditory	100	MFG IFG Insula SPL IPL	23.8, 51.5, 19.5 51.5, 8.5, 14.3 43.6, 14.8, -14.2 23.8, -47.4, 61.3 55.4, -34, 20.1	16.69 14.07 18.34 12.42 21.25
Bunzeck and Düzel, 2006	Visual	14	Insula MFG IPL	33.7, 23.3, -1.2 39.6, 0.8, 16.5 39.6, 30.9, 35.3 61.4, -22.1, 23.2	9.3 4.44 5.88 4.72
Lagopoulos *et al*, 2006	Auditory	6	IPL	38, -52, 36	6.72
Gur *et al,* 2007	Visual	36	IPL MFG Insula	52, -26, 44 32, 50, 12 40, -2, 16	4.57 4.32 4.38
Williams *et al*, 2007	Auditory	16	IFG IPL	59.4, 18.4, 17.5 59.4, -41.2, 31.5	4.14 3.47

Strobel *et al*, 2008	Auditory	14	MFG IFG Insula IPS	40, 37, 29 33, -5, 60 48, 16, 1 34, 20, 7 47, -41, 51 33, -58, 41	3.3 2.8 4.5 6.7 5.2 4.5
Friedman *et al*, 2009	Auditory	15	IFG Insula STG	31.7, 23.1, -4.5 33.7, 25.6, 6.1 47.5, -18.6, 17.5 31.7, 17.7, 4.6 57.4, -42.1, 13.2 67.3, -37.8, 20.3 51.5, -21.1, 4.7	4.5 4.57 4.61 4.58 4.67 5.45 5.3

Table 1.2. Meta-analysis of studies assessing target-related salience detection (legend).

This meta-analysis included tasks performed at a *single location in space* only in healthy control subjects. Stimuli could be presented in any sensory modality. Only right hemisphere frontal and parietal activations are listed here and illustrated in Figure 1.5.

Z/t scores given where available.

IPL: inferior parietal lobe, IFL: inferior frontal lobe, MFG: middle frontal gyrus, IFG: inferior frontal gyrus, SPL: superior parietal lobe, dPMA: dorsal premotor area, DLPFC: dorsolateral prefrontal cortex, STG: superior temporal gyrus, VPMA: ventral premotor area

1.3.2. Novelty

New events or objects, which have not been encountered in a particular behavioural context before, are highly salient and also easily attract attention. This is an essential feature of a nervous system which encourages exploration of the surrounding environment. Like target-related salience, novelty has been studied using the oddball paradigm. In such tasks, in addition to infrequently occurring targets which require a response, there are occasional new stimuli which have not been presented previously. Subjects are instructed to respond only to the targets and are usually not given any instructions about the novel stimuli. Like targets, novel stimuli elicit a P3 ERP response over parietal and frontal cortex, even when no response to these items is required. However, the positive wave occurs slightly earlier (sometimes referred to as the P3a) than that which occurs to targets (P3b) (Courchesne, Hillyard et al. 1975; Squires, Squires et al. 1975). Lesions of the TPJ lead to abolition of both the P3a and P3b (Knight, Scabini et al. 1989).

While the areas of activation obtained with functional imaging studies in healthy subjects seem to occur more posteriorly in response to novelty than targets, they too predominantly involve the IPL, TPJ and ventral frontal lobe (Kiehl, Laurens et al. 2001; Downar, Crawley et al. 2002; Kiehl, Stevens et al. 2005; Bunzeck and Duzel 2006; Gur, Turetsky et al. 2007; Strobel, Debener et al. 2008; Friedman, Goldman et al. 2009). This is demonstrated in Figure 1.7, which plots the results of a meta-analysis I performed of functional imaging studies (also listed in Table 3) using the oddball paradigm to determine the anatomy of brain regions associated with processing of stimulus novelty. Again, all of

the investigations included presented stimuli at a single central location only, but a variety of sensory modalities were employed (Singh-Curry and Husain 2009).

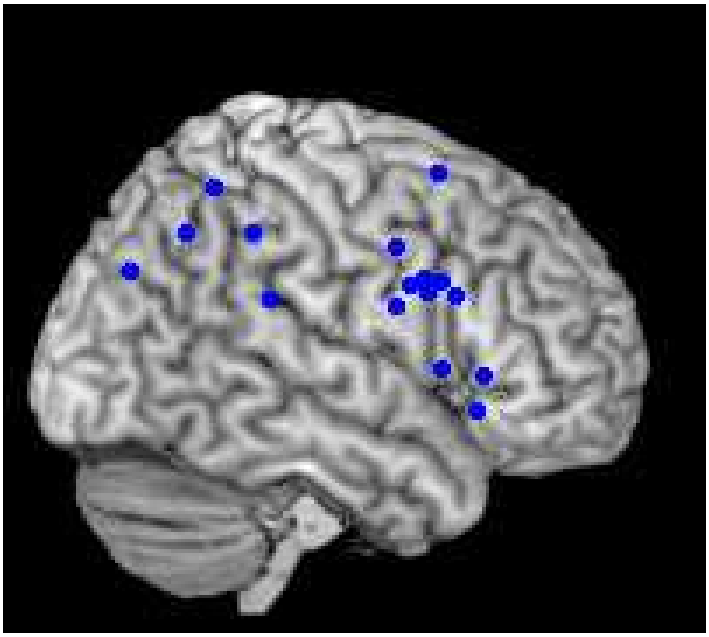


Figure 1.7. Activation sites associated with novelty detection.
Meta-analysis (performed in MRIcro – www.sph.sc.edu/comd/rorden/mricro) of brain regions associated with novelty detection during the oddball paradigm in control subjects. Only right hemisphere regions in the frontal and parietal lobes are demonstrated here.

Study	Modality of task	No of subjects	Regions activated	Talairach coordinates (x,y,z)	Z/t score of activation
Downar *et al*, 2002*	Visual, auditory and somatosensory	10	TPJ/IPL IFG Insula	56, -36, 24 53, 9, 26 42, 0, 22 43, 13, 4	4.77 4.34 4.36 4.27
Kiehl *et al*, 2001	Visual and auditory	10	I/MFG IPL Precuneus	48, 4, 28 32, -52, 56 28, -76, 32	5.33 6.51 9.5
Kiehl *et al*, 2005	Auditory	100	IFG IPL SPL	47.5, 16.8, 25 47.5, 22.4, -7.9 35.6, -60, 43.5 47.5, -40.6, 42.6	14.64 13.91 14.14 11.87
Bunzeck and Düzel, 2006	Visual	14	Insula IFG MFG	29.7, 25.4, 2.4 41.6, 13.1, 28.8 45.5, 0, 38.7	4.67 3.48 3.69
Gur *et al*, 2007	Visual	36	IFG	44, 6, 32	4.22
Strobel *et al*, 2008	Auditory	14	IFG Insula PreCS STG	45, 20, 27 48, 16, 1 40, -2, -8 47, 6, 35 54, 1, 2 59, -19, 9 57, -36, 9	7.8 2.6 5.1 4.3 3.9 10.2 9.4
Friedman *et al*, 2009	Auditory	15	STG	64.4, -25.7, 10.5 52.5, -16.3, 3.6 62.4, -11.8, -1.9 62.4, -36.3, 12	5.55 5.07 4.32 3.94

Table 1.3. Meta-analysis of studies assessing orientation to novel distracters

Only right hemisphere activations within the frontal and parietal lobes are listed here. Investigations included all presented stimuli at a single location

*Downer *et al*, 2002 did not use an oddball paradigm, but a similar task in which they were able to compare activity in response to novel stimuli to that obtained with a baseline familiar stimulus.

TPJ: temporoparietal junction, IPL: inferior parietal lobe, IFG: inferior frontal gyrus, MFG: middle frontal gyrus, PreCS: precentral sulcus, SPL: superior frontal gyrus, STG: superior temporal gyrus.

Importantly, ventral frontal and parietal regions were found to be active in response to task-irrelevant novel events, even in the context of subject engagement in an ongoing task (Kiehl, Laurens et al. 2001; Kiehl, Stevens et al. 2005; Bunzeck and Duzel 2006; Gur, Turetsky et al. 2007; Strobel, Debener et al. 2008; Friedman, Goldman et al. 2009). This contradicts Corbetta and Shulman's most recent ideas regarding the ventral network only responding to salient events which are relevant to performance of the current task (Corbetta, Patel et al. 2008). Hence, even in the context of stimulus-driven reorienting, the Corbetta and Shulman scheme fails to capture the full extent of right IPL functionality. As with orienting to target stimuli in the oddball paradigm, it might be argued that detection of novel events occurs in a primarily stimulus-driven or 'bottom-up' fashion. However, memory of previous items also needs to be maintained in order that a novel stimulus can be correctly judged as new. Therefore, even a process, which at first glance appears to be purely exogenous, can be seen on closer inspection, to be more complex than previously thought.

The detection of novel events is also associated with activity in the midbrain dopaminergic nuclei, the substantia nigra (SN) and ventral tegmental area (VTA), as well as the hippocampus and ventral striatum (Bunzeck and Duzel 2006). In fact the SN/VTA, ventral striatum and hippocampus are thought to form a mesolimbic loop, which together with input from prefrontal areas (which forms a parallel and interacting mesocortical loop) is instrumental in controlling entry of information into long-term memory (Lisman and Grace 2005). Activity in the hippocampus is likely to be crucial in implementing the comparison of incoming information with stored memories, in order to compute whether

incoming stimuli are actually new, while goal-related information from frontal regions may be critical in attaching importance (or salience) to novel stimuli (Lisman and Grace 2005). The dopaminergic contribution to novelty processing will be discussed further later on in this chapter (see Section 1.8.1).

1.3.3. Phasic alerting

The final aspect of salience I will discuss is phasic alerting, a process that has usually not been considered in this context, but separately under intensity aspects of attention. Phasic alerting refers to a readiness to detect and respond to environmental changes occurring as a result of an exogenous warning stimulus (Posner and Boies 1971), which may be in the same modality as the subsequent target stimulus or a different one. In this respect, it may be considered to be a category of salience which is primarily 'bottom-up' or stimulus-driven in nature (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008).

There may be a predefined association between an alerting stimulus and one which follows it, for example a cue presented a set interval before a visual target, or the ringing of an emergency alarm indicating there is a hazard in the building and that it must be evacuated. In such cases, where there are predefined associations between an alerting cue and a subsequent target or event, a goal-driven element of processing is also introduced. In terms of psychological studies, Posner and Boies demonstrated that reaction times to targets following phasic alerting cues were least if the interval between cue and target was 500-1000ms (Posner and Boies 1971).

On the other hand, there may not be any predefined stimulus-stimulus or stimulus-response association, in which case the alerting cue becomes very similar to a novel one. Such alerting events may be considered to be primarily 'bottom-up' in nature, however, as discussed in the previous section, memory of earlier stimuli is necessary in order to correctly judge that an event is new. It can therefore be appreciated that subdividing brain networks on the basis of whether they deal with processes that are primarily 'bottom-up' or 'top-down' in nature (Corbetta and Shulman 2002) is just as arbitrary, and at times unhelpful, as segregating them on the basis of whether they are engaged by action versus perception (Milner and Goodale 1995), or 'what' versus 'where' (Ungerleider and Mishkin 1982).

In fact, in some respects, all salient stimuli may be considered phasic alerting, to varying degrees. Here, I will consider a phasic alerting stimulus to be one which warns the subject of an impending target, but is of no other informational value. It has of course been shown that an alerting cue which orients the subject to the location of an impending target, activates the right IPS and TPJ (Kastner, Pinsk et al. 1999; Corbetta, Kincade et al. 2000; Shulman, Astafiev et al. 2009). However, it is important to note that there are also studies that suggest these regions are important in the detection of cues which provide no such predictive information (Fan, McCandliss et al. 2005; Thiel and Fink 2007).

In one such study (Thiel and Fink 2007), a simple target detection paradigm was used in which some targets were preceded by a visual or auditory cue (variable cue-target interval so as not to be temporally predictive). The other investigation (Fan, McCandliss et al.

2005) employed the attention network test (ANT) which is designed simultaneously to probe the effect of a non-informative cue (*alerting* condition), a spatially informative cue (*orienting* condition) and a condition in which the target arrow stimulus is flanked by either congruent or incongruent arrow stimuli (*conflict* situation, obtained by subtracting the effect of congruent from incongruent). Figure 1.8 plots in MRICro the right fronto-parietal activations obtained in these two studies (the only ones found in the literature to list coordinates of activation in response to a non-spatially informative alerting cue). Also not included are the more complex designs used by Coull and colleagues, which used several different types of cue (Coull, Nobre et al. 2001). Again, the IPL and TPJ are implicated; although in the right frontal lobe, the activation centroids appear to be in the middle, rather than inferior, frontal gyrus (Singh-Curry and Husain 2009).

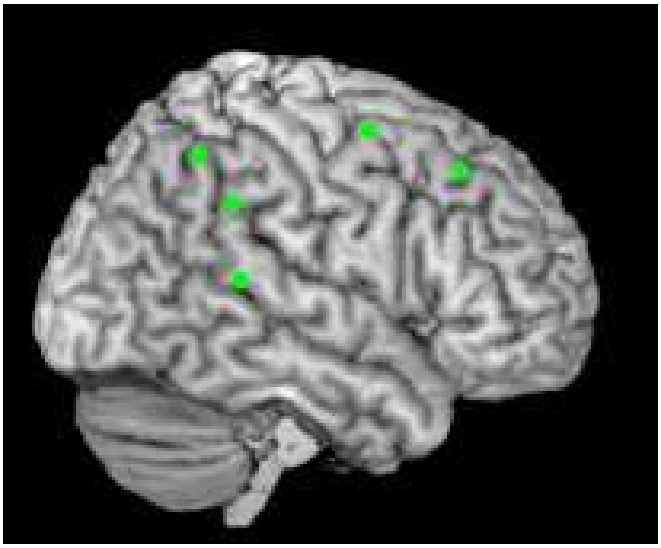


Figure 1.8. Activation sites associated with phasic alerting.

Meta-analysis (performed in MRIcro – www.sph.sc.edu/comd/rorden/mricro) of regions activated by non-informative warning cues in healthy control subjects. Right hemisphere frontal and parietal regions only are demonstrated here.

Lesions of the right hemisphere have long been known to impair alerting responses, measured with galvanic skin responses (Heilman, Schwartz et al. 1978) or heart rate changes to warning cues (Yokoyama, Jennings et al. 1987). Conversely, patients with hemispatial neglect following right hemisphere lesions benefit from an alerting tone during a task designed to assess the severity of their leftward inattention (Robertson, Mattingley et al. 1998). Posner and Petersen argued that ascending noradrenergic pathways from the locus coeruleus (LC) play a key role in alertness, specifically their innervation of right frontal and parietal regions (Posner and Petersen 1990), with the parietal cortex in particular appearing to receive a dense projection (Foote and Morrison 1987). They pointed to electrophysiological studies which suggested a crucial function of LC noradrenergic cells in arousal. For example, the activity of these neurons is reduced in states of low arousal (Aston-Jones, Gonzalez et al. 2007).

Recently, however, our understanding of the role of the LC noradrenergic system has been revised to a more sophisticated formulation. Aston-Jones and colleagues argue that the LC contributes to the regulation of attention between a focused, selective attention state (that facilitates responses to targets and filters out distractors) and a scanning, labile state that allows flexible responding to new events, i.e. to stimuli which are not targets, but may nevertheless be important (Aston-Jones and Cohen 2005; Aston-Jones, Iba et al. 2007). As I have discussed in the previous sections, there is evidence for the involvement of the right IPL in both of these modes of operation: maintaining attention and responding to novel, salient events.

In summary, the evidence points to a role of the right IPL in phasic alerting, which may be a special case of a response to a salient stimulus in the environment that acts to reconfigure task goals, possibly via interactions involving a noradrenergic input from the LC. I have also discussed that although many cases of detecting salient environmental stimuli have previously been considered more 'bottom-up' in nature, all additionally involve processes which can be thought of as 'goal-related'. Segregating brain networks on this basis may therefore not be a particularly useful enterprise.

1.4. The process of reconfiguration

How does this process of reconfiguration occur? One way to examine this question is to look at the data on task-switching. Functional imaging data and ERP evidence suggests a role for the IPL – as well as frontal regions – in task set reconfiguration, although not necessarily lateralised to the right hemisphere (Buchsbaum, Greer et al. 2005; Rushworth, Passingham et al. 2005; Travers and West 2008).

Tests assessing how we switch between two or more tasks involve the reconfiguration of a number of discrete processes (Wager, Jonides et al. 2004). Task-switching may involve a shift in the *rule* used to process stimuli in search of behavioural targets: for example from spatial location to object attributes of items. It may also involve a change in the *motor response*, e.g. which hand to respond with following target stimuli. Unfortunately, most paradigms assessing task-switching involve both of these processes, as well as differing degrees of working memory load, and a variety of bilateral frontal and parietal foci of

activation are found in such studies. For this reason, meta-analysis may be particularly useful in elucidating the critical regions underlying reconfiguration.

One fairly recent review, performed by Buchsbaum and colleagues, undertook meta-analyses of neuroimaging studies of three types of paradigm: the Wisconsin Card-Sorting Task (WCST), task-switching studies and the go/no-go task, as well as a critical conjunction analysis of all three paradigms (Buchsbaum, Greer et al. 2005). The WCST requires subjects to sort cards according to a rule which they must learn by trial and error. After a set number of trials, this rule changes and participants must 'shift set' in order to determine the new way in which they must sort the cards. This task was originally developed to probe human abstraction and the ability to switch set. However, it clearly involves other cognitive processes, including working memory and the ability to learn from positive and negative feedback. This is in contrast to 'purer' tests of task-switching in which an instructional cue specifies explicitly which of two rules should be used. Finally, in the go/no-go task, subjects are instructed either to respond (go) or not to respond (no-go) to a predefined set of stimuli embedded in a stream of rapidly presented items. The stimuli are presented such that the 'go' response predominates, so that when a 'no-go' stimulus occurs, the subject has to overcome a predisposed tendency to respond. This ability to inhibit a pre-potent, conflicting response is also a key component of both task-switching and the WCST.

The right IPL and ventral frontal cortex were identified as major foci of activation in all three meta-analyses, along with their left-sided counterparts. However, in a conjunction

analysis of all three types of study, the right – and not the left – IPL and ventral frontal cortex were found to be substantially activated (see Figure 1.9). This finding suggests that a process common to all three of these paradigms – such as the ability to overcome conflict between a previous response and a new one – depends upon the right, rather than the left, IPL.

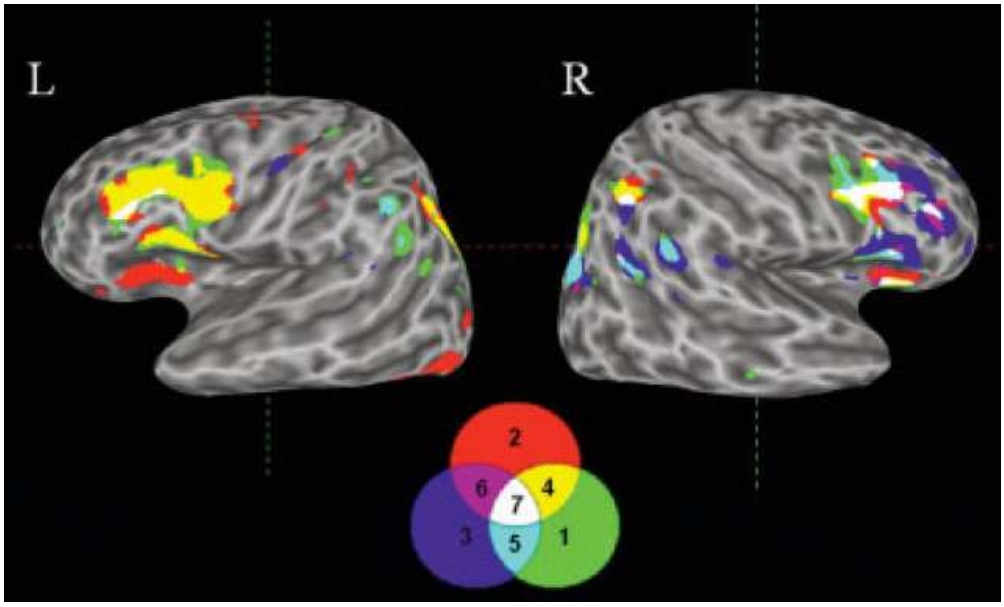


Figure 1.9. Conjunction analysis of studies using the WCST, task-switching and go/no-go paradigms (from Buchsbaum *et al,* 2005).
Three-dimensional surface rendered views of meta-analyses and all possible conjunctions of the following paradigms:1 = WCST, 2 = task-switching, 3 = go/no-go task, 4 = WCST and task-switching, 5 = WCST and go/no-go, 6 = task-switching and go/no-go, 7 = WCST, task-switching and go/no-go.

As with the process of reconfiguration, most studies investigating the effect of potentially conflicting responses, have focused on the frontal lobes (Botvinick, Cohen et al. 2004; Nachev, Rees et al. 2005; Rushworth, Buckley et al. 2007). It is however, becoming clear that this crucial component of the reconfiguration process, is also associated with PPC activity (Liston, Matalon et al. 2006; Jaffard, Longcamp et al. 2008; Karch, Mulert et al. 2009).

One recent study performed with neglect patients also supports this contention (Coulthard, Nachev et al. 2008). Coulthard and colleagues used a (vertical) directional flanker task, to demonstrate that patients with posterior parietal lesions show a paradoxical *facilitation* of rightward movements in the presence of conflicting leftward response plans. In contrast, neglect patients with frontal damage had increased costs of conflict for both leftward and rightward movements.

The authors argue that the findings suggest that the right PPC normally acts at a crucial stage in the automatic activation of competing motor plans, whilst frontal regions act to inhibit action plans which are not relevant to current task goals. Importantly, patients with left parietal lesions did not demonstrate a similar facilitation of leftward movements in the context of conflicting rightward response plans. This, like the conjunction meta-analysis of WCST, task-switching and go/no-go paradigm (Figure 1.9) suggests that the resolution of response conflict may be predominantly a function of right, rather than left, parietal cortex, in addition to the more characteristic frontal regions.

Neurophysiological evidence suggests that task-switching is accompanied by a parietal slow wave which appears to be a P300 or P3 response (Rushworth, Passingham et al. 2005; Travers and West 2008). As discussed earlier, detection of salient targets is also associated with a parietal P3 (P3b) response, as is the detection of novel stimuli (designated the P3a). However, the P3a in response to novel stimuli occurs slightly earlier and more anteriorly (Herrmann and Knight 2001) than the P3b evoked by task-relevant events. Moreover, the P3a is generally of smaller amplitude and/or of shorter latency than the P3b, with a greater rate of habituation, particularly over parietal regions (Courchesne, Hillyard et al. 1975; Yamaguchi and Knight 1991; Katayama and Polich 1998; Comerchero and Polich 1999; Polich and Comerchero 2003; Volpe, Mucci et al. 2007).

There are circumstances in which novel, or other infrequently occurring distractors, are capable of producing a P3a which is of larger amplitude than the P3b produced by the target stimulus in an oddball task (Katayama and Polich 1998; Comerchero and Polich 1999; Combs and Polich 2006). These, however, seem to be limited to situations in which the target is difficult to distinguish perceptually from the frequently occurring non-target stimuli, whilst the novels, or rare distractors, are far more salient. In these instances however, although the amplitude of the P3b is reduced, the latency is increased. Also note that in such situations more errors occur, suggesting that subjects are less effectively engaged by the task. Thus there is a difference between the P3 response to salient *task-related* stimuli – the P3b – and to novel stimuli that may not be relevant to the task – the P3a.

Intriguingly, converging evidence from animal neurophysiological, pharmacological and lesion studies, as well as some human studies, suggests that the P3 recorded over cortical regions reflects phasic activity of the LC noradrenergic system, which sends dense projections to the parietal cortex (Nieuwenhuis, Aston-Jones et al. 2005). For example, lesions of the LC in monkeys lead to abolition of P3-like cortical responses (Pineda, Foote et al. 1989). Consistent with these findings, computational modelling by Dayan and Yu has suggested the possibility that phasic noradrenergic activity might act as a 'neural interrupt signal', resetting or reconfiguring ongoing processing, leading to a shift in behaviour towards a task-engaged state (Dayan and Yu 2006). As mentioned earlier, Corbetta and Shulman have incorporated some of these findings into their most recent formulation of their dorsal versus ventral dichotomy (Corbetta, Patel et al. 2008). However, as previously discussed, their argument becomes confused at times, but more importantly they fail to include important processes such as sustained attention and responses to novel events in their proposal. I hope that what follows here is a little more coherent and attempts to account for more of the extant literature.

1.4.1. The role of the locus coeruleus in the process of reconfiguration

It has been generally acknowledged that noradrenergic LC cells fire en masse either phasically or tonically in response to afferent input (Berridge and Waterhouse 2003; Aston-Jones and Cohen 2005; Aston-Jones, Gonzalez et al. 2007). Aston-Jones and colleagues have proposed that *phasic* noradrenergic activity facilitates focused, selective responding, with effective filtering out of distractors. On the other hand, an increase in

tonic LC activity (associated with reduced phasic activity) shifts behaviour into an exploratory, more distractible state (Aston-Jones and Cohen 2005).

The computational modelling work performed by Dayan and Yu extends this concept, suggesting that alterations in the tonic activity of the LC noradrenergic system signals unexpected events in the surrounding environment, for example, changes in the nature of a task or the behavioural context in which it is being performed (Yu and Dayan 2005; Dayan and Yu 2006). They envisage phasic activity (which correlates with the P3) to signal the occurrence of uncertain events *within* a task, alerting the subject to the presence of a goal-relevant stimulus (such as a target or a pre-determined signal to switch stimulus-response contingencies) and interrupting the default state (Dayan and Yu 2006). In this way, phasic noradrenergic activity facilitates sustained and accurate performance of a task.

The relationship between tonic noradrenergic activity and function is thought to follow an inverted U-shaped curve, with an optimal level of focused performance being associated with a moderate level of noradrenaline, while low noradrenergic levels are associated with drowsiness and high levels with distractibility (Aston-Jones and Cohen 2005). Importantly, the level of tonic activity appears to influence the extent of *phasic* noradrenaline release. At low tonic levels, when the animal is drowsy, there is very little phasic activity, and similarly at very high tonic levels. But between these two extremes – at moderate tonic noradrenergic levels – phasic LC bursts are most effective and are strongly correlated with accurate target detection (Aston-Jones, Rajkowski et al. 1994), and by inference, the P3b potential recorded over parietal cortex in response to salient,

task-related stimuli (Figure 1.10). It is in this condition that behaviour seems to be most easily maintained on task demands, corresponding to the view of the state of sustained attention in human observers developed in this chapter so far.

Under these circumstances, I hypothesise that *novel* task-irrelevant stimuli also cause phasic bursts of LC activity within LC neurons, but of smaller amplitude or shorter duration. Studies in humans, show that under such conditions the P3a recorded over cortical regions is of smaller amplitude and/or of shorter latency (Yamaguchi and Knight 1991). If baseline tonic noradrenergic levels were to increase, then I envisage that responses to novel or distracting stimuli would become more prominent. Thus behaviour becomes more exploratory or distractible in nature and disengagement from the task occurs, accompanied by a reduction in LC phasic activity and parietal P3b potentials to targets (Aston-Jones, Rajkowski et al. 1994; Usher, Cohen et al. 1999; Aston-Jones and Cohen 2005).

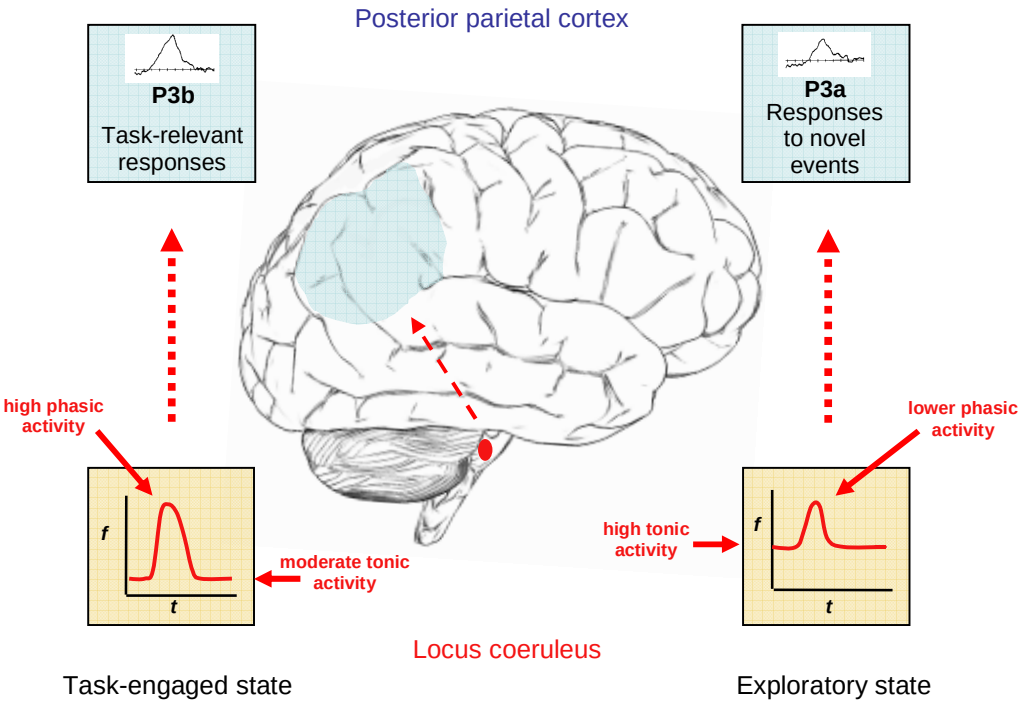


Figure 1.10. Reconfiguration of behaviour between task-engaged and exploratory states.

In the ***task-engaged state,*** locus coeruleus (LC) tonic or baseline activity is moderate, with optimal phasic bursts occurring in response to task-related events (*f*: firing rate of LC neurons, *t*: time or latency). This leads to a *P3b* potential in the posterior parietal cortex (PPC), facilitating accurate task performance.

Novel events (of no task-relevance) can also produce phasic LC responses. These are associated with a *P3a* potential in PPC, which is generally smaller than the P3b potential. The P3a does not correlate with behavioural responses when performance is task-engaged, but may be more likely to do so as behaviour becomes more ***exploratory***, with higher baseline LC tonic activity. If a novel stimulus is found to be of behavioural significance, a new goal or task may be formulated, reducing tonic LC activity (through input from medial frontal cortical regions), with optimal phasic bursts to new goal-relevant events. Note that, in contrast to either target or infrequent novel stimuli, *frequently* occurring task-irrelevant stimuli do not evoke P3 responses.

In summary, I argue here that *phasic* bursts of LC noradrenergic activity (on a background of moderate tonic levels) induce, via parietal regions, a goal-focused, task-engaged state, enhancing sustained attention to task demands and facilitating the detection of task-relevant events (indexed by the P3b). On the other hand, increases in LC *tonic* activity shift behaviour towards a more distractible and exploratory state, favouring responses to novel environmental stimuli. These are the two, broadly complementary, aspects of attention: maintaining attentive control on current task goals and responding to salient new or alerting stimuli in the environment – which I hypothesise to be a crucial aspect of right IPL function.

But what drives LC noradrenergic input to the parietal cortex and what governs the interplay between phasic and tonic modes of functioning? The answers to these questions remain to be established. However, it may be important to note that in addition to receiving subcortical afferents, there are prominent cortical projections to the LC from medial frontal and orbitofrontal structures (Rajkowski, Lu et al. 2000; Aston-Jones, Rajkowski et al. 2002), which may a key role in modulating its responses. These frontal regions might provide a site for the integration of sensory information with input from limbic structures (Carmichael and Price 1995; Devinsky, Morrell et al. 1995; Carmichael and Price 1996; Morecraft and Van Hoesen 1998; Ongur and Price 2000), placing them within a network that is also modulated by dopamine and capable of encoding the reward associations of sensory stimuli. Indeed, it has been demonstrated that the amplitude of LC phasic responses to targets on a signal detection task is altered by the motivational significance – i.e. associated reward – of the stimulus (Aston-Jones, Rajkowski et al.

1994; Rajkowski, Majczynski et al. 2004). Frontal afferents to the LC may therefore be capable of signalling the *motivational salience* of environmental events and act to bias the noradrenergic innervation to parietal cortex accordingly. The PPC of course also receives its own connections from frontal regions (Selemon and Goldman-Rakic 1988; Schmahmann, Pandya et al. 2007), enabling a direct frontal modulation of parietal activity.

In fact, the PPC seems to be an important hub where several different types of information – sensory, motor, goal-related and reward – converge. Indeed, recent evidence demonstrates that the IPL is at the heart of a 'structural core' of the human cerebral cortex, as one of the most densely interconnected cortical regions (Hagmann, Cammoun et al. 2008). Such connectivity ideally places the IPL at the centre of a network where these different types of information may compete, with signals from the LC biasing the outcome of the competition depending upon whether the subject is in a task-engaged state (with high sustained attention) or a distractible exploratory mode.

1.5. The role of the right inferior parietal lobe in controlling behaviour

In the preceding sections, I have discussed how the IPL plays a central role in networks that underlie both sustained attention and various forms of response to salient stimuli in the environment. Maintaining attention on current task goals is crucial for successful accomplishments, but just as important is the ability to adapt to changing circumstances, by reconfiguring task goals should the need arise, based on salient new information. The

brain needs to engage in both these activities and switch between them flexibly. As discussed, there is evidence for both of these modes of operation within the right IPL.

Importantly, neither of these processes are considered in several existing models of the visual system (Ungerleider and Mishkin 1982; Milner and Goodale 1995; Rizzolatti and Matelli 2003; Glover 2004). Moreover, each of these modes of operation receives input from what might be termed 'goal-directed' as well as 'bottom-up' mechanisms. It therefore becomes difficult to view the functions of the SPL and IPL as goal-driven and stimulus-driven respectively (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008), when both of these processes seem to rely so heavily on IPL activity.

I would rather conceptualise the IPL as contributing to two broadly different, but complementary, aspects of attention. Evidence suggests it plays an important role both in responding to salient events as well as maintaining attention on the task at hand. The weight given to these processes appears to differ between the two hemispheres. This is most evident from consideration of two syndromes, hemispatial neglect and limb apraxia, which result from damage to the right and left IPL respectively (De Renzi, Motti et al. 1980; Vallar and Perani 1986; Goldenberg 1996; Haaland, Harrington et al. 2000; Halsband, Schmitt et al. 2001; Heilman and Watson 2001; Mort, Malhotra et al. 2003; Buxbaum, Kyle et al. 2005; Buxbaum, Kyle et al. 2007; Pazzaglia, Smania et al. 2008).

Neglect or disorders of attention following right hemisphere damage, may be associated with deficits in sustaining attention and detecting salient events (Lhermitte, Turell et al.

1985; Hjaltason, Tegner et al. 1996; Rueckert and Grafman 1996; Robertson, Manly et al. 1997; Friedrich, Egly et al. 1998; Rueckart and Grafman 1998; Robertson 2001; Husain and Rorden 2003; Buxbaum, Ferraro et al. 2004; Husain and Nachev 2006; He, Snyder et al. 2007), whereas there is no evidence of similar deficits with limb apraxia following left hemisphere lesions. Spatial or directional biases in attention may also follow left hemisphere lesions, but they tend to be less pronounced and less persistent (Stone, Halligan et al. 1993). I would suggest that the severity of neglect is generally far less in such individuals, compared to their right hemisphere counterparts because they do not also suffer from comparably severe deficits in sustaining attention or responding to salient items.

1.6. Hemispatial neglect and investigation of right IPL function

The defining feature of hemispatial neglect is, of course, a difference in responding to stimuli in contralesional versus ipsilesional space (Mesulam 1999; Heilman, Valenstein et al. 2000; Kerkhoff 2001). Such a spatial or directional impairment clearly cannot simply be explained by a global deficit in sustaining attention or detecting salient events. My argument therefore, is not that these functions explain all of the neglect syndrome, or indeed all of IPL function, but rather that they may contribute to or exacerbate any spatial biases produced by unilateral lesions (Husain and Rorden 2003; Husain and Nachev 2006; Singh-Curry and Husain 2009).

Consequently, a major purpose of my thesis will be to investigate the non-spatial deficits associated with the neglect syndrome and how these affect the more characteristic spatial impairments. On the basis of the proposal I have outlined here, I hypothesise that right hemisphere patients with neglect should demonstrate deficits in the ability to sustain attention, as well experiencing problems detecting and orienting to salient or novel stimuli, wherever they occur in space – i.e. that these impairments are not simply lateralised to the contralesional side of space. Importantly, I would expect neglect patients to demonstrate a *vigilance decrement* over the time course of even simple tasks, rather than just an overall deficit (Whyte, Polansky et al. 1995; Parasuraman, Warm et al. 1998). For it could be argued that initial poor performance continuing throughout a task, simply indexes difficulty due to the specific cognitive demands of that task, rather than problems maintaining attention on it.

Furthermore, although it is accepted that non-spatial deficits may be an important component of the neglect syndrome (Samuelsson, Hjelmquist et al. 1998; Robertson 2001; Husain and Rorden 2003), little is understood about how they contribute to the manifestation of the spatial problems. For example do they interact, or are they merely additive in nature? If all of these processes are indeed critically dependent on IPL functionality, we may expect to see interactions among them. Using lesion analysis techniques it may also be possible to identify subregions within inferior parietal and frontal areas that are associated with particular deficits. If these regions are found to overlap, such areas may represent candidate foci, crucial in the mediation of such interactions.

Additionally, because I consider phasic alerting stimuli to act as salient inputs, evoking their behavioural effects through the IPL (Fan, McCandliss et al. 2005; Thiel and Fink 2007), alerting tones may serve to ameliorate the deficits associated with hemispatial neglect. It has previously been reported that alerting auditory stimuli can improve the spatial impairment (Robertson, Mattingley et al. 1998). However, I would hypothesise that such events should also be capable of affecting the non-spatial problems. Such a benefit might occur through a boost of phasic activity from the LC to parietal cortex, and indeed it has been shown that alerting stimuli can enhance the amplitude of target-related P3b potentials (Miniussi, Wilding et al. 1999; Griffin, Miniussi et al. 2002). The noradrenergic agonist guanfacine has been shown in a small proof-of-principle study to improve the ability of some neglect patients to sustain attention, in addition to ameliorating the spatial deficit (Malhotra, Parton et al. 2006). One of its possible mechanisms of benefit may also be to increase phasic activity from the LC to parietal and frontal regions.

As discussed earlier, the detection of novel stimuli activates the mesolimbic dopaminergic system (Bunzeck and Duzel 2006; Bunzeck, Schutze et al. 2007; Wittmann, Bunzeck et al. 2007) in addition to inferior parietal and frontal regions. Parkinson's disease is caused by degeneration of dopaminergic neurons in the substantia nigra/ventral tegmental area (SN/VTA) and may therefore represent a second neurological condition in which to examine novelty processing.

1.7. Parkinson's disease and novelty processing

Parkinson's disease (PD) is a neurodegenerative condition, primarily affecting dopaminergic neurons which project to the basal ganglia and is classically considered a disorder of movement. As such its core deficits encompass a triad of motor symptoms: tremor, brady/akinesia and rigidity. More recently, however, it has been recognised that PD also involves cognitive (Burn, Rowan et al. 2006; Verbaan, Marinus et al. 2007), mood and behavioural (Marras, McDermott et al. 2008; Aarsland, Bronnick et al. 2009) difficulties which can be a major source of disability. These additional problems may be caused by degenerative changes extending beyond the SN/VTA to other brain-stem nuclei, as well as to cortical regions (Del Tredici, Rub et al. 2002; Braak, Del Tredici et al. 2003; Parkkinen, Pirttila et al. 2008), and/or due to disordered mechanisms (disease-related or compensatory) within the dopaminergic system itself (Muller, Wachter et al. 2000; Remy, Jackson et al. 2000), in addition to the effects of drugs used to treat the motor symptoms (Cools, Barker et al. 2001; Cools, Barker et al. 2003).

Behavioural problems in PD consist of impulsive and compulsive behaviour, often termed impulse control disorders or ICD (Potenza, Voon et al. 2007), such as pathological gambling (Gschwandtner, Aston et al. 2001; Avanzi, Baratti et al. 2006; Gallagher, O'Sullivan et al. 2007) and compulsive medication overuse (Evans, Pavese et al. 2006). ICD are estimated to affect approximately 5% of PD patients at any one time (Grosset, Macphee et al. 2006; Weintraub, Siderowf et al. 2006) and between 5 and 10% at some point during the course of the disease (Voon, Hassan et al. 2006; Weintraub, Siderowf et

al. 2006). It has also been estimated that PD patients may be approximately 25 times more likely to develop an ICD compared to age- and sex-matched healthy controls (Avanzi, Baratti et al. 2006).

Both impulsive and risk-taking personality profiles have been linked to high scores in sensation (or novelty) seeking (Llewellyn 2008), and it has often been asserted that there is a characteristic 'Parkinsonian personality' profile. This is considered to be low in impulsivity and novelty-seeking and instead dominated by introversion, cautiousness and moral rigidity (Glosser, Clark et al. 1995; Tomer and Aharon-Peretz 2004). Needless to say, this is somewhat at odds with the fact that this population appears particularly sensitive to developing ICD. It has been suggested that such behavioural difficulties in PD may be related to the use of dopamine agonists (Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007). However, this argument fails to explain why some individuals, using these drugs for the same indication, develop these problems, whilst others do not.

Likewise, there is inconsistency in the literature regarding whether or not PD patients, without ICD, demonstrate risky behaviour. Some studies employing gambling tasks, such as the Iowa Gambling Task (IGT) (Bechara, Damasio et al. 1994), suggest that they do (Thiel, Hilker et al. 2003; Perretta, Pari et al. 2005; Pagonabarraga, Garcia-Sanchez et al. 2007; Kobayakawa, Koyama et al. 2008) while others have failed to find any evidence of risk-prone decisions (Stout, Rodawalt et al. 2001; Czernecki, Pillon et al. 2002; Mimura, Oeda et al. 2006).

PD, however, is not a homogeneous condition. In terms of the motor phenotype, two quite distinct subgroups have been described: the *akinetic-rigid* group – in whom the main symptoms are stiffness and slowness of movement – and the *tremor dominant* group – in whom tremor is the principal finding (Jankovic, McDermott et al. 1990; Kang, Bronstein et al. 2005).

Importantly, post-mortem evidence supports this distinction, with the brains of akinetic-rigid patients demonstrating more extensive neuronal loss and gliosis within the midbrain (Paulus and Jellinger 1991) and greater reductions in dopamine levels within the internal segment of the globus pallidus (Rajput, Sitte et al. 2008), compared to those who are tremor dominant. Critically, all of the patients included in the study by Rajput and colleagues were followed-up over a number of years (range: 4.9-24.6) and persistently demonstrated the pattern of symptoms consistent with their sub-grouping. There is also evidence that tremor dominant patients may be less susceptible to the development of cognitive dysfunction (Allcock, Kenny et al. 2006; Burn, Rowan et al. 2006), as well as autonomic problems (Allcock, Kenny et al. 2006).

Accordingly, I hypothesise that there may be further differences between these two subgroups, in terms of their ability to process novelty and in their willingness to take risks, which might, at least in part, explain why some PD patients are susceptible to developing ICD while others are not. Examination of behavioural differences between these sub-groups may therefore help elucidate key features of novelty processing and risk-taking in

different patients with PD. This is the area of research that I will focus on in Chapters 6 and 7 of this thesis.

1.8. The interplay between novelty, reward and risk-taking

1.8.1. The role of dopamine and the basal ganglia

ICD in PD patients are often associated with the presence of dyskinesias (Voon, Potenza et al. 2007; Voon, Fernagut et al. 2009), involuntary movements that are due to excessive dopaminergic stimulation. Furthermore, ICD symptoms are often found to abate after reductions in dopaminergic treatments (Weintraub 2008; Antonini and Cilia 2009; O'Sullivan, Evans et al. 2009). Hence it would seem that elevated levels of dopamine neurotransmission may play a role in the development of ICD.

It is possible to distinguish separate sensorimotor, cognitive and limbic regions of the striatum, based on their connections with the cerebral cortex (Parent 1990), a finding that has also been seen *in vivo* in the human brain using MRI tractography techniques (Draganski, Kherif et al. 2008) – see Figure 1.11. The ventral striatum receives input from limbic areas, such as the hippocampus, amygdala and orbitofrontal cortex, and has been implicated in drug addiction (Robbins and Everitt 1999). It is therefore possible that excessive limbic dopaminergic stimulation is involved in the development of ICD. If this is the case, PD patients with relative preservation of ventral striatal dopamine projections may be at increased risk of developing such problems (Dagher and Robbins 2009).

Indeed, it has been documented that in PD, dopamine neurons projecting to the ventral striatum are less severely affected by the disease process (Kish, Shannak et al. 1988). This therefore raises the possibility that pharmacological restoration of dopamine transmission in the *dorsal* (motor) striatum may lead to *overdosing* of the *ventral* striatum, with excessive dopamine receptor stimulation leading to adverse effects (Swainson, Rogers et al. 2000).

This hypothetical difference in baseline dopamine levels between the dorsal and ventral striatum may also account for the finding that levodopa improves performance on cognitive tasks thought to involve the dorsal striatum, such as working memory and task-set switching, whilst causing deficits in tests thought to depend on the ventral striatum, such as reversal learning and gambling tasks (Cools, Barker et al. 2001). This *ventral overdose* hypothesis is further supported by neuroimaging studies, which show that the normal signal that arises from the ventral striatum when subjects must reverse a previously learned response is abolished in PD patients treated with levodopa, in parallel with impaired task performance (Cools, Lewis et al. 2007).

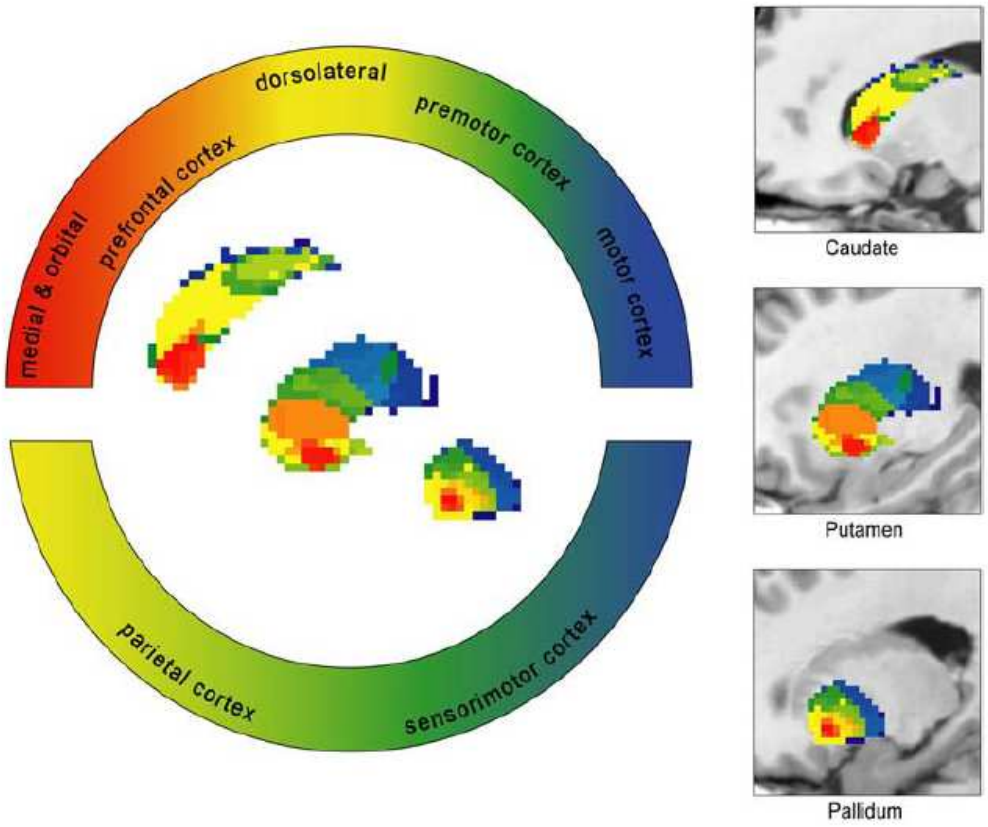


Figure 1.11. Cortical connectivity patterns of the human basal ganglia (from Draganski *et al,* 2008).

A 'rostrocaudal' gradient of frontal cortical connectivity in the caudate, putamen and pallidum of the basal ganglia has been revealed using probabilistic MRI tractography in the human brain. Sagittal views of the basal ganglia are shown superimposed on a T1-weighted sagittal image.

Ventral parts of the striatum show predominant connections to prefrontal cortical regions, especially medial prefrontal cortex and the orbitofrontal cortex. These regions are thought to be less severely affected by the PD disease process. The central and caudal portions of the striatum are preferentially connected with dorsolateral prefrontal cortex, premotor, sensorimotor and parietal cortices.

Another factor which may contribute to mesolimbic overdosing is sensitisation, which refers to an increased effect of stimulant drugs with repeated administration (Paulson and Robinson 1995). Sensitised animals are more likely to self-administer drugs and there is also evidence that PD patients with addiction (compulsive medication overuse) express sensitisation in the ventral striatum (Evans, Pavese et al. 2006). In this study, PET was used to measure dopamine release in response to a single dose of levodopa in PD patients with and without compulsive medication overuse. Levopdopa caused dopamine release in the motor striatum in both groups in equal measure. However, only the addicted group demonstrated significant dopamine release in the ventral striatum, indicating sensitisation. Sensitisation to amphetamine has also been shown in the ventral part of the striatum in control subjects using PET (Boileau, Dagher et al. 2006), with this being proportional to novelty-seeking as measured by Cloninger's personality questionnaire (Cloninger 1987).

As discussed earlier, phenotypically and on the basis of some pathological studies, there appear to be at least two distinct subgroups of PD – akinetic-rigid and tremor dominant. If one of these subgroups were found to have differential levels of degeneration within the dorsal and ventral subdivisions of the striatum – or in the subdivisions of the SN/VTA that project to these regions – such that the mesolimbic pathway was relatively spared to a greater degree, this could in theory account for such a group being more vulnerable to the development of impulse control problems. This theory is something which will be explored in Chapters 6 and 7 of this thesis.

Organisms engage in various forms of approach behaviours in order to obtain resources for homeostatic and reproductive needs. Such resources may be considered as ‘rewards’, which elicit and reinforce particular behaviours. During the evolution of higher mammals development of the functions of rewards have supported increasingly sophisticated forms of individual and social behaviours. Biological and cognitive needs therefore define the nature of reward, with the availability of these shaping the organism’s life conditions. Much evidence from monkey studies, which has been reviewed by Shultz (Schultz 1998), indicates that dopaminergic projections from the midbrain to the striatum and frontal cortex, play a central role in mediating the effects of rewards on learning and behaviour. Most dopamine neurons show phasic bursts of activation after rewards (Romo and Schultz 1990; Schultz, Apicella et al. 1993; Mirenowicz and Schultz 1994), which are transferred to other stimuli if they reliably predict the occurrence of a subsequent reward (Ljungberg, Apicella et al. 1992; Mirenowicz and Schultz 1994) – see Figure 1.12. They also show biphasic activation-depression responses to stimuli that resemble reward-predicting events (Schultz and Romo 1990) and demonstrate activation in response to novel events (Horvitz, Stewart et al. 1997).

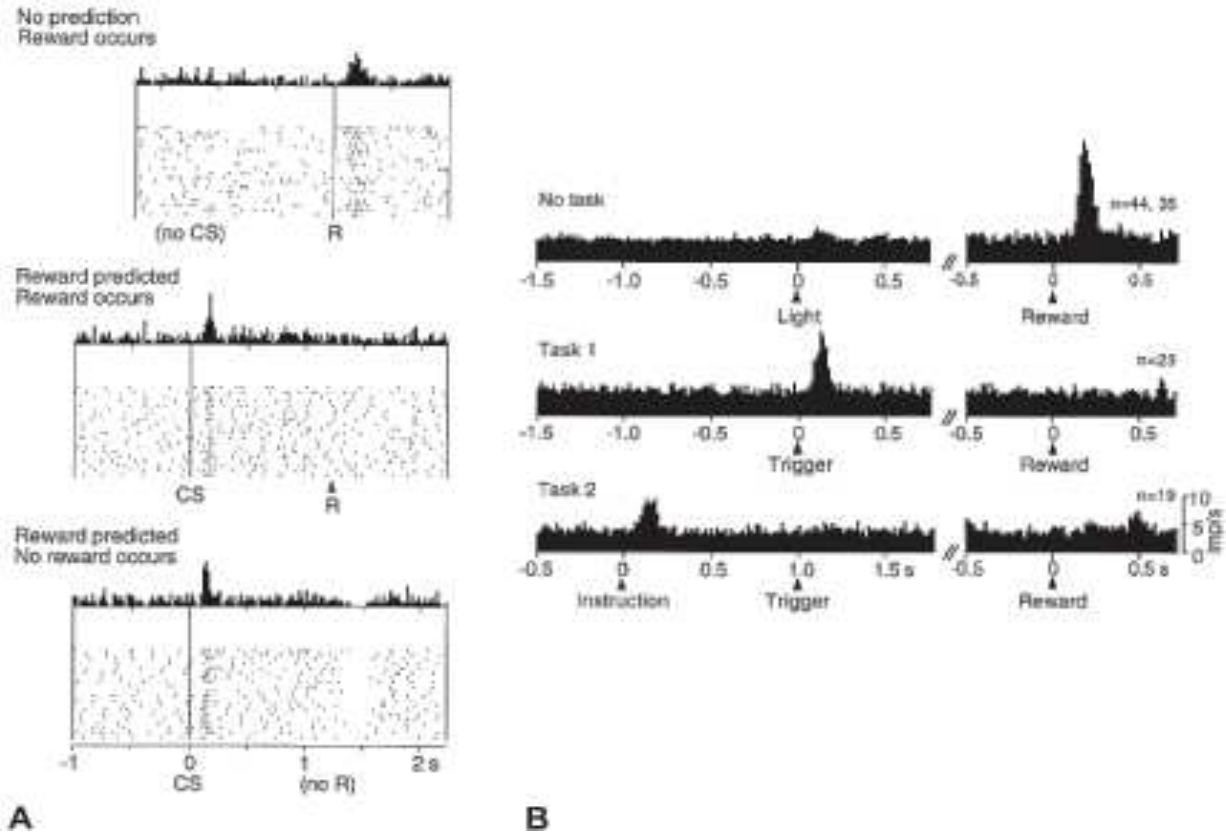


Figure 1.12. Characteristics of dopamine cell firing (from Schultz, 1998).

A. Dopamine neurons report rewards according to reward prediction. *Top*: an unpredicted reward (R) occurs, causing activation of the dopamine neuron. *Middle*: a conditioned stimulus (CS) reliably predicts a reward. In this case the dopamine neuron is not activated by the reward, but by the reliable reward predictor. *Bottom*: a conditioned stimulus predicts a reward, causing activation of the neuron, but the reward fails to occur. Activity of the dopamine neuron is depressed at the time the reward was predicted to occur.

B. The dopamine response is transferred to the earliest predictive stimulus. Displays here show averaged population histograms of a number (n) of neurons recorded from in a given behavioural situation. *Top*: outside of a task, neurons do not respond to a light stimulus, but 35 (of 44) neurons respond to a juice reward. *Middle*: response occurs to a reward predicting trigger stimulus, but not to the reward itself, in the context of the same task. *Bottom*: dopamine neuron response is transferred to an instruction cue preceding the reward-predicting trigger stimulus by a fixed interval of 1 second, with no response to the reward-predicting stimulus or the reward.

Generalisation of responses by dopamine neurons to stimuli that resemble reward-predicting events generally evoke activations which are lower in magnitude and engage fewer neurons than true reward-predicting stimuli, and are frequently followed by immediate depressions (Schultz 1998). It has been suggested that ambiguity regarding the possibility of reward – due to similarity to a known reward predictor – may cause the initial activation, while the subsequent dip in activity may reflect a cancelling of the erroneous reward assumption (Kakade and Dayan 2002). In contrast, dopaminergic responses to novel stimuli may allow a new stimulus to be stored in working memory until its potential for future reward has been explored and evaluated (Kakade and Dayan 2002).

In humans too, phasic bursts and depressions of dopamine have been inferred to occur during positive and negative feedback respectively during neurophysiology studies (Holroyd and Coles 2002), as well as neuroimaging investigations (Delgado, Nystrom et al. 2000; Frank, Woroch et al. 2005). By failing to discriminate between different types of reward, dopamine neurons appear to produce an 'alerting' signal about the unexpected presence or absence of rewards. They appear to be highly influenced by predictability, demonstrating increases in activation in response to rewarding events that are better than expected or occur earlier than predicted, being unaffected by rewards that are only as good as predicted and depressed by events that are worse or occur later than expected (Ljungberg, Apicella et al. 1991; Hollerman and Schultz 1996). They are therefore considered to signal *prediction error*, which has been postulated to underlie the teaching signal in reinforcement learning theories, where learning is driven by deviations or 'errors'

between the predicted time and amount of rewards and their actual experienced times and magnitudes (Schultz, Dayan et al. 1997).

In computer models, such as the *temporal difference model* (Schultz, Dayan et al. 1997; Kakade and Dayan 2002), the reward prediction error signal gradually optimises behaviour by changing the synaptic strengths of action selection neural networks. Indeed, it has been shown that dopamine acting at synapses in the basal ganglia can affect long-term potentiation and long-term depression (Bear and Malenka 1994; Calabresi, Saiardi et al. 1997; Nishi, Snyder et al. 1997; Kerr and Wickens 2001), the neurophysiological processes thought to underlie learning and memory formation.

However, other theories take into account evidence that dopamine also appears to have motivating and activating effects independent of learning, with the emphasis being on dopamine enhancing reward-seeking behaviours by acting on arousal, attention, movement and effort (Salamone, Correa et al. 2005; Robbins and Everitt 2007). Such an example is the incentive salience hypothesis put forward by Berridge and Robinson, in which dopamine firing is thought to exaggerate the incentive properties of environmental stimuli, turning them into ‘objects of desire’ (Berridge and Robinson 1998).

It is important to note however, that these two types of model are not mutually exclusive. It has been shown in some learning paradigms that changes in phasic dopamine bursts occur immediately before a reward-seeking action and again once the reward is actually received (Phillips, Stuber et al. 2003). Hence phasic dopamine may act both as a learning

signal and as an incentive signal. One computational approach by McClure and colleagues has tried to reconcile the two models, suggesting that the reward prediction error signal also biases neural activity in favour of actions or stimuli predictive of reward (McClure, Daw et al. 2003). In their scheme, dopamine not only encodes reward prediction error for the purpose of learning, but also the expected future reward rate, which is highly similar to incentive salience (with the incentive salience of an environmental stimulus being equal to its reward prediction).

This scheme has been expanded by Niv and colleagues, who propose that dopaminergic stimulation is a running average of recent rewards and therefore an index of likely future rewards (Niv, Daw et al. 2007). Such a proposal would suggest that in states of high dopaminergic activity, choices may be biased towards reward-predicting actions or stimuli, but may also energise and invigorate the individual, such that when expected rewards are high, there is a cost of inactivity.

A conceptual link between the learning model described here and addictive, or novelty-seeking, behaviour is supported by recent human and animal studies examining naturally occurring variations in dopamine function. In humans, two polymorphisms that determine dopamine D2 receptor expression have been associated with impulsivity and vulnerability to drug addiction, and both appear to influence performance in a probabilistic task that distinguishes positive from negative feedback learning (Klein, Neumann et al. 2007; Jocham, Klein et al. 2009). The TAQ-1A polymorphism modulates D2 receptor density in the striatum. The A1 allele, which is associated with lower expression of D2 receptors, is

also associated with impulsivity, addiction and compulsive behaviours, including pathological gambling (Comings, Rosenthal et al. 1996). Individuals with this allele are better at learning from positive feedback, but worse at learning from negative feedback, than subjects without the allele, and the two groups differ in their reward-related response in the ventral striatum as measured with fMRI (Klein, Neumann et al. 2007). Poorer learning from negative feedback has also been reported for the C957T polymorphism of the D2 receptor gene, which is also associated with reduced expression of D2 receptors.

Impulsivity, addiction and other risky behaviours may therefore be partly explained by an inability to learn from negative feedback. As discussed earlier, negative reward prediction errors (i.e. when an expected reward fails to arrive) are signalled by pauses in dopamine neuron firing. Persistent postsynaptic dopamine stimulation may therefore reduce the ability of these pauses to influence learning, accounting for the difficulty medicated PD patients have in negative feedback learning (Frank, Seeberger et al. 2004; Cools, Lewis et al. 2007), which is a consistent feature of the human (Frank, Moustafa et al. 2007; Klein, Neumann et al. 2007) and animal dopamine-related impulsive phenotypes (Belin, Mar et al. 2008). Indeed, it is easy to see how insensitivity to the adverse consequences of an action may promote the taking of disproportionate risks.

These theories are further supported by recent findings on the cellular neurophysiology of striatal dopamine. A well-validated model of the cortico-striatal system divides it into direct and indirect pathways (Albin, Young et al. 1989) – see Figure 1.13. The direct pathway contains D1 dopamine receptors and is involved in action selection, while the

indirect pathway contains D2 receptors and is primarily involved in response inhibition (Mink 1996).

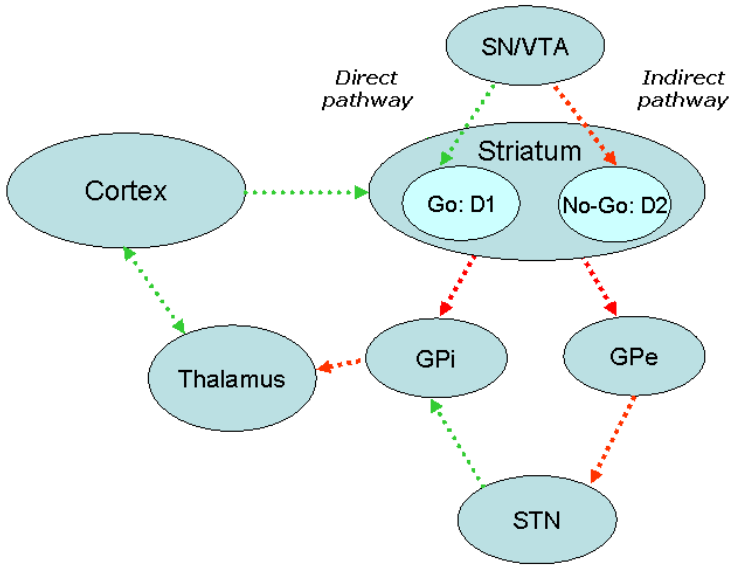


Figure 1.13. Basal ganglia loops including the direct and indirect pathways. Striatal neurons are divided into two subclasses based on differences in biochemistry and efferent projections. The 'Go' cells, which express D1 dopamine receptors, project directly to the internal segment of the globus pallidus (GPi) and have the effect of disinhibiting the thalamus, thereby facilitating the execution of an action (or process) represented in the cortex. The 'No-Go' cells, which express D2 dopamine receptors, are part of the indirect pathway to the internal segment of the globus pallidus, via its external segment (GPe) and subthalamic nucleus (STN), and have an opposing effect, suppressing actions from execution. Thus SN/VTA activity differentially modulates activity in the direct and indirect pathways via D1 and D2 dopamine receptors.

Dopamine signalling (like noradrenaline) also occurs in two modes. In addition to the phasic bursts already described, slow bursts of dopamine neuron activity control tonic dopamine levels, which act via the D2 receptor. The large transient increases in dopamine, which occur after phasic bursts, are able to activate the lower affinity D1 receptor (Grace 2008). A further model has been proposed in which the phasic bursts that follow unexpected rewards promote positive reinforcement within the direct pathway, via the D1 receptor, whilst withheld rewards or punishments, by reducing tonic dopamine levels, lead to negative reinforcement via reduced D2 signalling in the indirect pathway (Cohen and Frank 2009).

In fact, it has recently been shown that D1 stimulation and lack of D2 stimulation both promote long-term potentiation at the cortico-striatal synapses of the direct and indirect pathways respectively (Shen, Flajolet et al. 2008). Thus it is likely that both tonic and phasic dopamine signalling shape striatal synaptic plasticity, whether in the normal situation – learning – or pathological situation – addiction or compulsive behaviours. Persistent pharmacological stimulation, as is the case in medicated PD patients, could therefore potentiate positive reinforcement learning and impair learning from punishments, increasing engagement in reward-seeking behaviours and at the same time reducing the ability to disengage from risky behaviours leading to negative consequences (Dagher and Robbins 2009).

In my opinion, such an account of vulnerability to ICD in medicated PD patients does not preclude the ventral overdose hypothesis (Dagher and Robbins 2009). Rather it suggests to

me that relative ventral overdose may render these patients particularly susceptible to the development of such problems. Nevertheless, this theory would suggest that these behaviours may be seen even in the absence of ventral striatal hyperstimulation, although this situation is likely to be less common.

1.8.2. Parietal contributions to reward processing

I have discussed earlier in this chapter, evidence which suggests the PPC plays a crucial role in detecting novel stimuli, as indeed the dopaminergic system does too. Expectations about the delivery of reward also appear to activate parietal cortex, in addition to the dopaminergic system.

For example, Platt and Glimcher have examined the activity of neurons in the lateral intraparietal area (LIP) in monkeys in response to reward-related information (Platt and Glimcher 1999). Monkeys were given a task in which the amount of reward associated with different visual stimuli was varied. The animal had to fixate on a central spot while two stimuli were presented, one inside the response field of the LIP neuron being recorded from, and one outside. The animal then received a cue instructing which stimulus it should make a saccade to, but had to wait for a go signal before making its response. Consistent with previous studies, LIP neurons were more active when the monkey was cued to make a saccade to the stimulus inside the neuron's response field.

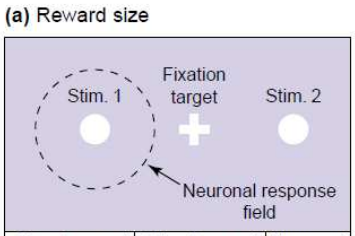
However, in another version of this task, the reward size associated with each stimulus was varied across blocks of trials. This produced activity of LIP neurons which was

greater in blocks in which the target stimulus was associated with larger rewards and smaller in blocks where reward was smaller (see Figure 1.14(a) for a schematic of this type of study). In a further version, the size of the reward was fixed, but the probability of reward attached to the target stimuli was varied between blocks from 20% to 80% of trials. Most LIP neurons demonstrated greater activity when it was more likely that a saccade to the response field would result in reward (Figure 1.14(b)). The authors therefore interpreted these modulations in activity as showing that LIP neurons encode reward-related variables associated with expected gain and outcome probability.

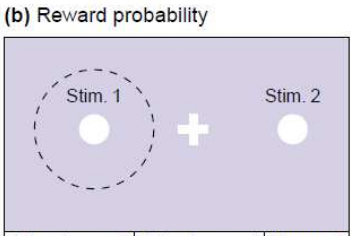
Other studies have described similar findings (Coe, Tomihara et al. 2002; Bendiksby and Platt 2003; Newsome 2003; Sugrue, Corrado et al. 2004), with neuronal modulations in LIP interpreted as being associated with reward contingencies and the animal's expectations of the amount of reward it was likely to receive. However, alternative interpretations of this data are possible. Specifically, the phenomena described in experiments of reward manipulation may be closely related to those seen in studies examining neuronal mechanisms related to attention (Figure 1.14(c)).

For example, it is only natural to expect that subjects will allocate more attention to stimuli or locations that are more likely to be rewarding. Often, the neurophysiological and behavioural consequences of shifting attention and changing reward expectations do not provide a clear basis for distinguishing between these processes (Maunsell 2004). Behavioural performance, indexed by reaction times or detection thresholds, is superior for attended stimuli (Posner 1980), with similar improvements seen for stimuli associated

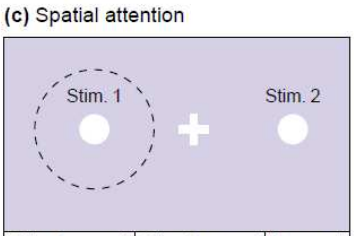
with larger rewards (Hollerman, Tremblay et al. 1998; Leon and Shadlen 1999; Kobayashi, Lauwereyns et al. 2002). Although there are differences between the designs of most attention and reward experiments, these are frequently unable to provide a basis for attributing affects to one process or the other. For example, most attention studies manipulate attention in an all-or-none way by rewarding one target reliably and the others not at all. Whereas some reward studies have adjusted reward parametrically to show that neuronal modulations vary continuously with expected reward (Platt and Glimcher 1999), this may simply be due to stimuli associated with higher reward being effectively more salient and attracting greater attention.



Stim. 1 reward		Stim. 2 reward		Neuronal activity
Size	Prob.	Size	Prob.	
8	0.5	2	0.5	high
2	0.5	8	0.5	low



Stim. 1 reward		Stim. 2 reward		Neuronal activity
Size	Prob.	Size	Prob.	
5	0.8	5	0.2	high
5	0.2	5	0.8	low



Stim. 1 reward		Stim. 2 reward		Neuronal activity
Size	Prob.	Size	Prob.	
5	1.0	0	0.0	high
0	0.0	5	1.0	low

Figure 1.14. Primate LIP responses due to reward and spatial attention are difficult to disentangle (from Maunsell, 2004).

Schematics from typical reward and attention tasks, illustrating the essence of stimulus and reward contingencies used in these experiments.

(a) Reward size task. The top half of the panel demonstrates a visual display consisting of a central fixation cross and two peripheral stimuli, one of which lies within the response field of the neuron being recorded. When reward size is manipulated, both stimuli are equally likely to be selected as the response target on a given trial. In some blocks, correct responses to one target receive a large reward (8), while correct responses to the other target receive a small reward (2). The activity of many neurons is modulated by reward size, with activity being greater for stimuli in the neuronal response field that are associated with high rewards.

(b) Reward probability task. When reward probability is manipulated, rewards are always the same size, but in some blocks one neuron is more likely to be selected as the response target (0.8), while in others that stimulus is less likely to be selected (0.2). The activity of neurons is modulated by reward probability, with higher activity during trials in which the stimulus in the response field is more likely to be selected.

(c) Spatial attention experiment. Targets appear on both sides, but rewards are given only for responses to the 'correct' side, with responses to the wrong side (distractors) being unrewarded. The rewarded side alternates between blocks. Neuronal activity is stronger during blocks in which the stimulus in the response field is rewarded.

As can be seen the structure of these experiments is very similar.

More recent studies have attempted to parse the effects of reward and attention related processes on parietal activity. For example one study employing a rewarded saccadic-cueing task in monkeys, found that while the activity of LIP neurons was modulated by reward size, neuronal responses were also correlated with reaction times independently of reward magnitude (Bendiksby and Platt 2006). The authors argue that this indicates that LIP is a crucial area for integrating reward-related information with attention and saccade planning, but that information regarding reward expectation and attentional processes may be separate.

Indeed, another group of authors have found that reversible activation of LIP does not affect reward evaluation processes, but does affect the ability to use reward in a spatially unbiased manner (Balan and Gottlieb 2009; Peck, Jangraw et al. 2009). Some human studies have also attempted to assess the combined effects of attention and motivation on the performance of visual tasks (Small, Gitelman et al. 2005; Engelmann and Pessoa 2007; Engelmann, Damaraju et al. 2009). Importantly, rewards or incentives have been shown to interact with attentional processes, with the impact of incentive being greater on invalidly cued trials – that necessitate reorienting – compared to validly cued trials. Furthermore, this effect of motivation on reorienting led to an increase in target-evoked signals in the TPJ (Engelmann, Damaraju et al. 2009).

The idea of parietal cortex playing a role in integrating reward information – or motivational salience – with attentional processes is consistent with the theory of IPL function that I developed earlier in this chapter. As discussed in Section 1.4.1, signals

regarding motivational salience may come from noradrenergic input to the PPC – which in turn receives afferents from orbitofrontal and medial frontal areas (Rajkowski, Lu et al. 2000; Aston-Jones, Rajkowski et al. 2002), which are closely connected to the mesolimbic dopaminergic system (Carmichael and Price 1995; Devinsky, Morrell et al. 1995; Carmichael and Price 1996; Morecraft and Van Hoesen 1998; Ongur and Price 2000). Evidence has also been accumulating for a more direct dopaminergic input to PPC, with the parietal lobe appearing to receive input (via the thalamus) from the SN/VTA (Yeterian and Pandya 1993; Middleton and Strick 2000; Middleton and Strick 2000; Clower, Dum et al. 2005).

The point I would like to make here, however, is that parietal dysfunction, which may also occur in PD (Antonini, De Notaris et al. 2001; Matsui, Udaka et al. 2006; Beyer, Janvin et al. 2007; Nobili, Abbruzzese et al. 2009), may influence *reward-related* and *risk-taking behaviour*, in addition to the processing of novel stimuli. Indeed, the right IPL has been shown to be significantly activated during the outcome phase of the Iowa Gambling Task in normal subjects (Lin, Chiu et al. 2008). To the best of my knowledge, there has only been one study which has examined the effects of parietal lesions on reward-related decision-making (Gomez-Beldarrain, Harries et al. 2004). This investigation suggested that while parietal patients were good at assessing task-related information, they were poor at using this information to inform their judgements.

1.9. Parietal and frontal dysfunction in Parkinson's disease

One of the most common neuropsychiatric presentations of PD is general cognitive decline, including dementia which can affect from 20% to 40% of this patient population (Hughes, Ross et al. 2000; Aarsland, Andersen et al. 2001; Korczyn 2001). Traditionally, dementia in PD has been considered to be mainly driven by reduced dopaminergic input to the frontal lobes. However, more recently it has become clear that diffuse cortical abnormalities may be found in PD patients, particularly those with dementia; with diffuse Lewy bodies, as well as Alzheimer-like changes reported at neuropathological examination (Brown, Dababo et al. 1998). Imaging studies have also demonstrated changes in the frontal, parietal and temporal lobes in PD patients with dementia (Antonini, De Notaris et al. 2001; Derejko, Slawek et al. 2006; Beyer, Janvin et al. 2007).

Importantly, compared to healthy control subjects, PD patients with mild cognitive impairment (who do not meet the criteria for dementia) also demonstrate hypoperfusion (Derejko, Slawek et al. 2006; Nobili, Abbruzzese et al. 2009) and atrophy (Beyer, Janvin et al. 2007) of parietal, frontal and temporal regions. In fact, even PD patients with no evidence of cognitive difficulties demonstrate a significant reduction in perfusion of *right* frontal and parietal cortex in comparison to controls, which is not significantly different from that of PD patients with dementia (Derejko, Slawek et al. 2006).

The potential importance of parietal dysfunction in PD has also been highlighted by recent studies (Matsui, Udaka et al. 2006; Matsui, Nishinaka et al. 2007). These investigations

suggest that impaired performance on tests traditionally thought of as reflecting frontal function, such as the frontal assessment battery and the WCST, are actually associated with hypoperfusion (Matsui, Udaka et al. 2006) and reduced fractional anisotropy (Matsui, Nishinaka et al. 2007) in the parietal, rather than the frontal lobes in PD.

Furthermore, in PD patients without dementia, impairments in several neuropsychological tests have been found to correlate with a decrease in metabolic activity in frontal and parietal areas, with these regions forming part of a PD-related cognitive network (Huang, Mattis et al. 2007; Hirano, Eckert et al. 2009). This metabolic network is defined by subjecting ^{18}fluorodeoxyglucose PET images to spatial covariance analysis and has been found to be highly reproducible in individual patients (see Figure 1.15).

Consistent with the existence of parietal dysfunction in PD, visuospatial problems are often reported in these patients. For example, they may have difficulty with tasks such as mental rotation, perceptual closure, line bisection and left-right decisions (Cronin-Golomb and Amick 2001). However, the extent and nature of visuospatial impairment has been unclear, in part because some studies have failed to confirm the existence of such deficits (Brown and Marsden 1986; Cooper, Sagar et al. 1991).

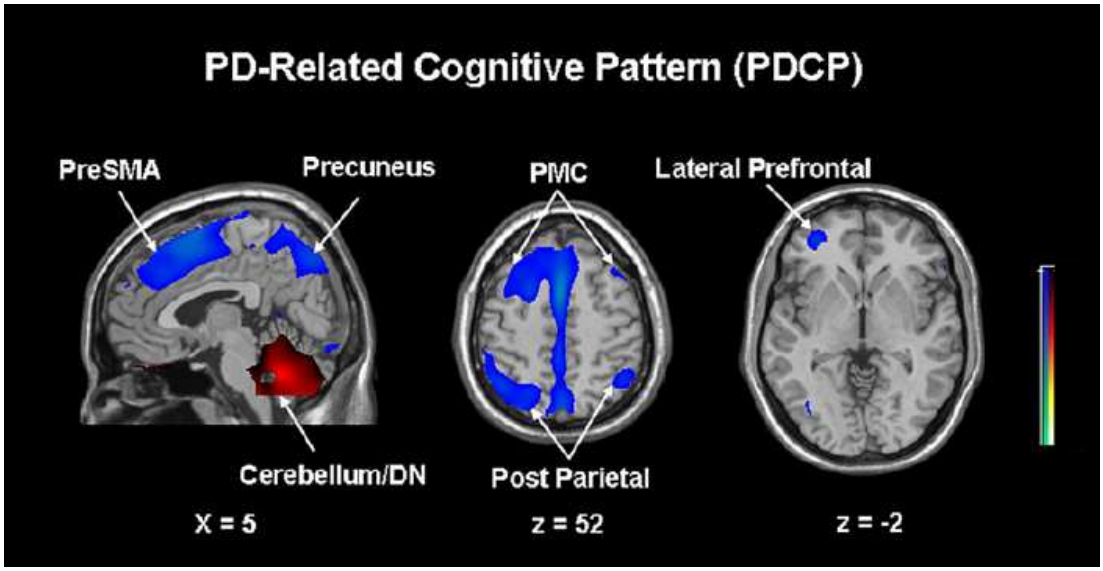


Figure 1.15. Parkinson's disease-related cognitive pattern of metabolic activity (Huang *et al,* 2007).

This PD-related cognitive pattern of metabolic activity was identified by covariance analysis of ^{18}F-fluorodeoxyglucose PET scans of 15 PD patients. This pattern was characterized by covarying metabolic reductions in the rostral supplementary motor area (pre-SMA) and precuneus (left figure), as well as in the dorsal premotor (PMC) and posterior parietal regions (middle figure) and in the left prefrontal cortex (right figure). Relative metabolic increases were seen in the cerebellar vermis and dentate nuclei (DN). Voxels with positive region weights (metabolic increases) are coloured red and those with negative region weights (metabolic decreases) are coloured blue.

These discrepancies may be explained, at least to some extent, by inattention to the potentially critical factor of body side of motor symptom onset. The asymmetrical motor symptoms in PD have been associated with an asymmetry in dopamine depletion in the

SN/VTA (Kempster, Gibb et al. 1989), which results in a similar asymmetry of striatal, and hence striato-cortical, dysregulation (Middleton and Strick 2000; Middleton and Strick 2000). These considerations may be particularly important when considering visuospatial function, which is considered to be lateralised to the right parietal lobe.

One recent study has explored this idea (Schendan, Amick et al. 2009). In this study, PD patients with left-sided symptom onset (right hemisphere dysfunction) were shown to have difficulty processing hierarchical stimuli at the global level, while patients with right-sided onset of symptoms (left hemisphere dysfunction) demonstrated abnormal local level processing. These findings are consistent with previous lesion studies, which have shown that global processing of such stimuli is dependent of an intact right parietal lobe, with local processing relying on the left side (Robertson, Lamb et al. 1988; Lamb, Robertson et al. 1989).

On this basis, it is therefore possible that PD patients may also demonstrate some of the deficits that I earlier argued depend crucially on the right IPL, such as the ability to sustain attention and detect salient events, in addition to visuospatial impairments. However, in light of the findings discussed above, I would hypothesise that only PD patients with left-sided symptom onset are likely to be susceptible to these problems.

However, the important point to take from this literature – in terms of this thesis – is that parietal dysfunction may represent a further mechanism of vulnerability of PD patients to the dysregulation of reward information.

1.10. Summary and outline of remaining chapters

In this chapter I have examined evidence which suggests that previous models of cortical visual attentional processing (Ungerleider and Mishkin 1982; Milner and Goodale 1995) have difficulty incorporating the human IPL. More recent models have attempted to rectify this (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008), but I argue, fail to capture the full extent of IPL functionality. I have reviewed evidence which suggests that the right IPL plays a crucial role in two broadly different, but complimentary, aspects of attention: maintaining attentive control on current task goals, in addition to responding to salient new information or alerting stimuli in the environment. I have argued that findings from functional imaging, electrophysiological and lesion studies are all consistent with the view that this region is a vital part of a system that allows the flexible adaptation of behaviour between these two contrasting modes of operation, and that noradrenergic input to the IPL may be particularly important in this regard. Patients with hemispatial neglect, the syndrome which frequently occurs following damage to the right IPL (Vallar and Perani 1986; Mort, Malhotra et al. 2003), represent an ideal population in which to investigate this proposal further.

The processing of salient new, or novel, stimuli also involves activation of the mesolimbic dopaminergic system (Bunzeck and Duzel 2006), the neuromodulatory network which is crucial in signalling reward-related information (Schultz 1998). PD, the neurodegenerative condition characterised by loss of dopaminergic cells in the midbrain, therefore represents

another neurological condition, investigation of which may help reveal how the brain processes stimulus novelty.

In fact, a subgroup of medicated PD patients, go on to develop impulse control problems, which are associated with risk-taking behaviour and novelty-seeking (Wu, Politis et al. 2009). The use of dopamine agonists has been implicated in the genesis of ICD (Voon, Potenza et al. 2007), however, this does not explain why some patients using these drugs develop such problems, whilst others do not. One possibility is that pathophysiological differences between the akinetic-rigid and tremor dominant subgroups of PD may go some way to explaining a difference in susceptibility between them.

These pathological differences may occur within the dopaminergic system itself. However, patients with PD may additionally demonstrate pathology outside the midbrain and basal ganglia, including the parietal and frontal lobes. These changes, of course, may also contribute to a vulnerability to behavioural and cognitive problems.

The aim of my thesis will be to investigate these proposals by examining patients with neglect and PD.

In Chapter 2, I will probe some of the *non-spatial* deficits which may be associated with neglect and investigate how these influence the characteristic spatial component of the disorder. This will be achieved by comparing the ability of neglect patients, with right hemisphere stroke control and healthy elderly subjects, to *sustain attention* and *encode*

salient events at a single central location, as well as in left and right sides of space. Lesion analysis techniques will be employed to examine the anatomical correlates of the impairments identified. Chapter 3 will extend these findings, by assessing the effect of salient stimuli – *phasic alerting tones* – on the spatial and non-spatial deficits established in Chapter 2.

Chapter 4 will present a report of a single case with persistent neglect and severe difficulties sustaining attention, secondary to bilateral thalamic lesions. I will discuss the effects of continued use of the noradrenergic agonist guanfacine on these deficits.

In Chapter 5, I will investigate *novelty processing* in right hemisphere stroke patients with and without neglect. The ability of these patients to encode novel stimuli will be compared with their processing of non-novel perceptual salience. Again, the anatomical correlates of any deficits will be probed using lesion analysis techniques.

Chapter 6 will examine *novelty processing and risk-taking behaviour in patients with PD*. The performance of patients with akinetic-rigid and tremor dominant PD, without ICD, will be compared. Additionally, their performance will be contrasted with that of PD patients with ICD, as well as healthy elderly control subjects. In Chapter 7, I will present the results of a magnetisation transfer imaging study performed in PD patients with and without ICD. Correlations between the imaging and behavioural data will be assessed, in addition to information regarding motor subgroup.

Finally, in Chapter 8, I will discuss the implications of my research, in the context of the proposals I have outlined in this introduction, and suggest future avenues of investigation.

Chapter 2

2.1. Introduction

As discussed in Chapter 1, there have been a number of influential attempts at the functional segregation of the cortical visual system (Ungerleider and Mishkin 1982; Milner and Goodale 1995). These dorsal versus ventral stream dichotomies, however, have found it difficult to incorporate the inferior parietal lobe (IPL) (Rizzolatti and Matelli 2003; Nachev and Husain 2006), which may at least in part, be explained by the fact that these proposals were based on experiments in the monkey, in which there may not be a complete, functional equivalent of the human IPL (Orban, Van Essen et al. 2004; Orban, Claeys et al. 2006). However, an important model which attempts to account for IPL functionality has been proposed by Corbetta and Shulman (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008), who propose the existence of anatomically distinct *frontoparietal* networks, which are thought to be specialised for the control of contrasting attentional processes.

Corbetta and Shulman's dorsal frontoparietal network, which includes the intraparietal sulcus (IPS), the superior parietal lobule (SPL) and dorsal frontal cortex, is considered to be specialised for the control of goal-directed processes. On the other hand, their ventral network which consists of the IPL, temporoparietal junction (TPJ) and ventral frontal cortex is thought to be primarily concerned with reorienting attention to behaviourally

salient environmental events and, they argue, is not associated with task preparatory mechanisms or goal-directed processes.

This model, however, fails to accommodate a major section of the current evidence base regarding IPL function. Studies with healthy human subjects demonstrate that the right IPL is involved in *sustaining attention* over time, so that focus can be maintained on the task at hand (Pardo, Fox et al. 1991; Johannsen, Jakobsen et al. 1997; Paus, Zatorre et al. 1997; Coull, Frackowiak et al. 1998; Coull and Frith 1998; Hager, Volz et al. 1998; Sturm, de Simone et al. 1999; Adler, Sax et al. 2001; Vandenberghe, Gitelman et al. 2001; Foucher, Otzenberger et al. 2004; Sturm, Longoni et al. 2004). This, in my view, is a 'top-down' function of the IPL, which occurs in addition to its crucial role in the detection of salient (Linden, Prvulovic et al. 1999; Clark, Fannon et al. 2000; Huang, Lee et al. 2005; Kiehl, Stevens et al. 2005; Lagopoulos, Gordon et al. 2006; Williams, Felmingham et al. 2007) or novel events in the environment (Weis, Fimm et al. 2000; Downar, Crawley et al. 2002; Kiehl, Stevens et al. 2005; Bunzeck and Duzel 2006; Gur, Turetsky et al. 2007). Together such studies implicate the right IPL in intensity, or 'top-down', aspects of attentional control, as well as stimulus-driven, or 'bottom-up', elements. In other words, it appears to play a role in processes segregated into Corbetta and Shulman's dorsal *and* ventral networks.

Functional imaging studies (Buchsbaum, Greer et al. 2005), as well as neurophysiological studies (Rushworth, Passingham et al. 2005; Travers and West 2008) further suggest that the right IPL is activated during experiments involving switching between tasks, a

function that has traditionally been considered goal-directed in nature and to be purely the remit of frontal structures. In fact meta-analysis has shown that the right – rather than the left – IPL is a crucial focus of activation during this process (Buchsbaum, Greer et al. 2005). Collectively, I consider this body of evidence to be consistent with my own alternative scheme, which attempts to integrate these findings by proposing that the right IPL acts as a pivotal module in the flexible reconfiguration of behaviour between two opposing functional states. These are a task-engaged state, in which attention is focussed upon current task goals, and a more exploratory state, which enables the identification of potentially important novel environmental events (Singh-Curry and Husain 2009).

I aim to investigate this proposal further in this chapter by examining the syndrome of hemispatial neglect, which occurs most frequently as a result of damage to the ventral attention network, including the right IPL and inferior frontal cortex (Vallar and Perani 1986; Husain and Kennard 1996; Mort, Malhotra et al. 2003). It has previously been reported that patients with neglect have difficulty detecting, or maintaining attention upon, events throughout space and not just the left (Heilman, Schwartz et al. 1978; Hjaltason, Tegner et al. 1996; Samuelsson, Hjelmquist et al. 1998; Robertson 2001; Buxbaum, Ferraro et al. 2004). However, it may be argued that problems with sustaining attention are best demonstrated through a *decline* in performance with the duration of a task (See, Howe et al. 1995; Whyte, Polansky et al. 1995), rather than simply a global deficit – a finding that has not previously been shown in neglect on non-spatial tasks.

Furthermore, although it is accepted that non-spatial impairments occur in neglect (Robertson 2001; Husain and Rorden 2003), little is understood about how they contribute, e.g. whether they interact with or are merely additive with the spatial deficits. The aim of the experiments described in this chapter is to probe how difficulty sustaining attention might articulate with the detection of stimuli of high and low perceptual salience, presented centrally and in left and right sides of space. If my proposal is correct (Singh-Curry and Husain 2009), it might be predicted that deficits in all three of these factors – sustaining attention, salience encoding and the spatial orientation of attention – might interact in the neglect syndrome.

In this chapter, two tasks based on an 'oddball paradigm' (Barcelo, Suwazono et al. 2000) were employed to examine the functions of the ventral attention network. In these experiments, infrequently occurring target stimuli – of high or low salience – were embedded within a stream of frequently occurring non-targets. By combining behavioural data with recently developed lesion analysis techniques, I investigated within the same individuals whether the right IPL plays an important role in the mediation of sustained attention, detection of salient targets (salience encoding) and spatial orienting of attention.

2.2. General Methods

2.2.1. Participants

Patients were recruited from stroke and neurological units with local ethics approval. Overall, a total of 16 right middle cerebral artery (MCA) stroke patients with neglect

(mean age: 59.4, range: 39-83; one left-handed) and 14 right MCA patients without neglect (mean age: 57.7, range: 32-82; all right-handed) were included in the study. Exclusion criteria included cognitive impairment such that there was difficulty following assessment or task instructions, and active medical comorbidity. 12 healthy elderly control participants with no neurological or psychiatric history were also recruited (mean age: 73 years, range: 59-82; 2 left-handed); see Table 2.1 for further patient demographic information.

2.2.2. Assessment of neglect

A visual neglect battery was performed on all of the patients to determine the presence or absence of neglect (Malhotra, Greenwood et al. 2004). Patients with neglect demonstrated neglect behaviours in their activities of daily living, as well as on the Mesulam cancellation test (Mesulam 1985) and/or line bisection task (Stone and Greenwood 1991). Neglect was identified by an asymmetry of cancellation of 2 or more items on the Mesulam task and a mean rightward deviation of 5mm or more on line bisection of three 17cm lines.

Subject	Age	Time since stroke (months)	Field defect	Mesulam (R-L difference)	Line bisection (cm to right of midline)	Task(s) performed
N1	83	1	No	15	3.9	C & B
N2	61	4.5	No	4	2	C
N3	40	0.1	No	8	1.4	C & B
N4	46	2	No	7	1	C & B
N5	74	0.3	No	4	1	C & B
N6	66	10	Partial left lower quadrantanopia	20	1	C & B
N7	66	3	Left hemianopia	22	3.2	C
N8	68		No	1	1.4	B
N9	75	0.7	No	2	0.7	C & B
N10	39	1	Partial left lower quadrantanopia	22	0.8	C & B
N11	58	3	Left hemianopia	20	2	C
N12	53	2	No	14	1.2	C & B
N13	59	0.7	Left hemianopia	13	4.3	C
N14	60	1.7	No	7	0.8	B
N15	44		No	10	1.2	B
N16	58	2	No	1	0.6	B
mean	**59.4**	**2.2**		**10.6**	**1.7**	
SC1	40	2	No	0	0.1	C & B
SC2	57	0.5	No	0	-0.4	C & B
SC3	82	0.1	Left hemianopia	-1	-0.4	C
SC4	59	2	No	0	-0.2	C & B
SC5	70	2	No	0	-0.2	C & B
SC6	63	1	No	0	0.5	C
SC7	50	0.5	No	1	0.2	C & B
SC8	71	2	No	-1	0.2	C & B
SC9	61	5	No	0	-0.2	C & B
SC10	37	0.2	No	0	-0.7	C & B
SC11	32	0.5	No	-4	-0.2	C & B
SC12	68	0.5	No	0	-0.3	C & B
SC13	76	0.6	No	0	-0.3	B
SC14	42	36	No	-2	-0.3	B
mean	**57.7**	**3.8**		**-0.4**	**-0.2**	

Table 2.1. Patient demographics.

N = patient with neglect

SC = stroke control patient

C = central task

B = bilateral task

2.2.3. Apparatus and stimuli

Participants depressed the central bottom button of an RB-530 Cedrus response box in response to the presentation of target stimuli. A Dell Latitude D820 laptop with a 15 inch screen and bilateral integral speakers was used for stimulus presentation. Both tasks were programmed using E-Prime software (Psychology Tools Software Inc.). Stimuli consisted of red and green coloured triangles, subtending approximately 2.5 x 2 º of visual angle when viewed from a distance of about 60cm, and were presented on a grey background. These were presented either centrally or at a parafoveal location (1 degree to the left or right of centre) depending on the task being performed. Subjects tested had no problems identifying parafoveal stimuli when fixating centrally.

2.2.4. General experimental design

Both tasks were based on an 'oddball paradigm' (Barcelo, Suwazono et al. 2000) in which infrequently occurring target stimuli (inverted triangles) were presented randomly intermixed with frequently occurring non-target stimuli (upright red triangles). There were two types of target: a green inverted triangle and a red inverted triangle. The green targets were designated *high salience* because they differed from the non-targets along two feature dimensions – orientation and colour. Red targets were of lower salience, differing from the non-targets in orientation only. Reaction time data supports this contention (see, for example, Figure 2.7) demonstrating clearly that participants responded significantly faster to green (high salience) targets compared to red (low salience) targets.

Subjects were instructed to respond as quickly as possible with their preferred hand whenever they saw an inverted triangle target, whatever its colour (green or red). The two target types were therefore identical in terms of task goal but differed in terms of perceptual salience.

In each of the experiments, non-targets (red upright triangles) comprised 75% of stimuli, whilst the low and high salience targets each made up 12.5%. Stimulus presentation time was 500ms, with inter-stimulus interval varying between 1000 and 1500ms. Responses were collected for 1500ms after visual stimulus onset and were discarded if they occurred within 200ms after stimulus onset (classified as anticipations). Each task consisted of 320 stimuli, lasting for approximately 10 minutes duration. Task order was counterbalanced across subjects, with each task preceded by a short practice comprising 20 stimuli, which was repeated if necessary. Subjects were monitored visually throughout the tasks, to ensure they maintained central fixation.

2.2.5. Data Analysis

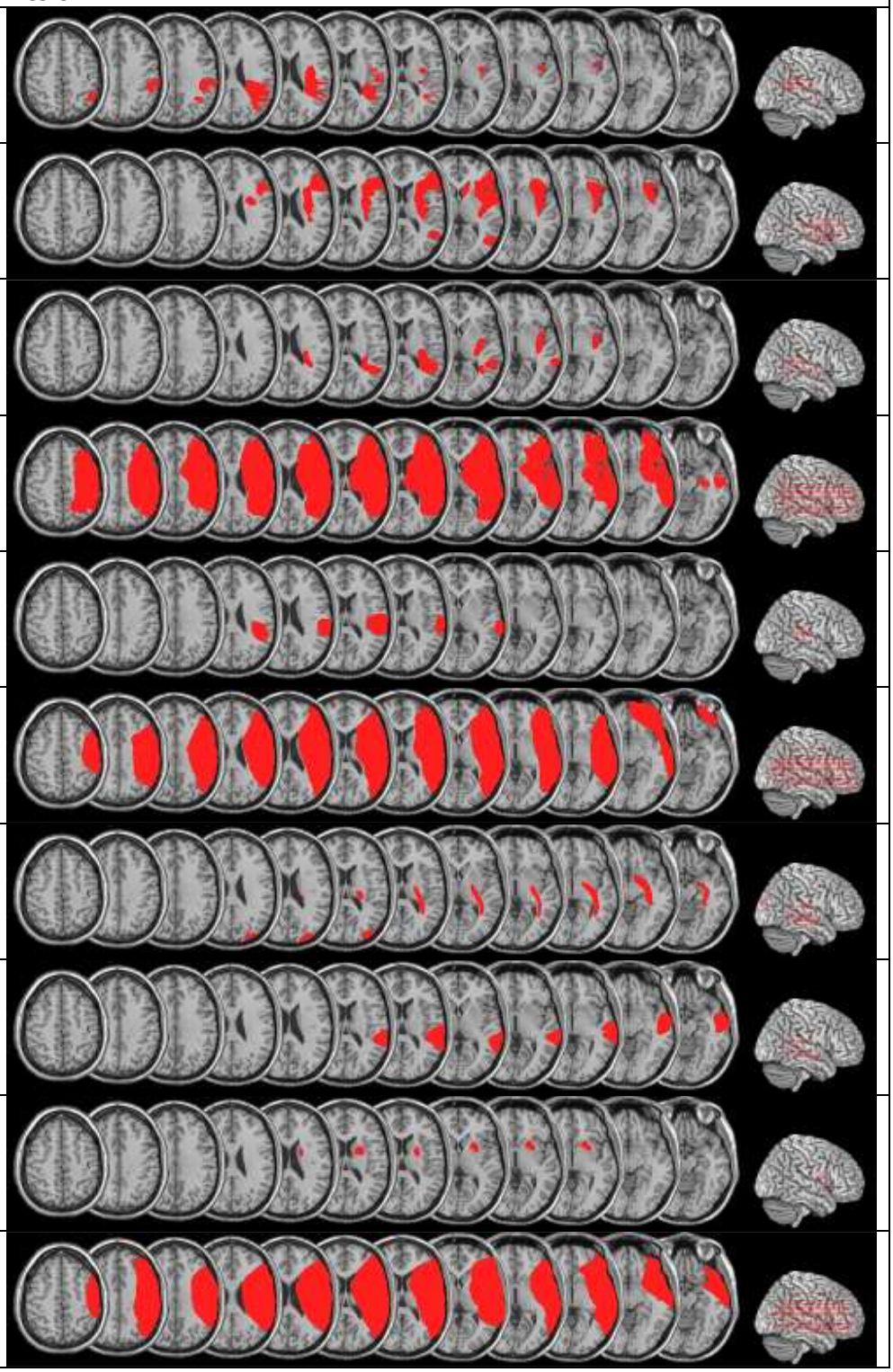
The median hit rates, false alarm rates and reaction times for each subject were analysed. All data presented on graphs represents the mean of individual subject medians. Repeated-measures ANOVAs were used to examine for significant effects between groups (neglect, stroke control and healthy control) as well as for additional within-group effects for each of the two tasks (see below) and for each behavioural outcome measure.

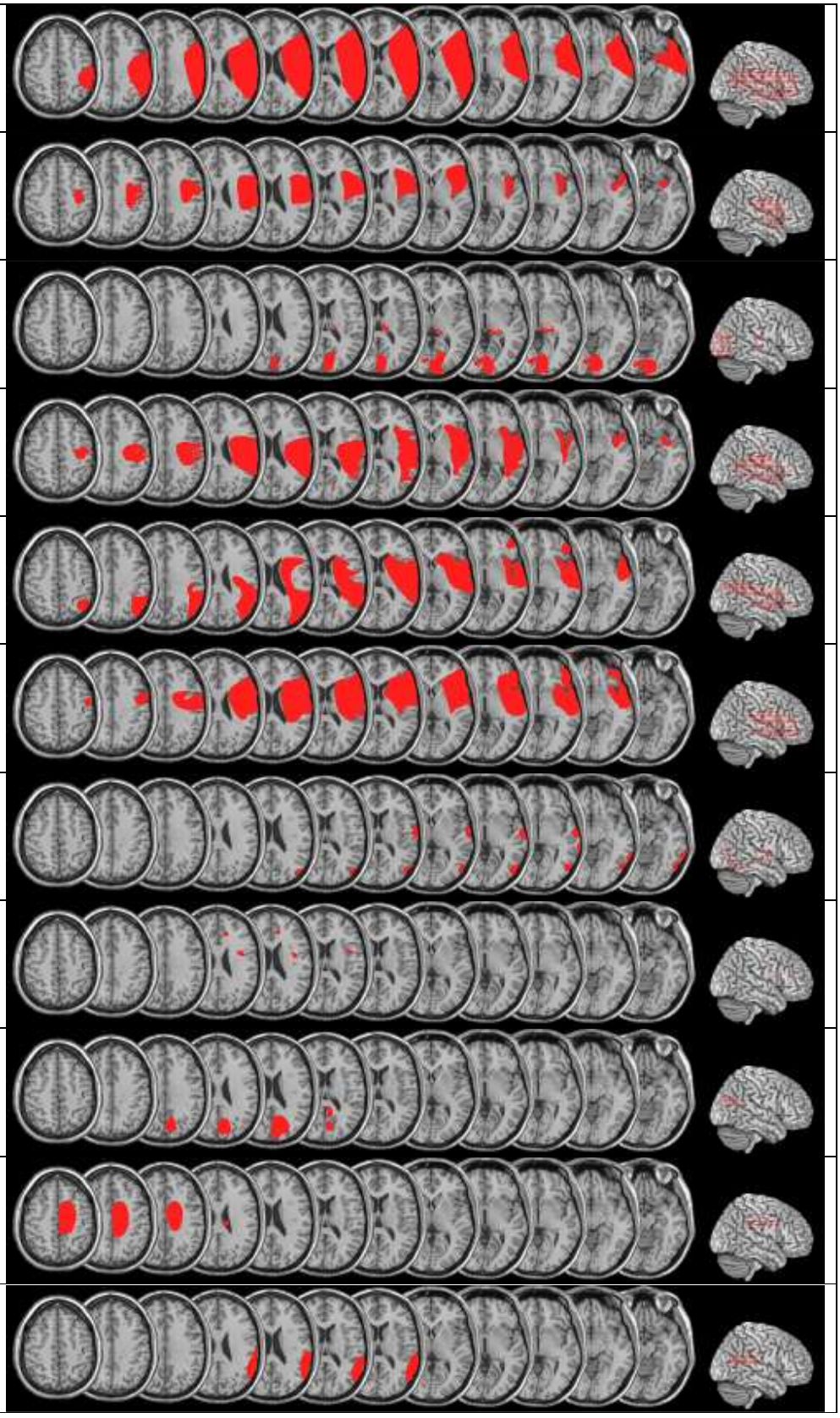
2.2.6. Lesion analysis

Lesions were plotted from clinical MR or CT scans (23 MR and 7 CT) on to a CH2 template using MRICro software (available from www.mricro.com), to produce a region of interest (ROI) on the axial images at MNI Z coordinates 56, 61, 66, 69, 75, 85, 88, 92, 96, 102, 108, 120. The lesions of individual patients are shown in Table 2.2.

Overlays and 3-D renderings were carried out in MRICron software (available from www.sph.sc.edu/comd/rorden/mricron) after conversion of the ROIs to smoothed volumes of interest (VOIs).

Voxel-based lesion symptom mapping (VLSM) was used to interrogate the behavioural and lesion data for the whole stroke group (neglect and stroke control patients combined) using MRICron and non-parametric mapping software (NPM for windows also available from www.sph.sc.edu/comd/rorden/mricron). The advantage of VLSM is that subjects are not grouped *a priori* according to behavioural measures (neglect or non-neglect), or according to site or size of lesion. Instead, it takes behavioural and lesion data from all patients and asks which voxels, when damaged, are associated with particular impairments (Bates, Wilson et al. 2003; Rorden, Karnath et al. 2007).

Subject	Lesion
N1	
N2	
N3	
N4	
N5	
N6	
N7	
N8	
N9	
N10	

N11	
N12	
N13	
N14	
N15	
N16	
SC1	
SC2	
SC3	
SC4	
SC5	

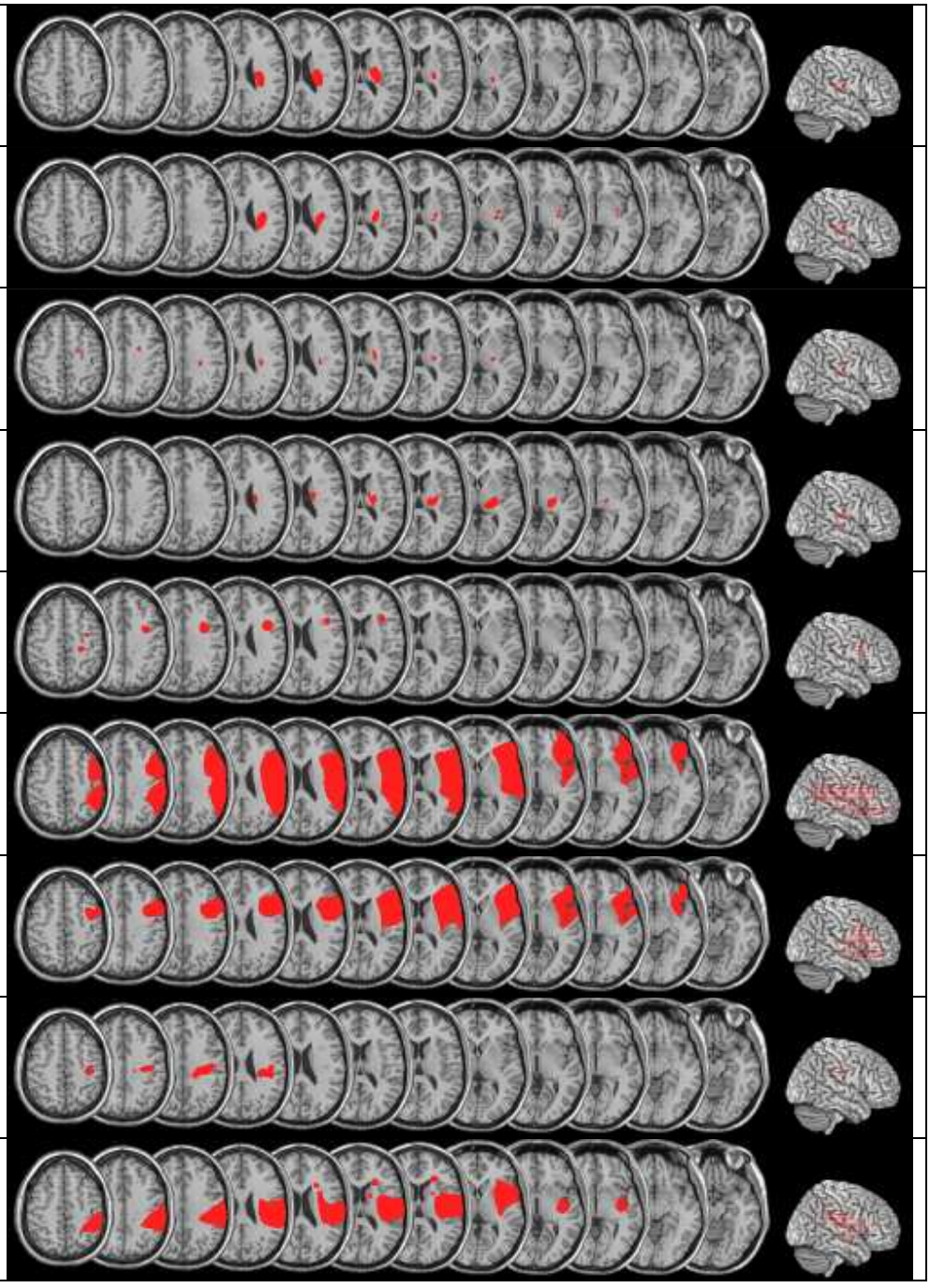
SC6	
SC7	
SC8	
SC9	
SC10	
SC11	
SC12	
SC13	
SC14	

Table 2.2. Patient lesions

N = neglect patient

SC = stroke control patient

VLSM therefore provides a relatively assumption-free measure of whether or not damage to a particular voxel is associated with a specific behavioural deficit. For each voxel subjects were divided into two groups according to whether that particular voxel was damaged or not. Behavioural scores were then compared using the Brunner-Munzel rank order analysis, which is incorporated within the MRICron and NPM software, to produce a statistic for each voxel. These Brunner-Munzel values were then overlain on the MNI template as colour Z maps, revealing the degree of involvement of each voxel in the behavioural process under investigation. The colour Z maps were then smoothed, automatically within the MRICron software, to produce a 3-D rendering.

Unlike the *t*-test, the Brunner-Munzel rank order test is a non-parametric analysis which is robust to violations of normality and has been considered the statistical test of choice in patient studies such as this (Rorden, Karnath et al. 2007). An earlier version of this test in MRICron/NPM has been recently criticized for producing large Type I errors in small groups (Medina, Kimberg et al. 2010). However, use of the Brunner-Munzel in conjunction with a permutation derived correction available in the most recent version of MRICron/NPM is considered to produce reliable *z* scores (Medina, Kimberg et al. 2010).

Only voxels lesioned in at least 15% of the stroke group were included in the analyses, with a permutation derived familywise error (FWE) correction (at the 0.05 level) performed automatically within the MRICron and NPM software.

In order to examine the potentially confounding effect of larger lesions in the neglect group compared to the stroke control group on the results, correlations between lesion size and the behavioural measures employed in the VLSM analyses were assessed. The volume of lesions was calculated using MIPAV software (available from www.mipav.cit.nih.gov), after conversion of each ROI to a VOI.

2.3. Experiment 1 – Sustained attention to central stimuli of high and low salience

2.3.1. Behavioural task design

In experiment 1, demonstrated in Figure 2.1, all stimuli were presented at a single central location on the display screen, aligned to the participant's vertical midline. This allowed assessment of responsiveness to salient items – targets which were of high or low salience – as well as of the ability to and sustain attention in central vision, over the 10 minutes' task duration.

Some investigators consider that an impairment of sustained attention is best demonstrated through decline in performance – a *vigilance decrement* – over time rather than simply an overall deficit (Whyte, Polansky et al. 1995; Parasuraman, Warm et al. 1998) because it could be argued that initial poor performance that simply continues throughout a task indexes difficulty due to the specific cognitive demands of that task (in this case, detecting salient items), rather than problems sustaining attention. Thus to assess sustained attention I examined performance as a function of time-on-task. 12 neglect patients, 12 stroke controls and 12 healthy elderly subjects took part in this experiment.

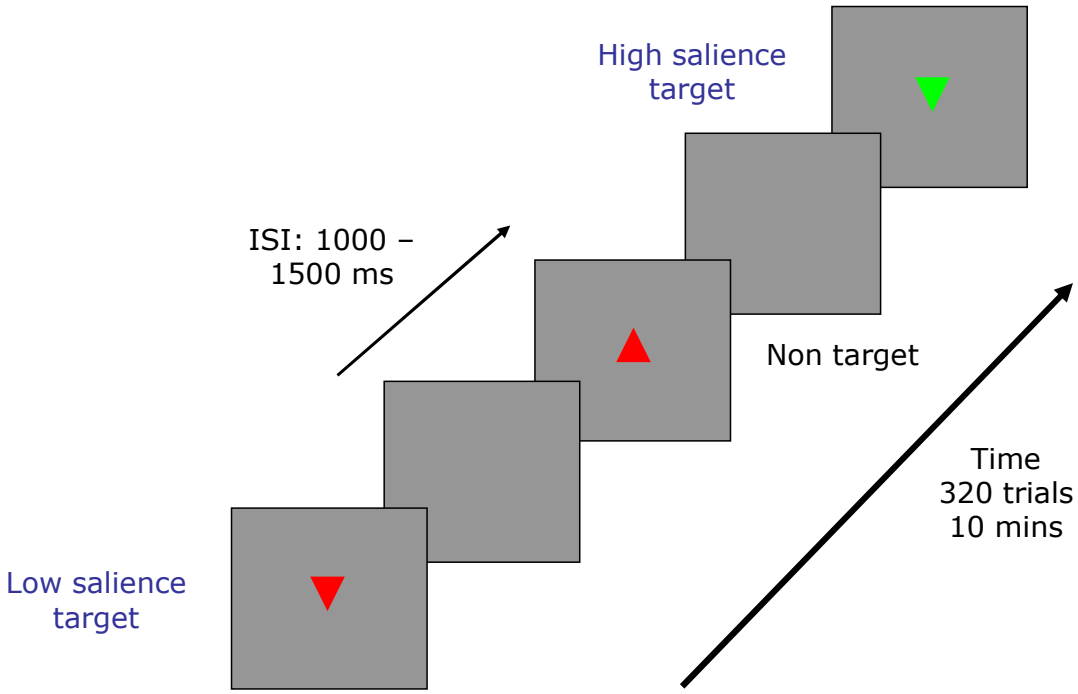


Figure 2.1. Central Task

Subjects were instructed to respond with a button press whenever they saw an inverted triangle, whether this was red (low salience) or green (high salience).

12.5% of stimuli were low salience targets, 12.5% were high salience targets and 75% of stimuli were non-targets. Each stimulus was presented for 500ms, with an interstimulus interval (ISI) of 1000-1500 ms. The task consisted of 320 stimulus presentations, lasting for approximately 10 minutes.

2.3.2. Results

2.3.2.1. Errors – hit rate and false alarm rate

The hit rate and false alarm rate for high and low salience events over time on the task are shown by group in Figure 2.2.

A repeated measures ANOVA was performed across the 3 groups (neglect, stroke control and healthy control) with within-group measures of time (divided into 2 equal halves) and target salience (high and low) for the hit rate. The performance of the neglect patients was significantly poorer than that of either control group (effect of group: $F(2,33)=5.635$, $p=0.008$) with *post hoc* Bonferroni tests revealing that the neglect group had significantly lower hit rates than the stroke controls ($p=0.022$) and healthy controls ($p=0.017$).

Furthermore, there was a main effect of time-on-task ($F(1,33)=7.723$, $p=0.009$) with a significant interaction between time and group ($F(2,33)=3.45$, $p=0.044$). Crucially, a within group ANOVA revealed that the performance of neglect patients deteriorated further with time-on-task ($F(1,1)=5.109$, $p=0.045$; see Figure 2.2A). This illustrates that neglect patients, in addition to an overall performance deficit in detecting salient targets, demonstrate a *vigilance decrement* over time, i.e., they show an impairment in the ability to sustain attention, even for stimuli presented at a single central location. Importantly, this effect of time-on-task was not observed within either of the control groups (stroke control: $F(1,11)=2.099$, $p>0.17$; healthy control: $F(1,11)=3.667$, $p>0.08$ – see Figure 2.2B&C). However, as can also be seen from Figure 2.2, in terms of the error data, the control groups were performing at ceiling.

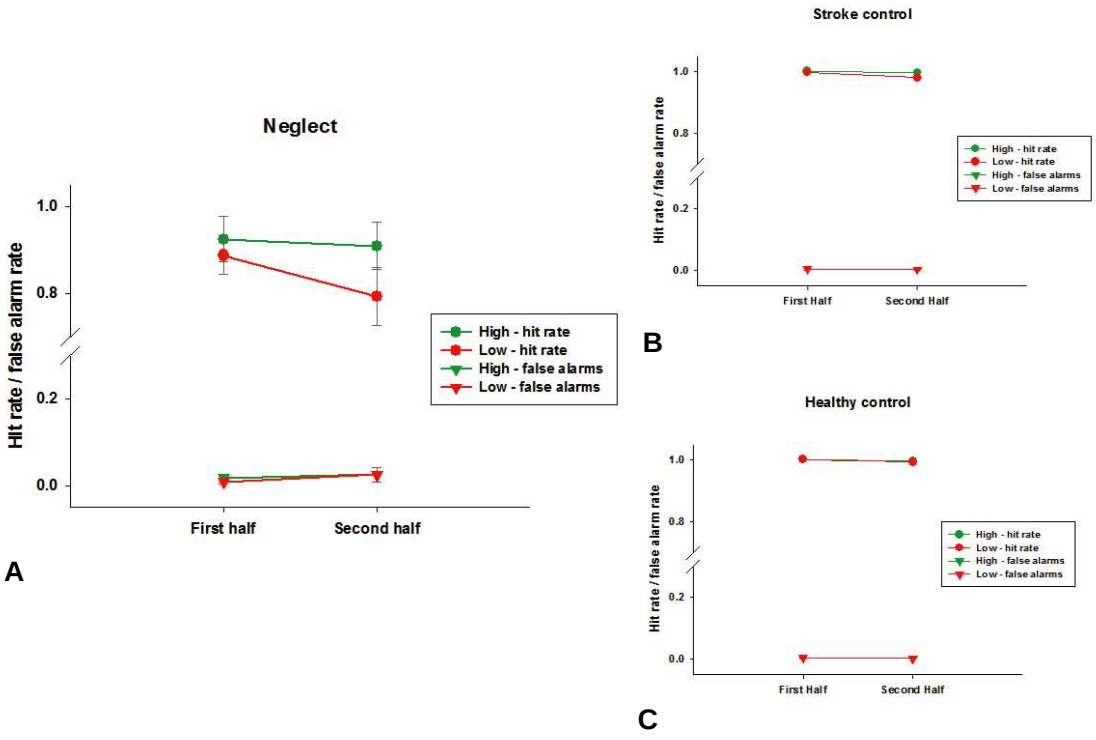


Figure 2.2. Impaired sustained attention and salience processing in neglect.
Neglect patients (A), unlike stroke controls (B) and healthy elderly control subjects (C), demonstrate a significant decline in performance over time. They are also deficient at detecting targets of lower perceptual salience, particularly as time-on-task progresses. This decline in effective task performance is driven by a reduction in accurate target detection (hit rate), rather than inaccurate responses to non-targets (false alarms).

High – high salience targets (inverted green triangles)
Low – low salience targets (inverted red triangles)

Error bars indicate the standard error of the mean.

The between groups ANOVA also revealed a main effect of salience ($F(1,33)=18.924$, $p<0.001$) with a significant interaction between salience and group ($F(2,33)=12.35$, $p<0.001$). Neglect patients were worse at detecting targets of low compared to high salience ($F(1,11)=15.172$, $p=0.002$). This was not the case in the healthy control group ($F(1,11)=0.314$, $p>0.5$), although the stroke control group showed a significant but lesser effect of salience ($F(1,11)=7.857$, $p=0.017$) as compared to the neglect patients – see Figure 2.2 – although, again it should be noted that the control groups were generally performing at ceiling.

Importantly, the between groups ANOVA revealed a significant interaction between time-on-task and salience ($F(1,33)=6.298$, $p=0.017$) in addition to a three-way interaction between time, salience and group ($F(2,33)=3.576$, $p=0.039$). Crucially, the interaction between time and salience reached significance in the neglect group alone, ($F(1,11)=3.4054.783$, $p=0.05$), with ability to sustain attention being significantly impaired for low salience ($t(11)=2.37$, $p=0.037$) compared to high salience targets ($t(11)=1.0$, $p>0.3$; Figure 2.2A). Thus, in neglect patients, the impairment in sustained attention interacts with the ability to respond to salient items (low salience targets compared to high salience ones), rather than merely acting in an additive fashion.

This finding demonstrates that neglect patients suffer an impairment in encoding salient items over time. Note that although the red, low salience targets are not as salient as green, high salience targets (see Figure 2.7 for supportive reaction time data), they are nevertheless salient with respect to the frequent non-targets. All groups, including the

neglect one, found detection of high salient targets to be relatively easy but it was responses to low salience targets that particularly discriminated between groups. The deficit in responding to low salience items, which worsened over time, was crucially only observed in the neglect group. This finding demonstrates a deficit in encoding salience which interacts with the impairment in sustaining attention over time in neglect patients.

The existence of this interaction between sustaining attention and detecting salient, task-related items can be criticised on the basis of an apparent ceiling effect, even in the neglect group, for the detection of high salience targets (Figure 2.2A). However, if the duration of the task is broken down into quartiles (see Figure 2.3), it can be seen that the neglect patients begin to manifest an impairment in the detection of even the high salience targets. Furthermore, despite this deterioration in the detection of high salience targets at the very end of the task, the separation between the detection of high and low salience targets seems to further increase, suggesting that such an interaction may in fact be real. However, in an analysis comparing performance in the first quartile to the final quartile, this interaction failed to reach significance ($F(1,11)=2.979$, $p=0.11$), although it should also be bourne in mind that that in the quartile analysis, due to a halving of the contributory data-points, the power of the analysis was reduced.

As can be seen from Figure 2.2, all three subject groups made very few false alarms. Repeated measures ANOVA across the groups, with within-group measures of time and target salience, on the false alarm rate revealed no significant effects.

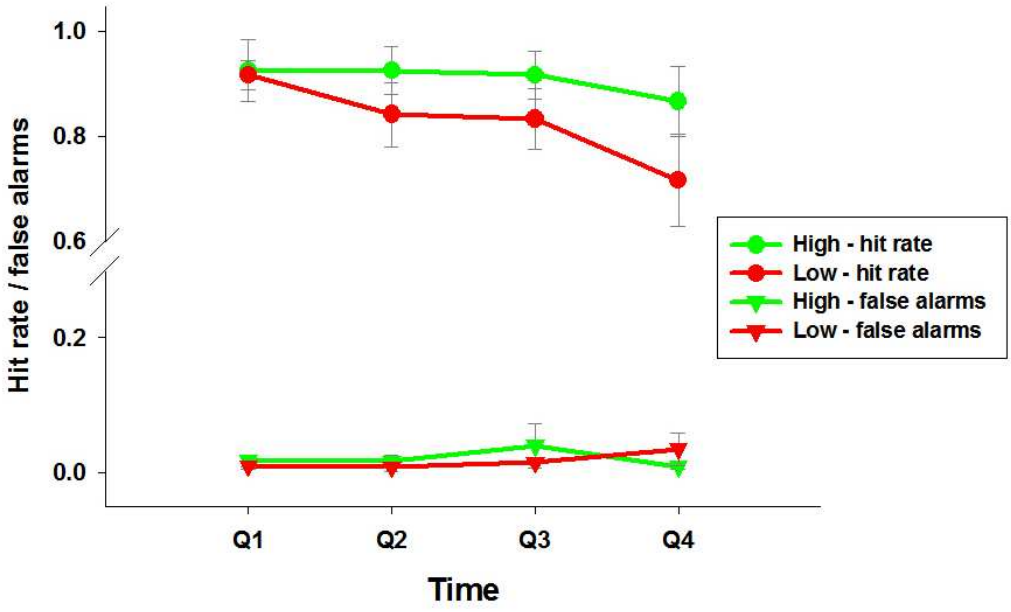


Figure 2.3. Deficit in detection of high salience begins to manifest at the end of the task in neglect patients.

Further subdividing the duration of the task into quartiles (Q1-Q4), reveals that at the end of the task, a deficit in detection of the high salience targets begins to manifest. Furthermore, despite the appearance of this deficit, the separation of performance to low and high salience targets appears to be increasing, supporting the notion of an interaction between the ability to sustain attention and detect stimulus salience. Unfortunately the interaction between time and salience fails to reach significance in the quartile analysis (see text). However, the total number of data points is halved in this analysis, leading to lower power.

Error bars indicate the standard error of the mean.

The decline in hit rate to low salient targets over time in the neglect group cannot be explained simply by slowing of responses, some of which might not even have been made within the 1500 ms time window in which we collected reaction times. Figure 2.4A demonstrates the frequencies of reaction times for low salience targets in the neglect group. The median reaction time of this group to low salience targets was approximately 600 msec, with the majority of responses falling between 400 and 800 msec. There were very few responses to low salience targets over 800 msec. Furthermore, out of the small number of total false alarms across the neglect group (Figure 2.4B), very few were of very short reaction time – which would have suggested that they might have been delayed responses to previous targets. In sum there is no evidence that delayed responses to targets significantly contributed to the observed error rate.

The reaction time data will be discussed more fully in Section 2.3.2.3.

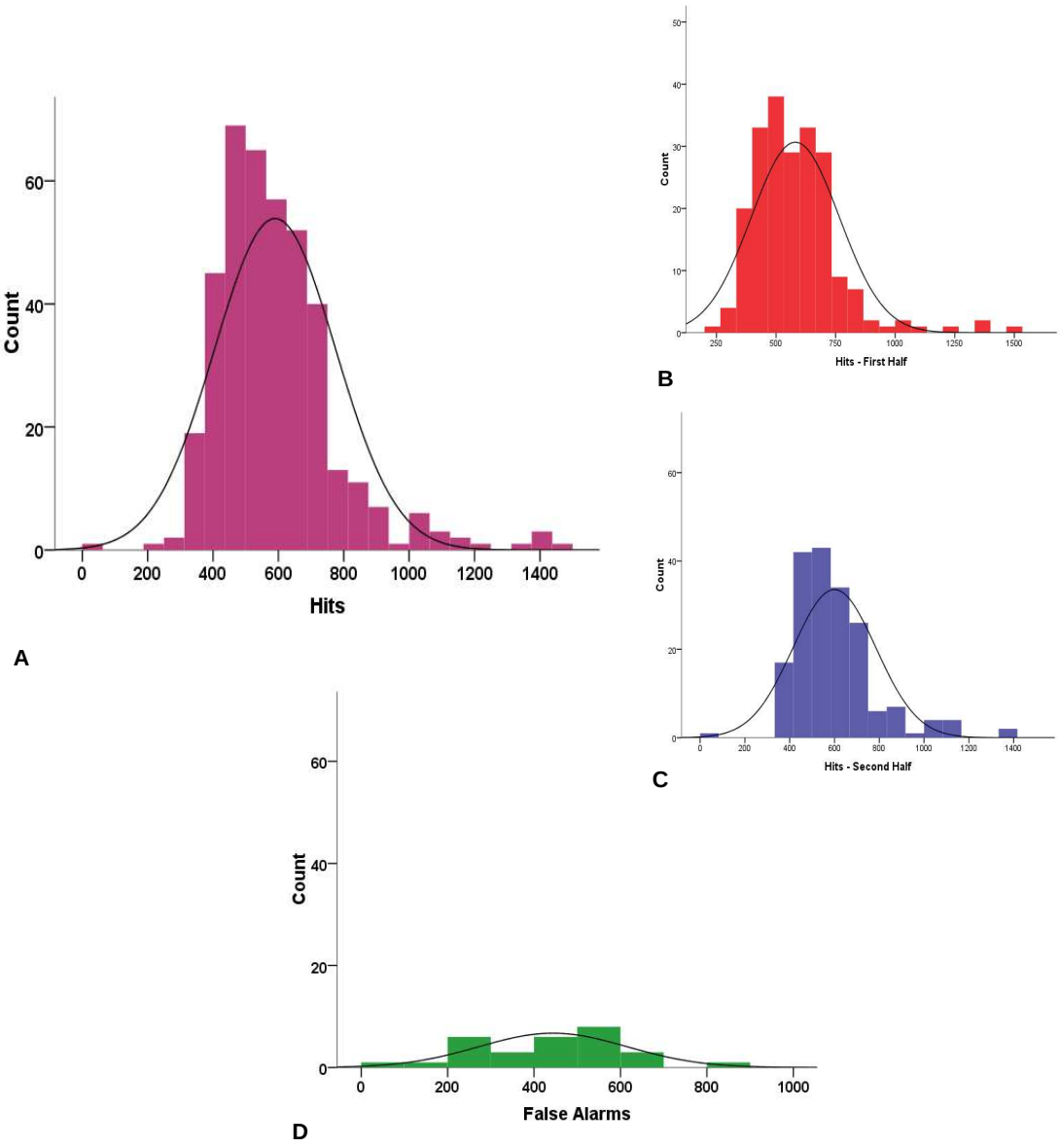


Figure 2.4. Reaction time distributions in the neglect patients.

A. Reaction time distributions during the central task to all of the low salience targets (red inverted triangles) detected. The reaction time distribution for hits during the first half of the task are shown in **B** and those during the second half of the task are shown in **C**. The median reaction time to low salience targets in the neglect group was approximately 600 msec, with the majority of responses falling between 400 and 800 msec. As can be seen from the small number of low RT hits, there were very few anticipatory responses. Importantly, the low number of high RT hits and very small number of low RT false

alarms (shown in **D**), argues against the possibility of 'time-outs' or very long target response times contributing significantly to the error rate. In fact, if anything there were more long RT hits during the first, compared to the second half of the task.

It has been argued that measures derived from signal detection theory (such as perceptual sensitivity - calculated by computing the distance between the signal and noise distribution means in standard deviation units (Stanislaw and Todorov 1999)) may be more sensitive to differences in performance on tests of sustained attention and vigilance than either hit rate or false alarm rate alone (Lam and Beale 1991). This is because such measures take into account both the hit rate and the false alarm rate in their computation. As discussed above, there were very few false alarms made on this task, by any of the groups, hence the calculation of these measures would add little extra value to the hit rate alone, and therefore have not been added here.

To investigate the anatomical correlates of performance differences between patient groups (discussed in the next section), two simple behavioural measures were used. First the hit rate during the final quartile of the task was used to probe the lesions of neglect and stroke control patients for deficits in sustaining attention because there were significant differences between the two groups during the final quartile of the task ($t(22)=-2.83$, $p=0.009$), but not during the first quartile ($t(22)=-1.79$, $p>0.05$). The performance of patients in the final quartile, rather than the final half, were chosen for this analysis

because the difference between groups here was greatest (difference between groups in the final half of the task ($t(22)=-2.309$, $p=0.03$)

Second, the hit rate for low salience targets was the behavioural measure used to investigate the anatomical correlates of difficulty identifying low salience items. There were significant differences between the two patient groups in the correct identification of low salience targets ($t(22)=-2.854$, $p=0.009$), but not for the identification of high salience targets ($t(22)=-1.554$, $p>0.1$).

2.3.2.2. Lesion analysis

VLSM was used to investigate the anatomy of the deficits in sustained attention and salience encoding identified in the preceding section. For the reasons discussed above, the hit rate during the final quartile of the task was used to probe the lesions of neglect and stroke control patients for deficits in sustaining attention, while the hit rate for low salience targets was the behavioural measure used to investigate the anatomical correlates of difficulty identifying low salience events.

The deficit in sustaining attention during the final quartile of the task was associated with damage to a network of frontal and parietal areas including the supramarginal gyrus (SMG) and angular gyrus (AG) of the IPL, in addition to the middle frontal gyrus, but particularly prominently the inferior frontal gyrus (IFG) (see Figure 2.5A).

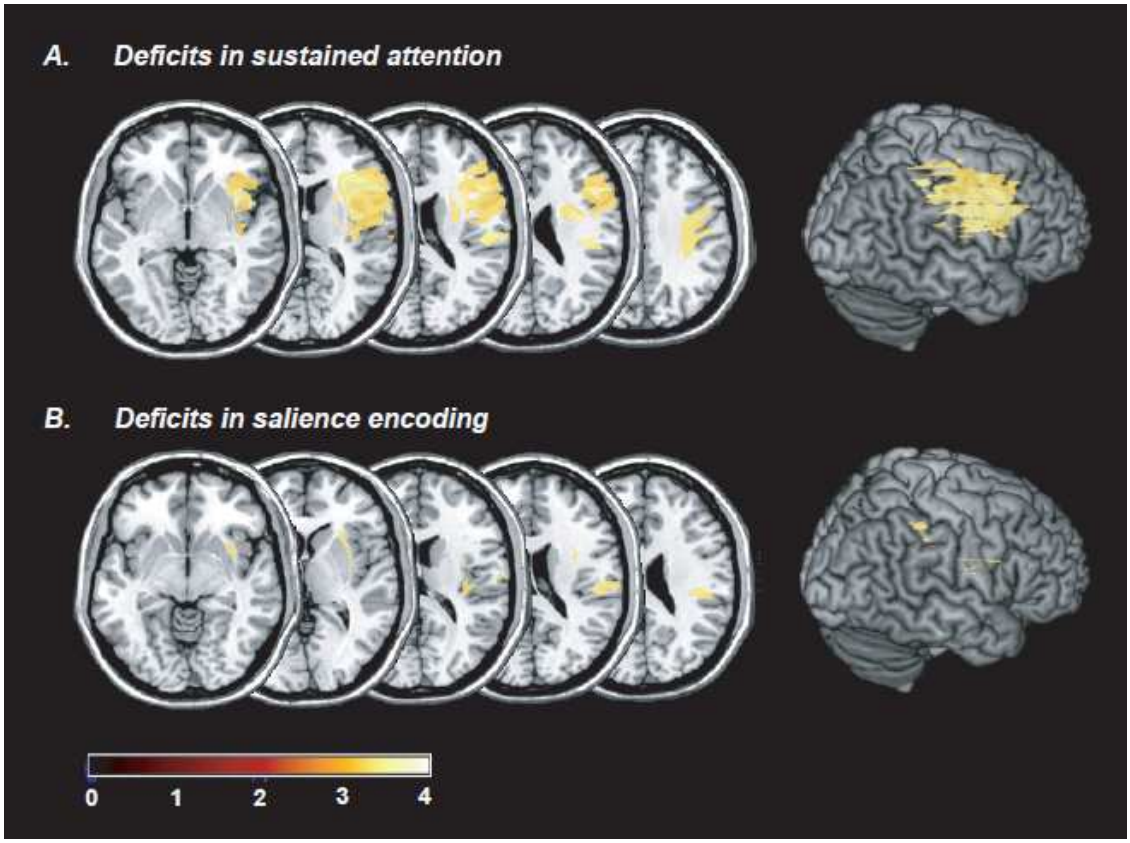


Figure 2.5. Regions associated with deficits in sustained attention and salience encoding.

A. Deficits in sustained attention were primarily associated with damage to the inferior frontal gyrus (IFG) and to a lesser extent with lesioned voxels in the middle frontal gyrus in addition to the supramarginal gyrus (SMG) and angular gyrus (AG) of the IPL. Z scores > 3.15 are significant at the 0.05 level after permutation derived FWE correction.

B. In contrast, difficulty detecting targets of lower perceptual salience was principally associated with damage to the IPL, involving the AG. Z scores > 3.26 are significant at the 0.05 level after permutation derived FWE correction.

Only significant voxels are shown.

It is important to note, however, that damage to posterior regions *alone* may be sufficient to cause an impairment of sustained attention. Figure 2.6A presents data from an individual patient from the neglect group, included in the analyses described above, whose lesion was centred on the IPL (see Figure 2.6B) and which crucially did not extend into the frontal lobe. This patient demonstrated a decline in performance with time, even for stimuli presented at a single central location.

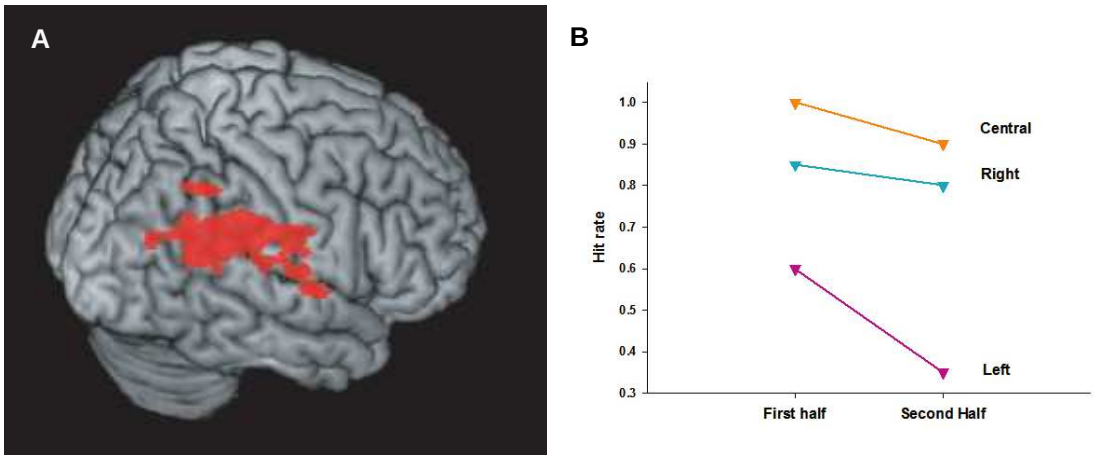


Figure 2.6. A neglect patient with posterior damage demonstrates a vigilance decrement.

A. Lesion anatomy of this patient. The lesion is largely confined to the IPL and importantly, does not extend to the frontal lobe.

B. The patient demonstrates a decline in hit rate over the time course of the tasks, centrally, as well as in the left and right sides of space.

The deficit in detecting low salience targets was found to be significantly associated with parietal damage only, centering on the angular gyrus (AG) of the IPL (Figure 2.5B). This finding suggests that the right IPL is crucial in detecting target-related salience, but as has been seen, it is also implicated in playing a role in sustained attention (Figure 2.5A).

There was a significant difference between the neglect and stroke control groups in terms of lesion volume ($t(22)=2.237$, $p=0.036$), with the neglect patients having larger lesions. Importantly, however, lesions volume did not significantly correlate with the ability to sustain attention during the final quartile of the task ($r=-.310$, $p=0.14$) or the ability to correctly identify the low salience targets ($r=-.367$, $p=0.08$).

2.3.2.3. Reaction time data

The reaction time data for this task are shown by subject group in Figure 2.7.

A repeated measures ANOVA was performed across the three subject groups, with within group measures of time (half task) and salience (high versus low). The difference in overall reaction time between the groups failed to reach significance ($F(2,33)=2.742$, $p=0.078$). However, there was a highly significant effect of salience ($F(1,33)=70.533$, $p<0.001$) with all three groups demonstrating slower reaction times to low salience targets – Figure 2.7. Importantly, this finding supports the contention that the red coloured (low salience) targets were indeed of lower perceptual salience than the green (high salience) targets; even healthy control subjects were *slower* to respond to the red (low salience) targets, although they did not demonstrate a *deficit in detection*.

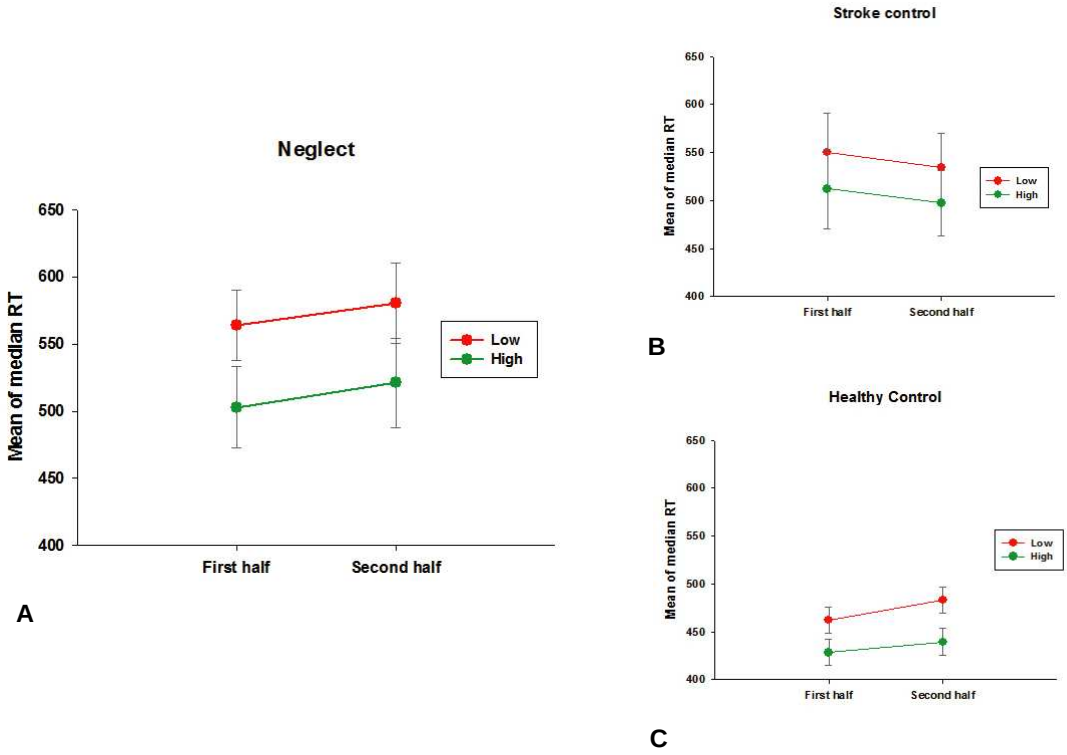


Figure 2.7. Reaction time data across the three subject groups.

Unlike the error data, there was a significant effect of salience in all groups, with all three demonstrating increased reaction times to the low salience (red) targets. The healthy controls, in addition to the neglect patients, developed slower reaction times with increasing time on task.

Low – low salience targets (red inverted triangle)
High – high salience targets (green inverted triangles)

Error bars indicate the standard error of the mean.
RT is measured in msec.

There was also a significant interaction between time-on-task and group ($F(2,33)=3.908$, $p=0.03$). The effect of time-on-task was significant in the healthy control group ($F(1,11)=5.714$, $p=0.036$), just failed to reach significance in the neglect group ($F(1,11)=3.692$, $p=0.08$) and was non-significant in the stroke control group ($F(1,11)=1.728$, $p>0.2$) – see Figure 2.7. Hence, as previous studies have shown (Berardi, Parasuraman et al. 2001), healthy subjects do manifest vigilance decrements, although this is of a much smaller magnitude (delayed reaction time compared to failure to detect) than that demonstrated by neglect patients with frontoparietal lesions.

2.3.3. Discussion

To summarise, the principal findings of this experiment indicate that there might be differences in the contributions of two critical nodes of the ventral attention network: the right IFG and IPL. The IFG appears to play the key role in sustained attention, consistent with classical findings (Wilkins, Shallice et al. 1987). However, although the IPL was found to be crucial in encoding stimulus salience as suggested by Corbetta and colleagues (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008), it too appears to play a role in sustained attention. This proposed function of the right IPL is strengthened by the observation that a patient with a predominantly parietal lesion, which did not extend to the frontal lobe, also demonstrated a vigilance decrement.

Furthermore, the results demonstrate that in neglect, the deficits in encoding stimulus salience and sustaining attention may interact – with one impairment serving to exacerbate the severity of the other, rather than merely acting in an additive fashion. Together, these

results are consistent with a new formulation of right IPL function (Singh-Curry and Husain 2009), rather than the scheme of Corbetta and colleagues (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008).

However, how does the impairment in sustained attention affect the characteristic deficit of the neglect syndrome, namely difficulty orienting to the left? The next experiment was designed to address this question.

2.4. Experiment 2 – Sustained attention to left and right sided stimuli of high and low perceptual salience

2.4.1. Behavioural task design

In this experiment, shown diagrammatically in Figure 2.8, a central white fixation cross subtending 1º x 1º visual angle, was continuously displayed. During this task, stimuli were presented at a parafoveal location, 1º left or right of this. Targets and non-targets were the same as those previously used in experiment1. This permitted examination of interactions between spatial processes (left versus right), salience encoding (high versus low) and sustained attention (over time).

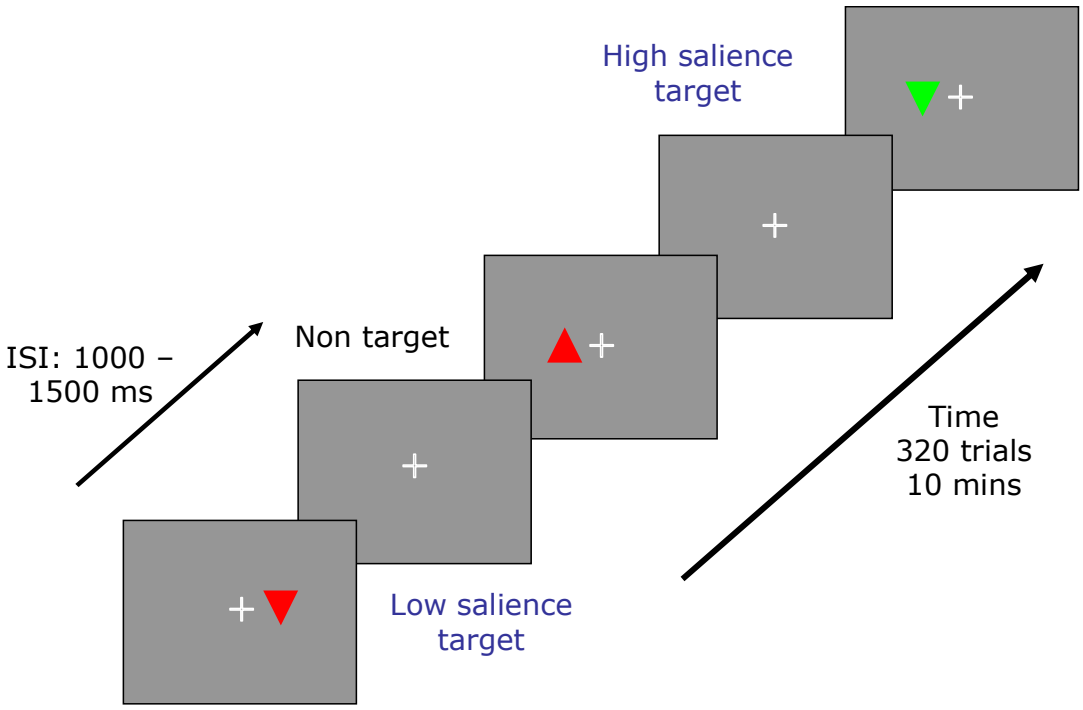


Figure 2.8. Bilateral Task

Subjects were instructed to respond with a button press whenever they detected an inverted triangle, whether this was red (low salience) or green (high salience), or appeared on the left or right side of space. Participants were monitored visually throughout the task, to ensure they maintained fixation on the central cross. 12.5% of stimuli were low salience targets, 12.5% were high salience targets and 75% were non-target stimuli. Equal numbers of these stimuli occurred on the left and right sides of space.

Subjects were instructed to fixate the central cross throughout, so that stimuli on the left and right were easily visible parafoveally. It was established that subjects were able to do this during a practice block preceding the main experiment and they were monitored visually throughout the duration of the task. Patients who were unable to maintain fixation, due to deviation of gaze to the right, were excluded. Two neglect patients also had their eye position monitored at 1000 Hz using a frame-mounted infra-red eye tracker (SR Research, Ontario, Canada). Stroke patients with a hemianopia were naturally excluded from this version of the experiment. 12 neglect patients, 12 stroke controls and 12 healthy elderly subjects participated in this task.

2.4.2. Results

2.4.2.1. Errors – hit rate and false alarm rate

The hit rate and false alarm data for each of the three subject groups is shown graphically in Figure 2.9.

A repeated measures ANOVA was performed across the 3 groups (neglect, stroke control and healthy control), with within group measures of time (first half compared to second half), salience (low versus high) and position (left versus right) on the hit rate data.

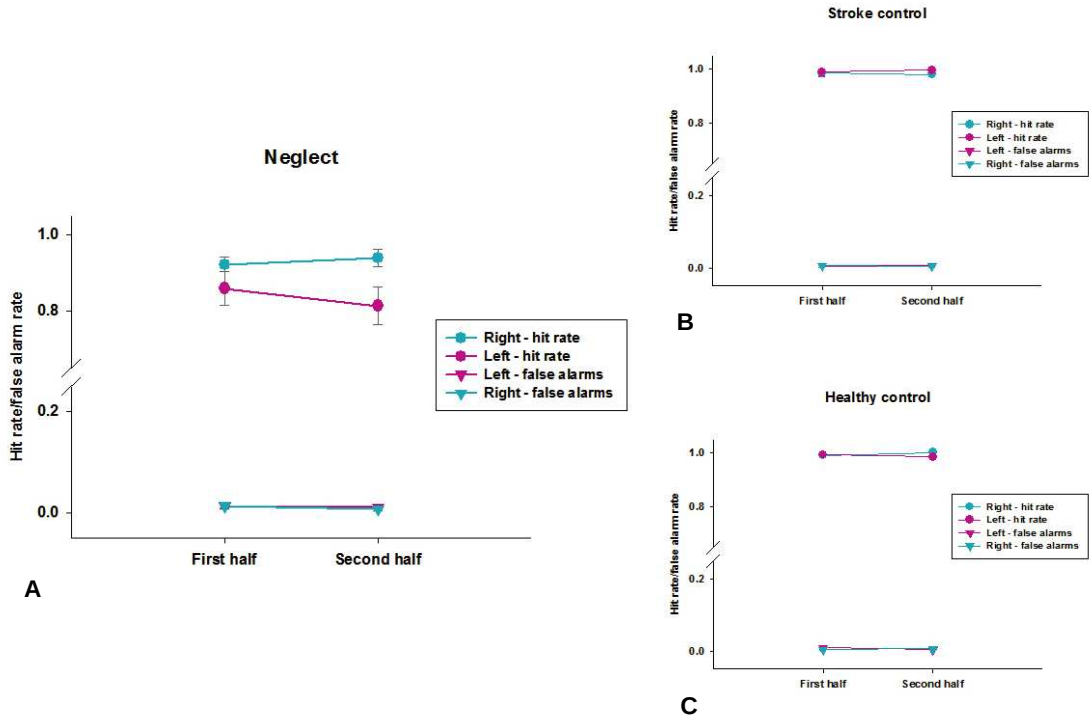


Figure 2.9. The spatial deficit in neglect is exacerbated by difficulty sustaining attention.

Neglect patients are significantly impaired at detecting left-sided stimuli, with a significant exacerbation of this deficit with time-on-task (A), unlike stroke control subjects (B) and healthy control subjects (C). Importantly, these deficits are driven by a failure to detect stimuli rather than an increase in false alarms.

Error bars indicate standard error of the mean.

As in experiment 1, neglect patients exhibited significantly poorer overall performance than either control group (effect of group: $F(2,33)=14.378$, $p<0.001$) with *post hoc* Bonferroni testing revealing that the neglect group had significantly lower hit rates than the stroke control and healthy control groups (both $p<0.001$). Again, the control groups generally performed at ceiling in terms of error rate.

Unsurprisingly, there was a main effect of position ($F(1,33)=4.796$, $p=0.036$) and a significant position by group interaction ($F(2,33)=5.613$, $p=0.008$), with the neglect patients alone demonstrating a significant impairment in detecting left compared to right-sided targets ($F(1,11)=5.456$, $p=0.039$ – Figure 2.9). Crucially, however, there was also an interaction between time-on-task and stimulus position ($F(1,33)=6.721$, $p=0.014$) and a significant interaction between time-on-task, position and group ($F(2,33)=5.674$, $p=0.008$), with this interaction between time and position reaching significance in the neglect group alone ($F(1,11)=6.022$, $p=0.032$). Hence, the left-sided spatial deficit in neglect was exacerbated by difficulty sustaining attention

It should again be noted that the neglect patients were close to ceiling in terms of their detection of right-sided stimuli (Figure 2.9A). However, although there was a significant difference in detection of left and right stimuli throughout the whole task in the neglect group (see above), this difference seems to be driven by performance during the second half of the task ($t(11)=-2.66$, $p=0.022$), whilst the difference in detection of left and right sided stimuli during the first half of the task failed to reach significance ($t(11)=-1.71$,

p=0.11). Therefore, while the prescence of ceiling effects must be acknowledged, the ability to sustain attention clearly influences the spatial deficit in neglect.

Importantly, the results of the two additional neglect patients who had their eye movements tracked, suggested that these deficits were not associated with occasional eye movements to the experimental stimuli. Figure 2.10 demonstrates that there was no association between the number or pattern of errors made by these patients and the eye movements they made. The total number of eye movements during each task quartile did not correlate significantly with the corresponding total number of omission errors made ($r=0.395$, $p=0.332$). Moreover, the number of rightward saccades to stimuli did not correlate significantly with the number of left-sided omission errors during each task quartile for the individual subjects ($r=0.396$, $p=0.332$).

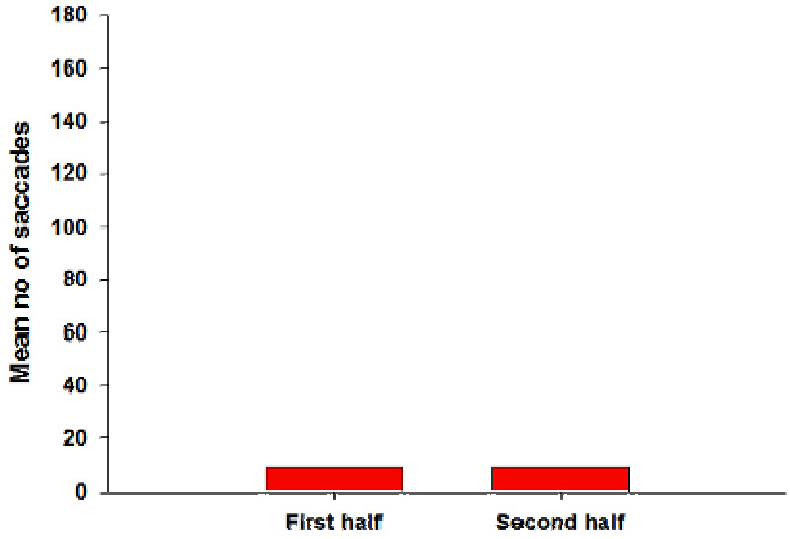


Figure 2.10. Eye position data.

Eye movement data from two additional neglect patients. Although subjects made some saccades to the experimental stimuli, these occurred relatively infrequently.

The mean numbers of saccades to experimental stimuli across each half task is shown. There was no increase in eye movements over the course of the task, which consisted of a total of 360 stimuli (i.e. 180 in each half task).

As in experiment 1, there was also a main effect of stimulus salience ($F(1,33)=25.972$, $p<0.001$) and a significant interaction between salience and group ($F(2,33)=11.622$, $p<0.001$), with neglect patients, unlike stroke control patients demonstrating a significant impairment in the detection of low compared to high salience stimuli ($F(1,11)=17.072$, $p=0.002$).

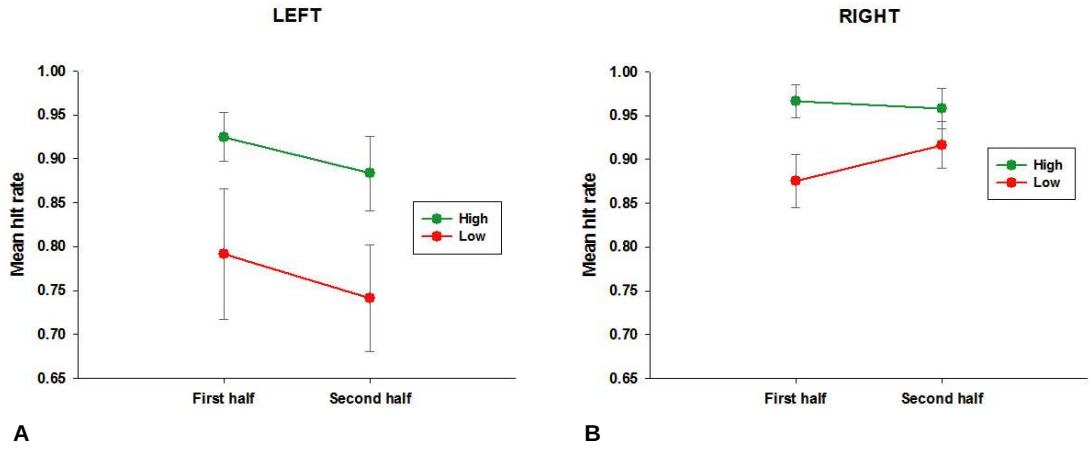


Figure 2.11. Detection of low salience stimuli is impaired in both sides of space in neglect.

Neglect patients demonstrate impairment in the detection of low salience targets, compared to high salience targets, in the right (B) as well as the left (A) sides of space.

Low – low salience targets (red inverted triangles)
High – high salience targets (green inverted triangles)

Error bars indicate the standard error of the mean.

The absence of an interaction between salience and side of stimulus presentation ($F(1,11)=1.935$, $p>0.19$) in the neglect group indicated that this was true for both left *and* right sided targets (Figure 2.11), suggesting suboptimal processing of low salience stimuli, even when presented to the right. This was in fact confirmed by a t-test indicating a significant difference in hit rate to low and high salience targets ($t(11)=3.752$, $p=0.003$) occurring in the right side of space, in addition to the left ($t(11)=2.93$, $p=0.014$).

Figure 2.11B also appears to demonstrate an improvement in sensitivity on the right side, particularly for the detection of low salience targets, over time. However, the difference in perceptual sensitivity even for *low* salience targets presented on the right, in the first compared to the second half of the task, was not significant ($t(11)=-1.313$, $p>0.19$).

As can be seen from Figure 2.9, all three subject groups made very few false alarm errors. Indeed, a repeated measures ANOVA across the groups, with within group measures of time (half task), position (left versus right) and salience (low versus high) revealed no significant effects.

2.4.2.2. Lesion analysis

VLSM was used to investigate the anatomical correlates of the deficit in detecting left sided stimuli and in sustaining attention to left-sided events. The hit rate to left-sided targets was used as the behavioural measure of the spatial deficit and the hit rate to left-sided targets during the second half of the task as the index of the spatial deficit with time.

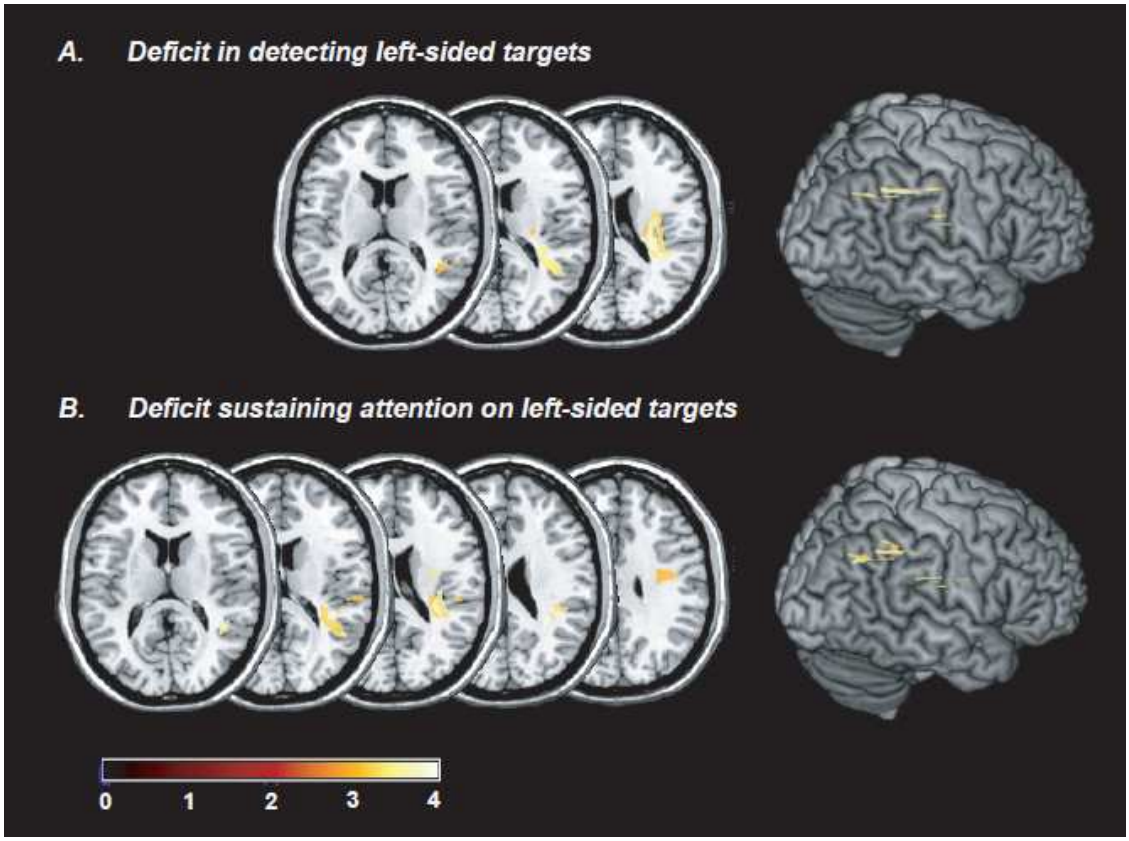


Figure 2.12. The anatomy of spatial attention.

A. The impairment in detecting left-sided stimuli was strongly associated with lesioned voxels in the angular and supramarginal gyri. Z scores >3.21 are significant at the 0.05 level after permutation derived FWE correction.

B. Exacerbations in detecting left-sided targets *with time* were also associated with damage to the angular and supramarginal gyri of the IPL, in addition to the underlying white matter. Z scores > 3.12 are significant at the 0.05 level after permutation derived FWE correction.

Consistent with previous reports (Vallar and Perani 1986; Mort, Malhotra et al. 2003), the deficit in orientation of spatial attention to left-sided targets was significantly associated with damage to voxels in the angular and supramarginal gyri of the IPL in addition to the underlying white matter (Figure 2.12A).

Perhaps more importantly, however, the deterioration in detecting left-sided events with time-on-task was also significantly associated with damage to the angular and supramarginal gyri of the IPL, as well as the underlying parietal white matter (see Figure 2.12B). Of course, as discussed above, the deficit in sustaining attention, in this task, appears to have contributed to the the overall spatial deficit, which perhaps explains the similarity of the lesion analyses illustrated in Figure 2.12. Although, the lesioned voxels associated with deficit in sustaining attention to left-sided targets are a little more extensive than those associated with the spatial impairment.

As was the case for experiment 1, there was a significant difference in lesion volume between those patients who had neglect and those who did not ($t(22)=2.375$, $p=0.027$). However, neither the deficit in detecting left-sided stimuli ($r=-.357$, $p=.09$) nor the difficulty maintaining attention on left-sided stimuli as the task progressed ($r=-.247$, $p>0.24$) correlated significantly with lesion volume.

2.4.2.3. Reaction time data

The reaction time data for this task is shown by subject group in Figure 2.13.

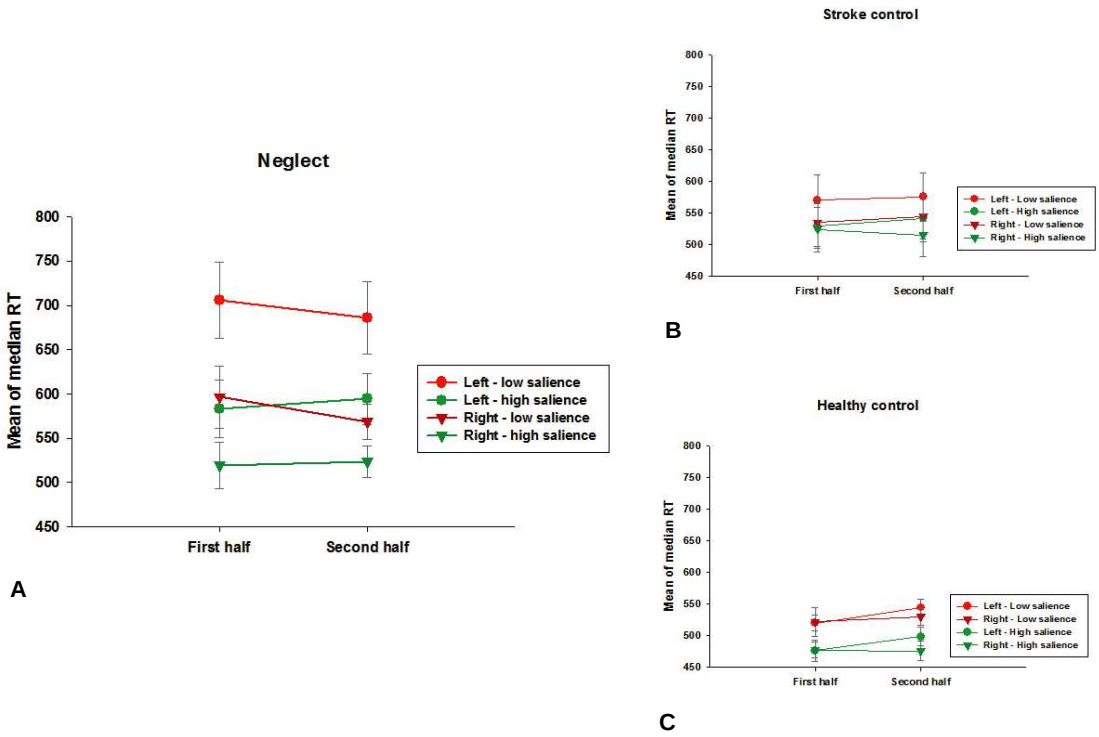


Figure 2.13. Reaction time data across groups on the bilateral task.

Unlike the error data, analysis of reaction times revealed a significant effect of stimulus salience and position in all three groups. Interestingly, in the healthy control group (C), there was an interaction between time and position with higher reaction times to left-sided stimuli with increasing time-on-task.

Low salience targets – red inverted triangles

High salience targets – green inverted triangles

Error bars indicate the standard error of the mean.

RT is measured in msec.

A repeated measures ANOVA was performed across the three subject groups, with within group measures of time (half task), position (left versus right) and salience (high versus low). The difference in overall reaction time between the groups just failed to reach significance ($F(2,33)=3.066$, $p=0.06$).

There was, however, a main effect of position ($F(1,33)=32.991$, $p<0.001$) and a significant interaction between position and group ($F(2,33)=12.194$, $p<0.001$). The effect of position was significant in both the neglect ($F(1,11)=22.083$, $p=0.001$) and stroke control group ($F(1,11)=14.505$, $p=0.003$), while there was an interaction between time and position in the healthy control group ($F(1,11)=6.613$, $p=0.026$).

It is possible that some of the stroke control patients had very mild lateralised deficits, which manifest as an increase in reaction times to left-sided targets, but not a significant reduction in hit rate. Some authors have argued that while the representation of left space is unilateral (residing in the right hemisphere), the representation of right space is bilateral (Bisiach 1993; Mesulam 1999). This might partly explain why neglect is much more common following right hemisphere lesions (Vallar and Perani 1986; Mort, Malhotra et al. 2003). Such an account might also explain why healthy control subjects developed slower reaction times to left-sided events with increasing time-on-task here.

Again, as in experiment 1, there was a main effect of target salience ($F(1,33)=79.854$, $p<0.001$) and a significant interaction between salience and group ($F(2,33)=7.433$,

p=0.002), although each group demonstrated significantly quicker reaction times to the high salience targets ($F(1,11)>14.0$, $p<0.003$) – Figure 2.13.

2.4.3. Discussion

As expected, patients with neglect were found to be deficient in the detection of left-sided stimuli, an impairment which was associated with damage to the IPL. However, more importantly, this deficit was found to interact with the difficulty sustaining attention over time, i.e. the two problems exacerbated each other – in fact difficulty sustaining attention likely contributed to the evident spatial deficit. This interaction was also found to be dependent on the integrity of the IPL. This region would therefore seem not only to be crucial in the detection of left-sided events, as is well established, but also in *maintaining attention* on, and sustaining goal-related activity, for left-sided locations. Again, this is inconsistent with the scheme of Corbetta and Shulman (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008), which suggests that ventral regions are primarily responsible for reorienting attention to behaviourally relevant stimuli. Instead, these findings are consistent with the proposal that the right IPL has additional goal-related or 'top-down' functions (Singh-Curry and Husain 2009).

Importantly, plotting the results of the lesion analyses from both experiments on the same rendered brain template (Figure 2.14), demonstrates that there is a crucial area of overlap at the border of the angular and supramarginal gyri of the IPL. This region is represented by the white coloured voxels within the circle shown in Figure 2.14. The IPL would therefore clearly seem to be involved in both goal-directed and stimulus-driven processes.

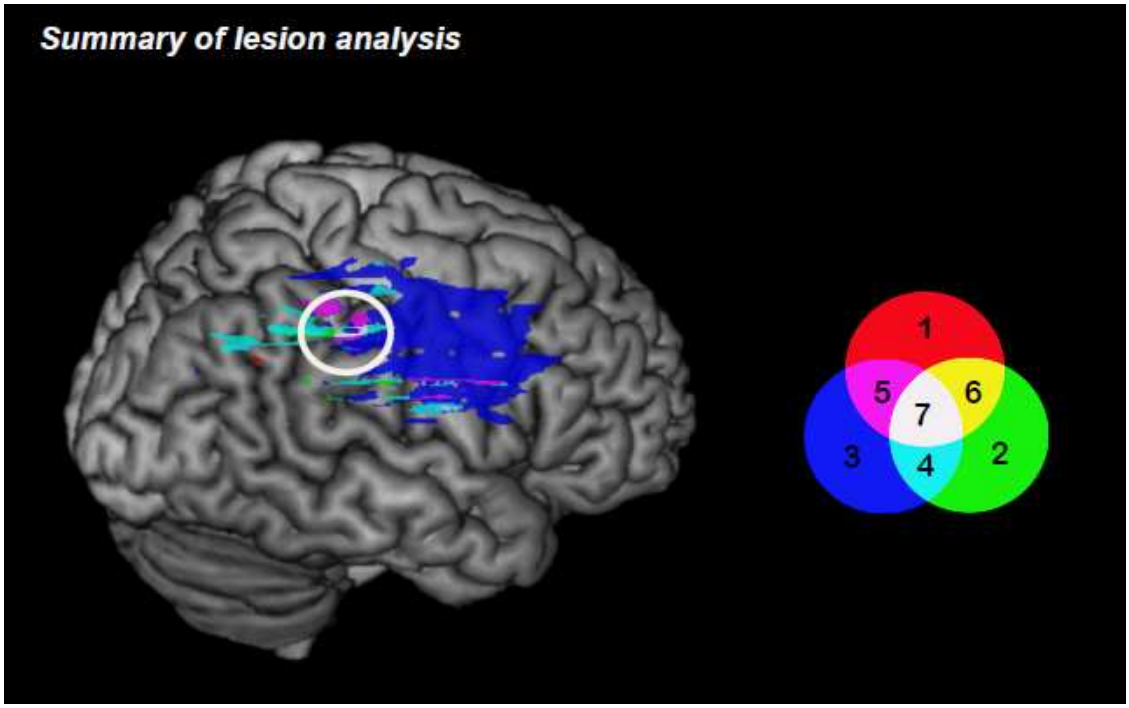


Figure 2.14. Summary of lesion analysis.

Results from all lesion analyses are plotted together on the same rendered brain template. The white circle indicates a crucial area of overlap at the border of the supramarginal and angular gyri in the IPL. Damage to the white coloured voxels within this area are significantly associated with deficits in salience encoding, detection of left-sided stimuli and sustaining attention to left-sided, as well as central events. Note that although the IPL is implicated in the ability to sustain attention to central locations, it appears to be the IFG which is dominant in this respect.

Colour code of cognitive deficits:
1 – salience encoding
2 – detection of left-sided stimuli
3 – sustaining attention
4 – sustaining attention to left-sided stimuli
5 – overlap of salience encoding and sustaining attention
6 – overlap of salience encoding and detection of left-sided stimuli
7 – overlap of salience encoding, detection of left-sided stimuli and sustaining attention to left-sided and centrally presented stimuli

2.5. General discussion

The aim of this chapter was to probe the functions of the ventral attention network – IPL, TPJ, superior temporal sulcus and ventral frontal regions – by examining deficits associated with hemispatial neglect, the syndrome that often follows damage to these areas (Vallar and Perani 1986; Husain and Kennard 1996; Mort, Malhotra et al. 2003). Using variants of an 'oddball paradigm' (Barcelo, Suwazono et al. 2000), I have demonstrated that neglect patients have difficulty sustaining attention over time, particularly for stimuli of lower perceptual salience (Figure 2.2). More importantly, however, I found that the deficit in sustaining attention interacts with difficulty detecting salient targets (Figure 2.2), as well as with the spatial orientation of attention (Figure 2.9). Although ceiling effects may have confounded these findings to a certain extent, closer examination of the data (subdividing the duration of the task into quartiles – Figure 2.3) suggests that the interaction between salience detection and sustaining attention may be real, although statistical analysis of the quartile data may have been adversely affected by power. If interactions between these behavioural measures are accepted, it suggests that these functions may be dependent upon an interrelated brain network.

Consistent with this notion, lesion analysis indicates that the ventral attention network is crucial in the mediation of all these processes (Figure 2.14). However, the findings suggest that there might be differences in the contributions of two critical nodes – frontal and parietal – in the ventral attention network. My data point to the right IFG playing a key role in sustained attention (Figure 2.5A), consistent with classical finding**s** (Wilkins,

Shallice et al. 1987), but a feature that is not a prominent in the model advanced by Corbetta and Shulman (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). By contrast, although the right IPL plays a role in the direction of spatial attention (Figure 2.12A) and encoding stimulus salience (Figure 2.5B), as suggested by Corbetta and colleagues, it also contributes to sustaining attention over time (Figure 2.5A), especially for left-sided events (Figure 2.12B).

These differences suggest a division of function between the frontal and posterior nodes of the ventral attention network that has previously not been established. Moreover, the results suggest that the right IPL may not simply have a role in reorienting attention or detecting salient events. Rather, this region also appears to play a role in sustaining attention. Furthermore, neglect patients show a deficit in salience encoding that may interact with the ability to maintain vigilant attention. These findings are consistent with a new hypothesis, which proposes that the right IPL plays a important role in the flexible adaptation of behaviour, between a task-engaged state, in which attention is sustained on task goals, and an exploratory state that facilitates identification of novel, salient events of potential behavioural significance (Singh-Curry and Husain 2009).

2.5.1. Sustained attention and the ventral network

Sustained attention may be considered an *intensity* aspect of attention – rather than a selectivity component (Posner and Boies 1971). It involves holding current goal or task instructions in mind, in order to monitor environmental information and produce appropriate motor responses that satisfy goal demands. Some authors consider that an

impairment in sustained attention is best demonstrated through a *vigilance decrement*, i.e. a decline in performance over the duration of a task, rather than simply an overall deficit (Whyte, Polansky et al. 1995; Parasuraman, Warm et al. 1998). For example, it could be argued that initial poor performance continuing throughout the duration of a task, simply indexes difficulty due to the specific cognitive demands of that task, rather than problems maintaining attention on it. But what would such a vigilance decrement mean in terms of underlying neural mechanisms?

Just as neural resources can be envisaged as being distributed over items in space or concurrently on different stimulus-response processes during dual-task paradigms (Bunge, Klingberg et al. 2000; Bays and Husain 2008), they also need to be maintained over time for optimal performance (Warm, Parasuraman et al. 2008). Such resources might be essential for protecting task goals, stored in working memory from distraction. Indeed, behavioural evidence shows that increasing working memory load leads to more rapid vigilance decrements over time (Parasuraman 1979). If task goals can not be adequately maintained, people may become distracted and switch to exploring novel task-irrelevant environmental stimuli (Singh-Curry and Husain 2009). In this way, sustaining attention can be considered to be an active process (Warm, Parasuraman et al. 2008).

Previous evidence (Wilkins, Shallice et al. 1987; Pardo, Fox et al. 1991; Rueckart and Grafman 1998; Vandenberghe, Gitelman et al. 2001) suggests that sustained attention may be associated with right parietal and frontal regions, and that neglect patients, who have lesions here (Vallar and Perani 1986; Husain and Kennard 1996; Mort, Malhotra et al.

2003), may be impaired at maintaining attention on tasks that do not require spatial shifts of attention (Hjaltason, Tegner et al. 1996; Robertson, Manly et al. 1997). In accordance with this, I have demonstrated a vigilance decrement on a non-spatial task associated with damage to the ventral attention network. In sum, these findings suggest a key role for this system in sustaining attention, a function for which there is no clear role in the model of Corbetta and colleagues (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). Instead, in their model, these regions are important in detecting salient stimuli in the environment, which may require reorienting of spatial attention.

2.5.2. Salience detection and the ventral attention network

Salience refers to the properties of a stimulus which make it stand out, due to goal-relevance or to task-irrelevant perceptual characteristics, such as stimulus novelty. Salient targets have been shown to strongly activate the right IPL in normal subjects (Linden, Prvulovic et al. 1999; Clark, Fannon et al. 2000; Foucher, Otzenberger et al. 2004; Kiehl, Stevens et al. 2005; Gur, Turetsky et al. 2007; Friedman, Goldman et al. 2009), and to produce a characteristic positive event-related potential, 300-500 ms after stimulus onset over the parietal lobe, termed the P3b (Ritter, Vaughan et al. 1968; Vaughan and Ritter 1970). Furthermore, parietal lesions lead to reduced or absent phasic P3b potentials and inaccurate target detection (Knight, Scabini et al. 1989; Verleger, Heide et al. 1996).

Consistent with this, I was able to show that neglect patients demonstrate difficulty detecting behaviorally salient targets – particularly the low salient items – and that this was associated with damage to the IPL. Moreover, increasing the perceptual salience of

targets (higher salience targets) improved performance. Interestingly, neurophysiological studies have shown that stimuli of higher perceptual salience can produce larger P3b potentials (Katayama and Polich 1998; Comerchero and Polich 1999). Hence high salience targets may have been more capable of initiating the appropriate response in parietal patients by evoking a larger P3b potential.

In this respect, my findings would be consistent with the view that the ventral network plays a key role in encoding salience (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008), although the data presented here suggest that this may be largely a right IPL function. One previous lesion study (Barcelo, Suwazono et al. 2000) demonstrated a small contralesional deficit in the detection of salient targets on an 'oddball' task following prefrontal lesions. However, the impairments reported in this investigation might have been due to poor sustained attention rather than salience encoding, as these participants were assessed over two long (one hour) sessions. Furthermore, only one type of target was used in this study, not two with different levels of salience as was used here.

My results therefore demonstrate how, in neglect patients, impaired detection of target stimuli may be modulated by perceptual salience (Figure 2.2), as well as spatial location (Figure 2.9). Crucially, these deficits did not depend upon spatial reorienting of attention, as they were evident even for stimuli presented consecutively at central fixation.

2.5.3. Interactions between attentional processes within the ventral system

In addition to identifying deficits in sustained attention and salience detection as components of ventral network function and the neglect syndrome, my findings in this chapter suggest that these processes may interact with each other. But why should these apparently independent functions be related? My own hypothesis proposes that the right IPL might play a crucial role in flexibly reconfiguring behaviour: between a task-engaged, 'exploitative' state in which attention is sustained on task goals, and an 'exploratory state', which enables the identification of potentially important novel or salient environmental events. Consistent with this view, task-switching, the process by which current behaviour is interrupted and engagement in a new task facilitated – and which is traditionally considered the remit of frontal areas – activates the IPL in several different types of study (Buchsbaum, Greer et al. 2005). It is also associated with a parietal P3 potential (Rushworth, Passingham et al. 2005; Travers and West 2008).

It has been proposed that noradrenergic input to the parietal cortex, from the locus coeruleus (LC) may be important in the flexible reconfiguration of behaviour between these two opposing functional states (Aston-Jones and Cohen 2005; Singh-Curry and Husain 2009). It is argued that *phasic* bursts from the LC, on a background of moderate *tonic* activity, may be important in mediating the task-engaged state, whilst higher *tonic* levels enable the exploratory mode and low tonic levels are associated with drowsiness. The relationship between tonic LC activity and effective task-engagement, or sustained attention, therefore follows an inverted U-shaped function, with both low and high tonic levels being associated with suboptimal phasic bursts and task-engagement.

Importantly, converging evidence suggests that the parietal P3 may reflect phasic activity of the LC noradrenergic system (Nieuwenhuis, Aston-Jones et al. 2005). By inference, therefore, effective phasic LC bursts on a background of moderate tonic levels, should be correlated with the P3b event-related potential recorded over parietal cortex, in response to salient, task-relevant events (Aston-Jones, Rajkowski et al. 1994; Dayan and Yu 2006).

I have argued, therefore, that *phasic* bursts of LC noradrenergic activity, on a background of moderate *tonic* activity, may induce, via parietal regions, a task-engaged state, enhancing sustained attention to task demands and facilitating detection of task-relevant events. By contrast, increases in LC *tonic* activity may shift the behavioural emphasis towards a more distractible, exploratory state (Singh-Curry and Husain 2009).

Neglect patients tend to be characterized by hypo-arousal rather than hyper-arousal, being more prone to drowsiness than distractible exploratory behaviour. Indeed, in this study, the errors made by neglect patients were principally omission errors rather than false alarms to non-target stimuli, suggesting that their deficit in sustained attention is driven by low levels of tonic noradrenergic activation of parietal cortex, rather than high levels. It is known that even normal subjects eventually experience a decrement in vigilance or sustained attention after prolonged periods on a repetitive task (Mackworth 1957) – and indeed the healthy controls demonstrated an increase in reaction time with time-on-task on the short experiments described here (Figures 2.7C & 2.13C) – hence it can be anticipated that less effective engagement at the start of the task, due to low tonic activation, would also be associated with subsequent faster decline.

Low levels of tonic noradrenergic activation of parietal cortex could result from lesions to parietal cortex itself, or alternatively from a reduction in tonic input from the LC. Efferent activity from the LC would in turn be affected by its afferent input, a large part of which appears to be derived from frontal regions (Rajkowski, Lu et al. 2000; Aston-Jones, Rajkowski et al. 2002) and would therefore be susceptible to damage here. Of course, it should be remembered that posterior parietal cortex also receives direct afferents from frontal areas (Schmahmann, Pandya et al. 2007), so that frontal lesions could reduce baseline parietal activity in this way too. In fact, this is consistent with the results of my lesion analysis, which, although suggesting that the parietal lobe is crucial in mediating interactions between sustained attention and other cognitive processes I examined, implicates frontal lesions more strongly in the sustained attention deficit.

If the deficit in sustained attention is indeed due, in part, to a reduction in baseline parietal activity, it can be envisaged how this may interact with and exacerbate the deficit in detecting task-related salience. Lower baseline parietal activity would mean the smaller P3b potentials have even less chance of crossing the threshold for initiation of appropriate motor output. This could also explain the interaction between difficulty detecting left-sided events, known to be dependent on right parietal integrity, and the sustained attention deficit.

In fact, posterior parietal cortex seems to be an important 'hub', where several different types of information – sensory, motor, goal and reward related – converge. Indeed, recent evidence suggests that the IPL represents a 'structural core', being one of the most densely

interconnected cortical regions (Hagmann, Cammoun et al. 2008). Such connectivity ideally places the IPL at the centre of a network where these different types of information may compete and interact to bias the functional state.

In sum, the findings presented here suggest that the functions of the ventral attention network are more complex than the proposal advanced by Corbetta and Shulman would suggest (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). Hypotheses regarding the contribution of these areas to behaviour need to take into account their role in sustaining attention over time, as well the encoding of salient events requiring evaluation of new environmental information. Furthermore, they provide new insight into the way in which non-spatial cognitive deficits associated with neglect, can interact with the characteristic visuospatial problems to exacerbate the severity of the syndrome.

Chapter 3

3.1. Introduction

Chapter 2 explored some of the functions of the ventral attention network, by examining the cognitive deficits associated with hemispatial neglect, the syndrome that commonly results from damage to these regions (Vallar and Perani 1986; Husain and Kennard 1996; Mort, Malhotra et al. 2003). It was concluded, on the basis of lesion-symptom analysis techniques, that the functions of the ventral attention network, particularly those of the right inferior parietal lobe (IPL), may be more complex than previous proposals have suggested (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). In fact, the findings from Chapter 2 indicate that this area plays an important role in both goal-directed attention and the stimulus-driven reorienting of attention – processes which these authors have traditionally segregated into functionally opposing dorsal and ventral fronto-parietal networks (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008).

Instead, the results provided support for the scheme developed in Chapter 1, whereby the right IPL is considered to act as a pivotal module in the flexible adaption of behaviour, switching the mode of operation between two broadly opposing functional states: a task-engaged mode, in which attention is focussed on goal or task demands and a more exploratory state, which enables the identification of potentially significant novel or salient environmental events (Singh-Curry and Husain 2009). In this chapter I extend

these findings by examining the effect of phasic alerting tones on the spatial and non-spatial deficits associated with neglect.

Phasic alerting refers to a readiness to detect and respond to environmental changes, due to the occurrence of an exogenous warning stimulus (Posner and Boies 1971). This may be in the same modality as the subsequent target stimulus or an alternate one. In this respect, it may be considered as a category of stimulus salience, rather than as a purely intensity aspect of attention (Singh-Curry and Husain 2009).

There may be a predefined association between an alerting stimulus and one which follows it. For example, a cue presented a set interval before a visual target, or the ringing of an emergency alarm indicating a potential hazard in a building and that it must be evacuated. In such cases, where there are predefined associations between an alerting cue and a subsequent target or event, a goal-driven element of processing is introduced. On the other hand, there may not be any predefined stimulus-stimulus or stimulus-response associations, in which case the alerting cue becomes very similar to a novel one. Although such alerting events may be considered to be primarily 'bottom-up' in nature, memory of previous events clearly needs to be available in order to correctly judge a stimulus as new. In this way, phasic alerting, like other categories of stimulus salience appears to incorporate a variable mix of goal-directed – or 'top-down' – and stimulus driven – or 'bottom-up' – processes.

It has been shown that an alerting cue which orients a subject to the location of an impending target activates the right intraparietal sulcus (IPS) and temporoparietal junction (TPJ) (Kastner, Pinsk et al. 1999; Corbetta, Kincade et al. 2000; Shulman, Astafiev et al. 2009). However, there are also functional imaging studies that suggest that parietal areas are important in the detection of cues which provide no such predictive information (Fan, McCandliss et al. 2005; Thiel and Fink 2007).

In one such study (Thiel and Fink 2007), a simple target detection paradigm was used in which some targets were preceded by a visual or auditory cue (with a variable cue-target interval so as not to be temporally predictive). The other investigation (Fan, McCandliss et al. 2005) employed the attention network test, which is designed to simultaneously probe the effect of a non-informative cue (*alerting* condition), a spatially informative cue (*orienting* condition) and a condition in which the target arrow stimulus is flanked by either congruent or incongruent arrow stimuli (*conflict* situation, obtained by subtracting the effect of congruent from incongruent). Both of these studies demonstrated prominent activation in the right IPL to be associated with alerting.

Lesions of the right hemisphere have long been known to impair alerting responses, as measured with galvanic skin responses (Heilman, Schwartz et al. 1978) or heart rate changes to warning cues (Yokoyama, Jennings et al. 1987). Conversely patients with hemispatial neglect, who usually have lesions involving the IPL (Vallar and Perani 1986; Mort, Malhotra et al. 2003), have been shown to benefit from an alerting tone on a task designed to assess their visuospatial deficit (Robertson, Mattingley et al. 1998).

Neglect, however, may also be associated with other non-spatial impairments (Samuelsson, Hjelmquist et al. 1998; Robertson 2001; Husain and Rorden 2003), such as the ability to sustain attention and encode stimulus salience, as demonstrated in Chapter 2. It has yet to be shown whether alerting stimuli can also ameliorate these difficulties, in addition to the spatial deficits. However, because I consider phasic alerting stimuli to act as salient inputs, and have demonstrated that increasing the salience of stimuli can modulate the ability of neglect patients to correctly identify target events and even improve their ability to sustain attention to them (Chapter 2), I hypothesise that alerting tones might serve to ameliorate all of these deficits – not just the spatial problems.

Using further versions of the 'oddball paradigm' (Barcelo, Suwazono et al. 2000) employed in Chapter 2, here I aim to investigate the effect of phasic alerting tones on the ability of neglect patients to sustain attention and encode stimulus salience. I will also examine how such effects might interact with the more characteristic spatial difficulties of neglect.

3.2. General methods

3.2.1. Participants

Patients were recruited from stroke and neurological units with local ethics approval. Overall, a total of 13 right middle cerebral artery (MCA) stroke patients with neglect (mean age: 59.8 years, range: 31-78; one left-handed and one ambidexterous) and 10 right MCA patients without neglect (mean age: 57.7 years, range: 32-76; all right-handed) were

included in the study. Exclusion criteria included cognitive impairment such that there was difficulty following assessment or task instructions, and active medical comorbidity. 10 healthy elderly control participants with no neurological or psychiatric history were also recruited (mean age: 73.5 years, range: 59-82; 2 left-handed); see Table 3.1 for further patient demographic information.

3.2.2. Assessment of neglect

A visual neglect battery was performed on all patients to determine the presence or absence of neglect (Malhotra, Greenwood et al. 2004). Patients with neglect demonstrated neglect behaviour in their activities of daily living as well as on the Mesulam cancellation test (Mesulam 1985) and/or the line bisection task (Stone and Greenwood 1991). Neglect was identified by an asymmetry of cancellation of 2 or more items on the Mesulam task and a mean rightward deviation of 5mm or more on line bisection of three 17cm lines.

Subject	Age	Time since stroke (months)	Field defect	Mesulam (R-L difference)	Line bisection (cm to right of midline)	Tasks performed
N1	74	0.3	No	4	1	C
N2	66	10	Partial left lower quadrantanopia	20	1	C & B
N3	66	3	Left hemianopia	22	3.2	C
N4	63	0.7	No	3	1.3	C
N5	75	0.7	No	2	0.7	C
N6	39	1	Partial left lower quadrantanopia	22	0.8	C & B
N7	58	3	Left hemianopia	20	2	C
N8	53	2	No	14	1.2	C & B
N9	78	0.5	No	18	0.8	C & B
N10	60	1.7	No	7	0.8	C & B
N11	31	2	No	20	0.1	B
N12	57	2	No	2	0.5	B
N13	58	2	No	1	0.6	B
mean	**59.8**	**2.2**		**11.9**	**1.1**	
SC1	70	60	No	1	0.3	C & B
SC2	70	2	No	0	-0.2	C & B
SC3	50	0.5	No	1	0.2	C & B
SC4	71	2	No	-1	0.2	C & B
SC5	61	5	No	0	-0.2	C & B
SC6	37	0.2	No	0	-0.7	C & B
SC7	32	0.5	No	-4	-0.2	C & B
SC8	68	0.5	No	0	-0.3	C & B
SC9	76	0.6	No	0	-0.3	C & B
SC10	42	36	No	-2	-0.3	C
mean	**57.7**	**10.7**		**-0.5**	**-0.2**	

Table 3.1. Patient demographics.

N = patient with neglect

SC = stroke control patient

C = central task

B = bilateral task

The central and bilateral alerting tasks are described in full in the text.

3.2.3. Apparatus and stimuli

Participants depressed the central bottom button of an RB-530 Cedrus response box in response to the presentation of target stimuli. A Dell Latitude D820 laptop with a 15 inch screen and bilateral integral speakers was used for stimulus presentation. Both tasks were programmed using E-Prime software (Psychology Tools Software Inc.). Stimuli consisted of red and green coloured triangles, subtending approximately 2.5 x 2 º of visual angle when viewed from a distance of about 60cm, and were presented on a grey background. These were presented either centrally or at a parafoveal location just left or right of centre, depending on the task being performed. Subjects had no problems identifying parafoveal stimuli when fixating centrally. Auditory tones (22kHz, 350ms duration and 85dB) were presented bilaterally through the integral laptop speakers.

3.2.4. General experimental design

Both tasks were based on an 'oddball paradigm' (Barcelo, Suwazono et al. 2000) in which infrequently occurring target stimuli (inverted triangles) were presented randomly intermixed with frequently occurring non-target stimuli (upright red triangles). As in the experiment described in Chapter 2, there were two types of target: a green inverted triangle and a red inverted triangle. The green targets were designated *high salience* because they differed from the non-targets along two feature dimensions – orientation and colour. Red targets were of lower salience, differing from the non-targets in orientation only. Subjects were instructed to respond as quickly as possible with their preferred hand whenever they saw an inverted triangle target, whatever its colour (green or red). The two

target types were therefore identical in terms of task goal but differed in terms of perceptual salience.

In both of the experiments, non-targets (red upright triangles) comprised 75% of stimuli, whilst the low and high salience targets each made up 12.5%. Stimulus presentation time was 500ms, with inter-stimulus interval varying between 1000 and 1500ms. Alerting auditory tones (22kHz, 350ms duration and 85dB) were presented bilaterally through the laptop speakers with visual stimulus onset for some of the visual stimuli (12.5% in the first experiment and 20% in the second). They had equal probability of occurring with the targets as non-targets, and on the left and right sides of space during the bilateral task. Auditory tones paired with target stimuli were equally distributed among those of high and low perceptual salience.

Responses were collected for 1500ms after visual stimulus onset and were discarded if they occurred within 200ms after stimulus onset (classified as anticipations). Each task consisted of 320 stimuli, lasting for approximately 10 minutes duration. Task order was counterbalanced across subjects, with each task preceded by a short practice comprising 20 stimuli, which was repeated if necessary. Subjects were monitored visually, to ensure they maintained central fixation, throughout the tasks.

3.2.5. Data Analysis

The median hit rates, false alarm rates and reaction times for each subject were analysed. All data presented on graphs represents the mean of the individual subject medians.

Repeated-measures ANOVAs were used to examine for significant effects between groups (neglect, stroke control and healthy control) as well as for additional within-group effects for each of the two tasks (see below) and for each behavioural outcome measure. Within group ANOVAs and *t*-tests were used to explore significant effects obtained in the group ANOVAs where appropriate.

3.3. Experiment 1 – The effect of alerting tones on responses to central stimuli

3.3.1. Behavioural task design

All visual stimuli were presented at a single central location on the display screen, aligned to the participant's vertical midline. In order to assess the effect of phasic alerting on salience encoding and sustaining attention during the 10 minute task duration, auditory tones were presented with 12.5% of the visual stimuli, as described above (see Figure 3.1).

Alerting tones were equally distributed among target and non-target stimuli and had equal probability of occurring with low and high salience targets. Subjects were instructed to respond with the same button press whenever they saw an inverted triangle, regardless of its colour or whether it was accompanied by a tone. Participants were warned beforehand that tones could occur with non-targets as well as targets. 10 neglect patients, 10 stroke control and 10 healthy elderly individuals performed this task.

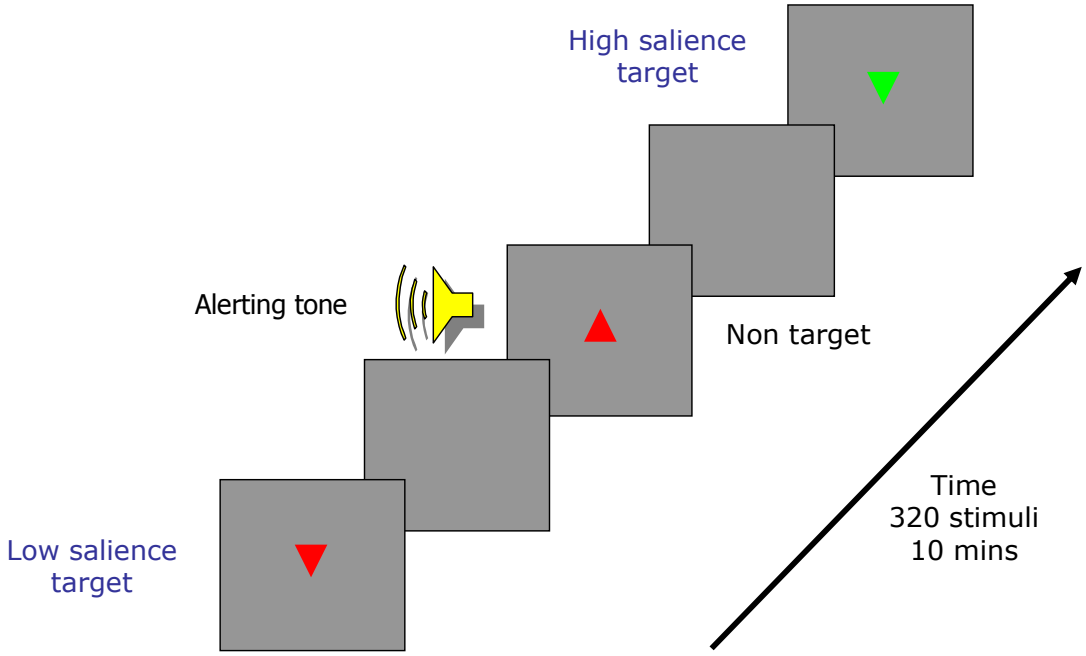


Figure 3.1. Alerting task – central presentation.

Subjects were instructed to respond with a button press whenever they saw an inverted triangle, whether this was red (low salience) or green (high salience).

12.5% of visual stimuli were low salience targets, 12.5% were high salience targets and the remaining 75% of stimuli were non-target stimuli. An auditory tone (22 kHz, 350 ms) was presented bilaterally at visual stimulus onset on 12.5% of stimulus presentations. These alerting tones were equally distributed amongst non-targets and targets and were equally likely to occur with low as high salience targets.

Each stimulus was presented for 500 ms, with an interstimulus interval (ISI) of 1000-1500 ms. The task consisted of 320 stimulus presentations, lasting for approximately 10 minutes.

3.3.2. Results

3.3.2.1. Errors – hit rate and false alarm rate

The hit rate and false alarm rate for high and low salience stimuli, with and without a tone, over time on the task are shown by group in Figure 3.2.

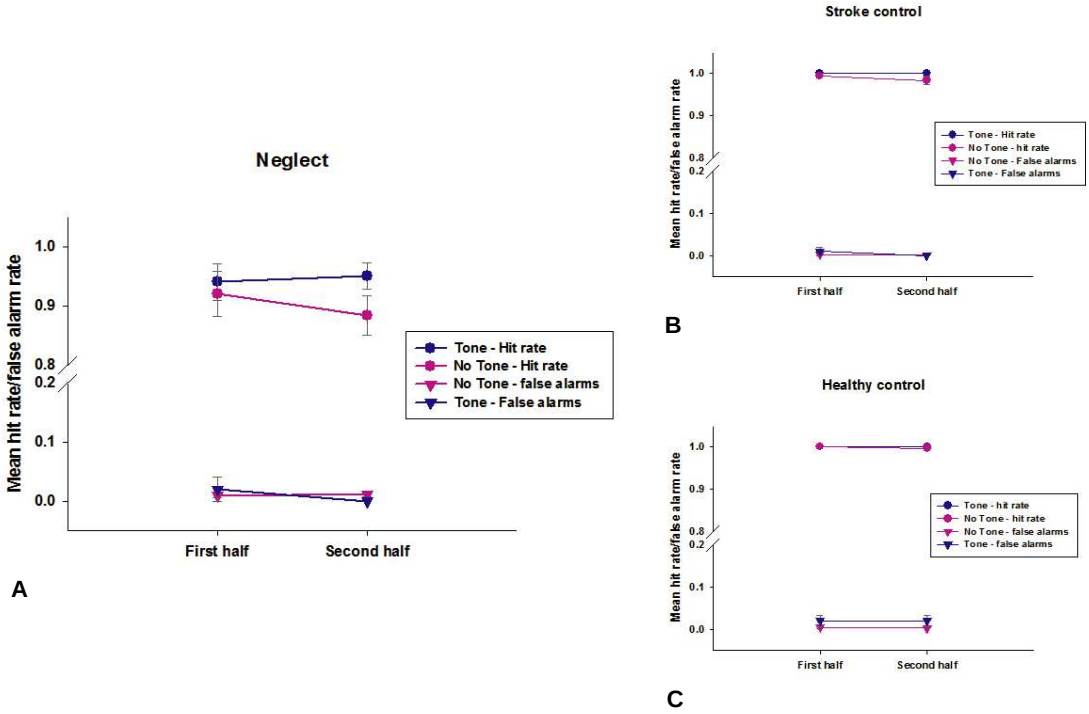


Figure 3.2. The effect of an alerting tone on hit rate across the three subject groups.
The presence of an alerting tone served to ameliorate the deterioration in hit rate seen over time without a tone in the neglect group (A). There was no effect of the alerting tone in the control groups (B and C), however, their performance was already at ceiling. All groups made very few false alarms and this was not significantly affected by the presence of an alerting tone**.**
Error bars indicate standard error of the mean.

A repeated measures ANOVA was performed on the hit rate data across the 3 groups (neglect, stroke control and healthy control), with within group factors of time (first half compared to second half), tone (tone versus no tone) and salience (high versus low).

Neglect patients demonstrated overall poorer performance than either of the control groups (effect of group: $F(2,27)=7.296$, $p=0.003$), with *post hoc* Bonferroni tests revealing the neglect group to have significantly lower hit rates than the stroke control ($p=0.011$) and healthy control groups ($p=0.006$).

There was a significant main effect of tone ($F(1,27)=5.495$, $p=0.027$) and although there was not a significant interaction between tone presence and subject group ($F(2,27)=2.429$, $p=0.107$), Figure 3.2 indicates that the performance of *only* neglect patients was ameliorated by an alerting tone. However, the performance of the control groups in terms of hit rate can be seen to be close to ceiling.

Although Figure 3.2A seems to indicate that an alerting tone acted to ameliorate the deterioration in hit rate seen over time in the absence of alerting tones, there was no interaction between time-on-task and tone presence ($F(1,27)=2.186$, $p=0.15$), nor was there an interaction between time, tone and subject group ($F(2,27)=0.992$, $p=0.384$).

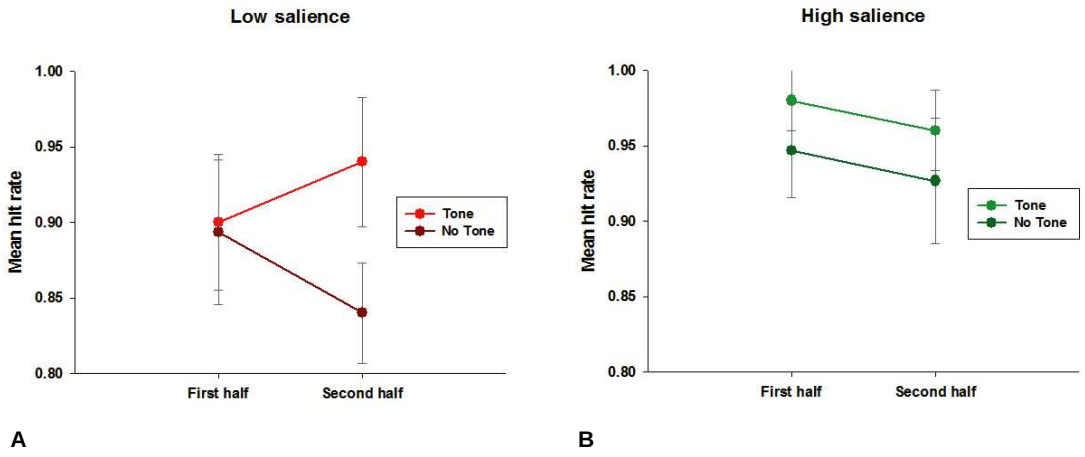


Figure 3.3. The effect of an alerting tone on the ability of neglect patients to sustain attention on salient target stimuli.

An alerting tone ameliorates the deficit neglect patients have in sustaining attention on target stimuli, particularly targets of lower (A), as opposed to higher (B) salience.

Low salience targets – red inverted triangles
High salience targets – green inverted triangles

Error bars indicate standard error of the mean.

However, similar to the experiments presented in Chapter 2, there was a significant effect of stimulus salience ($F(1,27)=16.852$, $p<0.001$) and an interaction between salience and subject group ($F(2,27)=9.147$, $p=0.001$). Only the neglect patients demonstrated a significant effect of target salience ($F(1,9)=12.624$, $p=0.006$), with hit rate being lower for low salience stimuli as compared to higher salience targets (see Figure 3.3). This was

partially ameliorated by the presence of an alerting tone, particularly as time-on-task progressed. This amelioration was, however, also apparent for the detection of the higher salience stimuli, which would explain why there was no interaction between stimulus salience and tone presence ($F(1,27)=1.042$, $p=0.317$) or indeed salience, tone and subject group ($F(2,27)=0.165$, $p=0.849$).

As can be seen from Figure 3.2, there were few false alarm errors made on this task, despite the fact that whenever an alerting tone occurred, it was equally likely to be accompanied by a non-target as a target. A repeated measures ANOVA on the false alarm data across the three patient groups, with within group factors of time (half task), tone (present or absent) and salience (low versus high) did not reveal any significant effects. This therefore suggests that the beneficial effect of alerting tones could not have been produced by an encouragement merely to respond whenever a tone was encountered.

3.3.2.2. Reaction time data

The reaction time data for this task is shown by subject group in Figure 3.4

A repeated measures ANOVA was performed across the three subject groups on the reaction time data, with within group measures of time (half task), tone (presence or absence) and salience (low versus high). There was a significant difference between the groups ($F(2,27)=4.332$, $p=0.023$), with *post hoc* Bonferroni testing revealing a significant difference between the neglect patients and healthy controls ($p=0.021$) but not the stroke controls ($p>0.7$).

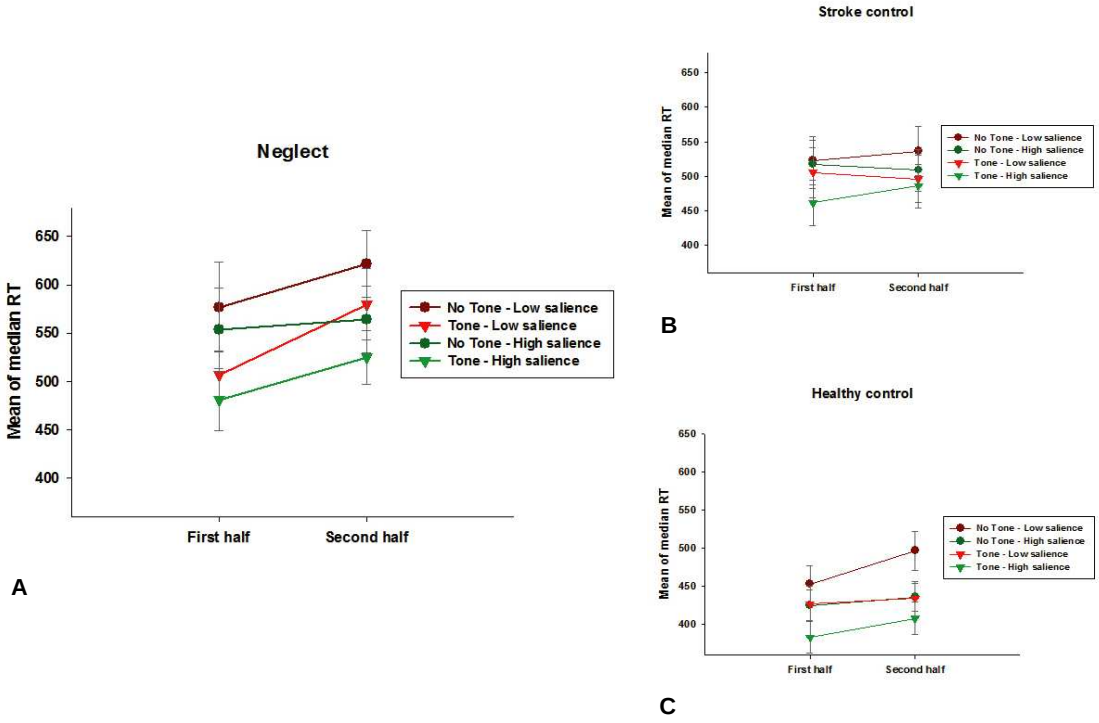


Figure 3.4. The effect of an alerting tone on reaction time to salient targets over time over the three subject groups.

The presence of an alerting tone reduced the reaction time to salient target stimuli in all three subject groups.

Low salience targets – red inverted triangles

High salience targets – green inverted triangles

Error bars indicate the standard error of the mean.

RT is measure in msec.

There was a significant effect of tone presence ($F(1,27)=33.392$, $p<0.001$), with all three subject groups demonstrating quicker reaction times to target stimuli when they were accompanied by an alerting tone ($F(1,9)>7.4$, $p<0.023$) – see Figure 3.4.

As demonstrated in Chapter 2, there was a main effect of time ($F(1,27)=15.217$, $p=0.001$) and a significant interaction between time-on-task and subject group ($F(2,27)=3.433$, $p=0.047$). The effect of time was significant in the neglect group ($F(1,9)=7.687$, $p=0.022$), as we might have anticipated, but interestingly it was also evident in healthy controls ($F(1,9)=14.694$, $p=0.004$), with both groups of subjects demonstrating higher reaction times with time-on-task (see Figure 3.4). Also as previously identified, there was a significant effect of stimulus salience ($F(1,27)=33.654$, $p<0.001$), present in all three subject groups ($F(1,9)>6.65$, $p<0.03$), with quicker reaction times for targets of higher salience, again confirming that these stimuli were more salient than the targets classified as being of low salience.

Importantly, there was a significant interaction between time-on-task, target salience and tone presence ($F(1,27)=4.533$, $p=0.043$), but this interaction reached significance within the healthy control group only ($F(1,9)=5.712$, $p=0.041$). From Figure 3.4C, it can be seen that in this group, there was an increase in reaction time with time-on-task for the low salience stimuli unaccompanied by a tone only ($t(9)=-3.588$, $p=0.006$), with time-on-task failing to significantly affect reaction time either for low salience stimuli accompanied by a tone ($t(9)=-.742$, $p>0.47$) or for high salience stimuli accompanied ($t(9)=-2.13$, $p>0.6$) or

unaccompanied by a tone ($t(9)=-1.671$, $p>0.12$). Hence a reduction in the ability to sustain vigilant attention, as measured by an increase in reaction time with time-on-task, was only observed for visual stimuli of particularly low perceptual salience and not for those of higher salience, either due to the stimulus properties (i.e. colour) or the presence of an additional auditory alerting stimulus.

3.3.3. Discussion

It has previously been shown that alerting tones can improve the spatial orienting of attention in neglect (Robertson, Mattingley et al. 1998). However, here it has been demonstrated that an amelioration of the deficit in sustained attention can occur at a single central location in patients with neglect; to the extent that in the presence of an auditory tone, performance becomes similar to that of control subjects (Figure 3.2).

I did, however, fail to demonstrate a significant interaction between the presence on an alerting tone and time-on-task on the hit rate data, although this might be attributable to a lack of power, with there being only a small number of targets actually accompanied by an alerting tone (in fact only 5 targets of high and 5 of low salience in each half task). The obvious way in which to overcome this limitation would have been to make the task longer or increase the rate at which stimuli were presented, although this would have made the task more demanding for neglect patients.

The next experiment, will aim to examine the effect of alerting tones on the interaction, that I demonstrated in Chapter 2, between the ability of neglect patients to sustain

attention and orient attention to the left side of space. In other words, I will investigate whether the presence of alerting tones can also ameliorate the more severe problems neglect patients have in detecting left-sided stimuli which manifest themselves over the duration of a task – the ability to *sustain attention* to left-sided events.

3.4. Experiment 2 – The effect of alerting tones on responses to left and right sided stimuli

3.4.1. Behavioural task design

This task was similar to that of experiment 1, except that the visual stimuli occurred at a parafoveal location, 1º left or right of a central fixation cross (see Figure 3.5), permitting the examination of alerting on salience detection, sustained attention and spatial attention. Alerting tones accompanied 20% of visual stimuli and were equally likely to be presented with targets as non-targets, high salience and low salience events and left-sided compared to right-sided stimuli. Subjects were monitored visually throughout the task to ensure they maintained fixation. Those unable to maintain central fixation, and those with a hemianopia, were excluded from this experiment. 8 neglect patients, 9 stroke control and 9 healthy elderly subjects participated in this task.

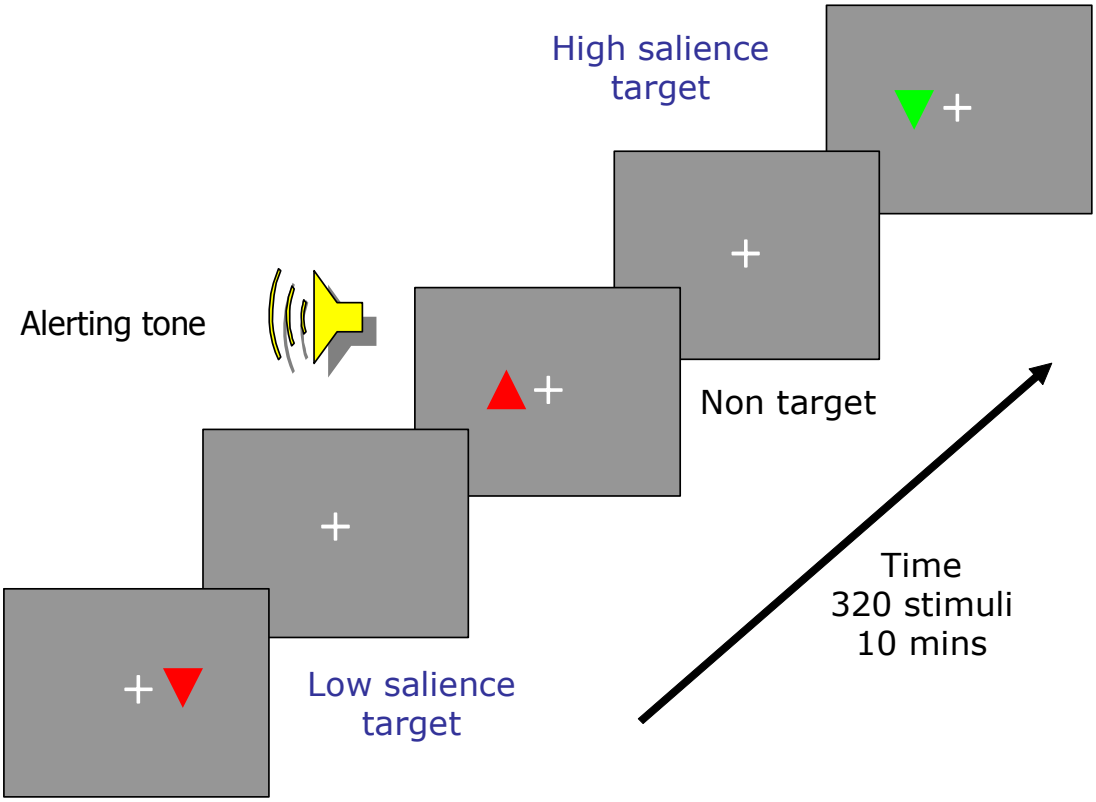


Figure 3.5. Alerting task – bilateral presentation.

Subjects were instructed to respond with a button press whenever they saw an inverted triangle, whether this was red (low salience) or green (high salience).

12.5% of visual stimuli were low salience targets, 12.5% were high salience targets and the remaining 75% of stimuli were non-target stimuli. Stimuli were presented 1º left or right of the central fixation cross.

An auditory tone (22 kHz, 350 ms) was presented bilaterally at visual stimulus onset on 20% of stimulus presentations. These alerting tones were equally distributed amonst non-targets as targets and were equally likely to occur with low as high salience targets and left as right-sided stimuli.

Each stimulus was presented for 500 ms, with an interstimulus interval (ISI) of 1000-1500 ms. The task consisted of 320 stimulus presentations, lasting for approximately 10 minutes.

3.4.2. Results

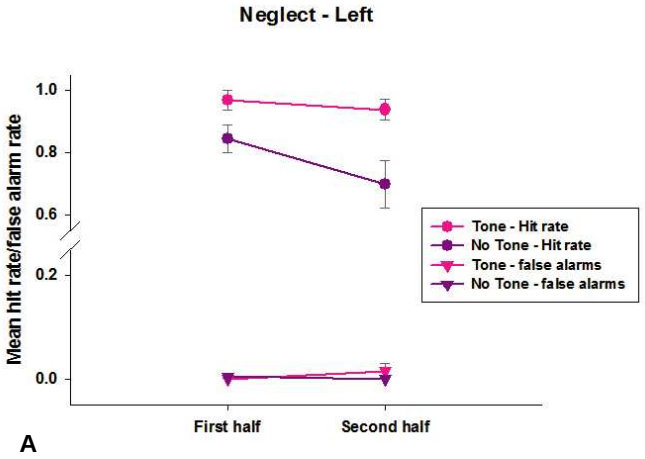
3.4.2.1. Error – hit rate and false alarm rate

The hit rate and false alarm rate for left and right sided stimuli, with and without an alerting tone, over time on the task are shown by group in Figure 3.6.

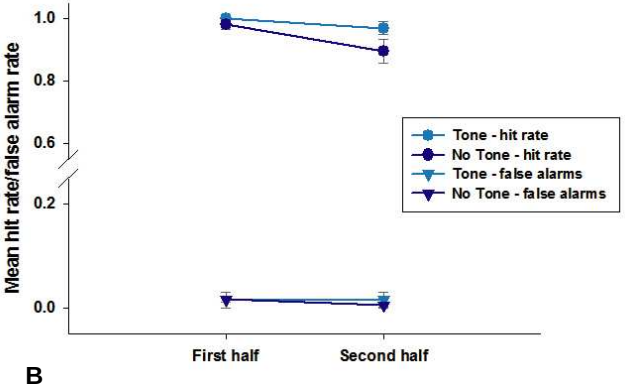
A repeated measures ANOVA was performed on the hit rate data across the 3 groups (neglect, stroke control and healthy control) with within group factors of time (first half versus second half), position (left versus right), tone (tone versus no tone) and salience (low versus high).

As in experiment 1, neglect patients demonstrated significantly poorer performance than either of the control groups (group effect: $F(2,23)=17.605$, $p<0.001$), with *post* hoc Bonferroni contrasts between neglect and stroke control groups, and neglect and healthy control groups (both $p<0.001$) revealing that neglect patients had significantly lower hit rates.

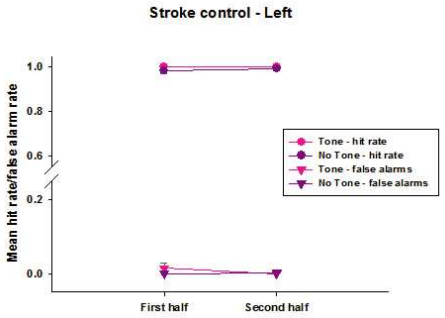
There was a significant effect of tone ($F(1,23)=17.918$, $p<0.001$) and an interaction between tone and subject group ($F(2,23)=11.684$, $p<0.001$), with *only* the neglect patients demonstrating a significant amelioration of performance in the presence of an alerting tone ($F(1,7)=13.247$, $p=0.008$) – see Figure 3.6.


Neglect - Left
Mean hit rate/false alarm rate
1.0
0.8
0.6
0.2
0.0
First half
Second half
Tone - Hit rate
No Tone - Hit rate
Tone - false alarms
No Tone - false alarms

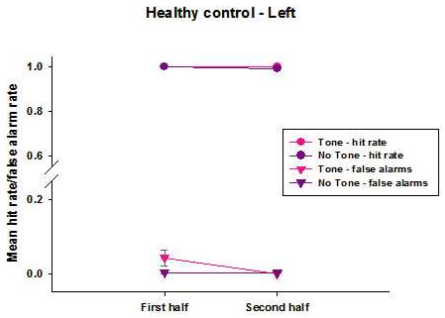
A


Neglect - Right
Mean hit rate/false alarm rate
1.0
0.8
0.6
0.2
0.0
First half
Second half
Tone - hit rate
No Tone - hit rate
Tone - false alarms
No Tone - false alarms

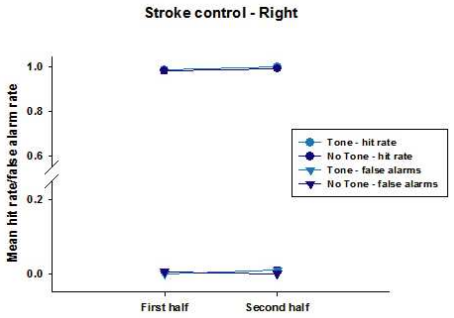
B


Stroke control - Left
Mean hit rate/false alarm rate
1.0
0.8
0.6
0.2
0.0
First half
Second half
Tone - hit rate
No Tone - hit rate
Tone - false alarms
No Tone - false alarms

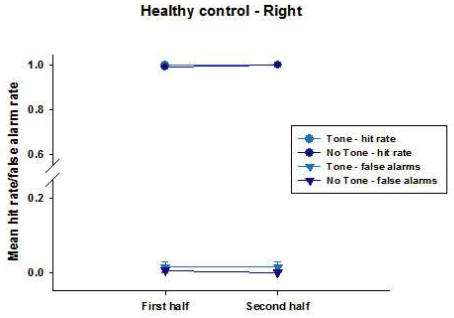
C


Healthy control - Left
Mean hit rate/false alarm rate
1.0
0.8
0.6
0.2
0.0
First half
Second half
Tone - hit rate
No Tone - hit rate
Tone - false alarms
No Tone - false alarms

E


Stroke control - Right
Mean hit rate/false alarm rate
1.0
0.8
0.6
0.2
0.0
First half
Second half
Tone - hit rate
No Tone - hit rate
Tone - false alarms
No Tone - false alarms

D


Healthy control - Right
Mean hit rate/false alarm rate
1.0
0.8
0.6
0.2
0.0
First half
Second half
Tone - hit rate
No Tone - hit rate
Tone - false alarms
No Tone - false alarms

F

Figure 3.6. The effect of alerting tone on hit rate and false alarm rate on the bilateral task across the three subject groups.

The presence of an alerting tone served to ameliorate the deterioration in hit rate seen over time without an alerting tone in the neglect group (A and B), particularly for stimuli presented on the left side of space. There was no significant effect of tone in stroke control (C and D) or the healthy control (E and F) groups, although these subjects were already at ceiling. All groups made very few false alarms and this was not significantly affected by the presence of an alerting tone.

Error bars indicate the standard error of the mean.

There was also a main effect of time-on-task ($F(1,23)=7.038$, $p=0.014$) and an interaction between time-on-task and group ($F(2,23)=9.683$, $p=0.001$). Again, there was a significant deterioration with time-on-task in the neglect group alone ($F(1,7)=8.005$, $p=0.025$) – see Figure 3.6. However, it should again be noted that the performance of the control groups, in terms of the error data, was at ceiling.

Importantly, there was also a significant interaction between time-on-task and presence of an alerting tone ($F(1,23)=5.577$, $p=0.027$) and a triple interaction between time-on-task, presence of alerting tone and subject group ($F(2,23)=5.88$, $p=0.009$), with *only* the neglect group demonstrating this interaction ($F(1,7)=5.861$, $p=0.046$).

As can be seen from Figure 3.6, the presence of an alerting tone ameliorated the deterioration in hit rate over time in the neglect patients. This was confirmed by t-tests, which revealed a significant difference in the second half of the task between stimuli accompanied by a tone and those not paired with an alerting tone ($t(7)=3.12$, $p=0.017$), while there was no difference between tone and no tone during the first half of the task ($t(7)=1.323$, $p=0.227$).

As would be expected, there was also a main effect of stimulus position ($F(1,23)=10.049$, $p=0.004$) and an interaction between position and subject group ($F(2,23)=10.76$, $p=0.001$), with neglect patients alone being significantly poorer at correctly detecting left sided targets ($F(1,7)=9.555$, $p=0.018$) – see Figure 3.6.

Importantly, however, there was also a significant interaction between stimulus position and presence of an alerting tone ($F(2,23)=8.016$, $p=0.009$) and a triple interaction between stimulus position, presence of alerting tone and subject group ($F(2,23)=6.631$, $p=0.005$), with the interaction between position and tone presence reaching significance in the neglect group alone ($F(1,7)=6.551$, $p=0.038$). As can be seen from Figure 3.6, alerting tones significantly improved the detection of left-sided stimuli to the extent that, in the presence of an alerting tone, there was no difference in the hit rate to right and left sided stimuli ($t(7)=-1.08$, $p=0.316$), while there was a clear difference in detection of left and right sided stimuli unaccompanied by an alerting tone ($t(7)=-3.266$, $p=0.014$).

Consistent with the results from experiment 1 and those presented in Chapter 2, there was a main effect of stimulus salience ($F(1,23)=14.9$, $p=0.001$) and an interaction between salience and subject group ($F(2,23)=6.272$, $p=0.007$). Neglect patients only were found to be significantly less accurate in the detection of low compared to high salience stimuli ($F(1,7)=8.488$, $p=0.023$) – see Figure 3.7. It must again be noted that the control groups were performing at ceiling.

There was also a significant interaction between stimulus salience and tone presence ($F(1,23)=8.091$, $p=0.009$) with the interaction between salience, tone and group just failing to reach significance ($F(2,23)=2.865$, $p=0.077$). This interaction approached significance in the neglect patients only ($F(1,7)=4.936$, $p=0.062$). In the neglect group, there was a significant difference in hit rate between high and low salience targets when they were unaccompanied by an alerting tone ($t(7)=2.763$, $p=0.028$), with performance to high and low salience stimuli becoming more similar in the presence of an alerting tone ($t(7)=1.871$, $p=1.04$).

In summary, alerting tones were found to ameliorate the deficit in sustaining attention to stimuli over the course of the task, in addition to improving detection of left-sided targets and low salience targets in both left and right sides of space.

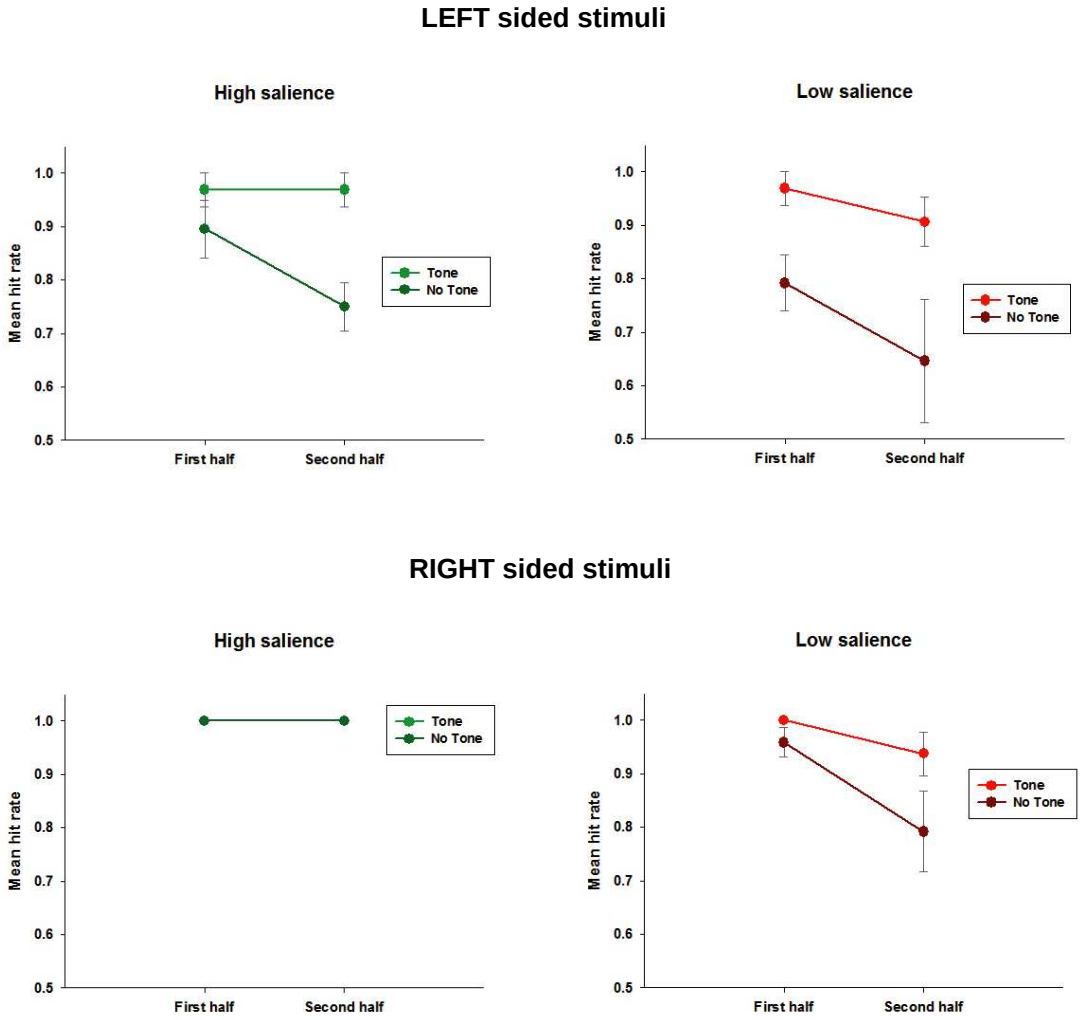


Figure 3.7. Effect of an alerting tone on detection of high and low salience stimuli in left and right sides of space in the neglect patients.

Presence of an alerting tone improved detection of left-sided targets of high (green inverted triangles) and low (red inverted triangles) salience. Alerting tones also improved detection of low salience targets appearing in the right side of space, but not those of higher perceptual salience. However, performance to high salience targets on the right was already at ceiling.

Error bars indicate standard error of the mean.

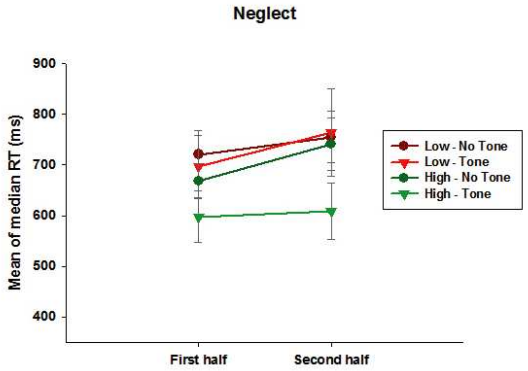
As can be seen from Figure 3.6, there were few false alarm errors made on this task, as was the case for experiment 1, despite the fact that alerting tones were equally likely to ccur with non-targets as targets. A repeated measures ANOVA on the false alarm data across the three patient groups, with within group factors of time (half task), tone (present or absent), position (left and right) and salience (low versus high) did not reveal any significant effects. Again, this suggests that the beneficial effect of alerting tones in the neglect patients could not have been produced by an encouragement to merely respond whenever they encountered a tone.

3.4.2.2. Reaction time data

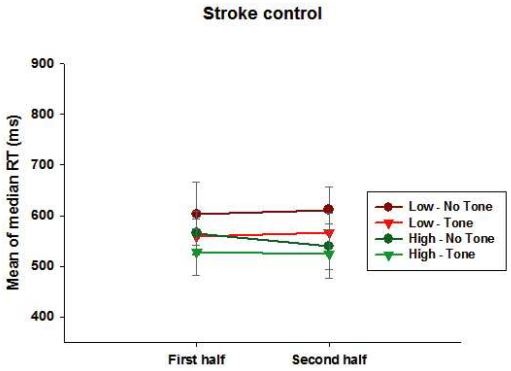
The reaction time data for this task is shown in Figure 3.8.

A repeated measures ANOVA was performed across the three subject groups on the reaction time data, with within group measures of time (half task), tone (presence or absence), position (left versus right) and salience (low versus high). There was a significant difference between the groups ($F(2,22)=5.851$, $p=0.009$), with *post hoc* Bonferroni testing revealing a significant difference between the neglect patients and healthy controls ($p=0.007$) but not the stroke controls ($p>0.2$).

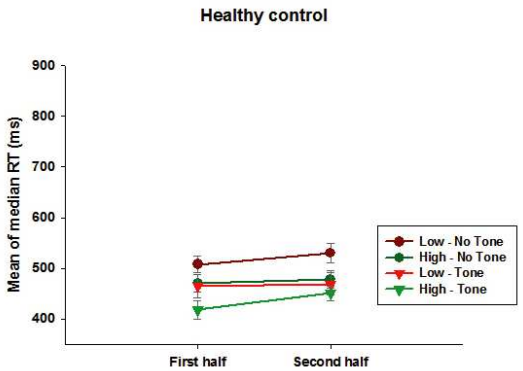
LEFT sided stimuli



A

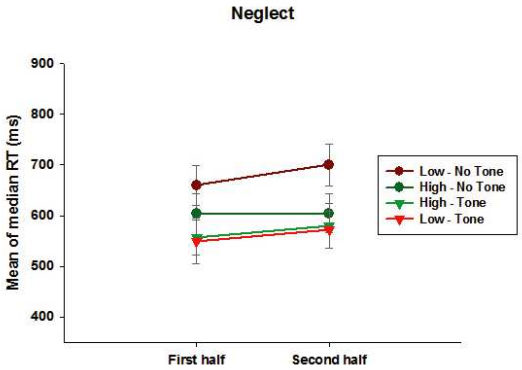


C

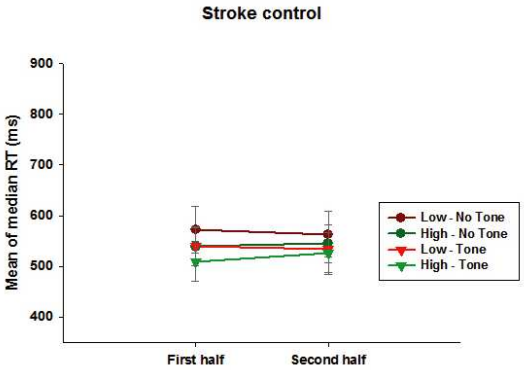


E

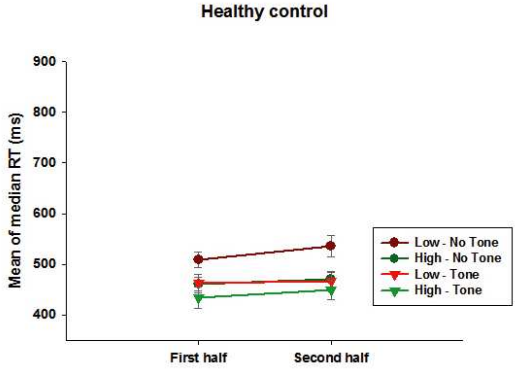
RIGHT sided stimuli



B



D



F

Figure 3.8. The effect of an alerting tone on reaction times on the bilateral task across the three subject groups.

The presence of an alerting tone served to reduce the reaction time to salient target stimuli in left and right sides of space across all three subject groups.

High – high salience targets (green inverted triangles)
Low – low salience targets (red inverted triangles)

Error bars indicate standard error of the mean.

There was a main effect of tone ($F(1,22)=42.555$, $p<0.001$), but no interaction between tone presence and subject group ($F(2,22)=1.776$, $p>0.19$) indicating a significant effect of tone in all the groups, which was indeed the case (neglect: ($F(1,7)=8.813$, $p=0.025$; stroke control: $F(1,8)=13.86$, $p=0.006$; healthy control: $F(1,8)=55.712$, $p<0.001$) – see Figure 3.8.

There was also a main effect of stimulus position ($F(1,22)=22.161$, $p<0.001$) and an interaction between position and subject group ($F(2,22)=11.675$, $p<0.001$). The effect of stimulus position, as expected, reached significance in the neglect group ($F(1,7)=14.302$, $p=0.009$) but also, to a lesser extent, in the stroke control group ($F(1,8)=7.285$, $p=0.027$). It is therefore possible that some of the stroke control patients had very mild lateralised deficits, which manifest as an increase in reaction times to left-sided targets, but not a significant reduction in hit rate.

As identified in the earlier experiments in this and the preceding chapter, there was a main effect of stimulus salience on reaction time ($F(1,22)=28.71$, $p<0.001$). This effect was present in the stroke control ($F(1,8)=20.627$, $p=0.002$) and healthy control ($F(1,8)=42.129$, $p<0.001$) groups, but failed to attain significance in the neglect group ($F(1,7)=3.855$, $p=0.097$). This lack of effect may be explained by the effect of alerting tones, particularly in the right side of space (Figure 3.8B), causing reaction times to high and low salience stimuli to become very similar.

In fact, there was a significant interaction between stimulus position, stimulus salience and presence of an alerting tone ($F(1,22)=5.672$, $p=0.026$) and an interaction between position, salience, alerting tone and subject group ($F(2,22)=4.526$, $p=0.023$). This interaction approached significance in the neglect group alone ($F(1,7)=5.24$, $p=0.062$). Indeed, in the neglect group there was only a significant difference in reaction time to low and high salience targets in the left side of space when the target stimuli were unaccompanied by an alerting tone ($t(7)=2.556$, $p=0.038$), with all other comparisons being non-significant ($t(7)<2.1$, $p>0.072$).

3.4.3. Discussion

The results of experiment 2 confirm those obtained in experiment 1 of this chapter: exogenous alerting tones are able to ameliorate the deficit in sustained attention that can occur in patients with neglect. However, they extend these findings. The impairment in detection of left-sided targets of low salience was improved throughout the duration of the task, and the ability to *sustain attention* on left-sided stimuli, as well as right-sided stimuli

of lower perceptual salience was also ameliorated. Alerting tones therefore seem capable of enhancing the suboptimal responses of neglect patients to low salience stimuli, as well as improving their ability to maintain attention on such events over time. Hence phasic alerting tones do improve the ability of neglect patients to sustain attention to left-sided events, although this appears to be true for stimuli wherever they occur in space – even the right.

As in experiment 1, power limitations must also be bourne in mind. The low frequency of tones, when distributed across high and low salience targets in left and right sides of space, meant that for each stimulus type, only 4 were accompanied by an alerting tone. Despite, this limitation, however, significant effects were obtained in the neglect group for the hit rate data.There were also ceiling effects apparent in the control groups, suggesting that some of the effects manifest in the reaction time data may have been evident in the error data had the tasks been more demanding.

3.5. General discussion

The aim of this chapter was to assess the effect of phasic alerting tones on the ability of neglect patients to sustain attention and encode stimulus salience, and examine how this may interact with the more characteristic deficit in the spatial reorientation of attention. Like previous investigators (Robertson, Mattingley et al. 1998), the results of this chapter have shown that non-informative alerting tones enhanced detection of left-sided targets. However, it was also demonstrated that alerting tones can ameliorate the deficits in

sustained attention and detection of low salience stimuli throughout space, and not just those occurring on the left (Figures 3.3 and 3.7).

How might this amelioration of non-spatial deficits throughout space occur? Phasic alerting can be considered to represent a category of stimulus salience, having much in common with stimulus *novelty* (Singh-Curry and Husain 2009). As discussed in Section 3.1, the term refers to a readiness to detect and respond to events of behavioural significance and can occur in an alternate stimulus modality as the target event (as was the case here) or the same modality. Alerting stimuli can be informative, predicting in some way the occurrence of a target event, or non-informative, when they may be considered to have most in common with novel events. Those used in this chapter were non-informative in nature, being equally likely to occur with a target as with a non-target stimulus. Like novel stimuli, phasic alerting events evoke a parietal P3a event-related potential, which occurs slightly earlier than the target-related P3b potential and is not necessarily accompanied by a motor response (Courchesne, Hillyard et al. 1975; Squires, Squires et al. 1975).

During task-engaged activity, novel stimuli are unlikely to be associated with motor responses (Barcelo, Suwazono et al. 2000). This was true of the alerting stimuli used in this chapter, as confirmed by the low false alarm rate in response to non-target stimuli paired with alerting tones and the fact that there was no effect of alerting tone presence on false alarm rate. When paired with a target stimulus, however, it is possible that a P3a ERP (discussed in chapter 1) immediately preceding a P3b potential can potentiate the

P3b, making initiation of a motor response more likely. Indeed, it has been shown that when novel stimuli are unpredictably associated with a target, the amplitude of both the P3a and subsequent target-related P3b increase (Suwazono, Machado et al. 2000). Alerting stimuli too, have been shown to enhance P3b amplitude (Miniussi, Wilding et al. 1999; Griffin, Miniussi et al. 2002).

This suggests that the parietal cortex may be crucial in mediating the alerting effect, a proposal which is supported by the findings of this chapter. The neglect group of patients demonstrated a three-way interaction that approached significance, between stimulus position, salience and presence of alerting tones, suggesting that all of these processes may be served by the same or closely linked neural systems. Furthermore, I was able to show in Chapter 2 that damage to the supramarginal gyrus of the IPL was significantly associated with deficits in salience encoding, orienting attention to left-sided stimuli and sustaining attention to left-sided, as well as central events. Given that these processes interact with the alerting effect, the IPL would therefore seem a likely candidate for its mediation. In fact, as discussed in Section 3.1, functional imaging studies in healthy participants have suggested that the right IPL is indeed involved in this process (Fan, McCandliss et al. 2005; Thiel and Fink 2007).

All of these findings suggest that the functions of the IPL can not be classified as purely stimulus driven (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). Indeed, as discussed earlier, even processes such as salience detection and phasic alerting can not truly be considered as only ‘bottom-up’, as they also involve components which can be

thought of as more ‘top-down’ in nature. As argued in the preceding two chapters, I consider the right IPL to play a crucial role in the processes enabling the adaptation of behaviour, allowing a switch between opposing functional states: a task-engaged, ‘exploitative’ state, in which attention is effectively focused on task demands, and a more ‘exploratory’ state, which enables potentially important novel or salient environment events to be identified. The fact that the IPL seems to be one of the most densely connected cortical regions (Hagmann, Cammoun et al. 2008), ideally places it to mediate interactions between numerous cognitive processes and perform such a ‘reconfigurational’ role.

I have also reviewed evidence which suggests that noradrenergic input from the locus coeruleus (LC) to parietal cortex may be vital in this flexible reconfiguration of behaviour (Aston-Jones and Cohen 2005; Singh-Curry and Husain 2009). Indeed, convergent evidence from monkey studies suggests that the parietal P3 potential may represent *phasic* input from the LC (Nieuwenhuis, Aston-Jones et al. 2005). However, a moderate level of *tonic* noradrenergic activity is necessary in order to produce phasic activity that results in effective task-engagement (Aston-Jones and Cohen 2005). It can therefore be envisaged that alerting stimuli – accompanied by their own parietal P3a and capable of enhancing the amplitude of target-related P3b potentials (Miniussi, Wilding et al. 1999; Griffin, Miniussi et al. 2002) – mediate their beneficial effect in neglect by effectively boosting noradrenergic input to parietal cortex.

If this hypothesis is correct, one would expect that noradrenergic agonists may also ameliorate the spatial and non-spatial deficits associated with neglect. In fact there is some evidence that this may indeed be the case. A small proof-of-principle trial recently demonstrated that neglect patients may benefit from a single dose of the noradrenergic agonist guanfacine, in terms of visuo-spatial exploration, but perhaps also their ability to sustain attention (Malhotra, Parton et al. 2006).

In the next chapter, I will examine the continued use of guanfacine in a single case with persistent neglect, in addition to a severe impairment of sustained attention.

Chapter 4

4.1. Introduction

Chapter 2, provided evidence which supports a new theory of right IPL function, whereby this region is considered to play a vital role in the flexible adaptation of behaviour, enabling a modulation of the prevailing cognitive state of the individual between a task-focussed state and a more exploratory mode of functioning which facilitates responses to new environmental events and challenges (Singh-Curry and Husain 2009). I consider noradrenergic input from the locus coeruleus (LC) to parietal cortex to be a crucial factor in this reconfigural process. The study reported in Chapter 2 demonstrated that lesions of the right IPL, such as occur in hemispatial neglect (Vallar and Perani 1986; Mort, Malhotra et al. 2003), can be associated with a variety of interacting non-spatial, as well as spatial, cognitive deficits that are important in mediating these contrasting behavioural states.

Chapter 3 demonstrated that phasic alerting tones are capable of ameliorating both the spatial and non-spatial deficits associated with neglect, leading to the speculation that this may occur through an augmentation of phasic noradrenergic activity to parietal cortex. If this hypothesis is correct, noradrenergic agonists should also be capable of improving these impairments. Indeed, there is evidence to suggest that the α-2-noradrenergic agonist guanfacine is capable of enhancing visuospatial exploration and sustained attention in some patients with neglect (Malhotra, Parton et al. 2006).

In monkeys, guanfacine has been shown to improve performance on spatial delayed response tasks (Franowicz and Arnsten 1998), by modulating dorsolateral prefrontal cortex (Avery, Franowicz et al. 2000), most likely through its actions at post-synaptic alpha-2A adrenergic receptors (Arnsten and Goldman-Rakic 1985; Arnsten, Steere et al. 1996). Guanfacine, which is a highly selective alpha-2A agonist (Uhlen and Wikberg 1991), has also been shown to improve planning and working memory performance in normal human subjects (Jakala, Riekkinen et al. 1999), while continued use of guanfacine has been demonstrated to be efficacious in the treatment of inattentiveness in children and adolescents with attention deficit/hyperactivity disorder (Biederman, Melmed et al. 2008; Sallee, McGgough et al. 2009).

Although neglect is most frequently associated with right IPL and inferior frontal lesions (Vallar and Perani 1986; Husain and Kennard 1996; Mort, Malhotra et al. 2003), damage to subcortical regions, particularly the pulvinar nucleus of the thalamus (Karnath, Himmelbach et al. 2002), as well as other medial thalamic nuclei (Watson, Valenstein et al. 1981; Schmahmann 2003), may also cause the syndrome – especially if affecting these structures in the right hemisphere. Thalamic lesions, particularly those involving the medial nuclei – including the pulvinar – are also frequently associated with impairments in arousal and the ability to sustain attention (Schmahmann 2003).

The thalamus is thought to act as a key processing node between other subcortical regions and the cortex. Specifically, the medial thalamic nuclei may function to enhance or habituate transmission of sensory information to parietal and frontal areas (Asanuma,

Andersen et al. 1985; Schmahmann and Pandya 1990; Romanski, Giguere et al. 1997), depending on motivational input they receive from medial frontal structures (Chiba, Kayahara et al. 2001) and information regarding arousal from midbrain nuclei such as the LC (Asanuma 1992; Vogt, Hof et al. 2008). As such, the medial thalamic nuclei can be thought of as important components of a functional loop between parietal and frontal cortices and neuro-modulatory nuclei such as the LC, with damage to the medial thalamic nuclei being capable of leading to similar deficits as seen following lesions of the cortical regions with which they connect (Watson, Valenstein et al. 1981).

This chapter will present the case report of a patient with bilateral thalamic lesions, secondary to acute disseminated encephalomyelitis (Bernarding, Braun et al. 2002), with severe difficulties sustaining attention associated with persistent hemispatial neglect. The patient's performance on tests assessing the ability to sustain attention, as well as tests of neglect, will be examined before and after the continued use of guanfacine.

Acute disseminated encephalomyelitis (ADEM) is a relatively rare neuroinflammatory disorder associated with multifocal lesions, frequently preceded by a viral prodrome (Shoji, Kusuhara et al. 1992) and occasionally by vaccination (Saito, Endo et al. 1980). Histologically, ADEM is similar to multiple sclerosis, with a predominantly T-lymphocytic perivascular infiltrate producing focal areas of demyelination. Unlike multiple sclerosis, however, it is usually a monophasic illness, with many patients recovering well, although up to half followed up long-term have been reported to have persistent neurological deficits (Schwarz, Mohr et al. 2001). MRI usually reveals

asymmetrical subcortical white matter lesions, however, the deep grey matter nuclei, such as the thalamus and basal ganglia, may also be affected (Bernarding, Braun et al. 2002).

There are few studies of ADEM documenting the neuropsychological and cognitive sequelae of the condition, with most focussing on the motor disabilities (Sunnerhagen, Johansson et al. 2003). The patient reported here developed bilateral lesions of the thalamus secondary to ADEM, causing persistent left-sided neglect and difficulty sustaining attention. I describe here how these problems were subsequently ameliorated by guanfacine.

4.2. Case report

A 38 year-old male presented with a right-sided facial droop and hemiparesis following a two-week prodrome of headache, fever, cough and right hemisensory symptoms. Soon after admission, he developed tonic-clonic seizures, necessitating intubation and ventilation and treatment with the anticonvulsant phenytoin. MRI revealed patchy signal changes in the thalamus, cerebellum, temporal and occipital lobes bilaterally, while MR angiogram revealed normal extra and intra-cranial blood flow. Cerebrospinal fluid examination, vasculitic blood screen and transoesophageal echocardiogram were all normal. Electroencephalography demonstrated features consistent with encephalopathy and a diagnosis of ADEM was made. He subsequently received two courses of intravenous methylprednisolone, intravenous immunoglobulin, plasma exchange and

antibiotics. He was also anticoagulated for a deep venous thrombosis of the leg and required surgical treatment for an associated compartment syndrome.

The patient remained in intensive care, due to persistent epileptiform activity, for four months, until seizures were stabilised on a regimen of levetiracetam 2 g, phenytoin 700 mg and prednisolone 30 mg. He was then transferred to a rehabilitation unit, at which time he had a tetraparesis, with predominant left-sided weakness.

Neuropsychological testing also revealed significant cognitive impairments, including left-sided neglect (with intact visual fields on confrontation), reduced arousal and difficulty sustaining attention. In addition there were significant impairments in verbal memory (chance performance on the short and easy Recognition Memory Test for verbal material and low average performance on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span subtest) and naming (5/15 correct on the Graded Naming Test). There was also evidence of dysfunction on tests of executive function (concrete performance on Proverb Interpretation and perseveration on Single Letter Reading and Similarites subtest of the WAIS-R). On the basis of educational and occupational background, he was estimated to have been functioning in at least the superior range premorbidly and had therefore suffered severe intellectual deterioration.

Admission for reassessment occurred two years later, at which time anticonvulsant medication consisted of levetiracetam 750 mg and gabapentin 300 mg, both twice daily (the total dose of levetiracetam was 1250 mg at 6 months follow-up, with a further

reduction to 1000 mg 10 months later). Cranial nerve examination was normal, except for a mild upper motor neuron left-sided facial weakness. Examination of the limbs revealed a severe hemiparesis, with increased tone on the left and a pyramidal distribution of weakness, worse distally. The limb reflexes were all brisk with bilaterally extensor plantar responses. There was severe left-sided hemispatial neglect and impairments in sustained attention and arousal (quantitative measures are given below in section 4.3), with the patient spending 20 hours a day in bed due to drowsiness. A decision was taken to trial guanfacine, with the hypothesis that this might improve these cognitive deficits.

4.3. Assessment measures

MRI was repeated to determine the extent of lesions (see Figure 4.1). This demonstrated bilateral thalamic lesions, involving the medial thalamic nuclei – including the medio-dorsal nucleus – as well as the pulvinar on the left, in addition to the pulvinar on the right (Schmahmann 2003). Lesions of the right pulvinar have previously been linked to the pathogenesis of neglect (Karnath, Himmelbach et al. 2002). The patient also had additional small lesions in the cerebellum, the occipital and temporal lobes, which all lie outside of areas commonly implicated in neglect, such as the IPL, temporoparietal junction and inferior frontal lobe (Vallar and Perani 1986; Husain and Kennard 1996; Mort, Malhotra et al. 2003).

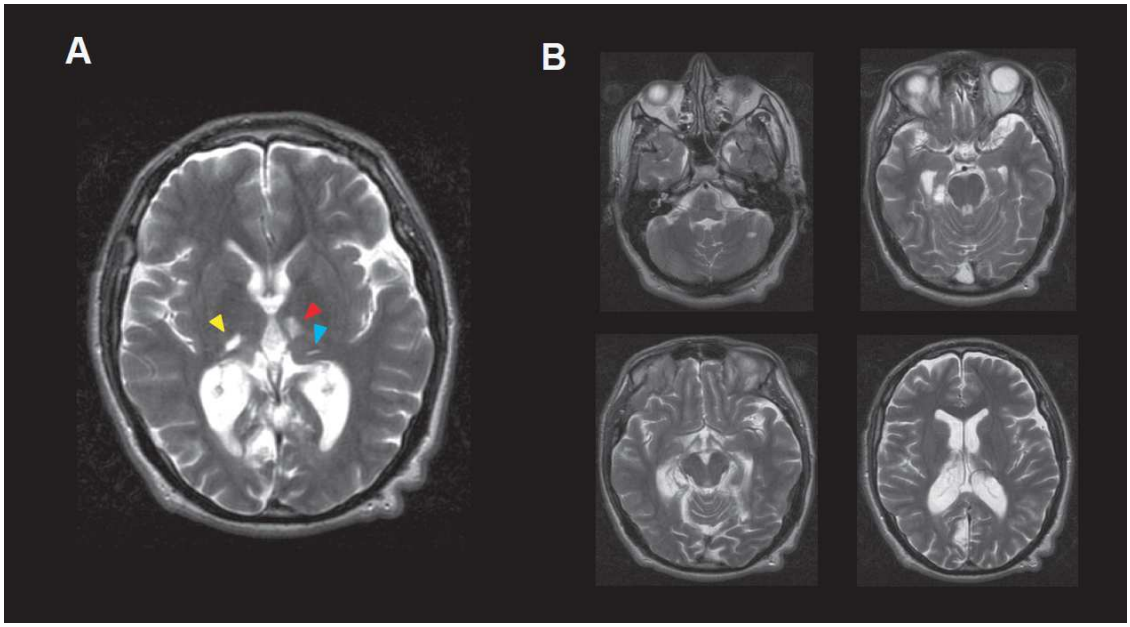


Figure 4.1. Patient's lesions.

A. Bilateral thalamic lesions as demonstrated by T2-weighted MRI scanning. The red arrow indicates a left-sided lesion involving the medial thalamic nuclei, including the medio-dorsal nucleus. There is also a smaller adjacent lesion in the left pulvinar (blue arrow). The yellow arrow indicates the right-sided lesion, also in the pulvinar.

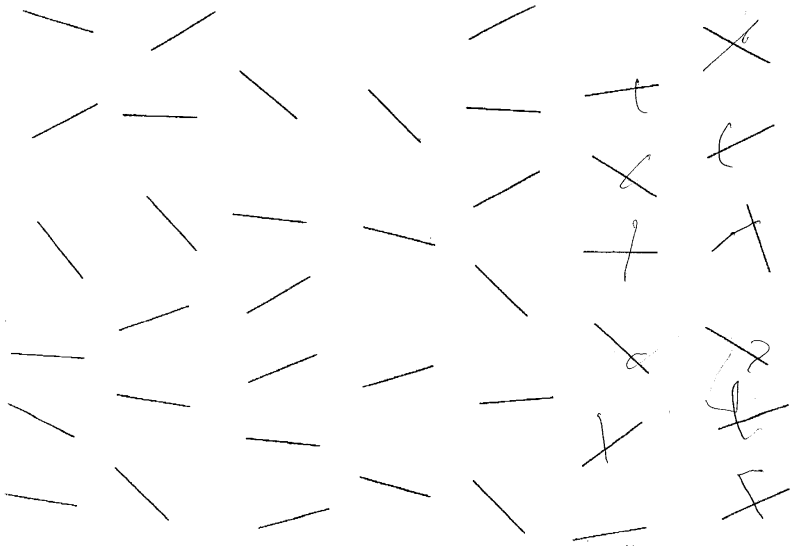
B. The patient also had additional small lesions in the cerebellum, occipital and temporal lobes. Importantly lesions of these other sites are generally not associated with neglect.

Two standard bedside measures of neglect were used to assess neglect, while a computerised task was used to measure the deficit in sustained attention.

4.3.1. Neglect tests

The neglect tests used were line cancellation and line bisection. On the line cancellation task (Albert 1973), subjects are instructed to cancel all the lines they can find (total 40) distributed across a landscape oriented A4 sheet of paper. Examples of line cancellation tests performed by the patient, before and after the introduction of guanfacine are shown in Figure 4.2. Line bisection requires the participant to mark their perceived midpoint of 17 cm horizontal lines (Stone and Greenwood 1991). The mean deviation rightwards from centre is then taken from three attempts.

A



B

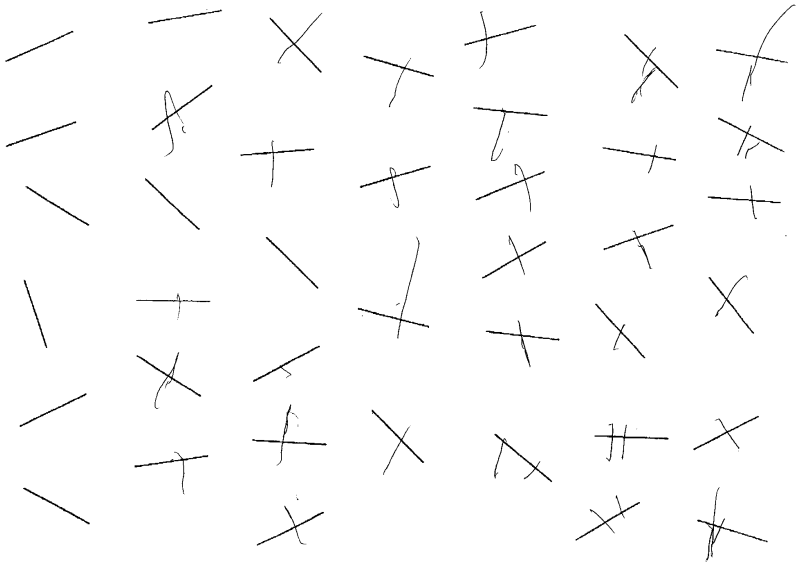


Figure 4.2. Patient's performance on the line cancellation test

A. Before introduction of guanfacine – the patient only managed to cancel 11 lines on the right hand side of the A4 sheet.

B. After commencement of guanfacine – the patient has managed to cancel all 18 lines on the right side of the sheet, as well as the 4 lines in the middle and 9 of the left-sided lines.

4.3.2. Sustained attention task

The computerised task, which has been used previously (Malhotra, Coulthard et al. 2009), was programmed using E-Prime software (Psychology Tools Software Inc.) and presented on a Dell Latitude D820 laptop computer. It entailed the subject depressing the central button on a response box (RB-530 Cedrus Corp.) as quickly as possible, whenever an infrequently occurring black circle (8mm diameter) occurred. The circle remained on the screen for 1 second and was presented on a grey background with interstimulus intervals of 1-7s. 100 stimuli were presented over a total period of eight minutes (see Figure 4.3).

Responses quicker than 100 ms were classified as anticipations, and therefore as commission errors, as were responses occurring more than 1600 ms after target onset. Perceptual sensitivity, or d-prime (d'), which is derived from signal detection theory (Stanislaw and Todorov 1999) and takes into account commission as well as omission errors (both of which the patient made a number of), was the behavioural outcome measure of this task and was calculated according to the formula below:

$$d' = \Phi^{-1}(H) - \Phi^{-1}(F)$$

H is the hit rate, F is the false alarm rate and Φ^{-1} is the inverse of the cumulative Gaussian distribution. The higher this value the better the perceptual sensitivity of the subject.

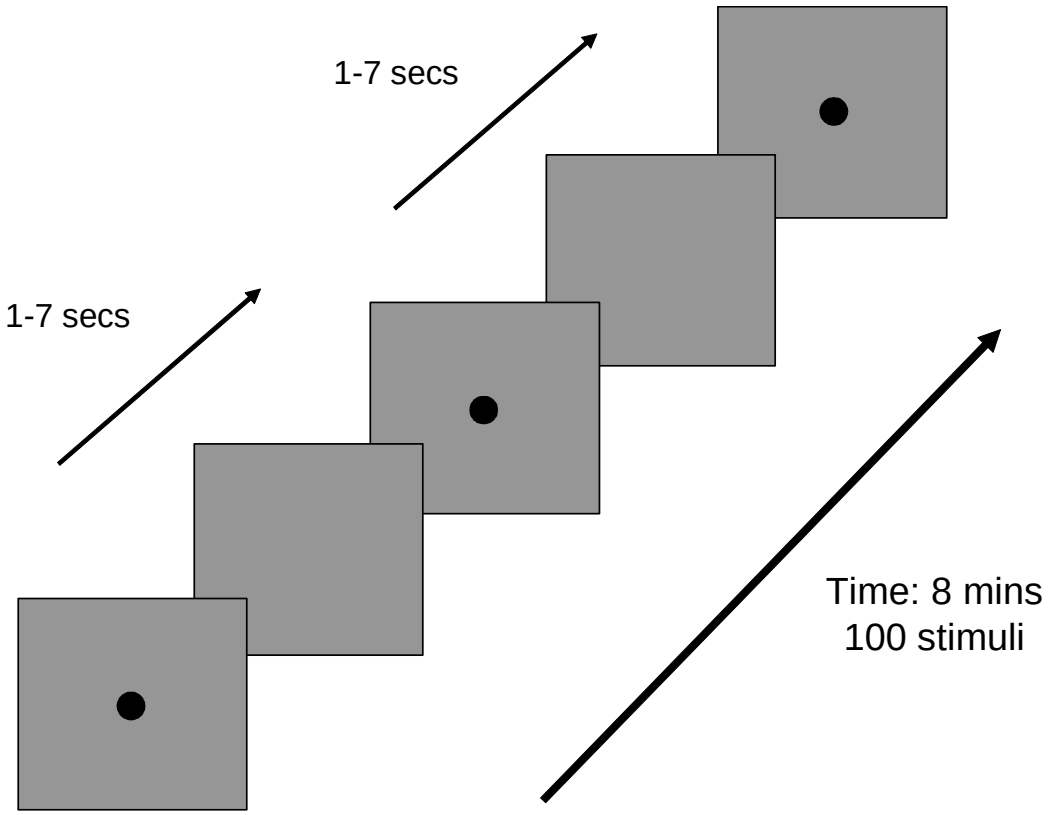


Figure 4.3. Sustained attention task.

The subject was required to respond with a button press as quickly as possible whenever a black circle appeared on the screen. A total of 100 stimuli were presented, with an inter-stimulus interval between 1 and 7 seconds. The task lasted for approximately 8 minutes.

4.4. Introduction of guanfacine

All assessment measures were performed on two consecutive days prior to commencing oral guanfacine, as well as at several time points after its introduction, including one session when it had been temporarily discontinued.

The dose of guanfacine was titrated up slowly over three days in small increments. The initial dose was 0.5mg, followed by 1mg the next day and 2mg on the third day of treatment. The guanfacine was given as single daily doses, administered orally in the morning. The first on-guanfacine testing session was performed on day three when a dose of 2mg had been reached. See Table 4.1 for a summary of the dosing and assessment schedule.

The patient continued on 2 mg guanfacine daily as an outpatient. However, an additional testing session off-guanfacine was performed two months later (due to initial difficulty obtaining the drug locally), at which point the patient had not received guanfacine for two weeks. Three on-guanfacine testing sessions were performed 6 months after the initial commencement of 2mg guanfacine daily and a final session occurred a further 10 months later. Therefore, in total, the patient underwent three testing sessions off and five on guanfacine. Testing was always performed during the early afternoon, as this was the time of day during which the patient was at his most alert.

Time	Activity
Day 1	Baseline assessments 1
Day 2	Baseline assessments 2
Day 3	0.5 mg guanfacine administered
Day 4	1 mg guanfacine administered
Day 5	2 mg guanfacine administered
	On guanfacine assessment 1
2 months	Off guanfacine assessment
6 months	
Day 1	On guanfacine assessment 2
Day 2	On guanfacine assessment 3
Day 3	On guanfacine assessment 4
16 months	On guanfacine assessment 5

Table 4.1. Assessment and dosing schedule.

Two sets of baseline assessment measures were performed on consecutive days prior to commencing guanfacine, which was titrated up to a final dose of 2 mg per day over three days. This was followed by five on-guanfacine assessment sessions – the first of these was performed the day 2 mg guanfacine was reached.

Two months later, due to initial difficulty obtaining the drug locally, the patient spent a period of just over two weeks off guanfacine – a third testing session off the drug was performed at the end of this period.

Three further on-guanfacine testing sessions were performed 6 months after initial commencement of guanfacine and one further set after another 10 months of continued use of 2 mg guanfacine daily.

Guanfacine was administered in the morning and assessment always occurred in the early afternoon.

4.5. Data analysis

Permutation testing was used to investigate whether the effects of guanfacine were statistically significant. This established procedure has specifically been used in single case designs and works by considering all possible recombinations of the data (Todman and Dugard 2001; Todman 2002) - see Figure 4.4.

The purpose of considering these recombinations, or permutations, is to attempt to account for fluctuations in assessment scores which may occur over time, unrelated to the effects of treatment. It has previously been reported that the performance of neglect patients may indeed fluctuate over short periods of time (Small and Ellis 1994), which may be related to fatigue, the time of day and previous activities, as well as patient learning. Although other studies have failed to find evidence of significant fluctuations on behavioural tests in neglect (Levy, Blizzard et al. 1995) and the patient was always tested at the same time of day to minimise this effect, the use of permutation testing allows further control of possible fluctuations.

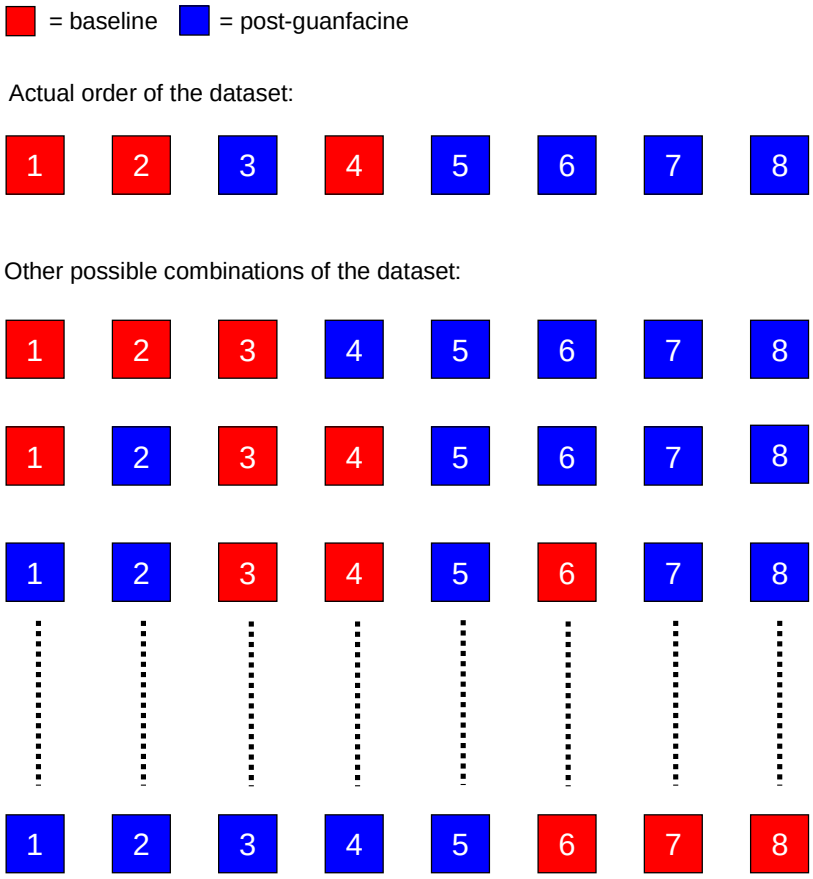


Figure 4.4. Permutation testing.

The mean difference between the actual off and on-guanfacine scores on a particular test was calculated (top row of coloured boxes). The numbers indicate the order in which these scores were obtained. This was then compared to the mean difference between off and on treatment observations for all other possible recombinations of the dataset (additional rows) if guanfacine had been introduced at different time points in the series. If the actual difference between pre and post-treatment means is greater than that for any other combination, it is possible to calculate how often this could occur by chance. In this study, the total number of permutations for the three off and five on-guanfacine observations is 56. Therefore, if the actual difference between off and on-guanfacine means is greater than the mean difference for all other possible combinations of the dataset, the probability of this occurring by chance is 1/56=0.018.

First the difference between the actual baseline and treatment mean score on a particular test is calculated. Then the mean difference for every other possible combination of the data if the treatment had been introduced at different time points in the data set is computed – see Figure 4.4. If the actual difference between pre and post-treatment means is greater than that for any other combination, it is possible to calculate how often this could happen by chance. In general, the obtained difference between means will be statisitically significant at the 5% level if this difference falls in the 5% most extreme differences in the (real) distribution of possible recombinations of the data (Todman and Dugard 2001; Todman 2002).

In this study, the total number of permutations for the three off and five on-treatment observations is 56. Therefore, if the actual difference between baseline and treatment means is greater than the mean difference for all the other possible recombinations of the dataset, the probability of this occurring by chance is 1/56 = 0.018.

4.6. Results

As discussed in Section 4.3, the patient's thalamic lesions localise to the medial thalamic nuclei (including the medio-dorsal nucleus) and the pulvinar on the left and to the pulvinar on the right (Schmahmann 2003). Damage to the right pulvinar has previously been associated with neglect, while the remaining small lesions – in the cerebellum, occipital and temporal lobes – all lie outside regions commonly implicated in the pathogenesis of neglect (Vallar and Perani 1986; Husain and Kennard 1996; Mort, Malhotra et al. 2003).

Pre and post-guanfacine scores on line bisection (A), line cancellation (B) and the computerised sustained attention task (C) are shown in Figure 4.5. Performance on all measures improved after guanfacine. On line bisection, before guanfacine the mean rightward deviation was 30.3 mm (SEM: 3.3 mm), compared to 19.4 mm (SEM: 2.18 mm) post-guanfacine. On line cancellation the mean number of items cancelled pre-guanfacine was 11.7 (SEM: 3.5), compared to 23.2 (SEM: 3.87) on treatment. Finally, on the sustained attention task, mean perceptual sensitivity pre-guanfacine was 0.3 (SEM: 0.09), compared to 1.32 (SEM: 0.28) post-guanfacine.

Permutation testing revealed that the rightward deviation on line bisection reduced significantly (Figure 4.5A) after commencing guanfacine ($p=0.018$ – no other recombination of the dataset produced a mean difference greater than that observed between the actual baseline and treatment means), demonstrating clear amelioration of the spatial bias most characteristic of neglect.

Although the number of lines identified on line cancellation also increased (Figure 4.3 and 4.5.B), this did not reach statistical significance ($p=0.071$ – with three of the other possible recombinations of the dataset producing a larger mean difference than the actual mean difference between baseline and treatment observations).

On the other hand, perceptual sensitivity over the 8 minute computerised sustained attention task was significantly enhanced ($p=0.018$) – Figure 4.5C – revealing that, in

addition to ameliorating the spatial bias of neglect, guanfacine was able to improve the deficit in sustained attention.

Furthermore, clinical observation was consistent with these data, with the patient's overall level of alertness and arousal improving following introduction of guanfacine. Moreover, after a period of 6 months on the drug, his carers reported an "improvement in his awareness and conversation…" to the extent that he was able to "…contribute significantly to crossword puzzles and enjoy his music CDs". As a result of these persistent benefits the patient continues to take 2 mg guanfacine daily.

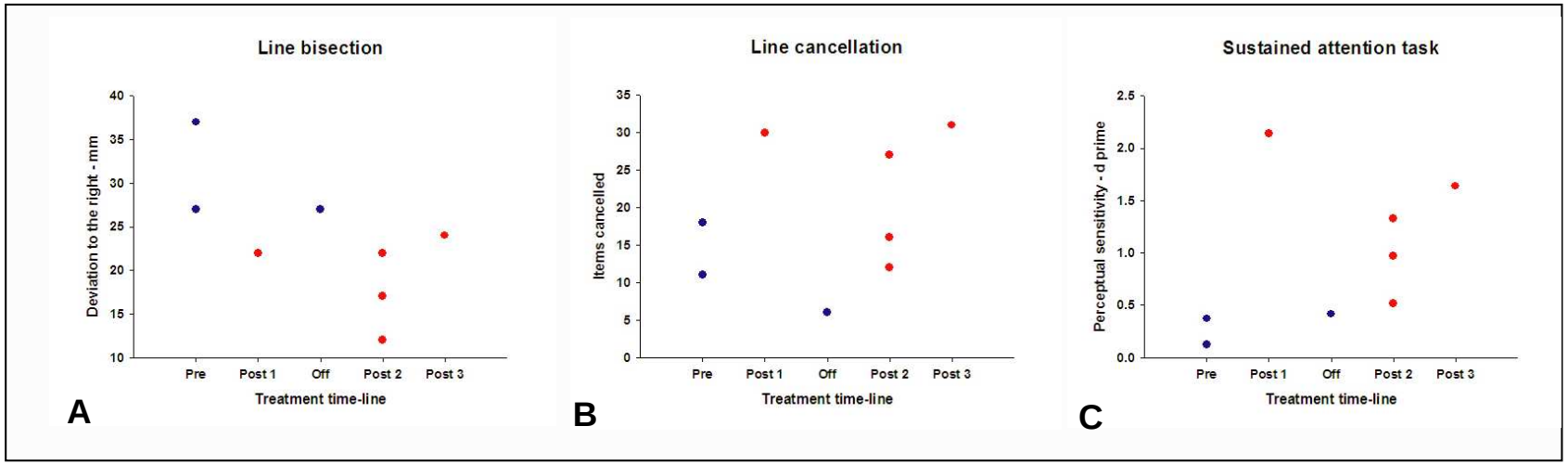


Figure 4.5. Behavioural outcome measures.

A. Line bisection. The rightward deviation on bisecting 17 cm lines decreased significantly on guanfacine (deviation in mm).

B. Line cancellation. The total number of lines cancelled by the patient increased on 2 mg guanfacine.

C. Perceptual sensitivity on the sustained attention task significantly improved after commencement of guanfacine.

Pre: pre-guanfacine

Post 1: initial assessment on 2 mg guanfacine

Off: assessment at 2 months after guanfacine treatment had been ceased for 2 weeks

Post 2: assessments at 6 months after initiation of guanfacine

Post 3: assessment at 16 months after initiation of gaunfacine

4.7. Discussion

This chapter has presented the case of a patient with persistent hemispatial neglect and severe difficulty sustaining attention, secondary to bilateral thalamic lesions caused by ADEM, which improved following the introduction of the noradrenergic agonist guanfacine.

Thalamic lesions are most frequently associated with deficits in arousal, although neglect is also often reported (Watson, Valenstein et al. 1981; Karnath, Himmelbach et al. 2002), particularly following lesions of the medial dorsal nucleus and pulvinar (Karnath, Himmelbach et al. 2002; Schmahmann 2003), as was the case here. In contrast, these deficits have rarely been referred to in the literature as a consequence of ADEM (Sunnerhagen, Johansson et al. 2003).

As discussed in Chapter 2, problems with arousal and the ability to sustain attention may be intimately linked with difficulty with the spatial orientation of attention, the characteristic deficit of the neglect syndrome. It has been proposed that arousal, or the endogenous maintenance of alertness, so that attention can be sustained on task goals, is dependent on activity within networks involving noradrenergic input from the LC in the midbrain, to inferior parietal and frontal cortex and indirectly to these regions via the thalamus (Watson, Valenstein et al. 1981; Mottaghy, Willmes et al. 2006).

Similar patterns of activation have been found within these networks in response to tasks assessing sustained attention at single locations and tasks in which the spatial distribution of attention is required (Sturm, Schmenk et al. 2006). Furthermore, damage to these areas is implicated in the pathogenesis of neglect, with the IPL (Mort, Malhotra et al. 2003) most frequently associated with the syndrome, and inferior frontal (Husain and Kennard 1996) and thalamic lesions (Karnath, Himmelbach et al. 2002) also being quite common.

In fact, difficulty sustaining attention is increasingly accepted as a component of the neglect syndrome (Samuelsson, Hjelmquist et al. 1998; Robertson 2001; Husain and Rorden 2003; Malhotra, Coulthard et al. 2009), with deficits in sustained attention capable of predicting the severity of the spatial bias (Robertson, Manly et al. 1997). This is supported by my findings from Chapter 2, which suggest that deficits in sustained attention can exacerbate the problems with the spatial orientation of attention. Furthermore, phasic alerting can improve both the visuospatial (Robertson, Mattingley et al. 1998) and non-spatial deficits (Chapter 3) associated with neglect, as can alertness training (Sturm, Thimm et al. 2006).

Single doses of guanfacine have previously been shown to enhance sustained attention, in addition to the spatial deficits in neglect (Malhotra, Parton et al. 2006). Although continued guanfacine use may be efficacious in the treatment of inattentiveness in children and adolescents with attention deficit/hyperactivity disorder (Biederman, Melmed et al. 2008), this case is the first demonstration of a <u>persistent</u> amelioration of the spatial deficit

in neglect with a noradrenergic agonist. But how might guanfacine produce such an amelioration?

I have already proposed that noradrenergic input from the LC to the IPL may play an important role in sustaining attention on task-focussed activity, in detecting novel, potentially important – but task-irrelevant – events in the environment and in the modulation or reconfiguration of behaviour between these opposing functional states (Singh-Curry and Husain 2009). It is therefore possible that boosting noradrenergic activity in regions such as the IPL and prefrontal cortex, with agonists like guanfacine, might enhance these processes, and in the case of thalamic lesions, increase the excitatory input in response to sensory stimulation that may normally be potentiated by thalamic input (Watson, Valenstein et al. 1981). Of course, lesions involving particular subregions of the IPL or prefrontal cortex, may preclude the behavioural benefit of such pharmacological manipulations, which is indeed what previous preliminary evidence suggests (Malhotra, Parton et al. 2006).

Furthermore, based on the interaction between deficits in sustained attention and the spatial orientation of attention which were demonstrated in Chapter 2, it is possible that an amelioration of a deficit in sustained attention may also act to improve the exploration of space in neglect.

In summary, I have reported in this chapter a case of ADEM causing severe deficits in arousal and sustained attention associated with hemispatial neglect, due to bilateral

involvement of the medial thalamus. The noradrenergic agonist guanfacine led to an amelioration of these difficulties, I speculate by enhancing activity within a network which involves the IPL, inferior frontal regions, the thalamus and the LC. However, larger studies are required in the future to fully establish the efficacy of guanfacine in the rehabilitation of neglect.

Chapter 5

5.1. Introduction

Chapters 2 and 3 explored some of the functions of the ventral attention network, by examining the cognitive deficits associated with hemispatial neglect, the syndrome that commonly occurs following damage to these regions (Vallar and Perani 1986; Husain and Kennard 1996; Mort, Malhotra et al. 2003). The results of these chapters suggested that the functions of the ventral attention network, particularly those of the right inferior parietal lobe (IPL), may be more complex than previous proposals have suggested (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). In fact, I believe the findings from Chapters 2 and 3 indicate that this area plays an important role in both goal-directed attention and the stimulus-driven reorientation of attention – processes which have been segregated into functionally opposing dorsal and ventral fronto-parietal streams (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008).

Instead, I believe the results provide support for the scheme developed in Chapter 1, whereby the right IPL is considered to act as an important module in the modulation of behaviour, facilitating a flexible switching between two functional states: a task-engaged mode, in which attention is focussed on current goals or task demands and a more exploratory state, which enables the identification of salient or novel environmental events (Singh-Curry and Husain 2009).

However, although the results from Chapters 2 and 3 suggest that the right IPL plays a crucial role both in salience detection and the ability to sustain attention, they did not examine the role of the ventral attention network in the processing of novel stimuli. The main purpose of this chapter will therefore be to probe novelty processing in right hemisphere stroke patients with and without neglect and to investigate the anatomy of any such deficits using voxel based lesion-symptom analysis techniques.

5.1.1. Novelty processing

An essential feature of the nervous system is to encourage exploration of the surrounding environment. As such, new events or objects, which have not been encountered in a particular behavioural context, are highly salient and easily attract attention. Like target-related salience, novelty processing has previously been studied with the 'oddball' paradigm. In many of these tasks, in addition to infrequently occurring targets which require a response, there are occasional new stimuli which have not previously been presented. In the context of event-related potential (ERP) studies, subjects are instructed only to respond to the targets and are usually not given any prior information regarding the novel stimuli. Like targets, novel stimuli have been found to elicit a P3 ERP response over parietal and frontal cortex, even when no response to these events is required. However, this potential occurs slightly earlier (sometimes referred to as the P3a) than that which occurs to targets – the P3b (Courchesne, Hillyard et al. 1975; Squires, Squires et al. 1975). Importantly, lesions of the temporoparietal junction (TPJ) abolish both the P3a and P3b (Knight, Scabini et al. 1989).

Functional imaging studies in healthy subjects also implicate the IPL, TPJ and ventral frontal regions in the detection of novel events (Kiehl, Laurens et al. 2001; Downar, Crawley et al. 2002; Kiehl, Stevens et al. 2005; Bunzeck and Duzel 2006; Gur, Turetsky et al. 2007; Strobel, Debener et al. 2008; Friedman, Goldman et al. 2009). Such activation is even seen in the context of engagement in an on-going task (Kiehl, Laurens et al. 2001; Kiehl, Stevens et al. 2005; Bunzeck and Duzel 2006; Gur, Turetsky et al. 2007; Strobel, Debener et al. 2008; Friedman, Goldman et al. 2009), contrary to recent functional formulations regarding the ventral attention system, which suggest it is only involved in reorienting to salient events which are relevant to the current goal or task state (Corbetta, Patel et al. 2008).

In fact stimulus novelty may be more complex than a first glance would suggest. For example, it might be argued that the detection of novel events occurs in a primarily stimulus-driven or exogenous fashion. However, memory of previous items also needs to be maintained in order that a novel stimulus can be correctly judged as new. For this reason, the right IPL – within the ventral attention network – may be a particularly important locus for novelty processing, given 1) its high connectivity with other brain regions (Hagmann, Cammoun et al. 2008), including the medial temporal lobe which is important for memory and novelty detection (Lisman and Grace 2005); and 2) overlap of goal-directed and stimulus-driven processes here (as demonstrated in Chapter 2 and Figure 2.14).

5.1.2. Aims

The principal aim of this chapter will be to investigate how patients with the neglect syndrome secondary to right hemisphere damage process novel stimuli. Specifically, I predict that neglect patients will process novel stimuli more poorly than right hemisphere stroke control and healthy control subjects and that this deficit will be associated with damage within the ventral attention network.

Because the identification of novel stimuli may be more complex than detecting perceptually salient events – necessitating comparison with previous items in order to correctly judge the stimulus as new – damage to the IPL and other ventral regions – which appears to be an important hub for the interaction of endogenous and exogenous processes – may be particularly deleterious for this process. Detection of novel stimuli may therefore also be impaired in comparison to identification of perceptually salient stimuli.

5.2. Methods

5.2.1. Participants

Patients were recruited from stroke and neurological units with local ethics approval. A total of 14 right middle cerebral artery (MCA) stroke patients were included in the study; 7 with (mean age: 58.3, range: 39-78; one left-handed) and 7 without neglect (mean age: 62.3, range: 50-71; all right-handed). Exclusion criteria included cognitive impairment such that there was difficulty following assessment or task instructions, and active medical comorbidity. 10 healthy elderly control participants with no neurological or psychiatric

history were also recruited (mean age: 64.8 years, range: 51-73; 1 left-handed; 4 male). A one-way ANOVA revealed that there were no significant differences between the subject groups in terms of age ($F(2,23)=0.912$, $p>0.4$). See Table 5.1 for further patient demographic information.

5.2.2. Assessment of neglect

A visual neglect battery was performed on all of the patients to determine the presence or absence of neglect (Malhotra, Greenwood et al. 2004). Patients with neglect demonstrated neglect behaviours in their activities of daily living, as well as on the Mesulam cancellation test (Mesulam 1985) and/or line bisection task (Stone and Greenwood 1991). Neglect was identified by an asymmetry of cancellation of 2 or more items on the Mesulam task and a mean rightward deviation of 5mm or more on line bisection of three 17cm lines.

Subject	Age	Time since stroke (months)	Field defect	Mesulam (R-L difference)	Line bisection (cm to right of midline)
N1	66	10	Partial left lower quadrantanopia	20	1
N2	39	1	Partial left lower quadrantanopia	22	0.8
N3	78	0.5	No	18	2
N4	60	1.75	No	7	0.8
N5	53	1	No	3	1
N6	68	2	No	2	1.2
N7	44	0.5	No	10	1.2
mean	**58.3**	**2.39**		**11.7**	**1.14**
SC1	70	2	No	0	-0.2
SC2	71	0.5	No	0	0.2
SC3	50	0.5	No	1	-0.2
SC4	61	5	No	0	-0.2
SC5	65	10	No	-3	-0.3
SC6	54	0.5	No	-3	0
SC7	65	22	No	-1	-0.3
mean	**62.8**	**5.8**		**-0.86**	**-0.14**

Table 5.1. Patient demographics.

N = patient with neglect

SC = stroke control patient

The time since stroke at which patients underwent testing was not significantly different across the two patient groups ($t(12)=-1.038$, $p=0.32$).

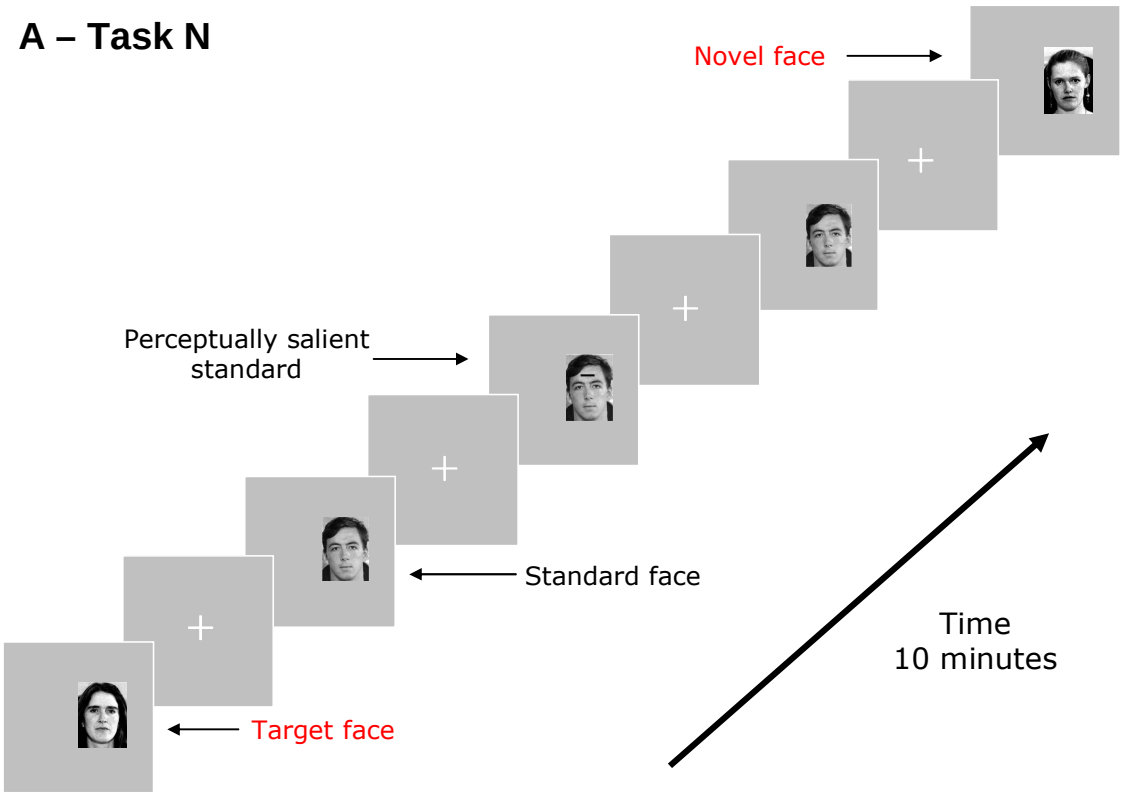
5.2.3. Apparatus and stimuli

Participants depressed the central bottom button of an RB-530 Cedrus response box in response to the presentation of target stimuli. A Dell Latitude D820 laptop with a 15 inch screen was used for stimulus presentation. Behavioural tasks were programmed using E-Prime software (Psychology Tools Software Inc.). Stimuli were presented on a grey background and consisted of greyscale male and female faces with neutral expressions taken from the Psychological Image Collection at Stirling (PICS) database, provided by the University of Stirling Psychology department (http://pics.psych.stir.ac.uk/). Stimuli subtended approximately 7º x 9.5 º when viewed from a distance of 60cm. Male and female faces were used in an equal proportions across each task.

5.2.4. Behavioural tasks

5.2.4.1. 'Oddball' tasks

Two versions of an 'oddball' task were used to probe novelty processing, which were adapted from a previous version used in healthy young control subjects (Bunzeck and Duzel 2006). The general design of each task was identical, with each task incorporating three types of infrequently occurring 'oddball' face, which were presented randomly intermixed with frequently occurring standard faces. 10% of stimuli consisted of a target face, 10% were novel faces and 10% were perceptually salient standard faces. Standard faces were made perceptually salient by a black bar positioned across the face (which did not interfere with recognition of the face – see Figure 5.1), and which varied in exact position between presentation of these stimuli. The remaining 70% of stimuli consisted of the unaltered standard face.


A – Task N
Novel face
Perceptually salient standard
Standard face
Target face
Time
10 minutes

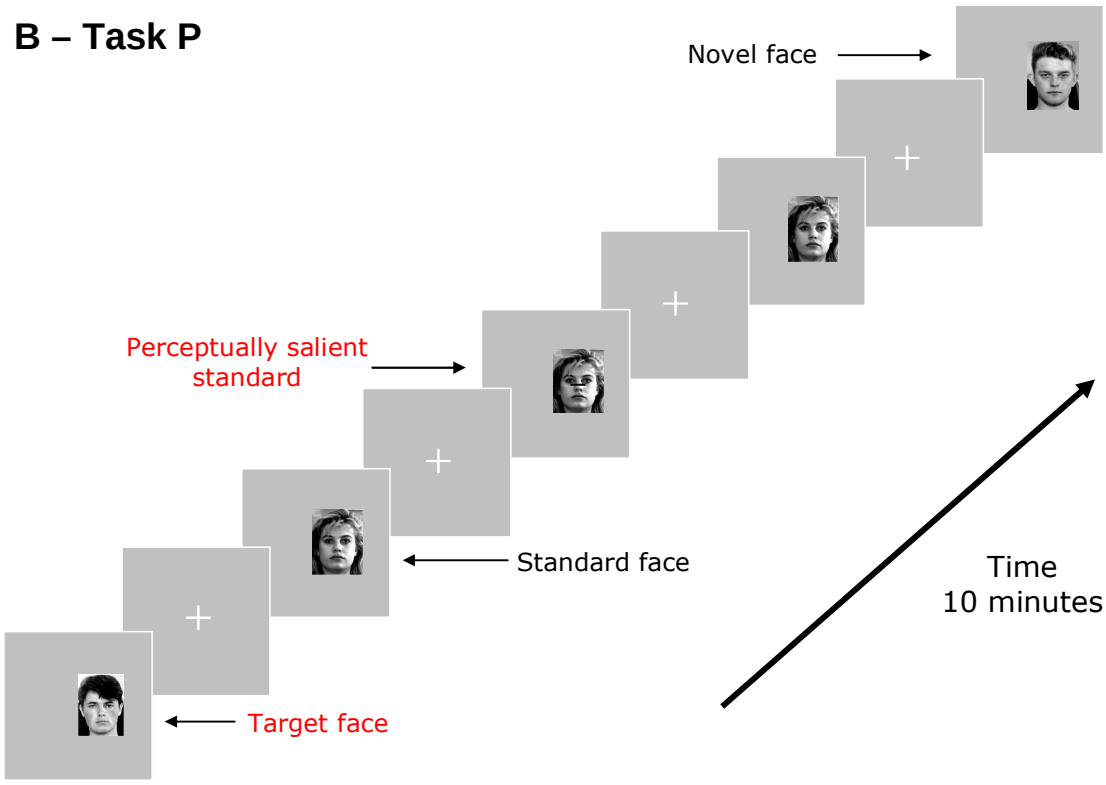

B – Task P
Novel face
Perceptually salient standard
Standard face
Target face
Time
10 minutes

Figure 5.1. 'Oddball task' design.
A. *Task N.* Subjects were instructed to respond with the same button press whenever they detected a target face or a novel face, and to withhold responses to the perceptually salient standard faces and standard face.
B. *Task P.* Participants were asked to respond to the target faces and the perceptually salient standard faces, and withhold responses to the novel and standard faces.

Each stimulus was presented for 2500 ms, with the interstimulus interval varying from 1000 to 1500 ms. Each task consisted of 150 stimuli and lasted for approximately 10 minutes. The stimuli were presented just right of the midline, with the left border of the stimulus positioned in the centre of the display screen.

Each face was presented for 2500 ms, with interstimulus interval varying between 1000 and 1500 ms. The faces were presented just right of central fixation (with the left border of the stimulus positioned in the centre of the screen), with a central fixation cross displayed during the interstimulus interval. This stimulus position was chosen to help ensure that even patients with severe neglect would explore the complex face stimuli.

Both tasks consisted of 150 stimulus presentations, lasting for approximately 10 minutes duration. The target face was displayed at the start of each task for as long as individual subjects required and was followed by a short practice session before proceeding to the main task. The practice session consisted of 20 stimulus presentations, which was repeated if necessary until subjects were confident of the task instructions – see below.

The two tasks were termed *task N* – for novelty – and *task P* – for perceptual salience. On task N, subjects were instructed to respond with the same button press whenever they detected the *target face* and whenever they encountered a *novel face*, and to withhold responses to the perceptually salient standard and unaltered standard faces – Figure 5.1A. On task P, they were instructed to respond to the *target face* and to the *perceptually salient standard faces*, and withhold responses to the unaltered standard face and novel faces – Figure 5.1B.

In order to ensure that participants examined all faces, and did not merely respond to the presence of a black bar on task P, 40% of novel faces on both tasks also had a black bar, with subjects being informed of this in advance. Both tasks were therefore identical in terms of design and the perceptual experience of subjects, differing only in terms of the responses subjects were instructed to perform. The order of task presentation was counterbalanced across the participants of each group.

5.2.4.2. Memory task

Participants' memory for the novel faces presented in each task was assessed following a 5 minute break. This memory task consisted of the 30 novel faces presented during the course of tasks P and N, randomly intermixed with an additional 30 faces which had not previously been shown. Subjects were instructed to indicate with a button press whether or not they had seen each face before. Each face stimulus remained on the screen until a decision had been made.

5.2.5. Data analysis

As in a previously published study using this task (Bunzeck and Duzel 2006), median reaction time and hit rate were used to analyse the behavioural results, in addition to false alarm rates. As will be detailed in the results section, there was a significant difference between the subject groups in terms of false alarm rate. For this reason perceptual sensitivity, or d prime (d'), was also calculated.

The d' index is derived from signal detection theory and computes the distance between the signal and noise distribution means in standard deviation units. It therefore represents the ability of the subject to discriminate between signals (or targets) and non-signals (or non-targets) (Stanislaw and Todorov 1999). Thus, by taking into account both the hit and false alarm rate in its computation, it may be more sensitive as a behavioural measure of deficit than using either of these measures alone, particularly when there are differences in both measures between subject groups. A d' value of 0 would indicate an inability to distinguish a target (signal) from a non-target (noise) stimulus, whereas higher values indicate better perceptual sensitivity. The formula used to calculate d' was as follows:

$$d' = \Phi^{-1}(H') - \Phi^{-1}(F')$$

H' is the corrected hit rate, F' is the corrected false alarm rate and Φ^{-1} is the inverse of the cumulative Gaussian distribution, the function which converts probabilities into Z scores. Corrections were used in order to protect against ceiling effects in the control groups (Snodgrass and Corwin 1988) and were as follows:

$$H' = (h + 0.5) / (h + m + 1)$$
$$F' = (f + 0.5) / (f + cr + 1)$$

Where *h* is the percentage of hits, *m* is the percentage of misses, *f* is the percentage of false alarms and *cr* is the percentage of correct rejections on noise trials.

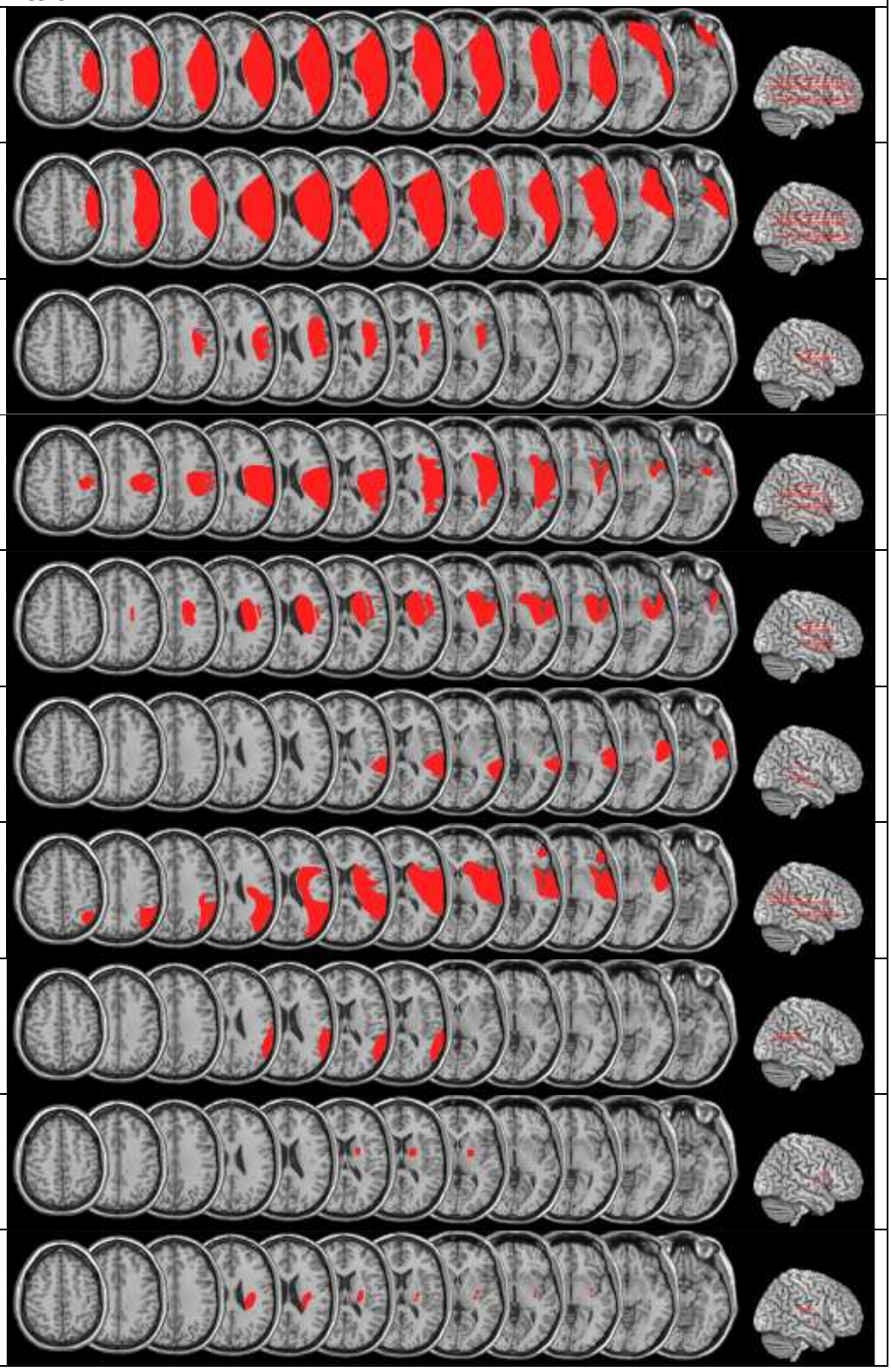
Repeated-measures ANOVAs were subsequently used to examine for significant effects between groups (neglect, stroke control and healthy control), which were followed up with t-tests where appropriate.

5.2.6. Lesion analysis

Lesions were plotted from clinical MR or CT scans (11 MR and 3 CT) on to a CH2 template using MRICro software (available from www.mricro.com), to produce a region of interest (ROI) on the axial images at MNI Z coordinates 56, 61, 66, 69, 75, 85, 88, 92, 96, 102, 108, 120. The lesions of individual patients are shown in Table 5.2.

The volume of lesions was calculated using MIPAV software (available from www.mipav.cit.nih.gov), after conversion of the ROI to a volume of interest (VOI). Importantly, there was not a statistically significant difference between the neglect and stroke control groups in terms of lesion volume ($t(12)=2.007$, $p=0.068$).

Overlays and 3-D renderings were carried out in MRICron software (available from www.sph.sc.edu/comd/rorden/mricron) after conversion of the ROIs to smoothed VOIs.

Subject	Lesion
N1	
N2	
N3	
N4	
N5	
N6	
N7	
SC1	
SC2	
SC3	

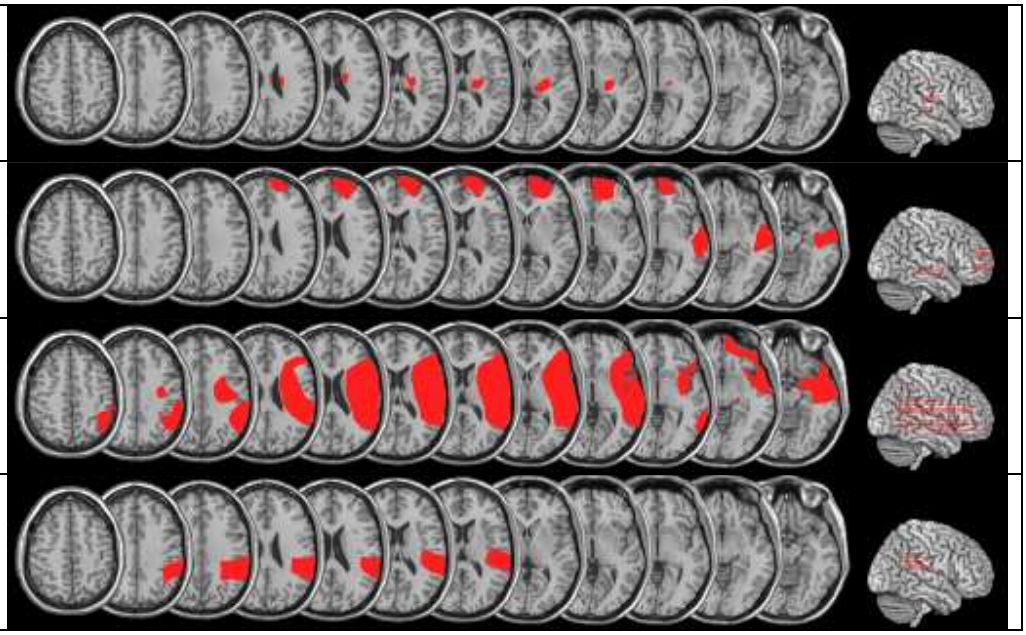
SC4	
SC5	
SC6	
SC7	

Table 5.2. Patient lesions.

N – neglect patient

SC – stroke control patient

Voxel-based lesion symptom mapping (VLSM) was used to interrogate the behavioural and lesion data for the whole stroke group (neglect and stroke control patients combined) using MRICron and non-parametric mapping software (NPM for windows also available from www.sph.sc.edu/comd/rorden/mricron). The advantage of VLSM is that subjects are not grouped *a priori* according to behavioural measures (neglect or non-neglect), or according to site or size of lesion. Instead, it takes behavioural and lesion data from all

patients and asks which voxels, when damaged, are associated with particular impairments (Bates, Wilson et al. 2003; Rorden, Karnath et al. 2007).

VLSM therefore provides a relatively assumption-free measure of whether or not damage to a particular voxel is associated with a specific behavioural deficit. For each voxel subjects were divided into two groups according to whether that particular voxel was damaged or not. Behavioural scores were then compared using the Brunner-Munzel rank order analysis, which is incorporated within the MRICron and NPM software, to produce a statistic for each voxel. These Brunner-Munzel values were then overlain on the MNI template as colour Z maps, revealing the degree of involvement of each voxel in the behavioural process under investigation. The colour Z maps were then smoothed, automatically within the MRICron software, to produce a 3-D rendering.

The Brunner-Munzel rank order test is a non-parametric analysis which is robust to violations of normality and has been considered the statistical test of choice in patient studies such as this (Rorden, Karnath et al. 2007). An earlier version of this test in MRICron/NPM has been recently criticized for producing large Type I errors in small groups (Medina, Kimberg et al. 2010). However, use of the Brunner-Munzel in conjunction with a permutation derived correction available in the most recent version of MRICron/NPM is considered to produce reliable *z* scores (Medina, Kimberg et al. 2010). Only voxels lesioned in at least 15% of the stroke group were included in the analyses, with a permutation derived familywise error (FWE) correction (at the 0.05 level) performed automatically within the MRICron and NPM software.

5.3. Results

5.3.1. Oddball tasks P and N

5.3.1.1. Error data

The hit rate and false alarm rate data across the three subject groups is shown in Figure 5.2.

A repeated measures ANOVA was performed on the hit rate data across the three subject groups (neglect, stroke control and healthy control) with a within group measure of task (task P versus task N). There was a significant effect of group ($F(2,21)=6.805$, $p=0.005$), with *post hoc* Bonferroni testing revealing that the neglect patients demonstrated significantly lower hit rates than either the stroke controls ($p=0.017$) or the healthy controls ($p=0.005$) – see Figure 5.2A. It should be noted that, in terms of the error data, the control groups performed at ceiling.

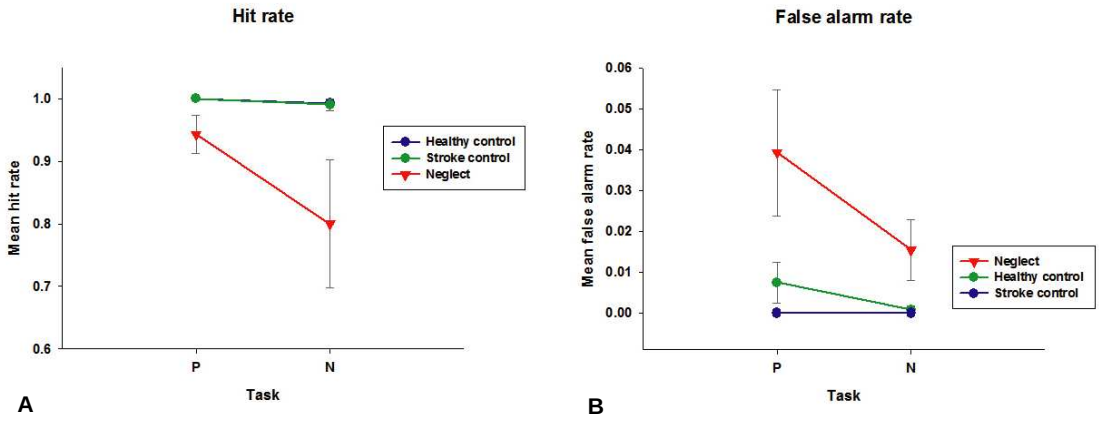


Figure 5.2. Hits and false alarms across subject groups.

The neglect group made significantly more errors than either of the control groups, both in terms of omission errors, giving a lower hit rate, and false alarms.

Error bars indicate the standard error of the mean.

Despite the neglect patients appearing to demonstrate a lower mean hit rate on task N, when they had to respond to the novel faces (Figure, 5.2A), there was, however, no significant effect of task ($F(1,21)=2.717$, $p>0.11$) or an interaction between task and subject group ($F(2,21)=1.854$, $p>0.18$). This therefore suggests that there was no consistent difference between the tasks in terms of the hit rate data in any of the subject groups.

A repeated measures ANOVA was also performed on the false alarm rate data across the three subject groups, with a within group measure of task (task P versus task N). There was a significant effect of group ($F(2,21)=9.645$, $p=0.001$), with *post hoc* Bonferroni testing revealing that neglect patients made significantly more false alarms than either the stroke control ($p=0.002$) of healthy control ($p=0.004$) groups – see Figure 5.2B.

Again, the effect of task failed to reach significance ($F(1,21)=3.273$, $p=0.085$), as did the interaction between task and subject group ($F(2,21)=1.457$, $p>0.25$), indicating inconsistent differences in false alarm rate across all three subject groups, including the neglect group, for novel and non-novel perceptually salient stimuli.

5.3.1.2. Perceptual sensitivity

Due to the presence of significant differences between the groups for both the hit rate and false alarm data, the perceptual sensitivity (d') data was also analysed, in order to assess how overall performance differed between the groups and across the tasks. This data is presented in Figure 5.3.

A repeated measures ANOVA was performed on the perceptual sensitivity data across the three subject groups (neglect, stroke control and healthy control) with a within group measure of task (task P versus task N). The performance of the neglect patients was significantly poorer than that of either control group (effect of group: $F(2,21)=12.626$, $p<0.001$) with *post hoc* Bonferroni tests revealing that the neglect group had significantly lower sensitivities than the stroke controls and healthy controls (both $p=0.001$).

There was no effect of task ($F(1,21)=0.734$, $p>0.4$) or a task by group interaction ($F(2,21)=1.163$, $p>0.33$), indicating that sensitivity was similar for novel stimuli (task N) and non-novel perceptually salient stimuli (task P) in all three groups, including the neglect group – see Figure 5.3.

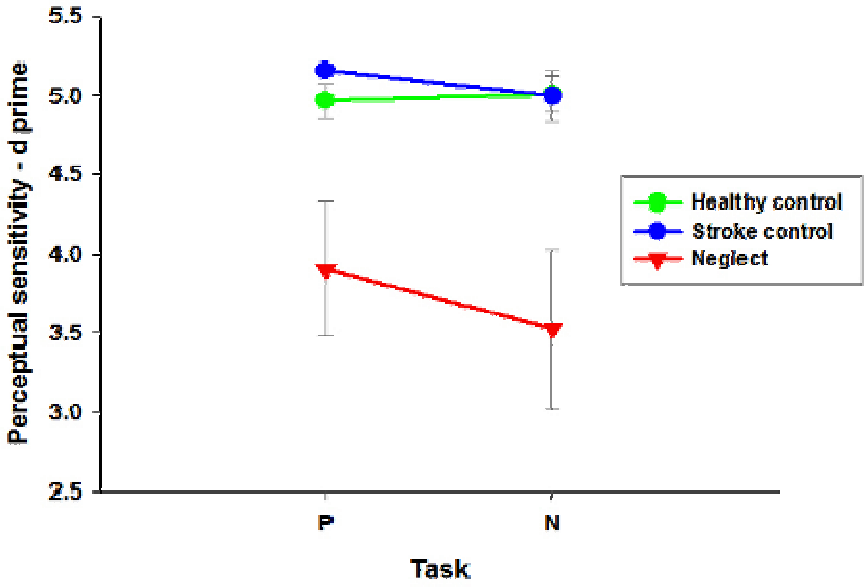


Figure 5.3. Perceptual sensitivity to novel and non-novel perceptually salient stimuli. Neglect patients demonstrated impaired perceptual sensitivity, compared to stroke control and healthy control subjects, to salient items on both tasks. They were at least equally deficient at detecting novel (task N) as compared to non-novel yet perceptually salient (task P) stimuli.

Error bars indicate the standard error of the mean.

In summary, therefore, neglect patients appear at least as deficient at detecting novel as non-novel but perceptually salient stimuli.

In order to demonstrate voxels which, when lesioned, were associated with an impairment in novelty processing, the d' value for the detection of novel stimuli during task N was used. This value for all of the neglect and stroke control patients was used by the Brunner-Munzel rank order test, instantiated within MRICron, to interrogate lesions in order to reveal areas necessary for the detection of novel stimuli.

This VLSM analysis revealed that the deficit in the detection of novel stimuli was associated with damage to the inferior frontal gyrus (IFG) and, to a lesser extent, the supramarginal and angular gyri of the IPL – Figure 5.4. This suggests a crucial role of the IPL, but particularly the IFG in novelty detection.

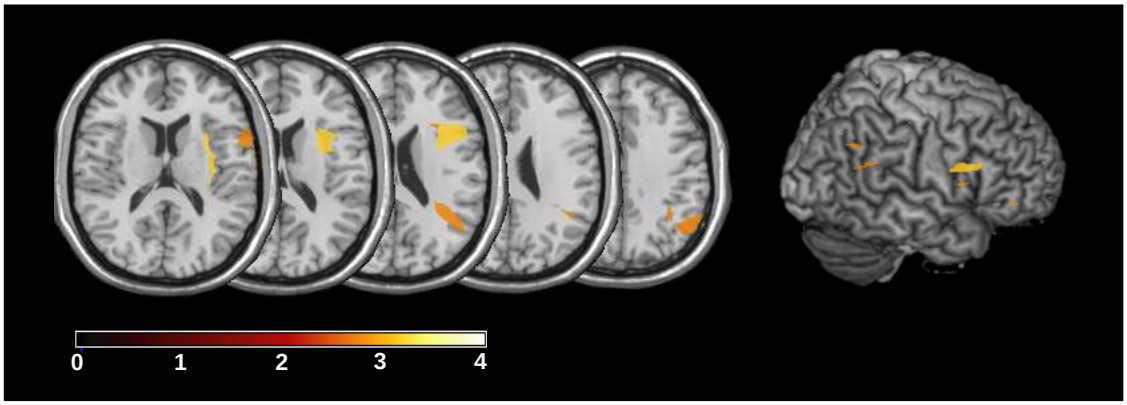


Figure 5.4. Regions associated with a deficit in novelty detection.
The deficit in novelty detection was associated with damage to voxels in the inferior frontal gyrus and to a lesser extent, the supramarginal and angular gyri of the IPL.
Z scores >2.98 are significant at the 0.05 level after permutation derived FWE correction.

5.3.1.3. Reaction time data

The reaction time data to target stimuli presented during task P and perceptually salient stimuli were collapsed together for task P, and the data for target stimuli presented during task N and novel stimuli were collapsed together for task N. There were no significant differences between target stimuli or perceptually salient standard stimuli presented during task P ($t(23)=1.498$, $p=0.148$) and target stimuli or novel stimuli presented during task N ($t(23)=-1.35$, $p=0.19$).

A repeated measures ANOVA was performed on the reaction time data across the 3 subject groups (neglect, stroke control and healthy control), with a within group measure of task (task P versus task N). This revealed a significant effect of group ($F(2,21)=5.531$, $p=0.012$), with *post hoc* Bonferroni testing revealing that the neglect group ($p=0.024$), as well as to a lesser extent the stroke controls ($p=0.045$), were significantly slower than the healthy controls.

Importantly, there was also a main effect of task ($F(1,21)=11.971$), in addition to a significant task by group interaction ($F(2,21)=11.877$, $p<0.001$). *Post hoc* t-tests revealed that the neglect patients were significantly slower to respond to novel compared to non-novel perceptually salient stimuli ($t(6)=-3.421$, $p=0.014$), while stroke controls ($t(6)=0.666$, $p=0.53$) and healthy control subjects ($t(9)=-0.798$, $p=0.446$) were equally quick to respond to both types of stimuli.

This suggests that in neglect, not only is novelty detection impaired, but that it may be affected more severely than the detection of non-novel perceptual salience – see Figure 5.5.

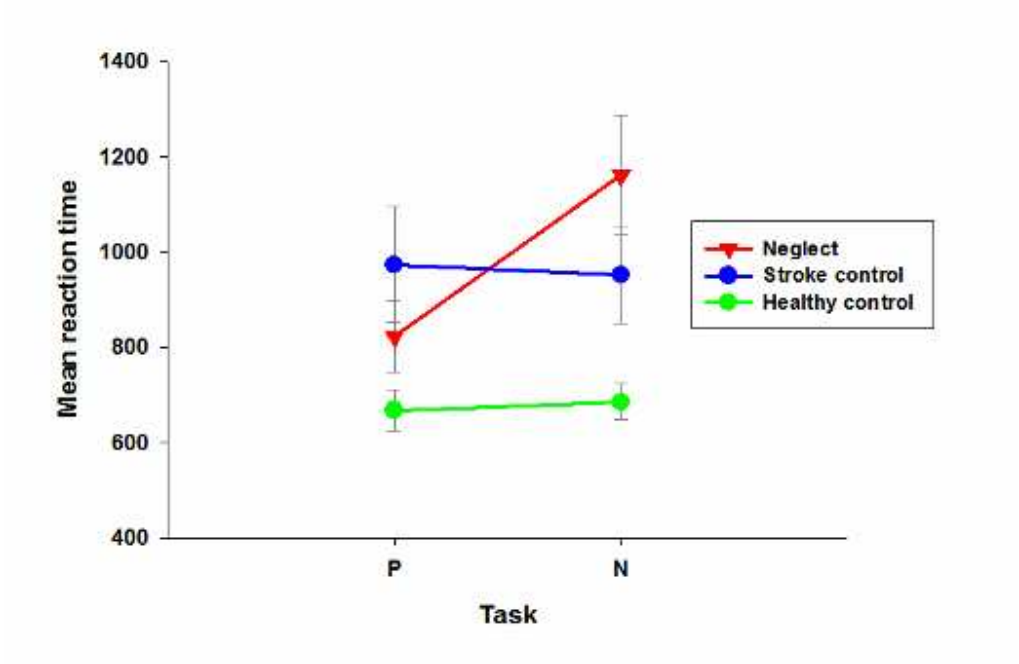


Figure 5.5. Reaction time to novel and non-novel perceptually salient stimuli. Unlike the stroke control and healthy control subjects, neglect patients were significantly slower to detect novel stimuli (task N) compared to non-novel yet perceptually salient stimuli (task P).

Error bars indicate the standard error of the mean.

In order to demonstrate voxels which, when lesioned, are associated with slower detection of novel compared to non-novel perceptually salient stimuli, the difference in median reaction time for the two types of stimuli was used. This value for all of the neglect and

stroke control patients was used by the Brunner-Munzel test to interrogate lesions in order to reveal areas associated with slower detection of novelty.

This VLSM analysis revealed that slower detection of novelty compared to non-novel perceptual salience was associated with damage predominantly in the IFG, but also the supramarginal gyrus of the IPL – see Figure 5.6. This suggests that damage to these regions may be particularly detrimental to the processing of stimulus novelty.

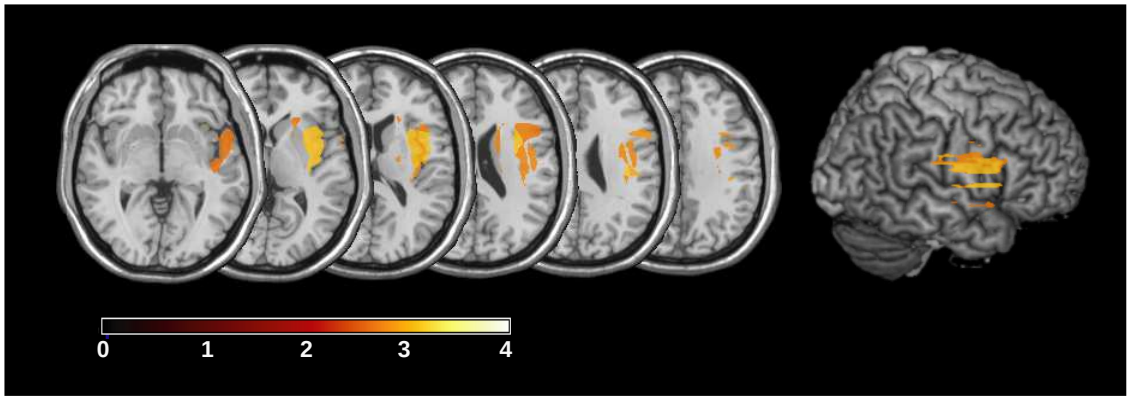


Figure 5.6. Regions associated with impaired detection of novelty compared to non-novel perceptual salience.
Impairment in detection of novel compared to non-novel perceptually salient stimuli was predominantly associated with damage to voxels in the inferior frontal gyrus. Additionally, injury to voxels in the supramarginal gyrus of the IPL was associated with this relative impairment.
Z scores >2.807 are significant at the 0.05 level after permutation derived FWE correction.

5.3.2. Memory Task

5.3.2.1. Error data

The hit rate and false alarm data for the memory task are shown in Figure 5.7.

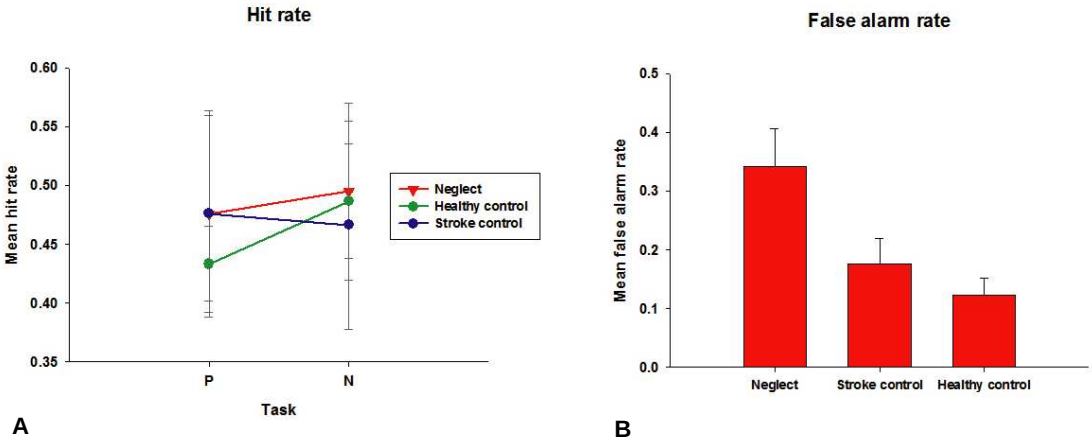


Figure 5.7. Hit rate and false alarm rate on the memory task across the three subject groups.

There was a significant difference between the three subject groups in terms of the false alarm errors made (B), but not the hit rate (A).

Error bars indicate the standard error of the mean.

A repeated measures ANOVA was performed on the hit rate data from the memory task across the three subject groups (neglect, stroke control and healthy control), with a within group measure of task (task P versus task N) during which the previously encountered novel faces had been earlier presented. There was no significant effect of group ($F(2,21)=0.047$, $p>0.9$), nor was there an effect of task ($F(1,21)=0.403$, $p>0.5$) – see Figure 5.7A.

A one-way ANOVA was used to analyse the false alarm data for the memory task, as false alarms were equally distributed amongst the novel faces from task N and task P. There was a significant difference between the three subject groups – neglect, stroke control and healthy control – ($F(2,23)=6.66$, $p=0.006$), with *post hoc* Bonferroni testing revealing that there was a significant difference between the neglect patients and the healthy controls ($p=0.005$) and a difference which just failed to reach significance between the neglect patients and the stroke controls ($p=0.06$), with neglect patients making a greater number of false alarm errors – see Figure 5.7B.

The hit rate and false alarm data were subsequently combined by examining perceptual sensitivity on the memory task.

5.3.2.2. Perceptual sensitivity

A repeated measures ANOVA was performed on the perceptual sensitivity data from the memory task across the three subject groups (neglect, stroke control and healthy control), with a within group measure of task (task P versus task N) during which the previously

encountered novel faces had earlier been presented. The effect of group just reached statistical significance ($F(2,21)=3.445$, $P=0.05$), with *post hoc* Bonferroni testing revealing a significant difference between neglect and healthy controls ($p=0.048$), but non-significant differences between the neglect and stroke control patients ($p=0.608$) and the stroke and healthy control subjects ($p=0.736$) – see Figure 5.6.

There was no effect of task ($F(1,21)=1.387$, $p=0.252$) and no task by group interaction ($F(2,21)=0.015$, $p>0.9$), indicating that having to make a motor response (task N) to a novel face, as opposed to having to withhold a motor response (task P) to a face, did not influence the accuracy with which it was subsequently detected by any of the subject groups.

Patients with neglect therefore demonstrated a global deficit in the recognition of previously encountered novel faces, in comparison to healthy age-matched subjects, but not stroke control patients, and this deficit was not affected by their impaired detection of novel stimuli during the oddball tasks.

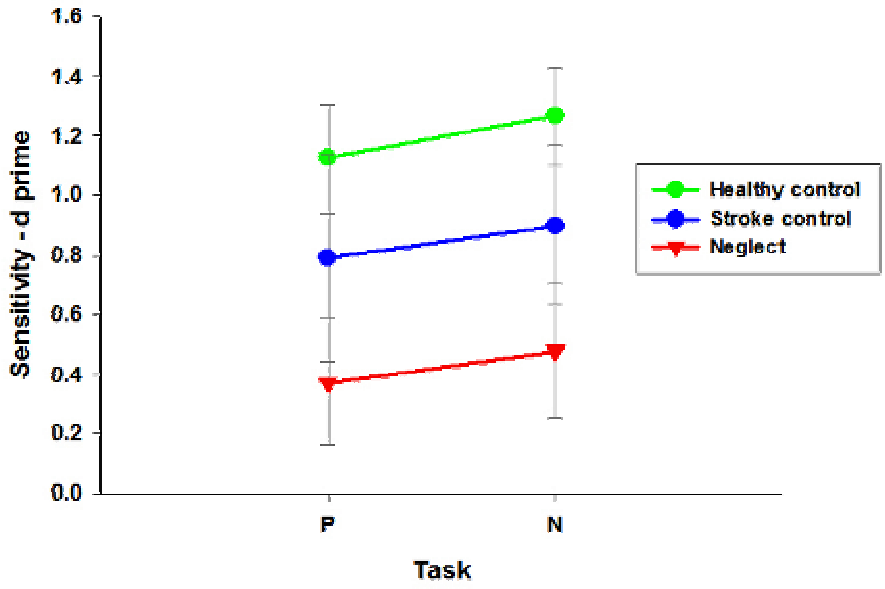


Figure 5.8. Sensitivity on the memory task.

Neglect patients were significantly impaired at correctly identifying faces they had previously encountered during the oddball tasks compared to the healthy control subjects. However, there was there was not a significant effect of oddball task – whether novel faces previously required a motor response (task N) or not (task P) – nor a significant task by group interaction.

Error bars indicate the standard error of the mean.

5.4. Discussion

One of the principal findings of this chapter is that neglect patients, in addition to demonstrating impairment in the accurate detection of non-novel perceptually salient stimuli, are also at least equally deficient at the accurate detection of novel stimuli (Figures 5.2 and 5.3). However, neglect patients were significantly *slower* at detecting novel compared to non-novel yet perceptually salient stimuli (Figure 5.5).

It could be argued that response inhibition plays an important part in the accurate performance of these tasks. The inclusion of novel stimuli in task P and perceptually salient non-novel stimuli in task N meant that the perceptual experience of subjects during each task was identical, with only the responses they were instructed to make differing between tasks. However, this meant that during task P, responses to novel stimuli had to be inhibited, while on task N, responses to perceptually salient standard stimuli had to be suppressed. This point is particularly pertinent during the second task that subjects performed, when the type of stimulus responded to during the previous task must be ignored in order to perform the task well. It must, however, be remembered that the order in which tasks were performed was counterbalanced across the subjects of each group. This effect, when considered at the group level, should therefore have been minimized. Furthermore I would argue that response inhibition is a vital cognitive component of all tasks during which selective responses are required and is certainly an important component of real-life behavioural choices.

Impairment in the accurate detection of novel stimuli (Figure 5.4), as well as the slower detection of novel compared to non-novel perceptually salient stimuli (Figure 5.5), was associated with damage within a ventral network of brain regions, including the IPL, but particularly the IFG (Figure 5.6).

These findings therefore support the proposed role of the right IPL and ventral attention network in the processing of novel stimuli, in addition to non-novel salience detection and the ability to effectively sustain attention as identified in Chapter 2 of this thesis.

Importantly, a role of the right IFG and IPL in the detection of novel stimuli is not a feature incorporated within a previous model of ventral attention network function, proposed by Corbetta and colleagues (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). In fact, their most recent formulation (Corbetta, Patel et al. 2008) seems to suggest that this network is important only in responding to salient task-relevant events and not novel or task-irrelevant stimuli. The novel faces used in the paradigms employed in this chapter were, of course, task-relevant. However, the fact that reaction times to novel stimuli were significantly *slower* than those to non-novel perceptually salient stimuli in neglect patients with right-sided ventral network damage – in the context of otherwise identical experimental requirements – suggests that stimulus novelty itself is important.

Taken together, I believe the results of this chapter adds support to the proposal that the right IPL and ventral attention network play an important role in the reconfiguration of behaviour, facilitating flexible switching between a task-engaged state – where attention is

sustained on current task goals and demands, with responses to items irrelevant to the current task being inhibited – and a more labile, exploratory state – during which attention is reoriented away from previous task goals and towards novel or salient environmental events of potential behavioural significance (Singh-Curry and Husain 2009).

5.4.1. Novelty processing and the ventral attention network

As discussed in the introduction to this chapter, evidence from both neurophysiological (Courchesne, Hillyard et al. 1975; Squires, Squires et al. 1975; Knight, Scabini et al. 1989) and functional imaging studies (Kiehl, Laurens et al. 2001; Downar, Crawley et al. 2002; Kiehl, Stevens et al. 2005; Bunzeck and Duzel 2006; Gur, Turetsky et al. 2007; Strobel, Debener et al. 2008; Friedman, Goldman et al. 2009) suggest an important role for the ventral attention network in the identification of novel stimuli. Because of the relative complexity of identifying novel events, necessitating a functional interplay between exogenous and endogenous information, and the highly connected position of the IPL (Hagmann, Cammoun et al. 2008), including to the medial temporal lobe which has a role in memory and novelty processing (Lisman and Grace 2005), it was hypothesized that this region might be particularly crucial in the detection of stimulus novelty. While the right IPL was identified as an important locus in novelty processing in this chapter, damage to the IFG was, however, more strongly associated with impairment in this process.

As discussed in Chapter 1, noradrenergic input from the locus coeruleus (LC) to the IPL and IFG – but particularly the IPL (Foote and Morrison 1987) – has long been considered

to play a key role in alertness (Posner and Petersen 1990), for example the activity of LC neurons is reduced in states of low arousal (Aston-Jones, Gonzalez et al. 2007). More recently, however, it has been argued that the LC contributes to the regulation of attention between a focused, selective attentional state (facilitating responses to targets and the filtering out of distractors) and a more scanning, labile state that allows flexible responding to new events (Aston-Jones and Cohen 2005; Aston-Jones, Iba et al. 2007; Singh-Curry and Husain 2009).

It has generally been acknowledged that noradrenergic LC cells fire en masse, either phasically or tonically in response to afferent input (Berridge and Waterhouse 2003; Aston-Jones and Cohen 2005; Aston-Jones, Gonzalez et al. 2007). Aston-Jones and colleagues have proposed that *phasic* noradrenergic activity (on a background of moderate tonic activity) facilitates focused, selective responding, with effective filtering out of distractors. On the other hand, an increase in *tonic* LC activity (associated with reduced phasic activity) shifts behaviour into an exploratory, more distractible state (Aston-Jones and Cohen 2005).

Intriguingly, converging evidence from animal neurophysiological, pharmacological and lesion studies, as well as some human studies, suggests that the P3 potential, recorded over cortical regions in response to task-relevant and novel salient events, reflects phasic activity of the LC noradrenergic system, which sends dense projections to the parietal cortex (Nieuwenhuis, Aston-Jones et al. 2005). Accordingly, it has been hypothesised that the interplay between phasic and tonic modes of noradrenergic afferent activity to the right

IPL may play a crucial function in permitting the flexible modulation of behaviour between a focussed, task-engaged state on one hand and a more exploratory mode of functioning on the other (Singh-Curry and Husain 2009).

As discussed earlier, novel stimuli are associated with P3a potentials (Courchesne, Hillyard et al. 1975; Squires, Squires et al. 1975; Knight, Scabini et al. 1989). Hence it can be predicted that novel *task-irrelevant* stimuli, in addition to salient task-relevant stimuli, might be associated with phasic bursts of LC noradrenergic activity (Singh-Curry and Husain 2009). Neurophysiological studies in humans have shown that the P3a in response to novel stimuli is of smaller amplitude and/or latency as compared to the P3b potential recorded in response to task-relevant events (Yamaguchi and Knight 1991). If baseline tonic noradrenergic levels were to increase, however, then I envisage that responses to novel or distracting stimuli would become more prominent. Thus behaviour becomes more exploratory or distractible in nature and disengagement from the task occurs, accompanied by a reduction in LC phasic activity and parietal P3b potentials to targets (Aston-Jones, Rajkowski et al. 1994; Usher, Cohen et al. 1999; Aston-Jones and Cohen 2005).

In the paradigm employed in this study, however, the novel stimuli in task N required a behavioural response and were therefore *task-relevant*. However, the lesion analysis shown in Figure 5.6 demonstrates areas which, when damaged, are associated with increased reaction times compared to perceptually salient, but non-novel task-relevant events and can therefore be considered as subtracting out the influence of task-relevance.

Like impaired detection of task-relevant novel events (Figure 5.4), slower responses to novel stimuli were associated with damage in inferior frontal and parietal regions (Figure 5.6).

In summary, the findings presented in this chapter support a role of the ventral attention system in the processing of novel stimuli. However, while the right IPL clearly played an important role in the detection and response to stimulus novelty, the IFG appeared to be more significantly associated with this process.

As discussed earlier, the detection of stimulus novelty is likely to be more complex than the detection of perceptually salient events, as it requires keeping track of and comparison with earlier stimuli in order to correctly judge the novel event as new. Indeed, novelty processing is also associated with activity in the midbrain dopaminergic nuclei the substantia nigra (SN) and ventral tegmental area (VTA), as well as the hippocampus and ventral striatum (Bunzeck and Duzel 2006).

In fact the SN/VTA, ventral striatum and hippocampus are thought to form a mesolimbic loop, which together with input from prefrontal areas (which forms a parallel and interacting mesocortical loop) is instrumental in controlling entry of information into long-term memory (Lisman and Grace 2005). Activity in the hippocampus is likely to be crucial in implementing the comparison of incoming information with stored memories, in order to compute whether incoming stimuli are actually new, while goal-related information from frontal regions may be critical in attaching importance (or salience) to

novel stimuli (Lisman and Grace 2005). This is therefore in accordance with my findings in this chapter which are consistent with a particularly prominent role of inferior frontal regions in novelty processing.

Novelty processing would therefore seem to involve input from the LC and ventral attention system, in addition to afferent information from the dopaminergic system, ventral striatum and hippocampus. The IFG and other ventral regions such as the IPL may play a particularly critical role in synthesising this information and incorporating it into behaviour. However, the remaining experimental chapters of this thesis will aim to explore novelty processing in the dopaminergic system, by examining a different neurological population: patients with Parkinson's disease, in whom the principal pathological process is the degeneration of the midbrain dopaminergic system.

Chapter 6

6.1. Introduction

Parkinson's disease (PD) is a neurodegenerative condition, primarily affecting dopaminergic neurons which project to the basal ganglia, and is classically considered a disorder of movement. Accordingly, its core deficits encompass a triad of motor symptoms: tremor, brady/akinesia and rigidity. More recently, however, it has become increasingly apparent that PD also involves cognitive (Burn, Rowan et al. 2006; Verbaan, Marinus et al. 2007), mood and behavioural difficulties (Marras, McDermott et al. 2008; Aarsland, Bronnick et al. 2009), which can represent a major source of disability. These additional problems may be caused by degenerative changes extending beyond the SN/VTA to other brain stem nuclei, as well as cortical regions (Del Tredici, Rub et al. 2002; Braak, Del Tredici et al. 2003; Parkkinen, Pirttila et al. 2008) and/or due to disordered mechanisms (disease-related or compensatory) within the dopaminergic system itself (Muller, Wachter et al. 2000; Remy, Jackson et al. 2000), in addition to the effects of drugs used to treat motor symptoms (Cools, Barker et al. 2001; Cools, Barker et al. 2003).

Behavioural problems in PD consist of impulsive and compulsive behaviour, termed impulse control disorders (ICD) (Potenza, Voon et al. 2007), such as pathological gambling (Gschwandtner, Aston et al. 2001; Avanzi, Baratti et al. 2006; Gallagher, O'Sullivan et al. 2007) and compulsive medication overuse (Evans, Pavese et al. 2006). Such problems are estimated to affect approximately 5% of PD patients at any one time

(Grosset, Macphee et al. 2006; Weintraub, Siderowf et al. 2006) and between 5 and 10% at some point during the course of the disease (Voon, Hassan et al. 2006; Weintraub, Siderowf et al. 2006). It has also been estimated that PD patients may be approximately 25 times more likely to develop an ICD compared to age and sex matched healthy controls (Avanzi, Baratti et al. 2006).

ICDs may also encompass behaviours which are referred to as *punding* or *hobbyism*. Punding involves an intense fascination with excessive, non-goal-oriented, unproductive, repetitive actions that are usually simple (e.g. manipulating or sorting common objects). Hobbyism is defined as repetitive behaviour which is more complex in nature, e.g. hoarding or excessive gardening, cleaning or computer use (Evans, Katzenschlager et al. 2004). These behaviours may be due to disinhibition of previously overlearned behaviours, for example an accountant has been reported to be more likely to shuffle papers, while housewives are more likely to clean. The behaviours are defined as pathological by their disruptive nature and interference with normal functioning, while interruption of the behaviour leads to irritability or dysphoria (Evans, Katzenschlager et al. 2004; Voon, Fernagut et al. 2009).

ICDs in general are characterised by the maladaptive nature of the preoccupations of the patient, the inability to control impulses or urges, and other pathological behaviours, such as lying or stealing, which may result from these preoccupations. Although these behaviours have different levels of severity, pathology is defined by the consequences of

distress or interference with social, financial or occupational functioning (Voon, Fernagut et al. 2009).

In the general population, impulsive and risk-taking personality profiles have been linked to high scores in sensation (or novelty) seeking on questionnaires (Llewellyn 2008). It has often been asserted that there is a characteristic 'Parkinsonian personality' profile. However, this is considered to be *low* in impulsivity and novelty-seeking and instead dominated by introversion, cautiousness and moral rigidity (Glosser, Clark et al. 1995; Tomer and Aharon-Peretz 2004). Needless to say, this is somewhat at odds with the fact that this population appears particularly sensitive to the development of ICD. It has been suggested that such behavioural difficulties in PD may be related to the use of dopamine agonists (Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007). However, this argument fails to explain why some individuals using these drugs for the same indication develop these problems, while others do not.

Similarly, there is inconsistency in the literature regarding whether PD patients, without ICD, demonstrate risky behaviour. Some studies which have used gambling tasks, such as the Iowa Gambling Task (IGT) (Bechara, Damasio et al. 1994), suggest they do (Thiel, Hilker et al. 2003; Perretta, Pari et al. 2005; Pagonabarraga, Garcia-Sanchez et al. 2007; Kobayakawa, Koyama et al. 2008), while other studies have failed to find any evidence of risk-prone decisions (Stout, Rodawalt et al. 2001; Czernecki, Pillon et al. 2002; Mimura, Oeda et al. 2006).

However, PD is not a homogeneous condition. In terms of the motor phenotype, two quite distinct subgroups have been described: the *akinetic-rigid* group – in whom the main symptoms are stiffness and slowness of movement – and the *tremor dominant* group – in whom tremor is the main finding (Jankovic, McDermott et al. 1990; Kang, Bronstein et al. 2005).

Importantly, post-mortem evidence supports this distinction, with the brains of akinetic-rigid patients demonstrating more neuronal loss and gliosis within the midbrain (Paulus and Jellinger 1991) and greater reductions in dopamine levels within the internal segment of the globus pallidus (Rajput, Sitte et al. 2008), compared to those who are tremor dominant. Critically, all the patients included in the study by Rajput and colleagues were followed up over a number of years (range: 4.9-24.6) and persistently demonstrated the pattern of symptoms consistent with their sub-grouping. There is also evidence to suggest that tremor dominant patients may be less susceptible to the development of cognitive dysfunction (Allcock, Kenny et al. 2006; Burn, Rowan et al. 2006), as well as autonomic problems (Allcock, Kenny et al. 2006).

A further large (250 cases) post-mortem study, with extensive post-diagnosis follow-up, also supports the existence of pathological differences between the brains of akinetic-rigid and tremor dominant PD patients (Selikhova, Williams et al. 2009). This investigation reported that an akinetic-rigid onset of PD is strongly associated with a higher load of cortical Lewy-bodies, in comparison to a tremor dominant onset, which may underlie the

higher propensity akinetic-rigid patients have for the development of cognitive problems (Allcock, Kenny et al. 2006; Burn, Rowan et al. 2006; Selikhova, Williams et al. 2009).

It is important to note that the study by Selikhova and colleagues used the pattern of symptoms during the first five years of disease, with particular importance given to those evident at diagnosis, to divide their patients into sub-groups (Selikhova, Williams et al. 2009), rather than only including those who consistently demonstrated either an akinetic-rigid or tremor dominant motor pattern. However, although it has been documented that the motor subtype of PD patients may change with disease progression, this appears to be predominantly from tremor dominant to akinetic-rigid, with the reverse scenario (akinetic-rigid to tremor dominant) occurring only rarely (Alves, Larsen et al. 2006). Hence the PD patients classified as akinetic-rigid at disease onset by Selikhova and colleagues are likely to have remained akinetic-rigid throughout the course of their disease.

There is also electrophysiological evidence of a distinction between akinetic-rigid and tremor dominant PD. It has been shown that dopaminergic medication can reduce oscillatory activity in the subthalamic nucleus, a finding which correlates with a reduction in akinesia and rigidity, but *not with tremor* (Kuhn, Kupsch et al. 2006; Kuhn, Tsui et al. 2009).

I therefore hypothesise that there may be further differences between the akinetic-rigid and tremor dominant PD subgroups, in terms of their ability to process novelty and in their willingness to take risks. This might, at least in part, explain why some PD patients are

susceptible to developing ICDs while others are not. Examination of behavioural differences between these sub-groups may therefore help elucidate key features of novelty processing and risk-taking in different patients with PD.

My aim in this chapter will therefore be to investigate possible behavioural differences in these two subgroups of PD patients, in terms of their ability to process novel stimuli and their willingness to take risks, and to compare their functioning to PD patients with ICDs. In order to probe novelty processing I will use a task based on the 'oddball paradigm', adapted from a previous version used in healthy control subjects (Bunzeck and Duzel 2006). Performance on this task will be compared to risk-taking behaviour, as measured on gambling tasks, including the IGT (Bechara, Damasio et al. 1994) and Cambridge Gambling Task (CGT) (Rogers, Everitt et al. 1999).

6.2. Methods

6.2.1. Participants

Patients were recruited from movement disorders and general neurological outpatient departments with local ethics approval. Overall 14 akinetic-rigid (mean age: 67.4, range: 55-87; all right-handed) and 15 tremor dominant patients (mean age: 65.7, range: 42-84; all right-handed) without ICD were recruited, in addition to 14 PD patients who had been diagnosed by their neurologist as having an ICD (mean age: 61.4, range: 36-73; one left-handed). Defining criteria for these groups is given below in Section 6.2.1.2. The PD patients were all assessed and underwent testing on their usual medication. 15 healthy

elderly controls, with no neurological or psychiatric history were also recruited (mean age: 69.1, range: 51-82; 2 left-handed). A one-way ANOVA revealed that there was no significant difference between the groups in terms of age ($F(3,57)=1.638$, $p=0.191$).

6.2.1.1. Exclusion criteria

Exclusion criteria included cognitive impairment such that there was difficulty following assessment or task instructions and/or a Mini-Mental State Examination (MMSE) score of less than 25. To provide a more detailed measure of cognitive function in the PD patients, the Addenbrooke's Cognitive Examination – Revised (ACE-R) was also performed (Mioshi, Dawson et al. 2006) - see Table 6.1. There were no significant differences between PD groups in terms of MMSE score ($F(2,42)=2.031$, $p>0.1$) or ACE-R score ($F(2,42)=0.3$, $p>0.7$).

Subject	Sex	Age	Time Dx	Time Sx	UPDRS	Subtype ratio	MMSE	ACE-R	BDI	LEU	DA
Akinetic-rigid/mixed											
AR1	F	64	3.5	4	26	0.4	30	95	10	300	0
AR2	M	79	8	9	54	0.7	29	73	9	867	67
AR3	M	63	4	5	44	0.7	30	95	9	67	67
AR4	F	62	2	4	29	0.7	29	93	6	268	268
AR5	M	87	2	3	23	1	30	77	16	300	0
AR6	F	62	17	18	21	0.4	30	95	10	351.25	83.75
AR7	F	55	8	9	69	0.8	29	92	17	602	402
AR8	F	76	0.1	3	49	1	30	95	16	0	0
AR9	F	58	2	4	11	0.94	30	95	5	201	201
AR10	F	69	0.1	1	28	0.8	30	95	4	0	0
AR11	M	65	0.6	2	19	0.8	30	95	1	200	0
AR12	M	64	5.5	6.5	30	0.25	30	86	6	720	120
AR13	M	69	2	4	37	0.625	30	95	1	246.9	46.9
AR14	M	71	9	9	49	0.357	30	90	4	600	0
Means/Ratio	**7:7**	**67.4**	**4.6**	**5.8**	**34.9**	**0.677**	**29.8**	**90.8**	**8.1**	**337.37**	**89.69**
Tremor dominant											
TD1	M	71	7	8	50	2.1	30	97	12	830	280
TD2	M	73	10	11	34	2.5	29	87	9	520	120
TD3	M	66	3	3	38	1.3	29	93	15	167.5	167.5
TD4	M	70	2	4	29	5	27	84	11	301	201
TD5	M	56	1	1	18	1.6	30	99	4	0	0
TD6	F	62	4	5	28	1.3	30	98	10	301.5	201
TD7	F	67	1.5	2	22	1.1	30	91	13	501	201
TD8	M	79	4	4	28	2.7	30	84	5	300	0
TD9	M	50	5	6	42	2.7	30	99	20	0	0
TD10	M	62	7	10	48	1.3	30	97	8	1334.7	268
TD11	F	68	5	6	32	2.1	30	96	8	300	0
TD12	F	42	0.25	0.5	27	1.7	30	86	19	0	0
TD13	F	75	3	4	34	2.4	30	96	10	0	0
TD14	M	60	2.5	5.5	21	1.6	30	91	8	167.5	167.5
TD15	F	84	0.1	0.8	27	1.25	30	93	3	0	0
Means/Ratio	**9:6**	**65.7**	**3.69**	**4.7**	**31.9**	**2**	**29.7**	**92.7**	**10.3**	**314.88**	**107.1**

Subject	Sex	Age	Time Dx	Time Sx	UPDRS	Subtype ratio	MMSE	ACE-R	BDI	LEU	DA
Impulse control disorder											
ICD1	M	69	13	17	93	0.24	30	85	29	500	400
ICD2	F	64	27	28	71	0.2	27	83	14	607	340
ICD3	F	65	12	15	75	0.313	28	78	26	812.5	0
ICD4	M	73	20	22	81	0.16	30	91	6	980	180
ICD5	M	61	16	17	73	0.26	29	91	8	2800	2800
ICD6	M	51	17	17.5	68	0.625	30	92	13	1201	201
ICD7	M	65	19	20	79	0	30	94	8	400	0
ICD8	F	62	20	23	78	0	25	81	14	1023.2	123.2
ICD9	F	58	17	20	74	0.85	30	93	15	500	0
ICD10	M	36	1.5	5	54	0.19	29	95	29	180	180
ICD11	M	63	12	15	36	0	29	87	14	747	80
ICD12	M	59	7	8	44	0.54	30	84	16	200	0
ICD13	M	69	3	10	15	3	30	81	6	0	0
ICD14	M	65	4.5	5	42	2.4	30	93	8	500	0
Means/Ratio	**10:4**	**61.4**	**13.5**	**15.9**	**63.1**	**0.627**	**29.1**	**87.7**	**14.7**	**746.5**	**307.4**

Table 6.1. Patient demographics.

Time Dx – time since diagnosis in years

Time Sx – time since symptom onset in years

UPDRS – Unified Parkinson's Disease Rating Scale score (maximum 199)

Subtype ratio – calculated as discussed in Section 6.2.1.2

MMSE – Mini-Mental State Examination score (maximum 30)

ACE-R – Addenbrooke's Cognitive Examination – Revised score (maximum 100)

BDI – Beck Depression Scale score (maximum 63)

LEU – L-dopa Equivalent Units – calculated as discussed in Section 6.2.1.3 (including L-dopa and dopamine agonisits)

DA – total dose of dopamine agonist in LEU

Significant depression was the other principal exclusion factor. PD patients *without* ICD and healthy control subjects were excluded if they had a Beck Depression Inventory (BDI) score of 21 or more. Patients *with* an ICD were only excluded if their BDI score was 30 or more. In the normal population, scores of 21 and above are thought to indicate depression, while scores above 30 indicate moderate-severe depression in people who have already been diagnosed as depressed. As disordered mood is common in PD (Marras, McDermott et al. 2008; Aarsland, Bronnick et al. 2009) and seems to be particularly so in those with ICD (Pontone, Williams et al. 2006; Voon, Hassan et al. 2006), this higher cut-off point was used for this group, in order to avoid the exclusion of excessive numbers in this already difficult to recruit population.

Accordingly, there was a significant difference between groups in terms of BDI score as revealed by a one-way ANOVA ($F(3,56)=3.563$, $p=0.02$), which was driven by significant differences between the ICD group and the other groups (ICD versus akinetic-rigid: $t(26)=-2.565$, $p=0.016$; ICD versus tremor dominant: $t(27)=-2.454$, $p=0.021$; ICD versus healthy control: $t(26)=2.249$, $p=0.033$). There was no difference between the control group and the PD patients without ICD (control versus PD without ICD: $t(41)=-0.05$, $p>0.9$; akinetic-rigid versus tremor dominant: $t(27)=0.726$, $p>0.7$). BDI scores of individual patients are shown in Table 6.1. Depression should therefore be bourne in mind as a possible confounding factor in interpreting differences between the ICD patients and other subject groups.

6.2.1.2. Sub-groups of PD

PD patients were placed into either akinetic-rigid/mixed or tremor dominant subgroups on the basis of the motor examination (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn 1987). Subgroups were defined according to the ratio of each patient's UPDRS III tremor score (sum of items 20 and 21 divided by 4) to their UPDRS akinetic/rigid score (sum of items 22-27 and 31 divided by 15) after the method proposed by Kang and colleagues (Kang, Bronstein et al. 2005). Patients with a ratio of >1.0 were classified as tremor dominant, those with a ratio of <0.8 as akinetic-rigid and 0.8-1.0 as mixed. See table 6.1 for detailed patient demographic information, including subtype ratios.

Impulse control problems were diagnosed in PD patients by the neurologist managing their PD. This occurred in the context of clinical interview during routine follow-up appointments and by administration of questionnaires such as the Minnesota Impulse Disorder Interview (Christenson, Faber et al. 1994) for compulsive buying, gambling and sexuality. The impulse control problems identified in the ICD patients studied here are detailed in Table 6.2. At the time of testing, all patients were subjectively in either full or partial remission.

Subject	Impulse control behaviour	Remission status	Motor subtype	Dyskinesias
ICD1	Pathological gambling	Full	AR	Yes
ICD2	Hobbyism and punding	Partial	AR	Yes
ICD3	Hobbyism and punding	Partial	AR	Yes
ICD4	Hobbyism and punding	Partial	AR	Yes
ICD5	Compulsive eating, compulsive medication overuse, hypersexuality, hobbyism	Partial	AR	Yes
ICD6	Hobbyism and punding	Partial	AR	Yes
ICD7	Hobbyism and punding	Full	AR	Yes
ICD8	Compulsive shopping	Partial	AR	Yes
ICD9	Hobbyism and punding	Partial	AR	No
ICD10	Pathological gambling	Full	AR	No
ICD11	Hypersexuality	Full	AR	Yes
ICD12	Pathological gambling	Full	AR	No
ICD13	Pathological gambling	Full	TD	No
ICD14	Hypersexuality	Full	TD	No

Table 6.2. Impulse control problems in the ICD group.

The impulse control problems of the individual ICD patients. The most common difficulty was with hobbyism and punding, followed by pathological gambling. Remission status was assessed by self-reports from the patients.

AR – akinetic-rigid/mixed

TD – tremor dominant

6.2.1.3.Demographic differences between the PD groups

There was a significant difference between the 3 PD groups in terms of their UPDRS scores ($F(2,42)=15.776$, $p<0.001$), driven again by the ICD group (ICD versus PD without ICD: $t(41)=-5.646$, $p<0.001$), with the 2 sub-groups without ICD being well-matched for severity of parkinsonian symptoms (akinetic-rigid versus tremor dominant: $t(27)=0.632$, $p>0.5$). This was mirrored by differences in duration of PD ($F(2,42)=13.94$, $p<0.001$), with the ICD group having a significantly longer disease duration compared to those without ICD ($t(41)=-5.302$, $p<0.001$), while the akinetic-rigid and tremor dominant groups were similarly matched ($t(27)=0.491$, $p=0.491$).

The total dose of dopaminergic medication of the PD patients was quantified by using l-dopa equivalence units after Evans and colleagues (Evans, Katzenschlager et al. 2004), which was defined as follows: l-dopa dose + l-dopa dose x 1/3 if on entacapone + bromocriptine (mg) x 10 + cabergoline or pramipexole (mg) x 67 + ropinirole (mg) x 20 + pergolide (mg) x 100 + apomorphine (mg) x 8.

Consistent with the demographic data regarding disease duration and severity of parkinsonian symptoms, a one-way ANOVA revealed that there were significant differences between the three PD groups in terms of LEU ($F(2,42)=3.488$, $p=0.04$), with the ICD group being on significantly more dopaminergic medication than the PD patients without ICD ($t(41)=-2.673$, $p=0.011$). The akinetic-rigid and tremor dominant sub-groups of PD without ICD were, however, well-matched for total dose of dopaminergic medication ($t(27)=-0.91$, $p>0.9$).

Isolating the contribution of dopamine agonists to the LEU of the patients, revealed no significant differences between the three PD groups in terms of dopamine agonist use ($F(2,42)=1.055$, $p=0.358$).

In summary, although the PD groups without ICD – the akinetic-rigid and tremor dominant groups – were well matched on all measures, the ICD group were more likely to suffer from depressive symptoms and had more severe parkinsonian symptoms, with longer disease duration and higher doses of dopamine replacement therapy. This is consistent with previous reports (Pontone, Williams et al. 2006; Voon, Hassan et al. 2006; Voon, Fernagut et al. 2009). These differences between ICD patients and the PD patients without ICD should be considered as potential confounding factors when considering differences between them.

Interestingly, as can be seen from Table 6.2, 12 of the 14 ICD patients were akinetic-rigid/mixed in terms of their motor subtype, with only 2 of these patients being tremor dominant.

6.2.2. Behavioural tasks

A series of computerised tasks were used to assess novelty processing and risk-taking. All tasks were presented using a Dell Latitude D820 laptop with a 15 inch screen and bilateral integral speakers.

6.2.2.1. Novelty processing

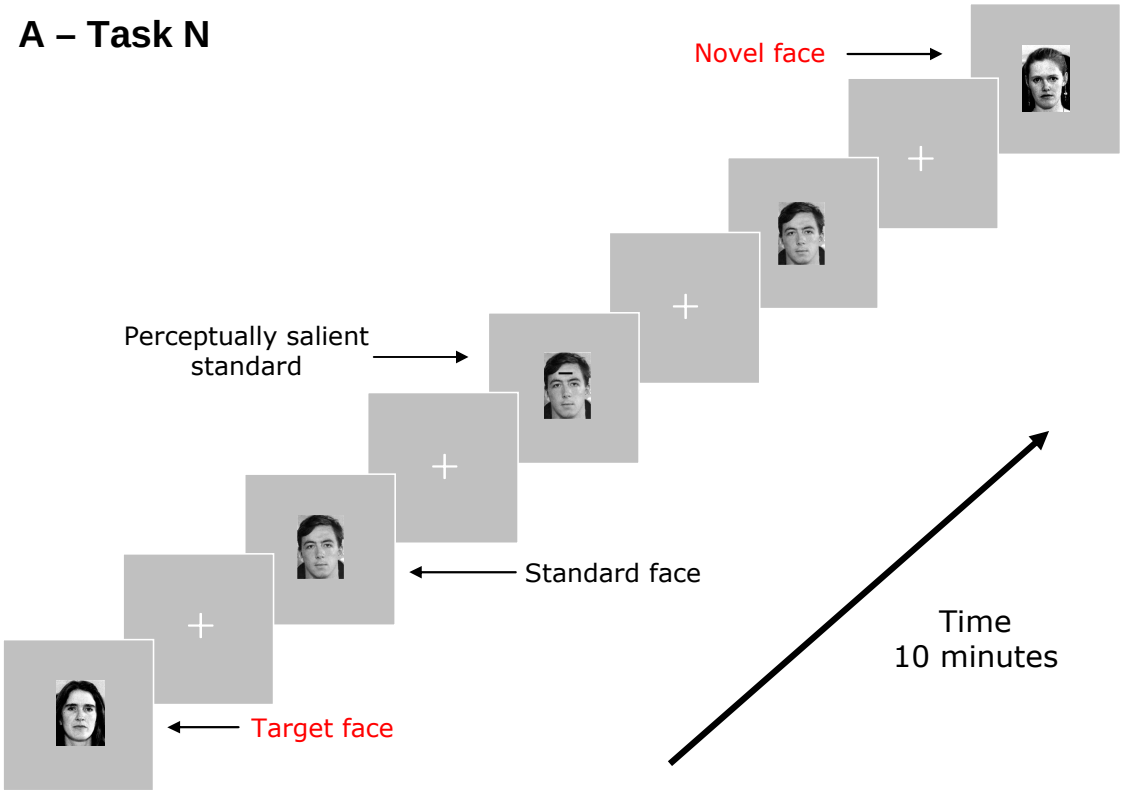
Two versions of an 'oddball' task were used to probe novelty processing, which were adapted from a previous version used in healthy young control subjects (Bunzeck and Duzel 2006). The tasks were programmed using E-Prime software (Psychology Tools Software Inc.). Stimuli were presented on a grey background and consisted of grey scale male and female faces with neutral expressions taken from the Psychological Image Collection at Stirling (PICS) database, provided by the University of Stirling Psychology department (http://pics.psych.stir.ac.uk/). Stimuli subtended approximately 7º x 9.5 º when viewed from a distance of 60cm. Male and female faces were used in an equal distribution across both tasks and subject responses were collected using an RB-530 Cedrus response box.

The general design of each task was identical. Three types of infrequently occurring 'oddball' faces were presented randomly intermixed with frequently occurring standard faces. 10% of stimuli consisted of a target face, 10% were novel faces and 10% were perceptually salient standard faces. Standard faces were made perceptually salient by a black bar positioned across the face (which did not interfere with recognition of the face – see Figure 6.1), and which varied in exact position between presentation of these stimuli. The remaining 70% of stimuli consisted of the unaltered standard face.

Each face was presented for 2500 ms, with interstimulus interval varying between 1000 and 1500 ms. Both tasks consisted of 150 stimulus presentations, lasting for approximately 10 minutes duration. The target face was displayed at the start of each task

for as long as individual subjects required and was followed by a short practice session before proceeding to the main task. The practice session consisted of 20 stimulus presentations, which was repeated if necessary until subjects were confident of the task instructions – see below.

The two tasks were termed *task N* – for novelty – and *task P* – for perceptual salience. On task N, subjects were instructed to respond with the same button press whenever they detected the *target face* and whenever they encountered a *novel face*, and to withhold responses to the perceptually salient standard and unaltered standard faces – Figure 6.1A. On task P, they were instructed to respond to the *target face* and to the *perceptually salient standard faces*, and withhold responses to the unaltered standard face and novel faces – Figure 6.1B.


A – Task N
Novel face
Perceptually salient standard
Standard face
Target face
Time
10 minutes

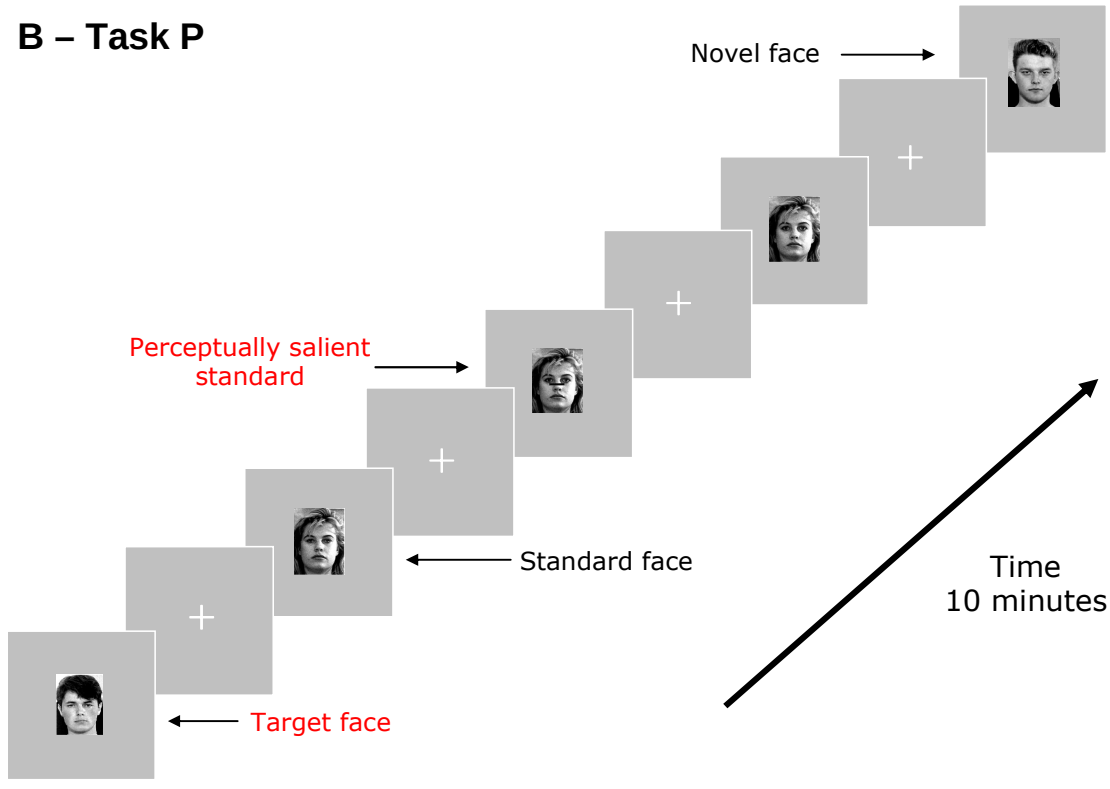

B – Task P
Novel face
Perceptually salient standard
Standard face
Target face
Time
10 minutes

Figure 6.1. 'Oddball task' design.

A. *Task N.* Subjects were instructed to respond with the same button press whenever they detected a target face or a novel face, and to withhold responses to the perceptually salient standard faces and standard face.

B. *Task P.* Participants were asked to respond to the target faces and the perceptually salient standard faces, and withhold responses to the novel and standard faces.

Each stimulus was presented for 2500 ms, with the interstimulus interval varying from 1000 to 1500 ms. Each task consisted of 150 stimuli and lasted for approximately 10 minutes.

In order to ensure that participants examined all faces, and did not merely respond to the presence of a black bar on task P, 40% of novel faces on both tasks also had a black bar, with subjects being informed of this in advance.

Both tasks were therefore identical in terms of design and the perceptual experience of subjects, differing only in terms of the responses subjects were instructed to perform. The order of task presentation was counterbalanced across the participants of each group. Median reaction time was the principal outcome measure of these tasks. Measures assessing errors made – hit rate, false alarm rate and perceptual sensitivity (see below) – were also calculated.

Participants' memory for the novel faces presented in each task was assessed following a 5 minute break, during which time they completed the Barratt Impulsiveness Scale, version 11 (BIS-11 (Patton, Stanford et al. 1995)). This memory task consisted of the 30 novel faces presented during the course of tasks P and N, randomly intermixed with an additional 30 faces which had not previously been shown. Subjects were instructed to indicate with a button press whether they had seen each face before or not. Each face stimulus remained on the screen until a decision had been made.

In addition to hit rate and false alarm rates, perceptual sensitivity, or d prime (d') was used as a behavioural outcome measure. These measures were calculated separately for faces presented on task N compared to those presented on task P. The d' index is derived from signal detection theory and computes the distance between the signal and noise distribution means in standard deviation units (Stanislaw and Todorov 1999). A d' value of 0 would indicate an inability to distinguish a target (signal) from a non-target (noise) stimulus, whereas higher values indicate better perceptual sensitivity. The formula used to calculate d' was as follows:

$$d' = \Phi^{-1}(H') - \Phi^{-1}(F')$$

H' is the corrected hit rate, F' is the corrected false alarm rate and Φ^{-1} is the inverse of the cumulative Gaussian distribution which converts probabilities into Z scores. Corrections were used in order to protect against ceiling effects (Snodgrass and Corwin 1988) and were as follows:

$$H' = (h + 0.5) / (h + m + 1)$$
$$F' = (f + 0.5) / (f + cr + 1)$$

Where *h* is the percentage of hits, *m* is the percentage of misses, *f* is the percentage of false alarms and *cr* is the percentage of correct rejections on noise trials.

Repeated measures ANOVAs were used to examine for group differences in (1) median RT on tasks P and N and (2) error data – hit rates, false alarm rates and perceptual sensitivity – on tasks P and N and (3) error data – hit rates, false alarm rates and perceptual sensitivity – on the memory task for faces presented on task N compared to those presented on task P. This was followed by *post-hoc t*-tests were appropriate.

6.2.2.2. Risk-taking

Two computerized tasks were used to assess risk-taking behaviour: the Iowa Gambling Task (IGT) and Cambridge Gambling Task (CGT). The IGT (Bechara, Damasio et al. 1994) is an established decision-making task, which has previously been used with PD patients, although with inconsistent results regarding whether or not this patient population demonstrates risk-prone decision-making (Czernecki, Pillon et al. 2002; Thiel, Hilker et al. 2003; Perretta, Pari et al. 2005; Mimura, Oeda et al. 2006; Pagonabarraga, Garcia-Sanchez et al. 2007; Kobayakawa, Koyama et al. 2008). The design of the IGT, however, makes it difficult to distinguish between different components of decision-making which may contribute to performance of the task. For example, the risk profile of

the four ‘decks of cards’ are not explicit, instead their utility must be learnt over a number of trials (see below and Figure 6.2).

In contrast, the CGT (Rogers, Everitt et al. 1999) makes the ‘odds’ of winning on a particular trial explicit and permits the separation of a number of decision-making components: quality of decision-making, risk adjustment with odds and impulsivity. However, this task has not previously been used with PD patients. For these reasons I employed both of these gambling tasks.

6.2.2.2.a. The Iowa Gambling Task

A ready-made computerized version of the IGT was used, obtained from the Psychology Experiment Building Language (PEBL) website (http://pebl.sourceforge.net/). Subjects were instructed to select cards from four decks labeled 1-4 (see Figure 6.2) in order to gain as much play money as possible. Decks 1 and 2 were associated with a large immediate reward ($100), while decks 3 and 4 produced a smaller reward ($50). However, decks 1 and 2 were also associated with larger and more frequent penalties ($-50 to $-1150), resulting in an average loss over ten trials of $-250. On the other hand, decks 3 and 4 produced smaller and less frequent penalties ($-25 to $-200) and led to an average gain over ten trials of $250. Decks 1 and 2 may therefore be termed the high risk, disadvantageous decks, while decks 3 and 4 are more conservative and advantageous.

The outcome of each trial, in terms of reward received, any associated penalty and overall gain or loss for that trial were displayed in a box in the bottom left corner of the screen.

The total amount of play money received was indicated as a figure and along a bar gauge at the bottom of the screen throughout the task, which ended automatically after 100 trials.

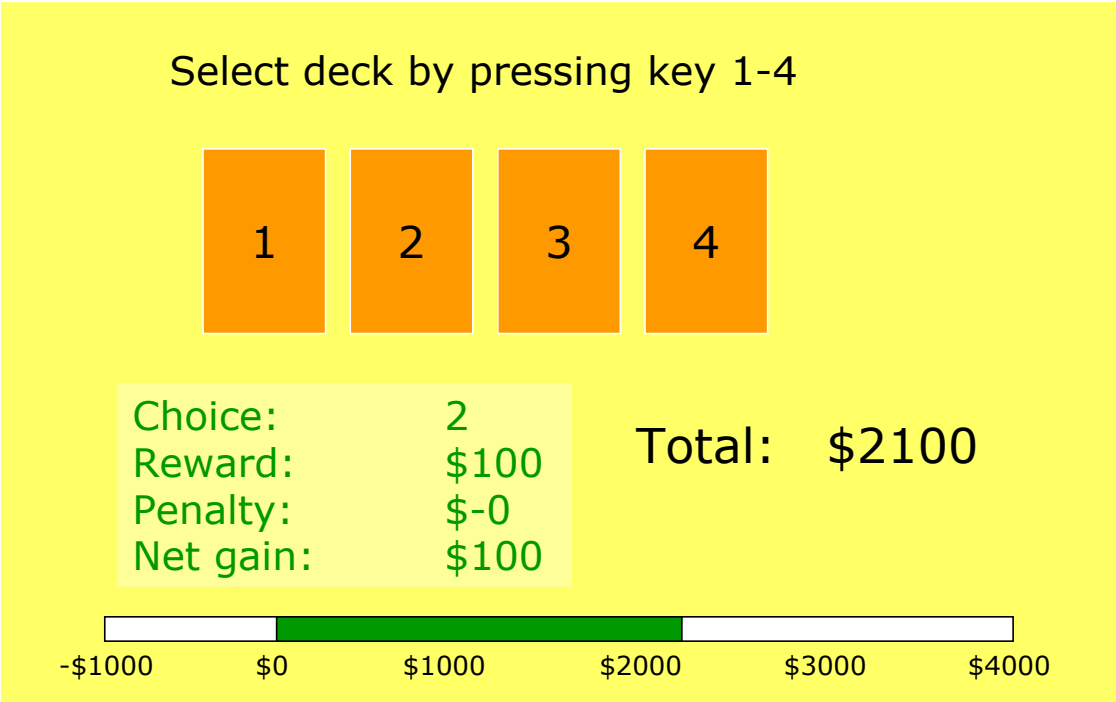


Figure 6.2. Iowa Gambling Task.

Subjects were instructed to choose cards from decks 1 to 4, by pressing keys 1 to 4 on a keyboard, in order to earn as much play money as possible. Decks 1 and 2 consistently gave out high rewards ($100), but were associated with high and frequent penalties. On the other hand, decks 3 and 4 gave out smaller rewards ($50), but were associated with smaller and less frequent penalties, so that over time, they led to higher gains. Decks 1 and 2 can therefore be considered as *disadvantageous*, while decks 3 and 4 are *advantageous*.

Subjects were not informed of this structure of gain and loss and instead had to figure it out for themselves by observing the outcome of their selections over the course of the task. Hence normal individuals typically start by sampling the high risk, disadvantageous decks most frequently at the start of the task. However, as they learn the task structure, switch to sampling the low risk, advantageous decks most often by the end of the task (Bechara, Damasio et al. 1994). Hence, in addition to assessing risk-based decision-making, the task also assesses the ability of subjects to switch set. Unlike the CGT, there is no easy way to separate these different processes.

The total number of advantageous – disadvantageous decks sampled and this difference in the first 20 compared to the last 20 trials were taken as the outcome measures of this task.

6.2.2.2.b. Cambridge Gambling Task

The CGT was obtained from Cambridge Cognition as part of a CANTAB software license. An Elo 1537L 15 inch LCD touch-screen was used for stimulus presentation and for collecting subject responses.

Subjects were told that a yellow token was hidden, on a random basis, in one of ten coloured boxes presented at the top of the display screen (see Figure 6.3). A variable proportion of the boxes were coloured red and blue and the participant had to indicate whether they thought it would be in red or blue box by touching the ‘RED’ or ‘BLUE’ panel at the bottom of the screen. The proportion of red to blue boxes varied through all of

the possible scenarios (i.e. 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9), with each scenario appearing once, in a random order, during each block of nine trials.

After making the initial choice of ‘RED’ or ‘BLUE’, the subject attempted to increase a total points score, shown on the left side of the screen, by placing a ‘bet’ on this choice being correct. The available bets appeared in a sequence, one after another, centered in a box which was displayed on the right side of the screen. Each bet was displayed for 5 seconds before being replaced by its successor, and the subject could select any bet by touching the box in which the bets were presented at any point.

Immediately following this selection, one of the red or blue boxes opened to reveal the yellow token, accompanied by either a ‘You win!’ message and a short rising musical scale or a ‘You lose!’ message with a low tone. If the participant chose the correct colour, the bet placed was added to the total point score, but if they chose the wrong colour, the bet was subtracted. Subjects were instructed to treat the points as valuable and to try to earn as many as possible, however, no monetary significance was attached to the point score.

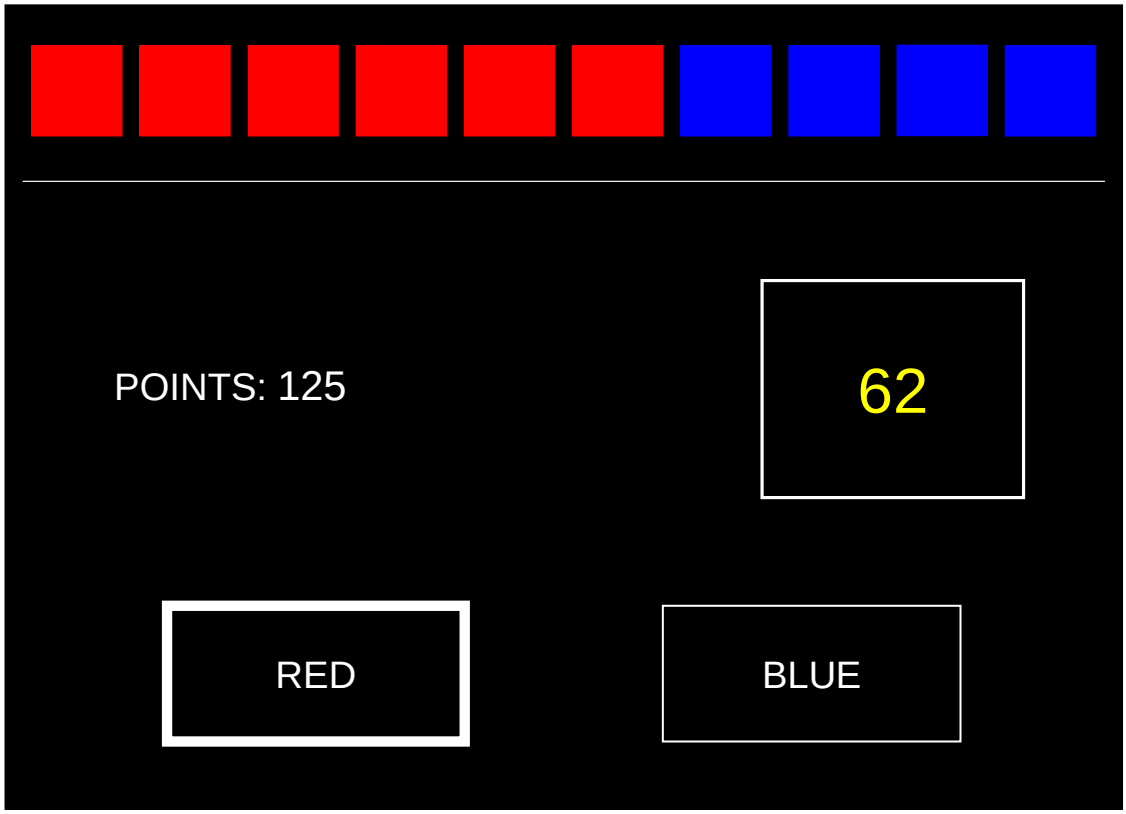


Figure 6.3. Cambridge Gambling Task.
Subjects were instructed to choose 'RED' or 'BLUE' depending on the colour box they thought was most likely to contain a yellow token. In this display, the subject has chosen the slightly more probable (6:4) 'RED' option. Note that the ratio of red to blue boxes changed from trial to trial.

Participants then had to gamble a percentage of their points (right sided box). In the *ascending* condition the points available to bet slowly increased, while in the *descending* condition the points slowly decreased. If the correct colour was chosen the number of points bet was added to the total score (on the left side of the display), but if they were wrong, these points were subtracted from the accumulated total.

Each subject performed a total of eight blocks of the task separated into two consecutive *ascending* and *descending* conditions (i.e. four ascending blocks followed by four descending blocks or vice versa). In the ascending condition, the first bet offered was small, but replaced by larger and larger bets until the subject made a selection. In the descending condition, the first bet offered was large and replaced by smaller and smaller bets until a selection was made. Each bet represented a percentage of the current total points score. Five bets were offered on each trial, so that in the ascending condition the order of available bets was: 5%, 25%, 50%, 75% and 95%; with this sequence being reversed in the descending condition. In both conditions, each bet was presented with a short tone, whose pitch corresponded to the size of the bet – higher tones accompanied larger bets and lower tones accompanied smaller bets. If the participant failed to select a bet by the end of the sequence, the last bet was automatically chosen.

Subjects commenced each block of nine trials with 100 points and were asked to try to increase this total as much as possible. If a subject's score fell to just 1 point, the current block was ended prematurely and the next begun. These events were classified as *bankruptcies*. The order of ascending and descending conditions was counterbalanced across the subjects within each group.

As discussed earlier, three features of this task are important. Firstly, the manipulation of the ratio of red to blue boxes from trial to trial makes it possible to examine the *quality of the subject's decision-making* over a variety of differentially weighted contingencies. For example, some ratios (e.g. 9 red : 1 blue) presented two contingencies that were quite

unequal in terms of the probabilities associated with their respective outcomes. In contrast, other ratios (e.g. 6 red : 4 blue) presented contingencies that were more balanced. Thus a subject's choice of contingency, speed of choice and size of bet were expected to differ as a function of the ratio of red to blue boxes.

Secondly, by allowing subjects to determine for themselves how much of their points score they wished to bet after each red/blue decision, it is possible to assess individual willingness to place already-accumulated reinforcement at risk in the hope of acquiring more reward. For example, one might suppose that a ratio of 9 red : 1 blue represents an opportunity to bet more points on a red decision in order to gain more reward, while a ratio of 6 red to 4 blue may represent a situation where more conservative behaviour is more appropriate. Finally offering bets in ascending and descending conditions affords the possibility of isolating merely impulsive behaviour from genuine risk seeking (Miller 1992). If a participant were impulsive in terms of being unable to withhold manual responses to the sequence of bets as they were presented then they would be expected to choose early bets in both the ascending and descending conditions. However, if they were actively risk-seeking, then they would be expected to choose late bets in the ascending condition, but early bets in the descending condition.

There were therefore five main outcome measures of this task:

- *Quality of decisions* – how often the subject chose the most likely outcome, i.e. the colour with the most number of boxes. The total was taken, as well as the difference between favourable (9:1) and unfavourable (6:4) conditions.

- *Risk adjustment* – the rate at which the subject increases the percentage of points bet in response to more favourable ratios (i.e. 9:1 versus 6:4).
- *Speed of decision-making* – the length of time a participant takes to choose a box colour. The median across conditions was taken, as well as the difference between favourable (9:1) and unfavourable (6:4) conditions.
- *Impulsivity* – the median difference bet between ascending and descending conditions.
- *Bankruptcies* – the number of times the subject let their point score drop to 1 or less. As the total number of blocks was eight, this was also the maximum number of times bankruptcies could occur.

6.2.3. Questionnaires

In addition to the UPDRS, ACE-R and BDI already discussed in Section 6.2.1, participants were asked to complete the 30 point Barratt Impulsiveness Scale, version 11 (BIS-11 (Patton, Stanford et al. 1995)) and the 100 point Tridimensional Personality Questionnaire (TPQ (Cloninger, Przybeck et al. 1991)). The BIS-11 provides a measure of general impulsiveness with four options for each item (rarely/never, occasionally, often and almost always/always), while the TPQ assesses novelty-seeking, harm avoidance and reward dependence with true/false items.

6.3. Results

6.3.1. Novelty processing

6.3.1.1. Reaction time data for task N and task P

A repeated measures ANOVA was used to assess differences in the mean (of median) reaction times on task P compared to task N between the four groups. Although there was no overall group effect on reaction time ($F(3,54)=1.253$, $p=0.3$), this did reveal a significant effect of task ($F(1,54)=20.864$, $p<0.001$) and importantly a significant interaction between task and group ($F(3,54)=4.302$, $p=0.009$).

As can be seen from Figure 6.4, neither the control group ($t(14)=0.885$, $p=0.391$) nor the tremor dominant group ($t(14)=0.334$, $p=0.743$) demonstrated a difference in reaction time between these two tasks. In contrast, the akinetic-rigid group ($t(13)=5.316$, $p<0.001$) and the ICD group ($t(13)=3.645$, $p=0.003$) both performed significantly more slowly on task P, when they had to respond to non-novel perceptually salient stimuli, compared to task N, when they had to respond to novel stimuli.

This suggests that PD patients with an ICD may demonstrate enhanced processing of novelty, compared to non-novel perceptual salience, as may have been predicted. However, more importantly, akinetic-rigid patients without impulse control problems also show this pattern of behaviour, in contrast to PD patients who are tremor dominant.

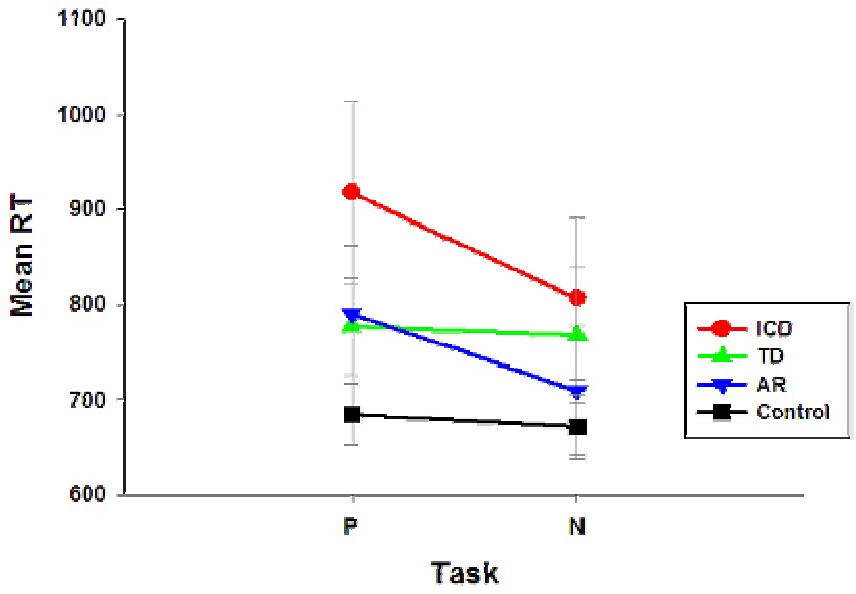


Figure 6.4. Novelty processing compared to salience processing in PD.
In contrast to healthy control subjects and tremor dominant (TD) patients, akinetic-rigid (AR) and impulse control disorder (ICD) patients performed significantly more slowly on task P, when they had to respond to non-novel perceptually salient stimuli, compared to task N, when they had to detect novel stimuli.

AR – akinetic-rigid PD patients without impulse control disorders
TD – tremor dominant PD patients without impulse control disorders
ICD – PD patients with an impulse control disorder
Control – healthy elderly control subjects

RT is measured in msec.
Error bars indicate the standard error of the mean.

Importantly, slower responses on task P (or quicker responses on task N) – across all the PD patients without ICD – were not associated with higher dose of total dopaminergic replacement therapy (r= -.271, p=0.155). The ICD patients were excluded from this analysis due to potentially confounding differences in terms of demographic variables such as duration of disease and therefore motor function. There was a significant correlation between difference in reaction on task N compared to task P with dose of *dopamine agonist* medication alone. However, this was in the <u>*opposite*</u> direction to what may have been expected given my hypotheses, with quicker responses on *task P* (to *non-novel* perceptually salient stimuli) associated with higher drug doses (r= -.404, p=0.03). Dopaminergic medication therefore did seem capable of speeding the reaction times of PD patients, but for *non-novel perceptually salient* stimuli more so than *novel* stimuli.

6.3.1.2. Error data for task N and task P

In general, few errors were made during 'oddball' tasks N and P. A repeated measures ANOVA on the hit rate data (see Figure 6.5A) revealed no significant difference between the three subject groups ($F(3,54)=1.133$, $p>0.34$). Nor was there a significant effect of task ($F(1,54)=0.073$, $p>0.78$) or an interaction between task and subject group ($F(3,54)=0.179$, $p>0.9$).

Analysis of the false alarm data (Figure 6.5B), however, did reveal a significant difference between the subject groups ($F(3,54)=3.838$, p0.015), with *post hoc* Bonferroni testing demonstrating a significant difference between the ICD patients and control subjects (p=0.032) and between the ICD and tremor dominant patients (p=0.042). There was also a

significant effect of task ($F(1,54)=7.16$, $p=0.01$), with subjects demonstrating fewer false alarms on task N – in response to novel stimuli – compared to task P – when they had to detect non-novel perceptually salient stimuli (Figure 6.5B). There was therefore no significant interaction between task and subject group ($F(3,54)=0.531$, $p>0.66$).

The hit rate and false alarm data were combined in the form of perceptual sensitivity, or d' (Figure 6.5C). A repeated measures ANOVA on this data revealed a trend towards a difference between the two tasks ($F(1,54)=3.084$, $p=0.085$), but no group effect ($F(3,54)=1.964$, $p=0.13$) or group by task interaction ($F(3,54)=1.223$, $p=0.31$).

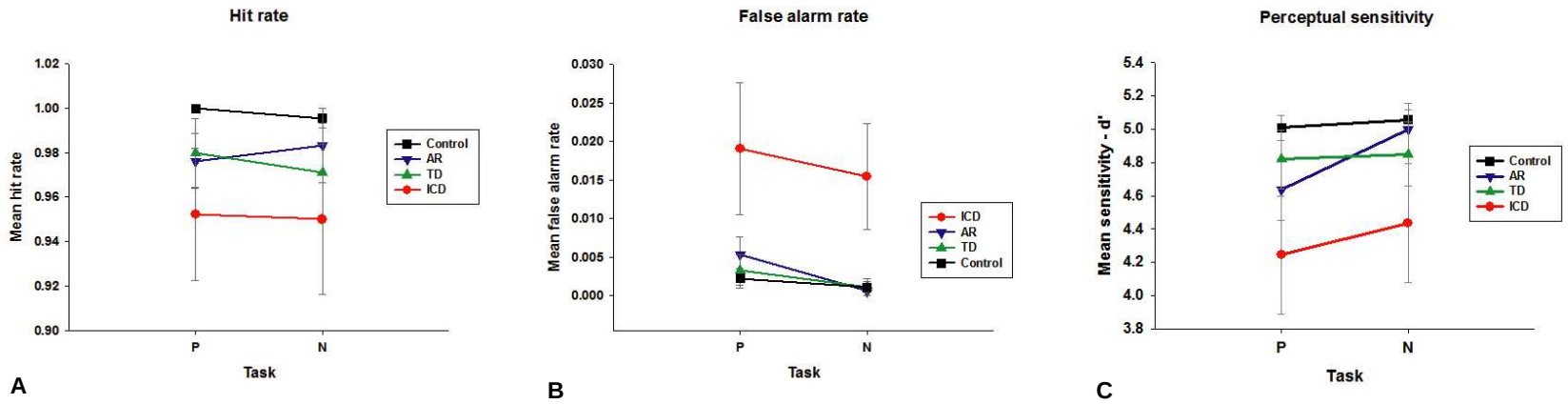


Figure 6.5. Error data on task N compared to task P.

In addition to responding more quickly on task N – when novel stimuli had to be detected – compared to task P – when non-novel perceptually salient stimuli had to be responded to – akinetic-rigid patients tended to have a higher hit rate (A), make fewer false alarms (B) and demonstrate a higher perceptual sensitivity on this task.

AR – akinetic-rigid PD patients without ICD

TD – tremor dominant PD patients without ICD

ICD – PD patients with an impulse control disorder

Control – healthy elderly control subjects

Error bars indicate the standard error of the mean.

As can be seen from Figure 6.5C, the trend towards a task effect on the d' data seems to have been driven primarily by the akinetic-rigid group being better at detecting stimuli on task N compared to task P, with a two-tailed t-test in this group just failing to reach statistical significance ($t(13)=-2.04$, $p=0.062$ – in the three remaining groups $t<0.5$ and $p>0.65$).

In summary of the error data, there is some evidence to suggest that not only were akinetic-rigid PD patients significantly quicker at detecting novel stimuli compared to non-novel perceptual salience, they also tended to be more accurate at this.

6.3.1.3. Memory Task

This enhanced speed of processing for novel stimuli in akinetic-rigid and ICD patients, was not, however, accompanied by improved recognition of the novel faces presented during task N, as can be seen from Figure 6.6.

A repeated measures ANOVA on the hit rate data from this task did not reveal a significant effect of group ($F(3,54)=0.325$, $p>0.8$), nor a significant effect of task ($F(1,54)=2.067$, $p>0.15$) or task by group interaction ($F(3,54)=1.779$, $p>0.16$). Similarly, although the akinetic-rigid and ICD patients tended to make more false alarms than the tremor dominant patients and control subjects (Figure 6.6B), a one-way ANOVA did not reveal a significant difference between subject groups ($F(3,54)=0.941$, $p>0.42$).

Likewise, a repeated measures ANOVA on the perceptual sensitivity data did not demonstrate a significant effect of group ($F(3,54)=0.709$, $p>0.5$), task ($F(1,54)=0.864$, $p=0.357$) or a group by task interaction ($F(3,54)=2.142$, $p=0.106$). In fact, there was a trend in both the ICD group and the akinetic-rigid group for memory of the faces presented in task N to be more poorly recognized. This effect, however, did not approach significance in either group (akinetic-rigid: $t(13)=0.556$, $p=0.581$; ICD: $t(13)=0.718$, $p=0.486$).

On the other hand, the tremor dominant group ($t(14)=-2.767$, $p=0.015$) and control group ($t(14)=-2.049$, $p=0.06$) were better at recognizing the faces from task N, compared to those from task P. However, it should be remembered that these faces elicited a motor response from subjects, in contrast to those presented during task P.

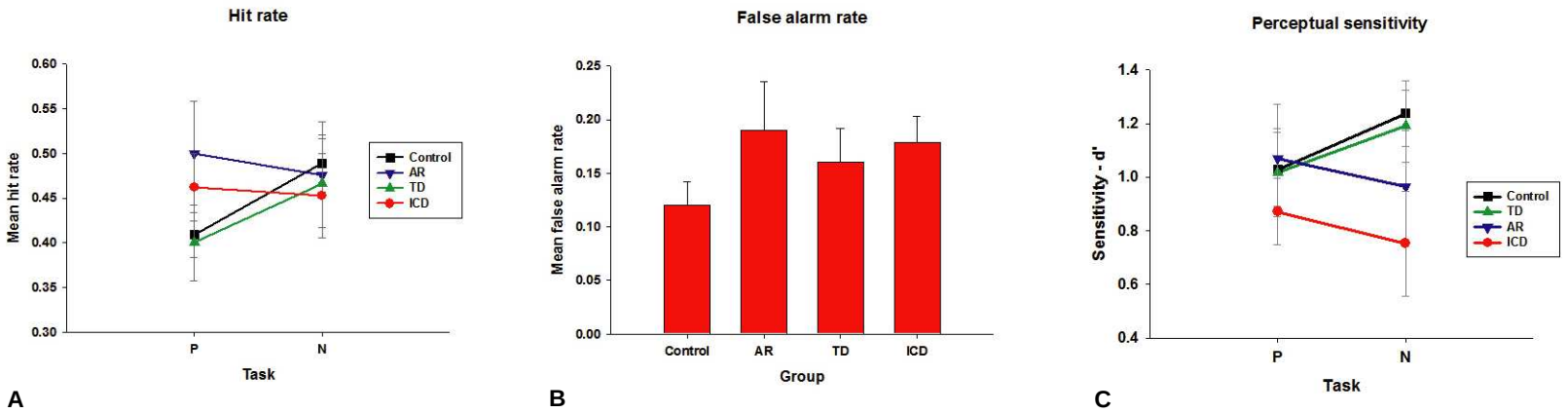


Figure 6.6. Performance on the memory task.

Despite having an enhanced speed of detection on task N, the novel faces on this task were not better recognized by the akinetic-rigid (AR) or ICD patients, in terms of hit rate (A) or perceptual sensitivity (C). The trend for these faces to be more *poorly* recognized by these patients did not reach statistical significance. Akinetic-rigid (AR) and ICD patients tended to make more false alarms than the tremor dominant (TD) patients and control subjects, although on task P, they tended to have a higher hit rate. However, neither of these effects reached significance. Error bars indicate the standard error of the mean.

AR – akinetic-rigid PD patients without ICD

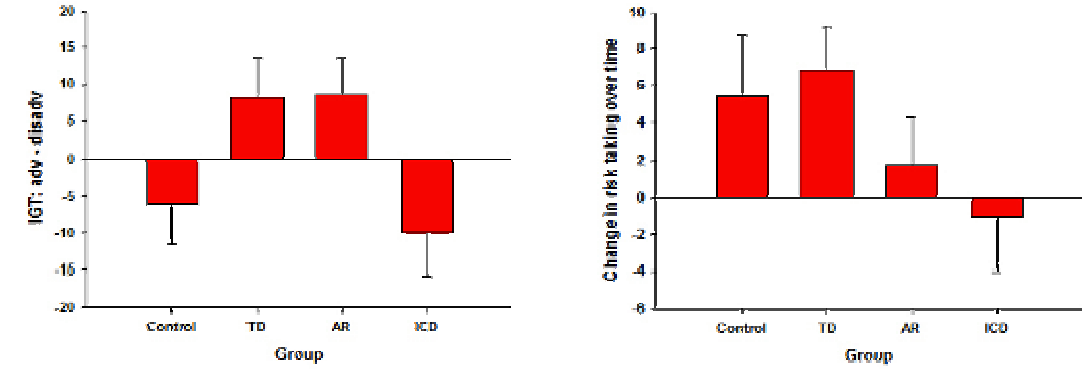
TD – tremor dominant PD patients without ICD

ICD – PD patients with an impulse control disorder

Control – healthy elderly control subjects

6.3.2. The Iowa Gambling Task

There were no significant differences between the four groups in terms of the number of advantageous versus disadvantageous decks sampled over the course of the whole task ($F(3,55)=1.492$, $p=0.227$ – Figure 6.7A). Nor was there a significant difference across the four groups in terms of the change (or switch) in sampling of the risky decks at the end (last 20 trials) compared to the start (first 20 trials) of the task ($F(3,55)=1.869$, $p=0.146$). There was, however, a trend for the ICD patients to choose the risky decks more often with time compared to the PD patients without impulse control problems ($t(40)=1.855$, $p=0.071$ – see Figure 6.7B). Importantly, there was no correlation in the ICD group between this tendency to choose risky decks more often with time and either total dose of dopaminergic medication ($r= -0.072$, $p>0.8$) or dose or dopamine agonist ($r= -0.013$, $p>0.9$).



A B

Figure 6.7. Group performance on the IGT.

A. The y-axis corresponds to the mean of the total number of advantageous – the total number of disadvantageous decks sampled by each of the groups. Negative values therefore indicate greater sampling of the disadvantageous, or risky, decks throughout the task. There were no significant group differences, although both the controls and the ICD patients tended to sample the riskier decks more often the PD patients without impulse control problems.

B. The y-axis here corresponds to the mean difference in advantageous – disadvantageous decks sampled at the start (first 20 trials) compared to the end (last 20 trials) of the task. Negative values here indicate greater sampling of the risky decks at the end (by which time the risk structure of the decks should have become apparent) compared to the beginning of the task. The difference between the ICD patients and the PD patients without impulse control problems approached significance.

Error bars indicate the standard error of the mean.

The relationship between the difference in reaction time on the oddball tasks P and N and the overall tendency to sample risky compared to conservative decks on the IGT was examined. This measure was taken rather than the difference between risky and conservative decks *with time,* as this second measure more explicitly incorporates the effect (or not) of learning – or set-switching – which should occur at the end compared to the beginning of the IGT. The correlation between these measures was examined for each subject group (n=4).

There was a significant correlation in the akinetic-rigid group alone, between the total number of risky compared to conservative decks sampled and increased speed of processing of novel compared to non-novel perceptual salience on the oddball task ($r = -0.608$, $p=0.021$ – see Figure 6.8). In other words, the quicker they were to process novel stimuli on task N compared to task P, the more they were willing to sample the risky decks on the IGT. Furthermore, there was no correlation between risk-taking on the IGT and total dose of dopaminergic treatment ($r = -0.16$, $p>0.58$), or dose of dopamine agonist ($r = -0.2$, $p>0.49$), in this group.

The only other group to demonstrate a significant correlation between performance on the IGT and the novelty oddball tasks was the control group ($r=0.686$, $p=0.007$). However, this correlation was in the <u>*opposite*</u> direction, with *increased risk-taking* behaviour being associated with *slower responses to novel* compared to non-novel salient stimuli.

In summary, there were no significant differences in performance on the IGT across the four participant groups. However, importantly, in the akinetic-rigid patients only, there was a significant correlation between increased preference for the risky decks on the IGT and quicker processing of novel stimuli on the oddball tasks. It is somewhat surprising that this correlation was not also evident in the ICD patients. However, there may have been confounding variables within this group, such as greater motor disability and more depressive symptoms.

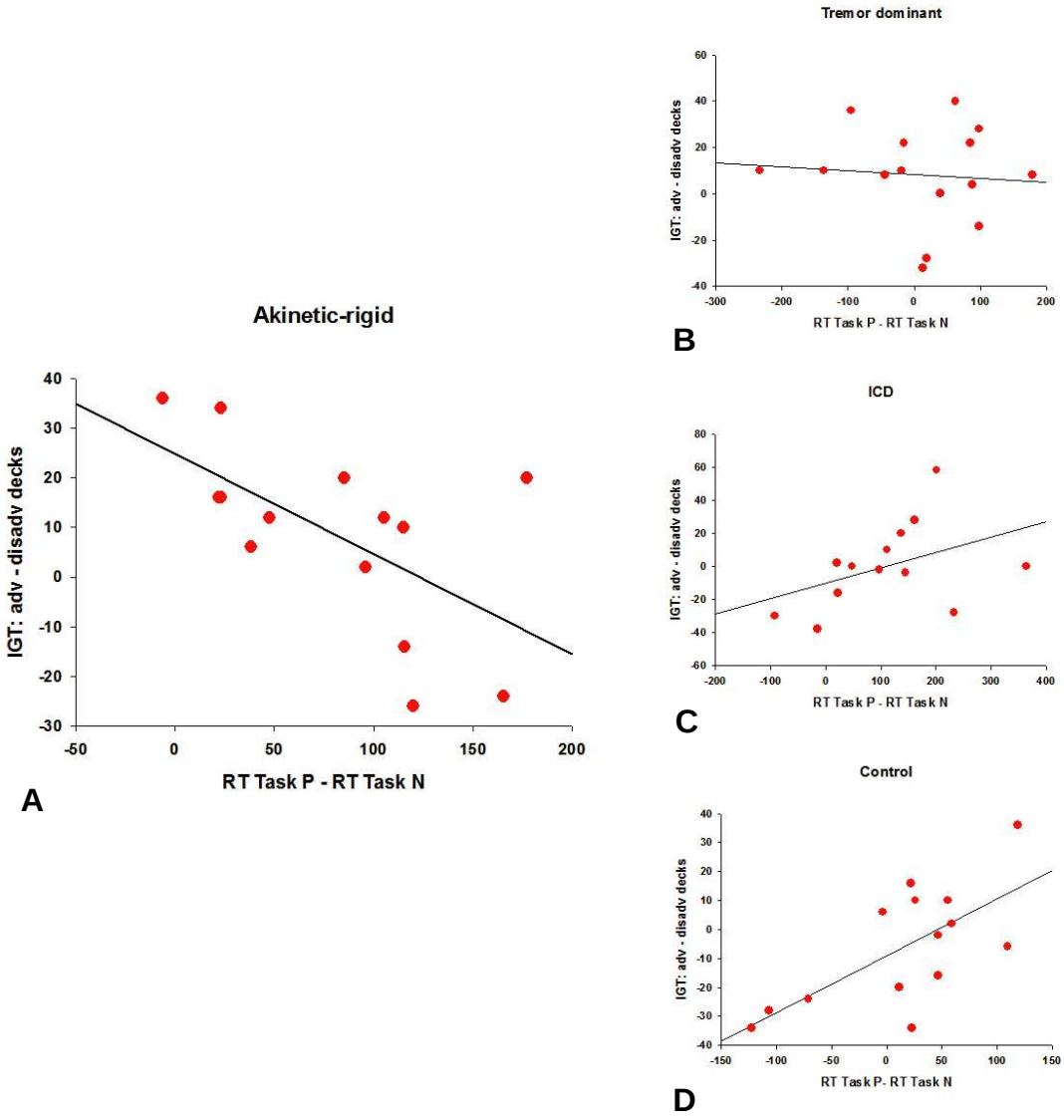


Figure 6.8. Correlation between risk-taking on the IGT and speed of novelty processing.

There was a significant correlation between increased speed of detection of stimuli on task N compared to task P (more positive values) and higher preference for the risky decks on the IGT (more negative values) – in the akinetic-rigid patients only (A). There was no correlation between these parameters in the tremor dominant (B) and ICD (C) patients. In the control subjects (D) the correlation was in the opposite direction – with speedier responses to novelty correlating with preference for the conservative decks on the IGT.

6.3.3. The Cambridge Gambling Task

There were a total of five outcome measures for this task, the results of which are summarised in Figure 6.9.

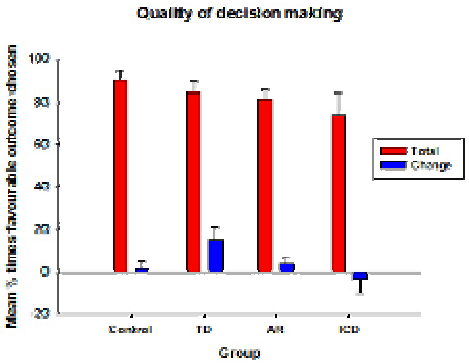
6.3.3.1. Quality of decision-making – Figure 6.9A

The total quality of decision-making was expressed as the percentage of trials on which the subject chose the box colour with the better odds. There were no significant differences between the groups on this measure ($F(3,55)=1.06$, $p=0.374$).

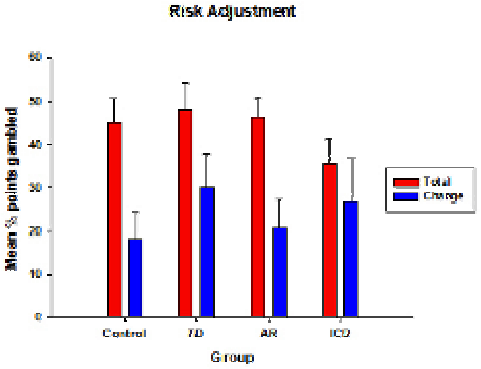
There was, however, a trend which approached significance for a difference between the groups regarding the way in which they changed their choice depending on the ratio of one box colour to another ($F(3,55)=2.673$, $p=0.057$) – i.e. highly likely to produce a win (9:1) compared to less likely to result in a win (6:4). Positive change values on Figure 6.9A indicate that the box colour with the better odds was chosen more often when the odds of winning were higher. The ICD patients demonstrated poor modulation of their decision-making being more likely to choose the box colour with the better odds when its odds of winning were *lower* rather than higher.

For all subsequent analyses, only those trials on which the box colour with the better odds was chosen are included.

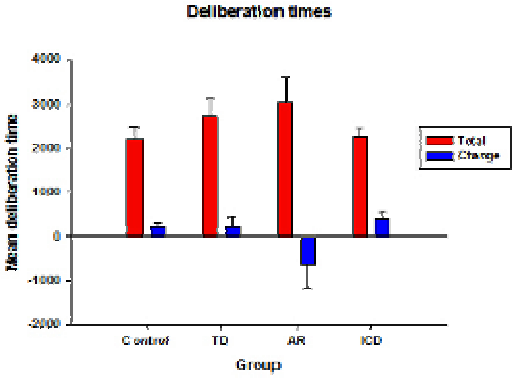
A

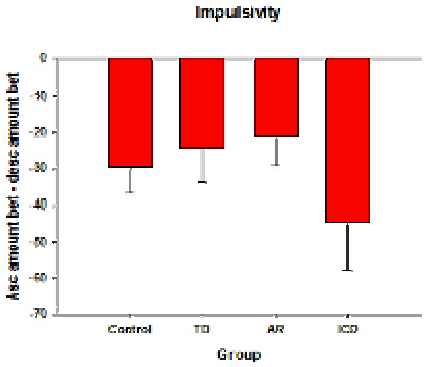

Quality of decision making
Mean % times favourable outcome chosen
100
80
60
40
20
0
-20
Total
Change
Control
TD
AR
ICD
Group

B

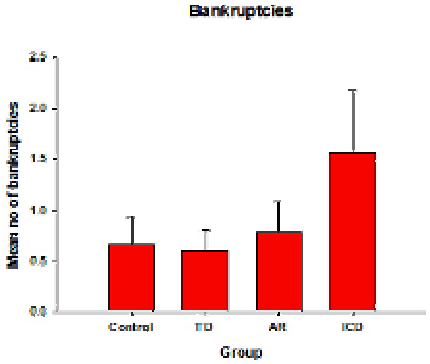

Risk Adjustment
Mean % points gambled
60
50
40
30
20
10
0
Total
Change
Control
TD
AR
ICD
Group

C


Deliberation times
Mean deliberation time
4000
3000
2000
1000
0
-1000
-2000
Total
Change
Control
TD
AR
ICD
Group


Impulsivity
Asc amount bet - desc amount bet
0
-10
-20
-30
-40
-50
-60
-70
Control
TD
AR
ICD
Group

D


Bankruptcies
Mean no of bankruptcies
2.5
2.0
1.5
1.0
0.5
0.0
Control
TD
AR
ICD
Group

E

Figure 6.9. Group performance on the CGT.

A. Total quality of decision-making is expressed as the percentage of trials on which the colour (red or blue) with the better odds was chosen by subjects The change in quality of decision-making refers to the mean of the difference in occasions when the colour with the better odds was chosen when the odds were high (9:1), compared to lower (6:4 odds). Positive change values indicate that the colour with the better odds was chosen more often when the odds were high (9:1) compared to when they were lower (6:4). Compared to the other groups, there was a trend for ICD patients to actually chose the colour with the better odds more often when the odds of winning were *lower*, rather than higher. Their overall quality of decision-making was also (non-significantly) poorer.

B. Total refers to the mean percentage of points gambled throughout the task, while change refers to the adjustment of risk-taking with the odds of winning a trial, i.e. the difference in the percentage of points gambled when the odds were high (9:1) compared to when they were low (6:4). The more positive this value, the larger the percentage of points gambled when the odds of winning were high. There were no group differences on this measure.

C. Total deliberation time refers to the mean time (ms) spent considering the colour of box to choose. Change in deliberation time refers to the difference in time considering which colour to choose when the ratio of one colour to the other was high (9:1) compared to when this was low (6:4). Higher values indicate that more time was taken when the outcome of the choice was less certain (6:4 ratio). There were no group differences on this measure.

D. Impulsivity was measured by taking the difference between the percentage of points bet on the ascending and descending conditions. Negative values here indicate higher levels of impulsivity. Although there was a trend for the ICD patients to be more impulsive here, this failed to approach significance.

E. Then mean number of bankruptcies refers to the number of times subjects let their points score fall down to one point or less. ICD patients encountered significantly more bankruptcies than the PD patients without impulse control problems. This perhaps relates to their tendency to make poorer decisions (graph A).

Error bars indicate the standard error of the mean.

6.3.3.2. Risk-taking and risk adjustment – Figure 6.9B

There were no significant differences between the groups in terms of the overall percentage of points they were willing to gamble ($F(3,55)=0.148$, $p>0.9$). Nor was there a group difference in the way in which this willingness to risk points was modulated by the odds of winning, i.e. a 9:1 colour ratio compared to a 6:4 colour ratio ($F(3,55)=0.554$, $p>0.6$) – all groups increased the amount they gambled with better odds, and to a similar extent.

6.3.3.3. Deliberation times – Figure 6.9C

There were no significant differences between the groups in terms of the length of spent deciding which box colour to choose ($F(3,55)=0.82$, $p>0.48$). Changes in deliberation time with the odds of winning (time spent deciding with 6:4 odds – time spent considering 9:1 odds) were also not significantly different across the groups ($F(3,55)=1.687$, $p=0.181$).

6.3.3.4. Impulsivity – Figure 6.9D

Impulsivity on the CGT can be measured by comparing the amount bet on the ascending and descending conditions. Negative values in Figure 6.9D indicate that more points were consistently gambled during the descending condition and that there was a tendency to respond earlier rather than later in both conditions, regardless of the number of points at stake. All groups appear to be impulsive on this task and although Figure 6.9D suggests that the ICD patients may be more inclined to respond impulsively, there are no significant group effects ($F(3,55)=1.011$, $p>0.39$).

The apparent impulsivity of all subjects may represent a flaw in the design of the CGT. The whole task takes about 30 minutes to complete and is somewhat repetitive, with the ascension and descension of points being quite slow. Subjects may therefore respond more quickly during the betting phase at the end of the task due to boredom rather than true impulsivity, a factor which is not accounted for with consecutive ascending followed by descending blocks (or vice versa). Placing bets earlier during either the last part of the ascending or descending condition will have the effect of making the subject appear more impulsive. Alternating ascending and descending blocks may therefore have improved the task in this respect by removing this bias.

6.3.3.5. Bankruptcies – Figure 6.9E

The difference between the four groups in terms of the number of times they let their point score drop down to one or less approached statistical significance ($F(3,55)=2.462$, $p=0.073$). Importantly, the difference in the number of bankruptcies between the ICD patients and the PD patients without impulse control problems did reach statistical significance ($t(39)=-2.481$, $p=0.018$).

The higher frequency of bankruptcies in the ICD patients likely relates to the trend they demonstrated towards poorer decision-making, as this was the only other measure on which they appeared to differ. The number of bankruptcies experienced by the ICD patients on this task did not correlate with either total dose of dopaminergic therapy ($r=0.345$, $p=0.272$) or dose of dopamine agonist ($r=0.229$, $p=0.475$).

To summarise, the principal finding from the CGT was that ICD patients demonstrated a higher likelihood of encountering bankruptcies compared to PD patients without impulse control problems, with this possibly being related to their tendency to make poorer decisions.

6.3.4. Questionnaires

There were no significant differences across the four groups on any of the three dimensions of the TPQ (Cloninger, Przybeck et al. 1991) or the BIS-11 (Patton, Stanford et al. 1995) - see Figure 6.10 ($F(3,54)<1.6$, $p>0.2$). There was, however, a trend for the ICD patients to be more reward dependent than the PD patients without impulse control problems ($t(38)=-1.403$, $p=0.169$) and for the tremor dominant patients to be more harm avoidant than the akinetic-rigid patients ($t(26)=-1.561$, $p=0.131$).

These questionnaires, however, rely on subjective responses and are therefore likely to be less sensitive than objective behavioural measures. The trends identified above, may have become statistically significant if larger groups of subjects had been used.

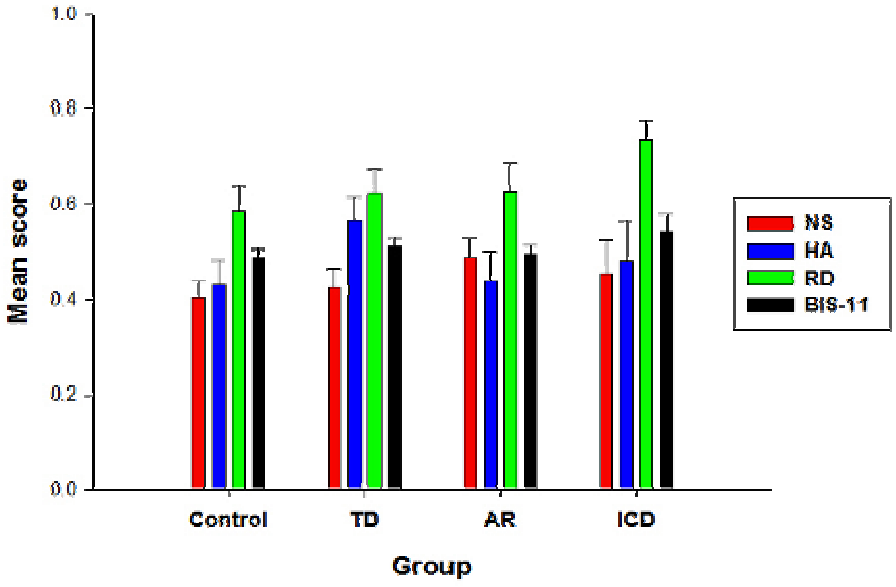


Figure 6.10. Personality questionnaires.

There were no significant differences between the groups on the three components (novelty-seeking, harm avoidance and reward dependence) of the Tridimensional Personality Questionnaire (TPQ) or the Barratt Impulsivity Scale (BIS-11). There was, however, a trend for the ICD patients to be more reward dependent than the other participants and for tremor dominant patients to be more harm avoidant than akinetic-rigid patients.

NS – novelty seeking on the TPQ
HA – harm avoidant on the TPQ
RD – reward dependent on the TPQ
BIS-11 – Barratt Impulsivity Scale

Error bars indicate the standard error of the mean.

6.4. Discussion

One of the principal findings of this chapter is that akinetic-rigid PD patients dissociate from tremor dominant patients in terms of their ability to process stimulus novelty. Akinetic-rigid patients were significantly slower on task P, when they had to respond to non-novel perceptually salient stimuli, compared to task N, when they were instructed to respond to novel stimuli (Figure 6.4), and by inference therefore, appeared able to process novelty more quickly.

On the other hand, tremor dominant PD patients, as well as healthy control subjects, responded equally quickly across the two tasks. These reaction time findings were mirrored by the perceptual sensitivity data from these tasks, with akinetic-rigid patients tending to be more accurate on task N compared to task P, while the tremor dominant patients and controls were equally accurate across the two tasks (Figure 6.5).

Importantly, the overall willingness to sample the risky compared to conservative decks on the IGT correlated with quicker reaction times on task N, in the akinetic-rigid patients only (Figure 6.8), although the akinetic-rigid patients were not significantly different in their performance on the IGT compared to tremor dominant patients. Crucially, neither faster responses to novelty, nor increased willingness to make risky decisions correlated with the total dose of dopaminergic medication or the dose of dopamine agonist in the akinetic-rigid group.

ICD patients too, were found to have quicker reaction times on task N compared to task P (Figure 6.4), as well as demonstrating a trend to sample the risky decks on the IGT more often *as time on the task progressed* (Figure 6.7B). This therefore suggests that an impairment in learning task contingencies and the ability to switch set may also be an important factor in the performance of this task, in addition to risk-taking per se. The ICD patients also encountered significantly higher numbers of bankruptcies on the CGT (Figure 6.9E), compared to the PD patients without impulse control problems, which may have been related to their trend to demonstrate poorer decision-making on this task (Figure 6.9A). There were not, however, any significant correlations between these measures and either total dose of dopaminergic medication or dose of dopamine agonist.

Interestingly, only 14% of the ICD patients tested here demonstrated a tremor dominant motor phenotype, with the remaining patients being classified as either akinetic-rigid or mixed. Another possibly important observation regarding my ICD patients is that the two tremor dominant patients both had disease durations of less than 5 years, whilst the akinetic-rigid ICD patients had generally received their diagnosis more than 10 years earlier (Table 6.1). As discussed in the introductory section of this chapter, tremor dominant patients may often progress to become mixed, or even akinetic-rigid, in motor phenotype with time, while the reverse scenario seems to occur only rarely (Alves, Larsen et al. 2006). It is therefore possible that these few tremor dominant ICD patients may subsequently progress to the akinetic-rigid motor phenotype, as longer disease duration seems to allow progression or conversion to akinetic-rigid PD.

This observation, together with the fact that akinetic-rigid patients appear to process novelty quicker that non-novel perceptual salience, a finding which correlated with risk-taking on the IGT, suggests that the akinetic-rigid sub-group of PD patients may be more susceptible to the development of impulse control problems than those who are tremor dominant. The fact that neither novelty processing, nor risk-taking behaviour, was found to correlate with dose of dopaminergic therapy suggests that *motor phenotype* – and the underlying neurobiology – (perhaps in addition to longer disease duration) may be more important in generating a vulnerability to impulse control problems than dopaminergic medication, contrary to previous reports (Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007). Of course, it may also be that an interaction between dopaminergic medication and neuropathological differences between akinetic-rigid and tremor dominant groups defines vulnerability to developing ICD.

Interestingly, faster reaction times by akinetic-rigid and ICD patients on task N (respond to the novel faces) was not accompanied by improved recognition of these faces, in comparison to the novel faces presented during task P, which did not require a motor response (Figure 6.6). This occurred even though these stimuli had reliably been associated with motor responses (indicated by the high perceptual sensitivity for task N compared to task P – Figure 6.5).

In fact, there was some indication that the faces from task N were more *poorly* recognised than those from task P by these patients, while tremor dominant and healthy controls

demonstrated the reverse trend – although these effects did not approach statistical significance in any of the groups (Figure 6.6C).

Nevertheless, it can be concluded that faster processing of stimulus novelty by akinetic-rigid and ICD patients seems not to have been associated with enhanced entry into memory. It is possible that this may be related to cortical Lewy body pathology and associated cognitive deficits, which are more likely to occur in akinetic-rigid patients (Selikhova, Williams et al. 2009); most of the ICD patients were in fact also of akinetic-rigid motor phenotype. Although there were no significant differences between the PD groups examined here in terms of the MMSE and ACE-R, it is possible that there may have been more subtle deficits in the ICD (and akinetic-rigid) patients, and that in the wider patient population this may play a role in the development of impulse control problems.

It should also be acknowledged that the potential confounding factors of longer disease duration and higher depression scores in ICD patients, although not manifesting in significant differences in terms of the MMSE and ACE-R, may have played a role in some of the effects observed – such as the higher number of bankruptcies on the CGT that the ICD patients demonstrated.

6.4.1. Akinetic-rigid and tremor dominant subtypes of PD

As discussed in the introduction to this chapter, evidence is accumulating for pathological differences between the akinetic-rigid and tremor dominant subgroups of PD. The brains

of akinetic-rigid patients have been shown to have higher levels of neuronal loss and gliosis within the midbrain (Paulus and Jellinger 1991), compared to those of tremor dominant patients, and greater reductions in dopamine levels within the internal segment of the globus pallidus (Rajput, Sitte et al. 2008). Akinetic-rigid patients have also been shown to have a higher cortical load of Lewy bodies (Selikhova, Williams et al. 2009), and to be more susceptible to cognitive decline (Allcock, Kenny et al. 2006; Burn, Rowan et al. 2006; Selikhova, Williams et al. 2009).

Single photon emission computed tomography (SPECT) (Vermeulen, Wolters et al. 1995; Asenbaum, Brucke et al. 1997) and positron emission tomography (PET) (Nahmias, Garnett et al. 1985; Brooks, Ibanez et al. 1990) studies demonstrate reduced ligand binding to dopaminergic receptors in the basal ganglia of patients with PD, indicating lower receptor density, compared to healthy control subjects. However, while the severity of bradykinesia and rigidity has been found to correlate with the reduction in ligand binding in the caudate and putamen in PD patients, *no such relationship has been found with the severity of tremor* (Eidelberg, Moeller et al. 1990; Antonini, Vontobel et al. 1995; Otsuka, Ichiya et al. 1996; Tissingh, Bergmans et al. 1998). Therefore, whilst functional degeneration of the nigrostriatal system seems to correlate with the severity of bradykinesia and rigidity in PD, the severity of tremor may relate to different mechanisms, perhaps involving thalamocortical circuits (Antonini, Moeller et al. 1998).

The recording of local field potentials (LFPs) from the subthalamic region of patients with PD, by macroelectrodes used for high frequency stimulation in advanced disease, have

demonstrated an exaggerated oscillatory synchronisation of neuronal activity mainly in the beta band (15-35 Hz), but also over a lower range (8-15 Hz) (Brown and Williams 2005; Hammond, Bergman et al. 2007). It has been suggested that excessive synchronisation in this band may contribute to some of the motor symptoms of PD (Brown 2003; Brown 2007). This theory is supported by the finding of a reduction in beta power which occurs before and during movement (Levy, Ashby et al. 2002; Kuhn, Williams et al. 2004), in addition to there being a strong relationship between reaction times and suppression of beta activity within the subthalamic nucleus (STN) of PD patients (Kuhn, Williams et al. 2004).

It has been shown that dopaminergic medication can reduce the LFP power recorded from the STN over the 8-35 Hz frequency range, and that this correlates with improvement in motor impairment, as assessed by the UPDRS. More importantly, however, is the fact that this medication-induced reduction in oscillatory activity correlates with improvement in akinesia and rigidity, but *not with tremor* (Kuhn, Kupsch et al. 2006; Kuhn, Tsui et al. 2009). It is possible that oscillations over the lower frequency ranges may correlate with tremor (Raz, Feingold et al. 1996; Levy, Hutchison et al. 2000). However, this evidence is not conclusive, with current opinion being that tremor may have evolved as a downstream compensatory mechanism, perhaps involving low frequency oscillatory activity in cortical loops with the basal ganglia *and* cerebellum (Rivlin-Etzion, Marmor et al. 2006).

In sum, these findings regarding basal ganglia oscillatory activity, in addition to the earlier SPECT and PET studies, provide further evidence of a distinction between akinetic-rigid

and tremor dominant PD. The pathological, biochemical and neurophysiological differences discussed here may underlie the dissociation I have found regarding novelty processing and risk-taking behaviour between these two subtypes of PD, as well as the difference in susceptibility to cognitive decline and motor phenotype. One particularly attractive theory regarding vulnerability to ICD, which I have found to be associated with speedier novelty processing and increased willingness to take risks, is the mesolimbic overdose hypothesis (Dagher and Robbins 2009). This situation may be more likely to occur in akinetic-rigid PD secondary to some of the pathophysiological differences described above.

6.4.2. The mesolimbic overdose hypothesis

It has been reported that ICD in PD patients is often associated with the presence of dyskinesias (Voon, Potenza et al. 2007; Voon, Fernagut et al. 2009), involuntary movements that are due to excessive dopaminergic stimulation. In fact, nine of the fourteen ICD patients reported in this chapter suffered from dyskinesias to varying degrees. Furthermore, ICD symptoms are often found to abate after reductions in dopaminergic treatments (Weintraub 2008; Antonini and Cilia 2009; O'Sullivan, Evans et al. 2009). Hence it would seem likely that elevated levels of dopamine neurotransmission may play a role in the development of ICD.

As discussed in Chapter 1, it is possible to distinguish separate sensorimotor, cognitive and limbic regions of the striatum, based on their connections with the cerebral cortex (Parent 1990), a finding that has also been reported *in vivo* in the human brain using MRI

tractography techniques (Draganski, Kherif et al. 2008). The *ventral striatum* receives input from limbic areas, such as the hippocampus, amygdala and orbitofrontal cortex, and has been implicated in drug addiction (Robbins and Everitt 1999). It is therefore possible that excessive limbic dopaminergic stimulation is involved in the development of ICD. If this is the case, PD patients with relative preservation of ventral striatal dopamine projections may be at increased risk of developing such problems (Dagher and Robbins 2009).

Indeed, it has been documented that in PD, dopamine neurons projecting to the ventral striatum are less severely affected by the disease process (Kish, Shannak et al. 1988; Goto, Hirano et al. 1989). This therefore raises the possibility that pharmacological restoration of dopamine transmission in the *dorsal* (motor) striatum may lead to *overdosing* of the *ventral* striatum, with excessive dopamine receptor stimulation leading to adverse effects (Swainson, Rogers et al. 2000).

This hypothetical difference in baseline dopamine levels between the dorsal and ventral striatum may also account for the finding that levodopa improves performance on cognitive tasks thought to involve the dorsal striatum, such as working memory and task-set switching, whilst causing deficits in tests thought to depend on the ventral striatum, such as reversal learning and gambling tasks (Cools, Barker et al. 2001; Cools 2006). This ventral overdose hypothesis is further supported by neuroimaging studies, which show that the normal signal that arises from the ventral striatum when subjects must reverse a

previously learned response is abolished in PD patients treated with levodopa, in parallel with impaired task performance (Cools, Lewis et al. 2007).

Another factor which may contribute to mesolimbic overdosing is sensitisation, which refers to an increased effect of stimulant drugs with repeated administration (Paulson and Robinson 1995). Sensitised animals are more likely to self-administer drugs and there is also evidence that PD patients with addiction (compulsive medication overuse) express sensitisation in the ventral striatum (Evans, Pavese et al. 2006). Evans and colleagues used PET to measure dopamine release in response to a single dose of levodopa in PD patients with and without compulsive medication overuse. Levopdopa caused dopamine release in the motor striatum in both groups in equal measure. However, only the addicted group demonstrated significant dopamine release in the ventral striatum, indicating sensitisation. Sensitisation to amphetamine has also been shown in the ventral part of the striatum in control subjects using PET (Boileau, Dagher et al. 2006), with this being proportional to novelty-seeking as measured by the TPQ (Cloninger 1987; Cloninger, Przybeck et al. 1991).

PD patients with ICD can therefore be hypothesised to have an overactive mesolimbic system (Dagher and Robbins 2009). So too might akinetic-rigid patients without ICD, on the basis of their behaviour as revealed in this chapter, although to a lesser extent. The observation that, at least in this sample, the majority of ICD patients were of akinetic-rigid motor phenotype supports this contention. The fact that akinetic-rigid patients seem to have the most severe pathology on post-mortem examination (Paulus and Jellinger 1991;

Rajput, Sitte et al. 2008; Selikhova, Williams et al. 2009) also suggests the possibility that greater degeneration in some areas, may lead to enhanced compensatory mechanisms, which may also occur in areas that are relatively spared – perhaps including the mesolimbic system – so that such regions become overactive. More advanced symptoms would also necessitate higher medication doses, which may compound the problem. The ICD patients tested here, did in fact have more severe parkinsonian symptoms than those patients without ICD (Table 6.1), in addition to a longer duration of disease.

The hypothesis that akinetic-rigid patients, as well as those with ICD, might have more advanced degeneration in the nigrostriatal system, as compared to the mesolimbic system, will be tested in the next chapter using structural MR imaging.

The mesolimbic dopaminergic system has been shown to be activated by novelty (Bunzeck and Duzel 2006; Bunzeck, Schutze et al. 2007) in addition to rewarding stimuli (Delgado, Nystrom et al. 2000; Holroyd and Coles 2002; Frank, Woroch et al. 2005). Hence the mesolimbic overdose hypothesis is also an attractive explanation for the findings regarding novelty processing in this chapter.

6.4.3. Mechanisms by which dopaminergic activity may modulate novelty processing and risk-taking behaviour

As discussed in Chapter 1, phasic dopaminergic activity has been considered to act as a reward *prediction error*. This has been postulated to underlie the teaching signal in reinforcement learning theories, where learning is driven by deviations or 'errors' between

the predicted time and amount of rewards and their actual experienced times and magnitudes (Schultz, Dayan et al. 1997).

However, other theories have taken into account evidence that dopamine also appears to have motivating and activating effects independent of learning, where the emphasis has been on dopamine enhancing reward-seeking behaviours by acting on attention, arousal, movement and effort (Salamone, Correa et al. 2005; Robbins and Everitt 2007). For example the incentive salience hypothesis, in which dopamine firing is thought to exaggerate the incentive properties of environmental stimuli, turning them into 'objects of desire' (Berridge and Robinson 1998).

These models are not, however, mutually exclusive. It has been shown in some learning paradigms that changes in phasic dopamine bursts occur immediately before a reward-seeking action and again once the reward is actually received (Phillips, Stuber et al. 2003). Hence phasic dopamine may act both as a learning signal and as an incentive signal. One computational approach by McClure and colleagues has tried to reconcile the two models, suggesting that the reward prediction error signal also biases neural activity in favour of actions or stimuli predictive of reward (McClure, Daw et al. 2003). In their scheme dopamine not only encodes reward prediction error for the purpose of learning, but also the expected future reward rate, which is very similar to incentive salience (with the incentive salience of an environmental stimulus being equal to its reward prediction).

This scheme has been expanded by Niv and colleagues, who propose that dopaminergic stimulation is a running average of recent rewards and therefore an index of likely future rewards (Niv, Daw et al. 2007). Such a proposal would suggest that in states of high dopaminergic activity, choices may be biased towards reward-predicting actions or stimuli, but may also function to energise and invigorate the individual, such that when expected rewards are high, there is a cost of inactivity.

A conceptual link between the learning model just described and addictive or novelty-seeking behaviour is supported by recent human and animal studies examining naturally occurring variations in dopamine function. In humans two polymorphisms that determine dopamine D2 receptor expression have been associated with impulsivity and vulnerability to drug addiction, and both appear to influence performance on a probabilistic task that distinguishes positive from negative feedback learning (Klein, Neumann et al. 2007; Jocham, Klein et al. 2009). The TAQ-1A polymorphism modulates D2 receptor density, with the A1 allele being associated with lower expression of D2 receptors, in addition to impulsivity, addiction and compulsive behaviours (Comings, Rosenthal et al. 1996). Individuals with this allele are better at learning from positive feedback, but poorer at learning from negative feedback, than subjects without the allele. The two groups also differ in their reward-related response in the ventral striatum as measured with fMRI (Klein, Neumann et al. 2007).

It is therefore plausible that impulsivity, addiction and other risky behaviours, as well as novelty-seeking, may partly be explained by an inability to learn from negative feedback –

a trait which the ICD patients from this chapter tended to demonstrate on the CGT (figure 6.10A). As discussed in Chapter 1, negative reward prediction errors (i.e. when an expected reward fails to arrive) are signalled by pauses in dopamine neuron firing. Persistent postsynaptic dopamine stimulation, as occurs when chronic dopaminergic medication is used – as in PD – may therefore reduce the ability of these pauses to influence learning.

This scheme accounts for reports of the difficulty medicated PD patients have in negative feedback learning (Frank, Seeberger et al. 2004; Cools, Lewis et al. 2007), which is also a consistent feature of the human (Frank, Moustafa et al. 2007; Klein, Neumann et al. 2007) and animal (Belin, Mar et al. 2008) dopamine-related impulsive phenotypes. It is in fact, easy to appreciate how insensitivity to the adverse consequences of an action may promote the taking of disproportionate risks.

These theories are also well supported by recent findings on the cellular neurophysiology of striatal dopamine. A well-validated model of the cortico-striatal system divides it into direct and indirect pathways (Albin, Young et al. 1989). The direct pathway contains D1 dopamine receptors and is primarily involved in action selection, while the indirect pathway contains D2 receptors, with the principal role of response inhibition (Mink 1996). In addition to phasic bursts of dopamine, slow bursts of dopamine neuron activity control tonic dopamine levels, which act via the D2 receptor. The large transient increases in dopamine, which occur following phasic bursts, are able to activate the lower affinity D1 receptor (Grace 2008). A further model proposes that phasic bursts following unexpected

rewards promote positive reinforcement within the direct pathway, via the D1 receptor, whilst withheld rewards or punishments, by reducing tonic dopamine levels, lead to negative reinforcement via reduced signalling in the indirect pathway (Cohen and Frank 2009).

In fact, it has recently been shown that D1 stimulation and lack of D2 stimulation both promote long term potentiation at the cortico-striatal synapses of the direct and indirect pathways respectively (Shen, Flajolet et al. 2008). Thus it is likely that both tonic and phasic dopamine signalling shape striatal synaptic plasticity, whether in the normal situation – learning – or pathological situation – addiction or compulsive behaviours. Persistent pharmacological stimulation, as is the case in medicated PD patients, could therefore potentiate positive reinforcement learning and impair learning from punishments, increasing engagement in reward-seeking behaviours and at the same time reducing the ability to disengage from risky behaviours leading to negative consequences (Dagher and Robbins 2009).

Such an account sits well with the association of dopaminergic medication, particularly the use of dopamine agonists, with the development of ICDs in PD patients (Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007). However, it does not preclude the mesolimbic overdose hypothesis discussed earlier (Dagher and Robbins 2009). Instead, it suggests to me, that possible mesolimbic, or ventral, overdose in akinetic-rigid PD may render these patients relatively more susceptible to the development of these problems. Nevertheless, this theory would suggest that these behaviours may be seen even in the

absence of ventral striatal hyperstimulation (tremor dominant patients perhaps), although this situation is likely to be less common.

6.4.4. Summary

The results of this chapter suggest that PD patients with ICD process stimulus novelty more quickly than non-novel perceptual salience, in addition to demonstrating riskier behaviour on gambling tasks compared to PD patients without impulse control problems. More interestingly, however, is that akinetic-rigid PD patients (without impulse control problems), unlike tremor dominant PD patients and control subjects, also demonstrated quicker processing of novel compared to non-novel yet salient stimuli. The akinetic-rigid patients did not perform significantly differently on the gambling tasks compared to tremor dominant patients. However, quicker processing of novel events correlated with increased risk-taking on the IGT in this group of PD patients only. Importantly, neither quicker processing of novelty nor increased risk-taking behaviour correlated with dose of dopaminergic medication in either the akinetic-rigid or ICD patients.

I believe these results suggest that akinetic-rigid patients may be more vulnerable to the development of ICD, a proposal supported by the high proportion of my ICD patient sample found to be of the akinetic-rigid motor phenotype.

I hypothesise that novelty seeking and impulsive, risk-taking behaviour may be related to relative overdose of the mesolimbic dopaminergic system in PD. Accordingly, I predict that ICD patients, as well as akinetic-rigid patients without ICD, may have relative

preservation of the mesolimbic system in the context of more severe degeneration of the nigrostriatal system. I would hypothesise tremor dominant PD patients on the other hand, to have more equal levels of degeneration in mesolimbic and nigrostriatal systems, making them less susceptible to impulse control problems. This proposal will be investigated in the next chapter using structural MR imaging techniques.

Chapter 7

7.1. Introduction

The results obtained in Chapter 6 suggest that the two major subgroups of patients with Parkinson's disease (PD) – the akinetic-rigid and tremor dominant subtypes – may differ in terms of their behaviour, in addition to their motor phenotype. Like PD patients with impulse control disorders (ICD), akinetic-rigid patients (without ICD) were found to process novel stimuli more quickly than non-novel perceptually salient stimuli. Unlike the ICD patients, however, the akinetic-rigid patients without ICD did not demonstrate riskier behaviour on gambling tasks. Nevertheless their willingness to take risks on the Iowa Gambling Task (IGT) did correlate significantly with faster responses to novel stimuli compared to non-novel yet salient stimuli. Importantly, neither quicker processing of novelty nor increased willingness to take risks, correlated with dose of dopaminergic medication or dose of dopamine agonists.

Accordingly, I hypothesised that the akinetic-rigid motor phenotype may be important in generating a susceptibility to the development of impulse control problems, a proposal supported by the fact that the majority of my ICD sample in Chapter 6 were of the akinetic-rigid motor phenotype. This hypothesised susceptibility may interact with factors previously identified as being associated with the development if ICD, such as the use of dopamine agonists (Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007).

7.1.1. Pathophysiological differences between the akinetic-rigid and tremor dominant subtypes

As discussed in Chapter 6, there are various strands of pathophysiological evidence that support a distinction between the akinetic-rigid and tremor dominant subtypes of PD. Akinetic-rigid patients have been shown to have higher levels of neuronal loss and gliosis within the midbrain (Paulus and Jellinger 1991), compared to tremor dominant patients, and greater reductions in dopamine levels within the internal segment of the globus pallidus (Rajput, Sitte et al. 2008). Akinetic-rigid patients have also been shown to have a higher cortical load of Lewy bodies (Selikhova, Williams et al. 2009), which may also explain their increased vulnerability to cognitive decline (Allcock, Kenny et al. 2006; Burn, Rowan et al. 2006; Selikhova, Williams et al. 2009).

PET and SPECT studies have found that nigrostriatal degeneration in PD correlates with bradykinesia and rigidity, but *not with tremor* (Eidelberg, Moeller et al. 1990; Antonini, Vontobel et al. 1995; Otsuka, Ichiya et al. 1996; Tissingh, Bergmans et al. 1998), suggesting that tremor may relate to different mechanisms. Furthermore, it has been reported that dopaminergic medication can reduce oscillatory activity in the subthalamic nucleus, a finding which correlates with a reduction in akinesia and rigidity, but again, *not with tremor* (Kuhn, Kupsch et al. 2006; Kuhn, Tsui et al. 2009). These finding therefore provide further evidence of pathophysiological differences between akinetic-rigid and tremor dominant subgroups, which may underlie the contrasts in behaviour reported in Chapter 6.

7.1.2. The mesolimbic overdose hypothesis

One particularly attractive hypothesis regarding the vulnerability of PD patients to ICD is the mesolimbic overdose hypothesis (Dagher and Robbins 2009), which due to the pathophysiological differences described above, may be more likely to occur in akinetic-rigid patients.

It has been reported that ICD in PD patients is often associated with the presence of dyskinesias (Voon, Potenza et al. 2007; Voon, Fernagut et al. 2009), involuntary movements that are due to excessive dopaminergic stimulation. This is consistent with the clinical characteristics of my sample of ICD patients in Chapter 6, a high proportion of whom suffered from dyskinesias to variable extents – likely related to their long duration of disease. Furthermore, ICD symptoms are often found to abate following reductions in dopaminergic treatment (Weintraub 2008; Antonini and Cilia 2009; O'Sullivan, Evans et al. 2009). It would therefore seem that elevated levels of dopamine – or increased sensitivity to dopamine – may play a role in the development of ICD.

As previously discussed in Chapters 1 and 6, it is possible to distinguish separate sensorimotor, cognitive and limbic regions of the striatum, based on their connections with the cerebral cortex (Parent 1990), a finding that has also been reported *in vivo* in the human brain using MRI tractography techniques (Draganski, Kherif et al. 2008). The ventral striatum receives input from limbic areas, such as the hippocampus, amygdala and orbitofrontal cortex, and has been implicated in drug addiction (Robbins and Everitt 1999). It is therefore possible that excessive limbic dopaminergic stimulation is involved

in the development of ICD. If this is indeed the case, PD patients with relative preservation of ventral striatal dopamine projections may be at increased risk of developing such problems (Dagher and Robbins 2009).

In fact, it has been reported that dopamine neurons projecting to the ventral striatum from the medio-dorsal substantia nigra/ventral tegmental area (SN/VTA) are less severely affected by the disease process (Kish, Shannak et al. 1988; Fearnley and Lees 1991). This therefore raises the possibility that pharmacological restoration of dopamine transmission in the *dorsal* or motor striatum may lead to *overdosing* of the *ventral* striatum, with excessive dopamine receptor stimulation leading to adverse effects, such as the development of ICD (Swainson, Rogers et al. 2000).

PD patients with ICD can therefore be hypothesised to have an overactive mesolimbic system, as too might akinetic-rigid patients without ICD, on the basis of their behaviour in Chapter 6, although perhaps to a lesser extent. The observation that, at least in my sample, the majority of ICD patients were akinetic-rigid also supports this contention. The finding that akinetic-rigid patients also seem to have the most severe pathology on post-mortem examination suggests the possibility that greater degeneration in some areas may lead to enhanced compensatory mechanisms. This may occur in regions that are relatively spared – perhaps including the mesolimbic system – so that such areas become relatively overactive. More advanced symptoms would also necessitate higher medication doses which may compound the problem.

The aim of this chapter will be to investigate the hypothesis that ICD patients and akinetic-rigid patients (without ICD) have relative preservation of their mesolimbic system, in comparison to tremor dominant patients. I will examine this hypothesis using magnetisation transfer imaging.

7.1.3. Magnetisation transfer imaging

Magnetisation transfer imaging (MTI) depends on the exchange of proton magnetisation between mobile water protons and protons that are immobilised by macromolecules, such as myelin or cell membrane constituents (Wolff and Balaban 1989). To achieve MTI, the magnetisation of macromolecular protons is partially saturated using off-resonance radiofrequency pulses during standard proton density-weighted imaging (dependent primarily on the density of protons in the imaging volume). The interaction of these partially saturated macromolecular protons with the protons of mobile water in their immediate surrounding attenuates the observed water signal in the images.

This signal reduction depends on tissue properties, such as the concentration, structure and/or chemistry of macromolecules, and water content, in addition to image sequence parameters, and is therefore thought to provide a measure of tissue integrity. The amount of magnetisation transfer has been found to correlate positively with the degree of myelination (Rademacher, Engelbrecht et al. 1999) and with axonal density (van Waesberghe, Kamphorst et al. 1999).

Furthermore, MTI provides greater contrast of subcortical grey matter structures compared to standard T1-weighted methods. The basal ganglia and thalamic nuclei are connected by complex and intertwined axonal tracts below the resolution limits of standard T1-weighted imaging, thus reducing contrast by partial volume averaging. Additionally, the high iron content of the midbrain nuclei and basal ganglia further shortens and degrades T1 contrast. MTI is considered a more effective means of investigating the integrity of deep grey matter nuclei because it appears to be a more direct measure of myelin content and other macromolecules, such as iron-containing neuromelanin, than T1 relaxation, which mainly reflects the physical properties of tissue water (Helms, Draganski et al. 2009).

The measure most frequently taken during studies employing MTI is the magnetisation transfer ratio (MTR). This can be calculated on a voxel-by-voxel basis by taking two consecutive measurements with (MT) and without (no-MT) magnetisation transfer according to the following formula:

$$MTR = (no\text{-}MT - MT)/no\text{-}MT$$

Reductions in MTR have previously been documented in the SN/VTA of PD patients compared to control subjects (Tambasco, Pelliccioli et al. 2003; Eckert, Sailer et al. 2004; Seppi and Schocke 2005). This is in contrast to conventional structural MRI techniques which generally do not show differences between patients with idiopathic PD and healthy individuals especially in the earlier stages of the disease (Seppi and Schocke 2005; Hotter, Esterhammer et al. 2009). Volumetric MRI methods are also usually unable to distinguish

PD patients from controls (Huber, Chakeres et al. 1990; Schulz, Skalej et al. 1999), with the utility of these techniques generally being limited to the differentiation of atypical parkinsonian syndromes from PD (Kraft, Schwarz et al. 1999; Schrag, Good et al. 2000).

The same is also true in multiple sclerosis, where MTR reductions may be seen despite conventional MRI techniques indicating no abnormality, suggesting that MTI may be particularly sensitive in detecting early abnormalities (Iannucci, Tortorella et al. 2000; Traboulsee, Dehmeshki et al. 2002; Fernando, Tozer et al. 2005) likely related to alterations in myelination. The reason for SN/VTA MTR reduction in PD is not fully understood, but may be due to neuronal loss and degradation of the neuromelanin macromolecule (the pigment conferring the black colour to the SN/VTA) which is thought to occur during the PD disease process (Fasano, Bergamasco et al. 2006).

Importantly, mesolimbic haemodynamic responses to novelty – as measured during a paradigm similar to that employed in Chapter 6 – have been found to correlate positively with MTR in the SN/VTA in older healthy individuals (Bunzeck, Schutze et al. 2007). Furthermore, SN/VTA MTR has been found to correlate positively with verbal memory in younger and older healthy subjects (Duzel, Schutze et al. 2008).

In this chapter, however, instead of using MTR, which shows a residual T1 dependence, I will be using MT saturation, a novel semi-quantitative parameter, which separates MT from T1 effects (Helms, Dathe et al. 2008; Helms, Draganski et al. 2009). Such MT maps are corrected for confounding influences of proton density and T1 relaxation changes and

have been shown to provide good contrast of subcortical grey matter structures (Helms, Draganski et al. 2009) and hence may represent a more reliable measure of tissue integrity here.

7.1.4. Compartmentalisation of SN/VTA

In order to assess differences in the level of degeneration across mesolimbic and nigrostriatal dopaminergic systems, it will be necessary to divide the SN/VTA accordingly.

The distinction between the SN and VTA in the primate is not so clear cut as it is in the rat (Duzel, Bunzeck et al. 2009), where the SN represents the source of the nigrostriatal system and the VTA the mesolimbic system. In humans and primates, the SN is more continuous with the VTA (Lynd-Balta and Haber 1994), with dopaminergic projections to limbic regions unrestricted to the VTA and instead dispersed across the SN/VTA (Smith and Kieval 2000; Bjorklund and Dunnett 2007).

It is for this reason that I have hitherto referred to these regions jointly as the SN/VTA. Nevertheless, it is possible to distinguish a dorso-medial region of the primate SN/VTA that seems to be most representative of the rat VTA region (McRitchie, Cartwright et al. 1998), although the distinction between the ventro-lateral region is in the form of a gradient, rather than a clear boundary (Duzel, Bunzeck et al. 2009) – see Figure 7.1 for a comparison of the rat and primate compartmentalisation of the SN/VTA.

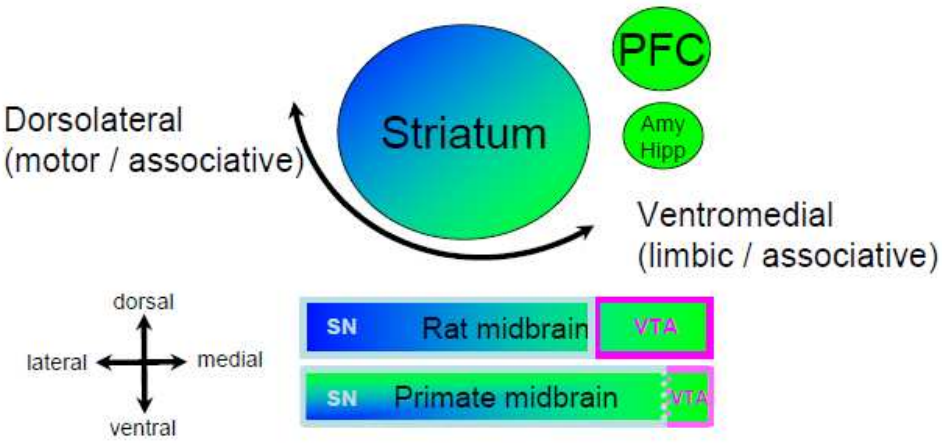


Figure 7.1. Compartmentalisation of the SN/VTA in the primate compared to the rat brain.

This figure demonstrates the comparative organisation of the efferent projections from the midbrain dopaminergic system in rats and primates. Unlike the rat, the primate SN/VTA distinction is not so clear cut and instead there is a dorso-medial versus ventro-lateral gradient of SN/VTA projections to ventro-medial and dorso-lateral portions of the striatum respectively (coloured from green to blue). The dotted border between the VTA and SN in the primate midbrain indicates that these two regions are more continuous in primates than in the rat.

Amy – amygdala
Hipp – hippocampus

Adapted from Düzel *et al*, 2009.

As previously mentioned, the mesolimbic overdose hypothesis is based on reports of more extensive dopamine neuron loss in the ventro-lateral SN/VTA (projecting to the dorsal striatum) compared to the dorso-medial compartment which projects to the ventral striatum (Fearnley and Lees 1991). Furthermore, neuronal loss in PD appears to begin in the ventro-lateral tier of the SN/VTA and throughout the course of the disease this region remains the most severely affected (Fearnley and Lees 1991).

Accordingly, patients who have higher levels of structural integrity within the dorso-medial, compared to the ventro-lateral, compartment of the SN/VTA may be more vulnerable to mesolimbic overdose. It may therefore be hypothesised that PD patients with ICD might have higher levels of structural integrity in the dorso-medial SN/VTA – as too might akinetic-rigid patients without ICD – compared to tremor dominant patients.

For this reason, the ideal would be to examine the SN/VTA with respect to ventro-lateral and dorso-medial compartments. However, the resolution of the MR acquisitions we used does not allow such precise compartmentalisation to be reliably made (Duzel, Schutze et al. 2008). It was, however, possible to divide the SN/VTA more grossly into medial and lateral compartments. The medial compartment will be taken to represent the highest density of mesolimbic dopaminergic neurons (see Figure 7.1), while the lateral region contains predominantly nigrostriatal neurons.

7.1.5. Aims

In summary, the aim of this chapter is to investigate structural differences in the SN/VTA and ventral striatum between PD patients with and without ICD. Differences between akinetic-rigid and tremor dominant patients without ICD will also be assessed. This will be performed using MTI. Specifically, I predict that ICD patients will have greater sparing (i.e. higher MT saturation) of the mesolimbic dopaminergic system (medial SN/VTA and ventral striatum) compared to PD patients without ICD. I further predict that, within those patients without ICD, akinetic-rigid patients may have greater mesolimbic sparing than tremor dominant patients.

I will also assess how these structural parameters relate to behavioural measures of novelty-seeking and risk-taking behaviour. I predict that increased levels of novelty-seeking and risk-taking will correlate with higher levels of structural integrity in the mesolimbic system.

7.2. Methods

7.2.1. Participants

Patients were recruited from movement disorders and general neurology outpatient departments with local ethics approval. Overall 10 akinetic-rigid (mean age: 66.3, range: 58-79; all right-handed) and 10 tremor dominant patients (mean age: 66.6, range: 42-84; all right-handed) without ICD were recruited, in addition to 7 PD patients who had been diagnosed by their neurologist as having an ICD (mean age: 60.3, range: 36-73; all right-

handed). The PD patients were all assessed, underwent behavioural testing and scanned on their usual medication.

Note that these groups of PD patients were the same as those used in Chapter 6, but excluding those who had contraindications to MRI scanning. An additional group of healthy elderly control subjects (n=12) were also recruited for MRI scanning (mean age: 64.7, range: 43-85; all right-handed). A one-way ANOVA revealed no significant differences between the groups in terms of age ($F(3,38)=0.586$, $p=0.628$).

7.2.1.1. Exclusion criteria

As in Chapter 6, exclusion criteria included cognitive impairment such that there was difficulty following assessment or task instructions and/or a Mini-Mental State Examination (MMSE) score of less than 25. To provide a more detailed measure of cognitive function in the PD patients, the Addenbrooke's Cognitive Examination – Revised (ACE-R) was also performed (Mioshi, Dawson et al. 2006) – see Table 7.1. There were no significant differences between PD groups in terms of MMSE score ($F(2,26)=0.099$, $p>0.9$) or ACE-R score ($F(2,26)=0.099$, $p>0.9$).

Significant depression was the other principal exclusion factor. PD patients *without* ICD were excluded if they had a Beck Depression Inventory (BDI) score of 21 or more. Patients *with* an ICD were only excluded if their BDI score was 30 or more. In the normal population, scores of 21 and above are thought to indicate depression, while scores above 30 indicate moderate-severe depression in people who have already been diagnosed as

depressed. As disordered mood is common in PD (Marras, McDermott et al. 2008; Aarsland, Bronnick et al. 2009) and seems to be particularly so in those with ICD (Pontone, Williams et al. 2006; Voon, Hassan et al. 2006), this higher cut-off point was used for this group, in order to avoid the exclusion of excessive numbers in this already difficult to recruit population. This consideration was particularly pertinent to subject recruitment in this chapter, due to the relatively high proportion of ICD patients with contraindications to MRI scanning, including the presence of moderate to severe dyskinesias. However, a one-way ANOVA did not reveal a significant difference between the patient groups in terms of their BDI score ($F(2,26)=3.317$, $p>0.05$).

Subject	Sex	Age	Time Dx	Time Sx	UPDRS	Subtype ratio	MMSE	ACE-R	BDI	LEU	DA
Akinetic-rigid/mixed											
AR1	F	64	3.5	4	26	0.4	30	95	10	300	0
AR2	M	79	8	9	54	0.7	29	73	9	867	67
AR3	F	62	2	4	29	0.7	29	93	6	268	268
AR4	F	62	17	18	21	0.4	30	95	10	351.25	83.75
AR5	F	58	2	4	11	0.94	30	95	5	201	201
AR6	F	69	0.1	1	28	0.8	30	95	4	0	0
AR7	M	65	0.6	2	19	0.8	30	95	1	200	0
AR8	M	64	5.5	6.5	30	0.25	30	86	6	720	120
AR9	M	69	2	4	37	0.625	30	95	1	246.9	46.9
AR10	M	71	9	9	49	0.357	30	90	4	600	0
Means/Ratio	**5:5**	**66.3**	**4.97**	**6.2**	**30.4**	**0.597**	**29.8**	**91.2**	**5.6**	**375.42**	**78.67**
Tremor dominant											
TD1	M	71	7	8	50	2.1	30	97	12	830	280
TD2	M	73	10	11	34	2.5	29	87	9	520	120
TD3	M	66	3	3	38	1.3	29	93	15	167.5	167.5
TD4	F	62	4	5	28	1.3	30	98	10	301.5	201
TD5	F	67	1.5	2	22	1.1	30	91	13	501	201
TD6	M	79	4	4	28	2.7	30	84	5	300	0
TD7	M	62	7	10	48	1.3	30	97	8	1334.7	268
TD8	F	42	0.25	0.5	27	1.7	30	86	19	0	0
TD9	M	60	2.5	5.5	21	1.6	30	91	8	167.5	167.5
TD10	F	84	0.1	0.8	27	1.25	30	93	3	0	0
Means/Ratio	**6:4**	**66.6**	**3.94**	**4.98**	**32.3**	**1.69**	**29.8**	**91.7**	**10.2**	**412.22**	**140.5**
Impulse control disorder											
ICD1	M	73	20	22	81	0.16	30	91	6	980	180
ICD2	M	51	17	17.5	68	0.625	30	92	13	1201	201
ICD3	M	65	19	20	79	0	30	94	8	400	0
ICD4	M	36	1.5	5	54	0.19	29	95	29	180	180
ICD5	M	63	12	15	36	0	29	87	14	747	80
ICD6	M	69	3	10	15	3	30	81	6	0	0
ICD7	M	65	4.5	5	42	2.4	30	93	8	500	0
Means/Ratio	**7:0**	**60.3**	**11**	**13.5**	**53.6**	**0.91**	**29.7**	**90.4**	**12**	**572.57**	**91.57**

Table 7.1. Patient demographics.

Time Dx – time since diagnosis in years

Time Sx – time since symptom onset in years

UPDRS – Unified Parkinson's Disease Rating Scale score (maximum 199)

Subtype ratio – for calculation see Section 7.2.1.2

MMSE – Mini-Mental State Examination score (maximum 30)

ACE-R – Addenbrooke's Cognitive Examination – Revised score (maximum 100)

BDI – Beck Depression Scale score (maximum 63)

LEU – L-dopa Equivalent Units (including L-dopa and dopamine agonisits) – see Section 7.2.1.3 for method of calculation

DA – total dose of dopamine agonist in LEU

7.2.1.2. PD subgroups

As in Chapter 6, PD patients were placed into either akinetic-rigid/mixed or tremor dominant subgroups on the basis of the motor examination (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn 1987). Subgroups were defined according to the ratio of each patient's UPDRS III tremor score (sum of items 20 and 21 divided by 4) to their UPDRS akinetic/rigid score (sum of items 22-27 and 31 divided by 15) after the method proposed by Kang and colleagues (Kang, Bronstein et al. 2005). Patients with a ratio of >1.0 were classified as tremor dominant, those with a ratio of <0.8 as akinetic-rigid and 0.8-1.0 as mixed. See Table 7.1 for detailed patient demographic information, including subtype ratios.

Impulse control problems were diagnosed in PD patients by the neurologist managing their PD. This occurred in the context of clinical interview during routine follow-up appointments and by administration of questionnaires such as the Minnesota Impulse Disorder Interview (Christenson, Faber et al. 1994) for compulsive buying, gambling and sexuality. The impulse control problems identified in the ICD patients studied in this chapter are detailed in Table 7.2. At the time of testing, all patients were subjectively in either full or partial remission.

Subject	Impulse control behaviour	Remission status	Motor subtype	Dyskinesias
ICD1	Hobbyism and punding	Parital	AR	Yes
ICD2	Hobbyism and punding	Partial	AR	Yes
ICD3	Hobbyism and punding	Full	AR	Yes
ICD4	Pathological gambling	Full	AR	No
ICD5	Hypersexuality	Full	AR	Yes
ICD6	Pathological gambling	Full	TD	No
ICD7	Hypersexuality	Full	TD	No

Table 7.2. Impulse control problems in the ICD group.

The impulse control problems of the individual ICD patients. Remission status was assessed by self-reports from the patients.

AR – akinetic-rigid/mixed

TD – tremor dominant

7.2.1.3.Demographic differences between the PD groups

There was a significant difference between the three PD groups in terms of their UPDRS scores ($F(2,26)=5.133$, $p=0.014$). This was driven by the ICD group who demonstrated significantly higher UPDRS scores than the PD patients without ICD ($t(25)=-3.254$, $p=0.003$), whilst the two subgroups without ICD were well-matched on this measure (akinetic-rigid versus tremor dominant: $t(18)=-0.361$, $p>0.7$). This was mirrored by duration of parkinsonian symptoms ($F(2,26)=5.397$, $p=0.012$), with the ICD group having a significantly longer duration of symptoms that those without ICD ($t(25)=-3.313$, $p=0.003$), while the akinetic-rigid and tremor dominant groups were similarly matched ($t(18)=0.489$, $p>0.6$).

The total dose of dopaminergic medication of the PD patients was quantified by using l-dopa equivalence units after Evans and colleagues (Evans, Katzenschlager et al. 2004), which was defined as follows: l-dopa dose + l-dopa dose x 1/3 if on entacapone + bromocriptine (mg) x 10 + cabergoline or pramipexole (mg) x 67 + ropinirole (mg) x 20 + pergolide (mg) x 100 + apomorphine (mg) x 8.

In these samples of patients, a one-way ANOVA did not reveal a significant group difference in total dose of dopaminergic medication ($F(2,26)=0.63$, $p>0.5$). Isolating the contribution of dopamine agonists to the LEU of patients also revealed no significant group difference ($F(2,26)=1.3$, $p>0.29$).

In summary, although the two PD groups without ICD – akinetic-rigid and tremor dominant – were well-matched, the ICD group had more severe parkinsonian symptoms, with a longer duration of these symptoms. This may have represented a confounding influence in the data.

7.2.2. Structural Magnetic Resonance Imaging

Structural MRI scans were performed on the PD patients and healthy elderly controls using a 3Tesla whole-body MRI system (Magnetom TIM Trio, Siemens Medical Systems, Erlangen, Germany) operated with a radio frequency body transmit and 12 channel receive head coil. Each scanning session lasted for a total of approximately 30 minutes.

All 3D datasets were acquired in sagittal orientation with 1 mm isotropic resolution (176 partitions, field of view (FOV) = 256 x 240 mm^2, matrix 256 x 240 x 176) and non-selective excitation.

7.2.2.1. T1-weighted anatomical images

T1-weighted structural scans were obtained using a 3D Modified Driven Equilibrium Fourier Transform (MDEFT) sequence: repetition time = 7.92 ms, echo time = 2.48 ms, inversion time = 910 ms (symmetrically distributed around the inversion pulse, quot = 50%), flip angle $\alpha = 16^{o}$, fat saturation, bandwidth 195 Hz/pixel). The sequence was specifically optimised for reduced sensitivity to motion, susceptibility artefacts and B1 field inhomogeneities (Deichmann, Schwarzbauer et al. 2004). These images were used to

identify possible lesions from strokes or other brain diseases and for anatomical localisation.

7.2.2.2. Magnetisation transfer imaging

As discussed in Section 7.1.3, in order to achieve MTI, the magnetisation of macromolecular protons is partially saturated using appropriate off-resonance radiofrequency pulses during standard proton density weighted imaging. The interaction of these partially saturated macromolecular protons with the mobile protons of water in their direct surrounding attenuates the observed water signal in the images. This signal reduction depends on tissue properties, such as the structure, integrity and chemistry of macromolecules and water content, as well as on image sequence parameters.

MT maps were calculated from a mutli-parameter protocol based on a 3D multi-echo fast low angle shot (FLASH) sequence (Weiskopf and Helms 2008). Three co-localised 3D multi-echo FLASH datasets were acquired with proton density weighting (repetition time/α = 23.7 ms/6º), T1-weighting (18.7 ms/20º) and MT-weighting (23.7 ms/6º; excitation preceded by an off-resonance Gaussian MT pulse of 4 ms duration, 220º nominal flip angle, 2 kHz frequency offset). The signals of six equidistant bipolar gradient echoes (at 2.2 ms to 14.7 ms echo time) were averaged to increase the signal-to-noise ratio (Helms and Dechent 2009) and a rather high acquisition bandwidth of 425 Hz/pixel was chosen to keep the susceptibility-related geometric distortions in brain and the chemical shift displacement of fat signals below one pixel. In order to speed up the acquisition, generalised autocalibrating partially parallel acquisition (GRAPPA) parallel imaging with

an acceleration factor of two in the phase-encoding direction (anterior-posterior) and 6/8 partial Fourier in the partition direction (left-right) was employed. Semi-quantitative MT parameter maps, corresponding to the additional saturation created by a single MT pulse, were calculated by means of the single amplitudes and T1 maps (Helms, Dathe et al. 2008), thereby eliminating the influence of relaxation and B1 inhomogeneity (Helms, Dathe et al. 2008).

7.2.2.3. Delineation of regions of interest

The SN/VTA and ventral striatal regions of interest (ROIs) were defined as described below using MRICro software (available from www.mricro.com). From each of these ROIs, the mean volume and MT values were extracted. This was performed twice for each ROI and each subject and the average of the two measurements taken, although the two sets of data were highly correlated for each ROI ($r>0.69$, $p<0.001$).

7.2.2.3.a. SN/VTA

All boundaries of the SN/VTA were selected visually based on the intense change in contrast between its bright grey colour and the dark grey colour of the adjacent tissue in the MT image (Duzel, Schutze et al. 2008). First the SN/VTA ROI was defined as a whole and then was later divided into a medial and lateral compartment (Fearnley and Lees 1991).

The upper limit of the SN/VTA ROI was taken at the level of the superior colliculi, where the cross-sectional area of the SN/VTA appears as an even bright grey coloured region in

the MT image and therefore excluding voxels that directly flank the adjacent tissue. The anterior part of the SN/VTA ROI was limited by the interpeduncular fossa and posterior borders by the lateral side of the cerebral peduncle. The medial and lateral boundaries of the SN/VTA ROI were extended until the contrast changed. The lower limit of the SN/VTA was identified as the last even grey coloured cross sectional area.

According to the study by Fearnley and Lees (Fearnley and Lees 1991), the medial and lateral compartments of the SN/VTA were defined by deleting a diagonal line of voxels within the SN/VTA-ROI. The junctures of this diagonal line was identified as the midpoint of the ventral side of the cerebral peduncle and its intersection with an imaginary line connecting the anterior and posterior intersection of the superior sagittal sulcus at an angle of about 45º. Fearnley and Lees, further subdivided the SN/VTA into dorsal and ventral tiers in their post-mortem study (Fearnley and Lees 1991), however, the resolution of the MT imaging used here did not allow for such fine-grained subdivision. Figure 7.2 demonstrates an example of the medial and lateral SN/VTA ROIs.

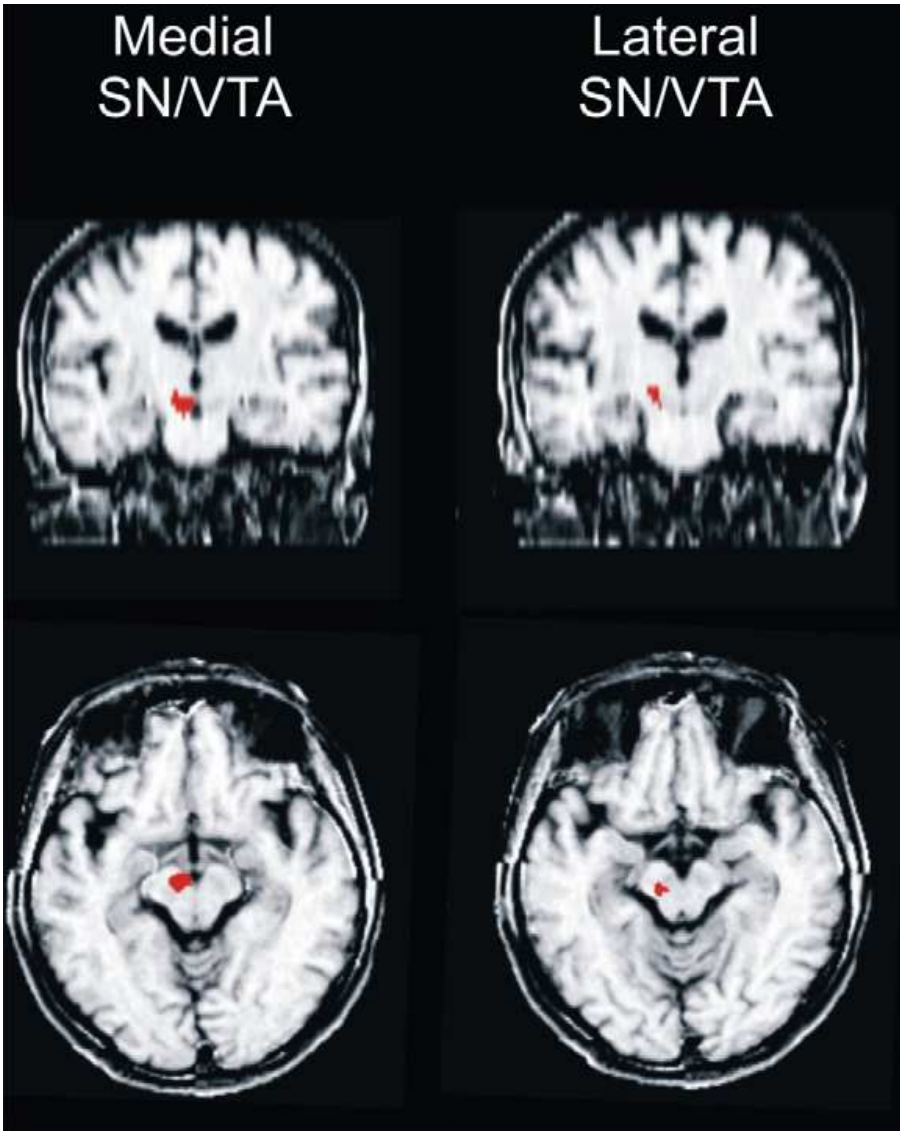


Figure 7.2. SN/VTA regions of interest.

An example of the medial and lateral SN/VTA regions of interest (ROIs). The top row indicates the ROI (shown in red) on a coronal section, and the bottom row, the ROI as seen on a transverse slice.

Adapted from Düzel *et al*, 2008.

7.2.2.3.b. Ventral striatum

In the primate, the ventral striatum includes the nucleus accumbens and the broad continuity between the caudate nucleus and putamen ventral to the rostral internal capsule, in addition to the olfactory tubercle and the rostolateral portion of the anterior perforated space adjacent to the lateral olfactory tract (Haber and McFarland 1999).

The following criteria were used to define the ventral striatal ROI, based on those described by Mawlawi and colleagues, see Figure 7.3 (Mawlawi, Martinez et al. 2001). The boundary between the ventral striatum inferiorly and the dorsal striatum superiorly was defined by a line joining the intersection between the outer edge of the putamen with a vertical line going through the most superior and lateral point of the internal capsule (point a in Figure 7.3) and the centre of the portion of the anterior commissure transaxial plane overlying the striatum (point b in Figure 7.3). This line was extended to the internal edge of the caudate (point c in Figure 7.3).

The other boundaries of the ventral striatum were visually determined by its dense grey signal, making it easy to distinguish from adjacent structures, and it was sampled from the anterior boundary of the striatum to the level of the anterior commissure coronal plane.

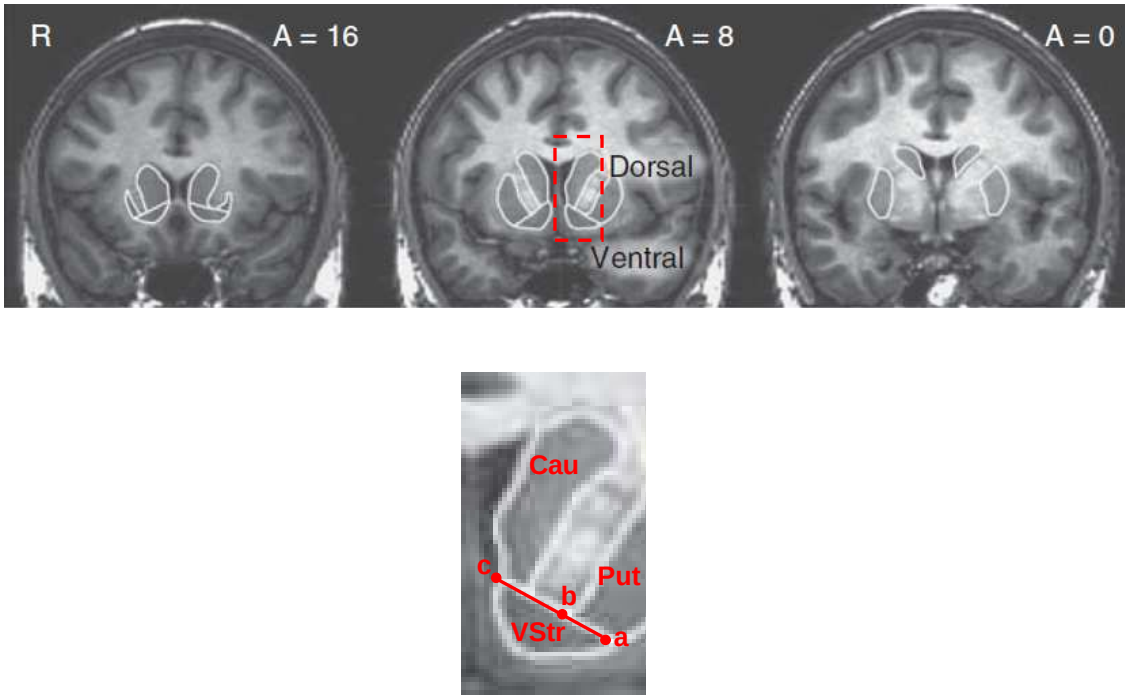


Figure 7.3. Ventral striatal region of interest.

The anatomical scheme used for identifying the ventral striatum is shown on coronal slices. The area within the red dashed box is magnified below. The boundary between the ventral striatum inferiorly and the dorsal striatum superiorly was defined by a line joining the intersection between the outer edge of the putamen with a vertical line going through the most superior and lateral point of the internal capsule (point a) and the centre of the portion of the anterior commissure transaxial plane overlying the striatum (point b). This line was extended to the internal edge of the caudate (point c).

Cau – caudate nucleus

Put – putamen

VStr – ventral striatum

Adapted from Malawi *et al*, 2001.

7.2.2.4. Data analysis

One-way ANOVAs, and t-tests where appropriate, were used to assess for statistically significant group differences regarding size and MT saturation of the ROIs.

7.2.3. Behavioural indices

The MTI data was also compared to some of the behavioural indices obtained from the computerised tasks described in Chapter 6. These were as follows.

7.2.3.1. Iowa Gambling Task

The IGT was used as the behavioural index of risk-taking behaviour as it produced more robust findings in Chapter 6 than the Cambridge Gambling Task. A ready-made computerized version of the IGT was used, obtained from the Psychology Experiment Building Language (PEBL) website (http://pebl.sourceforge.net/). This task is explained in detail in Section 6.2.2.2 and summarized again in Figure 7.4.

The difference in the number of advantageous – disadvantageous decks sampled in the first 20 compared to the last 20 trials was the measure which was compared against the imaging data obtained in this chapter. This measure was chosen, rather than the overall difference between advantageous and disadvantageous decks, as the ICD patients tended to demonstrate differences on this measure in Chapter 6. This measure was compared to MT saturation in the SN/VTA and ventral striatum across each of the subject groups.

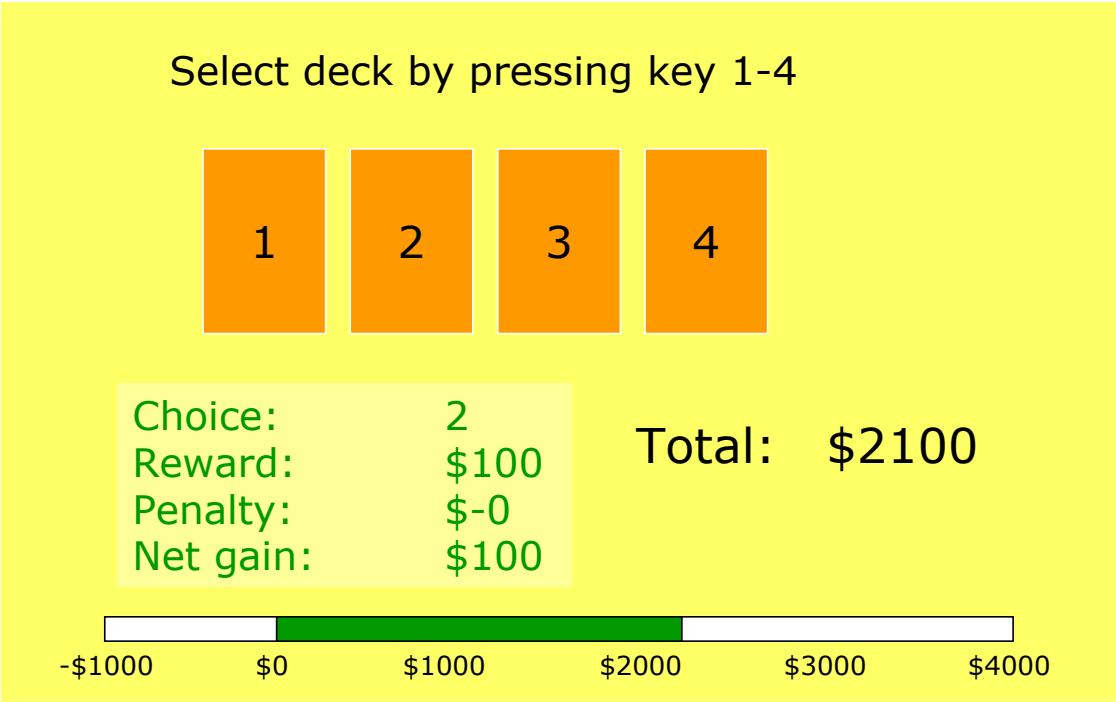


Figure 7.4. Iowa Gambling Task.

Subjects were instructed to choose cards from decks 1 to 4, by pressing keys 1 to 4 on a keyboard, in order to earn as much play money as possible. Decks 1 and 2 consistently gave out high rewards ($100), but were associated with high and frequent penalties. On the other hand, decks 3 and 4 gave out smaller rewards ($50), but were associated with smaller and less frequent penalties, so that over time, they led to higher gains. Decks 1 and 2 can therefore be considered as *disadvantageous*, while decks 3 and 4 are *advantageous*.

7.2.3.2. Tridimensional Personality Questionnaire – novelty-seeking

The novelty-seeking score from the Tridimensional Personality Questionnaire (TPQ (Cloninger, Przybeck et al. 1991)) was also compared to the structural imaging data. This measure of novelty-seeking was chosen as it has previously been shown to correlate with SN/VTA activation in response to novel cues (Krebs, Schott et al. 2009). This measure was compared to MT saturation across each of the subject groups.

7.3. Results

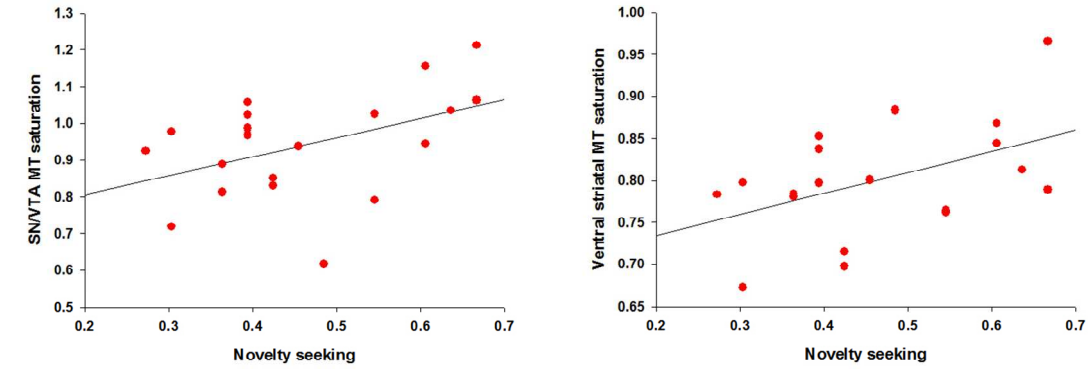
7.3.1. Correlations between MT saturation and behavioural parameters

7.3.1.1. Novelty seeking

In the PD patients without ICD, novelty seeking, as measured by the TPQ (Cloninger, Przybeck et al. 1991), was found to correlate with MT saturation in the whole SN/VTA (r= .454, p=0.045 – see Figure 7.5A), with little variation in this correlation across the medial (r= .435) and lateral (r= .452) compartments. Higher MT values were associated with an increased novelty seeking score on the TPQ.

Importantly, this correlation was unchanged when controlling for dose of dopamine agonist medication (r= .464, p=0.046) and actually improved when controlling for total dose of dopaminergic medication (r= .569, p=0.011) and duration of disease (r= .536, p=0.018).

The same association was also seen in the ventral striatum (r= .474, p=0.035 – see Figure 7.5B), again with preserved ventral striatal integrity correlating with a higher level of novelty seeking. This correlation too, was unaffected by controlling for total dose of dopaminergic medication (r= .547, p=0.015), dose of dopamine agonist (r= .471, p=0.042) and duration of disease (r= .499, p=0.03).



A B

Figure 7.5. Correlation between novelty seeking and MT saturation in the SN/VTA and ventral striatum.

A. In PD patients without ICD, novelty seeking (as measured by the TPQ) correlates with MT saturation in the SN/VTA, whereby higher novelty seeking scores are associated with a higher degree of SN/VTA integrity.

B. The same association was also seen between ventral striatal MT saturation and novelty seeking.

Although there was no variation in the correlation of novelty seeking with SN/VTA MT saturations across the medial and lateral subcompartments, the fact that there was also a correlation with ventral striatal MT saturation suggests that greater mesolimbic preservation may represent a structural correlate of a higher tendency towards novelty seeking.

7.3.1.2. Risk-taking behaviour

Although the ICD patients did not demonstrate any significant correlations between novelty seeking and MT saturation ($r<.4$, $p>0.38$), there was a highly significant correlation between risk-taking on the IGT and MT saturation in the medial compartment of the SN/VTA ($r= -.933$, $p=0.002$), which was less marked in the lateral compartment ($r= -.685$, $p=0.089$). An increased tendency to sample the high risk decks of the IGT with time was associated with preserved integrity of the medial SN/VTA – see Figure 7.6). This association between MT values in the medial SN/VTA and risk-taking was not observed in the PD patients without ICD ($r= -.013$, $p>0.9$).

Importantly this correlation remained significant when controlling for total dose of dopaminergic medication ($r= -.925$, $p=0.008$), dose of dopamine agonist ($r= -.909$, $p=0.012$) and duration of disease ($r= -.954$, $p=0.003$), factors which have previously been reported as increasing susceptibility to the development of ICD (Voon, Hassan et al. 2006; Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007). Instead, this result suggests that structural factors, specifically the integrity of the medial SN/VTA – the SN/VTA

compartment with the highest density of mesolimbic dopamine neurons – may be more important in mediating a vulnerability to risk-prone behaviours.

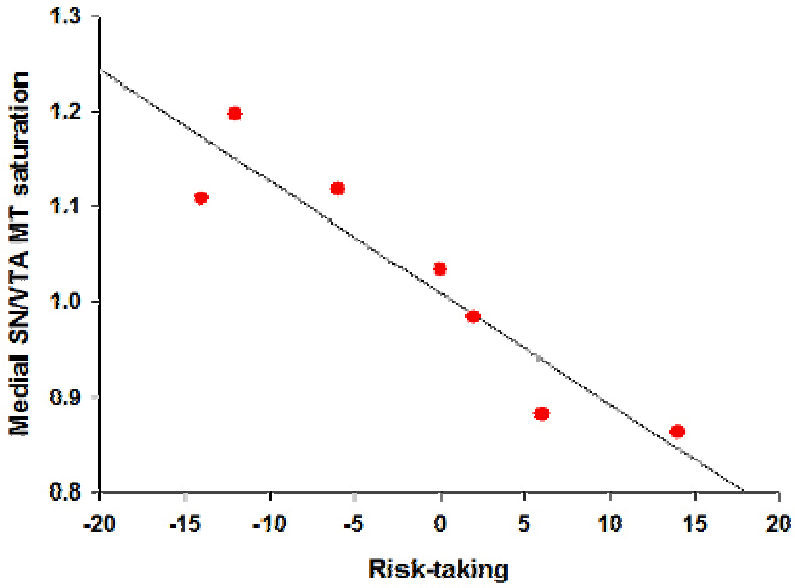


Figure 7.6. Correlation between risk-taking and medial SN/VTA MT saturation. In the ICD patients there was a significant correlation between risk-taking on the IGT and MT saturation in the medial SN/VTA. Increased preference for the risky decks on the IGT as the task progressed was associated with increased structural integrity of the medial SN/VTA.

In summary, in PD patients without ICD, increased novelty processing correlated with higher structural integrity of the SN/VTA and ventral striatum (Figure 7.5), indicating that preservation of the mesolimbic dopaminergic system in these patients may be associated with an increased tendency to novelty seeking. In the ICD patients on the other hand, increased risk-taking behaviour was associated with preservation of structural integrity in the medial compartment of the SN/VTA (Figure 7.6), the region likely to contain a higher proportion of mesolimbic dopamine neurons. Importantly, these correlations remained even when dose of dopaminergic medication was controlled for, suggesting that preservation of the mesolimbic system may be an important factor in mediating tendencies towards such behaviours.

7.3.2. Group differences in the structural imaging data

7.3.2.1. SN/VTA

A one-way ANOVA revealed a significant difference in the size of the whole SN/VTA ROI between the four groups ($F(3,38)=7.137$, $p<0.001$). This was driven by the control groups demonstrating a significantly larger SN/VTA than the PD patients ($t(37)=-4.615$, $p<0.001$), while there were no significant differences between the PD groups themselves ($t<0.94$, $p>0.36$). There was no significant difference in MT saturation in the SN/VTA ROI across groups, including controls ($F(3,38)=1.064$, $p=0.377$).

Examining the lateral and medial compartments of the SN/VTA, a one-way ANOVA revealed a significant difference in the size of both the lateral SN/VTA ($F(3,38)=6.748$,

p=0.001) and the medial SN/VTA ($F(3,58)=6.659$, $p=0.001$) between the groups (Figure 7.7 A and B).

Again, this was driven by the control groups demonstrating significantly larger volumes than the PD patients (lateral SN/VTA: $t(37)=-4.513$, $p<0.001$ medial SN/VTA: $t(37)=-4.354$, $p<0.001$). Again there were no significant differences between the PD groups in terms of lateral ($t<0.75$, $p>0.46$) or medial ($t<1.37$, $p>0.19$) SN/VTA size.

As was the case with the whole SN/VTA, there were no significant differences across the groups in terms of MT saturation in the lateral SN/VTA ($F(3,38)=0.423$, $p>0.73$). Although this was also the case in the medial SN/VTA ($F(3,38)=1.909$, $p=0.146$), here there was a trend for ICD patients ($t(15)=1.893$, $p=0.078$) – and to a lesser extent akinetic-rigid PD patients without ICD ($t(18)=1.668$, $p=0.113$) – to have larger MT values compared to tremor dominant PD patients.

Although these findings regarding medial SN/VTA MT values did not reach (two-tailed) statistical significance, the observed trends are in the direction predicted in Section 7.1. ICD patients demonstrated higher MT values – and by inference structural integrity – of the medial, or mesolimbic, SN/VTA in comparison to tremor dominant PD patients; as did the akinetic-rigid patients to a lesser extent. The use of larger group sizes, particularly in the ICD group, might have led to a statistically significant result here, but unfortunately many of my original ICD patient sample had contraindications to MRI scanning.

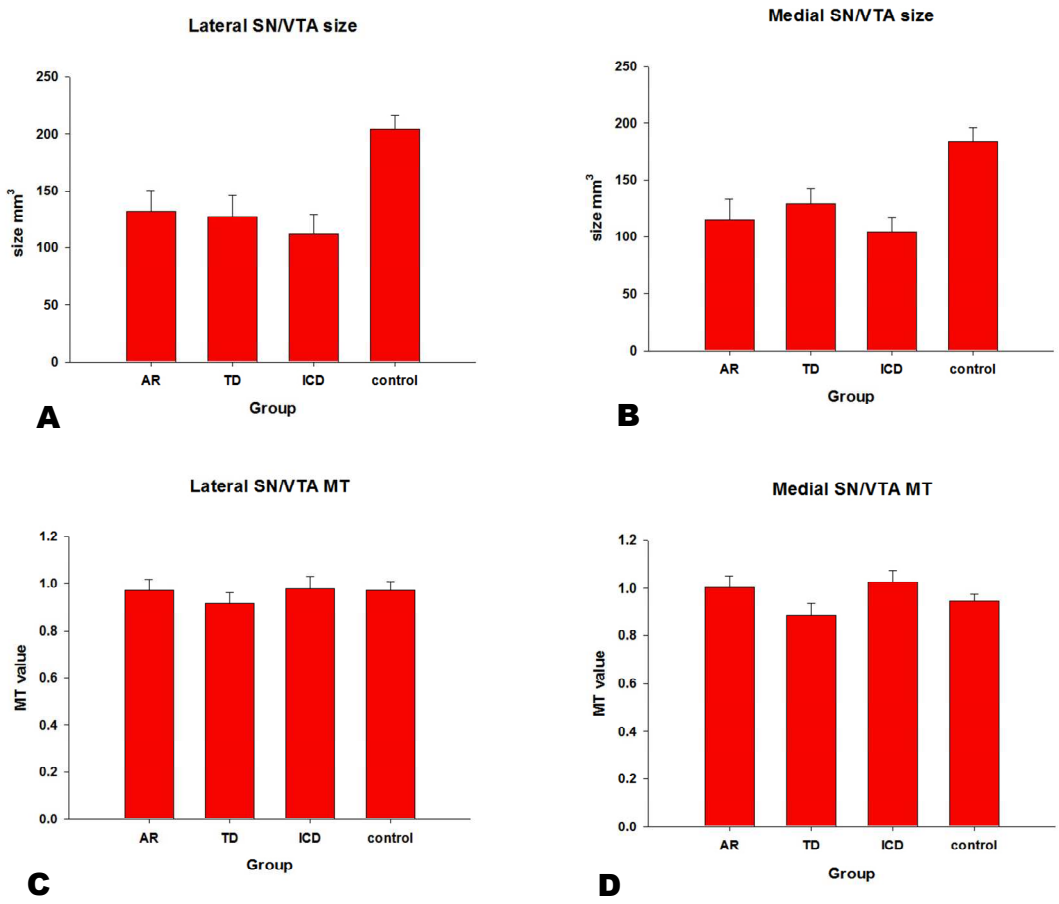


Figure 7.7. Group differences in the lateral and medial compartments of the SN/VTA.

A. PD patients had a significantly smaller lateral SN/VTA than control subjects.

B. This was also the case for the medial SN/VTA compartment.

C. There was no difference in the MT value of the lateral SN/VTA across the groups.

D. Although there were also no significant differences between the groups in terms of the MT value of the medial SN/VTA, there was a trend for ICD patients – and to a lesser extent the akinetic-rigid PD patients without ICD – to have higher MT values here than the tremor dominant PD patients. Error bars indicate standard error of the mean.

AR – akinetic-rigid patients without ICD

TD – tremor dominant without ICD

ICD – PD patients with an impulse control disorder

7.3.2.2. Ventral striatum

There were no significant differences between the groups in terms of either ventral striatal size ($F(3,38)=0.318$, $p>0.8$) or MT saturation ($F(3,38)=1.374$, $p=0.267$). As the striatum is downstream of the principal source of pathology in PD, structural changes here may be more subtle and difficult to discern with the current methods.

7.3.3. Correlations between structural imaging parameters and subtype ratio

In the PD patients without ICD (i.e. both akinetic-rigid and tremor dominant patients who were well-matched on all demographic measures, unlike the ICD patients), there was a trend towards higher MT values in the medial SN/VTA and lower subtype ratios ($r= -.403$, $p=0.078$). In other words, the more akinetic-rigid the patient was, the higher the MT saturation in (and by inference the more intact) the medial (or mesolimbic) SN/VTA (Figure 7.8A). Importantly, there was no such correlation in the lateral SN/VTA ($r= -.265$, $p=0.259$), suggesting that motor phenotype was less likely to influence structural integrity here.

No such correlation was observed in the small ICD group of PD patients regarding MT saturation and subtype ratio in either the lateral or medial SN/VTA compartments ($r<0.43$, $p>0.33$). However, in this group there was a correlation between the size of the lateral SN/VTA and subtype ratio ($r=.798$, $p=0.031$), with the akinetic-rigid ICD patients having a significantly smaller lateral SN/VTA than the tremor dominant ones (Figure 7.8B). This, however, is likely to be secondary to the akinetic-rigid ICD patients having a longer

duration of disease and more severe parkinsonian symptoms than the tremor dominant ICD patients (see Table 7.1).

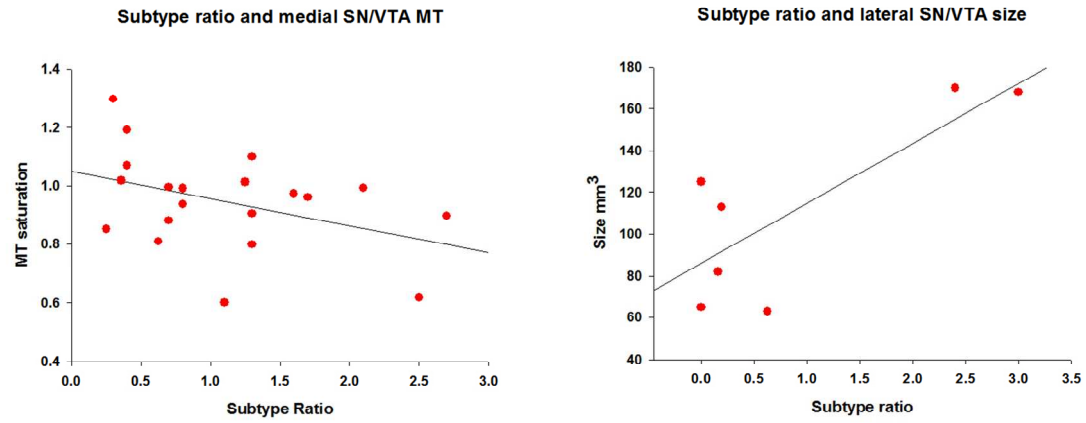


Figure 7.8. Correlation between subtype ratio and structural parameters.

A. In the PD patients without ICD, there was trend towards an association between lower subtype ratios (more akinetic-rigid parkinsonian signs) and higher MT values in the medial SN/VTA, suggesting that the more akinetic-rigid the patient, the greater structural preservation of the medial SN/VTA.

B. In the PD patients with ICD, there was a significant association between the size of the lateral SN/VTA and subtype ratio, whereby the akinetic-rigid ICD patients had smaller lateral SN/VTA ROIs.

This inhomogeneity of the ICD group may also explain why no correlation between MT saturation and subtype ratio was observed in this group: in the more advanced cases (which were also more advanced than the majority of cases in the PD groups without ICD) more severe and widespread degenerative changes may confound such associations.

In summary, this adds some support to the hypothesis that akinetic-rigid patients may have less neurodegeneration in the medial SN/VTA than tremor dominant patients, which is likely to contain the highest density of mesolimbic dopaminergic neurons.

7.4. Discussion

One of the most important findings of this chapter was that in the ICD patients there was a significant correlation between greater propensity to risk-taking behaviour (as measured by the IGT) and preserved structural integrity of the medial SN/VTA (Figure 7.6), the region of the SN/VTA likely to contain the highest density of mesolimbic dopaminergic neurons. Crucially, this association remained significant when controlling for dose of dopaminergic medication and duration of disease; factors which have previously been linked to the development of ICD in PD patients (Voon, Hassan et al. 2006; Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007). There was also a trend for ICD patients to have higher levels of structural integrity in the medial SN/VTA compared to tremor dominant patients without ICD (Figure 7.7D).

Although the PD patients without ICD did not demonstrate this association between risk-taking behaviour and structural integrity of the medial SN/VTA, they did show significant

correlations between higher scores of novelty-seeking (as measured by the TPQ) and preservation of structural integrity in the SN/VTA and the ventral striatum (Figure 7.5).

Again, these correlations remained significant when controlling for dose of dopaminergic medication and duration of disease. Furthermore, there was a trend for integrity of the medial SN/VTA to correlate with subtype ratio in the PD patients without ICD, with akinetic-rigid patients demonstrating higher levels of structural integrity here (Figure 7.8A).

In Chapter 6, akinetic-rigid patients were shown to process novel stimuli more quickly than non-novel yet perceptually salient stimuli (unlike tremor dominant patients and healthy controls, who processed both types of stimuli equally quickly), with this measure correlating with risk-taking behaviour on the IGT – although these patients did not demonstrate an increase in risk-taking per se. Increased novelty-seeking and speedier processing of novel stimuli may therefore represent a precursor to the development of risky behaviour and explain why there was no association between risk-taking and mesolimbic integrity identified in the PD patients without ICD.

In summary, in PD patients with ICD there was a correlation between mesolimbic preservation and risk-taking behaviour. By contrast, in PD patients without ICD there was a correlation between mesolimbic preservation and increased novelty-seeking. Both akinetic-rigid patients without ICD and PD patients with ICD – shown in Chapter 6 to process novel stimuli more quickly than non-novel salient stimuli – tended to have higher

levels of structural integrity within the medial compartment of the SN/VTA, the area containing the highest density of mesolimbic dopaminergic neurons.

These results therefore suggest that preservation of the mesolimbic dopaminergic system may indeed be crucial in generating a vulnerability to the development of ICD. Furthermore, akinetic-rigid patients, on the basis of their behaviour (Chapter 6) as well as their tendency towards increased preservation of the medial SN/VTA, may be more susceptible to these problems.

7.4.1. Contribution of dopaminergic medication

Previous reports have documented an association between ICD and the use of dopamine agonists (Voon, Hassan et al. 2006; Voon, Hassan et al. 2006; Weintraub, Siderowf et al. 2006; Weintraub 2008; Voon, Fernagut et al. 2009). Although the results obtained here suggest that integrity of the mesolimbic dopaminergic system may be a crucial factor in generating a susceptibility to ICD, this nevertheless occurred on a background of dopaminergic replacement therapy (Table 7.1).

Despite the possibility that generalized compensatory mechanisms (Creese and Snyder 1979; Zigmond and Stricker 1984; Zhang, Tilson et al. 1988) may contribute to some extent to *mesolimbic overdose* (Dagher and Robbins 2009), it seems likely that this should predominantly result from the use of dopamine replacement medication. Dopamine replacement therapy principally consists of the use of its precursor L-dopa (Yahr, Duvoisin et al. 1969; Hornykiewicz 2002) and more recently the use of dopamine agonists

which act predominantly at the D2 subclass of dopamine receptors (Rascol 1999; Seeman 2007). Importantly, it is the use of dopamine agonists, rather than L-dopa, which has been linked to the development of ICD in PD patients (Voon, Hassan et al. 2006; Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007).

Although these data implicate a more important role of structural integrity of the mesolimbic SN/VTA in risk-taking behaviour in ICD patients, some of the variance in risk-taking behaviour in this group could be accounted for by dose of dopamine agonist medication. The bivariate correlation between risk-taking on the IGT and medial SN/VTA MT fell from r= -.933, p=0.002 to r= -.909 p=0.012 when controlling for dose of dopamine agonist – in contrast to a correlation of r= -.925, p=0.008 when controlling for total dose of dopaminergic medication.

Together, these results provide considerable support for the mesolimbic overdose hypothesis in the development of impulse control problems (Dagher and Robbins 2009). But why should the use of dopamine agonists be more likely to lead to such problems?

As mentioned above, L-dopa is an amino acid precursor to dopamine which is converted in the brain to its active substrate (Hornykiewicz 2002). It may therefore be more capable of producing an effect which in some respects is closer to normal physiology than dopamine agonists which act directly at specific, predominantly D2 type, receptors (Rascol 1999). The mechanism of action of L-dopa is likely to be complex.

Acute administration of the L-dopa is associated with a robust increase in extracellular dopamine levels within the striatum in dopamine-depleted animals (Spencer and Wooten 1984; Orosz and Bennett 1992), which appears to correlate with the initial reduction in rigidity observed in parkinsonian patients (Juncos 1992). By contrast, repeated administration of L-dopa is necessary for improvements in complex motor behaviour (Juncos 1992).

Studies using *in vivo* microdialysis in rats with unilateral dopamine depletions have demonstrated that elevated extracellular dopamine levels in the dopamine-depleted striatum that occur in response to L-dopa administration are unaltered during the course of repeated drug administration, even though the behavioural response to L-dopa is enhanced over a 28-day period with the administration of successive doses of the drug (Wachtel and Abercrombie 1993). Therefore, the time course over which L-dopa administration induces maximal increases in striatal extracellular dopamine levels in rats does not appear to be correlated with its behavioural actions.

Other evidence suggests that the site of action of L-dopa may actually lie in areas other than the striatum. For example, augmentation of dopamine levels in the SN/VTA produced by L-dopa administration has been found to correlate more precisely with its behavioural actions in comparison to L-dopa induced changes in striatal dopamine levels (Robertson and Robertson 1989).

Indeed, studies have shown that repeated systemic administration of L-dopa can induce alterations in the electrophysiological activity of SN/VTA neurons (Harden and Grace 1995), such as a decrease in the sensitivity of dopamine neurons to dopamine agonist induced inhibition in intact rats (Jackson, Walters et al. 1982). Furthermore, electrophysiological studies in rats have also demonstrated that L-dopa administration can increase stimulation-induced release of dopamine in the striatum in both intact and dopamine depleted animals, suggesting that L-dopa is converted to dopamine by SN/VTA neurons (Keller, Kuhr et al. 1988; Wightman, Amatore et al. 1988). Importantly, this stimulation-induced release appears to occur in a phasic manner (Keller, Kuhr et al. 1988).

Therefore, in summary, L-dopa appears to act in a phasic manner by increasing dopamine release from dopaminergic neurons, in addition to producing tonic effects through other mechanisms leading to increased levels of striatal dopamine. L-dopa therefore seems capable of producing effects that are more physiologically adaptable than those associated with dopamine agonists, which are unlikely to exert any phasic effects and instead lead to tonic stimulation of specific dopamine receptor subtypes.

As discussed in Chapters 1 and 6, it has been suggested that persistent – or tonic – postsynaptic dopaminergic stimulation may block phasic dopamine dips that serve as a crucial component of the learning signal to negative reinforcement (Frank, Seeberger et al. 2004; Frank, Samanta et al. 2007). In PD patients receiving treatment with dopamine agonists, this situation could be further amplified in the context of greater levels of mesolimbic sparing, making learning from negative consequences particularly difficult – a

trait which the ICD patients investigated here tended to demonstrate on the Cambridge Gambling Task in Chapter 6.

Further support for this notion of enhanced mesolimbic dopaminergic activity in ICD patients comes from a recent PET study. Patients who had developed pathological gambling on dopamine agonists were found to have greater decreases in [^{11}C]-raclopride binding (indicating higher levels of dopamine release) in the ventral striatum during a gambling task than control patients, who were also taking dopamine agonist medication (Steeves, Miyasaki et al. 2009).

In addition to a possible effect on learning from negative consequences, it is possible that the enhanced tonic postsynaptic dopamine receptor stimulation associated with dopamine agonist use may also affect learning from positive outcomes. In fact, one further recently published study reports that ICD patients on dopamine agonists demonstrate faster learning about gain, or positive outcomes, than PD control patients also taking dopamine agonists (Voon, Pessiglione et al. 2010). Furthermore, dopamine agonists in ICD patients increased ventral striatal activity to positive prediction errors, resulting in a persistent 'better than expected' outcome. In contrast, dopamine agonists were associated with slower loss, or negative outcome, learning in the PD control patients.

To summarise, it appears that use of dopamine agonists, by persistently increasing mesolimbic dopaminergic activity, may be capable of enhancing learning from positive outcomes whilst also perhaps deleteriously affecting learning from negative outcomes. In

susceptible individuals, this may subsequently lead to the development of impulse control problems. On the basis of the results obtained in this chapter, preserved structural integrity of the medial SN/VTA, which appears to be a particular feature of akinetic-rigid PD, may represent one such important susceptibility factor.

Other factors, unrelated to PD and also occurring in the normal population, may of course also result in a vulnerability to the development of impulse control problems, such as genetic polymorphisms resulting in different dopamine receptor profiles. For example, the TAQ-1A polymorphism modulates D2 receptor density, with the A1 allele being associated with lower expression of D2 receptors, in addition to impulsivity, addiction and compulsive behaviours (Comings, Rosenthal et al. 1996). Nevertheless, in the context of PD, high levels of mesolimbic preservation, especially with concurrent use of dopamine agonists, may be a critical determinant in the development of ICD.

7.4.2. Summary

The results obtained in this chapter suggest that preserved integrity of the mesolimbic SN/VTA may be a crucial factor in mediating a vulnerability to the development of ICD in PD patients. They also suggest that akinetic-rigid patients may be more likely than tremor dominant patients to demonstrate preserved integrity of the medial (or mesolimbic) SN/VTA.

This finding dovetails with the findings from Chapter 6 which demonstrated that ICD patients were more likely to have an akinetic-rigid motor phenotype. Furthermore,

akinetic-rigid patients were shown to process novel stimuli more quickly than non-novel yet salient stimuli, with this increased speed of processing of novel stimuli correlating with risk-taking behaviour.

In sum, these results appear to suggest that akinetic-rigid patients may be particularly vulnerable to impulse control problems and that this vulnerability may be exacerbated by the use of dopamine agonists.

Chapter 8

8.1. Introduction

The principal aim of this thesis has been to explore some of the functions attributable to the right inferior parietal lobe (IPL) of humans. Chapter 1 examined two existing theories of *cortical visual processing streams* (Ungerleider and Mishkin 1982; Milner and Goodale 1995) and the cortical *control of visual attention* (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008) which, I argue, have failed to capture the full extent of the role played by the IPL. In particular the earlier models, although they addressed the visuospatial functions of this region, failed to accommodate non-spatial aspects (Ungerleider and Mishkin 1982; Milner and Goodale 1995). The more recent model advanced by Corbetta and colleagues (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008), while attempting to incorporate some non-spatial functions of this region, does not really offer a clear role for important components, such as the ability to sustain attention.

In Chapter 1, I reviewed evidence which suggests that the right IPL plays a crucial role in broadly different, but complimentary, aspects of attention: maintaining attentive control on current task goals *and* responding to salient new information or alerting stimuli in the environment. I argued that findings from functional imaging, neurophysiological and lesion studies are all consistent with the view that this region is a vital part of a system that allows the flexible reconfiguration of behaviour between these two contrasting modes of

operation, and that noradrenergic input to the IPL may be particularly important in this regard (Singh-Curry and Husain 2009).

This proposal was tested in earlier chapters of this thesis by investigating stroke patients with hemispatial neglect, the syndrome which frequently occurs following damage to the right IPL (Vallar and Perani 1986; Mort, Malhotra et al. 2003). The ability of such individuals to sustain attention on task goals, respond to salient stimuli and alerting tones, as well as orient spatial attention were all assessed in a series of experiments that sought also to determine lesion locations associated with deficits in these domains.

The processing of salient new, or novel, stimuli also involves activation of the mesolimbic dopaminergic system (Bunzeck and Duzel 2006), the neuromodulatory network which is crucial in signalling reward-related information (Schultz, Tremblay et al. 1998). Parkinson's disease (PD), a neurodegenerative condition characterised by loss of dopaminergic cells in the midbrain, therefore represents another disorder which may help reveal how the brain processes stimulus novelty as well as reward-related information.

In fact, a subgroup of medicated PD patients, go on to develop impulse control problems, which are associated with risk-taking behaviour and novelty-seeking (Wu, Politis et al. 2009). The use of dopamine agonists has been implicated in the genesis of impulse control disorders (ICD) (Voon, Potenza et al. 2007). However, this does not explain why only some patients using these drugs encounter such problems, while most others do not. One possibility is that pathophysiological differences between two well characterised

subgroups of PD – the akinetic-rigid and tremor dominant motor phenotypes – might at least partially explain a difference in susceptibility to these problems. Such pathophysiological differences may occur within the dopaminergic system itself. However, patients with PD may additionally demonstrate pathology outside of the midbrain and basal ganglia, including within the frontal and parietal lobes (Derejko, Slawek et al. 2006; Beyer, Janvin et al. 2007; Nobili, Abbruzzese et al. 2009), which may of course, also contribute to behavioural and cognitive problems. The purpose of this thesis was to investigate these proposals by examining patients with the neglect syndrome, following right hemisphere stroke, and PD.

8.2. Functions of the IPL and ventral attention network as revealed by neglect

8.2.1. Sustained attention and salience detection

The aim of Chapter 2 was to probe the functions of the ventral attention network – IPL, temporoparietal junction (TPJ), superior temporal sulcus and ventral frontal regions – by examining deficits associated with hemispatial neglect, the syndrome that often follows damage to these areas (Vallar and Perani 1986; Husain and Kennard 1996; Mort, Malhotra et al. 2003). Using variants of an 'oddball paradigm' (Barcelo, Suwazono et al. 2000), neglect patients were shown to have difficulty sustaining attention over time, or a *vigilance decrement*, even when no spatial shifts of attention were required. In other words, neglect patients were unable to adequately protect task-related goals in working memory over the time-course of the task.

This deficit in sustained attention was particularly evident for stimuli of lower perceptual salience (Figure 2.2). More importantly, however, the deficit in sustaining attention was found to interact with difficulty detecting salient targets (Figure 2.2), as well as with the orientation of spatial attention (Figure 2.9), suggesting that these functions may be dependent upon an interrelated brain network.

Consistent with this notion, the results of the lesion analysis indicated that the ventral attention network appears to be crucial in the mediation of all of these processes (Figure 2.14). However, the findings suggested that there may be differences in the contributions of two critical nodes – frontal and parietal – of this network. The right inferior frontal gyrus (IFG) appears to play the key role in the ability to sustain attention (figure 2.4A), consistent with classical findings (Wilkins, Shallice et al. 1987; Rueckert and Grafman 1996), but a feature which is of little prominence in the formulation of Corbetta and colleagues (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008).

By contrast, although the right IPL plays a role in the direction of spatial attention (Figure 2.12A) and encoding stimulus salience (Figure 2.5B) as suggested by Corbetta and colleagues, it also contributes to sustaining attention over time (Figure 2.5A), especially for left-sided events (Figure 2.12B).

These differences suggest a division of function between the frontal and posterior nodes of the ventral attention network which has not previously been established. Moreover, the results suggest that the right IPL may not simply have a role in reorienting attention or

detecting salient events, as is the central tenet of the Corbetta model (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008), but also in sustaining attention. Furthermore, neglect patients demonstrated a deficit in salience encoding that interacts with the ability to maintain vigilant attention. These findings are consistent with the hypothesis that the right IPL plays an important role in allowing the flexible adaptation of behaviour, permitting a modulation between a task-engaged state, in which attention is sustained on task goals, and an exploratory mode that facilitates the identification of novel, salient events of potential behavioural significance (Singh-Curry and Husain 2009).

8.2.2. Phasic alerting

The aim of Chapter 3 was to investigate the effect of phasic alerting tones on the ability of neglect patients to sustain attention and encode stimulus salience, and also to examine how this may interact with the more characteristic deficit in the spatial reorientation of attention. As previous investigators have found (Robertson, Mattingley et al. 1998), the results demonstrated that non-informative alerting tones enhanced detection of left-sided targets. However, alerting tones also ameliorated the deficits in sustained attention and the detection of low salience stimuli throughout space, not just those occurring on the left (Figures 3.3 and 3.7).

How might this improvement of non-spatial deficits occur? I have argued that phasic alerting can be considered to represent a category of stimulus salience, having much in common with stimulus *novelty* (Singh-Curry and Husain 2009). Salience refers to properties of a stimulus which make it stand out from the environment, due either to goal-

relevance or task-irrelevant perceptual characteristics. Phasic alerting refers to a readiness to detect and respond to events of behavioural significance and can occur in a different stimulus modality to the target (as was the case with the auditory tones used in Chapter 3).

Alerting stimuli can be informative, predicting in some way the occurrence of a target event, or non-informative, when they can be considered to have most in common with *novel events*. Those used in this thesis were non-informative, being equally likely to occur with a target as a non-target stimulus. Like novel stimuli, *phasic alerting events* evoke a parietal P3 potential: the P3a. This ERP occurs slightly earlier than the P3b potential (evoked by task-relevant salient targets) and does not have to be accompanied by a motor response (Courchesne, Hillyard et al. 1975; Squires, Squires et al. 1975).

When paired with a target stimulus, however, it is possible that a P3a ERP immediately preceding a P3b target-evoked potential can potentiate the P3b, making initiation of a motor response more likely. Indeed, it has been shown that when novel stimuli are unpredictably associated with a target, the amplitude of both the P3a and subsequent target-related P3b increase (Suwazono, Machado et al. 2000). Alerting stimuli too, have been shown to enhance P3b amplitude (Miniussi, Wilding et al. 1999; Griffin, Miniussi et al. 2002).

One way in which the findings regarding phasic alerting stimuli obtained in this thesis could be extended would be to record ERPs during the tasks. On the basis of the evidence discussed above, I would expect that P3b potentials to target stimuli, particularly those of

lower perceptual salience, would be of greater amplitude when paired with an alerting tone.

The findings obtained in this thesis, together with other evidence from the literature, suggest that the parietal cortex might be crucial in mediating the alerting effect. In fact, the neglect patients tested here demonstrated a three-way interaction that approached significance, between stimulus position, salience and presence of alerting tones, suggesting that all of these processes may be served by the same or closely linked neural systems. As discussed in the previous section, the IPL was significantly associated with deficits in salience encoding, orienting attention to left-sided stimuli and sustaining attention to left-sided, as well as central events. Given that these processes interact with the alerting effect, the IPL would therefore seem a likely candidate for its mediation. In fact, functional imaging studies in healthy participants have also suggested that the right IPL is indeed involved in this process (Fan, McCandliss et al. 2005; Thiel and Fink 2007).

Together, these findings suggest that the functions of the IPL cannot be classified as purely stimulus-driven (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). Indeed, even processes such as salience detection and phasic alerting cannot truly be considered as only 'bottom-up', as they also involve components which can be thought of as more 'top-down' in nature. As previously argued, the right IPL can be considered to play a crucial role in the flexibly reconfigurating behaviour, permitting adaptation between opposing functional states: a task-engaged, 'exploitative' state, in which attention is effectively

focused on task demands, *and* a more 'exploratory' state, which enables potentially important novel or salient environment events to be identified.

8.2.3. Novelty processing

One of the principal findings of Chapter 5 was that neglect patients, in addition to demonstrating impairment in the *accurate* detection of non-novel *perceptually salient* stimuli, are also at least equally deficient at the accurate detection of *novel* stimuli (Figures 5.2 and 5.3). Importantly, neglect patients were found to be significantly *slower* at the detection of novel compared to non-novel perceptually salient stimuli (Figure 5.5). Furthermore, impairment in the accuracy of detection of novel stimuli (Figure 5.4), as well as the slower detection of novel compared to non-novel perceptually salient stimuli (Figure 5.6), was associated with damage within a ventral network of brain regions, including the IPL, but particularly the IFG. These findings therefore also support the proposed role of the right IPL and ventral attention network in the processing of novel events, in addition to non-novel salience detection and the ability to effectively sustain attention.

Again, a role of the ventral attention network in the detection of novel stimuli is not a feature incorporated within the model of Corbetta and colleagues (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). In fact, in their most recent formulation (Corbetta, Patel et al. 2008), they appear to suggest that this network is important only in responding to salient task-relevant events and not novel or task-irrelevant items. The novel stimuli used in the experiments of this thesis were, of course, task-relevant. However, the fact that

reaction times to novel stimuli were significantly *slower* than those to non-novel perceptually salient stimuli in neglect patients with right-sided ventral network damage – in the context of otherwise identical experimental requirements – suggests that stimulus novelty itself is important.

I therefore conclude that the results of this particular experiment also add support to the proposal that the right IPL and ventral attention network play a crucial role in the reconfiguration of behaviour which allows flexible adaptation between task-engaged and exploratory modes of attentional functioning (Singh-Curry and Husain 2009).

8.2.4. The role of noradrenaline and the locus coeruleus

It has been proposed that noradrenergic input to the parietal cortex from the locus coeruleus (LC) may be important in the flexible reconfiguration of behaviour between these two opposing functional states (Aston-Jones and Cohen 2005; Singh-Curry and Husain 2009). Converging evidence suggests that the parietal P3 potential may reflect phasic activity of the LC noradrenergic system (Nieuwenhuis, Aston-Jones et al. 2005). By inference, therefore, effective phasic LC bursts on a background of moderate tonic levels should be correlated with the P3b ERP in response to salient task-relevant events (Aston-Jones, Rajkowski et al. 1994; Dayan and Yu 2006).

I have argued, therefore, that *phasic* bursts of LC noradrenergic activity, on a background of moderate *tonic* activity, may induce, via parietal regions, a task-engaged state, enhancing sustained attention to task demands and facilitating detection of task-relevant

events (Singh-Curry and Husain 2009). It can therefore also be envisaged that alerting stimuli – accompanied by their own parietal *P3a potential* and capable of enhancing the amplitude of target-related P3b potentials (Miniussi, Wilding et al. 1999; Griffin, Miniussi et al. 2002) – mediate their beneficial effect in neglect by effectively boosting noradrenergic input to the parietal cortex.

If this hypothesis is correct, one would expect that noradrenergic agonists may also ameliorate the spatial and non-spatial deficits associated with neglect. A small proof-of-principle trial previously demonstrated that neglect patients may benefit from a *single* dose of the noradrenergic agonist guanfacine, in terms of visuospatial exploration, but perhaps also their ability to sustain attention (Malhotra, Parton et al. 2006).

In Chapter 4, I described the case of a patient with persistent neglect and severe difficulty sustaining attention, secondary to bilateral thalamic lesions caused by acute disseminated encephalomyelitis (ADEM), which improved following the introduction of a regular dose of guanfacine. Although continuous use of guanfacine has been shown to be efficacious in the treatment of inattentiveness in children and adolescents with attention deficit/hyperactivity disorder (Biederman, Melmed et al. 2008), this case represents a first demonstration of a *persistent* amelioration of the spatial deficit in neglect with a noradrenergic agonist.

I speculate that guanfacine produced this amelioration by boosting noradrenergic activity in regions such as the IPL and, in the case of this patient with bilateral thalamic lesions, by

increasing the excitatory input in response to sensory stimulation that may normally be potentiated by thalamic input (Watson, Valenstein et al. 1981). Furthermore, based on the interaction between deficits in sustained attention and the spatial orientation of attention demonstrated in Chapter 2, it is possible that an amelioration of the deficit in sustained attention may also act to improve the exploration of space in neglect.

One way in which to attempt to gain support for this hypothesis would be to compare neurophysiological or functional imaging parameters during sustained attention tasks in such patients, comparing them on and off guanfacine. I would expect that improved performance on guanfacine would be paralleled by an enhancement of parietal P3b potentials and increased activation of parietal cortex.

8.3. The dopaminergic contribution to novelty processing and risk-taking behaviour as revealed by Parkinson's disease

One of the principal findings of Chapter 6 was that, in addition to differences in motor phenotype, akinetic-rigid PD patients dissociate from tremor dominant patients in terms of their ability to process stimulus novelty. Akinetic-rigid patients were significantly quicker to process novel stimuli than they were non-novel perceptually salient stimuli (see Figure 6.4), while tremor dominant PD patients and healthy controls responded to both types of stimulus equally quickly. Importantly, increased risk-taking behaviour, as measured by performance on the Iowa Gambling Task (IGT), correlated with quicker reaction times to novelty (as compared to non-novel perceptually salient stimuli) in the akinetic-rigid

patients only (see Figure 6.8). Crucially, neither faster responses to novelty, nor increased willingness to make risky decisions correlated with total dose of dopaminergic replacement therapy.

ICD patients too, were found to have quicker reaction times to novel compared to non-novel perceptually salient stimuli (Figure 6.4), as well as demonstrating a trend to sample the risky decks on the IGT more often as time on the task progressed (Figure 6.7B). There were not, however, any significant correlations between these measures and either total dose of dopaminergic medication or dose of dopamine agonist.

Interestingly, only 14% of the ICD patients tested were tremor dominant, with the remainder classified as either akinetic-rigid or mixed motor phenotype. This observation, together with the fact that akinetic-rigid patients appear to process novelty quicker than non-novel perceptual salience, a finding which correlated with risk-taking on the IGT, suggests that the akinetic-rigid sub-group may be more susceptible to ICD. The fact that neither novelty processing nor risk-taking behaviour correlated with dose of dopaminergic therapy suggests that *motor phenotype* – and the underlying neurobiology – may be more important in generating a vulnerability to ICD than dopaminergic medication, contrary to previous reports (Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007).

It is important to note that all of the patients tested here were taking their usual dopaminergic medications. Despite the lack of correlation between the behavioural parameters obtained and dose of dopaminergic medication, it would be important in the

future to demonstrate similar dissociations between akinetic-rigid and tremor dominant patients off their medications. Of course, it may also be that an interaction between dopaminergic medication and neuropathological differences between akinetic-rigid and tremor dominant groups defines vulnerability to developing ICD.

8.3.1. Akinetic-rigid and tremor dominant subtypes of PD

Evidence is accumulating for pathological (Paulus and Jellinger 1991) and neuropharmacological (Rajput, Sitte et al. 2008) differences between akinetic-rigid and tremor dominant PD patients. Moreover, while the severity of bradykinesia and rigidity has been found to correlate with the reduction in dopaminergic ligand binding in the caudate and putamen in PD patients, *no such relationship has been found with the severity of tremor* (Eidelberg, Moeller et al. 1990; Antonini, Vontobel et al. 1995; Otsuka, Ichiya et al. 1996; Tissingh, Bergmans et al. 1998). Therefore, whilst functional degeneration of the nigrostriatal system seems to correlate with the severity of bradykinesia and rigidity in PD, the severity of tremor may relate to different mechanisms, perhaps involving thalamocortical circuits (Antonini, Moeller et al. 1998).

Local field potentials (LFPs) from the subthalamic region of patients with PD have demonstrated an exaggerated oscillatory synchronisation of neuronal activity mainly in the beta band (15-35 Hz) (Brown and Williams 2005; Hammond, Bergman et al. 2007). Such excessive synchronisation may contribute to some of the motor symptoms of PD (Brown 2003; Brown 2007). Dopaminergic medication can reduce the LFP power recorded from the STN over the 8-35 Hz frequency range, and this effect correlates with improvement in

akinesia and rigidity, but *not with tremor* (Kuhn, Kupsch et al. 2006; Kuhn, Tsui et al. 2009).

Together, these findings from pathological, imaging and neurophysiological studies support the distinction between the akinetic-rigid and tremor dominant subgroups of PD They may also underlie the dissociation I found regarding novelty processing and risk-taking behaviour between these two motor phenotypes. A particularly attractive theory regarding vulnerability to ICD – which I have found to be associated with speedier novelty processing and increased willingness to take risks – is the mesolimbic overdose hypothesis (Dagher and Robbins 2009), a state that may be more likely to occur in akinetic-rigid PD secondary to some of the pathophysiological differences described above.

8.3.2. The mesolimbic overdose hypothesis

The *ventral striatum* receives input from limbic areas, such as the hippocampus, amygdala and orbitofrontal cortex, and has been implicated in drug addiction (Robbins and Everitt 1999). It is possible that excessive limbic dopaminergic stimulation is involved in the development of ICD. If this is the case, PD patients with relative preservation of ventral striatal dopamine projections may be at increased risk of developing such problems (Dagher and Robbins 2009).

In fact, dopamine neurons projecting to the ventral striatum are less severely affected by the disease process in PD (Kish, Shannak et al. 1988; Goto, Hirano et al. 1989). This

raises the possibility that pharmacological restoration of dopamine transmission in the *dorsal* (motor) striatum may lead to overdosing of the *ventral* striatum, leading to adverse effects (Swainson, Rogers et al. 2000). This ventral overdose hypothesis is further supported by neuroimaging studies, which show that the normal signal that arises from the ventral striatum when subjects must reverse a previously learned response is abolished in PD patients treated with levodopa, in parallel with impaired task performance (Cools, Lewis et al. 2007).

Another factor which may contribute to mesolimbic overdosing is sensitisation: an increased effect of stimulant drugs with repeated administration (Paulson and Robinson 1995). In PD patients with and without compulsive medication use, levodopa caused dopamine release in the dorsal striatum in equal measure in both groups. However, only the compulsive drug users demonstrated significant dopamine release in the ventral striatum, indicating sensitisation (Evans, Pavese et al. 2006). These findings suggest that PD patients with ICD may have an overactive mesolimbic system (Dagher and Robbins 2009). On the basis of the findings from Chapter 6 of this thesis, so too might akinetic-rigid patients without ICD, although probably to a lesser extent. The results obtained in Chapter 7 add further support to this proposal.

8.3.3. Correlations between the structural integrity of the mesolimbic system and novelty seeking and risk-taking in PD

The most striking finding from Chapter 7 was that in the ICD patients there was a significant correlation between risk-taking behaviour (as measured by the IGT) and

preserved structural integrity of the medial SN/VTA (as assessed by magnetisation transfer), the region of the SN/VTA likely to contain the highest density of mesolimbic dopaminergic neurons (Figure 7.6). Importantly, this association remained significant when controlling for dose of dopaminergic medication and duration of disease, factors which have previously been linked to the development of ICD in PD (Voon, Hassan et al. 2006; Weintraub, Siderowf et al. 2006; Voon, Potenza et al. 2007). There was also a trend for ICD patients to have higher levels of structural integrity in the medial SN/VTA compared to tremor dominant patients without ICD (Figure 7.7D).

Although the PD patients without ICD did not demonstrate this association between risk-taking behaviour and structural integrity of the medial SN/VTA, they did show significant correlations between higher scores of novelty-seeking (as measured by the TPQ) and preservation of structural integrity in the SN/VTA and the ventral striatum (Figure 7.5). Again, these correlations remained significant when controlling for dose of dopaminergic medication and duration of disease. Furthermore, there was a trend for integrity of the medial SN/VTA to correlate with subtype ratio in the PD patients without ICD, with akinetic-rigid patients demonstrating higher levels of structural integrity here. Increased novelty-seeking and speedier processing of novel stimuli, as they were found to correlate with risk-taking behaviour in some patients with PD in Chapter 6, may therefore represent a precursor to the development of risky behaviour and explain why there was no association between risk-taking and mesolimbic integrity identified in the PD patients without ICD.

These results therefore add support to the proposal that preservation of the mesolimbic dopaminergic system may be crucial in generating a vulnerability to the development of ICD. Furthermore, akinetic-rigid patients, on the basis of their behaviour, as well as their tendency towards increased preservation of the medial SN/VTA, may be more susceptible to these problems.

To investigate this proposal further it would be useful to examine dopamine release in the ventral striatum using PET during gambling and novelty processing tasks. It has, in fact, recently been shown that PD patients with pathological gambling demonstrate reduced [^{11}C] raclopride binding, and therefore greater dopamine release, in the ventral striatum during a gambling task compared to control PD patients (Steeves, Miyasaki et al. 2009). However, I would also speculate that akinetic-rigid patients without ICD may also demonstrate higher ventral striatal dopamine release in comparison to tremor dominant patients.

8.4. Novelty, reward and attention

The results of the early chapters of this thesis, I would argue, add support to the proposal advanced in Chapter 1: that the IPL plays a key role in the allowing the flexible adaptation of behaviour between a task-engaged state – where attention is focused on task demands – and a more labile, exploratory state in which novel, salient events of potential behavioural significance capture attention (Singh-Curry and Husain 2009). Phasic and tonic noradrenergic input from the LC to the IPL (part of the 'ventral attention network') is

thought to be crucial in this process of reconfiguration (Aston-Jones and Cohen 2005; Singh-Curry and Husain 2009).

The detection of stimulus novelty is a complex process, requiring the individual to keep track of and compare stimuli with earlier events, in order to correctly judge a novel stimulus as new. Novelty processing has also been associated with activity in the SN/VTA, as well as the hippocampus and ventral striatum (Bunzeck and Duzel 2006), which together form a mesolimbic loop. With input from prefrontal areas, this loop is considered to be instrumental in controlling entry of information into long-term memory (Lisman and Grace 2005). Data presented in the later chapters of this thesis, which suggest that novelty processing may be enhanced by relative overactivity of the mesolimbic dopaminergic system, would be consistent with such a view. Novelty processing therefore seems to involve the synthesis of information from the mesolimbic dopaminergic system as well as from the LC and ventral attention network.

There are prominent cortical connections to the LC from medial frontal and orbitofrontal cortex (Rajkowski, Lu et al. 2000; Aston-Jones, Rajkowski et al. 2002), which may play a key role in modulating its responses. These frontal regions might provide a site for the integration of sensory information with input from the mesolimbic system (Carmichael and Price 1995; Devinsky, Morrell et al. 1995; Carmichael and Price 1996; Morecraft and Van Hoesen 1998; Ongur and Price 2000), placing them within a network that is modulated by dopamine and capable of encoding the reward associations of sensory stimuli. In fact, it has been demonstrated that the amplitude of LC phasic responses to

targets is altered by the motivational significance or associated reward of the stimulus (Aston-Jones, Rajkowski et al. 1994; Rajkowski, Majczynski et al. 2004).

Frontal afferents to the LC may therefore be capable of signaling the *motivational salience* of environmental events and act to bias the noradrenergic innervation to parietal cortex accordingly. The PPC of course also receives its own connections from frontal regions (Selemon and Goldman-Rakic 1988; Schmahmann, Pandya et al. 2007), enabling a direct frontal modulation of parietal activity. Furthermore, there is also evidence for a more direct dopaminergic input to PPC, with the parietal lobe appearing to receive input (via the thalamus) from the SN/VTA (Yeterian and Pandya 1993; Middleton and Strick 2000; Middleton and Strick 2000; Clower, Dum et al. 2005).

Indeed, it has been shown that expectations about the delivery of a reward activate the parietal cortex in monkeys, with neuronal modulations here interpreted as being associated with reward contingencies and expectations regarding the amount of reward to be received (Platt and Glimcher 1999; Coe, Tomihara et al. 2002; Bendiksby and Platt 2003; Newsome 2003; Sugrue, Corrado et al. 2004). Although it may be difficult to separate out parietal responses associated with reward and those associated with attentional processes, more recent studies have attempted to do just this.

For example one investigation employing a rewarded saccadic-cueing task in monkeys, found that while the activity of parietal neurons was modulated by reward size, neuronal responses were also correlated with reaction times *independently of reward magnitude*

(Bendiksby and Platt 2006). The authors argue that this indicates that parietal cortex is a crucial area for integrating reward-related information with attention and saccade planning, but that information regarding reward expectation and attentional processes may be separate.

Some human studies have also attempted to assess the combined effects of attention and motivation on the performance of visual tasks (Small, Gitelman et al. 2005; Engelmann and Pessoa 2007; Engelmann, Damaraju et al. 2009). Importantly, rewards or incentives have been shown to interact with attentional processes, with the impact of incentive being greater on invalidly cued trials – that necessitate reorienting – compared to validly cued trials. Furthermore, this effect of motivation on reorienting led to an increase in target-evoked signals in the TPJ (Engelmann, Damaraju et al. 2009).

Parietal lobe function therefore also appears to influence reward-related and risk-taking behaviour, in addition to the processing of novel stimuli. Indeed, the right IPL has been shown to be significantly activated during the outcome phase of the Iowa Gambling Task in normal subjects (Lin, Chiu et al. 2008). To the best of my knowledge, there has only been one study which has examined the effects of parietal lesions on reward-related decision-making (Gomez-Beldarrain, Harries et al. 2004). This investigation suggested that while parietal patients were good at assessing task-related information, they were poor at using this information to inform their judgements.

I therefore further speculate that the parietal lobe may be an important area of convergence for attentional and reward related information and that, together with modulation from the noradrenergic and dopaminergic systems, it plays a key role in the flexible adaptation of behaviour in changing environmental circumstances (Figure 8.1). Indeed, this idea is supported by evidence demonstrating that the IPL is at the heart of a 'structural core' of the human cerebral cortex, as one of the most densely interconnected cortical regions (Hagmann, Cammoun et al. 2008).

An important avenue for further investigation of this proposal would be the use of reward related paradigms in neglect patients in whom damage is centred on the IPL. It would be important to investigate whether reward can modulate inattention, both spatial and non-spatial, in such individuals. Moreover, future studies might also explore the effects of dopaminergic drug modulation of inattention, with or without reward modulation, in neglect patients.

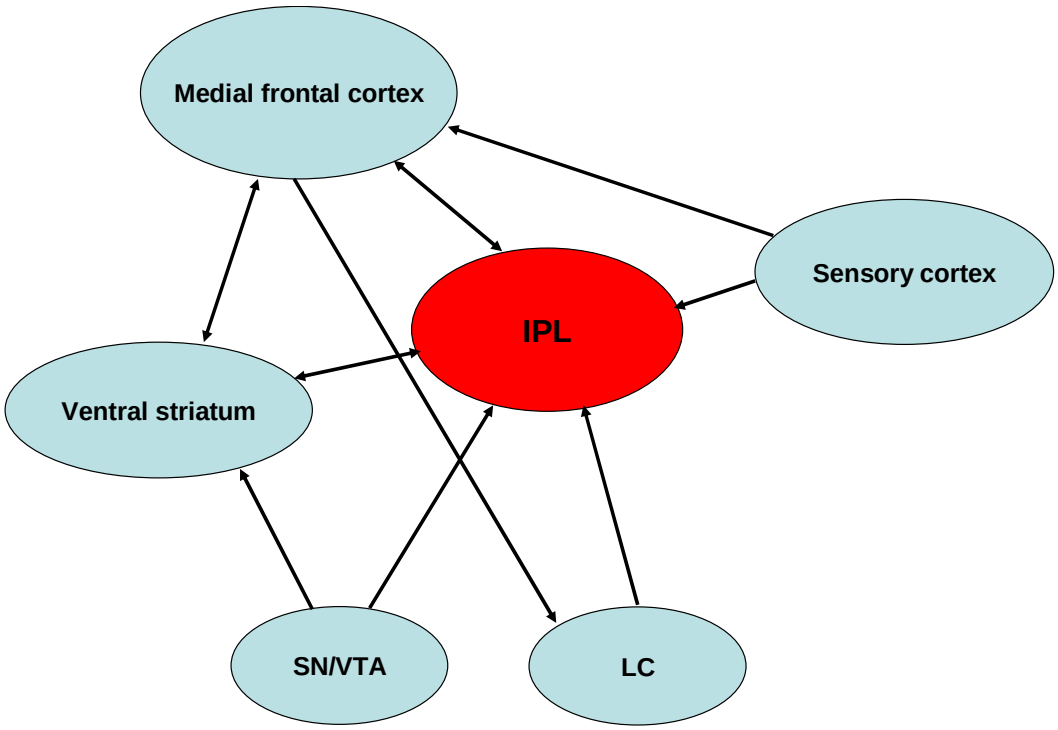


Figure 8.1. Convergence of attention and reward related input on to the IPL. Although simplified, this diagram aims to demonstrate the convergence of input from a variety of structures on to the IPL. In combination with modulation by both the noradrenergic and dopaminergic systems, the IPL is ideally placed to allow the flexible adaptation of behaviour according to environmental circumstances.

With respect to Parkinson's disease, the findings presented here suggest it would be important to pursue further whether motor phenotype (akinetic- rigid versus tremor dominant) is associated with risk for developing ICD on dopaminergic medication. Ideally, a longitudinal rather than cross-sectional study would need to be performed, but this would require a large number of patients, since only a relatively small percentage of PD patients develop ICD. The neurobiology of any differential effects in akinetic-rigid and tremor dominant patients can be investigated *in vivo* with existing ligand-based PET methodology (Steeves, Miyasaki et al. 2009).

The findings discussed in this thesis, linking the SN/VTA system and IPL to novelty processing, also suggest that it might be useful to investigate cortical function in PD patients, particularly with respect to visual attention. In fact, existing studies have demonstrated significant abnormalities in several aspects of attention, even in non-demented PD patients and perhaps independent of motor phenotype (Taylor, Rowan et al. 2008), with some of these deficits being linked to changes within the parietal lobe (Matsui, Udaka et al. 2006; Matsui, Nishinaka et al. 2007). But, to the best of my knowledge, there has been no systematic investigation of modulation of attention by behavioural manipulations of reward or novelty, or by pharmacological interventions with dopaminergic or noradrenergic drugs in such individuals.

The perspectives presented in this thesis have attempted to bring together some disparate elements of research on the contributions of cortical, LC and mesolimbic systems to novelty processing, reward modulation and attention. The findings suggest such a wide-

ranging view might be useful in considering not only the inter-connected functions of these regions, but also their modulation in two important neurological conditions: stroke and PD.

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