THE NEUROCOGNITIVE CONSEQUENCES OF NON-FUNCTIONING PITUITARY ADENOMA AND ITS TREATMENT

by

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Abstract

Patients with pituitary adenoma often report problems with cognitive function. However, the current literature is inconsistent on the types of cognitive deficits that patients experience. Chapter 1 of this thesis reviews the current literature and the questions that are still unanswered concerning the cognitive function of this patient group. Chapter 2 outlines the methodology used to assess the neurocognitive function of a group of patients with non-functioning pituitary adenoma. Chapters 3, 4 and 5 report and discuss the results of this assessment for general intellectual functioning, memory and executive functions. Chapter 6 discusses the physiological correlates of these results and finally, Chapter 7 presents the first fMRI experiment used to assess both content and context abilities in this patient group. The results of this thesis suggest that patients have intact general intellectual functioning and executive functions, in the presence of relative immediate memory impairment. Having hormone levels outside the normal range are a better predictor of dysfunction than treatment received. This thesis does not implicate surgery or radiotherapy as having adverse consequences to patients' neurocognitive functioning.

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Table of Abbreviations

ABP – Arterial Blood Pressure

ACC – Anterior cingulate cortex

AI-IV – Autoregulatory index between phase one and four

ARI – Autoregulatory index

ASI – Autoregulation slope index

CA – Cerebral Autoregulation

CBFV – Cerebral Blood Flow Velocity

CFA – Confirmatory factor analysis

CHC – Cattell-Horn-Carroll

CM – Conservatively managed

COWAT – Controlled Oral Word Association Test

CSF – Cerebrospinal fluid

CT – Computed Tomography

D-KEFS – Delis-Kaplan Executive Functions System

DLPFC – Dorsolateral prefrontal cortex

EF – Executive function

ERP – Event-related potential

FAA – Formally alcohol abusing

fMRI – functional magnetic resonance imaging

FSIQ – Full Scale Intelligence Quotient

g – General Intelligence

Gc – Crystallised intelligence

Gf – Fluid intelligence

GHD – Growth hormone deficiency

GSI – Global severity index

IMT – Intima-media thickness

IPG – Impaired performance group

IQ – Intelligence Quotient

MCA – Middle cerebral artery

MQ – Memory Quotient

MRI – Magnetic resonance imaging

MTL – Medial temporal lobe

NART – National Adult Reading Test

NFA – Non-functioning adenoma

NMDA – N-methyl-D-aspartate

NPC – Nasopharyngeal carcinoma

NPG – Normal performance group

OH – Hydroxide

PI – Proactive interference

PIQ – Performance Intelligence Quotient

PO – Perceptual Organisation

PS – Processing Speed

RT – Radiotherapy

SAS – Supervisory Attentional System

SCL-90R – Symptom Checklist-90 Revised edition

s.d. – standard deviation

SEM – Standard error of measurement

TBI – Traumatic brain injury

TCD – Transcranial Doppler

TIA – Transient ischemic attack

VC – Verbal Comprehension

VIQ – Verbal Intelligence Quotient

WAIS – Wechsler Adult Intelligence Scale

WCST – Wisconsin Card Sort Test

WM – Working Memory

WMS – Wechsler Memory Scale

WTAR – Wechsler Test of Adult Reading

Section 1 – Literature Review

What are the neurocognitive consequences of surgery and radiotherapy for tumours of the pituitary gland?

Background

Pituitary adenomas

Pituitary adenomas are benign tumours of the pituitary gland and account for about 15% of all intracranial tumours (Asa & Ezzat, 2002). They can affect any age group. In the absence of visual field disturbances adenomas can be difficult to diagnose. Patients are sometimes given unnecessary treatment such as anti-depressants because they have functional depression, which is secondary to the hormone imbalance caused by compression of the pituitary gland by the adenoma. There is a small but lifelong risk of adenoma recurrence, even after radiotherapy (RT). Patients require lifelong monitoring of endocrinological functioning and daily replacement of the hormones that their pituitary gland has ceased to produce. The fatigue and neurocognitive dysfunction previously found in patients treated for this disease can prevent them from enjoying their usual activities or continuing in their previous employment capacity. These outcomes are debilitating for the patient and their family and have significant health, social and economic consequences. The costs and benefits of the available treatments must be carefully assessed to ensure the best possible recovery for individual patients. It is therefore crucial that the neurocognitive consequences of each treatment protocol are fully understood. This will allow clinicians and patients to make informed decisions about the potential risks and benefits of various therapeutic interventions, and choose the option most appropriate for each patient.

Pituitary function and anatomy

The pituitary gland is regulated by the hypothalamus. It consists of two lobes: the anterior pituitary, which produces hormones that aid in the regulation of homeostasis, and the posterior pituitary. Whilst some hormones produced by the pituitary act directly on the body, others act indirectly by stimulating glands around the body to produce their own hormones. Due to this hierarchical nature of hormone regulation, the pituitary is therefore sometimes referred to as the 'master gland'. The pituitary regulates growth, blood pressure, gonad function, metabolism, electrolyte levels and thyroid function. Pituitary adenomas may produce hormones and cause complications related to hormone excess. For instance, in the condition of acromegaly, a growth-hormone secreting adenoma, formed during adulthood, will cause the hands, feet and jaw to grow in addition to increasing a person's risk of heart failure, diabetes mellitus and hypertension. Adenomas may also cause pressure effects. Pressure on the optic nerves reduces peripheral vision and can eventually lead to blindness. The pressure directly on the pituitary gland often results in the under-production of hormones, a condition known as hypopituitarism. This leads to diverse symptoms such as fatigue, weight loss or gain and a reduction of muscle mass. The symptoms experienced will relate directly to the hormones that are being under produced. More details on these hormones are given in the Physiology Chapter.

The Effects of Hormones on Neurocognitive Functions

Hormone receptors are present throughout the brain and hormone imbalance can be detrimental to brain tissue. There are receptors for many hormones throughout the brain. Glucocorticoid receptors are ubiquitous in the brain and modulate neurotransmitters, energy metabolism and nerve growth factors. Cortisol excess can cause steroid induced psychosis and depression whereas cortisol deficiency can cause a variety of cognitive symptoms including depression, confusion, apathy and paranoia. Growth hormone receptors are also found in the cortex and growth hormone deficiency is associated with memory impairment. Thyroxine increases the sensitivity of certain receptors to norepinephrine. Excess thyroxine can cause irritability and anxiety whereas thyroxine deficiency leads to fatigue and somnolence. Prolactin receptors have not been found in cortical tissue and so it is unlikely that prolactin will

have a direct effect on the brain. The location of the pituitary gland, along with other important nearby brain structures, is shown in Figure 1.

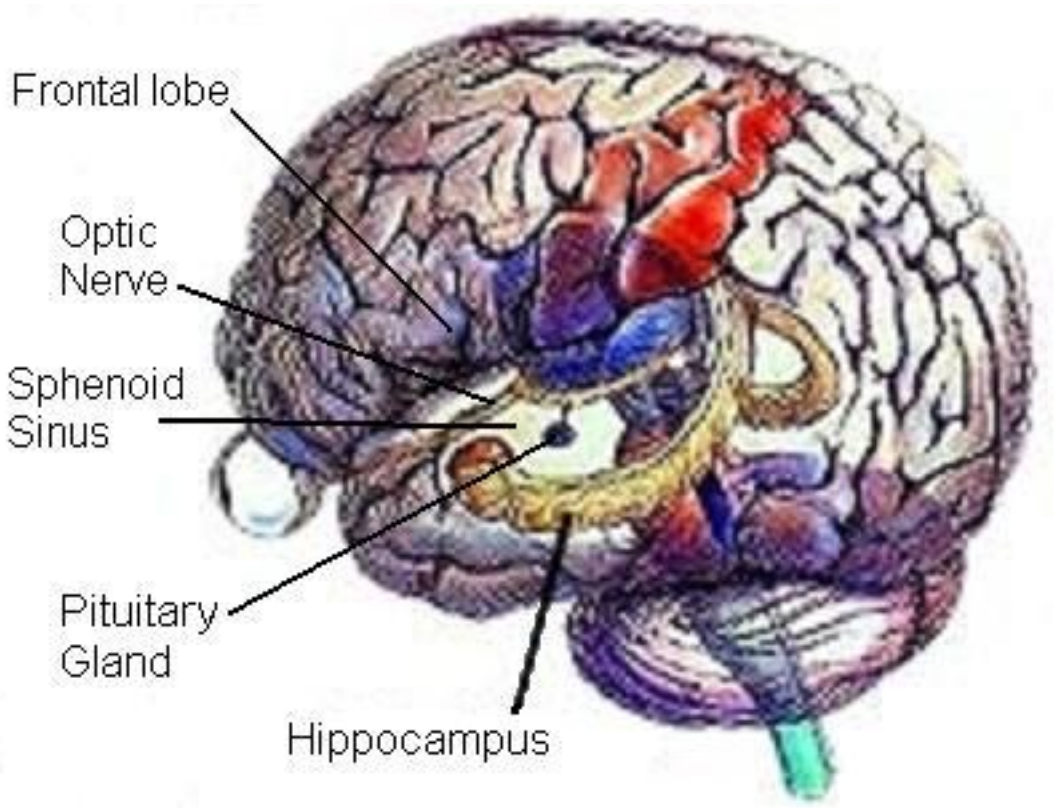

Figure 1: Diagram of the brain showing the structures surrounding the pituitary gland

Over a series of experiments, Lupien *et al*. (Lupien, Gillin, & Hauger, 1999; Lupien et al., 2002) found that administering 35mg of hydrocortisone in the morning via bolus injection had no significant effect on memory whilst the same dose of hydrocortisone in the afternoon improved the speed with which participants completed verbal memory tasks. They also found that when cortisol production was inhibited by metyrapone given in the afternoon, recall was impaired and that this observation was reversed by hydrocortisone administration. Others (Kuhlmann, Kirschbaum, & Wolf, 2005) have observed a reduction in delayed recall after cortisol administration for negative words more than for neutral words, suggesting inappropriate levels of cortisol replacement may exert different effects under different conditions. Patients with Cushing's disease have also been found to show poorer performance on several

subtests of learning, delayed recall, and visual-spatial ability associated with higher cortisol levels (Starkman, Giordani, Berent, Schork, & Schteingart, 2001).

Working memory, the ability to briefly hold and manipulate small amounts of information, such as mental arithmetic, appears unaffected by cortisol (Kuhlmann et al., 2005; Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000). This also seems to be the case with executive function (MacLullich et al., 2005). However, switching and selective attention has been shown to deteriorate when a person's cortisol level is lower (Vedhara et al., 2000), although studies that have experimentally manipulated cortisol levels have found that sustained attention is unaffected by cortisol (Wolkowitz et al., 1990; Lupien et al., 1999; Kuhlmann et al., 2005).

Administering exogenous levothyroxine to induce sub-clinical hyperthyroidism does not seem to affect cognitive performance in healthy individuals over a period of 45 days (Baethge et al., 2002). However, hypothyroidism has been shown to selectively impair delayed recall whilst leaving immediate recall intact (Burmeister et al., 2001). Difficulties with verbal memory retrieval have also been found but these resolved with levothyroxine replacement (Miller et al., 2006).

Event-related brain potentials are stereotyped electrophysiological responses caused by neurocognitive processes such as memory or attention, to any internal or external stimulus. The P300 is a positive deflection of voltage in the neurons that should occur about 300ms after an unpredicted event or stimulus is presented. Research using healthy adults who were made subclinically hyperthyroid found that reaction times on computer tasks did not vary with levothyroxine administration but the P300 component of their event-related potentials showed a significant reduction in amplitude suggesting a reduced ability to process information (Munte, Radamm, Johannes, & Brabant, 2001), although this reduction in amplitude has been shown to be reversible (Ozata, Ozkardes, Odabasi, Corakci, & Gundogan, 1997). Working memory and executive functions such as inhibition and task switching seem to be largely unaffected by hypothyroidism (Prinz et al., 1999; Baethge et al., 2002) although hyperthyroid patients have shown impairment on a test of inhibition, Trails B (Yudiarto, Muliadi, Moeljanto, & Hartono, 2006).

Childhood growth hormone deficiency (GHD) has been recognised as a significant variable leading to neurocognitive problems which can be improved by growth hormone (GH) replacement (Arwert, Deijen, Muller, & Drent, 2005; Deijen, de Boer, & van der Veen, 1998). Patients with adult-onset GHD also demonstrate impairment on immediate and delayed recall (Deijen, deBoer, Blok, & vanderVeen, 1996). Adult-onset GHD patient's have shown improvements in attention after six months of GH replacement suggesting the deficiency was previously impairing their attention (Oertel, Schneider, Stalla, Holsboer, & Zihl, 2004). Research into GHD has also found that patients have significantly lower scores than controls on spatial learning (Bulow, Hagmar, Orbaek, Osterberg, & Erfurth, 2002).

Sex hormones can affect cognition differently according to a person's age, (Mulnard et al., 2000) especially if age inappropriate levels are given to older adults (Espeland et al., 2004). Estrogen has been shown to have a positive effect on verbal memory in younger women who have recently experienced menopause, either naturally (Stephens, Bristow, & Pachana, 2006; Dumas, Hancur-Bucci, Naylor, Sites, & Newhouse, 2008) or surgically (Phillips & Sherwin, 1992). This is thought to be due to a protective effect on cholinergic neurones by oestrogen (Gibbs & Aggarwal, 1998). However, older women do not experience this protective effect. This may be due to a reduction in muscarinic receptors to which estrogen induces an increase in NMDA binding (Norbury et al., 2007). Testosterone may be beneficial to men in whom it correlates with switching attention (Thilers, MacDonald, & Herlitz, 2006). In a study of nearly 1400 individuals in the normal population, Thilers *et al*. (2006) also found verbal fluency to be positively correlated with free testosterone in men, yet negatively correlated with testosterone in women. Testosterone deprivation in men treated for prostate cancer has been associated with poorer recall (Beer et al., 2006) and recognition (Bussiere, Beer, Neiss, & Janowsky, 2005) of verbally presented semantic material. However, higher testosterone levels have also correlated with poorer performance on executive functioning tasks in men over 50 years of age (Martin et al., 2004).

Types of surgery for pituitary adenomas

The two main surgical approaches to the pituitary gland are transsphenoidal and transcranial. Transsphenoidal surgery is conducted transnasally (through the sphenoid

sinus) or sublabially (between the top lip and upper gum). This is the surgery of choice, as it is less invasive and carries less risk than a transcranial operation; which involves making an incision through the front of the cranium and retracting the frontal lobe to reach the pituitary gland. However, the transsphenoidal route only gives access to the midline of the pituitary fossa and so if the adenoma has a lateral supersella extension, it cannot be fully reached and transcranial surgery may be considered.

The main risks of either type of surgery are leakage of cerebrospinal fluid (CSF), hormonal disturbances and damage to the optic nerves. CSF leakage occurs quite frequently during pituitary adenoma operations but the source of the leak can usually be sealed by the surgeon if they occur. However, if CSF leaks go unnoticed during surgery or are not completely sealed, the brain is at risk of infection and developing meningitis. If a CSF leak is found post-operatively, a second operative procedure is required in order to seal the leak.

Hormone disturbance is likely to occur if a large amount of pituitary tissue is removed with the adenoma, and loss of vision can result if the optic nerve near the pituitary is damaged during the operation. The risk of optic nerve damage is greater during transcranial surgery because the surgical route passes closer to this nerve tissue. The increased risk posed by transcranial surgery is due to the potential contusion damage caused by retraction of the frontal lobe tissue during the operation.

The risks to the patient increase if adenomas reoccur, requiring a second operation using the same route. The first transsphenoidal operation partially modifies the anatomical markers that the surgeon uses as a guide, increasing the difficulty of remaining on the midline. The first transcranial operation will have left adhesions in the tissues causing them to bind together and thereby making tearing and blood vessel haemorrhage more likely.

Radiotherapy for pituitary adenomas

During surgery, the surgeon may be unable to excise all of the adenoma, leaving a remnant behind. In this instance, RT may be recommended to reduce the chance of adenoma regrowth. The x-rays that cause the required radiation damage in tissue are

delivered to the target area from three different directions (fields) so that the tumour and immediately surrounding tissue receive the full dose of radiation whilst healthy tissue further from the tumour incurs a progressively lesser dose. To ensure the radiation beams are always focused on the correct location, the patient's head is immobilised during treatment by a plastic mask. More recently, Gamma-Knife RT has also been used in the treatment of pituitary adenoma. This method directs radiation at the tumour from over 200 separate beams. However, this method of RT delivery has not been used in any of the studies discussed in this literature review chapter.

When the ionizing x-rays interact with tissue cells they dislodge electrons from water molecules. These negatively charged free electrons associate with polar water molecules, temporarily reducing their mobility. The water molecule that has lost its electron breaks down into a hydrogen ion and an OH radical. Oxygen then reacts with these free radicals to produce organic peroxy radicals that fix previous radiation damage in place. This damage is most likely to kill cells when it produces double-strand breaks in DNA. Each Gray of radiation produces approximately 40 initial double-strand breaks in each cell. The presence of oxygen reduces the amount of radiation needed to kill cells. Accordingly, hypoxic tumours are two to three times more radioresistant than well oxygenated cells. Tumours often become hypoxic when they outgrow their available blood supply. Cells are also more resistant during the S phase of their lifetime, when they are replicating DNA to make chromosomes from chromatids. Cells are most radiosensitive during the G2 phase, during which they create the structures needed to divide, and during mitosis, when there is reduced time for the cell to repair radiation damage before dividing into daughter cells. Tumours regrow after unsuccessful treatment if some neoplastic stem cells in the tumour have retained their ability to proliferate. Both hypoxia and irradiating cells during S phase will make this more probable. Giving radiotherapy in several fractions instead of one session reduces this problem. The normal 24 hour period between doses allows cells in the S phase to move into the later G2 phase, so a new portion of cells can be killed with each dose. When well oxygenated cells near the tumour's blood supply die it allows cells that are further from the supply to have greater access to oxygen, resulting in increased sensitivity to subsequent radiotherapy. The effect of RT is determined by the rate of cell turnover. This may result in a quick effect of RT on

tumour cells accompanied by a gradual effect of RT on neural tissue, which has a slower rate of cell turnover.

Effects of Surgery and Radiotherapy on Neurocognitive Function

It is unlikely that either form of pituitary surgery will *directly* damage the hippocampus due to its anatomical distance from the pituitary gland. However, transcranial surgery has the potential to cause damage to the anterior brain structures. During transcranial surgery it is necessary to retract the frontal lobe to access the pituitary gland, thereby increasing the risk of damage to the cortical tissue on the underside of the frontal lobe. Accordingly, transcranial surgery has a greater potential for impairment of executive functions than does transsphenoidal surgery.

During RT, the medial temporal and frontal lobes are within the field of radiation. The medial temporal lobe receives approximately 70-100% of the RT that the pituitary gland receives, amounting to about 32-45 Gy (Dr Ian Geh, personal communication, calculated from treatment plans). One of the most common side effects of therapeutic irradiation is dose dependent damage to blood vessels. The vasculature is the most vulnerable as the vessel walls largely consist of radiosensitive endothelial cells. CT and MRI may show focal neurological abnormalities in the form of demyelination of white matter. When patients experience radiation induced symptoms, cognitive impairments are prominent. It is possible that asymptomatic patients with white matter pathology are experiencing sub-clinical cognitive dysfunction.

Patient outcome may partially depend on how long ago they received treatment. For example, in a study of patients irradiated for base of skull tumours, it was found that the patients treated before 1985 experienced the poorest neurocognitive outcomes. Patients who received RT experienced a higher relative risk of mortality from cerebrovascular disease, although RT *per se* has not been confirmed as an independent risk factor. It is possible that pituitary RT is increasing the risk of cerebrovascular disease by disrupting normal vascular function; or by causing hypopituitarism, which is itself associated with an adverse cardiovascular risk profile; or a combination of both (Tomlinson et al., 2001).

Operational definition of the term 'neurocognitive'

The term 'neurocognitive' refers to the behavioural expression of brain functioning. This includes modalities such as selective attention, sustained attention, memory, language, executive functioning, fine motor function, spatial ability and processing speed. The neurocognitive deficits commonly highlighted in pituitary patients affect memory, sustained attention and executive functioning. This differs from the term 'neuropsychological', which refers to behaviour that is not necessarily a direct consequence of brain functioning. For example, depression could be the result of brain damage or a person's reaction to their circumstances and environment. The direct neurocognitive effects of pituitary adenoma, surgery and RT will be reviewed here. Secondary or reactive disabilities will not be discussed.

Aims of this Literature Review

The aim of this literature review chapter is to use the current literature to assess whether or not non-functioning pituitary adenoma and its treatment affects neurocognitive functioning. If this is the case, the review will explore which treatments are affecting neurocognitive functioning; which functions are affected; and the time course over which cognitive dysfunction becomes evident.

Method

Electronic searches were performed from the earliest dates available on PsychINFO (1806), Medline (1966), EMBASE (1980), The Cochrane Library (1800) and Web of Knowledge (1970) until September 2009 using the search terms PITU* and TREAT* and (COG* or NEUROCOG* or PSYCH* or NEUROPSYCH*) with articles limited to 'human' and 'English language'. The reference lists of any relevant articles were checked for other relevant studies. The National Research Register was also searched for recently undertaken and not yet published studies using the search terms PITU* and (COG* or NEUROCOG* or PSYCH* or NEUROPSYCH*). The investigators were contacted for any results they had. Six studies were found that tested patients after surgery and/or radiotherapy for pituitary adenomas. Two prospective studies

were found on radiotherapy for low grade neoplasms including some pituitary adenomas. These studies are shown in Table 1.

Table 1: Characteristics of samples

Study	Type of research	Patients (n)	Controls (n)	Surgery group (n)	RT group (n)	Surgery + RT group (n)	Drugs only group (n)	CM group (n)
Grattan-Smith et al. (1992)	Cross-Sectional	65	21	10	14	24	Unknown (10 unaccounted for)	7
Peace et al. (1997)	Cross-Sectional	36	36	9		18	2	7
Peace et al. (1998)	Cross-Sectional	69	23	21		25	23	
Baum et al. (1998)	Cross-Sectional	40		17	3	15	2	3
Guinan et al. (1998)	Cross-Sectional	90	19	21	10	41	18	
Armstrong et al. (2002)	Prospective	26			26			
Torres et al. (2003)	Prospective	17				17		
Noad et al. (2004)	Cross-Sectional	71		38		33		

CM = Conservatively managed; RT = Radiotherapy

RESULTS

Variations in the methods and analysis strategies between these studies have resulted in a heterogeneous literature that is difficult to amalgamate. Accordingly, each paper is summarised in chronological order, as some of the later studies have based aspects of their methodology on the findings of earlier studies.

Grattan-Smith, Morris, Shores, Batchelor & Sparks (1992)

Grattan-Smith et al. (1992) first highlighted potential neurocognitive problems in patients irradiated for pituitary tumour. They reviewed irradiated patients within a five year period, excluding only patients who had developed dementia. They compared these patients to patients with pituitary adenoma who had not received RT, in an attempt to separate the effects of RT from the effects of tumour and surgery. They compared both pituitary adenoma groups to chronic illness inpatient controls using measures of executive function and visual and auditory memory. They found no significant differences between the two treatment groups of patients with pituitary adenoma. However, both treatment groups performed below what Grattan-Smith et al. considered clinically acceptable norms. Both treatment groups also performed significantly worse than the inpatient controls on visual recall, delayed memory and the switching task, Trails B. Deficits were found in both groups of patients with pituitary adenoma, suggesting that executive and memory dysfunction is experienced by all patients with pituitary adenoma, regardless of whether they are treated with RT.

Due to the exploratory nature of the Grattan-Smith et al. study, many methodological considerations needed to be addressed. The wholesale grouping of patients who had or had not received RT resulted in patients who had received different types of surgery or medication being analysed together as one group. This resulted in the non-RT group having a greater number of patients who were treated less invasively, such as with medication only. The results of the study could, therefore, be skewed towards showing more impairment in the RT group due to treatments other than RT. Some patients that perhaps should have been excluded on the basis of alcohol abuse, regular marihuana use or stroke were included in the study. As these substances/conditions have been shown to have detrimental effects upon cognition (Loeber et al., 2009;

Solowij & Battisti, 2008; Donovan et al., 2008) their inclusion may have biased this study into highlighting cognitive dysfunction that was due to other brain insults not related to the pituitary adenoma or its treatment. The endocrine status of the patients was not given, so differences in the number of hormone deficiencies might have affected the results. Finally, only pre-morbid intelligence was assessed using the NART. There was no measure of current intellectual functioning (IQ). This prevented the comparison of memory functioning and IQ as pre-morbid IQ is unsuitable for the prediction of current memory function.

Peace et al. (1997)

Peace et al. (1997) rectified some of these methodological issues using a different analysis strategy. They compared patients who had received transsphenoidal surgery with patients who had received transcranial surgery as well as comparing patients treated with RT to patients treated without RT. They reported no difference between the patients on the basis of type of surgery or presence of RT. However, the surgically treated patients as a whole performed significantly worse than healthy controls on all measures of executive functioning and on recognition memory for faces. Surgically treated patients also performed significantly worse than non-surgically treated patients on some measures of auditory and visual memory. These results are commensurate with Grattan-Smith et al.'s original study, demonstrating deficits in executive function and to a lesser extent in memory. This study also implicates surgical treatment as a potential cause of these deficits. Unfortunately, this study did not mention some useful patient information including adenoma type or the number of patients in each surgery group who had received RT. Certain hormone producing adenomas such as Cushing's Disease are known to affect cognitive functioning, so a greater number of these patients in one group could bias the results. Again only the NART was used to measure pre-morbid IQ, with no measure of current IQ, and so no comparison with current memory performance could be made.

Peace, Orme, Padayatty, Godfrey & Belchetz (1998)

This research developed upon the methodology of Grattan-Smith et al. (1992) and Peace et al. (1997) by using a more structured approach to patient grouping, in order

to obtain a clearer contrast of the effects of different types of surgery. Peace et al. (1998) improved on their previous study design by grouping their patients according to the type of surgery they had received. This was to test the hypothesis that the type of surgery given to patients would affect the magnitude of deficits the patients experienced. By also including a group of patients only treated with medication, the possible effects of tumour and medication could be tested. This allowed for these effects to be controlled for within the statistical analysis of the effects of surgery, over and above the effects of adenoma. Peace et al. (1998) focused on the neurocognitive areas of attention, memory and executive function. They found no differences between any of the groups on measures of attention, but all the patient groups including the medication only group showed poorer performance on immediate and delayed auditory recall than the control group. Both surgery groups were poorer than the controls at list learning and recognition of faces suggesting both auditory and visual memory impairments. Interestingly, only the transsphenoidal group was poorer than the controls on block design. This counter-intuitive result means that patients who received the more invasive transcranial surgery performed slightly better, despite having received greater physical insult. The transcranially operated patients who had received RT also performed better at list learning than the transcranially operated patients who had not received RT. This could be due to the patients treated with surgery only having more invasive and potentially damaging surgery to remove all of their adenoma. They would, therefore, not require adjuvant RT. Peace et al. (1998) chose to measure impairment by comparing the number of patients in each group who scored below the tenth percentile on three or more subtests. Using this method a fifth of the non-surgical group, just under a third of the transsphenoidal surgery group and over 43% of the transcranial group were deemed to be impaired, compared to 4.3% of controls. This study again suggests that surgery is implicated in the memory deficits found in these patients whilst RT has not significantly affected these patients beyond any damage caused by their surgery. Disappointingly, whilst approximately 50% of the surgically treated patients had also received RT, Peace et al. again did not report which surgery group these patients were entered into, meaning any effect of surgery found could in fact be due to a greater number of RT treated patients being in one surgery group than the other. However, they found no differences between who had received RT and those who had not, rendering this less problematic.

Baum et al. (1998)

The Baum et al. (1998) study was not intended to assess the effects of RT, but as a study of the benefits of growth hormone. However the study is presented in a format that also allows comparison of neurocognitive functioning in patients who had been treated with RT versus those patients who had not. Baum et al. employed a superior selection of psychometric tests, comprising the WAIS-R, a large section of the WMS-R and several executive functioning tests. Both their RT and non-RT groups performed above average on tests of intelligence, executive functioning and the memory tests, with the exception of list learning in which they performed below average. The only difference found between the groups was on verbal fluency, where the RT group actually outperformed the non-RT group. This study differs from the previous research, in that the patients outperformed test norms, contradicting the evidence that patients have the neurocognitive deficits previously discussed, regardless of their treatment.

Guinan, Lowy, Stanhope, Lewis, & Kopelman (1998)

The most comprehensive and methodologically sound study published at this time is by Guinan et al. (1998). Their stated objective was to undertake a full comparison of all surgery and RT combinations by grouping their patients by type of surgery and/or treatment with RT. They also included medication only and control groups. The only group that was not included was a transcranial surgery without RT group, due to the lack of applicable patients available to them. Guinan et al. used the full WAIS-R and WMS-R, allowing a comparison between IQ and MQ, but only verbal fluency and a card sort test to measure executive function, giving a less extensive assessment of this domain. They found no difference between any of their groups and controls on attention/concentration, executive function, language or speed of mental processing. The patient groups did not show any absolute impairment because their general memory and delayed memory were within normal population limits. However, all of the patient groups except the RT only group demonstrated a poorer memory quotient (MQ) than would be predicted based on their IQs. The RT only group had a significantly lower IQ than the other groups and so this probably accounts for their lack of MQ-IQ difference; because the simple difference IQ-MQ comparison method

is less likely to show deficits in memory than the predicted difference method when used for people with a FSIQ of under 100.

Commensurate with previous studies, all the patient groups, excluding the medication only group, performed worse than the controls on the memory tests. The exception to this was for face recognition in which the transsphenoidal surgery without RT group achieved better scores than the controls. This may represent a selection bias in this group; however, this is unlikely as patients were matched closely for mean age and sex distribution in each group. When Guinan et al. re-analysed the results without the control group there was very little difference between the patient groups. The medication only group was less impaired on delayed recall but no other differences reached statistical significance.

The authors also re-analysed the data by both adenoma type and time since treatment and found no differences for either; although for the time since treatment comparison, patients treated within the last five years were compared with patients treated longer than five years ago. The five year cut-off appears to be somewhat arbitrary and it would perhaps have been preferable to conduct a more linear analysis rather than dichotomising the patients.

This study provides useful information when attempting to answer the aims of this review, mainly due to the large number of patients and groups. It found deficits only in the domain of memory and concluded that adenoma aetiology is unlikely to be significantly implicated in this area of impairment. In contrast, surgery, RT and to a lesser extent, medication was implicated as causes of memory impairment.

Armstrong et al. (2002)

Two prospective studies that have included pituitary adenoma patients in their samples of low-grade supratentorial brain tumours are Armstrong et al. (2002) and Torres et al. (2003). Both of these studies tested patients before RT. Some of the patients had unfortunately recently received surgery and this may have affected the baseline results. The Armstrong et al. (2002) study utilised an extensive test battery including visual and auditory attention, language, processing speed, visual and auditory memory, visuospatial perception, and a card sort test used to measure

executive function. Patients were tested every year after baseline, for six years, although only nine of the patients had participated in the study from baseline through to the six years of data collection. When comparing the baseline and year six assessment, patients showed a linear and constant improvement on tests of language, verbal fluency, processing speed, visual memory (both immediate and delayed) and auditory selective attention. There was also curvilinear improvement (steep improvement early on followed by a plateau into more shallow improvement) on another measure of processing speed. Curvilinear decline was seen on a different measure of visual memory, again in both the immediate and delayed conditions, and on sustained visual attention. These curvilinear declines, which at first showed improvement before deteriorating, are thought to reflect the late-delayed damaging effects of RT treatment. Whilst the results of the pituitary adenoma patients were not analysed separately, these patients had mean scores similar to or better than the overall group mean on the tests.

This study addresses both of the review questions. Some long term impairment occurred in the patients in some measures of memory and attention, whilst there were improvements on other measures of memory, attention and executive function. The study also describes a time course whereby patients experience a rebound effect from the acute symptoms of RT and improve until approximately four years after treatment when some of their scores start to decline again. This curvilinear decline is thought to reflect the late-delayed damaging effects of RT treatment. This article suggests that RT does not significantly damage cognitive functioning. Whilst this prospective data allows within-subject comparisons that are not possible from the retrospective data, the percentage of patients with pituitary adenomas was small (15%) and so the generalisability of these results to other pituitary patients is severely limited.

Torres et al. (2003)

The smaller second study (Torres et al., 2003) also attempted to map the time course of any changes in neurocognitive functioning. They tested 15 RT treated patients and two surgically treated controls for baseline and at least one follow-up assessment. Twelve of the RT treated patients were classified as ‘non-progressors’ as their adenomas did not regrow. The three ‘progressors’ suffered a recurrence of their

adenomas. After the baseline visit, reassessments were done at three months, six months, one year and two years. At three months, the non-progressor and surgery groups had improved from baseline on an auditory memory test. The progressors' performance declined on tests of immediate auditory recall, delayed auditory and visual recall, processing speed and inhibition. At six months, compared to three months the non-progressors and surgery groups improved on processing speed. At one year compared to six months the non-progressors improved on an inhibition task whilst the progressors declined further on visual delayed recall. Three comparisons were made with the final data collected on the non-progressors and surgery groups at two years. The first compared two years with the data collected at one year, the second compared two years versus baseline, and the third compared two years with three months in case immediate post-surgery effects had skewed the results of the baseline assessment. At two years versus one year the non-progressors improved on a measure of immediate verbal recall, digit span forward. At two years versus baseline the non-progressors improved on immediate and delayed verbal recall and on digit span backwards and at two years compared to three months there were no significant differences, suggesting post-surgery effects, which tend to last around three months may indeed have affected the baseline assessment. Overall, this study suggests that patients do not exacerbate any deficits they might already have from their adenoma surgery by having further treatment in the form of RT.

The Torres et al. (2003) study could be methodologically improved upon. There were only two surgically and not RT treated controls. This is too small a number to constitutes a control group. Two patients in the progressor group had also been treated with chemotherapy, which is not usual practice for pituitary adenoma patients, making this group less comparable to patients with pituitary adenoma in other studies. There was no test of intelligence used to compare to memory functioning and only trails A and B were used to measure executive function. Considering the very small number of patients in the study, a large amount of analysis was conducted without the use of any technique to reduce possible family-wise error. This increased the chance of the study finding a significant result which could have been a type 1 error.

Noad, Narayanan, Howlett, Lincoln & Page (2004)

The most recent publication on the neurocognitive effects of pituitary adenoma treatment is by Noad et al. (2004) who looked more narrowly at the possible effects of RT. They tested patients who received surgery between 1994 and 1997 by the transsphenoidal route and excluded patients who were either treated by the transcranial route or diagnosed with Cushing's Disease or craniopharyngioma. Just over half of the patients were given surgery only whilst the rest received surgery and RT. Noad et al. (2004) did not include control or medication only groups. They found no difference between the groups of pituitary patients on tests of memory. However, on the tests of visuo-spatial ability and visual memory (the Rey Figure Copy and recall) almost half of the patients scored below the tenth percentile on the copy task and over a quarter of patients scored below the tenth percentile on the recall. A fifth of the patients scored below the tenth percentile on immediate logical memory. There was a difference found between the two groups on a test of executive function, the Stroop test; on which the surgery and RT treated patients performed significantly worse than the patients treated with surgery alone.

In order to compare their results to Peace et al.'s (1998) study, Noad et al. also counted the percentage of patients who scored lower than the tenth percentile on three or more subtests. More than a quarter of the surgery and RT patients were impaired using this method of classification, compared to just 5% of the surgery only group, and this difference was significant. This is a much lower percentage than was found by the Peace et al. (1998) study. This could be due to technical advances in treatment, such as improvements in the quality of imaging (Gandhi, Christiano, Eloy, Prestigiacomo, & Post, 2009), that occurred during the time between the two studies, or simply because Peace et al. used slightly more subtests than Noad et al. and therefore three subtests represented a smaller proportion of the total number of tests administered, making it easier for patients to reach this threshold. Noad et al. drew no strong conclusions from their results. They suggested that both surgery and/or RT might separately affect cognitive function; that the patients' poor performance could be caused by the pituitary disease itself, or growth hormone deficiency. This addresses the question of whether or not patients experience cognitive deficits but not the question of what cause these deficits arise from. Although for executive function,

RT was implicated as a cause of reduced inhibition ability. Noad et al. chose to report all their results using medians and inter-quartile ranges instead of means and standard deviations. They did not state a reason for this unusual decision. They did not administer the WAIS-III and so no intelligence-memory comparison could be done. They also used only one test each to measure visual and auditory memory.

Effects of hormonal dysfunction on neurocognitive function

All of the studies into the neurocognitive effects of treatment for pituitary tumours have included patients with hormone producing tumours in their sample. This may have affected the results as several studies have found that abnormally high levels of some hormones can affect neurocognitive function. Over a series of experiments, Lupien *et al*. (Lupien et al., 1999; Lupien et al., 2002) found that administering 35mg of hydrocortisone in the morning via bolus injection had no significant effect on memory whilst the same dose of hydrocortisone in the afternoon improved the speed with which subjects completed verbal memory tasks. They also found that when cortisol production was inhibited by metyrapone given in the afternoon, recall was impaired and that this observation was reversed by hydrocortisone administration. Others (Kuhlmann et al., 2005) have observed a reduction in delayed recall after cortisol administration for negative words more than for neutral words, suggesting inappropriate levels of cortisol replacement may exert different effects under different conditions. Patients with Cushing's disease have also been found to show poorer performance on several subtests of learning, delayed recall and visual-spatial ability associated with higher cortisol levels (Starkman et al., 2001). Working memory, the ability to briefly hold and manipulate small amounts of information, such as mental arithmetic, appears unaffected by cortisol (Kuhlmann et al., 2005; Vedhara et al., 2000). This also seems to be the case with executive function (MacLullich et al., 2005). However, switching and selective attention has been shown to deteriorate when a person's cortisol level is lower, (Vedhara et al., 2000) although studies that have experimentally manipulated cortisol levels have found that sustained attention is unaffected by cortisol (Kuhlmann et al., 2005; Lupien et al., 1999; Wolkowitz et al., 1990). Administering exogenous levothyroxine to induce sub-clinical hyperthyroidism does not seem to affect cognitive performance in healthy individuals over a period of 45 days (Baethge et al., 2002). However, hypothyroidism has been

shown to selectively impair delayed recall while leaving immediate recall intact (Burmeister et al., 2001). Difficulties with verbal memory retrieval have also been found but these resolved with levothyroxine replacement (Miller et al., 2006). Event-related brain potentials are stereotyped electrophysiological responses caused by neurocognitive processes such as memory or attention, to any internal or external stimulus. The P300 is a positive deflection of voltage that should occur about 300ms after an unpredicted event or stimulus is presented. It is measured using electroencephalography. Research using healthy adults found that reaction times on computer tasks did not vary with levothyroxine administration but the P300 component of their event-related potentials showed a significant reduction in amplitude suggesting a reduced ability to process information (Munte et al., 2001), although this reduction in amplitude has been shown to be reversible (Ozata et al., 1997). Working memory and executive functions such as inhibition and task switching seem to be largely unaffected by hypothyroidism (Baethge et al., 2002; Prinz et al., 1999) although hyperthyroid patients have shown impairment on Trails B (Yudiarto et al., 2006).

Childhood GH deficiency (GHD) has been recognized as a significant variable leading to neurocognitive problems which can be improved by GH replacement (Arwert et al., 2005; Deijen et al., 1998). Patients with adult-onset GHD also demonstrate impairment on immediate and delayed recall (Deijen et al., 1996). Adult-onset GHD patients have shown improvements in attention after six months of GH replacement suggesting the deficiency was previously impairing their attention (Oertel et al., 2004). Research into GHD has also found that patients have significantly lower scores than controls on spatial learning (Bulow et al., 2002). Several previous studies examining the effects of pituitary adenoma and treatment have not stated whether patients were GH deficient (Grattan-Smith, Morris, Shores, Batchelor, & Sparks, 1992; Noad, Narayanan, Howlett, Lincoln, & Page, 2004; Guinan, Lowy, Stanhope, Lewis, & Kopelman, 1998; Armstrong et al., 2002; Torres et al., 2003), while others have stated that all patients had GH deficiency (Peace et al., 1997; Peace, Orme, Padayatty, Godfrey, & Belchetz, 1998).

Sex hormones can affect cognition differently according to a person's age (Mulnard et al., 2000), especially if age inappropriate levels are given to older adults (Espeland et

al., 2004). Estrogen has been shown to have a positive effect on verbal memory in younger women who have recently experienced menopause, either naturally (Stephens et al., 2006; Dumas et al., 2008) or surgically (Phillips & Sherwin, 1992). This is thought to be due to a protective effect on cholinergic neurones by estrogen (Gibbs & Aggarwal, 1998).

However, older women do not experience this protective effect. This may be due to a reduction in muscarinic receptors to which oestrogen induces an increase in NMDA binding (Norbury et al., 2007). Testosterone may be beneficial to men in whom it correlates with switching attention (Thilers et al., 2006). Thilers *et al*. (2006) also found verbal fluency to be positively correlated with free testosterone in men, yet negatively correlated with testosterone in women. Testosterone deprivation in men treated for prostate cancer has been associated with poorer recall (Beer et al., 2006) and recognition (Bussiere et al., 2005) of verbally presented semantic material. However, higher testosterone levels have also correlated with poorer performance on executive functioning tasks in men over 50 years of age (Martin, Wittert, Burns, & McPherson, 2008).

Two studies examining cognition in patients with pituitary adenoma have entered gender as a covariate into analyses (Grattan-Smith et al., 1992), but these studies did not report whether there were any differences on any of the outcome measures between females and males. The remaining research has not compared the performance of their female and male patients (Peace et al., 1997; Noad et al., 2004; Peace et al., 1998; Guinan et al., 1998; Armstrong et al., 2002; Torres et al., 2003). For the reasons outlined above, it is imperative to take into account the endocrine status of the patient to achieve reliable assessment of the impact of pituitary disease upon neurocognitive functioning, especially in regard to cortisol and GH, which consistently emerge as important for achieving full cognitive potential. It is inappropriate to group together patients with actively functioning tumours and patients with clinically non-functioning pituitary tumours. Instead, patients with non-functioning adenoma constitute a more homogenous group on which to identify the effects of treatment.

DISCUSSION

The questions that this review originally set out to answer was whether or not treatment of pituitary adenomas affects neurocognitive function and if so, what type of treatment and what type of function. The time course of the appearance of cognitive deficits was also questioned.

In general, researchers have administered tests of selective attention or sustained attention, executive function and memory. Most studies have found patients to be in normal ranges and not different to controls on measures of selective attention or sustained attention (Peace et al., 1997; Peace et al., 1998; Baum et al., 1998) whilst the prospective studies on RT (Armstrong et al., 2002; Torres et al., 2003) found improvement on some but not all attention subtests. It is the neurocognitive area of memory where researchers have consistently found deficits, whilst studies have shown disagreement on the executive functioning impairments that are or are not experienced by patients with pituitary adenoma.

Executive functioning

Grattan-Smith et al. (1992) and Peace et al. (1997) both found patients' performance to be worse than controls on a switching task and Peace et al. (1997) also found their patients to be worse than controls on all four of the executive functioning tasks administered. In contrast Guinan et al. (1998) found patients to be no different to controls on any of their executive functioning tasks, although some of the tasks they used were different. Variations between groups have also been found. In Peace et al.'s (1998) later study, it was only the transsphenoidally operated group that performed significantly worse than controls on block design, with the other patient groups performing somewhere in between the transsphenoidal group and the controls. Baum et al. (1998) found that their RT treated group actually outperformed the non-RT treated patients on verbal fluency, whilst Noad et al. (2004) found the opposite on the Stroop test, a measure of inhibition, with the surgery and RT treated patients showing poorer performance than the surgery only group. In the prospective studies patients showed improvement over six years in verbal fluency (Armstrong et al., 2002) and also improvement on a switching task between six and 12 months after treatment (Torres et al., 2003), although this improvement was not sustained with a non-

significant difference between baseline and the two year follow-up. Overall, the balance of evidence so far published would suggest that patients have some mild problems with various executive functions, regardless of treatment, although there appears to be a lot of variation between studies and patients. This variation could be due to the tests used being normed on a smaller number of the general population than newer tests (Wechsler, 1987; Wechsler, 1997b). The mechanism of injury for these deficits is unknown and could be due to a number of factors such as hormone disturbance, direct damage during surgery to brain tissue or surrounding blood vessels, or RT damage in the form of demyelination or white matter hyperintensities.

Memory

Recall of new material is the neurocognitive ability in which patients most frequently and reliably experience deficits. All of the retrospective studies found that patients performed worse than controls or test norms on at least one measure of memory; and most studies found patient groups to be worse on measures of both visual and auditory memory. There was also little difference found between the groups. Four studies found no differences between the groups at all whilst others found varying differences between treatment types. Peace et al. (1997) found that the non-surgically treated patients performed better than the surgically treated patients on tests of visual and auditory memory. However, they found no differences based on type of surgery or presence of RT treatment. Similarly, Peace et al. (1998) later found their surgery group to be worse than non-surgically treated groups on auditory memory and worse than controls on visual memory, but again there was no difference between the patients treated with surgery alone or surgery and RT. When comparing patients to test norms, Guinan et al. (1998) found that they were within normal limits. However, given their high IQs, all the patient groups except the RT only group showed a relative MQ-IQ deficit. The results are somewhat ambivalent for the first of the prospective studies. On one measure of visual memory patients showed linear improvement whilst on another they showed curvilinear decline. In the second prospective study, patients who did not suffer tumour regrowth showed improvements at various stages over two years and an overall improvement from baseline on two measures of auditory memory. A summary of the tests used and the findings of each study are shown in Table 2.

Table 2: Summary of the tests used and the findings for memory of the literature reviewed

Study	Tests used (visual)	Tests used (auditory)	COMMENTS
Grattan-Smith et al. (1992)	· WMS VR delayed · RMT faces · ROCFT recall	· WMS LM delayed · RMT words	· Both patient groups worse than controls on WMS LM and VR delayed and ROCFT recall
Peace et al. (1997)	· RMT faces	· AVLT · WMS LM	· Patients worse than controls on RMT faces · Surgery patients worse than non-surgery treated patients on AVLT and RMT faces
Peace et al. (1998)	· RMT faces	· AVLT · WMS LM	· Surgery patients worse than non-surgery patients on AVLT and controls on RMT faces · Patients worse than controls on LM
Baum et al. (1998)	· WMS-R VR · WMS-R SS · Continuous recognition test	· WMS-R LM · WMS-R DS · CVLT	· Patients scored within normal limits on all tests except the CVLT where they scored over one standard deviation below test norms
Guinan et al. (1998)	· RMT faces	· WMS-R · RMT words · AMI	· Relative MQ-IQ deficit in all groups except RT only and controls · All groups worse than controls on WMS-R, RMT words and faces (except TPS for faces)
Armstrong et al. (2002)	· SS forward · RBVRT · ROCFT · Biber FLT	· DS forward · Word span · AVLT	· Over six years, linear improvement on ROCFT immediate and delayed · Curvilinear decline on Biber FLT
Torres et al. (2003)	· 10/36 Spatial Recall Test	· SR procedure · WMS-R DS	· At two years versus baseline non-progressors improved on the SR procedure
Noad et al. (2004)	· Rey Figure Copy recall	· WMS-R LM	· 27% below 10th percentile on Rey Figure Copy recall · 20% below 10th percentile on immediate LM

WMS-R = Wechsler Memory Scale-Revised; LM = logical memory; VR = visual reproduction; RMT = Recognition Memory Test; AMI = Autobiographical Memory Interview; ROCFT = Rey-Osterrieth Complex Figure Test; AVLT = Auditory-Verbal Learning Test; SS = Spatial Span; DS = Digit Symbol; CVLT = California Verbal Learning Test; RBVRT = Revised Benton Visual Retention Test; FLT = Figure Learning Test; SR = selective reminding

Despite some promising results from the two prospective studies of RT, in which patients showed long-term improvement on many tests, it must be argued that pituitary adenoma patients have memory problems in both the visual and auditory domains, and due to the lack of treatment group differences found, these deficits seem to be present largely independent of treatment. The evidence for cognitive dysfunction in the domain of executive function is weaker than the evidence for memory dysfunction. Whether or not these deficits are caused by treatment, and if so, which one, is still unanswered. It is likely that there is a short-term rebound improvement from the resolution of acute post-treatment symptoms and this has been demonstrated by the two prospective studies but the long-term course of any effects is still unknown.

The literature produced so far has also raised some new questions. If the adenoma itself is to blame for any deficits; why? This could be due to pressure effects, hormonal disruption, a combination of both or an alternative explanation that has not yet been hypothesized in the current literature. To answer these questions, more sophisticated assessments by trained psychologists is required. Until then, endocrinologists, neurosurgeons and oncologists will not be able to properly advise their patients of the true risks and benefits of treatment.

Problems with the current literature

There are several problems with the current literature that make it difficult, if not impossible, to suggest the cause of any neurocognitive deficits in patients treated for pituitary adenoma. In most of the earlier studies several of the patients have either been treated some decades ago or the range of time since treatment has not been given. In one study, patients were treated as far back as 1966. Since this time, many advances in both surgical and RT techniques may mean that patients treated many years ago are not comparable to patients treated more recently. In several studies, one group was treated significantly more recently than another, whilst in others time since treatment for each group has not been stated. Age of diagnosis has not been stated (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Guinan et al., 1998; Baum et al., 1998; Armstrong et al., 2002; Torres et al., 2003; Noad et al., 2004), allowing the inclusion of patients with child-onset adenomas. In these patients, deficits could have been alleviated by brain plasticity which is greater at a younger age and can allow the redistribution of cognitive functions to nearby undamaged brain regions (Johnston, 2009; Johnston, 2004). Another detail omitted from all but the most recent study is the original size of the patients' adenomas and whether there was a difference in this between the groups, forcing the reader to speculate that group differences found could be due to the more impaired group having larger more invasive tumours that necessitated more aggressive treatment.

In some articles adenoma type has not been given and in other articles patients with Cushing's, craniopharyngioma and acromegaly have been included. Several articles have associated high cortisol levels with poorer neurocognitive performance in healthy individuals and this has also been found in patients with Cushing's disease. The inclusion of Cushing's patients could therefore affect the results, especially if

there were more Cushing's patients in one group than another. The inclusion of craniopharyngioma and acromegaly patients is also a potential problem. Whilst little research into the neurocognitive outcomes of these adenomas has been conducted, Tomlinson et al. (2001) found that craniopharyngioma patients had a standardised mortality ratio approximately four times higher than other pituitary adenoma types. If a craniopharyngioma and its treatment are causing this extent of damage to a patient's physical health then it is feasible that it could be affecting their neurocognitive function. Therefore, including craniopharyngioma in a study sample is adding a fundamentally different tumour type to other adenomas. The increased risk of stroke and diabetes mellitus that comes with acromegaly may also have a secondary effect on cognitive abilities (Moller & Jorgensen, 2009; Beeri, Ravona-Springer, Silverman, & Haroutunian, 2009).

In relation to this criticism, previous studies have not measured blood hormone levels on the day of testing. The relationship between hormone levels and cognition has therefore not been examined in these patients. Sex differences have also not been examined. Only two studies analysed for sex differences (Grattan-Smith et al., 1992; Armstrong et al., 2002) but they did not report any differences. They did, however, enter sex as a covariate to other analyses, suggesting that some difference between the sexes must have existed to make this analysis necessary.

The final criticism of the current literature is based on the range of tests used. Often it is only the NART which has been used as an estimate of pre-morbid intelligence with no measure of current intelligence. This fails to address whether treatment of pituitary adenomas has damaged intellectual functioning or if there is a difference between full scale IQ and memory. This is important because as demonstrated by Guinan et al. (1998), patients could show memory function within normal ranges and yet have memory deficits in comparison to their IQ. Of the studies that have used tests of intelligence, the number of tests has often been scant and not conducive of a memory-intelligence comparison. In most of the later research a greater selection of visual and auditory memory tests have been used. However, some studies have used too small a variety of memory tests to give a full and accurate picture of memory function. In contrast to the large amount of time and attention that potential memory deficits now receive, executive functioning has not been so closely examined. Despite earlier

research highlighting executive function as an area in which pituitary patients might experience dysfunction, most later studies have used three or less subtests to measure various aspects of executive functioning. Whilst this can be assumed to be a standard amount in clinical practice, the relative lack of subtests used to measure executive functions in comparison to memory may explain some of the variation in patients' executive function performance between studies.

Suggestions for future research

A 'gold standard' investigation of the neurocognitive effects of pituitary adenoma and its treatment would be a prospective study offered to all patients with newly diagnosed non-functioning macroadenomas who can be tested at baseline and following any treatment they receive, and then followed up annually or bi-annually. However, this is labour intensive and is unlikely to provide any firm answers in less than five years. In the meantime, a well-designed cross-sectional study could determine differences between groups of patients particularly in relation to time since treatment and should try to find patients with similar time since surgery, or most recent treatment, depending on which the researchers deem to be a more equivalent comparison. Future studies should look specifically for, and attempt to balance, differences between groups in original adenoma size to avoid being forced to speculate that any difference they have found between a surgery only and a surgery and RT group is possibly just due to one group having bigger adenomas that had to be more aggressively treated. Patients with craniopharyngioma should be studied separately, as their morbidity is so much higher than patients with pituitary adenomas that they are incomparable. If the effect of hormone excess on neurocognitive function is to be excluded, then studies should concentrate on patients with non-functioning adenoma whose endocrine status is stable. This should also be confirmed with blood tests on the day of testing. The use of only patients with non-functioning adenomas would also allow comparisons to be made between treated patients and patients who are being managed conservatively. This would give a true non-surgery group rather than a medication only group. Finally, better normed and more extensive neurocognitive testing is required. Whilst time consuming, Armstrong et al. (2002) demonstrated that it can be done. This will give a more rounded evaluation and thus, these improvements will form the basis of this thesis.

Statement of Intent

Previous studies into the effects of treatment for pituitary adenomas upon neurocognitive function have been unable to determine the causes of the impairments found in patients. This is due to the combination of a number of methodological difficulties in the existing literature. The inclusion of different tumour types has created heterogeneity within treatment groups. This is especially probable when tumour types which secrete hormones known to affect cognition are included. Patient groups have also differed in treatment variables including time since surgery or RT and original tumour size. These parameters have the potential to affect neurocognitive results. Previous studies have often omitted the testing of intelligence, instead using a premorbid estimate with the NART and have used abbreviated tests or shortened versions of full test batteries. Shortened test versions can systematically under or overestimate the function of interest (Axelrod, 2002). The methodological difficulties in existing literature severely curtail the conclusions that can be drawn from the results. The use of inappropriate or unstandardised test materials also limits or prevents comparisons across studies.

Aims

The aim of this thesis is to determine whether the presence or treatment of pituitary adenomas has negative consequences for cognition. If this is so, the mechanism of impairment will be investigated. It is aimed to establish the specific profile of neurocognitive deficits that may be associated with each treatment. In order to exclude the effects of hormone hypersecretion on cognition from skewing the results, only patients with non-functioning adenomas will be included. Previous research has highlighted the domains of memory and executive function as cognitive areas in which patients may experience deficits. Complete test batteries with good psychometric and interpretative reliability and validity will be used to achieve the aforementioned aims and exploration of functioning. Factors that are expected to have a potential effect on cognition and so will be included in analyses of treatment effects are: presence of surgery; type of surgery; presence of radiotherapy; number of hormone replacements; blood hormone levels and the size of the original tumour before surgical intervention.

Section 2 – Behavioural Data

Structure of Section

The next four chapters contain the neurocognitive outcome data obtained from the patient sample, arranged as follows:

General method: This describes the patient sample, the procedure used, the tests administered and the data preparation required before the data could be analysed.

Cognitive functioning: the three chapters dedicated to the individual areas of cognitive functioning will each discuss the area of function in question and the previous research conducted in this area. A hypothesis is given for how pituitary patients are expected to perform. The obtained data are presented and discussed in relation to previous research.

> *General intellectual functioning*: the concept of intelligence and how it is tested and used in the previous literature is discussed. The intelligence data of the current patient sample is analysed according to test procedures as well as by the Cattell and Horn (Horn & Cattell, 1966) Gc-Gf distinction of intelligence.
>
> *Memory*: The various processes subsumed within the term 'memory' are described. The test of memory used, the WMS-III is discussed in terms of which of these processes the test measures. Data are analysed according to the specified test procedure.
>
> *Executive Functions*: There are various models of EF which are explained in this chapter. The various tests employed by previous studies and the EFs they measure are discussed. The executive and posterior functions required for successful completion of each D-KEFS subtest are described and the current patient data is presented.

General Method

Participants

The participants who took part in this study may be classified as representing four different treatment groups. The four groups were treated with either surgery only, RT only, or both surgery and RT. A group of patients who were conservatively managed (who had not received surgery or RT) were also included. All patients receive annual blood tests to assess hormone levels, and hormone deficiencies are corrected with hormone replacements with the exception of GHD which was not corrected in every patient. The four treatment groups are outlined in Table 3. Surgery was conducted by the transsphenoidal or transcranial route to the pituitary gland and RT was given using the standard three-field technique.

Table 3: The tumour type and treatment received of each group

Group:	**Conservatively Managed**	**Surgery only**	**Radiotherapy only**	**Surgery & RT**
Tumour Type	NFA	NFA	NPC	NFA
Pituitary Surgery	No	Yes	No	Yes
Radiotherapy	No	No	Yes	Yes

NFA = non-functioning pituitary adenoma; NPC = nasopharyngeal carcinoma

Comparisons between groups

The comparisons made between the four groups are described below:

- The conservatively managed group acts as a control for the effects of having a non-functioning adenoma (NFA) when compared to the surgery only group and the surgery and RT group, because all three of these groups contain patients with adenomas, but only two groups received treatment.

- The surgery only group acts as a control for the effects of both NFA and surgical intervention when compared to the surgery and RT group, as the only difference between these groups is that the surgery and RT group has received additional radiotherapy.

- Finally, the RT only group serves a different purpose. Because patients with NFA are not treated with RT alone, it is not possible to recruit an RT only group containing patients with NFA. When patients with nasopharyngeal carcinoma (NPC) receive RT, the pituitary gland and the medial temporal lobe (MTL) lie within the fields of RT and therefore also receive a percentage of the RT dose, similar to RT given for NFA.

The RT only group therefore acts as a confirmation group for the effects of RT. If the surgery and RT group is more impaired than the surgery only group, this could be due to disease factors such as the more aggressive tumours necessitating the use of RT to stop regrowth. However, if any cognitive deficits found in the surgery + RT group are due to RT, and not tumour related factors, then a similar profile of deficits should be seen in the RT only group because they have also received RT treatment to similar regions of the brain.

Sample

Patients were recruited from the Queen Elizabeth Hospital Pituitary Clinic. All patients who met the inclusion criteria were asked to take part in the study. Approximately one third of the patients who were approached agreed to take part. The patients who declined most commonly cited distance to travel, time constraints and a dislike of hospitals as their reasons for not wishing to take part. All participants were diagnosed with a NFA or NPC when over the age of 18. Diagnoses were confirmed with blood tests and an MRI scan. Patients diagnosed under the age of 18 were not included in order to exclude the possibility of greater functional recovery due to brain plasticity in childhood. This may have masked the effects of tumour and/or treatment. Participants had been on stable hormone replacement therapy for at least three months and a minimum of 18 months had passed since surgery or RT in order to allow any acute post-treatment effects to resolve. Patients with impaired vision, diabetes mellitus or a history of stroke were excluded from participating. The exclusion of these co-morbidities, which are occasionally, but not rarely, found with pituitary disease, was designed to eliminate other explanations for any cognitive impairment found in participants. The exclusion criteria reduced the available sample by about 10%.

Some hormones, such as cortisol and growth hormone, have consistently been found to affect neurocognitive functions (Kuhlmann et al., 2005; Oertel et al., 2004; Arwert et al., 2005). The presence of either too little or too much of various hormones can affect memory and attention (Burmeister et al., 2001; Deijen et al., 1996; Starkman et al., 2001; Vedhara et al., 2000). Other hormones such as prolactin have not been found to have an effect on cognition. Patients with a hormone producing pituitary adenoma may experience neurocognitive effects due to the hyper-secretion of that hormone and not due to the adenoma itself or subsequent treatment (Starkman et al., 2001). In contrast, patients with a non-functioning pituitary adenoma may have several hormone deficiencies and therefore require hormone replacement to within the population normal range. Patients with a hormone producing pituitary adenoma were therefore excluded from this study; so that any deficits found could be more confidently attributed to tumour or treatment, without hormone hypersecretion as a confounding variable. This is intended to avoid the difficulty experienced by previous research which has been unable to draw such strong conclusions about the effects of the presence of tumour. The results of the current study will be generalisable to all patients with pituitary macroadenomas who follow the same treatment paths as the current sample.

The demographic data for the four treatment groups are shown below in Table 4. Surgically treated NFA patients were most available to recruit; with or without adjunct RT. Fewer conservatively managed NFA patients or patients with NPC attended the recruiting clinics. This is reflected in the treatment group sizes. The average age of the groups ranged from 49.4 to 58.1. A one-way ANOVA showed no significant difference in average age between the groups ($F = 0.801$, $p = 0.53$). There was however, a significant difference between the groups for years of formal education ($F = 2.81$, $p = 0.05$). This was due to the surgery + RT group remaining in formal education for significantly longer than the RT only group ($t = 2.27$, $p = 0.04$) and the conservatively managed group ($t = 3.93$, $p = 0.001$). 'Original tumour size' refers to the size of the tumour found on the scan that was used to diagnose the patient as with NFA or NPC. There was no difference between the groups on the size of original tumour ($F = 1.73$, $p = 0.20$). Most surgically treated patients received transsphenoidal surgery, however one patient in the surgery only group and four patients in the surgery + RT group received transcranial surgery. A Fisher's exact test

indicated that there was not a significant difference between the two groups in the distribution of patients across types of surgery (p=0.34). There was also no difference between the surgically treated groups for time since surgery using an independent samples t-test. This was the case regardless of whether time since first surgery (t = 1.66, p = 0.11) or time since most recent surgery (t = 0.81, p = 0.42) was entered into the analysis for the surgery + RT group. There was no difference between the RT only group and the surgery + RT group for time since RT (t = 1.15, p = 0.30). Nor was there a difference between the groups for the number of hormone replacements participants were taking (F = 2.53, p = 0.07). All of the patient and treatment variables shown in Table 4 were normally distributed using a Shapiro-Wilk test (p = 0.06 – 1.00). Further details of each individual patient are shown in Appendix 1.

Table 4: Patient and treatment variables.

Group:	**Conservatively Managed**	**Surgery only**	**Radiotherapy only**	**Surgery & RT**
N patients	7	19	7	19
Age (years)	58.1 (14.9)	54.7 (11.2)	49.4 (14.3)	51.2 (10.0)
Years education	10.2 (1.6)	13.1 (3.5)	12.0 (1.9)	14.8 (3.7)
Original tumour size (in cm^3)	6.4 (8.6)	10.5 (8.1)	Data not available	14.1 (4.7)
Type of Surgery	n/a	1TC/18TP	n/a	4TC/15TP
Time since surgery (in m)	n/a	74.2 (78.9)	n/a	93.5 (64.6)
N had a second surgery	n/a	0	n/a	7
Time since RT (in m)	n/a	n/a	70.4 (45.2)	58.3 (42.5)
RT dose (in Gy)	n/a	n/a	Data not available	46.7 (2.6)
N hormone replacements	1.5 (1.0)	1.9 (1.7)	0	2.2 (1.5)

TC = transcranial; TP = transsphenoidal; m = months; Gy = Gray

Procedure

Participants attended the Wellcome Trust Clinical Research Unit and completed tests of emotional and cognitive functioning. The order of presentation of the WAIS-III and WMS-III were counter-balanced so an equal number of patients in each group started the testing session with each test. This was because within subject comparisons of performance on the WAIS-III and the WMS-III were planned. Therefore this counter-balancing controlled for the effects of fatigue and prevented it from affecting the participants' performance on one test battery more than the other.

No within-subject comparisons of performance on the D-KEFS were planned (i.e., performance on the DKEFs was not compared to performance on the other tests). Therefore the D-KEFS was always administered last so that a minimal amount of data was lost if a participant chose to leave the research early. The entire test session took four hours to complete.

Measures of Emotional Functioning

Symptom Checklist-90 Revised (SCL-90R)

The SCL-90R Questionnaire is a 90 question self-report questionnaire of current mood state. Patients rate their distress in the previous seven days on each of 90 psychological and physical symptoms. The SCL-90R has nine symptom scales: somatisation; obsessive-compulsive; interpersonal sensitivity; depression; anxiety; hostility; phobic anxiety; paranoid ideation and psychoticism. It also has three severity scales: the Global Severity Index; the Positive Symptom Total and the Positive Symptom Distress Index.

The nine scales of the SCL-90R have good internal consistency (ranging from 0.77-0.90) and good test-retest reliability (range of 0.78-0.90) (Derogatis, 1983). The 'global severity index' correlates highly with the global score of a similar measure, the Middlesex Hospital Questionnaire (Bolelouc & Horvath, 1974), indicating good validity.

The SCL-90R has proved useful in distinguishing between primary and secondary depression, demonstrating the differential severity of symptoms between these patient groups (Weissman et al., 1977). It has also been highly sensitive to differences in stress levels between medication and control groups (Carrington et al., 1980). More globally, the SCL-90R has been found to be a useful measure of psychological and symptomatic distress following mild traumatic brain injury (TBI) (Hoofien, Barak, Vakil, & Gilboa, 2005; Westcott & Alfano, 2005).

Previous use of the SCL-90R in pituitary disease patient populations has focused on the effects of growth hormone replacement, to determine whether patients are at greater risk of mental health disorders than euhormonal persons and to compare the levels of anxiety and hostility between types of pituitary adenoma. Torres et al. (2003)

used the SCL-90R to examine the effects of RT over time in patients with low-grade brain neoplasms, including pituitary adenomas. They found an improvement in the global severity index between the baseline assessment, immediately prior to RT, and the three months post-RT assessment. No further differences were found during the two year follow up. In the current study, this questionnaire was used to ascertain whether any differences in cognitive scores between groups could be attributed to differences in mood or mental state.

Measures of Neurocognitive Functioning

Wechsler Test of Adult Reading (WTAR)

The WTAR provides a measure of pre-morbid functioning that estimates an individual's general intellectual functioning before injury or the onset of illness. It is composed of 50 irregularly spelt words, and therefore measures word recognition rather than phonetic reading. The WTAR was originally normed on 1134 neurologically normal people aged between 16 and 89 years with no history of psychiatric illness. This sample represents the expected age-adjusted performance in a neurologically intact population.

There is a strong association between word recognition and general intellectual functioning in the neurologically intact population. Further, it has been demonstrated that word recognition is relatively robust to the effects of acquired brain injury. Accordingly, this association allows premorbid general intellectual functioning to be estimated using tests of word recognition. When other cognitive functions decline due to age, neurological illness or brain injury, reading ability remains relatively stable and so can be used to predict what an individual's FSIQ would have been if they had not experienced a neurological impairment or brain injury.

For the WTAR to predict pre-morbid intelligence it should be relatively unaffected by traumatic or acquired brain injury and there should not be differences in scores obtained between groups of patients and matched controls. The test manufacturers (The Psychological Corporation, 2001) tested 83 patients with various neurological disorders and 83 controls individually matched on the demographic variables of education, ethnicity, sex and geographical region. Mild Alzheimer's dementia;

Parkinson's disease; Huntington's chorea and Korsakoff's syndrome did not adversely affect the performance of patients, relative to healthy controls. However, there was a significant difference between the patients with moderate Alzheimer's dementia and their matched controls. The test manufacturers also compared the patients' current FSIQs to their WTAR scores and their matched controls. There was only a negligible difference of 0.1-3.5 points between the WTAR IQs and WAIS-III FSIQs for each matched control group. However, both of the Alzheimer's groups obtained significant differences between their WTAR IQs and their WAIS-III FSIQs with FSIQs of up to 22 points less than their WTAR predicted pre-morbid IQs. This indicates significant decline in intellectual function compared to reading recognition.

Other researchers have obtained similar results. It has commonly been found that patients with head injury or minimal to mild dementia obtain WTAR scores which remain stable over time; or that patients score at the same level as matched controls (Watt & O'Carroll, 1999; Schmand, Geerlings, Jonker, & Lindeboom, 1998). WTAR scores are likely to under-estimate pre-morbid intelligence in cases of moderate dementia, but prediction can be improved with the addition of demographic variables (McFarlane, Welch, & Rodgers, 2006). Patients with pituitary adenoma are not more at risk of dementia than the normal population and do not present with the level of impairment found in mild dementia. Therefore, the WTAR is likely to be an accurate estimate of pre-morbid IQ.

The correlation between the WTAR score and the WAIS-III FSIQ has been estimated at 0.73 and regression analysis indicated that the WTAR score can accurately predict a person's FSIQ ($r^2 = 0.53$). The WTAR average SEM across age groups is +/- 4 points of the obtained score and the test-retest reliability of the WTAR ranges from 0.9 to 0.94. The mean difference in test-retest scores is -0.8 with a standard deviation of 5.4. The WTAR should not be used with participants with dyslexia or acquired language deficits.

Wechsler Adult Intelligence Scale (WAIS-III)

Intelligence may be broadly defined as the ability to deal effectively with the environment (Wechsler, 1944) and is considered as both a global capacity (*g*) and the combination of more specific and varied abilities. The WAIS-III measures both verbal

and performance intelligence with a diverse range of tasks which measure skills such as perceptual abilities and abstract reasoning. The WAIS-III was originally trialed on 2450 individuals to create standardised norms for use with people aged 16 – 89 years old. The test gives an overall Full Scale IQ (FSIQ), and can be separated into a two factor model of verbal IQ (VIQ) and performance IQ (PIQ). It can be further separated into a four factor model of verbal comprehension (VC), perceptual organisation (PO), working memory (WM) and processing speed (PS) (see Figure 2). Separating VIQ and PIQ into their four component indexes allows clinicians to differentially test potential causes for a low VIQ or PIQ score.

Confirmatory factor analysis (CFA) has demonstrated a good congruence between empirical and theoretical factor structure, and CFA in both clinical and normal populations has provided support for the four factor model (Arnau & Thompson, 2000; Taub, 2001; Saklofske, Hildebrand, & Gorsuch, 2000; van der Heijden & Donders, 2003; Dickinson, Iannone, & Gold, 2002). The higher order one factor model (*g*) has also been supported (Arnau & Thompson, 2000; Taub, 2001). *g* is conceptualised as encompassing such abilities as reasoning, abstract thinking, comprehending complex ideas and learning from experience (Gottfredson, 1997). The WAIS-III has good convergent validity with the WAIS-R (r=0.93) (Wechsler, 1997b) which allows results using the WAIS-III to be compared to results obtained by previous researchers using the WAIS-R.

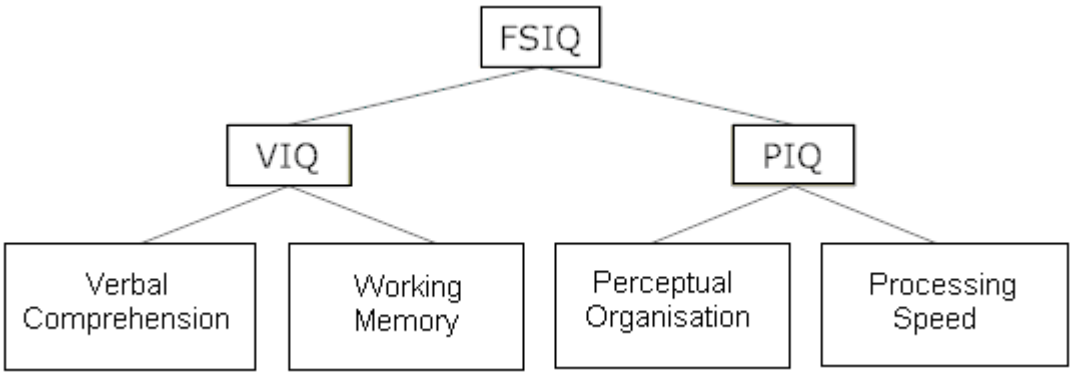

Figure 2: The composition of the WAIS-III indices

The 95% confidence interval (CI) of the WAIS-III is approximately four points either side of the obtained FSIQ. For example, if a person's obtained FSIQ score is 100,

then there is a 95% probability that their true score lies between 96 and 104. Each factor in the two factor and four factor models has a 95% CI of between five and seven points either side of the obtained score, with the exception of PS which is nine points either side.

Wechsler Memory Scale (WMS-III)

The third edition of the Wechsler Memory Scale (WMS-III) is a test of anterograde memory. Participants are asked to recall either verbally or visually presented stimuli immediately after it is presented and then again approximately 30 minutes later. This provides a measure of both immediate and delayed recall. There are also subtests measuring recognition as well as recall, which allows clinicians to assess whether a participant has encoded the information but is unable to retrieve the information without prompting.

The WMS-III gives six index scores as well as two composite index scores. The visual immediate index measures the recollection of visually presented information shortly after presentation, without interruption by intervening tasks. The auditory immediate index measures the recollection of aurally presented information in the same manner. The visual and auditory delayed indexes measure the recollection of this same information after approximately 30 minutes delay. During this delay, intervening tasks are completed. The auditory recognition delayed index measures the individual's ability to recognise previously presented information when it is again presented amongst novel distracter items.

The immediate memory index is an amalgamation of the visual immediate and auditory immediate indexes whilst the general memory index amalgamates the visual delayed, auditory delayed and auditory recognition delayed indexes.

Working memory indices are provided by both the WMS-III and the WAIS-III. Working memory refers to a person's ability to hold and manipulate temporarily stored information, sometimes in the service of another goal, for example, mental arithmetic. The ability to passively store items in working memory (capacity) and the ability to manipulate information are both assessed on the WMS-III.

The Auditory processing composites are derived from the auditory subtests. The composite scores are scaled from percentages rather than from raw scores. The Single-Trial Learning Composite assesses recall capacity after a single presentation of stimuli. The Learning Slope Composite is a measure of the relative increase from the first to the last trial of auditory immediate subtest material. The Retention Composite measures delayed free recall in relation to the participant's performance on the immediate recall condition. Low scores indicate high rates of forgetting. The Retrieval Composite is a comparison of delayed recall and delayed recognition and indicates how much a participant has benefited from cuing of information. These measures are shown in Table 5 with their standard errors of measurement (SEM) in index points for the age range 45-54 years old in brackets (Wechsler, 1997a).

Table 5: Measures given by the WMS-III (SEMs)

Immediate Primary Indexes	**Delayed Primary Indexes**	**Auditory Process Composites**
Visual Immediate (5.61)	Visual Delayed (5.41)	Single-Trial Learning
Auditory Immediate (3.67)	Auditory Delayed (5.41)	Learning Slope
Immediate Memory (3.67)	Auditory Recognition Delayed (8.22)	Retention
Working Memory (6.00)	General Memory (4.24)	Retrieval

The WMS-III was originally trialled on 1250 neurologically intact individuals, aged between 16 and 89 years and was co-normed with the WAIS-III.

The WMS-III was trialled on the same individuals as the WAIS-III, which means the correlations between these two tests could be evaluated to examine their relationships. The relatively high inter-correlations between intellectual functioning and memory allow the use of discrepancy analysis and an individual's IQ score becomes an estimate of their memory abilities. A person's actual memory scores can then be compared to the scores predicted by their FSIQ. Whilst there is not a straight relationship between FSIQ and memory, particularly in very high or low functioning individuals, FSIQ provides a more accurate predictor of memory functioning than any other index. In group studies, this method reduces within group variance as each person is being compared to their theoretical selves and it is possible to compare an individual group to its expected scores, not just other groups.

Delis-Kaplan Executive Functions System (D-KEFS)

The Delis-Kaplan Executive Function System (D-KEFS) contains nine subtests, which measure various executive functions such as inhibition, strategy use and problem solving. Each subtest is scored separately. The D-KEFS does not give index scores. Standardised norms were created using 1750 individuals for persons aged 8 – 89 years old. All tests have scaled score means of ten points and standard deviations of three points.

Trail Making Test: This test originates from the work of Partington (Brown & Partington, 1942) and also featured in the Army Individual Test Battery (1944). It is a visual-motor sequencing procedure in which participants must join up numbers and letters in order. The task measures cognitive switching and inhibition. The SEM for 50 to 59 year olds participants is 1.31 scale score points. The trails test has been found to be sensitive to the effects of brain injury (Spreen & Benton, 1965). Poor performance on the trails test was highly correlated with caudate atrophy in patients with Huntington's disease (Starkstein et al., 1988).

Verbal Fluency Test: The Verbal Fluency Test is a modification of the Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1989). It also incorporates Newcombe's (1969) category fluency and category fluency with switching procedures. Participants must generate as many words as they can, beginning with a specified letter or in a specified category in 60 seconds. These tasks measure the rapid retrieval of lexical items, strategy use and cognitive flexibility (Delis, Kaplan, & Kramer, 2001). The SEM of switching accuracy for 50 to 59 year olds is 2.06 points. Patients with Alzheimer's disease produce significantly less category words than controls (Sailor, Antoine, Diaz, Kuslansky, & Kluger, 2004) and a meta-analysis of the literature has shown that patients with focal frontal cortical traumatic brain injury (TBI) are equally impaired on both phonetic and semantic fluency tests. This was not the case for patients with focal temporal cortical TBI (Henry & Crawford, 2004) who present with greater deficits in semantic fluency than in phonological fluency. A meta-analysis of studies of patients with Huntington's disease has also found impaired phonetic and semantic fluency as part of patients' wider cognitive decline (Henry, Crawford, & Phillips, 2005).

Design Fluency Test: This procedure was originally developed by (Regard, Strauss, & Knapp, 1982). It measures design fluency and cognitive flexibility (Delis et al., 2001). Participants must create as many different designs as they can within 60 seconds and the given rules by connecting dots. The SEM for the most difficult condition, which involves switching between white and black dots, is 2.47 for all age groups combined. Patients with frontal lesions show a tendency to perseverate, and so produce less designs on this task (Jones-Gotman, 1991) and patients with traumatic brain injury produce fewer different designs than control subjects (Varney et al., 1996).

Colour-Word Interference Test: This is a modification of the Stroop (1935) test. It primarily measures the ability to inhibit a learnt verbal response and instead generate a conflicting response. A switching procedure has been added to enhance the sensitivity of the task to mild brain damage (Bohnen et al., 1992) and so the test now measures inhibition and cognitive switching. The SEM for participants aged 50 to 59 years is 1.13 points. Stuss & colleagues (1985) found the Stroop task to be sensitive to the effects of closed head injury and performance on this test is slowed in patients with multiple sclerosis, independent of their level of depression and disability status.

Card Sort Test: The participant must sort a set of cards into two groups as many ways as possible, based on within group similarity. The Card Sort Test contains two sets of cards to provide two trials. This test measures concept formation and problem-solving skills (Delis et al., 2001) and has been found to be sensitive to focal frontal damage (Dimitrov, Grafman, Soares, & Clark, 1999). It has also been used to document different profiles of spared and impaired executive function in patients with Parkinson's disease (Bondi, Kaszniak, Bayles, & Vance, 1993), Korsakoff's syndrome (Delis, Squire, Bihrle, & Massman, 1992) and unilateral brain damage (Crouch, Greve, & Brooks, 1996). The SEM for the number of different sorts generated is 1.13 points.

Twenty Questions Test: Participants must guess which one of a set of 30 objects the examiner has chosen, using only questions that can be answered 'yes' or 'no'. The Twenty Questions Test examines participants' ability to identify categories and subcategories (Delis et al., 2001). The SEM of the initial abstraction score (the usefulness of the participants first question) is 1.21 for participants aged 50 to 59

years old. In a study of patients with epileptic foci in different locations, the patients with bifrontal lesions made the most errors on this subtest and had the least efficient strategies (Upton & Thompson, 1999). Patients with severe closed head injury also have poor question asking strategy.

Word Context Test: The Word Context Test requires the participants to guess the missing word in a variety of sentences, using as few clues as they can. This test measures deductive reasoning, integration of information, hypothesis testing and flexibility of thinking (Delis et al., 2001). The SEM for 50 to 59 old participants is 1.59 points. This test is sensitive to damage caused by focal frontal lesions on either the left or right side but especially to lesions located on the left side of the frontal lobes (Keil, Baldo, Kaplan, Kramer, & Delis, 2005).

Proverb Test: Participants are asked to give the meanings of both common and uncommon sayings. This is a test of participants' verbal abstraction skills. The SEM for 50 to 59 year olds is 1.49 points. Benton (1968) showed that patients with bilateral frontal lobe disease performed very poorly on the multiple choice element of this test. Patients with agenesis of the corpus callosum produce fewer abstract interpretations to proverbs in both the free inquiry and multiple choice conditions.

Data preparation

All analyses were performed on scaled scores or index scores as provided by the relative tests. Scale scores are age corrected, allowing patient's of different ages to be compared to each other without age as a confounding variable. All of the abilities tested are normally distributed in the population (Wechsler, 1997b; Wechsler, 1997a; Delis et al., 2001). The data was checked for normality using the Shapiro-Wilk test and in cases where the data was not normally distributed, both parametric and the non-parametric equivalent statistics were conducted. If there was any discrepancy between the results then the non-parametric results were accepted. The predicted-difference method was used for estimating memory from FSIQ as it takes into account the reliabilities and correlations between the WAIS-III and the WMS-III and also corrects for regression to the mean (Wechsler, 1997a). In this method, FSIQ is used in a regression equation to calculate the predicted memory scores.

For all analyses, hormone levels of patients will be assessed as potential covariates. In the current sample, some hormones were found at significantly different levels in men and women. These hormones were testosterone (female $\bar{X}$ = 0.83, s.d. = 0.35; male $\bar{X}$ = 16.53, s.d. = 10.55; t = -7.57, p<0.001) and TSH (female $\bar{X}$ = 1.85, s.d. = 1.42; male $\bar{X}$ = 0.81, s.d. = 0.91; t = 2.97, p = 0.005). Therefore these hormones will be correlated with the outcome measures separately for men and women. Outcome variables will also be assessed for differences between the sexes. The hormones prolactin (female $\bar{X}$ = 262.62, s.d. = 172.75; male $\bar{X}$ = 313.81, s.d. = 327.57; t = -0.627, p = 0.533), IGF1 (female $\bar{X}$ = 24.66, s.d. = 35.96; male $\bar{X}$ = 17.79, s.d. = 8.88; t = 0.780, p = 0.438), oestrodial (female $\bar{X}$ = 137.33, s.d. = 124.08; male $\bar{X}$ = 95.50, s.d. = 59.38; t = 1.419, p = 0.167), FT3 (female $\bar{X}$ = 4.25, s.d. = 0.12; male $\bar{X}$ = 4.36, s.d. = 0.76; t = -0.628, p = 0.537) and FT4 (female $\bar{X}$ = 13.89, s.d. = 1.99; male $\bar{X}$ = 15.33, s.d. = 3.95; t = -1.648, p = 0.107) were not significantly different between the sexes. These hormones will be correlated with outcome variables for the whole sample.

There were no differences between the treatment groups on a one-way ANOVA for the levels of prolactin (F = 2.10, p = 0.114), IGF-1 (F = 0.40, p = 0.752), oestrodial (F = 0.60, p = 0.617), FT3 (F = 2.20, p = 0.116) or FT4 (F = 1.36, p = 0.269). For women, there were no differences between treatment groups for levels of testosterone (F = 0.43, p = 0.744) or TSH (F = 1.79, p = 0.186). For men, there were no differences between treatment groups for levels of testosterone (F = 0.08, p = 0.970). However, there was a significant difference between the treatment groups for the level of TSH with the RT only group having significantly higher levels than the surgery only group (t = -3.69, p = 0.04) and the surgery + RT group (t = 3.24, p = 0.008). Therefore, for analyses of treatment group differences, in which there is a correlation between the outcome measure and TSH for men, this hormone will be added to the analysis as a covariate.

Statistical correction

There is a convention in inferential statistics that null hypotheses are rejected if their probability can be demonstrated to be less than 0.05. In circumstances where a body of statistical tests are required to test a specific hypothesis (e.g., the comparison of a number of indices of memory function between multiple treatment groups) then the

overall error for the body of statistical tests is calculated by multiplying 0.05 by the number of individual tests undertaken. This is known as the family-wise error rate and is used when each test within the body of tests may be used to reject the null hypothesis. A common solution to the problem of family-wise error is to divide alpha (i.e., 0.05) by the number of tests undertaken to reject a null hypothesis (i.e., the Bonferroni correction).

Correcting for family-wise error using the Bonferroni correction reduces the chance of committing a type I error. However, this correction reduces the statistical power of an experiment and increases the chance of committing a type II error, and concluding that there is no impairment, when in fact, impairment does exist. Given the low numbers of participants in two treatment groups and therefore the already low statistical power, it was decided not to correct for family-wise error. Given that this research was funded by UHB Charities to inform patients of the potential risks of treatment, it was considered of greater ethical importance to protect against type II error than to commit a type I error and conclude that patients should be misinformed about the safety of their future treatments. Instead, the number of significant results expected from chance alone (1 in every 20) will be stated and compared to the number of statistical results obtained in each family of tests. For a full discussion on the reasons against using family-wise error correction, see O'Keefe (2003).

Intelligence

Introduction

In considering the possible impact of treatment on cognitive functions, I will turn to the broadest concept of cognitive function, general intelligence. This reflects the operation of a large and diverse number of brain regions orchestrating many cognitive modules and abilities and cannot be conceived as a neurocognitive outcome in and of itself.

Historical Developments in the Measurement of Intelligence

Charles Spearman first introduced the idea that a person's performance on all tests of individual intellectual faculties provided estimates of 'one great common Intellective Function' (Spearman, 1904) that became known as *g*. He believed that any correlation between different intellectual functions was due to *g*, and that *g* was best estimated using sample tests such as the ability to distinguish one sensation from another, for example, two musical tones of different pitch. This is quite different to the current concept of *g* which is conceptualised as encompassing such abilities as reasoning, abstract thinking, comprehending complex ideas and learning from experience (Gottfredson, 1997).

The WAIS-III is the most widely used intelligence test currently available (Camara, Nathan, & Puente, 2000). It has developed over many years and each version has been progressively improved and updated. Binet and Simon developed the first battery of intelligence tests (Binet & Simon, 1905) by studying children and discerning which tasks distinguished between children and adults or between normal from retarded children (Binet & Simon, 1908). In contrast to Spearman's work, Binet and Simon preferred to use more complex tests of intelligence rather than simple stimuli discrimination. The loss of inter-task correlation was compensated by the increased validity of using tests that were related to everyday function. The Binet-Simon Intelligence Scale was later updated and standardised, becoming the Stanford-Binet (Terman, 1916). During the First World War, the Army Alpha test was developed essentially by turning the Stanford-Binet into a group-administered test. It could be administered to groups of individuals simultaneously and was eventually normed and

validated on over 1.7 million men. In this battery, Binet's age-scale approach was displaced by a point scale on tests of functions that were thought to be important (Yerkes, 1917). The Army Performance Scale Examination was also developed, to which Wechsler's Performance Scale was added (Yoakum & Yerkes, 1920).

In the mid-1930s, David Wechsler amalgamated a variety of tests developed for non-clinical use to create a clinical test battery to meet the needs of practitioners. In 1939 he developed the Wechsler-Bellevue test battery for assessing adults and adolescents (Wechsler, 1939). This was the first battery to give verbal and non-verbal tests equal importance and equal contribution to the overall intelligence score. The Wechsler-Bellevue was later updated into the Wechsler Adult Intelligence Scale (WAIS) based on the results of norming studies, with more items added to subtests. These changes improved the reliability of the test's Full Scale IQ (FSIQ) from 0.90 to 0.97 (Derner, Aborn, & Canter, 1950; Wechsler, 1955). Minor changes were later made to the WAIS to create the WAIS-R (Wechsler, 1981). The WAIS-III contained many more changes (Wechsler, 1997b). Three new subtests were added bringing the total to 14 and a four factor model was reported as well as the usual VIQ/PIQ model and the overall FSIQ. With each update, subtests that did not load highly onto *g* were altered to improve them as measures of intelligence. The later versions of Wechsler's intelligence test are the most frequently administered tests by clinical psychologists (Camara et al., 2000).

Basic Developments of the Concept of Intelligence

Other researchers rejected the verbal/performance dichotomy in favour of the distinction between fluid intelligence (Gf) and crystallised intelligence (Gc) (Cattell, 1963; Horn & Cattell, 1966). The Cattell-Horn Gf-Gc theory follows Spearman's (1904) psychometric approach. However, instead of a single *g*-factor model, Cattell proposed a two factor model of general intelligence, Gf and Gc (Cattell, 1941). These two factors arose from many factor-analysis and correlation studies that were used to objectively identify the main constructs of cognitive ability (Horn & Noll, 1997). Gf is the ability to infer and understand the relationships between stimuli, without using acquired knowledge. Tests of Gf focus on the ability to solve novel problems; form and recognise concepts and extrapolate from one set of stimuli to another. Gc is the ability to utilise experience, knowledge and skills. Tests of Gc focus on a person's

acquired knowledge and whether they effectively use this knowledge. The Cattell-Horn Gf-Gc theory was later succeeded by the Cattell-Horn-Carroll (CHC) theory (Mcgrew, Keith, Flanagan, & Vanderwood, 1997). CHC theory conceptualises intelligence as consisting of acquired knowledge, thinking abilities and cognitive efficiency. Acquired knowledge contains the categories of: verbal comprehension knowledge/crystallised intelligence (Gc); reading and written language (Grw); and quantitative knowledge (Gq) which is the store of mathematical knowledge and the ability to use and work with numbers. Thinking abilities consists of: visual-spatial thinking (Gv), which is the ability to generate, manipulate, remember and think with visual patterns and stimuli; auditory processing (Ga), which is the ability to perceive, analyse and synthesize patterns of auditory stimuli including speech; long-term retrieval (Glr) from memory; and fluid reasoning/fluid intelligence (Gf). Cognitive efficiency consists of processing speed (Gs) and short-term memory (Gsm). CHC theory was used as the blueprint for the WJ-III intelligence test battery (Woodcock, Mcgrew, & Mather, 2001) with tests of at least two narrow abilities from each aforementioned category included.

Whilst the WAIS-III can be interpreted as a one factor (*g*); two factor (VIQ and PIQ) or four factor (VC, WM, PO and PS) test as intended by Wechsler, it can also be interpreted using the CHC theory. Only six of the nine CHC categories are represented by the subtests of the WAIS-III with no subtests that load onto the categories of Grw, Ga and Glr. The CHC categories and Psych Corp factors that each subtest loads onto are shown in Table 6 below.

Table 6: Factor-analysis of the WAIS-III

WAIS-III subtest:	Gc	Gq	Gv	Gf	Gs	Gsm	FSIQ	VIQ	PIQ	VC	PO	WM	PS
Picture C.	X		X				X		X				X
Vocab.	X						X	X		X			
Digit S-C.					X		X		X				X
Similar.	X						X	X		X			
Block D.			X				X		X		X		
Arithmetic		X		X			X	X				X	
Matrix R.				X			X		X		X		
Digit Span						X	X	X				X	
Inform.	X						X	X		X			
Picture A.	X		X				X		X		X		
Comp.	X						X	X		X			
Obj. Ass.			X				X		X		X		
Symbol S.					X		X		X				X
L.-N. S.						X	X	X				X	

Gc = Comprehension-Knowledge; Gq = Quantitative Knowledge; Gv = Visual Processing; Gf = Fluid Reasoning; Gs = Processing Speed; Gsm = Short-Term Memory; FSIQ = Full Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; VC = Verbal Comprehension; PO = Perceptual Organisation; WM = Working Memory; PS = Processing Speed; C. = Completion; Vocab. = Vocabulary; S-C. = Symbol-Coding; D. = Design; R. = Reasoning; Inform. = Information; A. = Arrangement; Comp. = Comprehension; Obj. Ass. = Object Assembly; S. = Search; L.-N. S. = Letter-Number Sequencing

In contrast to the original use of IQ scores to categorise people as normal or learning disabled, comtempory use of IQ scores reflect a number of interpretive functions. A person's FSIQ gives a midpoint of their overall performance which can be used for profile interpretation. A person's other neurocognitive functions can be compared to FSIQ to identify statistically significant strengths and weaknesses (Kaufman & Lichtenberger, 2005). FSIQ is also useful in making these comparisons in group studies. FSIQ can here be used to identify clinically relevant weaknesses across a homogenous group (Kaufman & Lichtenberger, 2005).

Intelligence can be differentially affected by diffuse or localised brain damage. Diffuse injury, caused by neurological disease or an insult that affects large volumes of cortical tissue, is likely to affect several functional distinct processing modules, reducing the general ability factor. Localised damage can have distinct or diffuse effects. Cognitive modules are arranged hierarchically so damage to one module (e.g., working memory) may affect many or few other modules.

Previous studies into the effects of RT on intellectual functioning have largely been confined to paediatric research. Whole brain RT has been found to be detrimental to children's intellectual functioning and this effect is thought to gradually increase over time as expected from the temporally delayed effects of RT. In adults, patients treated with radiotherapy for nasopharyngeal carcinoma had significantly lower IQ scores (12 point difference, $p<0.05$) an average of 5.5 years post-RT than matched controls awaiting RT (Lee, Hung, Woo, Tai, & Choi, 1989).

There are seven previous studies of the effects of treatment for pituitary disease or low-grade, supratentorial, brain tumours that have examined either pre-morbid intellectual functioning (Peace et al., 1998; Grattan-Smith et al., 1992; Noad et al., 2004; Peace et al., 1997; Torres et al., 2003), current intellectual functioning (Baum et al., 1998) or both (Guinan et al., 1998). Grattan-Smith et al. (1992) used the NART, a measure of pre-morbid intelligence, when assessing patients with pituitary adenoma who were treated with RT to patients treated without RT. They used the NART scores as a covariate in other analyses, but unfortunately did not report the NART scores per se. This does not allow the reader to compare the performance of their patients to those participating in other studies. Peace et al. (Peace et al., 1997; Peace et al., 1998) also used the NART in two studies. The patient groups all scored between 0.7 and 1.0 standard deviations (s.d.s) above the population average. Noad et al. (2004) found their surgery only group scored 0.6 s.d.s above average whilst their surgery + RT scored 0.4 s.d.s above the normal population. No differences were found between the groups in any of these studies; although potential differences were not reported in Grattan-Smith et al.'s study, and so are left unknown. Torres et al. (2003) used the Shipley living scale to estimate premorbid IQ. Unfortunately, they also did not report the outcome of this assessment, so no further comment can be made.

The use of the NART as a measure of intellectual function is likely to be insensitive to the effect of treatment, as the NART was originally designed as a measure of premorbid function which was robust to either acquired brain injury or dementia. Therefore, measures of current intellectual functioning should be included in the test battery chosen to assess the effects of tumour, hormone dysfunction or treatment.

Only two previous studies have used a full standardised test battery, the WAIS-R, to measure intelligence (Baum et al., 1998; Guinan et al., 1998). Baum et al. (1998)

reported that their patient groups achieved FSIQ scores between 0.7 and 0.9 s.d.s above the normal population. This is commensurate with the pre-morbid estimations of intellectual functioning reported by other studies. These scores also suggest that treatment with surgery and RT does not result in deficits in current intellectual functioning. Guinan et al. (1998) reported FSIQs of over 100 in all groups except the RT only treatment group. In three other treatment groups, FSIQ exceeded the population average by approximately one s.d.. It was not stated whether this was a significant difference from the population average. Guinan et al. also used the NART-R to assess pre-morbid functioning. Their patients obtained higher WAIS-R FSIQs than NART-R FSIQs in every treatment group. In the groups that achieved the highest WAIS-R FSIQs, this may have been partly due to the WAIS-R having a greater ceiling score than the NART-R. However, this should have affected the groups that achieved more average WAIS-R FSIQs. The results as a whole indicate that a pituitary adenoma and its treatment have adversely affected the patients' current intellectual functioning.

There is currently a dearth of research into the effects of surgery and/or RT for adult onset brain tumours and pituitary adenomas. Whilst two studies have found normal intellectual functioning in patients with pituitary adenoma, this was using an older version of the WAIS on patients with heterogeneous tumour types. This confounds the effects of treatment with the effects of hormone hypersecretion, reducing the strength with which conclusions can be drawn from the results. These studies have only used the FSIQ and have not more closely examined the index scores that the FSIQ consists of. This does not elucidate potential difficulties that patients may experience with one index, which may be masked by high performance on the other index scores that contribute to FSIQ. They have also not considered other interpretations such as differences between fluid and crystallised intelligence. Again, this may obscure deficits in a more specific area of intellectual functioning. This current study will examine the effects of surgery and radiotherapy in patients with only non-functioning adenoma and will consider FSIQ as well as the four factor model and the Gf-Gc comparison.

Hypothesis

Previous research on patients with pituitary adenoma has suggested that tumour and treatment do not negatively affect general intellectual functioning. Patients with pituitary adenoma have not demonstrated a difference in intelligence after surgery or RT from patients who have not received surgery or RT. This could mean that the lower doses of RT used to treat pituitary adenoma do not damage cerebral cortex and impair intellectual function. Therefore, it is hypothesised that the presence and treatment of non-functioning pituitary adenoma will not impair pituitary patients' general intellectual functioning. The FSIQ will also provide a necessary comparison for the results of the memory testing.

Method

Testing was conducted as described in the General Methods chapter. This is a cross-sectional independent groups design with four treatment groups: conservatively managed, surgery only, RT only, and surgery and RT. Patients were treated with RT alone if they were diagnosed with a nasopharyngeal carcinoma. The three other treatment groups exclusively contained patients treated for NFA.

One-way ANOVAs were used to examine any differences between groups on the pre-morbid WTAR scores, WAIS-III index scores or WAIS-III IQ scores. Potential correlations between WAIS-III scores, and several demographic and treatment factors were analysed. These factors were age; time in months since surgery; time in months since RT; size of original tumour volume; number of hormone replacements; years of education; and GSI T-score from the SCL-90R. There was a significant correlation between one or more WAIS-III scores and the factors of age; years of education; and GSI T-score. One-way ANOVAs were thus conducted to assess the distribution of the covariates between the treatment groups.

Results

There was a significant difference between the groups only for years of education, due to the surgery + RT group being significantly more educated than the conservatively managed group ($t = 3.93$, $p=0.001$). Years of education correlated with the WAIS-III scores of VIQ ($r=0.41$, $p=0.01$); FSIQ ($r=0.34$, $p=0.02$); VCI ($r=0.45$, $p=0.003$); and

WMI (r=0.34, p=0.03). Years of education was therefore entered into the analysis as a covariate for the WAIS-III scores with which it correlated and ANCOVA was used to compare treatment groups on these scores instead of ANOVA. There were no differences between men and women on any WTAR or WAIS-III index scores ($t \leq -1.53$, $p \geq 0.13$). Finally, for each treatment group, a paired sample t-test was used to compare the pre-morbid intelligence scores obtained from the WTAR to the current measure of intelligence given by the WAIS-III scores. The raw means and standard deviations achieved by each group are shown below in Table 7.

Table 7: The WAIS-III scores achieved by each treatment group

		Conservatively Managed	**Surgery Only**	**RT only**	**Surgery + RT**
	N	7	19	7	19
FSIQ	**Mean**	101.00	106.79	96.43	108.58
	Std. Dev.	11.58	17.36	17.62	17.52
VIQ	**Mean**	98.71	108.00	95.29	107.53
	Std. Dev.	6.29	17.54	14.82	15.96
PIQ	**Mean**	103.71	105.47	98.43	108.42
	Std. Dev.	18.67	15.93	19.98	19.33
VCI	**Mean**	97.00	106.58	95.43	105.95
	Std. Dev.	6.27	14.73	18.56	16.50
POI	**Mean**	104.86	106.68	98.00	109.74
	Std. Dev.	18.61	17.38	17.19	18.67
WMI	**Mean**	99.00	106.44	93.29	107.89
	Std. Dev.	9.97	18.23	9.53	14.76
PSI	**Mean**	101.57	98.95	97.43	102.00
	Std. Dev.	19.72	12.04	16.60	16.82

RT = Radiotherapy; FSIQ = Full Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; VCI = Verbal Comprehension Index; POI = Perceptual Organisation Index; WMI = Working Memory Index; PSI = Processing Speed Index

Absolute Impairment of Intellectual Functioning

To assess whether patients were impaired in comparison to the normal population, the percentage of patients scoring within each classification range was compared to the percentages found in the normal population. These values were provided by the test norms and not from a tested control group. This is shown in Table 8.

Table 8**:** Percentage of patients scoring within each IQ classification (RT = Radiotherapy)

FSIQ Classification	Normal Population	Conservatively Managed	Surgery Only	RT Only	Surgery + RT
Very Superior (130+)	2.2		10.5		10.5
Superior (120-129)	6.7		10.5	14.3	5.3
High Average (110-119)	16.1	28.6	15.8		26.3
Average (90-109)	50.0	57.1	42.1	42.9	52.6
Low Average (80-89)	16.1	14.3	15.8	28.6	
Borderline (70-79)	6.7		5.3	14.3	5.3
Extremely Low (69 or less)	2.2				

There were no patients in the extremely low classification for any of the groups. The RT only group was over-represented in terms of percentage in the 'borderline' and 'low average' groups, however, this may have been due to each participant in this group representing 14.3% and the normal population percentage of 'borderline' individuals is less than this figure. No other group was over-represented in the 'low average' or below classifications. The numbers in several of the cells were too low to conduct a chi-squared analysis.

To test for differences between the treatment groups, a one-way ANOVA was used for the WAIS-III PIQ, POI, WMI and PSI scores. There was no difference between the groups on any of these scores ($F \geq 2.01$, $p \geq 0.13$). An ANCOVA was used to test for differences between treatment groups on the WAIS-III FSIQ, VIQ and VCI scores, with years of education entered as a covariate. There was no main effect of group for any of these scores ($F \leq 1.04$, $p \geq 0.38$), showing that there is no significant difference between treatment groups on any of the WAIS-III scores.

Relative Impairment of Intellectual Functioning

In order to test for a reduction in intellectual functioning, WTAR scores, which are a measure of pre-morbid intelligence, were subtracted from the WAIS-III scores, creating a current - predicted premorbid discrepancy score. A positive discrepancy score represents better current intellectual functioning than estimated pre-morbid functioning and a negative discrepancy score represents poorer current intellectual functioning than pre-morbid functioning. This discrepancy score gives a more sensitive measure of cognitive decline because each score represents the participants' deviation from their own pre-morbid abilities. As all participants are positioned on the

same metric (with a null hypothesis value of 0), this test may reduce error variance attributable to within group variation in premorbid intellectual abilities. A one-sample t-test for each treatment group was used to calculate whether the discrepancy scores were significantly different to 0. Discrepancy scores were correlated with the variables of age; time in months since surgery; time in months since RT; size of original tumour volume; number of hormone replacements; the hormones LH and FSH in men, years of education; and GSI T-score from the SCL-90R. The factors of sex, age and time since surgery correlated with the visual delayed discrepancy score. Time since surgery also correlated with the visual immediate discrepancy score. A one-way ANOVA showed no difference between groups on any of these factors, except sex. Men scored significantly higher on the VIQ discrepancy score ($t = -2.72$, $p=0.009$) and the VCI discrepancy score ($t = -2.06$, $p = 0.045$). Therefore sex was entered as a covariate into the analysis of group differences for the VIQ discrepancy score and VCI discrepancy score. This is shown in Table 9.

Table 9: Pre-morbid intelligence for each treatment group ($P(t) \neq 0$ means the probability that the discrepancy score is different from 0 (two-tailed)).

		Conservatively Managed	**Surgery Only**	**RT only**	**Surgery + RT**
	N	6	18	6	18
FSIQ (WTAR)	**Mean**	97.83	100.78	94.50	102.72
	Std.Dev. (Mean)	7.25	9.63	14.03	8.72
	Discrepancy	4.33	5.72	4.20	5.72
	Std.Dev. (Disc)	9.40	10.68	10.62	12.30
	$P(t) \neq 0$	0.31	**0.04**	0.43	0.07
VIQ (WTAR)	**Mean**	97.83	100.61	94.67	102.67
	Std.Dev. (Mean)	6.97	9.59	13.82	8.42
	Discrepancy	1.33	6.83	0.80	3.50
	Std.Dev. (Disc)	5.09	10.24	7.50	8.72
	$P(t) \neq 0$	0.55	**0.01**	0.82	0.11
PIQ (WTAR)	**Mean**	99.83	102.11	96.83	104.11
	Std.Dev. (Mean)	6.18	8.95	12.53	7.51
	Discrepancy	6.00	3.44	6.00	4.44
	Std.Dev. (Disc)	16.86	12.97	13.66	16.12
	$P(t) \neq 0$	0.87	0.28	0.38	0.26
VCI (WTAR)	**Mean**	97.83	100.94	94.50	102.78
	Std.Dev. (Mean)	7.25	9.36	14.02	8.60
	Discrepancy	-0.33	5.00	2.20	2.83
	Std.Dev. (Disc)	5.75	7.37	10.47	10.34
	$P(t) \neq 0$	0.89	**0.01**	0.66	0.26
POI	**Mean**	100.83	103.00	97.83	105.11

		Conservatively Managed	Surgery Only	RT only	Surgery + RT
(WTAR)	**Std.Dev. (Mean)**	6.18	9.17	12.53	7.72
	Discrepancy	6.00	3.67	4.00	3.89
	Std.Dev. (Disc)	17.77	14.83	14.75	15.60
	P(t) ≠ 0	0.45	0.31	0.58	0.31
WMI	**Mean**	100.50	102.67	97.83	104.44
(WTAR)	**Std.Dev. (Mean)**	5.79	8.07	11.32	6.92
	Discrepancy	0.00	3.78	-5.40	3.56
	Std.Dev. (Disc)	7.51	12.89	1.67	11.86
	P(t) ≠ 0	1.00	0.23	**0.00**	0.22
PSI	**Mean**	98.17	99.61	96.33	101.00
(WTAR)	**Std.Dev. (Mean)**	3.97	5.82	8.12	4.92
	Discrepancy	5.67	-0.33	4.80	0.94
	Std.Dev. (Disc)	19.21	10.58	9.31	15.84
	P(t) ≠ 0	0.50	0.90	0.31	0.80

FSIQ = Full Scale Intelligence Quotient; WTAR = Wechsler Test of Adult Reading; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; VCI = Verbal Comprehension Index; POI = Perceptual Organisation Index; WMI = Working Memory Index; PSI = Processing Speed Index; N = Number; Disc = Discrepancy score; Std.Dev. = Standard Deviation; RT = Radiotherapy

Four discrepancy scores were significantly different to 0, indicating a change in level of functioning. The surgery only group had a significantly positive discrepancy score for the three related scores of FSIQ ($t = 2.27$, $p = 0.04$), VIQ ($t = 2.83$, $p = 0.01$) and VCI ($t = 2.88$, $p = 0.01$). The FSIQ score also approached a positive significant difference for the surgery + RT group ($t = 1.97$, $p=0.07$). However, the WMI discrepancy score for the radiotherapy only group was significantly negative indicating lower levels of current intellectual functioning than pre-morbid intellectual functioning ($t = -7.22$, $p = 0.002$). A one-way ANOVA found no differences in discrepancy scores for any measures of IQ ($F \geq 1.03$, $p \geq 0.39$).

The fluid (Gf) and crystallised (Gc) intelligence can be calculated by averaging the subtest scores that contribute to these indexes (see Table 7). The Gf and Gc scores for each group are shown below in Table 10. The population average is 10 scaled score points. All groups were in the normal range. There was no difference in scores between the groups ($F \leq 0.82$, $p \geq 0.49$). Paired sample t-tests showed no significant difference between Gf and Gc for any treatment group ($t \leq 1.52$, $p \geq 0.15$).

Table 10: The mean Gf and Gc scores for each group

		Conservatively Managed	Surgery Only	RT Only	Surgery + RT
Gf	**N**	7	19	7	19
	Mean	10.60	11.42	10.29	11.32
	Std. Dev.	2.23	2.56	2.10	2.22
Gc	**N**	7	19	7	19
	Mean	9.74	10.84	9.55	10.82
	Std. Dev.	2.01	2.45	3.05	2.32

Gf = Fluid Intelligence; Gc = Crystallised Intelligence; N = Number; Std. Dev. = Standard Deviation; RT = Radiotherapy

Discussion

The aim of this investigation was to test the impact of NFA and its treatment on intellectual functioning. The interpretation of the existent literature is confounded by problems relating to study design and patient sample. Methodological improvements on previous study design included the use of a comprehensive standardised neuropsychological test, the assessment of pre-morbid functioning to allow a within-subject comparison of previous and current functioning and more stringent patient inclusion criteria, such as the inclusion of only patients diagnosed after the age of 18.

No absolute impairment of intellectual functioning was found in any treatment group and no difference was found between the groups' WAIS-III scores. When relative impairment was assessed by comparing pre-morbid and current IQ, the surgery only group scored significantly higher for current IQ than pre-morbid IQ on the verbal measures of VCI and VIQ. Both the surgery only and the surgery + RT groups showed a trend towards higher current FSIQ than pre-morbid FSIQ. It is highly improbable that having an NFA or surgical treatment for it will improve a person's intelligence. This most likely represents a ceiling effect on the WTAR. The highest FSIQ that the WTAR can estimate is 119 and three patients in each of the surgery and surgery + RT groups scored above this on the WAIS-III measure of current functioning. Accordingly, it is likely that the measure of relative impairment is, in such cases, confound by the low ceiling of the WTAR.

A similar effect was found when the patient group as a whole was analysed for sex differences in discrepancy scores. Men had significantly higher VIQ and VCI discrepancy scores. However, both men and women had positive discrepancy scores, although men's scores were greater. It is again doubtful that being a man with a pituitary adenoma will improve your intelligence. Future researchers may benefit from the expanded word reading pre-morbid assessment included in the recently released WAIS-IV which has a higher ceiling limit of score.

The RT only group of patients with nasopharyngeal carcinoma had a decreased current WMI compared to their pre-morbid WMI. This was not seen in the NFA groups. Patients with nasopharyngeal carcinoma receive a greater amount of RT to more frontal areas of their cranium and brain. Therefore the prefrontal cortex of patients with nasopharyngeal carcinoma receives a higher dose of RT than patients treated for NFA. The decreased WAIS-III WMI score could indicate a deficit caused by RT induced damage to the prefrontal cortex. A negative effect of RT on working memory has been found previously in patients treated for nasopharyngeal carcinoma (Lam, Leung, & Chan, 2003).

When the treatment group scores were reanalysed using the factors of Gf and Gc, all groups were within the normal range, suggesting that patients do not have a particular impairment with either of these factors of general intellectual functioning. Within each group, there was no difference in Gf and Gc ability, except for the surgery only group in which the Gf index was significantly higher than the Gc index. As both of the group's index scores were above 10, this likely constitutes a relative strength in Gf rather than a weakness in Gc. It should also be noticed that whilst the factor of Gc is well represented in the WAIS-III with six subtests contributing to the index, only two subtests contribute to the Gf index. If future researchers wish to have a fuller measure of Gf, they should consider using the recently released WAIS-IV which incorporates an additional measure of Gf, instead of the WAIS-III.

The results of this study are commensurate with the previous literature. Baum et al. (1998) reported similar findings to the present study, showing intact current intellectual functioning in all treatment groups, whether or not patients were divided by the presence or absence of growth hormone replacement or by treatment with or without RT. Guinan et al. (Guinan et al., 1998) showed the same pattern of results

across assessments as the current study, with patients' WAIS-R FSIQs consistently exceeding their NART-R FSIQs, also adding to the evidence that pituitary adenoma and treatment do not impair intellectual functioning. Several other studies have assessed pre-morbid but not current intellectual functioning (Noad et al., 2004; Peace et al., 1998; Peace et al., 1997; Grattan-Smith et al., 1992). The pre-morbid estimates produced by these studies are commensurate with both the pre-morbid and current IQ scores achieved by the patients assessed in the current study.

The results of this study, combined with the evidence from the previous literature, supports the use of FSIQ to predict the memory scores that patients should be expected to achieve (Wechsler, 1997b). This method is based on the known correlations found between IQ and memory during the norming process for the WAIS-III and WMS-III. This provides a more sensitive measure of relative memory impairment and negates the issue of different treatment groups having different average FSIQs.

Memory

The previous chapter investigated the general intellectual functioning of patients with either non-functioning pituitary adenoma or nasopharyngeal carcinoma and found no evidence of impairment. However, it is far more frequent for patients to report difficulties with memory (McCord et al., 1997) and thus this cognitive function will now be examined in greater detail.

Introduction

Memory is not a unitary concept. It refers to a diverse range of cognitive abilities, which can be subdivided both conceptually and structurally. Different types of memory ability are measured in different ways, and are affected differently by hormone imbalance or by the presence or treatment of pituitary adenomas. The most commonly used subdivisions of memory in clinical assessment are shown below in Figure 3.

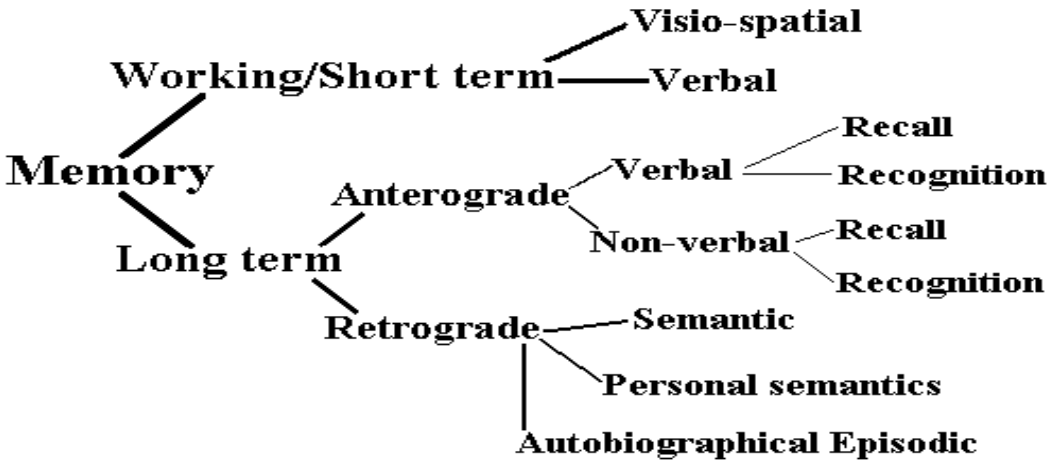

Figure 3: The most commonly used subdivisions of memory in clinical assessment

The broadest distinction of memory is between retrograde memory and anterograde memory. Retrograde memory refers to memories formed before a cerebral insult, usually a stroke or trauma. Conversely, anterograde memory refers to memories formed after such insult. Pituitary adenomas usually develop slowly over a number of years (Greenman & Stern, 2009) and so previous studies have rarely made reference

to retrograde and anterograde memory as a testable distinction. However, the distinction is important, as retrograde memory is dependent upon the retrieval of memories that had been encoded and stored prior to cerebral insult, whereas anterograde memory requires the encoding, storage and retrieval stages of memory. Accordingly, tests of retrograde memory may be susceptible to impairment of retrieval mechanisms, whereas tests of anterograde memory are susceptible to impairment of new learning in addition to impairment of retrieval mechanisms.

Guinan et al. (1998) used the Autobiographical Memory Inventory (Kopelman, Wilson, & Baddeley, 1990), a test of retrograde memory, to compare 90 patients grouped by treatment to a control group of neurologically normal individuals. They found no performance differences between any of the groups. This would suggest that memories encoded before a person develops an adenoma and receives treatment are unaffected.

A common way in which memory is often divided is between procedural, semantic and episodic. Procedural memory denotes knowledge of how to do something, usually a motor action such as riding a bike. Semantic memory is the knowledge of facts, unconnected to the memory of when or where the individual learnt them, whilst episodic memory refers to the recollection of events that happened to the person remembering them (Squire, 1982). Semantic and episodic memories together constitute the category of declarative memory. Most tests of memory, such as the various versions of the Wechsler Memory Scale (WMS) measure declarative memory. Participants are given new information to learn and are later tested on their ability to reproduce or recognise this material. The previous literature examining the effects of hormone dysfunction, adenoma and treatment on declarative memory is described below.

Declarative memory can be further subdivided into short-term and long-term memory systems. Short-term memory is typically depicted as a limited capacity memory system which is maintained for short periods of time without rehearsal (7 +/-2 chunks) (Miller, 1956). Perhaps the most well known model of short-term memory is that of Baddeley's (Baddeley & Hitch, 1974) working memory (WM) model, shown below in Figure 4. In this model WM is conceived as an active process involving two limited capacity short-term memory systems called the visuo-spatial sketchpad and

the phonological loop; the operation of which is controlled by a central executive system or systems. In functional terms, WM provides the ability to manipulate, as well as maintain, information in short-term memory in the service of ongoing problem-solving or transactions with the environment. Long-term memory can be conceived as memory for information that is no longer being actively rehearsed or stored in short-term memory. Long-term memory is typically measured with the use of delayed recall subtests in memory test batteries.

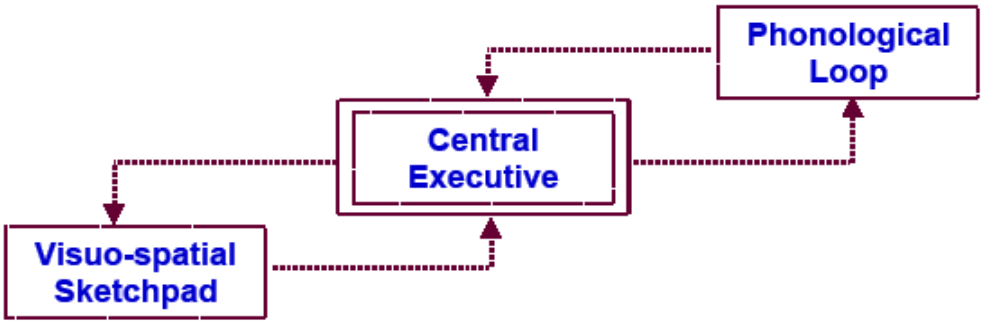

Figure 4: Baddeley's (1974) Working Memory model

Information can enter short term memory through any sensory route; however most memory tests use either visually or verbally presented material. Damage to sensory pathways can thus impair the encoding of to-be-remembered material. The left hemisphere is also more strongly associated with the processing of verbal material (Petrides, Alivisatos, & Evans, 1995) whilst the right hemisphere shows a greater involvement with spatial stimuli (Cadoret, Pike, & Petrides, 2001; Kostopoulos & Petrides, 2003; Petrides, Alivisatos, & Frey, 2002). This can mean that a person's memory abilities for material can be influenced by the manner in which it is presented, whether that person has damage to the brain areas that process this type of material, and that individual's premorbid preference for verbally or visually presented material (Henke et al., 1999). Although stimuli are presented either visually or verbally, the distinction between 'visual' and 'verbal' is dependent upon strategy use. This distinction needs to be treated with caution as it refers more to the input of the stimuli than the strategies used to encode it. For example, a participant may be asked to remember the conjunction 'star-ladder', and instead of encoding the words, imagines a picture of a ladder reaching up to a star, and encodes this image instead.

Accordingly, it is naïve to conceptualise performance on this task as reflecting verbal memory and being biased toward left hemisphere processing.

Although test batteries of memory often divide tasks between visually and verbally presented material, the neuropsychologist should be cautious about interpreting task discrepancies as reflecting process dissociations.

Memories that can be spontaneously brought to mind and reported during free recall represent the intact encoding and retrieval of the stimuli. Patients with prefrontal cortex damage often exhibit deficits in free recall in the presence of intact recognition (Shimamura, 1995). If a person is not able to freely recall novel stimuli, they may still find it familiar when it is represented (due to prior activation of the representation of the stimulus during the learning phase), indicating that the information had been encoded and consolidated but had failed to be retrieved in free recall. Functional magnetic resonance imaging (fMRI) studies have demonstrated that within the medial temporal lobe (MTL), the hippocampus and to a lesser extent the posterior parahippocampal region show greater activation during both encoding and retrieval of remembered versus forgotten stimuli, suggesting these areas support the process of recall. However, the majority of studies have not found activation in these areas correlated to familiarity based memory (Eichenbaum, Yonelinas, & Ranganath, 2007). The anterior parahippocampal gyrus shows the opposite pattern, with greater activation during encoding for stimuli that were later rated as highly recognised than for those that were not. Anterior parahippocampal activation is rarely reported for recall tasks (Eichenbaum et al., 2007). These results suggest that recall and familiarity are supported by different areas of the MTL. A similar pattern of dissociations between recall and recognition is observed studies of amnesic patients, who show intact familiarity judgement with poor recall memory (Yonelinas et al., 2002; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005). Memory test batteries usually contain both free recall and recognition tasks to differentiate between deficits of encoding and retrieval.

Various aspects of a visual stimulus can be separately encoded in the brain. From the occipital cortex the identity of an object is encoded along a ventral pathway, whilst the location of the object is encoded along the dorsal pathway (Dutton, 2003). Greater activation at encoding in the left anterior parahippocampal cortex and right anterior

medial temporal lobe is correlated with correctly remembering the location associated with an object (Sommer, Rose, Glascher, Wolbers, & Buchel, 2005; Sommer, Rose, Weiller, & Buchel, 2005). The right temporal lobe has also been implicated as processing spatial memory (Morris et al., 1999), whilst the ventromedial prefrontal cortex has been shown to be specifically involved in memory for objects (Szatkowska, Grabowska, & Szymanska, 2003). The memory of when a stimulus was presented has been associated with left prefrontal activity in humans (Suzuki et al., 2002) and the dorsal hippocampus in rats (Hoge & Kesner, 2007). Damage to different brain areas can therefore differentially impair the information a person can recall about a stimulus. They may show poor performance when tested on one aspect of the information (e.g. when it was shown) but not another (e.g. what is it).

As the term memory subsumes such a variety of function, the clinical assessment of memory has accordingly focused on a range of type of memory stores and processes. Most frequently, memory test batteries will assess the free recall and recognition of working, immediate (short-term) and delayed (long-term) memory for visually or verbally presented material.

Measurement of Memory using the WMS-III

The third version of the Wechsler Memory Scale (WMS-III) is one of the most widely used memory test batteries currently available (Wechsler, 1997a). It provides measures of immediate and delayed free recall and recognition for material presented in both the visual and verbal modalities. The subtests are outlined below in Table 11.

Table 11: The subtests of the WMS-III

Subtest Name	Input Modality	Time since Presentation at Test	Measure of
Logical Memory 1	Verbal	Immediate	Free Recall
Faces 1	Visual	Immediate	Recognition
Verbal Paired Associates 1	Verbal	Immediate	Free Recall
Family Pictures 1	Visual	Immediate	Free Recall
Letter-Number Sequencing	Verbal	Immediate	Free Recall
Spatial Span	Visual	Immediate	Free Recall
Digit Span	Verbal	Immediate	Free Recall
Logical Memory 2	Verbal	Delayed	Free Recall
Logical Memory Recognition	Verbal	Delayed	Recognition
Faces 2	Visual	Delayed	Recognition
Verbal Paired Associates 2	Verbal	Delayed	Free Recall
Verbal Paired Associates Recognition	Verbal	Delayed	Recognition
Family Pictures 2	Visual	Delayed	Free Recall

There has been considerable empirical interest in the factor structure of the WMS-III and the literature presents some variation in the number of factors that have been identified (Wilde et al., 2003; Hoelzle, Meyer, Pyykkonen, & Han, 2008), however, the majority of factor analytic solutions include factors for auditory memory (inclusive of immediate and delayed recall), visual memory (inclusive of immediate and delayed recall) and working memory (Price, Tulsky, Millis, & Weiss, 2002). This has also been replicated in a clinical sample of patients with epilepsy (Wilde et al., 2003; Bell, Hermann, & Seidenberg, 2004).

As the WMS-III indices have changed from the WMS-R, it is not possible to make a direct correlation but scores for individuals who were administered both tests did not differ by more than two points on similar indices, for example visual memory versus visual immediate memory (Wechsler, 1997a). This is important to consider when comparing the results of previous studies which have used the WMS-R to the current research.

Memory dysfunction often presents as an early indicator of pathology in neurological diseases such as Alzheimer's disease, and is a common cognitive complaint following a wide range of acquired neurological events (Schroeter, Stein, Maslowski, & Neumann, 2009; Zec et al., 1993; Leyhe, Muller, Milian, Eschweiler, & Saur, 2009;

Pirogovsky et al., 2007). The WMS-III has proved sensitive to these conditions. For example, a group of 35 patients with mild Alzheimer's disease scored in the impaired range (ie., <70 on all indexes except WM) whilst their FSIQs were in the low average classification range (Wechsler, 1997a). This study was later replicated by Lange and Chelune, (2006). A group of patients with Huntington's obtained slightly better scores, with an average immediate memory of 70.9 and general memory of 76.4. However, these were still considerably lower than their average FSIQ of 84 points (Wechsler, 1997a). The WMS-R was also shown to be highly sensitive to hippocampal damage. Reed and Squire (1997) tested six patients with lesions limited to the hippocampal region and found their average general memory index to be 33.7 points lower than their WAIS-R FSIQ.

The effects of hormone dysfunction, pituitary adenoma, and its treatment on memory functioning

Patients treated for pituitary adenomas sometimes report difficulties with anterograde memory. One study found that patients are more likely to report memory difficulties if they are treated with a combination of surgery and radiotherapy than if they were only given one treatment (McCord et al., 1997). This suggests several possible mechanisms of injury that could cause the reported memory impairment in patients with NFA; principally surgery, RT and hormone insufficiency (Samuels, Schuff, Carlson, Carello, & Janowsky, 2007b; Cheng et al., 2000; Arafah, Prunty, Ybarra, Hlavin, & Selman, 2000). Pituitary surgery is unlikely to directly damage the hippocampal complex due to its relative distance from the pituitary gland. However, transcranial surgery has the potential to cause damage to the anterior brain structures and although damage to anterior cortices may not have a direct effect upon memory consolidation systems, the overall efficiency of memory function may be compromised due to a failure to encode appropriate contextual information as a consequence of suboptimal goal orientation (Grafman, Partiot, & Hollnagel, 1995). During RT, the medial temporal and frontal lobes receive about 22.5-45 Gy (Sohn, Dalzell, Suh, Tefft, & Schell, 1995). One of the most common side effects of therapeutic irradiation is a dose dependent damage to blood vessels. The vasculature is most vulnerable to RT damage as the vessel walls largely consist of radiosensitive endothelial cells (Fajardo, 1999). Depletion of endothelial cells may result in demyelisation of axonal tissue and

consequently impairment of interneuronal communication. This may lead to cognitive impairment. When patients experience other radiation induced symptoms, cognitive impairments are also prominent. It is possible that asymptomatic patients with white matter pathology are experiencing sub-clinical cognitive dysfunction. Patients who receive RT have a greater chance of developing hypopituitarism (Gittoes, 2005) which is a deficiency in the production of one or various hormones. Hypopituitarism has been associated with reduced memory performance (Arwert et al., 2005; Arwert, Veltman, Deijen, van Dam, & Drent, 2006; Samuels et al., 2007b). Therefore, RT could cause anterograde memory deficits by damaging pituitary hormone production, with a secondary effect on memory, rather than by directly damaging the MTL.

Potential effects of hormone dysfunction

All of the studies into the neurocognitive effects of treatment for pituitary tumours have included patients with hormone producing tumours in their sample. This may have affected the results as several studies have found that abnormally high levels of some hormones can affect neurocognitive function. Cortisol administration can have a positive effect on memory performance in the afternoon, when levels are typically low, but the same effect is not found in the morning. If cortisol production is inhibited by metyrapone in the afternoon, recall is impaired (Lupien et al., 2002; Lupien et al., 1999). Others (Kuhlmann et al., 2005) have observed a reduction in delayed recall after cortisol administration for negative words more than for neutral words, suggesting inappropriate levels of cortisol replacement may exert different effects under different conditions. Patients with Cushing's disease have also been found to show poorer performance on several subtests of learning, delayed recall, and visual-spatial ability associated with higher cortisol levels. Working memory appears unaffected by cortisol level (Starkman et al., 2001).

Inducing sub-clinical hyperthyroidism does not seem to affect cognitive performance in healthy individuals over a period of 45 days (Baethge et al., 2002), however, hypothyroidism has been shown to selectively impair delayed recall (Burmeister et al., 2001). Difficulties with verbal memory retrieval have also been found but these resolved with levothyroxine replacement (Miller et al., 2006).

Childhood growth hormone deficiency (GHD) has been recognised as a significant variable leading to neurocognitive problems which can be improved by growth hormone (GH) replacement (Arwert et al., 2005; Deijen et al., 1998). Patients with adult-onset GHD also demonstrate impairment on immediate and delayed recall (Deijen et al., 1996).

Sex hormones can affect cognition differentially according to a person's age (Mulnard et al., 2000), especially if age inappropriate levels are given to older adults (Espeland et al., 2004). Estrogen has been shown to have a positive effect on verbal memory performance in younger women who have recently experienced menopause, either naturally (Stephens et al., 2006; Dumas et al., 2008) or surgically (Phillips & Sherwin, 1992). This is thought to be due to a protective effect of oestrogen on cholinergic neurones (Gibbs & Aggarwal, 1998). However, older women do not experience this protective effect. This could be due to a reduction in muscarinic receptors to which oestrogen induces an increase in NMDA binding (Norbury et al., 2007). Testosterone deprivation in men treated for prostate cancer has been associated with poorer recall (Beer et al., 2006) and recognition (Bussiere et al., 2005) of verbally presented semantic material.

Two studies examining cognition in patients with pituitary adenoma have entered gender as a covariate into analyses (Grattan-Smith et al., 1992; Armstrong et al., 2002), but these studies did not report whether there were any differences on the outcome measures between females and males. The remaining research has not compared the performance of their male and female patients (Peace et al., 1997; Peace et al., 1998; Noad et al., 2004; Guinan et al., 1998; Torres et al., 2003; Armstrong et al., 2002). For the reasons outlined above, it is imperative to take into account the endocrine status of the patient in order to achieve reliable assessment of the impact of pituitary disease upon neurocognitive functioning, especially in regard to cortisol and GH, which consistently emerge as important for achieving full cognitive potential.

Potential effect of the adenoma

The area in which patients most frequently and reliably experienced deficits is recall of new material. All of the retrospective studies found patients to be worse than test norms or controls on at least one measure of memory. Most studies found patient

groups to be worse on measures of both visual and auditory memory (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Guinan et al., 1998; Noad et al., 2004). However, there was no consistently found difference between patients grouped by the treatment they had received. Four studies found no differences between any of the patient treatment groups (Guinan et al., 1998; Grattan-Smith et al., 1992; Baum et al., 1998; Noad et al., 2004) whilst others found varying differences in memory abilities between treatment types (Peace et al., 1997; Peace et al., 1998).

Some studies have included a group of patients who were conservatively managed or treated with medication only (Peace et al., 1998; Guinan et al., 1998). They found that all patient groups performed worse than controls, indicating that the underlying tumour may be causally linked to their deficits. Peace et al. (1998) found all patient groups, including the medication only group, performed worse than the control group on immediate and delayed auditory recall. When comparing patients to test norms, Guinan et al. (1998) found that similar patient groups did not show any absolute impairment because their general and delayed memory were within the normal range. However, all of the patient groups except the RT only group, demonstrated a poorer memory quotient (MQ) than would be predicted based on their intelligence quotients (IQs). The RT only group had a significantly lower IQ than the other groups, and so there was a smaller difference between MQ and IQ in the RT only group than was demonstrated by the other patient groups. When Guinan et al. re-analysed the results without the control group there was very little difference between the patient groups. The medication only group demonstrated less impairment on delayed recall than the surgically and/or RT treated groups, but no other differences reached significance. In contrast to Peace et al., Guinan et al. concluded that memory deficits were due to damage to diencephalic structures such as the mammillary bodies, and are most likely to be caused by treatment rather than the tumour itself.

Potential effects of pituitary surgery

Peace et al. (Peace et al., 1997; Peace et al., 1998) reported that surgically treated patients as a whole performed significantly worse than healthy controls on recognition memory for faces. Surgically treated patients also performed significantly worse than non-surgically treated patients on some measures of auditory and visual memory. The same researchers later found that both their surgery groups were poorer than the

controls at list learning and recognition of faces suggesting both auditory and visual memory impairments. Therefore these studies implicate both surgery and the underlying tumour as being potential causes of patients' deficits.

Potential effects of combined surgery and RT

None of the retrospective studies found any significant deficit on tests in memory in patients treated with RT compared with other patient groups (Peace et al., 1998; Grattan-Smith et al., 1992; Peace et al., 1997; Baum et al., 1998; Guinan et al., 1998; Noad et al., 2004). Peace et al. found no difference in memory test performance between their patients on the basis of type of surgery or presence of RT. Guinan et al. did not find a difference between patients treated with or without RT. They also analysed their data by both adenoma type and time since treatment and found no differences for either. However, time since treatment was dichotomised as patients treated within the last five years and patients treated longer than five years ago. The dichotomisation by this criterion appears somewhat arbitrary and additional precision with regard to the effect of time since treatment may have been achieved if this factor had been measured and analysed as a continuous variable.

The first of the prospective studies reported somewhat ambivalent findings (Torres et al., 2003). On one measure of visual memory patients showed linear improvement whilst on another they showed improvement followed by decline. This delayed decline is thought to reflect the late or delayed effects of RT treatment. In the second prospective study, patients who did not suffer tumour regrowth showed improvements at various stages over two years and an overall improvement from baseline on two measures of auditory memory (Armstrong et al., 2002). These post-RT improvements may be due to a reduction of symptoms caused by pressure effects from the tumour. This may have been the case in one study, in which pre-RT baseline testing occurred an average of 53 days after surgery when some swelling may still have remained.

There are several flaws and omissions in the previous literature. Patients with functioning tumours have been included in the sample despite the potential effects of hormone excess on memory functioning. Different control groups have been used by previous studies. Some have used a small control group of neurologically intact individuals (Peace et al., 1997; Peace et al., 1998; Guinan et al., 1998), whilst others

have used a group of patients with a different chronic condition (Grattan-Smith et al., 1992). Only two studies have compared patient groups to standardised test norms (Guinan et al., 1998; Baum et al., 1998). Most studies compare only measures of absolute impairment (i.e. patient performance on memory tasks). This method may be insensitive as within group variation (i.e. natural variability in the general population) is likely to be substantial, relative to the between group variation attributable to treatment effects. An alternate strategy would be to use a relative impairment measure (i.e. difference scores relative to estimated premorbid function). However, such relative impairment measures have only been employed in one study; Guinan et al. (1998) use a measure of relative impairment obtained by subtracting current memory quotient from that individual's current intelligence quotient. This provides a measure of the discrepancy between memory function and general intellectual functioning. However, the relationship between memory and intellectual function is not linear across the range of intellectual performance, as measured by standardised IQ tests. Accordingly the simple discrepancy method used by Guinan et al. (1998) tends to over-estimate the discrepancy between memory function and general intellectual functioning in either high or low functioning individuals.

The current study employs a measure of relative impairment (i.e. the predictive discrepancy) which does not show bias if a person's general intellectual functioning is discrepant from age peers.

Aims

The literature discussed thus far would suggest that patients treated with surgery will perform worse than patients who have been conservatively managed. This has been found by all research to date except Baum et al. (1998). Patients treated with surgery and radiotherapy have not been found to consistently perform more poorly on memory tasks than patients treated with surgery alone. However, the small number of unconnected memory tests coupled with the small number of participants used by many studies makes this finding inconclusive. This study aims to provide robust and sensitive memory performance data to answer the question of whether the presence or treatment of a pituitary adenoma impairs memory functioning.

Null Hypotheses

- Memory scores in patients treated with surgery will not be significantly different from patients who have been conservatively managed up to the time of memory testing.

- Memory scores in patients treated with RT will not be significantly different patients who have been conservatively managed up to the time of memory testing.

- Memory scores in patients treated with surgery and RT will not be significantly different from patients treated with surgery alone or patients who have been conservatively managed up to the time of memory testing.

Method

Participant characteristics, general procedure and experimental design are discussed in the 'General Methods' chapter. This is a cross-sectional independent groups design with four treatment groups: conservatively managed, surgery only, RT only, and surgery and RT. Patients were treated with RT alone if they were diagnosed with a nasopharyngeal carcinoma. The three other treatment groups exclusively contained patients treated for NFA.

There is a moderate to strong correlation between WMS-III subtests and WAIS-III FSIQ (correlations range from 0.36 to 0.68). Learning and memory are assumed to be core components of general intellectual ability and therefore, significantly related to an individual's performance on tests of intelligence. Because of the relatively high intercorrelations between FSIQ and memory, the individual's FSIQ provides an estimate of their probable memory abilities. The FSIQ from the WAIS-III will be used to predict the premorbid memory scores. These expected scores will be subtracted from their achieved scores to give a discrepancy score. A positive discrepancy score indicates performance above that expected from the individual's FSIQ. A negative discrepancy score indicates impaired performance relative to that predicted by general intellectual functioning. This method provides a measure of relative impairment which is more sensitive to dysfunction than measuring absolute impairment by comparing to the population average. Because the relative impairment method

accounts for the individual's FSIQ, a person with a high level of intellectual functioning and previously commensurate high memory abilities will still be recognised as having an acquired memory dysfunction after a loss of several MQ points, even if this loss causes them to fall to the level of the population average and not below. Conversely, if a person has a below average level of general intellectual functioning, they will not be mislabelled as having an acquired memory functioning deficit when their memory scores are commensurate with their other cognitive abilities. Accordingly, the discrepancy score controls for variation in level of premorbid function.

In this study, the conservatively managed treatment group act as a control group for the effect of the presence of tumour, in both the surgery and surgery + RT groups. The surgery group acts as a control for the effect of surgery in the surgery + RT group. The RT group acts as a control for the effect of RT in the surgery + RT group. A difference between two groups would indicate an effect of treatment. Deficit due to tumour would be demonstrated by a significant negative discrepancy between the memory scores expected given the participants' FSIQ and the scores they achieve.

The battery of measures of memory and other cognitive functions is described in the General Methods chapter. These measures were selected because of the high quality normative data provided with the test and the measure of relative impairment that can be obtained from using the WMS-III and the WAIS-III together. The WMS-III allows the comparison of immediate and delayed memory for the same stimuli. These linked subtests provide extra data such as retention and retrieval scores as well as the data provided by the subtests per se. The use of the WMS-III in conjunction with the WAIS-III also provided a person's predicted memory scores which can be compared to their obtained scores, to allow the analysis of discrepancies.

One-way ANOVAs were used to examine any differences between groups on the memory index scores. Potential correlations between WMS-III index scores and several demographic and treatment factors were analysed. These factors were age; time in months since surgery; time in months since RT; size of original tumour volume; number of hormone replacements; TSH levels in men, years of education; and the GSI T-score from the SCL-90R.

Results

There was a significant correlation between one or more WMS-III scores and the factors of age; time in months since surgery, the number of hormone replacements patients were taking and TSH in men. One-way ANOVAs were thus conducted to assess the distribution of the covariates between the treatment groups. TSH was the only variable to differ between the groups. TSH correlated with auditory delayed memory (r = -0.38, p = 0.05) and working memory (r = -0.47, p = 0.01). There were no other significant differences between the groups on any of these variables. Therefore, level of TSH was the only covariate entered into the analyses.

Absolute Impairment of Memory Functioning

The distribution of the scores achieved by each treatment group is shown below in Table 12 and the average scores achieved by each group are shown in Table 13. Statistical analysis is not possible on the spread of scores due to low or zero numbers in many cells, however, it can be seen that the average range contains the most participants for each index score. A one-way ANOVA showed no difference between the groups on any absolute measure of memory functioning (Table 13).

However, an independent samples t-test showed a significant difference between men and women across the groups on both auditory delayed memory (female $\bar{X}$ = 106.2, s.d. = 16.8; male $\bar{X}$ = 96.5, s.d. 13.7; t = 2.31, p = 0.03) and visual delayed memory (female $\bar{X}$ = 104.9, s.d. = 7.2; male $\bar{X}$ = 95.3, s.d. = 12.2; t = 2.34, p = 0.02), with women achieving significantly higher scores than men.

Table 12: The distribution of scores achieved by each treatment group for each WMS-III index

		CM	S	RT	S+RT			CM	S	RT	S+RT
AIM	**V Sup**				1	**ADM**	**V Sup**			1	2
	Sup		1	2	1		**Sup**		2	1	1
	H Avge		2		2		**H Avge**	3	3		2
	Average	6	10	3	10		**Average**	3	9	3	10
	L Avge	1	4	1	4		**L Avge**	1	4	1	2
	Border		2	1			**Border**		1	1	2
	E Low				1		**E Low**				
VIM	**V Sup**		1			**VDM**	**V Sup**		1		1
	Sup		2				**Sup**		1	1	
	H Avge		2	1	2		**H Avge**	2	4	1	3
	Average	6	7	4	13		**Average**	3	8	3	11
	L Avge	1	5		2		**L Avge**	2	4	1	2
	Border		2	2	1		**Border**		1	1	1
	E Low				1		**E Low**				1
WM	**V Sup**		3		3	**ARDM**	**V Sup**	1	1		1
	Sup	1			4		**Sup**		2		2
	H Avge	1	8	1	1		**H Avge**	2	4	1	4
	Average	4	3	3	8		**Average**	3	9	3	9
	L Avge	1	4	3	2		**L Avge**	1	3	3	3
	Border				1		**Border**				
	E Low						**E Low**				

CM = Conservatively Managed; S = Surgery; RT = Radiotherapy; AIM = Auditory Immediate Memory; VIM = Visual Immediate Memory; WM = Working Memory; ADM = Auditory Delayed Memory; VDM = Visual Delayed Memory; ARDM = Auditory Recognition Delayed Memory; V = Very; Sup = Superior; H = High; Avge = Average; L = Low; Border = Borderline; E = Extremely

Table 13: The WMS-III scores achieved by each treatment group

		Conservatively Managed	Surgery Only	RT only	Surgery + RT	F	p(F)
	N	7	19	7	19		
AIM	**Mean**	95.00	97.21	96.86	99.47	0.20	0.90
	Std. Dev.	5.07	12.40	17.31	16.49		
VIM	**Mean**	96.14	98.05	95.43	93.89	0.27	0.85
	Std. Dev.	6.41	18.04	14.59	11.87		
ADM	**Mean**	102.14	100.58	98.57	101.32	0.07	0.97
	Std. Dev.	12.31	14.52	20.75	17.18		
VDM	**Mean**	96.43	100.05	100.29	99.89	0.11	0.96
	Std. Dev.	10.06	16.25	17.43	15.97		
ARDM	**Mean**	105.00	102.37	93.57	102.37	0.93	0.44
	Std. Dev.	14.14	14.66	10.69	14.57		
WM	**Mean**	103.43	108.94	96.14	110.79	1.43	0.76
	Std. Dev.	13.39	18.98	11.28	17.93		

AIM = Auditory Immediate Memory; VIM = Visual Immediate Memory; ADM = Auditory Delayed Memory; VDM = Visual Delayed Memory; ARDM = Auditory Recognition Delayed Memory; WM = Working Memory

Relative Impairment of Memory Functioning

In contrast to absolute impairment, which measures an individual's abilities compared to age matched peers, relative impairment relates to the discrepancy between an individual's memory function in relation to that same individual's general intellectual ability. Therefore, the FSIQ of each patient was used to predict the memory scores that each patient would be expected to achieve (Wechsler, 1997a). This is known as the predicted difference method and it represents a more sensitive measure of potential memory dysfunction. It reduces error variance attributable to within group variation, as each participant acts as their own control (using the formula: 'achieved memory score – predicted memory score = discrepancy score'). A negative discrepancy score indicates worse than expected performance and might indicate an acquired memory deficit. By predicting each patient's memory scores from their own general intellectual functioning, differences between the groups, resulting from baseline difference in general ability, will have a reduced effect on the results. This reduced effect results from a decrease in between group variance. A one-way ANOVA showed no difference in discrepancy scores between the groups, indicating no difference in the level of impairment between the treatment groups. To test for relative impairment within each group, the discrepancy between the expected scores of each group and their observed memory scores was compared to 0 (no difference between predicted and observed scores) using a one sample t-test. The results are shown in Table 14.

Table 14: The memory scores predicted for each group and the discrepancy from the achieved scores **(**P(t) ≠ 0 means the probability that the discrepancy score is different from 0 (two-tailed))

		Conservatively Managed	Surgery Only	RT only	Surgery + RT	F	p(F)
	N	7	19	7	19		
AIM	**Predicted Mean**	100.43	104.00	98.14	103.89	0.85	0.47
	Mean Discrepancy	-5.43	-6.79	-1.29	-5.16	0.33	0.81
	Std. Dev. (Disc)	6.97	11.82	9.64	15.37		
	p(t) ≠ 0	0.09	**0.02**	0.74	0.16		
VIM	**Predicted Mean**	100.43	102.37	98.57	102.47	0.95	0.42
	Mean Discrepancy	-4.29	-4.32	-3.14	-9.05	0.58	0.63
	Std. Dev. (Disc)	4.39	18.04	11.73	9.72		
	p(t) ≠ 0	**0.04**	0.31	0.51	**0.001**		
ADM	**Predicted Mean**	100.57	103.89	98.14	103.89	0.87	0.46
	Mean Discrepancy	1.57	-3.32	0.43	-2.89	0.27	0.85
	Std. Dev. (Disc)	9.62	14.00	13.10	17.64		
	p(t) ≠ 0	0.68	0.32	0.93	0.48		
VDM	**Predicted Mean**	100.43	102.84	98.43	103.00	0.96	0.42
	Mean Discrepancy	-4.00	-2.79	1.86	-4.53	0.37	0.78
	Std. Dev. (Disc)	8.62	16.33	13.42	13.12		
	p(t) ≠ 0	0.27	0.47	0.73	0.15		
ARDM	**Predicted Mean**	100.43	103.21	98.29	103.37	0.90	0.45
	Mean Discrepancy	4.57	-0.84	-4.71	-0.47	0.54	0.66
	Std. Dev. (Disc)	16.68	15.40	4.99	13.04		
	p(t) ≠ 0	0.50	0.81	**0.05**	0.88		
WM	**Predicted Mean**	100.71	104.58	97.57	104.63	0.91	0.45
	Mean Discrepancy	2.71	4.56	-1.43	3.63	0.47	0.71
	Std. Dev. (Disc)	10.16	13.14	7.09	11.68		
	p(t) ≠ 0	0.51	0.16	0.61	0.19		

AIM = Auditory Immediate Memory; VIM = Visual Immediate Memory; ADM = Auditory Delayed Memory; VDM = Visual Delayed Memory; ARDM = Auditory Recognition Delayed Memory; WM = Working Memory

All groups achieved scores that are commensurate with their FSIQs, with the exception of four variables. The surgery only (p=0.04) groups scored below expected for the auditory immediate discrepancy score. In contrast, both the conservatively managed (p=0.02) and the surgery + RT group scored below expected on the visual immediate discrepancy score (p<0.001). The RT only group scored below expected on the auditory recognition delayed discrepancy score (p = 0.05).

The predicted and achieved memory scores for each group are shown in Figure 5 below.

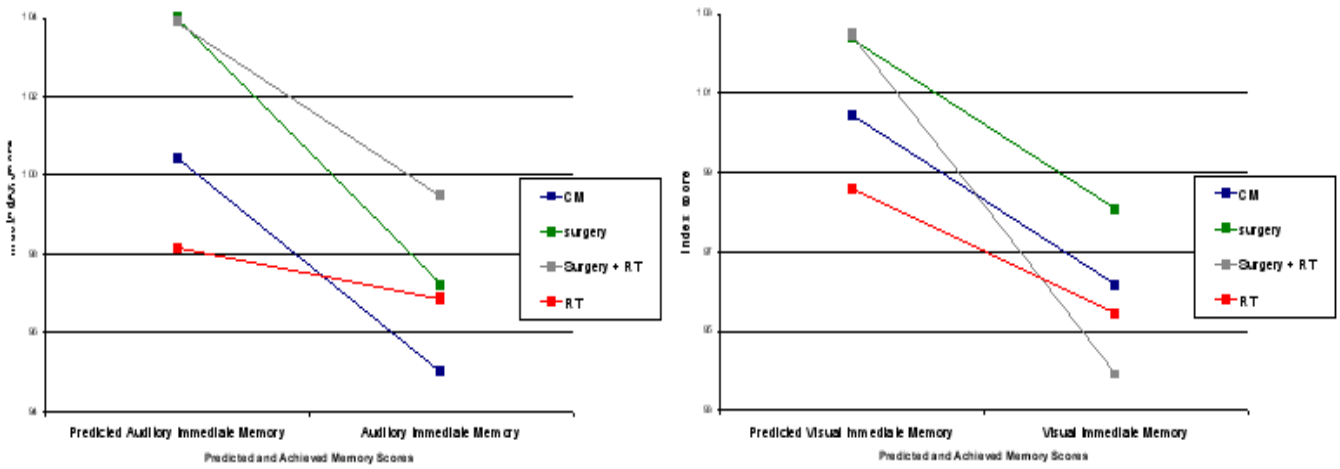

Figure 5: The mean predicted and achieved memory scores for each treatment group

The standard deviations of the discrepancy scores were less than the standard deviation of the raw ability scores within a treatment group. This is to be expected given that each patient's predicted score was estimated from their own level of general intellectual functioning and that the observed minus predicted score (i.e. the discrepancy score) was based upon estimates derived from the individuals own performance. However, there was still a considerable spread of discrepancy scores within each group. This is shown below in Figure 6. Whilst some participants achieved memory scores that were commensurate or above those predicted by their FSIQ, others achieved memory scores up to three standard deviations below expected, despite receiving the same treatment. Accordingly, there is considerable variability in this data set that cannot be attributed to treatment type. This is described in Table 15.

The patient data was again reanalysed by sex and it was discovered that men showed significantly poorer discrepancy scores than women on every measure of memory except auditory recognition and working memory. These scores are shown in Table 16. The auditory immediate discrepancy scores are shown in Figure 7 as a typical example of the distribution of scores of each discrepancy outcome measure. An ANCOVA showed that there was no significant sex by group interaction ($F = 0.21$, $p = 0.89$).

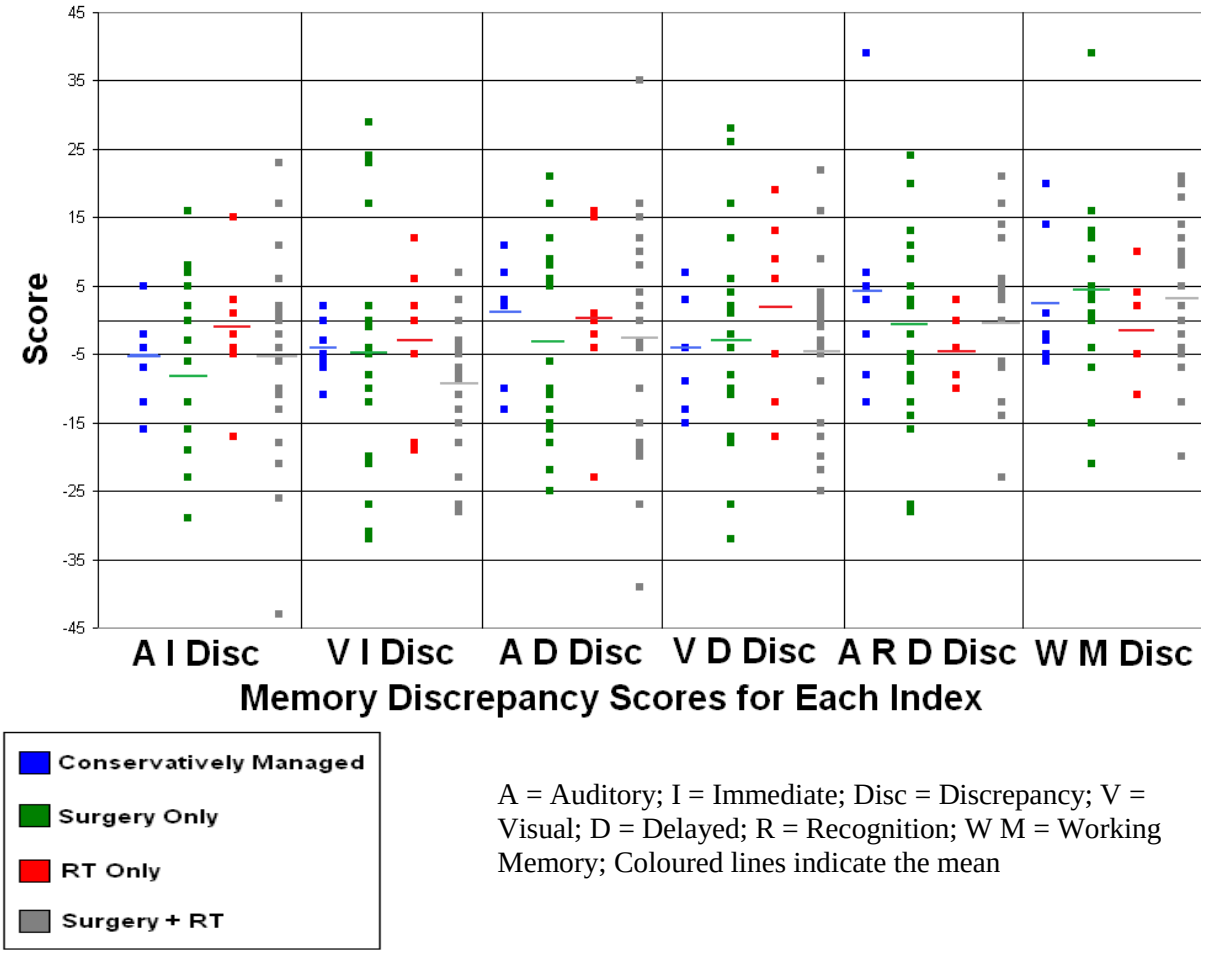

Figure 6: The spread of discrepancy scores within each treatment group

Table 15: The range of discrepancy scores within each treatment group

	CM				Surgery				RT				Surgery + RT			
	R	**Min**	**Max**	**IQR**	**R**	**Min**	**Max**	**IQR**	**R**	**Min**	**Max**	**IQR**	**R**	**Min**	**Max**	**IQR**
A I Disc	21	-16	5	10	45	-29	16	17	32	-17	15	8	66	-43	23	15
V I Disc	13	-11	2	7	61	-32	29	26	31	-19	12	24	35	-28	7	12
A D Disc	24	-13	11	21	46	-25	21	23	39	-23	16	19	74	-39	35	28
V D Disc	22	-15	7	16	60	-32	28	25	36	-17	19	25	47	-25	22	20
A R D Disc	51	-12	39	15	52	-28	24	22	13	-10	3	10	44	-23	21	24
W M Disc	26	-6	20	19	60	-21	39	16	21	-11	10	9	41	-20	21	17

CM = Conservatively Managed; RT = Radiotherapy; A = Auditory; I = Immediate; Disc = Discrepancy; V = Visual; D = Delayed; R = Recognition; W M = Working Memory; R = range; Min = Minimum; Max = Maximum; IQR = Inter-Quartile Range

Table 16: The discrepancy scores achieved by men and women across groups

	Sex	**N**	**Mean**	**Std. Dev**	**t**	**p(t)**
A I Disc	female	23	0.48	10.34	3.26	0.002
	male	29	-9.83	12.04		
V I Disc	female	23	-0.13	14.28	3.03	0.004
	male	29	-10.45	10.27		
A D Disc	female	23	5.70	11.74	3.80	0.000
	male	29	-8.10	13.91		
V D Disc	female	23	3.48	13.59	3.28	0.002
	male	29	-8.07	11.76		
A R D Disc	female	23	2.65	10.08	1.51	0.14
	male	29	-3.00	15.59		
W M Disc	female	23	3.86	10.39	0.39	0.70
	male	29	2.59	12.26		

A = Auditory; I = Immediate; Disc = Discrepancy; V = Visual; D = Delayed; R = Recognition; W M = Working Memory

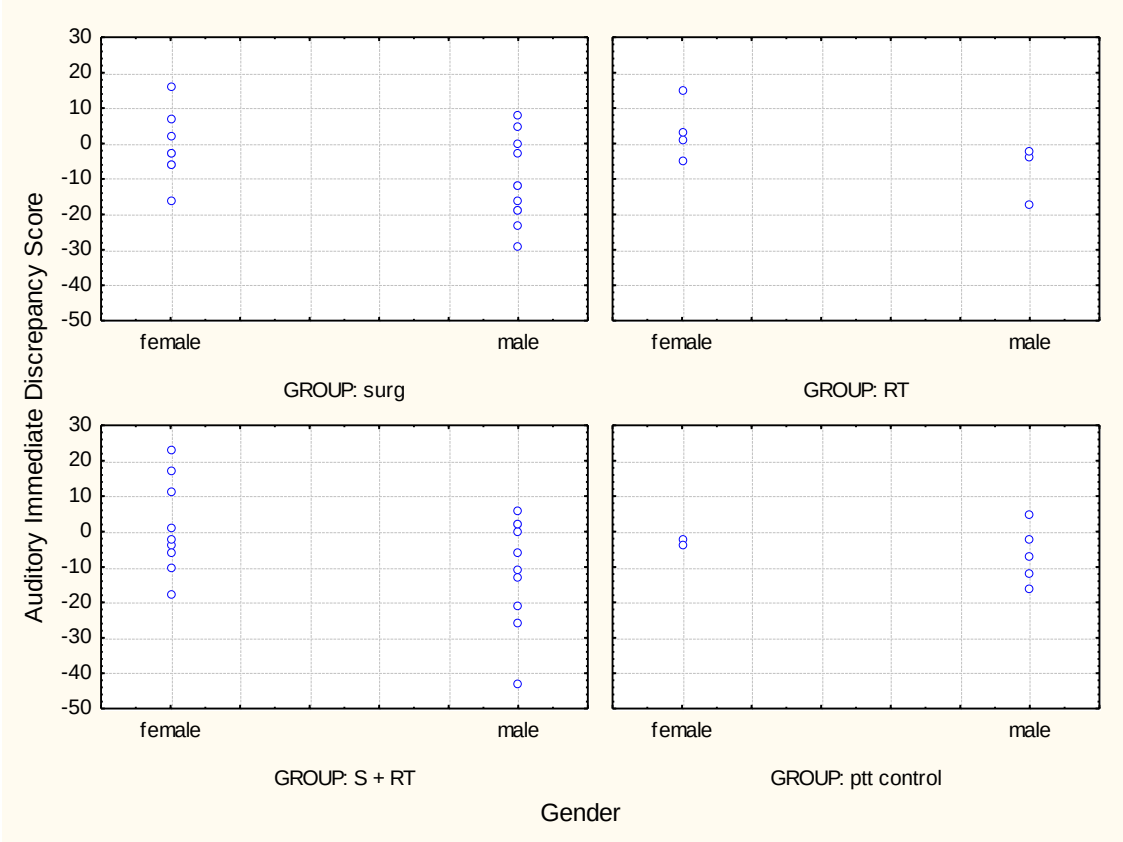

Figure 7: The distribution of auditory immediate memory scores separated by group and sex

In summary, whilst the treatment groups showed no absolute impairment of memory functioning and no difference between groups, relative impairment of some measures of immediate memory was evident. A sex difference was also found, with men achieving significantly poorer memory scores than women across the treatment groups.

Discussion

Patients in this study treated with or without surgery and RT achieved immediate memory scores below the scores predicted by their IQ. Delayed memory scores and recognition memory were commensurate with IQ.

Immediate memory impairment for different modes of stimulus presentation was found within the treatment groups, with the CM and RT treated NFA patients showing deficit for visually presented stimuli whilst NFA patients treated with surgery alone showed deficit for verbally presented material. There is no obvious reason for this dichotomy and it could represent a statistical artefact of the WMS-III test battery factor structure, as it is highly

unlikely that receiving RT treatment will increase a patient's auditory immediate memory abilities. The conservatively managed patients had a significantly poorer than expected visual immediate memory score with a sample size of only seven. This suggests that the cause of the patients' memory dysfunction is independent of treatment, although, a larger sample of conservatively managed patients would be required to confirm this finding.

Patients with nasopharyngeal carcinoma treated with RT showed a different pattern of results to the groups of patients with pituitary adenoma. Their achieved memory scores were commensurate with those predicted from their FSIQs except for a specific deficit in recognition memory. This is surprising given that their auditory free recall discrepancy score was commensurate with their predicted score. There is no conceptual basis as to why patients treated with RT for NPC would have intact free recall in the presence of impaired recognition. It is possible that this result is due to psychometric artefact, in that the auditory delayed recognition subtests suffer from a ceiling effect. As most people perform at near ceiling level, this results in the standard error of measurement of the raw scores on this scale being far less than the standard error of measurement on the free recall scales. Accordingly, the auditory delayed recognition subtests are sensitive to small variations in performance which in themselves may not constitute processing difficulties.

However, it should be noted that some individuals in this sample did present with memory impairment. Discrepancy scores that were significantly lower than expected ranged from -4.3 to -9.1 points. Discrepancies of this magnitude may translate into disabilities at everyday level. It has been shown by the use of questionnaire that patients do subjectively report memory problems (McCord et al., 1997). However, there is a paucity of literature on the objective impairment in day-to-day functioning caused for people with this level of discrepancy. Future research on the ecological disability caused by significant but small memory discrepancies is needed for patients with memory difficulties from any cause. Several participants in the current study reported that they had perceived memory decline since their treatment, which they attributed to surgery or RT. This attribution is not supported by the comparisons between treatment groups.

Given the statistical power of the studies reported in the current literature, it is highly likely that a discrepancy of the magnitude found in this study would not have reached the criteria for statistical significance if comparisons of raw performance data were analysed. In contrast, the within subjects discrepancy scores provide smaller estimates of standard error and a

measure of relative impairment independent of variation consequent on individual differences in functional ability prior to treatment.

The wide range of immediate memory discrepancy scores within each group suggests that factors other than treatment contribute to memory dysfunction. These factors could include hormone levels at the time of testing, time since treatment, original tumour size or vascular damage caused by RT; and will be discussed further in the Physiology chapter of this thesis.

The results of the current study are most similar to those found by Guinan et al. (1998) in which patients also demonstrated relative, but not absolute, memory impairment. Unfortunately, other studies have not used a measure of current intellectual functioning (Peace et al., 1997; Peace et al., 1998; Grattan-Smith et al., 1992; Noad et al., 2004) or have not made an IQ-MQ comparison to allow relative impairment to be assessed (Baum et al., 1998). However, four of the previous studies have shown absolute impairment of memory (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Noad et al., 2004) which was not found in the current study. Grattan-Smith et al. (1992) found impairment in both visual and verbal delayed memory. Peace et al. (Peace et al., 1997; Peace et al., 1998) have found patients to be worse than controls for remembering faces and lists and Noad et al. (2004) found that a greater percentage of their sample scored below the 10^{th} percentile on a test of visual recall and immediate verbal memory. Coupled with the high estimates of pre-morbid IQ that were also found, it is likely that patients demonstrating absolute impairment in these studies also experienced relative impairment. The current study is not commensurate with these findings of absolute impairment, but instead concurs with the Guinan et al. (1998) and Baum et al. (1998) studies, which also did not find any indication of absolute impairment.

There are several reasons why the absolute impairment found in other studies was not found in this sample. The most prominent reason for this is the inclusion of patients with hormone producing adenomas in previous samples. The cognitive deficits caused by hormone excess may have skewed the results. Long term cognitive deficits have been found in patients treated for cortisol excess even after hormone levels have been stabilised (Pivonello et al., 2007; Hook et al., 2007). The inclusion of patients with craniopharyngioma in some studies (Peace et al., 1997; Peace et al., 1998; Guinan et al., 1998; Grattan-Smith et al., 1992) is also unadvisable. This particular group of patients have a standardised mortality ratio 5.7 times greater than patients treated for pituitary adenoma (Tomlinson et al., 2001), suggesting the

effects of craniopharyngioma are fundamentally different from pituitary adenoma. Cognitive impairments have also been found in these patients (Garnett, Puget, Grill, & Sainte-Rose, 2007; Dhellemmes & Vinchon, 2006).

Some previous studies have found differences between treatment groups. Peace et al. (Peace et al., 1997; Peace et al., 1998) twice found that patients who were treated with surgery performed significantly worse than patients treated without surgery on two out of the three tests of memory they used. In contrast, other studies have not found group differences. Grattan-Smith et al. (1992), Baum et al. (1998) and Noad et al. (2004) found no differences between patients treated with or without RT, whilst Guinan et al. (1998) found no differences between any of their groups. The current study found no significant difference between any of the groups when comparing either raw or discrepancy memory scores. All three of the null hypotheses were therefore upheld in this study.

This study has clarified some of the issues left outstanding by the previous literature. Previous results should not be solely attributed to the inclusion of patients treated for hormone producing tumours or craniopharyngioma. However, the absolute impairment found by some studies may be a product of these inclusions. It is important that future studies include a measure of relative impairment to expose the more subtle deficits experienced by patients which may not be revealed by a measure of absolute impairment, especially when the individual tested has a high level of general intellectual functioning.

There are three main clinical implications of this study. Firstly, it should be recognised that patients may have immediate memory deficits prior to surgery or RT, and an absence of invasive treatment should not be assumed to guarantee an absence of deficit. Secondly, this study supports the use of surgery and RT as treatments which can be used for NFA without causing a consistent significant increase in memory deficit over and above that caused by tumour. Thirdly, the outcome literature could be improved by the use a measure of relative impairment to assess memory whenever testing an individual with pituitary adenoma.

Executive Functions

The previous chapters have shown evidence that suggests patients with non-functioning pituitary adenoma have intact general intellectual functioning in the presence of relative impaired immediate memory. This is, in some respects, commensurate with the current literature. However, previous research has been more discordant as to the effects of pituitary adenoma and treatment on executive functions. The following chapter examines this range of functions in patients with pituitary adenoma.

Introduction

There are several similar definitions of executive functions (EFs), reflecting a variety of conceptualisations and models. Lezak (2004) defined EFs as comprising of volition; planning; purposive action; and effective performance. Posner (Posner, 2004) construed EFs as the monitoring and resolution of conflicts between computations made by different neural areas. These included new behaviours; error detection; regulation of thoughts and emotion; planning and decision making. Burgess and Simons (2005) characterised EFs as high level functions that control and direct lower level, more automatic functions and Stuss (Stuss, 2006) termed EFs as an umbrella for a range of functions that allow individuals to plan and organise themselves over extended periods of time; control and organise their memories; and make complex and abstract judgements. Most researchers and clinicians could agree on this last definition of EF, postulating that EFs concern higher level functions that control behaviour.

Models of EF

The predominant models of EF may be encapsulated in a threefold typology. These are single system theories, construct-led theories and multiple process theories (Burgess & Simons, 2005). An example of a single system theory is Cohen et al.'s (2002) computational theory of working memory which postulates that the prefrontal cortex (PFC) actively maintains patterns of activity that represent goals and the methods of achieving them. These patterns of activity bias other brain areas and guide the neural activity needed to perform a task (Miller & Cohen, 2001). In contrast, Goldman-Rakic (1995) argues for a construct-led theory centred

on working memory processes, which are argued to be organised according to the modality of information. According to this theory DLPF regions are associated with spatial memory and ventrolateral regions subserve memory for the content of stimuli. This theory differs from others in that it is the informational domain, not the type of process, which is mapped to prefrontal regions (Goldman-Rakic, 1998).

However, there are several problems with a single system or construct theory. The correlations between executive tasks tend to be low in studies of either neurologically damaged patients or healthy individuals (Burgess & Shallice, 1994; Robbins et al., 1998). Greater correlations would be expected if EFs were a unitary function and the small correlations that are found can be attributed to the general intellectual functioning factor *g* (Duncan et al., 2000). Damage to different areas of the frontal lobes is associated with different types of impairment on a variety of executive tasks (Burgess, 2000; Foster, Eskes, & Stuss, 1994; Stuss & Alexander, 2000; Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998) and fMRI studies of healthy individuals have suggested a fractionation of the executive system (Buchsbaum, Greer, Chang, & Berman, 2005; Braver, Paxton, Locke, & Barch, 2009).

Multiple process theories generally propose that EFs consist of a number of soft modular systems (Posner, 1989) that collaborate in the achievement of everyday EF tasks (Burgess & Simons, 2005). Fuster (Fuster, 1997; Fuster, 2002) provides an example of this type of theory. He depicts the PFC as essential for formulating and executing novel plans or structures of behaviour. These plans of behaviour are represented as abstract schemas in the neuronal networks of the PFC. The PFC as a whole performs four functions: Selective attention; Working memory, mainly supported by the dorsolateral prefrontal cortex (DLPFC); Set, which is the selection and preparation of established motor behaviours and is also supported by DLPFC and the anterior medial cortex; and Inhibitory Control, which is supported by the orbitomedial PFC.

Other examples of multiple process theories have focused primarily upon the role of attention. Norman and Shallice (1986) proposed a ‘supervisory attentional system’ (SAS) that is responsible for the selection of context appropriate but subordinate behaviours (or thoughts) in response to novel situations. The original model of the SAS (Norman & Shallice, 1986) was developed to explain utilisation behaviours following ABI, and did not fractionate the mechanisms by which the SAS achieved this function. However, the model of the SAS

was later extended and modified by Shallice and Burgess (1996) and has become one of the most influential models of EF to date. This later model (see Figure 8 below) identified the multiple components and stages of the SAS that are required when faced with a novel situation:

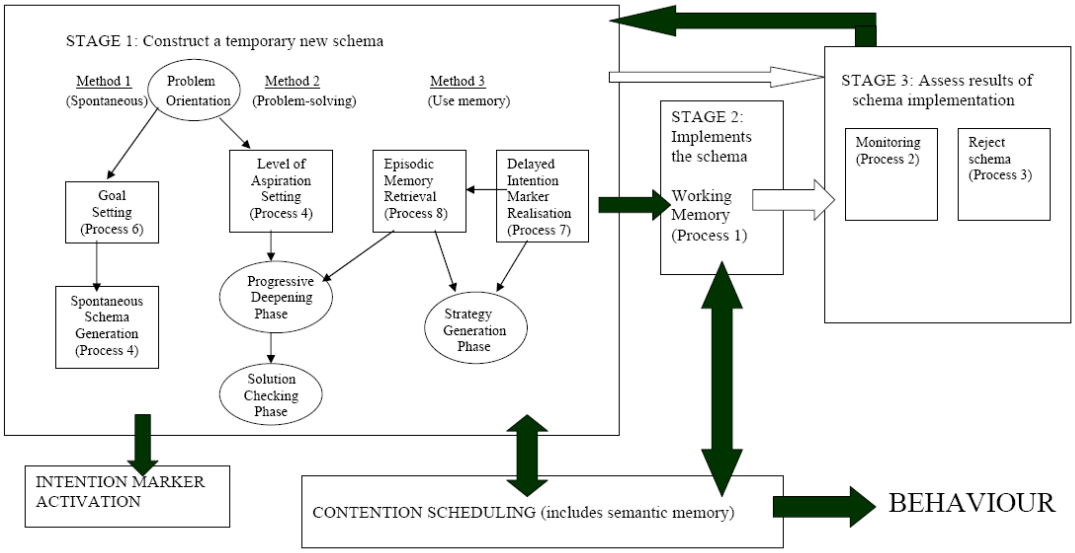

Figure 8: The stages of the SAS adapted from Shallice and Burgess (1996)

The SAS mediates many processes including monitoring; schema generation and/or rejection; goal setting; working memory; and episodic memory retrieval. There are three stages to the model: construction of a temporary schema, implementation of the schema, and assessment of the results from using the schema. During stage one there are three possible methods of schema construction. The problem itself may suggest a solution, and so a schema is spontaneously generated. An example of this would be the visual image of a door handle prompting a person to turn the handle and push the door without giving the action conscious thought. People with brain injury are often still able to complete these types of automatic actions (Schmitter-Edgecombe, 2006). Alternatively, an individual might use problem solving strategies to create a schema of action to take, using deliberative processing. However, sometimes an individual will have previously experienced a similar situation and can simply recall a previously used schema from episodic memory. During stage two, one schema is chosen from all the generated possible schemas and is carried out. At stage three, after the schema has been tested, its usefulness and suitability is reviewed. If the schema is not fit for purpose it may be rejected and stage one is repeated to generate a new more appropriate schema.

Stuss et al. (1995) fractionated EF into seven different attention functions, with each function possessing a distinct neuronal correlate. Sustaining attention is served by the right frontal cortex; concentrating served by the cingulate; sharing served by the cingulate and orbitofrontal cortex; suppressing served by the DLPFC; switching served by the DLPFC and medial frontal cortex; preparing served by the DLPFC; and setting is served by the left DLPFC.

The multiple process theories of EF emphasise the need for multiple tests of executive functioning. Although the multiple subsystems of EF may be functionally interdependent, different tests will tend to emphasise different functional components to different degrees. Accordingly, the multiple process theories can accommodate the observation that the correlations between executive tasks tend to be low (Burgess & Shallice, 1994; Robbins, 1998) and also the observation that damage to different areas of the frontal lobes is associated with different types of impairment on a variety of executive tasks (Burgess & Shallice, 1994; Foster et al., 1994; Stuss & Alexander, 2000; Troyer et al., 1998). The selection of measures of EF should therefore reflect this potential fractionation of EF.

Summary Of Theories

Cohen's (2001) single system theory focuses on the frontal lobes' ability to maintain patterns of activity and postulates that this represents the goals and methods required for adaptive behaviour. In contrast, Goldman-Rakic (1998) argues for a construct-led theory hypothesizing that the modality of information is important and dictates which frontal lobe region will process it. Multiple process theories assume a range of soft modular systems that collaborate to achieve behaviour. These systems create structures of behaviour or schemas and also select the most appropriate or activated schema to implement (Shallice & Burgess, 1996; Fuster, 2002).

The theoretical models have broadly tended to focus on either a single function such as attention or working memory. As the theory of EF has developed, this has led to the increased fractionation of functions and a shift in emphasis to using a variety of tests to measure multiple different functions. There is still no one dominant theory of EF. However, the various different theories indicate the type of functions that should likely be subsumed into the term of EF.

The Measurement Of EF

The Delis-Kaplan Executive Functioning System (D-KEFS) (Delis et al., 2001) samples a variety of different tests of EFs such as switching attention; verbal fluency with and without a switching element; design fluency with and without a switching element; response inhibition; abstract concept formation; and planning. The D-KEFS was assembled from tests that were deemed clinically useful by clinicians rather than created on the basis of what should be useful, according to a particular theory. However, the broad range of abilities that it samples, and the extensive number of neurologically intact and impaired individuals tested during the norming process, ensures that it adequately differentiates the various functions or processes postulated by most theories. Individual subtests may measure multiple EFs and non-EFs. However, they each bias towards one particular type of EF. The non-executive components of each task are tested separately to differentiate between executive and lower level dysfunction. For example, Colour-Word Interference first measures a person's reading ability and colour naming ability before conducting the interference task.

The D-KEFS subtests

The D-KEFS consists of nine subtests. The eight subtests used in the current research are described below and outlined in Table 17.

Table 17: The D-KEFS subtests and the EF they measure

D-KEFS subtest	**Cognitive functions measured**	**Brain areas thought to mediate these functions**
Trail making	visual motor flexibility of thinking	DLPFC
Verbal fluency	verbal fluent productivity	Left inferior frontal gyrus, DLPFC
Design fluency	spatial fluent productivity	Left frontal lobe
Colour-word interference	verbal inhibition	DLPFC, left PFC, ACC
Card sorting	problem solving, verbal and spatial concept formation, flexibility of thinking	DLPFC
Twenty questions	hypothesis testing, verbal and spatial abstract thinking	Left PFC
Word context	deductive reasoning	Left frontal lobe
Proverbs	metaphorical thinking and comprehending abstract thought	VMPFC

DLPFC = Dorsolateral prefrontal cortex; PFC = prefrontal cortex; ACC = anterior cingulate gyrus; VMPFC = ventral medial prefrontal cortex

Trails

The trails subtest involves five similar tasks which participants must complete as quickly and accurately as they can. The main scaled score for each task is derived from the time taken to complete the task. If an error is made, the participant is immediately informed and must go back to the last correctly connected number or letter and continue. For the first task, participants must draw a small diagonal line through 24 '3's located on an A3 page containing circled numbers and letters. This is to test for conditions such as visual neglect, which may lead a participant to miss the '3's on a particular part of the page, usually the left side (Ronchi, Posteraro, Fortis, Bricolo, & Vallar, 2009). This task will also highlight lower level difficulties such as visual problems, which could compromise the results of the remaining tasks. On the second task, participants must join up the numbers in order from lowest to highest, on a similar A3 page of numbers and letters. Thirdly, participants connect the letters in alphabetical order, whilst this time ignoring the numbers. These two tasks ascertain whether the participant is numerically and alphabetically literate, understands the basic 'connecting in sequence' premise of the task, and provides baseline scores with which to compare the switching task to. The fourth task is the measure of EF. Participants must now connect the numbers and the letters on the page, in numerical and alphabetical order, switching each time between joining the numbers and letters. Therefore participants start with '1' which they connect to the letter 'A', then to '2', to 'B' and so forth, finishing at the letter 'P'. If the participant has appeared to understand the tasks but has consistently slow overall times, there is a fifth task that can be used to assess motor speed. On the A3 page, empty circles are connected by dotted lines and the participant must simply trace over the lines in the order stated from start to finish.

The switching element of this task is thought to measure cognitive flexibility. The additional time participants take to complete the task is primarily due to the extra cognitive effort required to continually switch 'set' between numbers and letters (Arbuthnott & Frank, 2000). However, this test also requires the ability to inhibit the more learnt response of just joining numbers to numbers or letters to letters, in order that mistakes be minimised. The D-KEFS version of this test is superior to previous versions of Trails as it measures a participant's ability to sequence letters as well as numbers, prior to the switching component of the test. Neglect and motor difficulties can also be separately assessed.

Patients with DLPFC lesions make more errors on the Trails B task and this is thought to be due to difficulties in switching and sustaining attention (Stuss et al., 2001). Research using fMRI has revealed distinct left-sided dorsolateral and medial frontal activity when comparing Part B versus Part A (Zakzanis, Mraz, & Graham, 2005), and this prefrontal cortex task involvement has been confirmed by multichannel near-infrared spectroscopy (Shibuya-Tayoshi et al., 2007).

Verbal fluency

The verbal fluency subtest assesses a participant's ability to generate words from a stated letter or semantic category. The participant must first give the examiner as many words as they can that begin with a certain letter. There are one minute trials for the letters 'F', 'A' and 'S'. The participant then generates as many words as they can from the categories 'animals' and 'boys' names'. Again, they have 60 seconds for each category. The D-KEFS version of this subtest also has a third task in which participants switch back and forth between naming items from two different categories: fruit and furniture. This is designed to incorporate another measure of set switching into the D-KEFS.

Verbal fluency tests initiation, lexical production and organisation, working memory and inhibition of rule breaks (Strauss, Sherman, & Spreen, 2006). Therefore poor performance on this subtest must be cross-referenced with other subtest performances to generate a hypothesis of the underlying cause of difficulties. This task activates several brain regions in normal adults. However, Costafreda et al. (2006) used a meta-analysis of 22 fMRI experiments on verbal fluency and showed that the left inferior frontal gyrus was consistently activated during verbal fluency tasks. Broadmann's areas 46 and 47 of the frontal cortex are also prominent during task completion (Weiss et al., 2003).

Design Fluency

The design fluency subtest measures fluency in the non-verbal domain. On the first task, participants are given an A4 page containing 35 identical boxes; each containing five black dots. They must generate as many different shapes as they can in 60 seconds. To score points, each shape must be unique and composed of four straight lines that connect the dots. For the second task, participants must again create as many unique designs as possible. This time each box contains five hollow dots as well as the five filled black dots. The participant must only use the hollow dots to create the shapes. For the final task, participants are again given

boxes with 10 dots, five of which are hollow, five of which are filled, and must create designs in which the lines they draw connect different types of dot. This produces a situation in which participants must switch from connecting a hollow dot to a filled dot to a hollow dot and so forth.

The design fluency subtest measures creativity and visual-perceptual speed. The second task also incorporates the need to ignore extraneous stimuli. The third task adds another measure of set switching or cognitive flexibility to the D-KEFS, this time in the non-verbal domain (Delis et al., 2001). Patients with left lesional frontal lobe epilepsy have been found to be impaired on the design fluency with switching task. This only occurred with left sided lesions and only on the switching (McDonald, Delis, Norman, Tecoma, & Iragui, 2005).

Colour-Word Interference

The colour-word interference subtest contains four tasks. The first two tasks assess the lower level skills of colour vision and reading. On task one, participants look at five lines of different coloured blocks and name the colour of each block in order. For task two, participants simply read aloud five lines of the words 'blue', 'green' and 'red'. The time taken to read these words is taken as the baseline measure with which to compare the more complex tasks to. The third task contains five lines of the words 'blue', 'green' and 'red' printed in ink colours that are incongruent with the colour described by the word (e.g. the word 'blue' might be written in either red or green ink). Participants must name the colour of the ink, rather than read out the word. In the fourth task, some of the words are placed inside individual black boxes whilst others are not. All words are again printed in a different ink colour to that which they spell. Words in boxes must be read and the ink colour ignored. The ink colour should be named for all words not in boxes, as was required in task three.

Task three of this subtest mainly assesses a participant's ability to inhibit the highly learned response of reading a word and instead to name the ink colour it is printed in. The main scaled score is derived from the time taken to complete the task. Task four also includes a set switching element to the subtest (Delis et al., 2001).

Kaufmann et al. (2005) used fMRI to demonstrate DLPFC activation in healthy participants during the Stroop task, indicating a difficulty with inhibiting automatic responses. Similarly, Markela-Lerenc et al. (2004) measured high-density event-related potentials (ERPs) to show increased negativity in the left PFC during the processing of colour incongruent words

compared to colour congruent words. This was followed by positive ERPs in the ACC, suggesting that the PFC indicates when executive control is required for the task and the ACC actions this requirement.

Card Sorting

Participants are required to sort a set of six cards into two groups of three cards each, based on principles such as the colour of the cards or gender of the names printed on the cards. The total number of correct categorical sorts made, and the accuracy of the description used to describe these sorts are used to calculate the scaled scores. There are two trials with two sets of cards and participants must generate and explain as many sorts as they can in 240 seconds. In the second task, the cards are sorted into two groups by the examiner and the participant must guess and explain the link between the three cards in each group.

The subtest differentiates between the participant's ability to form basic conceptual sorts nonverbally and the ability to verbally describe those sorts. Problem solving and flexibility of thinking abilities will also aid the participant in successful completion of this subtest (Strauss et al., 2006).

There is limited empirical evidence regarding the Card Sorting task, principally because it is a relatively new test pre-dated by the similar Wisconsin Card Sort Test (WCST) (Grant & Berg, 1948) which has a much wider evidence base. However, the D-KEFS Card Sorting subtest has been shown to differentiate between patients with Multiple Sclerosis (MS) and education-matched controls, and unlike the WCST, continued to discriminate between these groups after depression levels were controlled for, suggesting it is a superior test for this patient group (Parmenter et al., 2007). Card Sorting correlates with MRI indices of brain atrophy in MS patients. The subtest measures concept shifting and so it is expected that the DLPFC will show increased activity during the task (Rogers, Andrews, Grasby, Brooks, & Robbins, 2000).

Twenty Questions

The participant is presented with an A4 page containing 30 equally spaced common objects. One of these objects is the target and the participant must ask the fewest number of 'yes/no' questions they can to identify the target. After twenty questions have been asked without the target being correctly identified, the participant is considered to have failed that trial of the

subtest. There are four trials in total. The total number of questions asked across the four trials forms one score. A second score is generated by adding together the number of items excluded from the target search by the participant's first question on each trial. For example, 'is it living?' would score the maximum of 15, as half the items are forms of life and half are not, whereas 'is it a fork?' would score only one point as there is only one fork on the page.

This subtest requires a participant to generate and test hypotheses, involving working memory abilities. Participants must form concepts, generate strategies and use the feedback given to refine these hypotheses (Strauss et al., 2006). This is an example of the second method of Shallice and Burgess' (1996) SAS model of EF: problem-solving.

Patients with right-sided frontal lobe epileptic dysfunction show poorer performance on the initial abstraction index of the Twenty Questions subtest than patients with left-sided frontal lobe epileptic dysfunction showing a particular importance of this part of the brain to the task (Upton & Thompson, 1999). Patients with focal prefrontal lesions also show a tendency to ask significantly more questions to find the target item, sometimes exhausting the 20 question limit. These questions often reflect ineffective categorisation strategies such as asking questions that refer to single items, signifying that the prefrontal cortex supports the on-line conceptualisation and organisation of category exemplars in concept-formation tasks (Baldo & Shimamura, 1998).

Word Context

During this subtest, five sentences are presented to the participant one at a time. The same word (e.g. 'apple') is present in each of these sentences. However, in all of the sentences this word has been replaced by a non-word (e.g. 'sev') and the participant must guess what the real word is, which the non-word has replaced. The participant must guess what they think the non-word is after each sentence is given to them. The sooner they guess correctly, the more points they receive on that trial, unless they later change their guess and spoil their score. There are ten trials of five sentences. This subtest measures verbal abstract thinking, deductive reasoning and hypothesis testing (Strauss et al., 2006). Patients with frontal lobe lesions have shown significantly impairment on this task compared to age and education matched controls. These deficits were particularly pronounced in patients with left-sided frontal lesions (Keil et al., 2005).

Proverbs

The participant is given eight proverbs, one at a time, and must state what they think each proverb means. Five of the proverbs are in common usage in the English language whilst three are not. Points are given for a response that is a correct interpretation of the proverb and additional points are given if that response is abstract, and not concrete. After the participant has reported or guessed the meaning of the proverbs, the examiner shows each proverb again along with four possible meanings. The participant then chooses which meaning they think best relates to the proverb. This subtest generates two scores. A free enquiry score and a multiple choice score. The proverbs subtest assesses metaphorical thinking and the two tasks allow the comparison of the participant's ability to generate versus comprehend abstract thought (Strauss et al., 2006). The proverbs subtest is a measure of abstract thinking and deductive reasoning. In unfamiliar or conflict situations, the ventral medial prefrontal cortex (VMPFC) are activated to resolve this conflict and make sense of unfamiliar materials (Feredoes, Tononi, & Postle, 2006).

The D-KEFS subtests provide age appropriate scaled scores for each task with a mean of 10 and a standard deviation of 3. Some subtests also provide contrast scaled scores, which aim to separate the EF component of the task from lower level processing components. This is particularly useful when participants' high scores on the lower level processing components may mask a comparative deficit on the task of EF. The contrast scores used for each subtest are shown below in Table 18.

Table 18: Contrast Scaled Scores

Subtest	**Contrast Scaled Score Name**	**Contrast Scaled Score Formula**	**Interpretation**
Trail Making	Switching – Lower Processes	Switching (task 4) – (Numbers (task 2) + Letters (task 3))/2	Inhibition, cognitive flexibility, 'set' shifting
Verbal Fluency	Letter Fluency – Category Fluency	Letter Fluency (task 1) – Category Fluency (task 2)	initiation, lexical production, working memory, inhibition
Verbal Fluency	Switching Category Fluency – Category Fluency	Switching Category Fluency (task 3) – Category Fluency (task 2)	initiation, lexical production, working memory, inhibition, 'set' shifting
Design Fluency	Switching – Lower Processes	Switching (task 3) – (Dots (task 1) + Hollow Dots (task))/2	Creativity, visual-perceptual speed, 'set' shifting
Colour-Word Interference	Inhibition – Colour Naming	Inhibition (task 3) – Colour naming (task 1)	Inhibition

Subtest	Contrast Scaled Score Name	Contrast Scaled Score Formula	Interpretation
Colour-Word Interference	Inhibition Switching – Lower Processes	Inhibition Switching (task 4) – (Colour Naming (task 1) + Word Reading (task 2))/2	Inhibition, switching
Card Sorting	Sort Recognition – Free Sort	Sort Recognition (task 2) – Free Sort (task 1)	Ability to recognise a greater amount of externally generated patterns than internally generated patterns

Individuals can fail tests of EF for a variety of reasons. Most importantly, they can fail because of damage to areas that mediate EF itself or because of damage to posterior brain areas which underlie lower level more basic information processing on which the EFs rely. If these posterior areas have afferent or efferent links to the frontal lobe, higher level behaviours could be impaired due to the dysfunction of required lower level behaviours. For this reason, several D-KEFS subtests measure both EFs and the lower level behaviours, such as reading, counting and motor control, required to complete the task.

Pituitary surgery by the transsphenoidal route avoids contact with the frontal lobes and its efferent and afferent pathways (Gandhi et al., 2009). It is therefore unlikely that transsphenoidal surgery will cause damage to frontal cortex or the functions it mediates. Pituitary surgery by the transcranial route involves opening the front of the skull and lifting the frontal lobe to reach the pituitary gland. This can cause bruising to the underside of the frontal lobe putting the orbitofrontal area, ventromedial PFC, and inferior prefrontal gyrus most at risk due to their ventral location. Damage to the orbitofrontal area could inhibit decision making ability because the OFC is associated with encoding the value judgements of various choices (Kringelbach, 2005). The ventromedial PFC is strongly associated with control of emotional processing and self-regulation (Nauta, 1971; Levine et al., 2005). This includes behavioural regulation that is controlled by the formation and, if necessary, reversal of stimulus-reward associations (Fuster, 1997; Rolls, 1996; Rolls, 2000). Damage to this area could inhibit an individual's ability to reverse learned associations, making them particularly vulnerable to poor decisions in tasks such as gambling. The inferior prefrontal gyrus has been associated with the selection of semantic knowledge (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). Insult to this area could impair the use of semantic knowledge. Damage to the left insular cortex has been associated with poor performance on verbal memory tasks (Manes, Springer, Jorge, & Robinson, 1999). Therefore if transcranial surgery causes cortical

damage, it is most likely to impair an individual's ability to make constructive decisions and their verbal memory.

Pituitary RT is delivered by a three-field technique. One of these fields passes through parts of the frontal lobe, taking care to avoid the optic nerves. Areas that may be included in the field of radiation are the frontal polar region, the orbitofrontal area, the ventromedial PFC and the insular cortex. The frontal polar region may be responsible for integrating information from other frontal lobe regions to plan and coordinate behaviour (Stuss & Alexander, 2000; Wallis, 2007) . Damage to this area could result in a difficulty appreciating humour (Shammi & Stuss, 1999) or making social judgements (Stuss, Gallup, & Alexander, 2001). Other impairments that RT could theoretically cause are similar to those suggested from transcranial surgery, as the brain regions affected are very similar. This includes the ability to make constructive decisions and verbal memory.

Previous research

Most of the previously conducted studies have predominantly used the switching task 'trail making test' and a measure of verbal fluency such as the COWAT. Using these tests, Grattan-Smith et al. (1992) found no difference between controls and patients on the COWAT (task 1 of the D-KEFS verbal fluency version), but poor patient performance on Trails B (task 4 on the D-KEFS version) in comparison to the controls. Given the heterogeneity of their sample, Grattan-Smith et al. only firmly concluded that patients with pituitary adenoma experience neuropsychological impairment, without commenting further on different treatment groups. Peace et al. (1997) used the same tests together with the Stroop (task 3 of Colour-Word Interference) and found patients to be impaired on all three measures of EF used. They concluded that patients with pituitary adenoma have EF impairment, especially in tests of rapid performance, which tend to be sensitive to frontal lobe pathology (Lezak, Howieson, & Loring, 2004). As the deficits were not contingent on treatment, Peace et al. (1997) concluded that they may arise from differences between patients and controls in endocrine status. In their later study, Peace et al. (1998) used only the COWAT and Trails B to compare patients treated with different types of surgery. Only transcranially treated patients had scores that tended towards a significant difference from controls ($p=0.07$ and 0.08 on the two tasks). This was due to a large amount of intragroup variance that showed some patients had intact EF whilst others had severely impaired EF, despite receiving the same treatment. Several non-surgically treated patients also showed mild cognitive

impairment, leading the researchers to conclude that the primary disease, resulting hormone abnormalities or nonspecific psychological factors associated with having a chronic illness were causes of cognitive dysfunction. In a later study, Noad et al. (2004) found that patients treated with surgery + RT showed poorer performance on the Stroop than patients treated with surgery alone. This difference was not found using the COWAT. Together, these studies suggest that patients with pituitary adenoma may suffer from EF deficits. However, this conclusion is complicated by large intragroup differences within studies and variance in findings between studies, with different researchers finding dysfunction on different measures.

Baum et al. (1998) used a larger variety of tests to measure EF. They included the previously used tests of COWAT, Trails B and Stroop, and added digit span backwards and the CVLT, which measures both memory and inhibition during the delayed list and list 2. They found that patients performed normally to above average on all tests compared to test norms and in contrast to previous research found no deficits. Similarly, Guinan et al. (1998) found no significant differences between patient groups and controls on any measure of EF. They used the COWAT, PASAT and modified card sort test. These two studies clearly suggest that patients with pituitary adenoma do not have EF dysfunction in any of the domains tested.

The two prospective studies both reported variable results throughout their follow-up period. Armstrong et al. (2002) reported that patients showed linear improvement over six years on the COWAT and curvilinear improvement on the auditory selective attention test and the PASAT. In contrast, results for the Continuous Performance Test, which measures sustained and selective attention, showed a curvilinear significant decline. Torres et al. (2003) found improvement on Trails B between six and 12 months after RT treatment. However, this improvement was not sustained and the difference between baseline and follow-up was non-significant. These results suggest that the discordant results found in the retrospective literature could be due to the time point after treatment at which patients were tested.

There are several issues with the previous literature which make it difficult to draw firm conclusions on the effects of pituitary adenoma and its treatment on EF. Primarily several studies have used only two tests of EF (Peace et al., 1998; Peace et al., 1997; Grattan-Smith et al., 1992). As each EF test is likely to employ many cognitive abilities, poor performance across a range of tests may be required to isolate the locus of dysfunction. The scatter of deficient results found across studies may be a result of lower level deficits whilst EF remains

intact. Sometimes small control groups have been used instead of test norms. The use of small comparison groups increases the chance of type II error, due to a lack of statistical power. Time since treatment is often not given, making it impossible to conclude whether the differences in results are indeed due to time since treatment and the post treatment rebound effect. The original tumour size and any extension into suprasella regions that may have affected the frontal lobe is often not stated (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Baum et al., 1998; Guinan et al., 1998). In some studies adenoma type has not been given and in other studies patients with Cushing's and craniopharyngioma have been included (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Baum et al., 1998; Guinan et al., 1998). High cortisol levels have previously been found to negatively correlate with EF performance (Egeland et al., 2005), although other studies have found negative effects of cortisol only for memory and not other cognitive functions (Mauri et al., 1993). Patients treated for craniopharyngioma have been found to be over a standard deviation below test norms on verbal fluency (Bawden, Salisbury, Eskes, & Morehouse, 2009). However, most neurocognitive research on patients with craniopharyngioma have been conducted on children and not the adults used in the current literature. The executive dysfunction found by these studies (Cavazzuti, Fischer, Welch, Belli, & Winston, 1983; Donnet, Schmitt, Dufour, & Grisoli, 1999) may not be relevant to adult onset craniopharyngioma.

From the above discussion it is evident that the existent literature provides a mixed pattern of EF deficits in pituitary tumour, with the principle question remaining unanswered; does the treatment of pituitary tumour by surgery, RT or a combination thereof result in impairment of EF?

Hypotheses:

- Scaled scores and contrast scaled scores will not be significantly different for patients treated with surgery from patients who have been conservatively managed up to the time of executive functions testing.

- Scaled scores and contrast scaled scores will not be significantly different for patients treated with RT from patients who have been conservatively managed up to the time of executive functions testing.

- Scaled scores and contrast scaled scores will not be significantly different in patients treated with surgery and RT from patients treated with each individual treatment or patients who have been conservatively managed up to the time of executive functions testing.

Method

Testing was conducted as described in the General Methods chapter. This is a cross-sectional independent groups design with four treatment groups: conservatively managed, surgery only, RT only, and surgery and RT. Patients were treated with RT alone if they were diagnosed with a nasopharyngeal carcinoma. The three other treatment groups exclusively contained patients treated for NFA. The number of patients in each group is shown in Table 19.

Table 19: The number of patients in each group

	Conservatively Managed	**Surgery only**	**RT only**	**Surgery + RT**
No. of patients	6	18	7	19

RT = Radiotherapy

Results

One-way ANOVAs were used to examine any differences between groups on the subtest scaled scores and subtest contrast scores. Potential correlations between D-KEFS scaled or contrast scores and several demographic and treatment factors were analysed. These factors were age; time in months since surgery; time in months since RT; size of original tumour volume; number of hormone replacements; TSH levels in men; years of education; and the GSI T-score from the SCL-90R.

There was a significant negative correlation between five of the EF scores and the GSI T-score of the SCL-90R. These were ‘Trail making: switching’ (r=-0.46, p=0.002); both correct responses (r=-0.42, p=0.005) and switching accuracy (r=-0.45, p=0.002) for the verbal fluency task; and both the ‘Stroop: Interference’ (r=-0.46, p=0.002) and the ‘Stroop: Interference/Switching’ tasks (r=-0.38, p=0.01). A one-way ANOVA were thus conducted to

assess the distribution of the GSI T-score between the treatment groups. There was no significant difference in GSI T-scores between groups ($F = 0.71$, $p = 0.55$). Correlations between the nine subscales of the SCL-90R and the five EF subtests which correlated with the GSI T-score were calculated and are shown in Table 20. Eight of the nine subscales significantly correlated with at least one of the EF subtests, whilst the obsessive-compulsive subscale did not correlate with any EF subtest. There were no significant differences between the treatment groups on any SCL-90R subscale ($F \leq 2.37$, $p \leq 0.08$).

There was a positive correlation between a participant's age when they received RT and EF scores on 'Trails Switching' ($r = 0.43$, $p = 0.04$), 'Verbal Fluency Switching' ($r = 0.48$, $p = 0.02$), 'Stroop Interference' ($r = 0.49$, $p = 0.02$), 'Card Sort – free sort description' ($r = 0.52$, $p = 0.02$) and 'Proverbs – free enquiry'($r = 0.50$, $p = 0.03$), suggesting that the older a person is when they receive RT, the better their EFs. However, there were no significant correlations between age at RT and the EF contrast scores. Age at RT did not differ between the two groups who received this treatment, and so this was not entered as a covariate. The number of hormone replacements positively correlated with '20 questions – initial abstraction score', but again there was no significant difference in the number of hormone replacements between groups and so this was not entered as a covariate. There were no differences in EF between men and women ($t \leq -1.79$, $p \geq 0.09$).

There was a significant difference between the groups only for years of education, with the surgery + RT group being significantly more educated than the conservatively managed group ($p=0.04$). Years of education correlated with the 'Trails: Switching – Lower Processes' score ($r = 0.331$, $p = 0.042$), the 'Word Context' score ($r = 0.326$, $p = 0.045$) and the 'Proverb – Free Inquiry' score ($r = 0.331$, $p = 0.042$). Years of education was therefore added as a covariate in analysis of these outcome variables. The male level of the hormone TSH ($r \leq -0.14$, $p \geq 0.35$) did not significantly correlate with D-KEFS outcome scores. Therefore there were no covariates entered into the analysis.

Table 20: The correlations between selected EF subtests and SCL-90R subscales

		TM S	VF S - CR	VF S - SA	Stroop - I	Stroop - I S
GSI T-score	Pearson Correlation	-0.46**	-0.42**	-0.45**	-0.46**	-0.38*
	Sig. (2-tailed)	0.00	0.00	0.00	0.00	0.01
	N	45	44	44	43	42
Somatization	Pearson Correlation	-0.27	-0.28	-0.37*	-0.42**	-0.35*
	Sig. (2-tailed)	0.07	0.06	0.01	0.00	0.02
	N	46	45	45	44	43
Obsessive Compulsive	Pearson Correlation	-0.23	-0.19	-0.20	-0.20	-0.27
	Sig. (2-tailed)	0.12	0.22	0.18	0.20	0.08
	N	46	45	45	44	43
Interpersonal Sensitivity	Pearson Correlation	-0.18	-0.33*	-0.39**	-0.28	-0.27
	Sig. (2-tailed)	0.23	0.03	0.01	0.06	0.08
	N	46	45	45	44	43
Depression	Pearson Correlation	-0.16	-0.32*	-0.31*	-0.30*	-0.25
	Sig. (2-tailed)	0.29	0.03	0.04	0.04	0.11
	N	46	45	45	44	43
Anxiety	Pearson Correlation	-0.32*	-0.31*	-0.38*	-0.40**	-0.30*
	Sig. (2-tailed)	0.03	0.04	0.01	0.01	0.05
	N	46	45	45	44	43
Hostility	Pearson Correlation	-0.33*	-0.27	-0.31*	-0.31*	-0.25
	Sig. (2-tailed)	0.03	0.07	0.04	0.04	0.11
	N	46	45	45	44	43
Phobic Anxiety	Pearson Correlation	-0.29*	-0.34*	-0.39**	-0.25	-0.13
	Sig. (2-tailed)	0.05	0.02	0.01	0.10	0.42
	N	46	45	45	44	43
Paranoid Ideation	Pearson Correlation	-0.20	-0.45**	-0.40**	-0.29	-0.30*
	Sig. (2-tailed)	0.18	0.00	0.01	0.05	0.05
	N	46	45	45	44	43
Psychoticism	Pearson Correlation	-0.38*	-0.28	-0.32*	-0.46**	-0.43**
	Sig. (2-tailed)	0.01	0.07	0.03	0.00	0.00
	N	46	45	45	44	43

TM = Trail Making; S = Switching; VF = Verbal Fluency; CR = Correct Responses; SA = Switching Accuracy; I = Inhibition ; ** indicates $p<0.01$; * indicates $p<0.05$

To examine the effects of GSI T-score on EF, the entire sample was split into two groups: above (high T-score) or below (low T-score) the mean GSI T-score of 56.3. The low T-score group scored significantly better on all of the measures of EF which correlated with the GSI T-score ($t \geq 2.01$, $p \leq 0.05$). There was no difference between the two groups on measures of EF which do not correlate with the GSI T-score. However, the low T-score group also had a significantly better Processing Speed Index score from the WAIS-III test battery ($t = 2.46$, $p=0.02$). When Processing Speed was added to the analysis as a covariate, the differences in EF scores were no longer significant. The difference between the low T-score and high T-score groups became as follows: 'Trail making: switching' ($F = 0.25$, $p = 0.28$); correct

responses (F = 0.73, p=0.48) and switching accuracy (F = -0.77, p = 0.44) for the verbal fluency task; and both the 'Stroop: Interference' (F = 1.08, p = 0.15) and the 'Stroop: Interference/Switching' tasks (F = 0.58, p = 0.45). A series of Sobel tests were undertaken in order to assess whether processing speed mediated the relationship between the SCL-90R GSI T-score and EFs. The relationship between the SCL-90R GSI T-score and 'Trail making: switching' showed significant mediation by processing speed (Sobel z = 2.04; p = 0.04). All of the other contrast scores showed trends toward significanct mediation (Verbal Fluency switching – correct responses (Sobel z = -1.78; p = 0.07); Verbal Fluency switching – switching accuracy (Sobel z = -1.90; p = 0.06); Stroop Inhibition (Sobel z = -1.91; p = 0.06); Stroop inhibition switching (Sobel z = -1.88; p = 0.06)). Accordingly, these tests of mediation, when considered en masse, suggest that the relationship between the SCL-90R GSI T-score and the EF contrast scores is mediated by processing speed.

A one-way ANOVA was used to compare the scaled scores and contrast scaled scores of each group. There were no differences between groups on any measure of EF. One-sample t-tests were used for each group to assess any significant differences from the subtest averages of 10. The 'inhibition - colour naming' contrast scaled score of the conservatively managed group was above average ($\bar{X}$ = 11, t = 3.16, p=0.03), indicating this group has intact to above average inhibition ability. The surgery only group demonstrated above average scores in all tasks of the verbal fluency subtest ($t \geq 2.07$, $p \leq 0.05$). However, their 'letter fluency - category fluency' contrast scaled score was below average ($\bar{X}$ = 8.47, t = -2.43, p=0.03), due to their 'verbal fluency: category fluency' score being over a standard deviation above the population average. This may be because the surgically treated patients found the category fluency task easier than the letter fluency task; which has also been repeatedly found in the normal population (Crowe, 1998; Klenberg, Korkman, & Lahti-Nuuttila, 2001; Riva, Nichelli, & Devoti, 2000). None of the contrast scaled scores were significantly different from the subtest averages of 10 for the radiotherapy only group. Finally, the surgery + RT group had a verbal fluency contrast scaled score 'switching category fluency – category fluency' that was significantly lower than the test average ($\bar{X}$ = 8.06, t = -2.39, p=0.03). The 'switching category fluency' was normal ($\bar{X}$ = 10.44) indicating that the low contrast score is due to a high 'category fluency' score ($\bar{X}$ = 12.17).

Discussion

Patients in the current sample did not show executive dysfunction. All three groups of pituitary patients showed above average functioning on at least one task of EF. The conservatively managed group showed above average inhibition on the colour-word interference task, whilst the surgery only group scored above average on all measures of verbal fluency. The surgery + RT group performed above average on three tasks of EF. This suggests that neither tumour nor treatment causes impairments of EF in patients with NFA. Patients with NPC also scored in the average range. It is probable that patients scored better than the population average on some EF tests due to their FSIQs also being above the population average of 100, rather than the unlikely scenario of tumour and treatment enhancing EFs. A correlation between FSIQ and a variety of EF tests has previously been found (Obonsawin et al., 2002).

Our results are commensurate with those of Guinan et al. (1998) and Baum et al. (1998). They also tested patients with FSIQs above the population average of 100 and found patients to be normal to above average compared to EF test norms (Baum et al., 1998) or scoring similarly to controls (Guinan et al., 1998). We did not find the impairment shown by some of the earlier studies (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998), nor the treatment group difference found by Noad et al. (2004). However, some of the studies finding impairment also found a large amount of intragroup variability (Peace et al., 1998) or impairment on only some tests (Grattan-Smith et al., 1992; Noad et al., 2004). This indicates a lack of consensus within the literature as to the affects of tumour and treatment on EF, even within the studies that have sometimes found dysfunction.

It is possible that psychological symptoms could have impacted on the EF test results. In the current study, there was a negative correlation between the GSI T-score, which measures overall symptom distress, and the switching tasks of several subtests. This was also found to be the case for many of the SCL-90R subscales. The switching tasks are considered the most taxing within each subtest. Patients with above average T-scores performed significantly poorer on these subtests than patients with below average T-scores. However, this difference was no longer significant when Processing Speed was added as a covariate. As all of the subtests which correlated with the GSI T-score are scored based on the speed with which they are completed, it is likely that low mood is impairing processing speed which in turn impacts on the scores of timed EF tests.

Mood, as measured by the SCL-90R has previously been found to correlate with both processing speed and EF in a study of 669 participants (van Hooren et al., 2005). Pre-treatment patients with Cushing's have been found to be significantly more depressed using the depression scale of the SCL-90R (Starkman et al., 2001) and the overall GSI T-score (Dorn et al., 1997). Unfortunately, Peace et al. (1997) did not report the percentage of patients in their sample with Cushing's or whether they had achieved endocrine remission, so the association between high levels of psychological distress and low EF performance cannot be excluded as a reason for the results of their study.

Three previous studies have not measured mood in their cohorts (Grattan-Smith et al., 1992; Peace et al., 1998; Guinan et al., 1998), whilst two others have compared treatment groups (Noad et al., 2004) or used their mood measure for before and after comparisons (Baum et al., 1998) rather than comparing results to the normal population. Peace et al. (1997) were the only researchers to compare patients and a control group on mood measures. They used the Beck Depression Inventory (BDI) (Beck, 1996) and the State-Trait Anxiety Inventory (S-TAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1970). 36% of their patients scored above the cut-off score on the BDI and were classed as depressed. However, the BDI score was not significantly different to controls ($t=1.5$, $p=0.07$). There was also no difference on the S-TAI and neither mood measures correlated with the neurocognitive tests. It is possible that the discrepancy between Peace et al.'s (1997) cohort and the current study is due to the use of different mood measures. The SCL-90R measures a variety of symptoms, not just depression and anxiety. Overall the previous literature does not clarify whether the executive dysfunction found in some previous studies is due to psychological distress. Future studies should include the SCL-90R whenever EF tests are used.

Section 3 - Physiological measures

The behavioural data chapters have outlined the intact and impaired neurocognitive functions of the current sample of patients with non-functioning pituitary adenoma. Intact general intellectual functioning and executive functions have been demonstrated in the presence of immediate memory deficit. However, it is unclear why this deficit exists. Type of treatment has not been a reliable predictor of deficit, as was hypothesized, and a large amount of within treatment group variance has been found. In the following chapter this variance is examined in the context of physiological variables such as hormone levels and cerebrovascular health, in an attempt to discover the causes of both the immediate memory deficit seen in the patient group as a whole, and the variance between patients who have received the same treatment.

Introduction

Physiological measures

One purpose of psychometric testing is to quantify the existence and extent of cognitive deficits that patients may experience. However, examining physiological measures concurrently can elucidate potential causes of cognitive dysfunction. This chapter will examine the relationship between two types of physiological data and cognitive function. Firstly, the level of hormones in the patients' blood will be correlated with cognitive measures. Patients with pituitary adenoma may be on a dose of hormone replacement which, whilst in the population normal range, is not optimum for their own cognitive functioning. Secondly, measures of cerebral blood flow will be taken and compared to cognitive performance. This is done to assess if the greater incidence of cerebrovascular disease found in patients treated with RT is also affecting cognitive functioning. Again, outcomes of both test types will be correlated.

The pituitary gland

The pituitary gland protrudes from the hypothalamus via the pituitary stalk and secretes a number of hormones, including tropic hormones which stimulate other endocrine glands. It is

comprised of two lobes called the anterior pituitary and the posterior pituitary. The hormones produced by the pituitary and the site of action and effect of those hormones are shown in Table 21.

Table 21: The hormones produced by the pituitary gland

Anterior Pituitary			
Hormone Name	**Acronym**	**Site of Action**	**Effect**
Adrenocorticotropic hormone	ACTH	Adrenal gland	Stimulates the secretion of glucocorticoids
Beta-endorphin		Opioid receptor	Inhibits the perception of pain
Follicle-stimulating hormone	FSH	Gonads	In women, it acts on the follicle to stimulate estrogen release. In men, it acts on the spermatogonia to stimulate sperm production
Luteinizing hormone	LH	Gonads	In women, it stimulates egg release and the development of the corpus luteum. In men, it stimulates the testes to produce and secrete testosterone
Growth hormone	GH	Liver	Stimulates the release of insulin-like growth factor-1 (IGF-1)
Prolactin	PRL	Breasts	Stimulates breasts to produce milk. Modulates immune system activity.
Thyroid-stimulating hormone	TSH	Thyroid gland	Causes the secretion of thyroxine (T4)
Posterior Pituitary			
Oxytocin		Certain smooth muscles	Stimulates uterine contractions at the time of birth. Stimulates milk release during breast feeding.
Vasopressin	ADH	Kidney nephrons	Facilitates the reabsorption of water into the blood stream

Hormone Levels and Cognition

The levels of several hormones that are produced or regulated by the pituitary gland have been associated with either cognitive potentiation or dysfunction. This can occur during periods of change associated with normal aging, such as puberty or menopause, but it can also be demonstrated in the short term by experimental manipulation. The effects of cortisol on memory are discussed in the 'Literature Review' chapter of this thesis, and can either inhibit or improve memory depending on the type of stimuli and time of day (Lupien et al., 1999; Lupien et al., 2002; Kuhlmann et al., 2005). The pituitary gland produces ACTH and disruption to this production affects the secretion of cortisol from the adrenal glands, so

whilst the pituitary does not directly produce cortisol, damage to the pituitary still results in cortisol insufficiency.

Sex hormones can affect cognition differently according to a person's age, (Mulnard et al., 2000). The positive effect of estrogen on verbal memory in younger women is thought to be due to a protective effect on cholinergic neurones by oestrogen (Gibbs & Aggarwal, 1998). However, older women do not experience this protective effect. This may be due to a reduction in muscarinic receptors to which estrogen induces an increase in NMDA binding (Norbury et al., 2007). Thilers *et al*. (2006) found verbal fluency and switching attention to be positively correlated with free testosterone in men; yet verbal fluency was negatively correlated with testosterone in women. Testosterone deprivation in men treated for prostate cancer has been associated with poorer recall (Beer et al., 2006) and recognition (Bussiere et al., 2005) of verbally presented semantic material. However, higher testosterone levels have also correlated with poorer performance on executive functioning tasks in men over 50 years of age (Martin et al., 2004).

The effects of hormone excess or deficiency can be particularly potent over extended periods of time. Patients with Cushing's disease have been found to show poorer performance on several subtests of learning, delayed recall, and visual-spatial ability associated with higher cortisol levels (Starkman et al., 2001; Forget, Lacroix, Somma, & Cohen, 2000). Sub-clinical hyperthyroidism does not seem to affect cognitive performance in healthy individuals over a period of 45 days (Baethge et al., 2002); however, hypothyroidism has been associated with impaired memory performance, even after months of appropriate thyroid replacement (Correia et al., 2008). Childhood growth hormone deficiency (GHD) has been recognised as a significant variable leading to neurocognitive problems which can be improved by growth hormone (GH) replacement (Arwert et al., 2005; Deijen et al., 1998). Patients with adult-onset GHD also demonstrate impairment on immediate and delayed recall (Deijen et al., 1996). Adult-onset GHD patient's have shown improvements in attention after six months of GH replacement suggesting the deficiency was previously impairing their attention (Oertel et al., 2004). Research into GHD has also found that patients have significantly lower scores than controls on spatial learning (Bulow et al., 2002).

Therefore, there is an extensive body of research that has shown cognition can vary with hormone function or dysfunction. When considering the impact of pituitary tumour and its treatment it is necessary to consider the effects these have on hormone secretion.

It is important to measure blood hormone levels on the day of neurocognitive testing to ensure that patients are not experiencing hormone levels which are outside the population normal range. As most patients with pituitary adenoma receive exogenous replacement of some hormones, it is possible that hormone excess or deficit on the day of testing could represent a chronic problem in blood-hormone levels. This can be identified by verifying any abnormal results against the patients' medical notes and self-report of current replacement consumption. Cortisol levels can be measured using a short-synacthen test. During this test, 250μg of synthetic ACTH is injected, and the amount of cortisol produced by the adrenal glands in response is measured. A cortisol level on or above 550 μg after 30 minutes is considered a normal result. Therefore, to understand an individual's performance it is important to understand whether this individual's performance is partially governed by hormone levels.

Cerebral Blood Flow and RT

Another mechanism by which cognitive impairment might occur is through damage to cellular structures of the vascular system through the administration of RT. Blood flow in healthy large vessels is generally laminar, which means the blood in the middle of the vessel is faster than the flow at the edge. Resistance to blood flow is determined by fluid viscosity and the length and diameter of the vessel. During standardised RT, x-rays are delivered to the target area through 'leaves' of a high atomic numbered material (multileaf collimation) into discreet beams. The x-rays can produce either double strand DNA breaks which, if unrepaired, will kill a cell; or single strand DNA breaks which are unlikely to kill a cell but may prevent successful mitosis at a later time and thereby prevent further tumour growth from this cell. Healthy tissue that lies in the pathway of the x-ray beam may also be damaged.

The level of radiation that biological tissue can tolerate depends on its radiosensitivity. Tissues which are highly radiosensitive, such as lung or kidney tissue show a 5% chance of pneumonitis or glomerulosclerosis if given 10 daily doses (fractions) of 2 Gray (Gy). In contrast, the brain shows a less than 1% chance of developing necrosis after 25 fractions of 2Gy (Steel, 2002). However, the endothelial cells in blood vessels are considered to be moderately radiosensitive (Rubin & Casarett, 1968). Capillaries are damaged by doses above approximately 40Gy. Generally, arteries are also more radiosensitive than veins (Hall & Giaccia, 2006).

Following RT, some cell death occurs rapidly. However, most damaged cells will continue to function until they enter mitosis but do not successfully split into new cells. Areas of blood vessel constriction occur from the abnormal proliferation of surviving cells. Denudation of the blood vessel surface can lead to thrombosis formation or capillary necrosis. Eventually, vessel walls lose their elasticity and blood flow is either diminished or occurs under higher pressure due to narrowing of the vessel lumen (Hall & Giaccia, 2006). This increase in hydrostatic pressure increases the pressure with which blood flows through the larger vessels feeding the capillary bed. Increased blood pressure has been associated with poorer or decreased cognitive function in all age groups (Elias, Wolf, Dagostino, Cobb, & White, 1993; Robbins, Elias, Croog, & Colton, 1994; Lande, Kaczorowski, Auinger, Schwartz, & Weitzman, 2003; Waldstein, Brown, Maier, & Katzel, 2005; Waldstein, Giggey, Thayer, & Zonderman, 2005) ranging from deficits in memory, executive functions, attention, psychomotor abilities and visuospatial skills.

Arterial blood pressure (ABP) can be measured using a small catheter inside the aorta. However, this is invasive and would prove very unpopular with participants. A suitable alternative is to non-invasively measure radial ABP with a Colin CBM-7000 monitor on the wrist, combined with the transcranial Doppler (TCD) technique. TCD uses probes that emit a beam of 2MHz ultrasound wave. This non-invasive procedure takes advantage of the penetrability of thinner areas of the skull to ultrasound. When the ultrasound wave collides with blood cells moving through the vessels it is reflected back towards the probe where the signal can be analysed.

Cerebral autoregulation (CA) is the term that describes the brain's intrinsic mechanism to keep cerebral blood flow (CBF) within the range of 50-150 mmHg. This is achieved by adjusting vascular resistance. The smaller blood vessels in the brain constrict or dilate to allow blood flow to pass through with greater or less resistance. CA can be induced by dynamic tests and the resulting changes in blood flow are visible in the Doppler signal. Two dynamic tests of CA were used. During the valsalva manoeuvre the patient must blow against pressure to 40mmHg for as long as they can up to a maximum of 30 seconds. In the second test, cuffs are inflated to 30mmHg above systolic blood flow around the patient's thighs. After two minutes the pressure is rapidly released. Both of these tests produce predictable physiological changes in normal individuals.

The middle cerebral artery (MCA) within the circle of Willis is ideal for measuring flow volume (FV) for two reasons. Firstly, it has been shown that, unlike smaller blood vessels, the diameter of the MCA does not alter under a variety of physiological changes such as change in oxygen levels or lower body negative pressure (Serrador, Houtman, Shoemaker, & Hopman, 2000). This is important, as it shows that an increase in FV within the MCA represents a change induced by the large vascular bed which the MCA serves, rather than a small change to the MCA itself. CA operates throughout the blood vessels of the brain and so for TCD to accurately measure changes due to CA, it must operate on a vessel that averages these changes, rather than being itself subject to the biological compounds that cause it. Secondly, the length of the MCA bisects the angle of the skin surface over the acoustic window at approximately 90 degrees. This means that the ultrasound beam produced by the probe passes directly through the vessel with a beam-vessel angle of or near to 0 degrees. At this angle, the measured Doppler frequency corresponds exactly to flow velocity. If the beam-vessel angle is changed from 0 degrees to 30 degrees, the measured Doppler frequency decreases by 13% (Li, Cheng, & Shen, 2000). The MCA is the only artery of the circle of Willis to offer such a low beam-vessel angle. In measuring CA across groups, it is more important to choose the artery to insonate based on the beam-vessel angle than on the vessel that supplies blood to the areas of brain which control the cognitive functions being measured. A typical resting TCD output is shown in Figure 9. The mean velocity of the blood flow through the vessels indicates whether a person has normal, hypo or hypertensive blood flow to the brain. The normal range for MCA blood vessels is between 50 to 65 cm/s (Lindegaard, Wiberg, Lundar, Aaslid, & Nornes, 1987; Lindegaard et al., 1987). Both hypo and hypertension have been associated with cognitive impairment. A community study of approximately 6000 older adults found that chronic hypotension correlated with mild cognitive impairment (Morris et al., 2002) whilst a recent review of the hypotension literature highlighted attention and memory as the cognitive skills most at risk from hypotension related impairment (Duschek & Schandry, 2007). Hypertension can also contribute significantly to cognitive impairment (Elias et al., 1993; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995). Therefore it is important to measure the blood flow velocity into the brain to assess its potential contribution to any cognitive impairment.

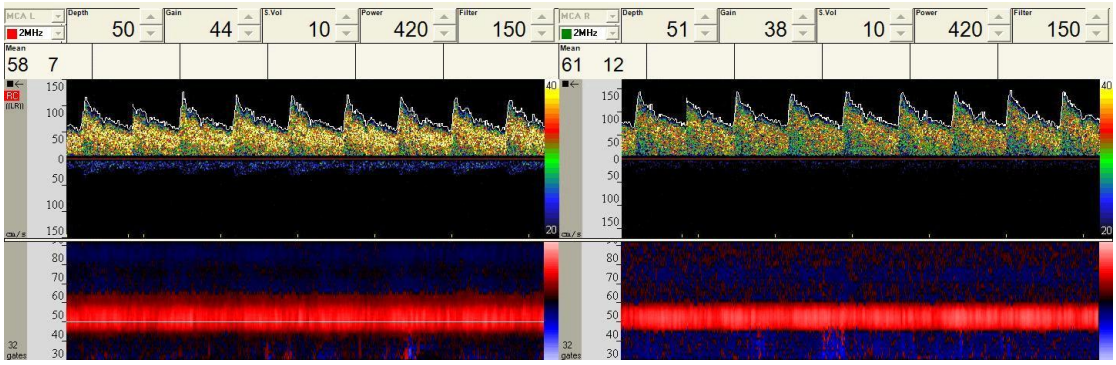

Figure 9: A typical TCD output during resting monitoring. The top pattern shows blood flow through the left and right MCAs and the bottom pattern shows the depth in mm at which this signal can be found (red bar).

Another potential cause of cognitive impairment through capillary damage is microemboli. These are either gaseous bubbles or solid fragments of atheromatous plaques (small thrombi). They are a risk factor for cerebrovascular disease (Rapp et al., 2000). Patients who have received RT are significantly likely to develop stenoses in large irradiated vessels, especially the carotid arteries (Martin et al., 2004; Smith & Magee, 2003; Cheng et al., 2000). Stenoses have been associated with the presence and production of microemboli (Wong, Gao, Hansberg, Chan, & Lam, 2002; Mayor, Comelli, Vassileva, Burkhard, & Sztajzel, 2003; Orlandi et al., 1999) which are considered a predictive parameter for the risk of stroke and transient ischemic attacks (TIAs) (Spencer, 1997; Levi et al., 1997; Valton, Larrue, le Traon, Massabuau, & Geraud, 1998; Goertler et al., 2002). Patients treated with RT have been found to have a standardised mortality ratio of 4.36 from death caused by cerebrovascular disease, including stroke (Tomlinson et al., 2001). It was hypothesised that microemboli would be a useful predictor of stroke risk. Microemboli themselves have been experimentally shown to cause neuronal cell death when introduced into the blood circulation of rats (Rapp et al., 2000). Microemboli can be detected using TCD. They appear as distinctive high intensity signals of short duration. Microemboli have been found to spontaneously occur in the TCD signal of resting patients with either intracranial carotid artery or MCA stenosis (Nabavi, Georgiadis, Mumme, Zunker, & Ringelstein, 1996; Droste & Ringelstein, 2002; Segura et al., 2001) and also extracranial carotid artery stenosis (Markus, Thomson, & Brown, 1995; Valton, Larrue, Arrue, Geraud, & Bes, 1995; Droste et al., 1999). Specialised software is used to detect potential microemboli during recording. After recording, the researcher must review each ‘event’ and determine whether it is a signal artefact or a microembolus. Artefacts occur across all depths of the same artery simultaneously and can be caused by movement of

the subject, for example coughing. Microemboli occur at a limited depth in the artery and will pass the different depths measured at different times (Droste et al., 1999; Moehring & Spencer, 2002; Molloy & Markus, 1996). The presence of microemboli after surgery correlates with greater cognitive impairment both eight days and eight weeks later (Pugsley et al., 1994) and an association between the number of microemboli detected and cognitive decline has frequently been noted in studies of heart surgery (Russell, 2002). This decline may be due to microemboli blocking and damaging cortex capillaries. In healthy individuals, microemboli are absent (Droste et al., 1997; Eicke, Vonlorentz, & Paulus, 1995; Daffertshofer, Ries, Schminke, & Hennerici, 1996).

There are thus several ways in which RT can damage blood vessels and therefore facilitate the development of cognitive dysfunction. Direct damage to capillary cell walls can limit the blood supply to surrounding neurons, especially when vessel dilation is required for local increases in blood flow. Alternatively, microemboli released during surgery or broken off from plaques formed in larger vessels may block capillaries and decrease blood supply to nearby areas. Hence, these variables are measured to assess whether changes in cognition are indeed mediated by hormonal disruption or whether the two-fold mortality rate found by Tomlinson et al. (2001) after RT is contributing to cognitive deficit.

Other Blood Characteristics

The elevation or depression of blood-born biological material can indicate physical health problems which may negatively impact on cognitive functioning. Lower hydration status has been related to reduced psychomotor processing speed and poorer attention and memory functioning in healthy adults aged 50 – 82 years (Suhr, Hall, Patterson, & Niinisto, 2004). As many of the potential participants for the current study were within this age range, plasma osmolality was measured. Cholesterol levels seem to have a bi-directional affect on cognition. Whilst the Framingham Heart Study found a positive relationship between total cholesterol (TC) and verbal fluency, attention and abstract reasoning in a sample of almost 1900 people. This relationship held even if TC levels were in a range considered to be unhealthily high (>240mg/dL). In a second longitudinal study, approximately 1500 were followed-up for an average of 21 years. High midlife TC was a risk factor for cognitive impairment in later life. However, a decrease of between 0.5 to 2 mmol/L from midlife to later life was also associated with poorer cognitive performance (Solomon et al., 2007). Total cholesterol, high-density lipoprotein cholesterol, triglycerides and lipoprotein subfractions

were therefore measured. A meta-analysis of six studies showed that high concentrations of C-reactive protein (CRP) are predictive of cognitive decline and dementia (Kuo et al., 2005) and a longitudinal study of 452 individuals found that fibrinogen independently predicted decline over four years in non-verbal reasoning. Thus, CRP and fibrinogen were measured.

Aims

The aim of this study is to evaluate the effects of several physiological factors on cognitive function. Hormone levels and cerebral blood flow velocity are expected to correlate with cognitive functioning. Higher scores in the three measures of cerebral autoregulation are also expected to positively correlate with cognitive function. The presence of microemboli will be negatively correlated with cognitive function.

Methods

Participants

Participants were chosen and recruited as described in the 'General Method' chapter. Additional exclusion criteria for physiological data collection were pregnancy or breast feeding as this would affect hormone levels and skew group averages.

Measures

The neurocognitive measures are described in the General Methods Chapter. These were measures of intelligence, memory and executive functions. Data such as time since surgery or RT was taken from the medical notes.

The following hormones were tested: oestradiol and testosterone (sex hormones); free triidothyronine (FT3) and free thyroxine (FT4) (FT4 is metabolised to FT3 which has biological effects); prolactin (mainly produced to induce lactation); insulin-like growth factor 1 (IGF-1) (a marker of growth hormone which promotes tissue growth); cortisol and cortisol 30 minutes after a short-synacthen injection. For patients on cortisol replacement, the dosage was noted instead.

The following blood contents were tested: plasma osmolality (a measure of the osmoles of solute per kilogramme of solvent. Solute is made up of substances such as sodium, glucose, potassium and urea); total cholesterol; high-density lipoprotein cholesterol (protects against cardiovascular disease); triglycerides (fatty acids); lipoprotein subfractions (a cerebrovascular disease risk factor); C-reactive protein (a marker of inflammation and a cerebrovascular disease risk factor) and fibrinogen (causes blood clotting and a cerebrovascular disease risk factor).

The transcranial Doppler technique yields the following scores: CBF velocity during resting monitoring (a measure of baseline cerebrovascular health); resting emboli detection (a measure of the risk of transient ischemic attack or stroke); the autoregulation index (ARI) provided by the thigh cuff technique described below (a measure of cerebral autoregulation (CA)); the AI-IV and the Autoregulatory Slope Index (ASI) are provided by the Valsalva manoeuvre and are also measures of CA. Higher scores indicate healthy CA whilst lower scores indicate the possible presence of pathology.

Procedure

Participants attended the Wellcome Trust Clinical Research Facility having fasted from midnight the previous day. The middle cerebral arteries (MCAs) were identified through the transtemporal window using the method described by Alexandrov and Neumyer (Alexandrov & Neumyer, 2007) and a transcranial Doppler (TCD) headset was individually fitted to each participants head. The equipment used was a digital M-mode 'DWL Compumedics Doppler Box' using 2MHz probes. Arterial blood pressure (ABP) was continuously measured using a 'Colin Medical CBM 7000'. The MCAs were insonated for thirty minutes whilst emboli detection and baseline measurements were conducted. Following this, the two CA studies were conducted. Each test was repeated three times with each repetition followed by 5 – 10 minutes rest before the next repetition.

Blood was drawn for evaluation of baseline endocrine status, cerebrovascular risk factors, and insulin and glucose estimation. Five participants were not taking hydrocortisone and had not received a short Synacthen test in the previous six months. These participants were administered a short Synacthen test to check for adequate cortisol production.

Each patient underwent carotid ultrasound to determine carotid intima-media thickness (IMT). This identified any plaques in the carotid which could be the cause of any microemboli found in the MCA rather than these microemboli being due to intracranial damage caused by RT. Carotid IMT is an early marker of atherosclerosis and is a well established measure of cardiovascular risk (del Sol et al., 2001) and for this reason the carotid IMT is measured rather than the IMT of any other artery in the body. This measurement was achieved using B-Mode ultrasound on a Philips Sonos 7500. The bifurcation of the common carotid artery into the internal and external arteries is identified and photographed. The IMT of the common and internal carotids as well as at the bifurcation is then measured using standard 'calliper' software provided on the equipment (Riley, 2002).

Data Pre-Processing

Calculating the Autoregulation index

A method was required to gain a measure of the autoregulation index (ARI) (Tiecks, Lam, Aaslid, & Newell, 1995) from TCD measurements of the MCA flow velocity (FV). The ARI is a dynamic measurement of Cerebral Autoregulation (CA) originally developed from the work of Aaslid et al. (1989). A rapid decrease in ABP is achieved by inflating cuffs around the thighs to 30mmHg above systolic blood pressure for 2 minutes and then rapidly deflating them using an air release valve. Immediately after the thigh cuff is released, the manner and speed with which equilibrium is achieved and the comparison between FV and ABP allow a specific ARI to be determined. The ARI itself is determined by solving a second order linear differential equation which is driven by changes in ABP and comparing the result to the FV, in a similar manner to that used by Tiecks et al. (1995). Each ARI was calculated using the software programme MatLab (Mathworks, 2009). The parameters of the second order differential equation that determine the resulting numeric solution (the ARI) are the time constant, T, the damping, D and the autoregulatory dynamic gain, K. The values of these and their corresponding ARI are shown in Table 1, taken from Tiecks et al. (1995) where the details of the solution to the differential equation can also be found.

Table 22: The values of the controlling variables in the second order linear differential equation and their corresponding ARI taken from Tiecks et al. (1995)

ARI	T/s	D	K
0	…	0	0
1	2.00	1.60	0.20
2	2.00	1.50	0.40
3	2.00	1.15	0.60
4	2.00	0.90	0.80
5	1.90	0.75	0.90
6	1.60	0.65	0.94
7	1.20	0.55	0.96
8	0.87	0.52	0.97
9	0.65	0.50	0.98

The data produced by the TCD apparatus are shown in Figure 10. This data are then filtered to remove the systolic and diastolic pressure and flow changes giving an indication of the mean behaviour. A low pass bilinear filter is used with an upper cut off frequency of 0.3 Hz. As most rapid shifts in ABP and FV due to a heart beat occur at much faster rates, of the order of 10-20 Hz, these are effectively smoothed from the resulting data. Of course, with the filtering process you effectively lose any information from the data at higher frequencies but, in the case of determining the ARI, one is only interested in the slower responses of the system. The region of interest is then selected from the data for further comparison. It is typical to take 10 seconds before the thigh cuff is released, to give an average of the initial ABP and FV in the system, and 15 seconds after the ABP has returned to equilibrium. This range of smoothed data are shown in Figure 11.

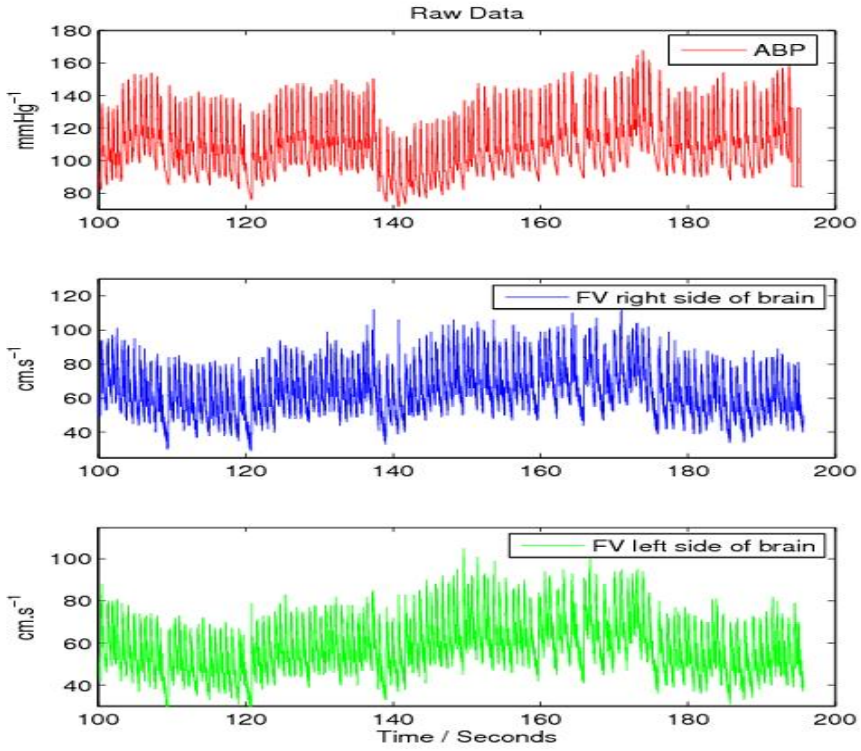

Figure 10: A typical data set of the FV and ABP values taken during a thigh cuff procedure. The rapid spiking is a result of the participant's heartbeat and there are minor changes in mean ABP and FV shown across the whole data range that are typical in all patients. After two minutes, the cuff was released at 137 seconds

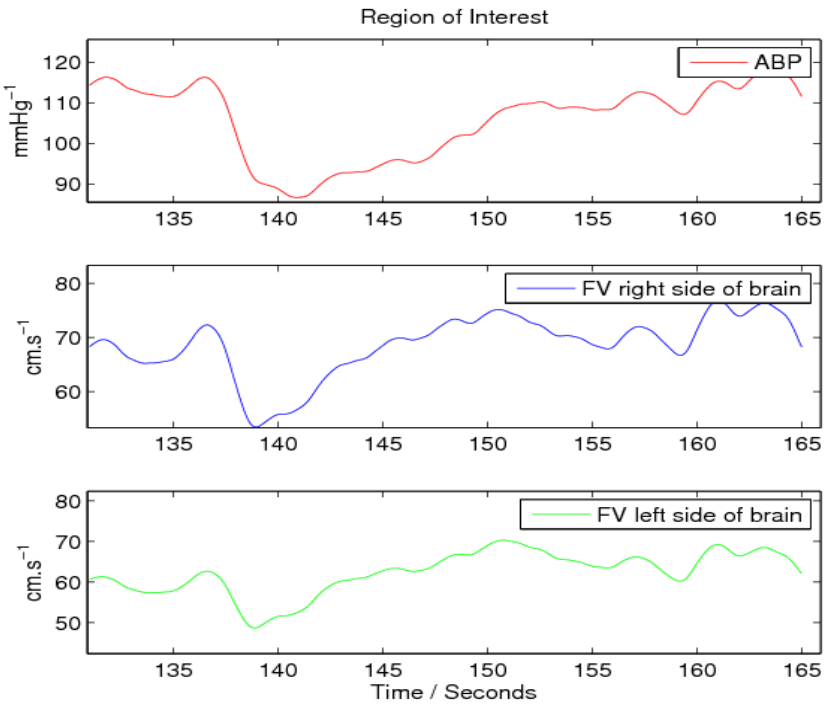

Figure 11: the region of interest from figure 10 before and after thigh cuff release. It has been filtered via a low pass bilinear filter with an upper cut off frequency of 0.3 Hz.

Calculating the Valsalva Manoeuvre

There are four distinct phases to the Valsalva manoeuvre which can be identified and used to calculate the efficiency with which the brain is autoregulating. At the start of the first phase, the participant inhales deeply before exhaling against pressure. This raises intrathoracic pressure causing a rise in arterial blood pressure (ABP). During the second phase, the output from the heart is reduced due to intrathoracic pressure, resulting in a drop in BP. In order to compensate, blood vessels constrict to raise ABP levels back to normal. The third phase occurs when the participant stops exhaling against pressure and inhales again. This causes a sudden decrease in intrathoracic pressure allowing the pulmonary arteries and aorta to expand, thereby causing a brief drop in ABP as cardiac output initially increases. The final and fourth phase occurs as blood which was previously suppressed from entering the heart by intrathoracic pressure returns. This causes a rapid increase in cardiac output and rise in ABP above normal before returning to the pre-Valsalva ABP. These phases are shown in Figure 12. The top picture in the diagram is taken from Tiecks et al. (1995), whilst the bottom part of the figure gives an example of the data obtained in the current study.

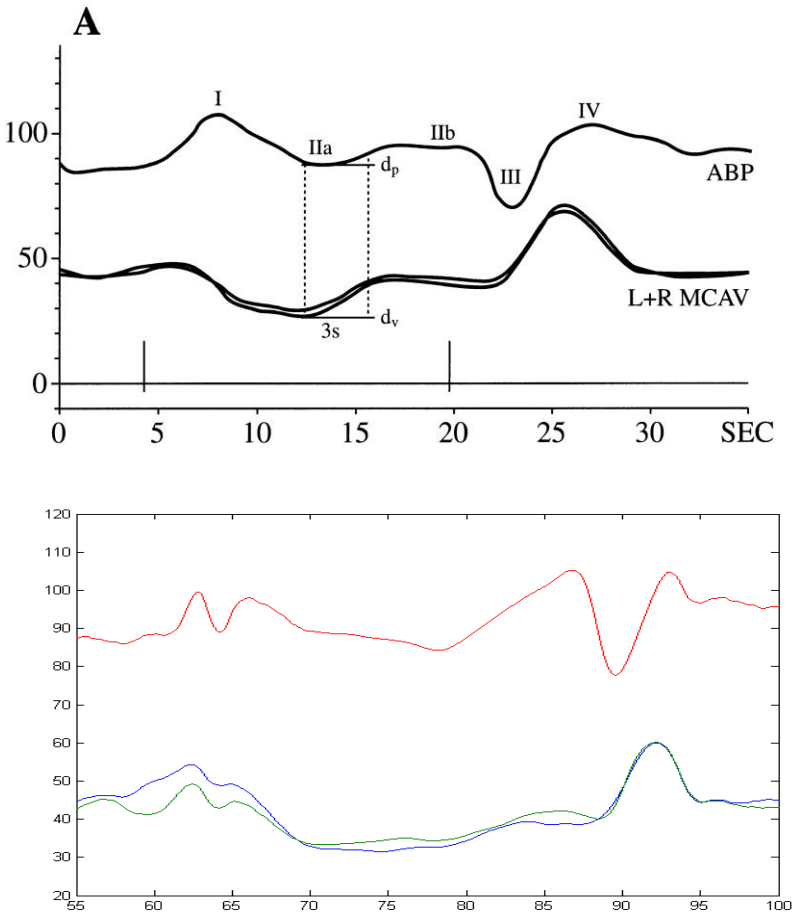

Figure 12: The four phases of the Valsalva manoeuvre (above) and an example of the data obtained in the current study (below)

The Valsalva manoeuvre provides two different measures of autoregulation. The 'AI-IV' gives an autoregulatory index based on the ratio of phase four and one of the Valsalva manoeuvre. The formula for calculating the AI-IV is taken from Tiecks et al. (1996) and is as follows:

$$AI - IV = \frac{CBFV\ (phase\ IV)/CBFV\ (phase\ I)}{ABP\ (IV)/ABP\ (I)} \times 100\%$$

In a healthy individual, it is expected that the increase in CBF volume (CBFV) in phase four will exceed the increase in ABP. It is also expected that both CBFV and ABP will be greater in phase four than in phase 1. Therefore, the result of the AI-IV formula should exceed 100%.

The second measure of CA obtained from the Valsalva manoeuvre is called the Autoregulatory Slope Index (ASI). The formula for calculating the ASI is as follows (Tiecks, Douville, Byrd, Lam, & Newell, 1996):

$$ASI = \left(\frac{CBFV_{(t+3s)} - CBFV_{(t)}}{CBFV_{(t)}} - \frac{ABP_{(t+3s)} - ABP_{(t)}}{ABP_{(t)}}\right) \times 100\%$$

During the second phase of the Valsalva manoeuvre, the body attempts to normalise ABP by constricting blood vessels. However, CA acts over and above this mechanism to normalise CBFV faster than ABP is normalised. The ASI is a measure of how much faster CBFV normalises than ABP by calculating the slope on and three seconds after the lowest point in ABP in phase two. In a healthy individual, the ASI would be expected to be above 0%. An ASI on or around 0% would indicate a passive rise in CBFV due only to the rise in ABP.

Microemboli

For microembolus detection, both MCAs was insonated simultaneously at two distances, 5mm apart, using multi-channel recording, for 30 minutes, as recommended in McGahan and Goldberg (Lao, Sharma, Katz, & Alexandrov, 2008). These distances were chosen by finding the strongest signal in the middle of the artery and then setting the two recording points equidistant from the artery centre. The average depths used were 47mm and 52mm on both the left and right MCAs. The detection threshold for a signal to be signposted by the emboli detection programme was 9dB. The high pass filter was set at 150Hz and the system power was set at 420mW/cm^2. The sample volume was set at 10mm for calculation of CBFV and CA and set to between 5 and 8mm for emboli detection. The fast Fourier Transform size was set at 256Hz and the headset probes transmitted on a frequency of 2MHz.

Statistical Analysis

For all analyses comparing patients treated with RT to patients treated without RT, the four treatment groups were amalgamated into two larger groups. The conservatively managed and the surgery only groups were amalgamated into a ‘non-RT’ group, whilst the RT only and surgery + RT groups were amalgamated into a ‘post-RT’ group. Where appropriate, data from the four original treatment groups is analysed separately also.

For group comparisons of physiological data, t-tests will be used to compare the ‘non-RT’ and ‘post-RT’ treatment groups whilst ANOVAs will be used if the four original treatment groups are analysed separately. For correlations between physiological data and cognitive

scores, the number of significant correlations will be compared to the number of type 1 errors expected.

Hypothesis

1) Hormone levels will correlate with memory discrepancy scores and executive functioning contrast scores.

2) Due to vessel narrowing, patients treated with RT will have significantly faster resting CBFV in the MCAs than patients treated without RT.

3) Patients treated with RT will present significantly more microemboli over the 30 minute resting monitoring period than patients treated without RT.

4) Patients treated with RT will perform significantly poorer on all measures of cerebral autoregulation than patients treated without RT.

5) There will be no difference on any resting or autoregulation measures between patients with NFA who have or have not received surgery.

6) Resting CBFV will be negatively correlated with memory discrepancy scores and executive functioning contrast scores.

7) Measures of CA will be positively correlated with memory discrepancy scores and executive functioning contrast scores.

Results

Hypothesis 1: Hormone levels and neurocognitive function

The hormone levels measured from the blood tests of the patient sample are shown in Table 23 along with the population normal range. FT3 was only calculated in some cases as some lab technicians followed the clinical protocol of only calculating FT3 when FT4 is abnormal, rather than the study protocol of always analysing FT3. Blood tests were mostly within population norms for each individual's gender and age. The proportion of each treatment group with hormone levels outside their peer group normal range is shown in Table 23. Using

a t-transformation of difference in proportions the number of abnormal results for women and for men was compared. Men had significantly more abnormal blood test results than women ($t = 2.17$, $p = 0.03$).

For other blood characteristics, only two correlations were found to be significant. Commensurate with the Framingham Heart Study (Elias et al., 1993), a positive association was found between total cholesterol level and the Card Sort 'Sort Recognition – Free Sort' score ($r = 0.34$, $p = 0.03$). The second positive association was between osmolarity and the Design Fluency 'Switching – Lower Processes' ($r = 0.33$, $p = 0.03$) which suggests that better hydrated patients performed better on this non-verbal EF task.

ANCOVAs were used with sex as a covariate to compare hormone levels across the treatment groups. These showed a significant difference between the groups for the hormone TSH ($F = 5.87$, $p=0.002$). The RT only group had significantly higher levels of TSH than all three other groups (CM group: $t = 2.29$, $p = 0.05$; Surgery only group: $t = 3.70$, $p = 0.001$; surgery + RT group: $t = 3.21$, $p = 0.004$). This is unsurprising as TSH deficiency is treated with replacement of thyroxine, rather than TSH itself. The RT only group experienced less pituitary insult and so have more normal hormone production. When the RT only group was removed from the analysis, there was no difference between the three groups of pituitary patients for the level of TSH ($F = 0.42$, $p = 0.66$).

Table 23: The hormone levels of the study sample

Hormone	**Female Group Average (range)**			
	CM (2)	**Surgery (8)**	**RT (4)**	**S + RT (9)**
Prolactin	168.5 (76-261)	146.3 (20-261)	198.0 (95-289)	395.6 (209-660)
% abnormal	50% below	25% below		22% above
IGF-1	21.7 (12.1-31.3)	17.2 (7.9-22.7)	16.8 (10.2-21.4)	34.6 (9.6-184)
% abnormal		13% below	25% below	11% below
Oestrodial	159.5 (120-199)	158.8 (34-427)	68.3 (35-113)	136.3 (20-358)
% abnormal				
Testosterone	0.6 (1-1)	0.9 (0-1)	1.2 (1-2)	0.8 (1-1)
% abnormal				
TSH	2.4 (2-3)	1.4 (0-4)	3.4 (2-5)	1.6 (0-4)
% abnormal		25% too low	25% above	
FT3	4.4 (4.4-4.4)	4.2 (4.1-4.3)	4.3 (4.3-4.3)	4.3 (4.1-4.4)
% abnormal				
FT4	13.5 (13.1-13.9)	14.6 (12.8-17.0)	13.0 (9.2-16.4)	13.7 (11.5-18.5)
% abnormal			25% below	
Cortisol (B)	338 (338-338)	371 (193-622)	151 (151-151)	340 (337-342)
Cortisol (30)	521 (521-521)	702 (601-828)	577 (577-577)	840 (836-843)
Cortisol (R)	n/a	20 (20-20)	n/a	23 (15-30)
	Male Group Average (range)			
	CM (5)	**Surgery (11)**	**RT (3)**	**S + RT (10)**
Prolactin	575.8 (112-1497)	249.1 (55-688)	142.7 (94-194)	325.1 (109-992)
% abnormal	20% above	22% above		30% above
IGF-1	12.4 (3.9-27.5)	19.2 (12.3-38.3)	20.4 (12.3-24.6)	17.8 (10.0-37.6)
% abnormal	20% below	11% above		10% above, 10% below
Oestrodial	96.5 (54-143)	116.2 (49-308)	95.7 (78-109)	76.4 (43-203)
% abnormal	20% above	33% above		10% above
Testosterone	16.8 (12-29)	17.9 (8-39)	15.3 (12-18)	15.6 (6-55)
% abnormal		11% below		20% below
TSH	0.7 (0-2)	0.6 (0-2)	2.5 (1-4)	0.6 (0-2)
% abnormal	20% below	22% below		50% below
FT3	4.5 (3.8-5.2)	4.7 (3.6-5.7)	4.9 (4.1-5.7)	3.9 (3.4-4.5)
% abnormal				20% below
FT4	14.0 (9.0-21.6)	16.9 (11.4-27.5)	13.9 (12.6-16.4)	14.7 (10.9-19.6)
% abnormal	20% above	11% above		
Cortisol (B)	281 (281-281)	311 (311-311)	n/c	223 (223-223)
Cortisol (30)	574 (574-574)	515 (475-544)	n/c	n/c
Cortisol (R)	20 (15-30)	28 (20-30)	n/a	25 (15-30)

CM = Conservatively Managed; RT = Radiotherapy; S = Surgery; F = female; M = male; PNR = Population normal range; IGF = Insulin-like Growth Factor; TSH = Thyroid-Stimulating Hormone; FT = Free Thyroid; B = baseline; 30 = 30 minutes after SST; R = Replacement Dose; n/c = Not Calculated; 'below' and 'above' are in relation to the normal range

General Intellectual Functioning

Only FT4 correlated with general intellectual functioning in the whole sample. It correlated with FSIQ ($r = 0.29$, $p = 0.04$), VIQ ($r = 0.30$, $p = 0.04$), VCI ($r = 0.32$, $p = 0.03$) and WM ($r = 0.29$, $p = 0.05$). For hormones which were found in significantly different amounts in men and women, the sample was split so that correlations could be assessed separately. These hormones were testosterone and TSH (as discussed in the 'General Methods' chapter). These two hormones did not significantly correlate with general intellectual functioning in women. However, TSH correlated negatively with FSIQ ($r = -0.46$, $p = 0.02$), VIQ ($r = -0.48$, $p = 0.01$), VCI ($r = -0.48$, $p = 0.01$), PSI ($r = -0.46$, $p = 0.02$) and WM ($r = -0.45$, $p = 0.02$) in men, meaning that the higher the TSH level, the lower the concurrent level of general intellectual functioning. The amount of cortisol replacement positively correlated with VIQ ($r = 0.42$, $p = 0.05$) and VCI ($r = 0.44$, $p = 0.04$) suggesting that the higher the replacement cortisol dose, the better a person's verbal intelligence. Cortisol levels at baseline and after SST in patients not receiving hydrocortisone replacement did not correlate with general intellectual functioning.

Memory

The hormones prolactin, IGF-1, Oestrodial, FT3, cortisol at baseline and cortisol replacement did not correlate with any of the memory discrepancy scores for the whole sample. Nor did testosterone or TSH correlate with memory discrepancy scores for men or women, assessed separately. However, FT4 correlated with the working memory discrepancy score ($r = 0.33$, $p = 0.02$) and cortisol 30 minutes after SST correlated with the auditory recognition delayed discrepancy score ($r = 0.70$, $p = 0.02$), suggesting the greater reaction to SST, the better the recognition memory. Surprisingly, there was a significant difference between men and women on several discrepancy scores across the treatment groups. This is shown in Table 24 below. This difference was only found on the tests of memory and was not found on the other tests of neurocognitive functioning. In order to test if the diverse range of abnormal hormone results were cumulatively affecting memory, and thereby contributing to the sex difference found, the entire sample was split into two groups; patients with at least one blood hormone result outside the age and sex appropriate normal range (28 patients) and patients with all blood hormone results within the normal range (22 patients). Independent t-tests were used to compare the discrepancy scores in these groups. The patient group with normal range hormone tests scored significantly better than patients with one or more abnormal results on

the auditory immediate discrepancy score (normal $\bar{X}$ = -1.27, abnormal $\bar{X}$ = -8.14, t = 2.03, p = 0.05) and the visual delayed discrepancy score (normal $\bar{X}$ = 2.14, abnormal $\bar{X}$ = -6.39, t = 2.25, p = 0.03). However, it is not clear whether the greater number of abnormal hormone results in men contributed to the sex difference found, or whether the greater number of men in the abnormal hormone level group contributed to this difference.

Table 24: The discrepancy scores achieved by men and women across groups

	Sex	N	Mean	Std. Dev	t	p(t)
A I Disc	female	23	0.48	10.34	3.26	0.002
	male	29	-9.83	12.04		
V I Disc	female	23	-0.13	14.28	3.03	0.004
	male	29	-10.45	10.27		
A D Disc	female	23	5.70	11.74	3.80	0.000
	male	29	-8.10	13.91		
V D Disc	female	23	3.48	13.59	3.28	0.002
	male	29	-8.07	11.76		
A R D Disc	female	23	2.65	10.08	1.51	0.14
	male	29	-3.00	15.59		
W M Disc	female	23	3.86	10.39	0.39	0.70
	male	29	2.59	12.26		

A = Auditory; I = Immediate; Disc = Discrepancy; V = Visual; D = Delayed; R = Recognition; W M = Working Memory

Executive Functions

The hormones prolactin, oestradiol, IGF-1, FT3, FT4, cortisol replacement and cortisol after SST did not correlate with any of the executive function contrast scores. For hormones assessed separately for men and women, no significant correlations between hormone and EF contrast scores were found. However, baseline cortisol did negatively correlate with the EF contrast scores of Verbal Fluency 'Switching Category Fluency – Category Fluency' (r = -0.66, p = 0.05) and Colour-Word Interference 'Inhibition – Colour Naming' (r = -0.66, p = 0.04). This suggests that higher baseline cortisol levels are associated with poorer inhibition and attentional switching ability. Conversely, baseline cortisol was positively correlated with the Card Sort 'Sort Recognition – Free Sort' score (r = 0.73, p = 0.02). However, this may indicate that patients who were better at initiating their own card sorts had lower baseline cortisol levels.

Hypothesis 1 was partially supported. FT4, cortisol and TSH correlated with several neurocognitive function scores. However, for general intellectual functioning, memory and

executive function analyses, there were nineteen neurocognitive scores, correlated with five hormones for the whole sample, three sets of cortisol measurements, and two hormones analysed separately for men and for women. This gives a potential total of 190 correlations. Given a 5% probability of a significant correlation occurring by chance alone, this analysis should provide ten significant correlations by chance. For the general intellectual functioning analysis, there were 11 significant correlations instead of an expected four, indicating several true results. For the memory analysis, there was one significant correlation instead of the expected three, indicating that this may constitute a type 1 error. For the executive function analysis, three correlations were found as expected, indicating a strong possibility that these were type 1 errors. Therefore these results must be interpreted with caution.

Hypothesis 2: Resting CBFV

An independent samples t-test showed no difference between the non-RT and post-RT groups in ABP ($t = -0.09$, $p = 0.93$) or in heart beats per minute ($t = 0.30$, $p = 0.76$). CBFV was however, significant faster for the post-RT group than the non-RT group in both the left (52.6cm/s versus 65.4cm/s; $t = -2.80$, $p = 0.008$) and the right (52.5cm/s versus 62.6cm/s; $t = -2.31$, $p = 0.026$) MCAs. This is shown in Table 25. Hypothesis 2 was therefore upheld.

Hypothesis 3: Microemboli and Carotid IMT

In the entire sample only one microembolus was detected in one patient (treated with surgery and RT). This is commensurate with the healthy general population. There was also no significant difference in any measure of carotid IMT between the groups ($t = 1.28$, $p \geq 0.24$). Hypothesis 3 was thus rejected in favour of the null hypothesis of no difference between groups.

Hypothesis 4: Cerebral Autoregulation

During the thigh cuff procedure, the average drop in ABP was 15.6mmHg for the non-RT group and 18.3mmHg for the RT group. An independent samples t-test showed a trend towards significance between the two groups ($t = -1.84$, $p = 0.07$). Drop in ABP was therefore entered as a covariate for the analysis of the ARI data. There was no difference between the non-RT and post-RT groups on the CA measures of ARI ($t = 0.04$, $p = 0.84$), ASI ($t = 0.65$, $p = 0.52$) and AI-IV ($t = 1.31$, $p = 0.20$). The ARI scores reflected the normal

population score of approximately 5 (Tiecks et al., 1995). Normal population scores for ASI are expected to be above 0 and AI-IV scores are expected to be above 100 (Tiecks et al., 1996). This was also achieved. All of the blood flow data are shown in Table 25. Hypothesis 4 was therefore rejected in favour of the null hypothesis.

Table 25: The mean values and standard deviations of the blood flow data

	non-RT		**post-RT**			
N	22		24			
	Mean	**S.D.**	**Mean**	**S.D.**	**t**	**p(t)**
ABP	89.2	10.1	89.5	9.8	-0.09	0.93
BPM	62.5	7.6	61.8	5.8	0.30	0.76
MCA left	52.6	14.7	65.4	15.4	-2.80	0.01
MCA right	52.5	14.6	62.6	13.8	-2.31	0.03
Average Drop	15.6	3.4	18.3	5.4	-1.84	0.07
ARI	4.8	1.1	4.7	1.0	0.04	0.84
ASI	8.0	6.8	6.6	6.4	0.65	0.52
AI-IV	127.0	15.5	120.4	15.5	1.31	0.20

RT = radiotherapy; ABP = arterial blood pressure; BPM = beats per minute; MCA = middle cerebral artery; ARI = autoregulatory index; ASI = autoregulation slope index; AI-IV = autoregulation phase one-to-four

Hypothesis 5: Individual treatment group differences

There was no difference between the CM and surgery only groups in CBFV. Nor was there a difference between the RT only and the surgery + RT groups. The two groups with smaller N size (CM and RT only) were not significantly different from any other group, possibly due to their lower statistical power. However, there was a statistically significant difference between the larger groups with the surgery + RT group demonstrating significantly faster CBFV in both the left (52.1cm/s versus 66.9cm/s; $t = -2.91$, $p = 0.007$) and right (50.5cm/s versus 61.5cm/s; $t = -2.20$, $p = 0.04$) MCAs. This shows that the overall effect of RT described above was not primarily due to the inclusion of patients with NPC. It can be found when comparing patients treated with surgery for NFA, where the only treatment difference is the presence or absence of RT. Hypothesis 5 was upheld.

Hypothesis 6: Resting CBFV and Neurocognitive Functioning

The left MCA CBFV significantly correlated with the auditory recognition delayed discrepancy score ($r = 0.41$, $p = 0.005$) and with the Processing Speed Index ($r = 0.34$, $p = 0.02$), whilst the right MCA CBFV correlated with the executive function Trail Making 'switching – lower processes' contrast score ($r = 0.32$, $p = 0.04$). This would indicate better

cognitive function scores for people with higher CBFV. The correlations between CBFV and memory discrepancy scores are shown in Table 26.

Two CBFV scores were correlated against 19 cognitive scores, giving a total of 38 correlations. Therefore two significant correlations would be expected by chance. Accordingly, it is not possible to dismiss the interpretation that these significant correlations might represent type 1 errors.

Table 26: The correlations between CBFV and CA data and the neurocognitive results

		MCA left	**MCA right**	**ARI**	**ASI**	**AI-IV**
A I Disc	Pearson Correlation	0.18	0.15	-0.01	-0.02	-0.32
	Sig. (2-tailed)	0.24	0.34	0.94	0.89	0.053
V I Disc	Pearson Correlation	-0.14	0.17	0.19	0.13	-0.18
	Sig. (2-tailed)	0.35	0.28	0.24	0.47	0.30
A D Disc	Pearson Correlation	0.22	0.19	-0.01	-0.04	-0.25
	Sig. (2-tailed)	0.14	0.23	0.94	0.84	0.14
V D Disc	Pearson Correlation	-0.09	0.18	0.04	-0.02	-0.44
	Sig. (2-tailed)	0.55	0.24	0.79	0.93	0.008*
A R D Disc	Pearson Correlation	0.41	0.17	0.19	0.12	-0.10
	Sig. (2-tailed)	0.005*	0.28	0.25	0.48	0.57
W M Disc	Pearson Correlation	-0.05	0.08	0.04	-0.26	-0.23
	Sig. (2-tailed)	0.74	0.61	0.82	0.13	0.19

* indicates $p \leq 0.05$; MCA = middle cerebral artery; ARI = autoregulatory index; ASI = autoregulation slope index; AI-IV = autoregulation phase one-to-four; A = Auditory; I = Immediate; Disc = Discrepancy; V = Visual; D = Delayed; R = Recognition; W M = Working Memory

Hypothesis 7: CA and Neurocognitive Functioning

There was only one significant correlation between CA and neurocognitive function. The AI-IV score negatively correlated with the visual delayed discrepancy score ($r = -0.44$, $p = 0.008$), suggesting that patients with poorer CA have better visual delayed memory. This is shown in Table 26. Given that 57 correlations were conducted, it is most likely that this represents a type 1 error. Therefore hypothesis 7 was not upheld.

Discussion

The three treatment groups of pituitary patients had similar hormone levels, whilst the RT only group had significantly more TSH. It should be noted that this result was to be expected.

The deficit in TSH renders the meaning of the negative correlation in men between general intellectual functioning and TSH questionable. TSH levels usually predict thyroxine levels, which act upon cells. However, in patients with TSH deficit, who are taking thyroxine replacement, this link is broken. Therefore this correlation is probably either a type 1 error or reflects the action of a confounding variable. The correlation between T4 and verbal intelligence scores somewhat differs from the previous literature. Whilst an association between verbal cognitive performance and T4 has often been found (Begin, Langlois, Lorrain, & Cunnane, 2008; Bono, Fancellu, Blandini, Santoro, & Mauri, 2004), this is usually for EFs such as verbal fluency rather than verbal intelligence. This result may therefore represent a variation on previous findings or a type 1 error. The correlation between T4 and working memory has been previously demonstrated by experimentally inducing subclinical hypothyroidism (Samuels, Schuff, Carlson, Carello, & Janowsky, 2007a) and has also been found in hypothyroid patients (Samuels et al., 2007b). However, cognitive deficits have also been attributed to hyperthyroidism (Yudiarto et al., 2006) so whilst these results suggest that patients might benefit from increased thyroxine replacement, care must be taken to achieve an appropriate balance.

The negative association between baseline cortisol levels and EFs in patients who do not require cortisol replacement has frequently been previously found for the general population (McCormick, Lewis, Somley, & Kahan, 2007; Lee et al., 2007) and for people with depression (Egeland et al., 2005). In tests on rats it has been found that elevations in cortisol level impair dopamine metabolism (Lindley, Bengoechea, Schatzberg, & Wong, 1999). The correlation between cortisol 30 minutes after SST and recognition memory is perhaps a type 1 error as the SST was conducted several hours before the recognition memory test, by which point cortisol levels would have returned to normal due to its half-life of 80-120 minutes (Peterson, 1971). In regards to the final positive correlation between amount of hydrocortisone replacement taken daily and VIQ, there is very little literature to inform the meaning of this result. Whilst hypocortisolism from childhood is associated with lower IQ scores in adults (Johannsen et al., 2006), this is not an appropriate comparison for patients with adult onset hypocortisolism. Nor is it reasonable to assume that patients on lower amounts of hydrocortisone are experiencing hypocortisolism. More research must be conducted before the reasons for this correlation can be hypothesised. It has also proven difficult to discount the possibility of type 2 errors in the non-significant correlations, due to the patient sample being split into patients on replacement and patients who had an SST. This

has reduced the N size used in the statistics and their subsequent power. However, it was not considered appropriate to stop any of the patients' medication on the day of testing and so this split became necessary.

The most surprising result is the gender difference found for memory discrepancy scores. Men performed significantly more poorly than women. This highly significant result would not be expected in the general population. This result could have occurred for two reasons. Firstly men had significantly poorer hormonal control with a greater number of results outside the normal range of their peers. The combination of abnormal hormone levels may have resulted in an overall difference between men and women. Secondly, the gender difference suggests the involvement of inappropriate levels of sex hormone replacement in men. The most noteworthy hormone present in the medial temporal lobe (MTL) is estrogen. In men, 60-75% of their estrogen is produced by the conversion of testosterone into estrogen by a process called aromatisation (Longcope, 1982). Aromatisation occurs within certain types of cell, such as brain or bone matter, rather than in the blood stream. Therefore it is not appropriate to attempt to measure estrogen levels in brain tissue by using a blood test, as circulating estrogen levels are not indicative of cellular levels within MTL tissue. This is unfortunate, as it prevents concrete conclusions on the potential effect on immediate memory of estrogen levels in the MTL of men in our sample. However, due to the wide ranging effects that estrogen has on the MTL and especially the basal forebrain, it is still the sex hormone most likely to affect immediate memory. Estrogen treatment of ovariectomized rats caused an increase in the cell soma size of cholinergic neurons in the band of Broca and in the basal nucleus of Meynert, which are areas that innervate the neocortex and amgdala. This was accompanied by improved performance on the Barnes Maze (Ping, Trieu, Wlodek, & Barrett, 2008). Estrogen also regulates the expression of the neurotrophin brain-derived neurotrophic factor (BNDF) in the hippocampus. BNDF helps maintain existing neurons whilst encouraging the growth of new neurons (Acheson et al., 1995). In addition to these effects, it is also thought that the presence of alpha type estrogen receptors in smooth muscle and vascular endothelial cells may contribute to the protective effect that estrogen has on blood vessels (Iafrati et al., 1997; Chen et al., 1999). These findings demonstrate the importance of appropriate hormone replacement, especially for sex hormones. However, it can be difficult for endocrinologists to find the right balance for each individual patient without the benefit of pre-morbid blood tests to guide them. The population normal range is

used instead; however this may not be the optimum level for some individuals leading to hyper or hypo hormone levels.

The faster CBFV in patients treated with RT could be due to vessel narrowing and loss of vessel flexibility. This suggests a reason for the increased risk of mortality from cerebrovascular disease in persons treated with RT (Tomlinson et al., 2001). RT to blood vessel walls can cause vasculopathy, and even without these creating microemboli, tissue necrosis, inflammation and scarring may still occur, compromising the diameter of the blood vessels and their ability to respond flexibly to changing blood flow requirements (Louis, McLoughlin, & Wortzman, 1974; Silverberg, Britt, & Goffinet, 1978). The lack of microemboli present suggests that patients are not at a higher risk of stroke from this cause. Similarly, the cognitive deficits noted in this study are unlikely to be the consequence of small vessel damage caused by microemboli.

The average arterial blood flow drop in mmHg achieved during the rapid deflation of thigh cuffs was typical of the current literature (Tiecks et al., 1995; Birch & Morris, 2003; Kolodjaschna et al., 2005). The CA measures were also within normal ranges. It is concluded that CA dysfunction is not the cause of the higher rate of cerebrovascular disease found in patients treated with RT. There was also a lack of correlation between CBFV and CA data and the cognitive data. The three correlations that were present suggested that faster CBFV and poorer CA had a positive impact on cognition. This is unlikely and thus these results may represent type 1 errors.

For the first time, this study has examined the associations between cognitive deficit and physiological variables on the day of testing. Thyroxine and cortisol were implicated as the hormones with the most significant impact on cognitive function. A sex difference for memory function may be a result of poorer hormonal control in men or be due to the amount of testosterone aromatised into estrogen locally in the brain. RT may be implicated in causing increased CBFV, however, CA has been found to be intact. For patients these results highlight the importance of reaching a stable hormone level within the normal range. Patients with lower levels of T4 replacement who are experiencing difficulties with working memory may wish to discuss an increase in dose with their Endocrinologist.

Section 4 – Functional Magnetic Resonance Imaging

All three treatment groups of patients with pituitary adenoma demonstrate impairment in immediate memory (IM) (see Memory' chapter). However, different treatment groups have experienced IM deficit in differing modalities of stimuli presentation. The conservatively managed and Surgery + RT groups have shown IM deficits for visually presented material, whilst the Surgery only group have shown the converse, experiencing IM deficits for only verbally presented material. This may be because whilst the WMS-III has good test reliability, the construct validity for the verbal-visual dichotomy is questionable, and the manufacturers have chosen to drop eight subtests when updating the test battery into the WMS-IV (Holdnack & Drozdick, 2009).

Intragroup as well as intergroup variability was also found. Within each group some patients achieved memory scores commensurate with the scores predicted from their FSIQs, whilst others scored up to three standard deviations below their predicted scores. The variance within treatment groups cannot be explained by correlating the level of impairment with other treatment variables such as time since surgery or RT, by the number of hormone replacements each participant requires or by blood hormone levels for many variables (see 'Physiology' chapter).

Whilst the WMS-III allows the assessment of patients' cognitive deficits, it does not investigate the reasons that these deficits occur. Nor can it define why some patients do not experience IM deficit whilst others do. Difficulties reporting back the given stimuli could indicate a deficit in encoding, or a deficit in retrieving stored information. Alternatively, some patients might successfully employ memory strategies which mask encoding or retrieval impairment. This would involve the greater engagement of executive functions (EFs) as compensatory processes, but would only show on the WMS-III as intact memory performance. Whilst this performance is technically intact, the brain regions that subserve memory may not be functioning as normal. To examine the reasons for a patient's poor memory performance, it is necessary to use brain imaging equipment which allows the researcher to measure the brain's response to and processing of a task, as well as performance on the task itself. Functional Magnetic Resonance Imaging (fMRI) allows the experimenter to

monitor changes in blood flow to different areas of the brain in response to a cognitive task. In the final experimental chapter, the methodology of fMRI will be explained, followed by the task used in an attempt to elucidate if there is a universal reason for the IM deficit experienced by some patients with pituitary adenoma.

Introduction to the fMRI Technique

Functional Magnetic Resonance Imaging (fMRI) is an imaging technique that overlays information about cerebral blood flow onto a structural scan of the brain that can be acquired using MRI. This is done by measuring the blood-oxygen-level dependent response (BOLD). An increase in blood flow to a particular area of the brain causes an increase in the concentration of oxygenated haemoglobin, which results in a higher BOLD signal intensity. Areas experiencing greater signal therefore have higher concentrations of oxygenated blood (Kwong et al., 1992).

Neurons in the brain do not store energy reserves, instead taking nutrients directly from the blood. When a region of the brain becomes more active in order to complete a task, the neurons use a greater amount of oxygen from the blood. Blood flow increases to this area to compensate for the oxygen use. This is known as the haemodynamic response. The increase in oxygen at the site of greater neuronal firing peaks at approximately 4-5 seconds, before returning to baseline. Over many repetitions of a task, a statistically significant difference in BOLD signal can be found between areas of the brain involved with the task, and areas which are not, as the BOLD signal is a correlate of neuronal activity (Logothetis, 2002). The use of fMRI allows baseline levels of regional blood flow to be identified. When the participant then attempts a cognitive task, the consequent change in regional blood flow can be attributed to the completion of the task. The ability to combine behavioural and anatomical data can give more specific insights into which brain regions are involved in the execution of different cognitive functions. For individuals demonstrating impairment of a certain cognitive function, fMRI may help elucidate the nature of the deficit and/or region of damage.

Differences between the regional blood flow demonstrated by individuals who achieve normal task performance and individuals showing impaired task performance may indicate the cause of this performance discrepancy, or alternatively, it may highlight brain areas in the normally performing individuals which are compensating for the underperformance of other

brain structures. The use of compensatory strategies is unlikely to be found in the neurologically intact population. However, the selective use of strategies by some patients to achieve normal performance may explain any differences found within a group of patients who all received the same treatment for the same condition.

Previous use of fMRI to advance the knowledge of memory systems

The main body of research using the fMRI technique is concerned with discovering which brain regions are involved in which cognitive tasks. Damage to brain structures that creates cognitive impairment has also been extensively studied using this technique (Lenzi, Raz, & Pantano, 2008; Pineiro & Matthews, 2001; Cook, Bookheimer, Mickes, Leuchter, & Kumar, 2007). A range of evidence now exists, based on different cognitive tasks, which has aimed to label the different structures in the brain that work in conjunction to encode and retrieve information. This evidence examines not only the brain's ability to recall prior material but also differentiates between medial temporal lobe (MTL) regions which process the content of the information and the context in which it occurred, such as location, colour and size (Wagner, Desmond, Glover, & Gabrieli, 1998; Zorrilla, Aguirre, Zarahn, Cannon, & DEsposito, 1996). Similar yet different processes such as familiarity and recollection have also been mapped onto different brain regions (Yonelinas et al., 2002; Ranganath et al., 2004).

Using the fMRI technique will allow the investigation of why some patients with pituitary adenoma perform significantly worse than others on tasks of immediate free recall. It may be that certain brain regions are not as active as would be expected during the IM task, and so poor performance results, or that other patients with normal performance are using their intact EFs to compensate for MTL underperformance. The different brain regions which are associated with various aspects of memory are outlined below, followed by the previous fMRI research into the effects of endocrine dysfunction on cognitive function. The IM task used in the current study is then described, together with a description of the brain regions that are expected to be activated by the task.

Brain regions associated with the encoding and retrieval of new information

Several fMRI studies have found that the left hippocampus is activated during both memory encoding (Henke, Buck, Weber, & Wieser, 1997; Henke et al., 1999; Lepage, Habib,

Cormier, Houle, & McIntosh, 2000; Yancey & Phelps, 2001) and retrieval (Giovanello, Schnyer, & Verfaellie, 2004; Preston, Shrager, Dudukovic, & Gabrieli, 2004). It has been hypothesized that anterior regions of the MTL have greater involvement in memory encoding whilst posterior regions are more involved in retrieval (Lepage, Habib, & Tulving, 1998; Schacter & Wagner, 1999) and that the hippocampus forms a converging region involved in both processes (Prince, Daselaar, & Cabeza, 2005). The regions of the MTL which appear to be the most critical for declarative memory formation are the hippocampal region including the dentate gyrus, CA 1-3 and the subicular complex, and the cortex of the parahippocampal gyrus comprising the entorhinal, perirhinal and parahippocampal cortices (Ranganath, Johnson, & D'Esposito, 2003). It has also been found that the success of encoding of information in specific brain regions is dependent upon the level of connectivity of that region with the hippocampus. Ranganath et al. (2005) found that the perihinal cortex, anterior inferior temporal cortex, medial orbitofrontal cortex, ventral frontopolar cortex, temporopolar cortex, insula and caudal ventromedial cortex all showed differential connectivity with the hippocampus during a short delay between encoding and retrieval. Enhanced coupling (greater mutual activation) between the perihinal cortex and the hippocampus was associated with successful memory retrieval. During retrieval, areas such as the parahippocampal cortex and posterior hippocampus (Prince et al., 2005) are most active. The prefrontal cortex is also typically activated during memory retrieval (Cabeza & Nyberg, 2000). These studies demonstrate the regions of the brain that would be expected to be activated during a short-term memory task. Different regions would be expected to exhibit greater neuronal firing and therefore oxygen requirements during encoding (anterior MTL) and retrieval (posterior MTL). It is also evident that greater activation is seen in these regions during successful memory formation (Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005).

Content versus Context memory

Memory relies on the ability to represent content and contextual information. Typically the various features (colour, shape, size) that comprise the stimuli to be encoded are referred to as content information. The term contextual information is generally used to refer to information that does not form a physical part of the stimulus to be encoded, but can still be used in the later identification of that stimulus; for example, remembering where on a computer screen a stimulus was presented, or remembering when it was presented (Jacoby, 1991). Some modern models of stimuli recognition posit that qualitative context information,

such as when the stimulus was encoded can only be retrieved through recollection if the signal level was great enough at encoding. If the signal falls below this level, the individual will not be able to retrieve this information (Yonelinas, 2002). Therefore, a stimulus' context information is considered more difficult to recall than the content of that stimulus. During the recognition phase of a task, a sense of familiarity alone provides enough information to allow a participant to indicate whether they have seen a stimulus previously. This is sufficient for stimuli which are only presented once as a target throughout the experiment; and must only be recognised among novel distracters. However, if the same stimuli are used repeatedly across different trials, sometimes as targets, sometimes as distracters, then the familiarity of a stimulus becomes increasingly less useful for making a target/distracter decision. Instead, participants must use the temporal context ('how recently did I see this item?') of the stimuli to make the target/distracter decision (Yonelinas, 2002). This allows the recollection of both the content and the more taxing context information of a stimulus to be tested within the same experiment.

Context memory can also be assessed separately from content memory by pairing stimuli at presentation and then asking participants to differentiate between pairs of items that are correctly matched and items that have been re-paired differently (Rhodes & Donaldson, 2007). Ranganath et al. (2004) found greater activation in the anterior prefrontal cortex and the hippocampus during an associative memory task than during a stimuli and procedure matched working memory task. This suggests that these brain regions are required for remembering the context in which stimuli appeared. Gold et al. (2006) found that activity in the hippocampal region, perirhinal cortex, and parahippocampal cortex was associated with both content memory and source memory. Therefore, these regions might be activated by a memory task, regardless of whether it measures content or context information.

fMRI studies of memory during endocrine dysfunction

There have been no previous fMRI studies directly assessing the effects of pituitary disease on cognitive function. However, researchers have examined the effects of hormone hypersecretion or hypoproduction on various aspects of memory. For instance, Zhu et al. (2006) used an 'n-back' task to test brain activity relating to working memory. Participants were grouped by their thyroxine levels. The groups were comprised of hyperthyroid, hypothyroid, subclinical hypothyroid (SCH) and euthyroid patients. A second group of SCH patients also participated after six months of thyroxine replacement. There was no significant

difference in group performance on the easiest version of the task (0-back). However, on the more difficult 1-back condition, the hypothyroid patients performed less accurately than the other groups. On the most difficult 2-back condition, the SCH group performed less accurately than the euthyroid and hyperthyroid groups, whilst the hypothyroid group performed worse than any other group ($p<0.001$). In contrast, the post thyroxine replacement SCH group did not show poorer accuracy than the other groups, indicating that working memory deficits caused by low thyroxine levels are reversible. The n-back task produced activation in a frontoparietal network of regions including the middle/inferior frontal gyri; the bilateral dorsolateral prefrontal cortices; the bilateral premotor areas; the supplementary motor area and anterior cingulate cortex; and bilateral parietal areas, regardless of task difficulty. However, when task load increased and the task became more difficult, the BOLD response changed in both the frontal and the parietal area of the euthyroid, hyperthyroid and SCH post thyroxine replacement groups. The SCH group only demonstrated BOLD changes in the parietal area and bilateral premotor areas. Whilst the results from the euthyroid and the hyperthyroid groups are consistent with previous fMRI studies on healthy participants (Owen, McMillan, Laird, & Bullmore, 2005), the SCH and hypothyroid groups demonstrated abnormal functions in the frontal gyri, implying that their working memory is impaired by SCH. This study indicates that if patients are not on an adequate thyroxine replacement dose, we may expect to see reduced activation in the frontal cortex accompanying poor task performance.

There is a relatively high density of cortisol receptors in the prefrontal cortex, amygdala and hippocampus (Gold, Drevets, & Charney, 2002) and cortisol can affect memory performance. Chronic hypercortisolism has a deleterious effect on the ability to remember new information (Forget et al., 2000; Hook et al., 2007; Starkman et al., 2001), however, an acute rise in cortisol during memory encoding can enhance recall performance of emotionally arousing stimuli, relative to neutral stimuli (Buchanan & Lovallo, 2001; Kuhlmann & Wolf, 2006). It has been proposed that high cortisol levels require the concurrent presence of noradrenaline in the amygdala in order to increase the amount of information remembered (Roozendaal, 2000; Roozendaal, 2002; Roozendaal et al., 2006). The use of a betablocker, propranolol, has been shown to decrease amygdala activation for emotional stimuli but not for neutral stimuli, suggesting that amygdala activation is indeed noradrenergic dependent (Hurlemann et al., 2005; Strange, Hurlemann, & Dolan, 2003). Van Stegeren et al. (2007) repeated this experiment but included a recall test of the stimuli two weeks after they were encoded inside

the scanner. Participants attended the experiment on two consecutive days to take part in a double-blind placebo-controlled protocol. Under placebo, high emotion stimuli were remembered more frequently two weeks later than neutral stimuli. This was not reported under betablockade. For highly emotional pictures, participants with naturally higher cortisol demonstrated greater amygdala activity in the placebo condition. In the betablockade condition, amygdala activity was not significantly different for emotional compared to neutral pictures. Participants with naturally low cortisol, did not show an amygdala activation difference comparing placebo to propranolol. This again suggests that a combination of high cortisol levels and noradrenaline in the amygdala is required for a memory encoding enhancement to occur for emotion inducing stimuli. The study also suggests that greater amygdala activation is associated with more successful memory encoding.

The majority of patients with pituitary adenoma have growth hormone deficiency (GHD) (Littley et al., 1989). Unlike other hormone deficiencies, some adults with GHD do not receive GH replacement. Only one study has used fMRI to examine the effect of GH replacement on patients with GHD (Arwert et al., 2006). They conducted a double-blind placebo-controlled study, conducting memory testing of patients with child-onset GHD before and after six months of GH replacement, both in, and more extensively, outside the scanner. In response to the working memory task they used, increased activation occurred in the DLPFC, the VLPFC, the anterior cingulate, the parietal, occipital and motor cortices, and the right thalamus. After six months of GH replacement, activation in the VLPFC was observed in the group given GH replacement compared to the group given placebo which indicated a decreased amount of effort required to complete the task. This was accompanied by an improvement in working memory and one hour delayed recall, and was thus thought to indicate decreased effort and more efficient functioning by the neural system involved in the tasks.

These studies indicate some of the brain regions which may be underactive if a patient's hormone replacement is suboptimal. This may even occur if a patient has hormone levels replaced to within the population normal range, but that this level is suboptimal for that individual.

IM task to be employed in this study

Within the fMRI scanner, it is preferable to use tasks which do not require speech as any movement of the head inside the scanner can disrupt the magnetic signal used to measure BOLD response. This negates the use of the verbal memory subtests from the WMS-III inside the scanner, and therefore does not allow a direct examination of the causes of the patients' previous poor memory performance on the WMS-III IM tasks. Therefore, an alternative task must be used that still taxes memory to varying degrees, but only requiring a button press response from participants. The task used is outlined in the methods section below. Non-words are used as stimuli. These are letter combinations that could feasibly be words but don't have any semantic meaning in the English language. Two conditions were created; one was intended to be more difficult than the other. In both conditions, six non-words were shown and the participant was asked to remember them. During the test phase, five of the six non-words were represented amongst five distracter items. Participants then had to indicate which of the ten words had been previously presented on that trial, and which had not. The easier condition measures content memory. Novel items are used on every trial so the participant must only decide whether or not a non-word seems familiar to them during recognition. On the more difficult condition, measuring context memory, the same group of non-words were repeated across trials. Sometimes a non-word appeared as a target to be remembered, and on other trials, the same non-word might be used as a distracter during the test phase. This condition was considered harder, because all repeated words would seem familiar and so a participant must instead make a decision on how recently they saw an item, instead of relying on its familiarity. Performance on both conditions is expected to decrease as the task progresses. This is due to proactive interference from earlier items interfering with the processing of later items (Kane & Engle, 2000). This occurs even in the novel items condition, as visually similar earlier items reduce the perceived novelty of later items.

Hypotheses:

1. The control group of patients who performed normally (NPG) on the WMS-III will perform better on the current IM task than patients who showed impaired performance (IPG) on sections of the WMS-III for novel/no-overlap stimuli.

2. Both the NPG and the IPG will perform at similar levels on the IM task for repeated/overlap stimuli.

3. The NPG will demonstrate greater cerebral blood flow (CBF) than the IPG in some areas of the medial temporal lobe; specifically the anterior MTL at encoding and the posterior MTL at retrieval of stimuli. This will suggest that the IPG show poorer IM performance due to the underperformance of MTL regions.

4. If hypothesis 3 is not found to be true, then the NPG will demonstrate greater CBF in the frontal lobes during encoding and retrieval. This will suggest that all patients have poor MTL function, but that patients performing IM tasks at normal levels are using compensatory strategies to achieve this.

Method

Participants

Six participants took part in the study. They were recruited from the previous cohort of patients described in the General Methods chapter based on their performance on the WAIS-III and WMS-III. The participants' demographic and treatment data are shown in Table 27 with the cognitive functioning scores pertinent to participant selection. All participants were required to have at least an average FSIQ and have previously received transsphenoidal surgery to debulk or remove their pituitary adenoma on only one occasion. Three participants had normal WMS-III memory scores with an IM index that was both commensurate with their FSIQ and within the 'normal' classification for the general population. These patients were termed the normal performance group (NPG). Three participants had impaired IM defined as a score that was at least one standard deviation below both the participants' FSIQ and the IM score predicted by the FSIQ, and within the 'below average' classification or lower. These patients were termed the impaired performance group (IPG).

Table 27: Participants details

Participant Number	**1**	**2**	**3**	**4**	**5**	**6**
Group	IPG	IPG	IPG	NPG	NPG	NPG
Sex	M	M	M	F	M	F
Age	64	51	57	46	45	40
FSIQ	126	104	118	104	110	102
IM score	87	84	73	102	110	96
Hormone Replacements	0	2	4	5	3	2
RT	No	No	Yes	No	No	Yes

IPG = Impaired performance group; NPG = normal performance group; RT = Radiotherapy

Stimuli

Non-words, taken from a computer generated database created by Müeller (2005), were all pronounceable and were 4, 5, or 6 letters in length.

Task Design

The task was designed by O'Sullivan and Humphyreys (2009). There were two conditions used: 'Overlap' of non-words and 'No overlap' of non-words. During the 'No overlap' condition the stimuli used were novel on every trial. During the 'Overlap' condition a small pool of non-words were used and these non-words were repeated across trials, on some trials being targets, on other trials being distracters. The 'Overlap' list consisted of 12 non-words. 6 of the non-words were presented 13 times and 6 of the non-words were presented 14 times during the scanning period: four or five times as a target and four or five times as a distracter. Performance in the no-overlap condition is more dependent on the ability to represent the content information of the stimuli. It is not necessary to remember when the non-word was presented; only that it has previously been seen. Performance in the overlap condition is more dependent on the ability to associate each item with the temporal context of its presentation.

Procedure

Participants were well practiced on the task before going in the scanner. The 'Overlap' stimuli were used during the task practice as well as during scanning, in order that participants would be familiar with these non-words from the first trial inside the scanner. The 'No overlap' practice stimuli were different from those used during the real task. In the scanner, the experiment was divided into three matched runs. Three trials of each condition

were presented in six sub-blocks within each of three runs/scans. The order of condition-presentation was randomised. Following the presentation of a fixation cross for two seconds, each trial took the following form: Six non-words appeared sequentially, with each item remaining on the screen for two seconds. A red fixation cross was then presented for two seconds to signify the start of the recognition test. During the recognition test, five targets from the encoding trial were interspersed among five distracters. These items were sequentially presented for two seconds each in a random sequence. Participants were instructed to press one key if they recognised an item as a target, and another key if they recognised an item as a distracter. A jittered inter-stimulus-interval of range two-six seconds followed each event.

Image acquisition and analysis

FMRI images were acquired using a 3T Philips Achieva MRI scanner, with an ascending multislice gradient echo EPI sequence (EPI factor 47). Each of the three runs consisted of 330 dynamics, and duration of 685 seconds. One volume of data was collected in each dynamic. Each volume consisted of 34 axial slices collected from the whole brain, with a field of view (FOV) of 225 x 117.5 x 225, and a slice thickness of 2 mm, with a 1.5 mm slice gap (matrix = 92 × 88, TR = 2 sec, TE = 35 msec, flip angle = 80°). A standard structural scan was also acquired (slices = 175, resolution 288 x 288). Analysis was performed using FSL 4.1.2 with the following standard pre-processing steps: motion correction, spatial smoothing (FWHM = 5 mm), slice-timing correction, and nonlinear high-pass temporal filtering (90 s). Statistical analysis used the FEAT and FLAME analysis packages (Woolrich, Ripley, Brady, & Smith, 2001).

Both the novel and repeated items had four types of events associated with it: correctly encoded items (the time series was back-sorted to exclude incorrectly recognised items); correctly recognised targets; correctly recognised distracters; delay between presentation and forced-choice response. The primary contrasts within each individual compared activation at each type of event as a function of being either novel or repeated items (Encode novel items> Encode repeated items; Encode repeated items > Encode novel items; Recognise novel targets > Recognise repeated targets; Recognise repeated targets > Recognise novel targets; Recognise novel distracters > Recognise repeated distracters; Recognise repeated distracters > Recognise novel distracters; Delay novel items > Delay repeated items; Delay repeated items > Delay novel items). In the next step of the analysis, the within participant contrasts

within each group (impaired, non-impaired) were averaged in a Fixed Effects model with cluster correction in order to compare the contrasts across the two groups. A region of interest mask was created encompassing the frontal lobe and MTL. This was used at the point the data was averaged to increase the power of the calculations.

Results

Behavioural data

Hypothesis 1 - Novel items

The normally performing group of participants (NPG) correctly indentified 78% of novel targets, and 93% of novel distracters. The impaired performance group (IPG) correctly identified 74% of novel targets and 84% of novel distracters. There was no significant difference between the two groups on total correct percentages although there was a trend towards significance for the distracter items overall percentage correct ($t = -1.88$, $p = 0.07$), with the NPG achieving a better score. Whilst the NPG improved their performance over the course of the experiment, the IPG showed the expected drop in performance across the blocks. This change was not significant for either group. However, by Block 3, this change resulted in the NPG achieving significantly more correct classification of stimuli than the IPG for both targets ($t = -2.46$, $p = 0.03$) and distracters ($t=-2.45$, $p = 0.03$). This is shown in Table 28.

There was no difference between the groups for the reaction times taken to categorise targets ($t = -0.49$, $p = 0.63$) or distracters ($t = -1.60$, $p = 0.13$). The NPG's increase in accuracy across blocks was accompanied by a decrease in reaction time; whilst the IPG's decrease in accuracy was accompanied by a corresponding increase in reaction time, showing that as the IPG found the task increasingly more difficult, they took longer to make a classification choice. By the third block the difference in reaction time was significant for distracter items ($t = -3.13$, $p = 0.006$) but not for target items ($t = -1.53$, $p = 0.15$). This data are also shown in Table 28.

Table 28: The percentage of correct responses and the reaction times for those responses for the novel items/no-overlap condition

	Targets (%)				Distracters (%)			
	Block 1	Block 2	Block 3	Overall	Block 1	Block 2	Block 3	Overall
NPG % correct	75	73	86*	79	94	90	96	93
NPG RT (s.d.)	1126.8 (127.7)	1122.1 (64.6)	1073.7 (121.4)	1107.5 (97.2)	1131.3 (143.1)	1107.5 (89.3)	1063.5* (76.1)	1100.8 (97.2)
IPG % correct	83	70	70*	74	88	80	82	83
IPG RT (s.d.)	1108.9 (104.6)	1118.3 (107.7)	1165.4 (142.2)	1130.9 (106.7)	1078.4 (139.1)	1267.0 (173.7)	1307.0* (244.6)	1217.5 (196.3)

* indicates $p<0.05$; NPG = Control group; IPG = Impaired group; RT = Reaction time; s.d. = standard deviation

Hypothesis 2 - Repeated items:

The NPG correctly identified 80% of repeated items when they were targets on a trial and 72% of repeated items when they were used as distracters. The IPG correctly identified 85% of repeated items when they were targets on a trial and 62% of repeated items when they were used as distracters. There were no significant differences between the groups on overall repeated item accuracy ($t \leq -1.37$, $p \geq 0.18$) or for accuracy on any individual block ($t \leq -1.48$, $p \geq 0.16$).

There was no difference between the groups for the reaction times taken to categorise targets ($t = 1.25$, $p = 0.23$) or distracters ($t = 0.46$, $p = 0.65$). There was also no difference between the groups for reaction times within each block ($t \leq 1.06$, $p \geq 0.31$) or within each group across blocks ($t \leq -3.50$, $p \geq 0.07$). This is also shown in Table 29.

Table 29: The percentage of correct responses and the reaction times for those responses for the repeated items/overlap condition

	Targets				Distracters			
	Block 1	Block 2	Block 3	Overall	Block 1	Block 2	Block 3	Overall
NPG % correct	78	84	78	80	80	73	63	72
NPG RT (s.d.)	1181.5 (96.3)	1127.3 (39.6)	1081.9 (209.7)	1130.2 (124.8)	1172.3 (91.0)	1260.4 (44.4)	1269.8 (62.2)	1234.2 (75.5)
IPG % correct	87	85	84	86	64	68	56	62
IPG RT (s.d.)	1087.9 (75.4)	1059.9 (134.6)	1026.7 (173.0)	1058.2 (118.9)	1280.6 (245.0)	1231.1 (184.5)	1096.0 (164.4)	1202.5 (192.7)

NPG = Control group; IPG = Impaired group; RT = Reaction time; s.d. = standard deviation

Brain regions activated by the task

In order to assess which brain regions are activated by the different versions a subtraction method is used. In this experiment there are two memory conditions, and so to separate the brain regions involved differentially in content or context memory, one condition must be subtracted from the other and vice versa. Secondly, the brain activation generated by each condition of the task in the NPG is subtracted from the activation generated by the same condition in the IPG, and vice versa, to investigate the activation differences which accompany variations in behavioural performance on the task. The areas showing increased activation for each condition are outlined below. This analysis is achieved by averaging across all blocks for all six participants.

1) Greater activation at encoding for the novel items/no-overlap condition than for the repeated items/overlap condition

Only the anterior cingulate gyrus showed greater activation for the encoding of novel stimuli. This increased activation was bilateral. The size, intensity and location of the activation cluster epicentre are shown in Table 30. The anterior cingulate gyrus is involved in both effortful attentional control and the resolution of conflict tasks (Posner & Rothbart, 2009; Pessoa, 2009; Barch et al., 2001). This indicates that the no-overlap condition generated more conflict, most likely in the form of proactive interference, and required greater attentional control to constantly update working memory with new items.

Table 30: The epicentre of cluster activation for greater activation at encoding in the no-overlap condition than the overlap condition

Cluster Name	**Voxels**	**p(Z)**	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Bilateral Anterior Cingulate Gyrus	3617	2.65E-005	3.54	14	-48	0

2) Greater activation at correct recognition of novel items/no-overlap targets than for the repeated items/overlap targets

Two areas of the brain showed greater activation for the retrieval of no-overlap items than for overlap items. These are shown in Table 31. The paracingulate gyrus was activated bilaterally. This area has been associated with the monitoring of one's own speech (Frackowiak, 2004), but also with the completion of executive function tasks (Fornito et al., 2004). The right planum polare is associated with syntactic processing in speech (Friederici,

Meyer, & Cramon, 2000). The activation of these regions may indicate that memory strategies and frontal lobe processing were required to complete this task, or may simply reflect the internal speech required to rehearse the easily pronounceable non-words.

Table 31: The epicentre of cluster activation for greater activation at retrieval in the no-overlap condition than the overlap condition

Cluster Name	**Voxels**	**p(Z)**	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Bilateral Paracingulate Gyrus	9170	3.06E-011	3.82	6	8	48
Right planum polare	1814	0.01	3.32	54	6	-6

3) Greater activation at correct classification of no-overlap distracters than for overlap distracters

Only the anterior cingulate gyrus showed greater bilateral activation for the correct classification of no-overlap distracters. The cluster epicentre is shown in Table 32. This may indicate that either the no-overlap distracters required more active effort to classify, or that the lower percentage of correct distracter classifications in the overlap condition is a result of reduces activity in necessary brain regions.

Table 32: The epicentre of cluster activation for greater activation for no-overlap distracters than for overlap distracters

Cluster Name	**Voxels**	**p(Z)**	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Bilateral Anterior Cingulate Gyrus	9318	2.23E-011	3.85	2	-2	46

4) Greater activation for the repeated items/overlap condition than for the novel items/no-overlap condition at correct encoding, retrieval, or for distracter items.

No MTL or frontal areas were more activated for the overlap condition than the no-overlap condition at encoding, retrieval or for distracter items. This may suggest that either, contrary to expectation, less effort was required to complete the context element of the task, or that there was greater inter-participant variance for this condition, and so when activation was averaged across participants, it no longer had the power required to survive the subtraction method. However, less overlap distracters were correctly classified than no-overlap distracters, so it may be that the reduced brain activation created the reduced performance.

Brain regions differentially activated in the NPG and the IPG

In this analysis, the same task condition is compared across the two groups. The activation generated by the NPG is subtracted from the activation of the IPG, and vice versa.

1) Greater activation for the IPG than for the NPG during the encoding of no-overlap items

The IPG showed greater activation than the NPG in several regions of the brain. The bilateral paracingulate gyrus was differentially activated, suggesting a greater reliance on executive functions to complete the task. The increased right anterior cingulate gyrus activation indicates greater effort and attention used to complete the task. The increased bilateral superior frontal gyrus is indicative of greater use of working memory and the executive control of working memory (Boisgueheneuc et al., 2006). The increased right supplementary motor cortex activation may is usually thought to be concerned with motor functions but has recently been implicated in working memory during a word task (Roth, Johnson, Raye, & Constable, 2009). The combination of this activation pattern for the IPG, in the presence of significantly poorer third block behavioural performance, suggests that despite increased effort and use of executive processing, IPG patients are still unable to achieve the memory abilities of the NPG for content memory. This is shown in Table 33.

Table 33: areas showing greater activation for the IPG than for the NPG during the encoding of no-overlap items

Cluster Name	**Voxels**	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Bilateral Paracingulate Gyrus	135	3.44	-2	26	44
Right Anterior Cingulate Gyrus	86	2.78	4	34	18
Bilateral Superior Frontal Gyrus	41	1.79	24	8	46
Right Supplementary Motor Cortex	35	2.52	6	6	48

2) Greater activation for the NPG than for the IPG during the encoding of no-overlap items

No greater activation was found for the NPG over the IPG for the encoding of no-overlap items. This may indicate that the NPG required less cognitive resources to achieve better performance on the task.

3) Greater activation for the IPG than for the NPG during the recognition of no-overlap targets

The IPG again showed greater activation than the NPG in several regions of the brain. The anterior cingulate gyrus (large area of activation that also included paracingulate gyrus) and superior frontal gyrus were again more greatly activated, as they were at encoding. Additionally, the frontal pole was activated bilaterally, which is usually associated with the cognitive emotional processing (Feinberg & Keenan, 2005). The bilateral superior temporal gyrus is involved in auditory processing including speech (Bigler et al., 2007) and probably indicates the lower processing of stimuli. The right hippocampus is reliably associated with both encoding and retrieval. It is most likely that the hippocampus was active for both groups, however, using the subtraction method, only the increased activation shown by the IPG was noted. This could indicate that a greater amount of hippocampal metabolism was required to correctly retrieve the stimuli. The putamen is part of the basal ganglia and is centrally involved in motor function (Orrison, 1995) and implicit learning (Grafton, Hazeltine, & Ivry, 1995; Hazeltine, Grafton, & Ivry, 1997; Willingham, Salidis, & Gabrieli, 2002).These regions are shown in Table 34 and Figure 13.

Table 34: areas showing greater activation for the IPG than for the NPG during the retrieval of no-overlap targets

Cluster Name	**Voxels**	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Bilateral frontal pole	792	4.51	40	44	28
Bilateral anterior cingulate gyrus	444	3.91	-2	20	34
Bilateral superior temporal gyrus	159	3.23	64	-2	-2
Left superior frontal gyrus	82	2.31	-16	18	50
Right hippocampus	18	2.13	28	-32	-10
Right putamen	17	2.87	28	0	-6

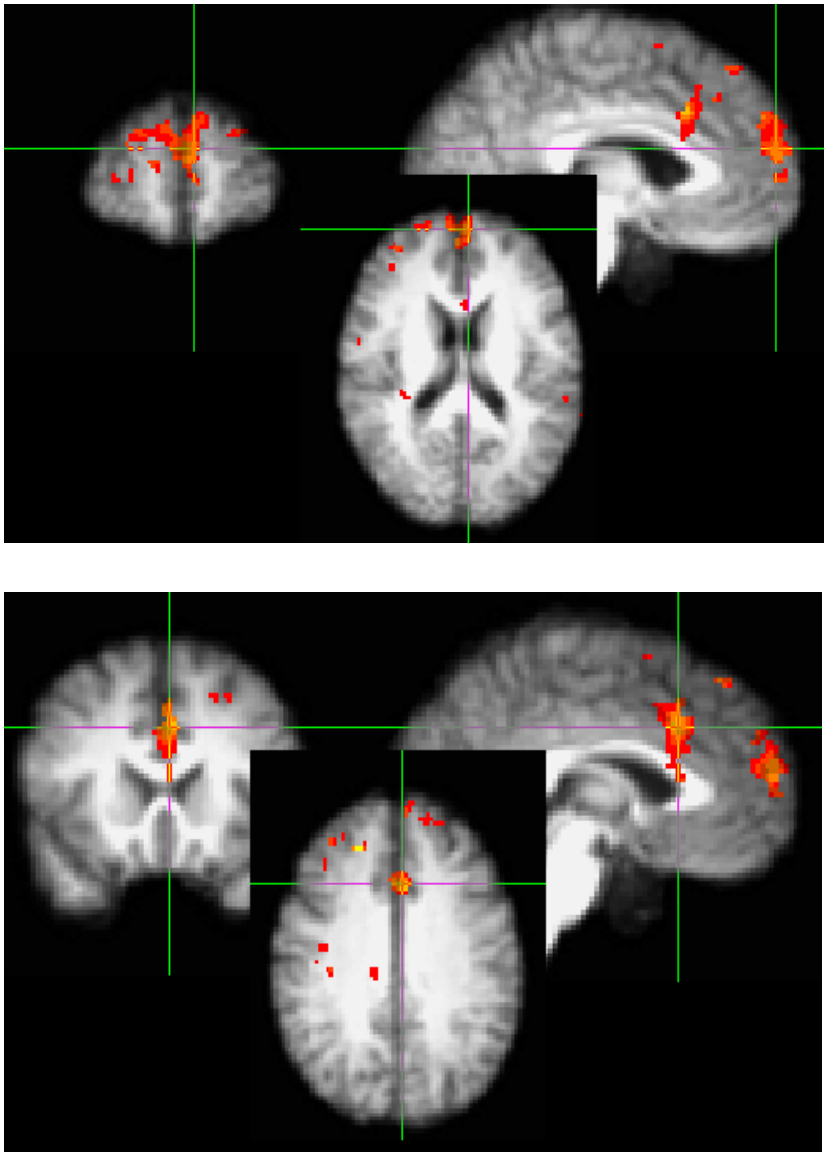

Figure 13: Increased frontal pole activation (top) and anterior cingulate gyrus (bottom) for the IPG than for the NPG during the retrieval of no-overlap targets

4) Greater activation for the NPG than for the IPG during the recognition of no-overlap targets

No brain areas showed greater activation using the cluster corrected Fixed Effects model. However, when a less conservative uncorrected Fixed Effects model is used, a large section of greater left inferior frontal gyrus activation for the NPG than IPG is present. The inferior frontal gyrus is active in many language tasks, however, the left inferior frontal gyrus is also implicated in preventing memory interference (Feredoes et al., 2006). This increased activation may explain the better behavioural performance achieved by the NPG over the IPG. This activation is shown in Figure 14.

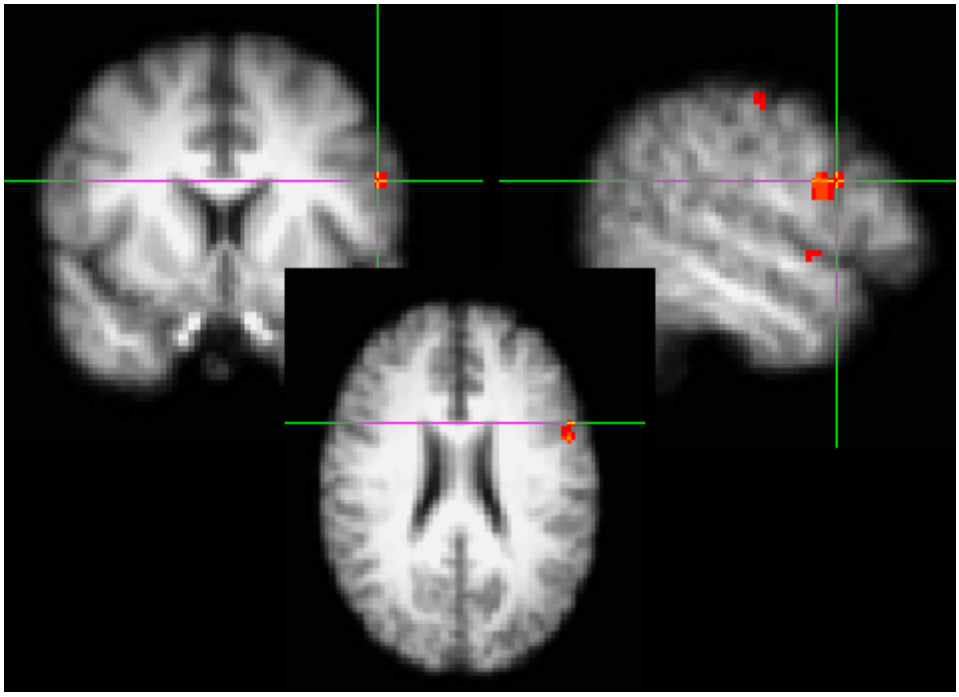

Figure 14: The increased inferior frontal gyrus activation for the NPG over the IPG during the recognition of no-overlap targets

5) Greater activation for the IPG than for the NPG during the recognition of no-overlap distracters

The bilateral anterior cingulate gyrus and the right insular cortex were both more activated for the IPG than the NPG during the recognition of no-overlap distracters. The insular cortex is involved in the perception of speech so this may indicate greater lower level processing of the stimuli (Manes et al., 1999) and the anterior cingulate activation indicates greater effort undertaken to complete the task. This is shown in Table 35.

Table 35: areas showing greater activation for the IPG than for the NPG during the retrieval of no-overlap distracters

Cluster Name	**Voxels**	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Bilateral anterior cingulate gyrus	327	3.49	2	-6	36
Right insular cortex	199	3.35	28	22	8

6) Greater activation for the NPG than for the IPG during the recognition of no-overlap distracters

For the recognition of distracters, several areas were more activated for the NPG than for the IPG. The left inferior frontal gyrus was more activated, again indicating a greater resolution

of proactive memory interference. The left temporal pole is associated with semantic memory (Grabowski et al., 2001). The left precentral gyrus is associated with movement and the right frontal orbital cortex is associated with smell, which may not be relevant to the current task (Rolls, 1999). These areas are shown in Table 36.

Table 36: areas showing greater activation for the NPG than for the IPG during the retrieval of no-overlap distracters

Cluster Name	**Voxels**	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Left inferior frontal gyrus	184	2.94	-46	18	22
Left temporal pole	103	3.67	-48	16	-14
Right frontal orbital cortex	34	2.52	18	14	-14
Left precentral gyrus	15	1.84	-52	6	16

7) Greater activation for the IPG than for the NPG during the encoding of overlap items

No greater activation was found for the IPG over the NPG for the encoding of overlap items.

8) Greater activation for the NPG than for the IPG during the encoding of overlap items

The NPG showed three areas with greater activation than the IPG for the encoding of overlap items. These are shown in Table 37. The right precentral gyrus is involved with the generation of movement and probably relates to the button press required to respond to each item. The right planum temporale is associated with the processing of language (Meyer, 2008) and the right middle temporal gyrus is believed to be involved in perceptual and memory integration (Orrison, 1995). Each of these areas subserves basic elements of the task such as stimuli perception that occur before memory encoding and thus it is unclear why these should be elevated in the NPG. Raised activation at perceptual levels was not accompanied by better behavioural performance.

Table 37: areas showing greater activation for the NPG than for the IPG during the encoding of overlap items

Cluster Name	**Voxels**	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Right Precentral Gyrus	345	3.43	42	-14	58
Right Planum Temporale	42	2.84	60	-34	16
Right Middle Temporal Gyrus	22	3.09	68	-50	8

9) Greater activation for the IPG than for the NPG during the recognition of overlap targets

No greater activation was found for the IPG over the NPG for the recognition of overlap targets.

10) Greater activation for the NPG than for the IPG during the recognition of overlap targets

No greater activation was found for the NPG over the IPG for the recognition of overlap targets.

11) Greater activation for the IPG than for the NPG during the recognition of overlap distracters

No greater activation was found for the IPG over the NPG for the recognition of overlap distracters.

12) Greater activation for the NPG than for the IPG during the recognition of overlap distracters

No greater activation was found for the NPG over the IPG for the recognition of overlap distracters. The lack of differences in activation between the two groups mirrors the similarity in behavioural performance.

Resolution of Proactive Interference

The NPG demonstrated better behavioural performance than the IPG by the third block of trials for the no-overlap condition. Whilst the IPG activated brain areas associated with memory and effortful attention to a greater degree than the NPG, the NPG showed greater activation in areas that resolve memory interference. However, this pattern of results was not present in the overlap condition, which has a greater emphasis on context rather than content memory. In order to examine brain areas preferentially involved in the resolution of proactive interference (PI) that increases as the task goes on, the brain activation stimulated by block 1 (low PI) is subtracted from the activation stimulated by block 3 (high PI) leaving only the activation preferentially stimulated by PI and not by the memory task itself. To compare this across the groups, the PI activation for the NPG is subtracted from the PI resolution for the IPG and vice versa; as it was in the previous analyses. It was necessary to use an uncorrected

model to compare the groups due to the multiple subtractions of activation to measure only PI activation.

No-overlap stimuli

Encoding

When comparing the PI resolution of the NPG and IPG at the encoding of stimuli, the NPG did not show any greater activation than the IPG. However the IPG showed greater activation in the areas shown in Table 38. These areas are associated with word recognition (Nobre, Allison, & McCarthy, 1994) and semantic memory (Grabowski et al., 2001).

Table 38: Areas showing greater activation during PI resolution for the IPG than the NPG (no-overlap encoding)

Cluster Name	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Left frontal pole	2.67	-48	6	-10
Right temporal fusiform gyrus	2.83	25	-10	-32
Right inferior temporal gyrus	1.81	40	-8	-48
Right amygdala	1.94	20	-4	-14
Left temporal pole	2.67	-50	6	-10
Left middle frontal gyrus	2.72	-40	14	54

Retrieval

At the correct recognition of no-overlap targets, the NPG again did not show any greater activation for PI resolution than the IPG. The IPG showed greater activation in the areas shown in Table 39. These areas are associated with language processing (Friederici, 2006), and cognitive emotional processing (Feinberg & Keenan, 2005), and their association with the current task is unclear.

Table 39: Areas showing greater activation during PI resolution for the IPG than the NPG (no-overlap retrieval)

Cluster Name	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Bilateral inferior temporal gyrus	1.98	54	-32	-22
Left frontal pole	1.96	-44	36	12
Left caudate	2.02	-16	18	0
Left frontal orbital cortex	1.82	-46	26	-16

Distracters

At PI resolution of correct recognition of no-overlap distracters the NPG showed greater activation than the IPG in the right putamen (Z-max = 2.01, x = 24, y = 14, z = 6) and the

superior frontal gyrus (Z-max = 3.57, x = 8, y = 14, z = 62). These areas are involved in implicit learning (Grafton et al., 1995; Hazeltine et al., 1997; Willingham et al., 2002) and the executive control of working memory (Boisgueheneuc et al, 2006). The areas that showed greater activation for the IPG than for the NPG are shown in Table 40. These areas are associated with both content and context memory (Gold et al., 2006) and word recognition (Nobre et al., 1994). These results suggest that for correct distracter classification, the IPG the regions of the brain normally associated with memory show greater metabolisation, whilst the NPG are using more frontal areas associated with the executive control of memory. This could result in more efficient information processing for the NPG and explain their better behavioural performance.

Table 40: Areas showing greater activation during PI resolution for the IPG than the NPG (no-overlap distracters)

Cluster Name	**Z-MAX**	**z-max X (mm)**	**z-max Y (mm)**	**z-max Z (mm)**
Bilateral parahippocampal gyrus	2.74	22	-30	-24
Right middle frontal gyrus	1.98	38	28	22
Right temporal fusiform cortex	2.66	30	-28	-28

Overlap stimuli

Encoding

During PI resolution of the encoding of overlap stimuli, the NPG showed greater activation than the IPG in the right putamen (Z-max = 2.02, x = 34, y = -10, z = -2), the inferior temporal gyrus bilaterally (Z-max = 2.77, x = -50, y = -42, z = -22) and the frontal pole bilaterally (Z-max = 1.89, x = 10, y = 58, z = -20). These regions are associated with implicit learning and cognitive emotional processing. The IPG showed greater activation than the NPG in the regions shown by Table 41. These areas are associated with the encoding and retrieval of explicit (Lepage et al., 1998) and implicit memories (Willingham et al., 2002; Grafton et al., 1995; Hazeltine et al., 1997). This showed that the IPG were again using areas normally associated with memory to a greater degree than the NPG to achieve similar amounts of resolution of PI.

Table 41: Areas showing greater activation during PI resolution for the IPG than the NPG (overlap encoding)

Cluster Name	Z-MAX	z-max X (mm)	z-max Y (mm)	z-max Z (mm)
Left putamen	3.79	-32	-14	8
Right hippocampus	1.95	28	-14	-16
Bilateral middle temporal gyrus	2.76	-58	-8	-30
Bilateral frontal pole	2.74	8	68	-6
Left frontal orbital cortex	2.00	-10	16	-24

Retrieval

During the correct recognition of overlap targets, the NPG showed greater activation than the IPG in the areas shown in Table 42. These areas are involved in speech perception and executive functioning tasks (Fornito et al., 2004).

Table 42: Areas showing greater activation during PI resolution for the NPG than the IPG (overlap retrieval)

Cluster Name	Z-MAX	z-max X (mm)	z-max Y (mm)	z-max Z (mm)
Right insular cortex	2.76	42	-8	8
Left paracingulate gyrus	1.95	-4	22	38
Bilateral frontal pole	2.77	-14	58	26

Areas showing greater activation for the IPG than the NPG at overlap target recognition were the right temporal fusiform cortex (Z-max = 2.88, x = 38, y = -14, z = -28), right insular cortex (Z-max = 2.04, x = 32, y = 4, z = 12) and right inferior frontal gyrus (Z-max = 1.92, x = 52, y = 14, z = 20). These areas are associated with word recognition (Manes et al., 1999) and PI resolution (Feredoes et al., 2006). This may indicate that the IPG are more successful at resolving context PI than content PI, which is reflected in the behavioural results.

Distracters

The NPG did not show any greater activation than the IPG for the resolution of PI generated by correct classification of overlap distracters. The IPG showed greater activation than the NPG in the left superior frontal gyrus (-max = 2.81, x = -12, y = 20, z = 56) and the frontal pole (Z-max = 2.66, x = 2, y = 66, z = 0). These areas are associated with the executive control of working memory (Boisgueheneuc et al., 2006).

Hypothesis 3: The NPG will demonstrate greater CBF than the IPG in some areas of the medial temporal lobe; specifically the anterior MTL at encoding and the posterior MTL at retrieval of stimuli.

There were not consistent differences between the groups for MTL activation. For the no-overlap content memory condition, the IPG group showed greater MTL activation at target recognition than the NPG, contrary to the expected activation pattern. For the overlap context memory condition, the IPG again showed greater MTL activation, specifically in the third block for PI resolution. Overall, hypothesis 3 was not upheld.

Hypothesis 4: The NPG will demonstrate greater CBF in the frontal lobes during encoding and retrieval. This will suggest that all patients have poor MTL function, but that patients performing IM tasks at normal levels are using compensatory strategies to achieve this.

The NPG and IPG showed considerable differences in frontal lobe activation. For the no-overlap content memory condition, the IPG group showed greater activation at encoding for areas associated with working memory and effortful attention, whilst at retrieval and for distracters, the NPG showed more inferior frontal gyrus activity, showing better resolution of conflict caused by prior items. For distracter recognition, the IPG showed greater activation for lower processing of stimuli and for effortful processing. For PI resolution, the IPG activated frontal regions associated with memory, whilst the NPG showed more activation for the executive control of memory.

For the overlap context memory condition, the NPG showed greater activation of areas related to executive functions during PI resolution, whilst the IPG showed greater inferior frontal gyrus activation, an area associated with successful PI resolution. The IPG also showed greater activation for PI resolution of distracter items in areas associated with executive functions.

Hypothesis 4 was therefore upheld in terms of CBF. However, the differing pattern of activation may have less to do with the NPG using more memory strategies but instead be due to the two groups using different frontal lobe brain areas to resolve PI, with differing success demonstrated by the behavioural data.

Discussion

An fMRI experiment was used in order to investigate the brain activation that correlated with the poorer immediate memory performance demonstrated by some patients on the WMS-III. Patients were grouped by their WMS-III performance, rather than by the treatment they had

received. Two versions of the same task measured the patients' ability for content and context memory. It was originally expected that overlap (context) condition would be more difficult, as it precluded the use of familiarity as the primary source of information on which to make a memory decision. However, the behavioural results suggested similar performance on both tasks. For the content (no-overlap) task, the IPG performed worse than the NPG by the third block of the experiment. However, this was not the case at the start of the experiment and so this drop in performance suggests that the IPG were less able than the NPG to resolve the PI generated by similar previous items. This poorer performance was accompanied by an increased use of brain regions associated with working memory and effortful attention. This pattern of activation shows that the lower performance level of the IPG was not simply due to a lack of effort by this group. On the contrary, they showed greater activation in the anterior cingulate; and yet this increased effort still did not enable them to perform at the level of the NPG. This would suggest that for patients experiencing memory problems in everyday life, simply "trying harder" (in the sense of increased attentional effort) will not resolve their difficulties. The NPG showed greater inferior frontal gyrus activation during the content task. This area is associated with PI resolution and so suggests that these patients are demonstrating both more efficient cognitive processing than the IPG and also the normal pattern of activation that would be expected in the neurologically intact general population.

The two groups performed at similar levels for the context element of the task. The IPG showed a greater propensity to classify a non-word as a target, demonstrated by better target recognition and poorer distracter recognition than the NPG. This was not significant in this pilot study, but may warrant further investigation. This reduced difference between the groups in behaviour performance was accompanied by fewer differences in activation pattern. Whilst the NPG showed greater activation in areas associated with EFs, the IPG showed greater activation areas associated with PI resolution. This was not so for the content element of the task, suggesting that the IPG resolved context PI better than content PI. This result is surprising, considering Yonelinas' (2002) assertion that when the strength of a memory signal at encoding falls below a certain level, the context of a memory is lost before the content. If this is so, it may indicate that the IPG struggle with content retrieval, rather than encoding. This proposal is supported by the equal MTL activation at encoding of no-overlap items between the groups, accompanied by increased MTL activation for the IPG at retrieval of no-overlap targets, without normalised performance. The hippocampus appears to be

showing greater matabolisation for the IPG at retrieval, yet the performance of this group suggests that target recognition is still less than the NPG.

The differing networks that the two groups employed to resolve PI have been noted previously in a recent study (Caplan, McIntosh, & De Rosa, 2007). Caplan et al. specifically investigated the brain regions involved in resolving PI and noted the presence of two functional networks that worked either separately or in conjunction to achieve this task. A more dominant network that depends on the medial septum and diagonal band of Broca (MS/DB) nuclei of the basal forebrain (BF) most reliably correlated with PI resolution in neurologically normal individuals. However, in formerly alcohol addicted (FAA) participants with compromised basal forebrain function due to cholinergic function at muscarinic receptors (De Rosa & Sullivan, 2003; De Rosa, Desmond, Anderson, Pfefferbaum, & Sullivan, 2004), this network did not reliably correlate with PI resolution. This was despite the task performance of the FAA participants being similar to controls. Instead, a second network which included additional areas normally involved in executive function, namely the lateral orbitofrontal cortex and left anterior cingulate, correlated with successful PI resolution. It was concluded that in neurologically normal individuals, these two networks work in concert. However, when the MS/DB network is compromised, the second, more frontal network is primarily engaged. It is interesting to note that the areas named in this second more frontal network were more greatly activated for the IPG during the content memory task. This may indicate that this group, for reasons unknown, has reduced use of the normal basal forebrain network. The sex hormone estrogen innervates the cholinergic neurons of the basal forebrain (Ping et al., 2008), suggesting an alternative method by which altered cholinergic function may have created a similar pattern of results to individuals who formally abused alcohol.

Limitations of the Current Study

The main limitation of this study is the small number of participants. These participants had to be chosen from a previous cohort who were tested using the WAIS-III and WMS-III, to ensure they had either normal general intellectual functioning and commensurate memory scores, or normal general intellectual functioning and an IM score at least one standard deviation below the score predicted by their FSIQs. Future researchers may wish to use a

short form version of the WAIS-III to screen potential participants, and then complete the test battery only with participants showing average estimated FSIQs, in order to create a larger pool of potential participants more efficiently.

The task used was recently created by O'Sullivan and Humphreys (2009). Whilst it succinctly measures the two types of memory information that were examined, it will be some time before extensive data on the full age range of neurologically normal adults is collected. When this occurs, it might be possible to reinterpret these results in comparison to neurologically intact same-age peers. However, this is unfortunately not possible at this time.

General Discussion

Position of the present research in the context of the existing literature

Pituitary adenomas account for approximately 15% of all intracranial tumours (Asa & Ezzat, 2004). These non-cancerous tumours can disrupt endocrine function and require life-long endocrine follow-up (Dehdashti, Garma, Karabatsou, & Gentili, 2008). Patients frequently report experiencing difficulties remembering new information (McCord et al., 1997) and in 1992 the first systematic comparison of patients treated with or without radiotherapy (RT) was conducted in Australia by Grattan-Smith et al. (1992). This study found no treatment group differences but highlighted cognitive deficits across the patient sample in a range of domains encompassing memory and executive functions (EFs). This seminal study inspired five further research projects in England and America which sought to improve on the methodology of Grattan-Smith et al. (1992) and thereby isolate the relative contribution of tumour, treatment and hormone dysfunction to the neurocognitive deficits found. These studies found that recall of new material was the cognitive ability in which patients most frequently and reliably experienced deficits. Every study found that patients performed worse than controls or test norms on at least one measure of memory; and most studies found patient groups to be worse on measures of both visual and auditory memory. However, few differences were found between patients receiving different treatments.

The findings concerning the presence or absence of EF deficit were more ambivalent. Whilst some studies found EF deficit on between one and all four of the EF tests they used (Grattan-Smith et al., 1992; Peace et al., 1997), others found no deficit on any EF measure (Guinan et al., 1998); and whilst one study found patients treated with RT performed worse than patients treated with surgery alone on one measure of EF (Noad et al., 2004), another study found that patients treated with RT actually outperformed those treated without RT (Baum et al., 1998). Many of the contradictions in the current literature may be due to methodological issues present within these studies. These issues relate to both patient selection and test selection. In terms of patient selection, age of diagnosis has not been stated (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Guinan et al., 1998; Baum et al., 1998; Noad et al.,

2004), meaning that patients with child-onset tumours may have been included. This has implications for the results as the paediatric brain has greater capacity for plasticity and functional reassignment to undamaged areas (Johnston, 2009; Johnston, 2004). The comparison of different treatment types has been confounded by the size of the original tumour which has not been stated in all but one study (Noad et al., 2004). Larger, more aggressive tumours require a combination of treatments, meaning that patients treated with RT who show greater impairment may have already been impaired due to a large tumour compressing the supra-sella region and disrupting hormone production, rather than due to the subsequent RT they received. In some articles adenoma type has not been given and in other articles patients with Cushing's and craniopharyngioma have been included. Both of these tumours are associated with a higher mortality rate (Tomlinson et al., 2001) and a greater degree of cognitive impairment (Starkman et al., 2001; Waber et al., 2006). The inclusion of patients with tumours that produce any hormone for which receptors are found in the brain is ill advised in studies investigating the effect of treatment. The effect of hormonal excess may skew the results and reduce the level of confidence with which conclusions about treatment can be made. In relation to this, hormone levels on the day of cognitive testing have not been measured meaning that any current over or under replacement of hormones will go unnoticed. Some studies have avoided this issue by insisting patients have been on stable hormone replacement for over one year (Peace et al., 1997; Peace et al., 1998), however, this method still does not allow associations between hormone levels and cognition to be assessed.

The tests selected to examine neurocognitive function have often been sub-optimal. The NART is frequently the only measure of intelligence used (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Noad et al., 2004). As this measures pre-morbid and not current intelligence, it is not possible to assess whether the presence of tumour or treatment have had a detrimental effect on general intellectual functioning. Nor is it possible to use each participant's current FSIQ to produce an individual prediction of current memory abilities (Wechsler, 1997a), which reduces variance within each treatment group. In most of the later research a greater selection of visual and auditory memory tests have been used. However, some studies have used too small a variety of memory tests to give a full and accurate picture of memory function (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998). The range of EFs has also not been closely examined. Most studies have used three or less subtests to measure the various aspects of EF (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Noad et al., 2004). The relative lack of assessment of the various different

types of EF may explain some of the variation in patients' executive function performance between studies.

The present studies aimed to improve on the methodology in the following ways:

- Only patients with non-functioning adenoma were included to remove variance in the results caused by the hyperproduction of hormone(s).
- Hormone levels were assessed on the day of testing to ensure appropriate replacement and to examine the relationship between hormone levels and cognitive abilities.
- Only patients diagnosed after the age of 18 were included to reduce variance caused by functional reassignment from damaged to undamaged brain tissue.
- Original tumour size was noted from scans and was not different across treatment groups of pituitary adenoma patients. This reduces the possibility of tumour related deficit being attributed to RT.
- Both current and pre-morbid general intellectual functioning was measured using the current 'Gold standard' test batteries available so that relative impairment in intelligence could be assessed.
- Memory was assessed using a 'Gold standard' test battery was co-normed with the measure of intelligence. This allowed both absolute and relative impairment of memory function to be examined. The more conservative 'predicted difference' method was used for the first time with this group of patients.
- Finally, EFs were tested with a full test battery of eight different subtests. This was double the amount of subtests ever used in the previous pituitary literature and allowed a wider range of EF abilities to be assessed.

Results of the Present Study

The present study demonstrated that no treatment group of patients with pituitary adenoma experienced either absolute or relative impairment of general intellectual functioning. This was still the case when the results were analysed using the Cattell-Horn-Carroll (CHC) theory

of fluid and crystallised intelligence. The RT only group of patients treated for nasopharyngeal carcinoma showed a relative impairment in working memory, which has been found previously (Lam et al., 2003) and is thought to be due to RT damage to the frontal lobe. No differences between the treatment groups were found on the measures of intelligence, memory or EF. In contrast, each treatment group showed relative impairment on a measure of memory. The three groups of pituitary patients showed a significant relative impairment of immediate memory, either for auditory or visual stimulus presentation. Given that this impairment was independent of treatment, it was concluded that alternative factors such as hormonal status might have contributed to this result, as well as to the gender difference found for memory discrepancy scores. Across the treatment groups, women achieved memory scores approximately commensurate with their FSIQs whereas men scored significantly lower. Patients treated with RT alone achieved delayed free recall scores appropriate for their FSIQs, and yet achieved delayed recognition scores below expected. This was thought to be due to test artefact, as the delayed recognition index has a low ceiling level and smaller standard error of measurement that the recall indices. This creates a situation where as little as two or three incorrect answers per person on any of the recognition subtests, in the presence of average FSIQ, can lead to a group relative deficit.

The SCL-90R GSI T-score was found to correlate negatively with five measures of EF. However this association showed a trend towards being mediated by processing speed, as measured by the WAIS-III. As higher scores on the five measures of EF are achieved the faster they are completed, it was concluded that low mood reduced processing speed on the task and thereby reduced EF scores. There was also an interesting correlation between the age at which a person received RT and several EF scores. This was not borne out in the contrast scores which could suggest that RT equally impairs EFs and the lower processes they require. The RT only group had contrast scores similar to the population norms, whilst the CM and Surgery only groups presented with some scores that were significantly better than the population average of 10. Both the Surgery only and the Surgery + RT groups had one contrast score significantly below average. However, in both cases this was due to a lower process score that was over one standard deviation (s.d.) above the population average, rather than a low EF score.

In an attempt to discover the relative contribution of various treatment related factors to the cognitive results found, hormone levels and cerebral blood flow characteristics were further

examined. This highlighted an association between free thyroxine (T4) and working memory, both directly and as a memory discrepancy score. Higher levels of T4 correlated with greater working memory ability suggesting that some patients in this sample might benefit from a higher dose of T4 replacement. T4 also correlated with the other verbal measures of general intellectual functioning, which is a variation on what is shown in the previous literature. T4 is more often associated with verbal measures of EF, such as Verbal Fluency (Begin et al., 2008). Cortisol replacement also correlated with verbal intelligence. There is a dearth of literature examining the effects of hydrocortisone dose on verbal intelligence for adult onset hypocortisolism, and so this result must await further research for interpretation. A correlation between cortisol, 30 minutes after SST, and the recognition memory discrepancy score was considered to be a type 1 error. However, the negative correlations between EFs and baseline cortisol have been found previously (McCormick et al., 2007; Lee et al., 2007). Finally, the difficulty of measuring the effect of cortisol when half of the sample was on hydrocortisone and the other half was not was noted. This creates two sets of cortisol results, both with smaller group sizes and potentially different meanings to the results. Other blood test results indicated a positive correlation between osmolarity and attentional switching, and between total cholesterol and association generation. These finding are commensurate with the previous literature, highlighting the importance of cholesterol to many brain processes, and of keeping hydrated.

The most significant result found during this study was the different memory outcomes for men and women. Whilst there were no significant differences between men and women for general intellectual functioning or EF, women scored significantly better on tests of memory. On average, women achieved actual and predicted memory scores that were commensurate with their peers. In contrast, whilst men scored actual memory scores that were indicative of no absolute impairment, they scored significantly below the scores that were predicted from their FSIQs. It was noted that across the sample, men had significantly more hormone blood test results outside the normal range than women, and poorer hormonal control may have contributed to this finding. The importance of estrogen in the brain and the difficulty of measuring cellular levels due to local aromatisation of testosterone to estrogen were also noted.

In order to examine the mechanisms by which RT might cause cognitive deficit through damage to blood vessels, the cerebral blood flood volume (CBFV) in the middle cerebral

arteries (MCAs), and the number of microemboli present were measured. The brain's ability to autoregulate its own blood flow and blood pressure (Cerebral Autoregulation: CA) was also assessed. This showed that those patients treated with RT had faster mean CBFV than patients who had not received RT treatment. This is potentially due to neurotic damage to small to medium sized blood vessels caused by RT (Fajardo, 1999; Martin et al., 2004). However, no microemboli were detected and all treatment groups achieved similar CA at normal population levels. Therefore, whilst RT may have had an effect on the diameter of some blood vessels, this has not been reflected in the brain's ability to regulate its own blood flow.

The reasons for the intra treatment group variability in immediate memory deficits were investigated using functional magnetic resonance imaging (fMRI). Patients who performed normally on immediate memory (IM) tasks (NPG) on the WMS-III were compared to patients who performed poorly on the WMS-III tests (IPG) of IM on measures of content and context IM. The ability to resolve proactive interference (PI) was also examined. Whilst little difference between the groups in behavioural performance was found for the context condition, in the content condition the NPG performed better by the third block of the experiment than the IPG. This suggested better PI resolution of content memory. This difference was supported by greater use of brain areas linked to EFs and PI resolution. Fewer differences in activation were found for the context condition and mainly comprised a greater use of areas associated with working memory for the IPG, and greater use of areas associated with EFs for the NPG. The IPG also showed greater use of PI resolution areas than the NPG for the context condition. These differing patterns of activation were thought to reflect the two networks of PI resolution discussed by Caplan et al. (2007). It suggests that poor immediate memory performance by some patients is not due to damage to or under-activation of specific structural areas, but instead due to differing use of the basal forebrain mediated network.

Comparison of Treatments

A primary concern of the present study was the potential contribution of treatment to any cognitive deficits found. This is of importance for all future patients, who should be informed of the potential risks and benefits of the treatments they are offered. The group comparisons were outlined in the 'General Methods' chapter and will be discussed here.

Conservatively Managed Patients

The conservatively managed group were included to control for the effect of having a non-functioning pituitary adenoma (NFA) when compared to the Surgery only and the Surgery + RT groups. Any cognitive dysfunction present in all three groups of pituitary patients would be most likely attributable to the tumour itself and any hormone dysfunction it caused, rather than to subsequent treatment.

All three NFA treatment groups showed intact general intellectual functioning and EFs, indicating that neither tumour nor treatment impairs these cognitive functions. However, these treatment groups demonstrated relative IM deficits which were not present in the RT only group of patients with nasopharyngeal carcinoma (NPC). This suggests that the NFA is the cause of this deficit, and not subsequent treatment. The effects of various hormone levels are discussed above and can be assumed to potentially affect all patients with NFA.

Patients treated with Surgery

Patients treated with surgery alone for NFA showed a similar pattern of results to the conservatively managed patients. This is reassuring for future patients for whom surgery may be necessary to avoid visual compromise.

Patients treated with Surgery and RT

Patients treated with RT after surgery showed a slightly different pattern of results to patients treated with surgery alone. Whilst they showed the same IM deficit as the other treatment groups, there was also a positive correlation between age at RT and several EF scores. However, this was not the case for EF contrast scores, indicating that the patients with better EF scores also had better scores for lower processes, making this result difficult to interpret.

Patients treated with RT also had significantly faster CBFV than patients treated without RT. This result is likely to be due to the necrotic damage to vessel walls which RT is known to cause (Martin et al., 2004; Fajardo, 1999). However, this CBFV increase is not associated with cognitive dysfunction.

How the Current Results Compare to the Previous Literature

This study found impairment of relative immediate memory, which is commensurate with the only previous study to use this method (Guinan et al., 1998). However, the absolute impairment found in previous studies (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Noad et al., 2004) was not repeated in the current research. Also, this study did not find deficits in delayed memory or in any EFs, as several prior studies have done (Grattan-Smith et al., 1992; Peace et al., 1997; Noad et al., 2004). This is most likely due to the methodological differences outlined earlier in this chapter.

Three previous studies included a non-surgically treated group. Both studies by the Peace et al. (Peace et al., 1997; Peace et al., 1998) group found that non-surgically treated patients performed better on tests of memory than surgically treated patients. In contrast the study by Guinan et al. (1998) found no difference between the non-surgically and surgically treated group for tests of immediate memory, but there was a difference for delayed recall in which the non-surgically treated group performed better. This group difference was not found in the current study. This could be due to the low numbers in the current CM group or because of the inclusion of patients with hormone producing tumours in previous studies. Commensurate with the current study, all previous studies have found no difference between patients treated with and without RT (Grattan-Smith et al., 1992; Peace et al., 1997; Peace et al., 1998; Guinan et al., 1998; Baum et al., 1998; Noad et al., 2004). For EFs, only the most recent study found that patients treated with RT performed worse than patients treated without it (Noad et al., 2004).

Implications for Patients

This research should be reassuring for patients and their physicians. Current first choice treatment for NFAs which cause visual compromise does not appear to systematically cause cognitive deficit. However, the level of cognitive variability between patients who have received the same treatment demonstrates that patients with NFA are far from a homogenous group. Physicians should not take this thesis as evidence that a patient's report of memory problems is unfounded.

Implications for Medical Practice

This research suggests that surgery used to debulk pituitary adenoma is not systematically associated with cognitive impairment. Physicians should consider the use of RT carefully, however. This study adds further evidence of its cerebrovascular risk, although this has not been shown to systematically impact on cognition. Finally, neuropsychologists are advised to consider the use of tests that allow the measurement of relative memory impairment when assessing this group of patients. Psychologists working in cognitive rehabilitation should also consider that the intact EFs observed in this patient group may be useful in teaching a client with NFA how to generate and consistently use strategies to circumvent impairment of memory.

Strengths and Weaknesses of the Current Study

The main strengths and methodological advances of this study are described in the bullet points above. However, there are several weaknesses that must also be drawn to the reader's attention. Firstly, the CM group and the RT only group were considerably smaller than the other treatment groups. This was due to the comparative rarity of CM patients in pituitary clinic and of patients with NPC. Also, the RT only group of patients with NPC did not provide as equivalent a control group for the patients treated with both surgery and RT for NFA, as a group of patients treated with RT alone for NFA would have done. The areas of the brain irradiated were not exactly the same in the two treatment groups and this is evidenced by the lack of hormone dysfunction present in patients with NPC. However, RT alone is not a treatment option that is offered for patients with NFA at University Hospital Birmingham and so it was not possible to recruit this treatment group consisting of patients with NFA.

As participation was voluntary, participants were self-selecting. The research took a full day for which patients had to attend the Queen Elizabeth Hospital. Therefore, patients needed to be both motivated and organised to attend. This may mean that patients with greater EF dysfunction or more fatigue may not have felt able to attend. Also, patients who simply could not/did not wish to take time off of work would also not participate.

Implications for Future Research

This thesis raises several possibilities for future research. The sex difference for the relative deficits in immediate memory found across treatment groups warrants further investigation. This may be due to a differing effect of hormonal dysfunction on men, cellular level estrogen metabolism in the brain or due to other reasons. In relation to this, the causes of the intra treatment group variance that was found are still unknown. It is surprising that individuals who receive virtually identical treatments for similar tumours should have such differences in memory outcome. Future studies may wish to recruit a larger conservatively managed group. This may necessitate a multi-centre project. Alternatively, patients treated with medication for prolactinoma may provide a viable recruitment option. Patients with NFA may often have raised prolactin levels due to stalk compression (Arafah et al., 2000). The reasons for different memory processing of stimuli may also warrant further investigation, especially as the implication of the basal forebrain as a pivotal area for this difference may suggest a hormonal contribution to immediate memory difficulties (Gibbs & Aggarwal, 1998).

Appendix 1: Patient details and results

Participant Number	Age	Sex	Group	Type of Surgery	Time since S (in months)	Age at First S (in years)	Dose of Radiotherapy	Time since Radiotherapy	Age at Radiotherapy
1	74	Male	CM						
2	55	Female	CM						
3	77	Male	CM						
4	44	Male	CM						
5	40	Female	CM						
6	68	Male	CM						
7	49	Male	CM						

CM = Conservatively Managed; S = Surgery; Not applicable cells are greyed out

Participant Number	Initial Tumour Size	Hormone Replacements	Suprasellar Extension	SCL-90R Clinical Distress	GSI T-score	PS Total T	CDS Raw	Years Education
1	15 diameter	1 (Te)	No	0	n/a	40	1	9
2	22x16x23	1 (E)	Not in notes	0	29	21	3	10
3	37x26x24	3 (Te, H, T4)	Yes	0	48	50	2	9
4	10x13x14	2 (H, Te)	No	7 (S, OC, IS, D, PA, PI, P)	81	67	17	10
5	10x10x12	0	No	0	47	49	5	13
6	Not in notes	Not in notes	Not in notes	0	45	47	2	Not done
7	12x8x7	2 (Te, T4)	No	2 (S, OC)	67	61	20	Not done

SCL = Symptom Checklist; GSI = General Severity Index; PS = Positive Symptoms; CDS = Cognitive Deficit Scale; Te = Testosterone; E = Estrogen; H = Hydrocortisone; T4 = Thyroxine; DP = Desmopressin; GH = Growth Hormone; Pr = Progesterone; S = Somatization; OC = Obsessive-Compulsive; IS = Interpersonal Sensitivity; D = Depression; A = Anxiety, Ho = Hostility, PA = Phobic Anxiety; PI = Paranoid Ideation; P = Psychotocism

Participant Number	Age	Sex	Group	Type of Surgery	Time since S (in months)	Age at First S (in years)	Dose of Radiotherapy	Time since Radiotherapy	Age at Radiotherapy
8	67	Male	Surgery Only	TP	31	64			
9	56	Female	Surgery Only	TP	96	48			
10	59	Male	Surgery Only	TC	344	30			
11	46	Female	Surgery Only	TP	40	43			
12	69	Male	Surgery Only	TP	130	58			
13	49	Female	Surgery Only	TP	34	46			
14	58	Male	Surgery Only	TP	31	55			
15	42	Female	Surgery Only	TP	83	35			
16	64	Male	Surgery Only	TP	62	59			
17	68	Male	Surgery Only	TP	43	64			
18	45	Female	Surgery Only	TP	51	41			
19	45	Male	Surgery Only	TP	146	33			
20	42	Female	Surgery Only	TP	21	40			
21	68	Female	Surgery Only	TP	69	62			
22	57	Female	Surgery Only	TP	21	55			
23	51	Male	Surgery Only	TP	33	48			
24	70	Male	Surgery Only	TP	Unknown	Unknown			
25	52	Male	Surgery Only	TP	Unknown	Unknown			
26	31	Male	Surgery Only	TP	26	29			

S = Surgery; Not applicable cells are greyed out

Participant Number	Initial Tumour Size	Hormone Replacements	Suprasellar Extension	SCL-90R Clinical Distress	GSI T-score	PS Total T	CDS Raw	Years Education
8	35x30x25	3 (Te, H, T4)	Yes	Not done	n/a	n/a	n/a	10
9	Not in notes	4 (H, E, T4, DP)	No	2 (S, OC)	62	59	20	15
10	Not in notes	4 (Te, H, T4, GH)	Yes	4 (S, OC, A, PA)	63	65	9	14
11	20 diameter	5 (H, T4, E, Pr, Dh)	Not in notes	0	47	45	4	17
12	Not in notes	0	Not in notes	0	53	58	2	10
13	Not in notes	0	Yes	2 (OC, IS)	64	60	20	11
14	Not in notes	3 (Te, H, T4)	Not in notes	1 (D)	63	64	7	14
15	20x25	Not in notes	Not in notes	0	60	60	6	14
16	20x23x13	0	Yes	0	41	43	3	12
17	Not in notes	Not in notes	Not in notes	0	55	53	7	11
18	26x22x16	0	Yes	1 (Ho)	61	61	13	10
19	Not in notes	3 (Te, T4, GH)	Yes	8 (S, OC, IS, D, A, Ho, PI, P)	81	73	19	17
20	Not in notes	Not in notes	Not in notes	0	55	53	7	14
21	Not in notes	1 (T4)	Yes	0	56	58	7	16
22	22x33	1 (T4)	Not in notes	9 (All scales)	81	75	24	Not done
23	Not in notes	2 (Te, T4)	Yes	0	45	48	2	10
24	Not in notes	Not in notes	Not in notes	4 (S, OC, PA, P)	67	67	11	7
25	Not in notes	Not in notes	Not in notes	0	41	43	1	21
26	30mm	1 (Te)	Yes	0	n/a	40	2	Not done

SCL = Symptom Checklist; GSI = General Severity Index; PS = Positive Symptoms; CDS = Cognitive Deficit Scale; Te = Testosterone; E = Estrogen; H = Hydrocortisone; T4 = Thyroxine; DP = Desmopressin; GH = Growth Hormone; Dh = Dehydroepiandrosterone; Pr = Progesterone; S = Somatization; OC = Obsessive-Compulsive; IS = Interpersonal Sensitivity; D = Depression; A = Anxiety, Ho = Hostility, PA = Phobic Anxiety; PI = Paranoid Ideation; P = Psychotocism

Participant Number	Age	Sex	Group	Type of Surgery	Time since S (in months)	Age at First S (in years)	Dose of RT (in Gray)	Time since Radiotherapy	Age at Radiotherapy
27	59	Female	RT only				50	16	58
28	34	Female	RT only				Unknown	121	24
29	50	Male	RT only				Unknown	41	47
30	30	Female	RT only				Unknown	62	25
31	51	Male	RT only				Unknown	403	17
32	50	Male	RT only				Unknown	Unknown	Unknown
33	72	Female	RT only				Unknown	112	63

S = Surgery; RT = Radiotherapy; Not applicable cells are greyed out

Participant Number	Initial Tumour Size	Hormone Replacements	Suprasellar Extension	SCL-90R Clinical Distress	GSI T-score	PS Total T	CDS Raw	Years Education
27	Not in notes	0	No	0	44	43	2	15
28	10x10x10	0	No	0	52	53	3	11
29	Not in notes	0	No	0	41	41	0	10
30	Not in notes	0	No	4 (OC, IS, D, Ho)	67	68	20	Not done
31	Not in notes	0	No	0	53	54	6	Not done
32	Not in notes	Not in notes	No	Not done	n/a	n/a	n/a	12
33	Not in notes	0	No	0	56	55	3	12

SCL = Symptom Checklist; GSI = General Severity Index; PS = Positive Symptoms; CDS = Cognitive Deficit Scale; Te = Testosterone; E = Estrogen; H = Hydrocortisone; T4 = Thyroxine; DP = Desmopressin; GH = Growth Hormone; Pr = Progesterone; S = Somatization; OC = Obsessive-Compulsive; IS = Interpersonal Sensitivity; D = Depression; A = Anxiety, Ho = Hostility, PA = Phobic Anxiety; PI = Paranoid Ideation; P = Psychotocism

Participant Number	Age	Sex	Group	Type of Surgery	Time since S (in months)	Age at First S (in years)	Dose of RT (in Gray)	Time since Radiotherapy	Age at Radiotherapy
34	58	Female	S + RT	TP x 2	147 and 72	46	not in notes	67	52
35	56	Male	S + RT	TC + TP	55 and 49	51	not in notes	38	53
36	40	Female	S + RT	TP	74	34	not in notes	61	35
37	47	Male	S + RT	TP	84	40	not in notes	40	44
38	64	Male	S + RT	TP x 2	181 and 37	49	not in notes	23	62
39	45	Male	S + RT	TP	89	38	not in notes	83	38
40	34	Female	S + RT	TP	99	26	45	40	31
41	53	Male	S + RT	TP + TC	61 and 58	48	50	51	49
42	42	Male	S + RT	TP	45	38	45	15	41
43	65	Male	S + RT	TP x 2	221 and 59	47	not in notes	52	61
44	57	Male	S + RT	TP	50	53	not in notes	19	55
45	42	Female	S + RT	TP x 2	92 and 79	34	not in notes	75	36
46	64	Male	S + RT	TP	108	55	50	Unknown	Unknown
47	35	Female	S + RT	TP	63	30	not in notes	Unknown	Unknown
48	41	Female	S + RT	TP	108	32	45	50	37
49	60	Female	S + RT	TP	103	51	not in notes	97	52
50	57	Male	S + RT	TP	79	50	not in notes	23	55
51	53	Female	S + RT	TC	308	27	45	60	48
52	59	Female	S + RT	TC + TP	235 and	39	not in notes	197	43

S = Surgery; RT = Radiotherapy

Participant Number	Initial Tumour Size	Hormone Replacements	Suprasellar Extension	SCL-90R Clinical Distress	GSI T-score	PS Total T	CDS Raw	Years Education
34	Not in notes	0	Yes	0	56	59	6	16
35	Not in notes	3 (Te, H, T4)	Yes	Not done	n/a	n/a	n/a	11
36	26x18	2 (E, GH)	Yes	0	56	59	10	20
37	Not in notes	2 (Te, H)	Yes	0	52	54	4	14
38	Not in notes	3 (Te, H, T4)	Yes	1 (Ho)	59	60	9	20
39	23x23x26	4 (Te, H, T4, GH)	Yes	0	55	54	5	11
40	Not in notes	1 (H)	No	0	50	52	4	11
41	20x30x40	4 (Te, H, T4, GH)	Yes	0	53	55	5	11
42	Not in notes	0	Yes	4 (IS, D, PA, PI)	66	62	4	19
43	Not in notes	3 (Te, H, T4)	Yes	2 (OC, P)	65	59	18	18
44	20x24x25	4 (Te, H, T4, GH)	Yes	0	48	47	4	16
45	21x24x30	1 (H)	Yes	1 (OC)	61	61	10	16
46	22 diameter	4 (Te, H, T4, GH)	Yes	0	55	58	6	14
47	Not in notes	1 (H)	Not in notes	0	58	56	1	19
48	19x24x28	2 (E, H)	No	6 (OC, IS, D, A, PA, P)	71	70	15	11
49	32 diameter	0	Yes	1 (OC)	61	61	16	10
50	Not in notes	3 (Te, H, T4)	Not in notes	3 (OC, D, PI)	67	66	13	Not done
51	Not in notes	2 (H, T4)	Yes	0	47	50	8	Not done
52	Not in notes	2 (H, T4)	Yes	0	n/a	33	1	Not done

SCL = Symptom Checklist; GSI = General Severity Index; PS = Positive Symptoms; CDS = Cognitive Deficit Scale; Te = Testosterone; E = Estrogen; H = Hydrocortisone; T4 = Thyroxine; DP = Desmopressin; GH = Growth Hormone; Pr = Progesterone; S = Somatization; OC = Obsessive-Compulsive; IS = Interpersonal Sensitivity; D = Depression; A = Anxiety, Ho = Hostility, PA = Phobic Anxiety; PI = Paranoid Ideation; P = Psychotocism

Participant Number	WCC	Hb	Plts	Neuts	Mono	Eosin	Bas	Fibrinogen	Urea	Creat	Glucose	Na	K	Alb	Bili	ALP
1	5.5	12.8	244	3.5	0.4	0.1	0	2.6	3.7	96	4.8	144	4	41	7	100
2	6.1	12.6	255	3.3	0.5	0.1	0	2.9	4.2	93	3.8	138	4.1	42	19	35
3	11.8	14.2	249	9.1	1	0.1	0	4.3	9	127	4.5	ND	ND	39	ND	ND
4	8.7	12.9	379	6.4	0.5	0.1	0	5.7	4.4	93	4.8	142	4.3	42	4	172
5	6.7	13.5	228	4.1	0.5	0.1	0	2.9	3.3	90	4.6	146	3.9	41	8	154
6	8.4	14.5	260	4.9	1.5	0.3	0.2	2.6	2.1	94	4.7	135	4.1	41	8	135
7	6.64	14.5	253	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	138	4.2	n/d	n/d	88

WCC = White blood Cell Count; Hb = Haemoglobin; Plts = Platelets; Neuts = Neutrophils; Mono = Monocytes; Eosin = Eosinophils; Bas = Basophils; Creat = Creatinine; Na = Sodium; K = Potassium; Alb = Albumin; Bili = Bilirubin; ALP = Alkaline Phosphatase; n/d = not done

Participant Number	Prol	IGF-1	Oest.	CRP	Test	FSH	LH	Total chol	HDL chol	LDL chol	Trigl	Osmol	TSH	FT3	FT4
1	522	13.2	143	<3	28.9	<0.5	<0.5	5.1	1.70	3.11	0.63	292	1.00	n/d	9.0
2	261	12.1	120	<3	0.6	10.7	3.7	5.4	1.83	3.00	1.24	287	1.8	n/d	13.1
3	112	5.1	54	48	11.9	2.0	<0.5	6.2	1.63	3.89	1.49	294	<0.1	3.8	21.6
4	1497	27.5	91	21	12.3	<0.5	<0.5	5.5	1.06	3.84	1.33	297	1.5	n/d	11.5
5	76	31.3	199	<3	n/d	4.6	7.8	4.7	1.66	2.37	1.48	290	2.9	4.4	13.9
6	172	3.9	98	5	14.0	3.4	n/d	2.7	1.32	0.91	1.04	265	0.2	5.2	14.0
7	n/d	n/d	n/d	n/d	n/d	1.3	0.2	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d

Prol = Prolactin; IGF = Insulin-like Growth Factor; Oest = Oestrogen; CRP = C- Reactive Protein; Test = Testosterone; FSH = Follicle Stimulating Hormone; LH = Luteinizing Hormone; chol = Cholesterol; Trigl = Triglycerides; Osmol = Osmolarity; TSH = Thyroid Stimulating Hormone; FT3 = Free Tri-iodothyronine; FT4 = Free Thyroxine; n/d = not done

Participant Number	WCC	Hb	Plts	Neuts	Mono	Eosin	Bas	Fibrinogen	Urea	Creat	Glucose	Na	K	Alb	Bili	ALP
8	8.5	16.0	216	5.5	0.8	0.2	0	2.1	8	133	3.9	139	3.9	139	11	157
9	7.9	14.2	219	4.6	0.5	0.2	0	2.5	6.7	103	4.5	136	3.9	43	8	134
10	10.9	15.0	215	8	0.6	0.2	0.1	n/d	5.7	120	6.9	140	4.5	43	7	213
11	5.6	13.4	302	3.7	0.4	0.1	0.1	1.5	4.2	83	4.9	140	3.8	42	10	108
12	5.7	11.6	285	3.4	0.5	0.4	0.1	4.5	4.6	93	5.1	139	3.6	43	8	193
13	4.6	13.0	300	3.1	0.3	0.1	0	1.6	4.2	86	3.8	141	4.0	44	13	113
14	4.2	15.1	231	2.3	0.3	0.1	0	2.3	4.8	115	5.1	137	3.7	42	9	111
15	6.5	12.7	279	3.6	0.5	0.1	0.1	2.9	5.3	78	4.6	138	3.5	40	6	193
16	4.3	13.0	300	1.8	0.6	0	0	2.7	5.2	98	4.4	130	4.0	43	11	109
17	8.6	15.9	341	4.8	1.1	0.2	0.1	2.4	5	103	5.1	138	4.4	42	16	99
18	4	11.7	208	2.4	0.4	0.1	0	2.7	3.7	88	5.1	141	4.2	40	8	140
19	5.2	15.0	200	2.7	0.7	0.2	0	2.8	5.7	93	5.4	139	4.0	45	12	200
20	7.4	12.2	315	4.7	0.05	0.3	0	1.4	3.5	76	5.5	142	4.5	39	6	195
21	5.1	12.8	182	3	0.5	0.1	0	3.1	4.1	90	4.4	143	3.7	45	17	166
22	6.8	12.8	243	4.2	0.5	0.2	0	3.3	4.3	88	4.1	n/d	n/d	39	17	n/d
23	6.7	15.9	286	2.6	0.7	0.3	0.1	3.4	3.2	90	4.9	141	4.5	43	9	154
24	8.7	13.9	212	5.6	0.9	0.5	0.1	2.3	6.3	114	4.8	144	3.6	43	11	100
25	5.5	13.7	210	3.1	0.5	0.1	0	3.4	4	102	4.6	n/d	n/d	44	n/d	n/d
26	7.52	15.0	235	n/d	n/d	n/d	0.03	n/d	n/d	n/d	n/d	139	3.8	n/d	n/d	n/d

WCC = White blood Cell Count; Hb = Haemoglobin; Plts = Platelets; Neuts = Neutrophils; Mono = Monocytes; Eosin = Eosinophils; Bas = Basophils; Creat = Creatinine; Na = Sodium; K = Potassium; Alb = Albumin; Bili = Bilirubin; ALP = Alkaline Phosphatase; n/d = not done

Participant Number	Prol	IGF-1	Oest.	CRP	Test	FSH	LH	Total chol	HDL chol	LDL chol	Trigl	Osmol	TSH	FT3	FT4
8	55	12.4	136	3	18.7	<0.5	<0.5	4.9	1.49	2.52	1.95	300	0.9	ND	13.1
9	<30	7.9	99	<3	<0.5	0.8	<0.5	3.6	1.47	1.51	1.35	288	<0.1	4.3	17.0
10	321	23.0	71	<3	19.1	2.5	0.7	5.6	0.83	3.78	2.17	298	0.9	n/d	20.0
11	<30	22.7	149	<3	1.0	6.5	3.7	5.4	1.77	2.93	1.54	297	0.3	4.2	15.6
12	112	31.0	49	<3	13.5	4.0	2.3	4.7	1.71	2.37	1.37	295	0.5	n/d	13.8
13	n/d	21.8	320	<3	1.2	n/d	11.0	4.6	2.03	2.20	0.80	286	0.9	n/d	14.5
14	688	17.6	185	4	18.7	0.6	<0.5	5.6	1.54	3.49	1.25	286	<0.1	4.7	14.5
15	159	17.2	121	8	0.8	6.3	6.1	4.6	1.63	2.65	0.70	295	1.5	n/d	14.3
16	100	16.1	75	<3	20.4	8.9	3.6	4.7	2.31	2.13	0.57	263	0.7	4.4	15.9
17	100	12.7	308	3	39.2	<0.5	<0.5	n/d	1.88	n/d	1.00	297	<0.1	5.7	20.1
18	244	15.9	81	3	n/d	8.7	4.3	4.3	1.43	2.46	0.91	290	3.2	4.2	13.3
19	227	14.1	n/d	3	8.1	3.1	2.7	7.3	1.41	3.63	4.97	270	<0.02	5.6	27.5
20	261	16.6	427	4	n/d	3.8	n/d	4.6	1.32	2.60	1.49	290	1.0	n/d	13.5
21	146	15.6	39	3	n/d	52.8	18.1	5.3	1.60	2.90	1.76	285	0.8	4.1	15.5
22	174	19.6	34	4	n/d	22.3	10.9	4.6	1.42	2.31	1.92	298	3.6	n/d	12.8
23	660	38.3	62	8	7.7	3.1	1.7	5.0	0.84	3.10	2.34	290	0.3	4.8	16.7
24	71	12.3	71	3	n/d	1.3	<0.5	4.3	1.38	2.43	1.07	292	1.8	3.6	11.4
25	157	14.1	89	<3	15.5	1.3	1.1	4.8	1.30	3.06	0.97	299	0.4	4.3	16.1
26	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d

Prol = Prolactin; IGF = Insulin-like Growth Factor; Oest = Oestrogen; CRP = C- Reactive Protein; Test = Testosterone; FSH = Follicle Stimulating Hormone; LH = Luteinizing Hormone; chol = Cholesterol; Trigl = Triglycerides; Osmol = Osmolarity; TSH = Thyroid Stimulating Hormone; FT3 = Free Tri-iodothyronine; FT4 = Free Thyroxine; n/d = not done

Participant Number	WCC	Hb	Plts	Neuts	Mono	Eosin	Bas	Fibrinogen	Urea	Creat	Glucose	Na	K	Alb	Bili	ALP
27	7.6	12.9	219	5	0.5	0.1	0	1.7	4.8	89	5.1	138	4.2	39	4	180
28	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d
29	8.8	13.9	311	5.4	0.7	0.2	0.1	4.2	3	90	7.7	143	3.7	40	4	261
30	4.5	8.1	218	2.6	0.3	0.1	0	3	4.3	97	4.3	139	3.9	43	5	131
31	5.9	14.6	186	3.9	0.5	0.1	0	2.5	4.4	89	5.1	141	4.1	45	7	154
32	5.7	14.6	261	2.1	0.5	0.1	0	2.1	5.6	142	5.5	140	4.1	48	15	148
33	4.7	11.8	262	3.1	0.5	0	0	4.1	7.1	105	6.4	140	4.1	40	6	152

WCC = White blood Cell Count; Hb = Haemoglobin; Plts = Platelets; Neuts = Neutrophils; Mono = Monocytes; Eosin = Eosinophils; Bas = Basophils; Creat = Creatinine; Na = Sodium; K = Potassium; Alb = Albumin; Bili = Bilirubin; ALP = Alkaline Phosphatase; n/d = not done

Participant Number	Prol	IGF-1	Oest.	CRP	Test	FSH	LH	Total chol	HDL chol	LDL chol	Trigl	Osmol	TSH	FT3	FT4
27	95	18.7	35	<3	1.2	49.3	25.0	4.2	1.82	2.19	0.41	297	1.7	4.3	16.4
28	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d
29	140	12.3	78	15	18.2	4.2	4.3	7.4	1.10	5.60	1.54	299	1.2	4.1	12.7
30	289	10.2	113	3	n/d	10.1	n/d	3.7	1.87	1.54	0.63	291	5.0	n/d	9.2
31	94	24.3	100	<3	15.4	6.4	5.0	5.0	1.44	2.97	1.29	295	4.0	n/d	12.6
32	194	24.6	109	<3	12.2	4.8	4.1	7.7	1.69	5.24	1.70	294	2.2	5.7	16.4
33	210	21.4	57	10	n/d	53.8	16.2	5.4	1.81	3.39	0.44	286	3.5	n/d	13.5

Prol = Prolactin; IGF = Insulin-like Growth Factor; Oest = Oestrogen; CRP = C- Reactive Protein; Test = Testosterone; FSH = Follicle Stimulating Hormone; LH = Luteinizing Hormone; chol = Cholesterol; Trigl = Triglycerides; Osmol = Osmolarity; TSH = Thyroid Stimulating Hormone; FT3 = Free Tri-iodothyronine; FT4 = Free Thyroxine; n/d = not done

Participant Number	WCC	Hb	Plts	Neuts	Mono	Eosin	Bas	Fibrinogen	Urea	Creat	Glucose	Na	K	Alb	Bili	ALP
34	5.5	13.0	323	3.1	0.4	0.2	0	4.2	5.1	78	4.3	140	4.1	38	6	140
35	6	14.9	180	4	0.5	0.1	0	2	5.4	104	4.3	140	3.6	42	13	154
36	7.2	12.2	324	3.9	0.5	0.2	0	2.8	4.2	92	3.8	na	na	43	na	na
37	5.6	13.8	221	2.9	0.4	0.3	0	2.3	4.7	108	4.8	138	4.1	44	9	122
38	3.9	12.9	195	2.1	0.4	0.2	0	2.5	5.8	113	4.6	142	3.7	39	9	121
39	5	13.5	154	2.6	0.4	0.3	0.1	2.6	5.8	101	4.3	141	3.6	42	9	160
40	8.3	12.5	232	6	0.3	0.3	0	3	4.4	77	4.1	137	3.4	42	9	95
41	9.4	14.1	245	7.3	0.5	0.1	0	2.8	4.6	116	5.1	139	4.1	41	7	129
42	5.3	12.5	265	1.9	0.4	0.6	0.1	3	4	135	4.6	142	3.7	44	8	181
43	5.4	13.6	260	4.1	0.3	0.1	0	2.8	4.6	108	5.2	143	4.0	47	14	111
44	5.7	13.5	230	3.9	0.4	0.1	0	2.2	4.2	106	4.9	143	3.8	41	12	95
45	7.9	12.1	264	3.1	0.5	0.2	0	3.3	5	82	4.6	139	4.0	44	9	112
46	9.2	14.0	195	6.6	0.8	0.3	0	4.1	8.8	132	4.6	140	4.0	39	11	101
47	5.7	10.8	248	3.8	0.5	0.1	0	2.3	4.2	74	4.3	140	3.8	41	11	137
48	8	12.2	241	5.2	0.4	0.1	0	3.5	4.2	90	4.6	139	4.2	44	5	117
49	8.3	12.8	281	5.9	0.5	0.1	0	5.2	4.8	91	4.1	140	4.4	41	8	163
50	5.7	13.5	188	3.4	0.6	0.4	0.1	3.2	5.2	107	5.6	141	4.0	43	10	281
51	6.3	11.7	281	4.6	0.4	0.1	0	n/d	3.1	81	4.3	146	4.2	41	5	134
52	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d

WCC = White blood Cell Count; Hb = Haemoglobin; Plts = Platelets; Neuts = Neutrophils; Mono = Monocytes; Eosin = Eosinophils; Bas = Basophils; Creat = Creatinine; Na = Sodium; K = Potassium; Alb = Albumin; Bili = Bilirubin; ALP = Alkaline Phosphatase; n/d = not done

Participant Number	Prol	IGF-1	Oest.	CRP	Test	FSH	LH	Total chol	HDL chol	LDL chol	Trigl	Osmol	TSH	FT3	FT4
34	454	15.1	31	3	0.6	30.9	10.0	5.7	1.60	3.64	1.00	292	2.1	n/d	12.1
35	155	12.9	203	<3	>50	1.4	0.9	5.0	1.58	2.89	1.14	295	0.4	4.2	14.4
36	412	18.1	358	10	1.3	1.0	0.8	6.5	1.53	3.34	3.58	294	3.2	n/d	11.5
37	184	14.2	56	<3	12.4	1.0	<0.5	7.1	n/d	n/d	2.93	292	1.2	3.4	13.5
38	109	10.0	78	3	13.0	1.9	0.7	5.5	1.29	2.44	3.90	299	<0.1	4.5	17.1
39	511	19.0	66	3	13.5	0.5	<0.5	5.3	1.35	3.60	0.68	289	1.8	3.7	11.5
40	242	184.0	46	3	<0.5	2.1	0.6	4.0	n/d	n/d	1.16	284	0.9	n/d	12.2
41	403	37.6	100	<3	16.5	<0.5	<0.5	6.1	1.01	2.79	5.07	294	0.2	4.5	16.3
42	327	11.5	53	<3	5.7	6.7	2.0	6.8	1.17	5.06	1.25	293	1.7	3.4	10.9
43	155	11.2	48	<3	5.6	<0.5	<0.5	5.2	1.61	3.09	1.11	n/d	0.2	3.5	19.6
44	163	20.8	58	<3	15.3	1.8	0.5	5.3	2.39	2.41	1.10	296	0.2	n/d	17.4
45	284	18.6	301	<3	n/d	1.1	1.3	5.5	1.86	3.28	0.79	286	4.2	4.1	14.1
46	992	28.4	59	8	8.5	<0.5	<0.5	6.4	1.13	4.24	2.25	295	0.2	3.8	12.7
47	355	16.8	259	<3	n/d	4.2	3.8	4.3	2.47	1.35	1.06	289	1.7	n/d	18.5
48	660	9.6	n/d	3	n/d	1.3	<0.5	7.2	1.34	5.15	1.57	288	1.3	4.4	12.6
49	294	21.1	37	8	n/d	52.7	24.9	6.1	1.88	3.73	1.08	297	0.5	n/d	12.8
50	252	12.3	43	5	10.4	1.3	<0.5	5.5	1.34	3.56	1.31	n/d	0.5	n/d	13.5
51	650	16.7	38	3	n/d	5.2	1.6	5.3	2.32	2.60	0.84	302	0.5	n/d	14.6
52	209	11.5	<30	n/d	n/d	<0.5	<0.5	n/d	n/d	n/d	n/d	n/d	0.2	n/d	14.6

Prol = Prolactin; IGF = Insulin-like Growth Factor; Oest = Oestrogen; CRP = C- Reactive Protein; Test = Testosterone; FSH = Follicle Stimulating Hormone; LH = Luteinizing Hormone; chol = Cholesterol; Trigl = Triglycerides; Osmol = Osmolarity; TSH = Thyroid Stimulating Hormone; FT3 = Free Tri-iodothyronine; FT4 = Free Thyroxine; n/d = not done

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