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The Neuropsychological Effects of Pituitary Macroadenomas and their Treatment

By

Daniella Mark MRKDAN002

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Declaration

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works, of other people has been attributed, and has been cited and referenced.

SIGNATURE

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DATE 26/01/2005

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ABSTRACT

Pituitary adenomas account for roughly 12% of all intracranial tumours and are treated either surgically or medically. Due to the prevalence, there have been many articles focusing on their treatment. Recently, a few studies have been published suggesting a link between pituitary tumours, their treatment and cognitive dysfunction. These articles challenge the texts put forward to date, texts that demarcate adenoma treatment effects to the realm of the physical. The mechanism(s) behind these supposed deficits have not yet been identified, largely because of problematic research designs and sampling. In the South African context, practitioners tend to encounter a greater proportion of macroadenomas than developed countries. Working on the assumption that the effects of adenomas are magnified in macroadenoma patients, the South African situation provides a base of extreme cases in which any potential dysfunction has the best chance to declare itself. This is particularly valuable given the controversy surrounding the presence of these cognitive deficits.

The aims of the present study were to evaluate the neuropsychological functioning of patients with pituitary macroadenomas as well as to compare the neuropsychological effects of the two primary modes of treatment: transsphenoidal surgery supplemented with radiotherapy, and medication. 40 participants aged 18 – 70 were recruited. 10 patients with newly diagnosed macroadenomas were recruited prior to treatment, 10 patients had undergone transsphenoidal surgery followed by radiotherapy and 10 patients were being medicated with dopamine agonists. 10 controls were used as a comparative base. Each participant was assessed with a neurocognitive test battery. Analysis of variance was used to evaluate macroadenoma patients against controls as well as to compare the performance of the two distinct treatment groups.

Results showed a significant difference between the four groups on only one neuropsychological measure, a result interpreted as indicative of type 1 error. The study suggests that neither adenomas themselves nor their treatment impact on cognitive functioning.

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INTRODUCTION

The pituitary gland lies at the base of the brain, in the pituitary fossa of the sphenoid bone, covered by the diaphragma sellae and just below the optic chiasma. It is bordered on each side by the cavernous sinuses. Pituitary tumours are common, accounting for roughly 12% of all intracranial tumours, and the great majority are benign. Adenomas are classified by size: the largest, those greater than 10mm in diameter, are labeled macroadenomas.

In the South African context, practitioners tend to encounter a greater proportion of macroadenomas than in developed countries. This is, in large part, due to a lack of resources in the South African population. Patients often cannot afford transportation to day hospitals. Many are members of the casual wage system, where payment per hour means they cannot take time off to visit a doctor. Moreover, the pervasive lack of education results in low disease awareness, meaning that presentation in general is lower than one would expect in more educated areas. Finally, there are insufficient medical resources in the country - low doctor-per-citizen ratios, widely spaced major hospitals and insufficient equipment. All of these factors lead to later diagnosis in the disease process. Working on the assumption that the effects of adenomas are magnified in macroadenoma patients, the South African situation provides an ideal (albeit unfortunate) base of extreme cases in which any potential dysfunction has the best chance to declare itself. This is particularly valuable given the controversy surrounding the presence of these cognitive deficits.

THE PITUITARY GLAND

The pituitary gland is a vital component of the endocrine system. It receives input from the hypothalamus and releases hormones, at the same time stimulating hormone secretion in the thyroid, adrenals and gonads. Pituitary adenomas - essentially a disruption of the gland itself and therefore its properties - present with any combination of hormone overproduction or suppression, with hypersecretion being the most common outcome.

The anterior pituitary is associated with the production of six hormones, namely growth hormone (GH), Prolactin (PRL), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Adrenocorticotropin (ACTH) and Thyroid-stimulating hormone (TSH). These hormones stimulate target organs at a distance from the pituitary. The nomenclature of pituitary adenomas is based on the premise that their clinical effects derive from endocrine imbalance, rather than their various histopathologies. Therefore pituitary adenomas are classified according to the particular hormone that they secrete in excess. Of the endocrinologically active adenomas, prolactinomas are the most common, making up 55% of all secreting adenomas. They are caused by the interruption of the hypothalamic inhibitory hormone, dopamine, which leads to excess secretion of PRL. GH-secreting adenomas make up 27% of endocrinologically active adenomas and lead to acromegaly in adults, while dual-secreting or mixed adenomas, secreting both PRL and GH, account for a further 12%. ACTH-secreting adenomas make up 4% of secreting adenomas and lead to steroid excess. Gonadotrophin-secreting adenomas, involving excess production of FSH and/ or LH, make up the last 1 - 2% of endocrinologically active adenomas. TSH-secreting adenomas do occur but are rare (Johnson and Lightman, 1996). Adenomas that are endocrinologically inactive are formally classified as non-functional. Because they may

remain clinically silent well into their growth, non-functioning adenomas tend to be discovered later in the disease process than secreting tumours, making them the most common type of macroadenoma (Yeh and Chen, 1997).

Adenomas can also cause hypopituitarism in two ways. First, the blood-flow between the hypothalamus and the pituitary gland (which normally contains hypothalamic releasing hormones which act on the pituitary) can be obstructed by the enlarging mass. Second, normal anterior pituitary tissue can be destroyed by the invading tumour. The latter is particularly common in non-functional adenomas (Leavens, 1973).

Aside from endocrine significance, the central location of the pituitary gland leads tumours of that region to exert mass effect on significant surrounding structures. The optic chiasma sits directly above the pituitary fossa and as the adenoma expands upwards and out of the diaphragma sellae it tends to compress the chiasma. Because of this, adenoma patients frequently present with reduced visual acuity and visual field defects, most notably bitemporal hemianopia (Yeh & Chen, 1997). With continued growth superiorly, adenomas may invade the third ventricle and the thalamus. An adenoma that spreads superiorly and anteriorly may compress the medial surface of the frontal lobes. Growth in an inferior direction can lead to invasion of the sphenoidal sinuses. Lateral spreading can involve compression of the cavernous sinuses and temporal lobes (Powell and Lightman, 1996).

Treatment options for pituitary macroadenoma patients vary, depending on the type and level of hormone secretion, tumour size, patient age, patient's past medical history, and the subjective

preference of both the clinician and patient. Since the introduction of the intraoperative microscope, and the development of newer antibiotics, surgical management of pituitary tumours has changed from the transfrontal craniotomy to the now-preferred transsphenoidal procedure. The sphenoidal sinus route lends easy access to the pituitary gland and poses less threat to the optic chiasma. While surgery does sometimes achieve complete tumour removal, in the case of macroadenomas in particular, cure based on surgery alone is very rare. In general, surgery aims to debulk the mass, thereby decompressing the chiasma and other local structures. Such partial removal of an adenoma usually improves vision considerably and can achieve what is normally a temporary endocrine cure (Powell, 1996). Repeat transsphenoidal surgery is common because of either tumour regrowth or insufficient tumour removal at the first procedure. The risk of mortality associated with neurosurgery for adenomas, although low, is regarded as its primary disadvantage. In 1996, Powell and Lightman reported that defense unions in the United Kingdom have approximately one case per year passing through the medicolegal system.

As a result of the surgical aim of debulking rather than complete ablation, transsphenoidal procedures are most often supplemented with radiotherapy. External radiotherapy is practiced, as are more focal techniques like proton beam radiation. External radiation uses photon energies, delivering dose of between 45 and 54 Gy over four to six weeks (Yeh & Chen, 1997). Rivaling conventional radiotherapy, proton beam radiation uses focused beams rather than generalized radiation. Heavy particles are delivered directly to the adenoma, sparing normal pituitary tissue and adjacent structures such as the optic chiasma, the hypothalamus and temporal lobes (Shalet and O'Halloran, 1996). This type of intense irradiation uses high-energy particles to overcome the pituitary gland's relative insensitivity to radiation, without administering large doses to a

broad area of vulnerable tissue (Lawrence et al., 1973). However, response to radiation tends to be slow and its benefits may take considerable time to be realized (Yeh & Chen, 1997).

Conventional radiation therapy in adenoma patients is associated with a risk of hypothalamic and optic chiasmal injury (Atkinson et al., 1979), and can injure the frontal and temporal lobe tissue (Sheline, Warra and Smith, 1980). There is also a small risk of radiation necrosis and radiation-induced seizures (Yeh & Chen, 1997).

Postoperatively, the incidence of hypopituitarism is said to be related to tumour size at surgery. For macroadenomas, the incidence is reported at 30%. Similarly, radiation can lead to hypopituitarism, with an incidence of up to 30% (Yeh & Chen, 1997). In a follow-up study undertaking endocrine evaluation of nineteen pituitary adenoma patients five to ten years after surgery and radiotherapy, Muhr, Bergstrom, Enoksson, Hugosson and Lundberg (1980) found 17 had thyroid insufficiency, 16 gonadal insufficiency and 12 adrenal insufficiency.

Certain pharmacological agents have been shown to decrease tumour size, suppress tumour regrowth and inhibit hormone secretion. This type of drug therapy is a much more recent advance in adenoma treatment than either surgery or radiotherapy. Dopamine agonists like bromocriptine have been in use since the 1970's and most clinicians now consider them to be the optimal treatment for prolactinomas, choosing to medicate rather than operate (Johnson & Lightman, 1996). Dopamine begins to inhibit prolactin secretion within one hour of administration, induces prolactinoma shrinkage, reverses visual abnormalities and restores normal pituitary functions (Yeh & Chen, 1997). A small number of authorities do however continue to uphold surgery as first-line treatment for macroprolactinomas. The rationale of the

pro-surgery camp is that surgery has the potential - however small - to act as a once-off cure, whereas dopamine agonist treatment is invariably life-long. In those cases where withdrawal from medication has been recommended, reports indicate a high incidence of tumour regrowth, increase in prolactin levels and recurrence of original symptoms (Lightman and Powell, 1996). Some GH-secreting tumours are also sensitive to dopamine agonists, as the drug appears to cause partial inhibition of growth hormone release. However, this regulation is usually temporary (Kontogeorgos, 1993). Pituitary-dependent Cushing's disease has been reported to respond to bromocriptine in individual cases (Johnson & Lightman, 1996; Yeh & Chen, 1997). Finally, there have been some reports of non-secreting adenoma shrinkage in response to bromocriptine, although pharmacological treatment tends not to be advocated for these adenomas as they tend to present as exceptionally large (Yeh & Chen, 1997). The dopamine analogue of first choice is generally bromocriptine, but pergolide, carbergoline and quinagolide are used as alternatives or in cases where bromocriptine is not tolerated (South African Medicines Formulary [SAMF], 2001).

More recently, somatostatin analogues have been used successfully in the treatment of acromegaly. Somatostatin, a 14-amino acid peptide, leads to the suppression of growth hormone release from the pituitary gland and the suppression of growth hormone releasing hormone from the hypothalamus (Yeh & Chen, 1997). Kontogeorgos (1993) suggests that somatostatin also blocks the release of prolactin and TSH. Specifically, the synthetic compounds ocreotide and somatuline have been used in acromegalic patients resistant to dopamine agonists, unsuitable for surgery or with continued high growth hormone levels following surgery and/ or radiotherapy (Johnson & Lightman, 1996). Somatostatin analogue therapy has some major disadvantages,

among them the need for frequent injections and the high cost involved. Long-term therapy appears not to effect tumour shrinkage (Kontogeorgos, 1993).

As far as Cushing's patients are concerned, the most common medical alternative to surgery has been metyrapone, with mitotane and ketoconazole following closely. However, the side effects associated with these treatments, such as virilism, hypercholesterolaemia and liver damage, have limited wide usage. On a case by case basis, certain other agents have been used and reported successful, namely cyproheptadine (a serotonin antagonist) and sodium valproate (a GABA transaminase inhibitor). Finally, as mentioned earlier, bromocriptine has been reported as occasionally successful in ACTH-secreting adenomas (Johnson & Lightman, 1996).

Due to the prevalence of pituitary adenomas, there have been many articles focusing on their treatment. Every possible aspect of adenoma intervention has been described in detail through extensive case reports. Since the publication of the first adenoma surgery texts dating as far back as the 1930's, there has been no mention of cognitive dysfunction resulting from treatment. Representative of the entire genre of pituitary intervention texts is a paper on the complications associated with transsphenoidal resection of pituitary adenomas by Ciric, Ragin, Baumgartner and Pierce (1997) in which the results of a large-scale national survey of neurosurgeons, an extensive review of the literature and an experiential outline are presented. In none of these sections is there even a subtle reference to possible cognitive effects of these masses.

NEW CLAIMS REGARDING COGNITIVE DEFICITS

Recently, a few studies have been published suggesting a link between pituitary tumours, their treatment and cognitive dysfunction. These four articles challenge the many texts put forward to date, texts that demarcate adenoma treatment effects to the realm of the physical. Whilst the claims made by the recent studies are engaging, the work needs to be interpreted with caution for three important reasons, not least being their novelty. Given the considerable attention received by the topic of intervention for pituitary adenomas, it would be surprising should it transpire that all prior, far-ranging descriptions had overlooked such an effect. Nonetheless, cognitive neuroscience is a particularly burgeoning field, given to unexpected findings, so this concern does not entirely negate the possibility of the validity of the new work. It is also true that the subject of cognition has, for the most part, been routinely disregarded by medical research in the past, and that science's cognizance of the area of late is conducive to fresh discoveries. The second caution, which should be applied to a review of the recent studies, involves a series of intra-article methodological issues, some of which impinge on the validity of the findings. The third and final consideration is that the new studies, while grouped together here as a homogeneous thesis of cognitive effects of adenoma treatment, do not reach consensus on certain basic points as regards the nature of the very cognitive deficits they describe as well as their basis(e). In what follows, the last two considerations will be expanded upon in relation to the new studies.

Grattan-Smith, Morris, Shores, Batchelor and Sparks (1992) assessed memory and executive functions in 65 patients who had been diagnosed with a pituitary tumour. The 65 patients were made up of two groups - 38 patients who had undergone radiotherapy and 27 who had not been

treated with radiotherapy. Both groups were compared with a control group made up of patients with chronic illness not involving the cerebrum. The study found that collectively, pituitary patients performed worse than controls in tests of visual and verbal memory as well as executive functions. There was however no difference between the radiotherapy and non-radiotherapy groups on any of the neuropsychological tests administered, nor a correlation between neuropsychological performance and surgical procedure.

Further analysis of the research design employed in the study reveals several critical methodological problems, which threaten the validity of the aforementioned findings. The most pressing issues can be ascribed to erroneous sampling. First off is the exclusion from the radiotherapy group of four cases of confirmed delayed radiation damage, one of the patients having been diagnosed with dementia. The reason for their exclusion was death in one case and chiasmal damage in the other three. While the practicalities responsible for the exclusion are plain and inflexible, the effects thereof are clear. Elimination of those patients affected by the most predictable form of damage incurred by radiation in an investigation designed to assess the damage associated with radiation would certainly have skewed the radiation group scores in a positive direction. The second criticism is the heterogeneity of the 'non-radiotherapy' group. Of the 27 patients making up the group, seven were assessed during investigations prior to intervention while the remainder had been treated with surgery and/ or medication. Because of the group's diversity, the authors were unable to reasonably attribute the cognitive impairments found to any particular variable such as the tumour itself or either of the forms of treatment received by members of the group. The third issue is that the radiotherapy and non-radiotherapy groups were not matched in terms of diseased type. For instance, the radiotherapy group

contained eight out of a total of 38 patients with Cushing's syndrome (21%), whereas the non-radiotherapy group included only two out of a total of 27 patients (7%). Finally, the patient sample included a number of participants with medical conditions already associated with cognitive dysfunction. Specifically, two reported a history of alcohol abuse, one had complex partial seizures and another had had a previous stroke. The paper does state that these conditions 'were also considered' (1992: 627) as possible contributors to the picture of cognitive dysfunction, but does not elaborate, and then goes on to attribute the cognitive deficits found to pituitary related factors only.

A further comment on the intra-article design is that the set of tests purported to assess executive functioning is altogether incomplete. The domain of executive functioning is particularly broad, and the three tests used to measure its presentation are clearly not exhaustive. Participant performance on certain key aspects of functioning, most notably abstraction and inhibition, was not established. One could argue that inhibition was assessed to some extent through COWAT and Trail Making B, but because the study design extracted only single measures from these tests, any disinhibition would have been assimilated into the word generation and flexibility scores of the respective tests, rather than being evident in its own right. A standard test of abstraction such as the Twenty Questions Task as well as some form of inhibition assessment like the Stroop Neuropsychological Screening Test (Trennery, Crosson, Deboe & Leber, 1989) would have completed the battery. Furthermore, despite the fact that only one of the three tests of executive functioning yielded a significant difference between pituitary patients and controls (Trails Making B), the conclusion presented by the paper is that executive functioning - that wide range of behaviours we know to encompass initiative, planning, self-verification, abstraction,

mental flexibility, reasoning and social-appropriateness in the most fluid manner of all cognitive functioning - was impaired.

In the second study, Peace, Orme, Thompson, Padayatty, Ellis and Belchetz (1997) assessed cognition and mood in 36 patients who had been treated for pituitary tumours and compared them with 36 healthy controls. Neuropsychological tests of memory and executive functions as well as standard self-report measures were used to assess cognition and mood respectively.

As with the first reported study, the patient group showed impaired memory and executive functions as compared with controls. Also in accordance with that study, there were no significant differences between patients who had had radiotherapy and those who had not. However, the finding that is incongruous with the first study is that the cognitive deficits were discovered to be related to surgery, whereas Grattan-Smith et al. (1992) found no correlation between neuropsychological performance and presence of surgery. Although surgery was implicated here, there was no difference found in a comparison of patients treated with transsphenoidal surgery and transfrontal surgery. The mood assessment revealed no difference between pituitary patients and controls.

Again, it is difficult to draw conclusions from this study due to the heterogeneity of the patient group. Of the 36 patients making up the group, 27 had had surgery (13 transsphenoidal and 14 transfrontal), and of this 27, 18 had had radiotherapy. Another two patients were receiving bromocriptine. While the authors state that another five patients were not receiving medication at the time of assessment, they do not disclose whether these patients had received medication in

the past or if they were still awaiting treatment. As for the remaining two patients, no mention is made of their treatment status. While the effects of surgery and radiation are examined through the formation of subgroups at the analysis stage, the neuropsychological consequences of medication are never considered, nor are the effects of the tumour itself. Once again, the diversity of the participant group meant that the paper was unable to attribute the deficits to any particular aspect of pituitary disease. In addition, while the four tests of executive functions constitute a list that is more inclusive than the first study and therefore a better representation of the broad domain of executive functioning, the key function of abstraction was also not accounted for in the assessment. As with the first study, it would have been prudent to use a standard test of abstraction such as the Twenty Questions Task.

The third study is a paper by Guinan, Lowy, Stanhope, Lewis and Kopelman (1998) who document two case studies of patients with pituitary adenomas who had received transsphenoidal surgery, one with and one without radiotherapy. In the same paper, the authors describe the findings from a neuropsychological investigation of 90 patients who had been treated for a pituitary adenoma as compared with 19 healthy controls. The patient sample was subdivided into four groups: those who had received transfrontal surgery with radiotherapy, transsphenoidal surgery with or without radiotherapy, radiotherapy only and a bromocriptine therapy group. In the two post-surgery case studies presented, memory impairments are described. This impression is in line with the previous study's finding that neuropsychological performance is related to presence of surgery but contradicts that of the Grattan-Smith et al. (1992) paper. In addition, the more severely affected patient had received radiotherapy which opposes the findings of both previous studies. The retrospective group study demonstrated significant memory deficits in the

patient group as compared with controls, which supports similar findings in both previous studies. However, unlike the previous publications, executive functions were found to be intact. Memory impairment was evident in the surgery groups, a finding compatible with the Peace et al. (1997) paper but opposing that of Grattan-Smith et al. (1992). Deficits were seen in the radiotherapy only treatment group relative to controls, a finding which is irreconcilable with both previous studies' conclusion that radiotherapy and neuropsychological performance are unrelated. Finally, while the bromocriptine group did perform significantly worse than controls, the degree of impairment was less than that of surgical and radiotherapy patients.

In the fourth study, Peace, Orme, Padayatty, Godfrey and Belchetz (1998) performed memory and executive function assessments on three groups of 23 pituitary patients who had been treated with transfrontal surgery, transsphenoidal surgery and medication respectively and compared them with healthy controls. Consistent with the first two reports but conflicting with the third, the study found impairments in both memory and executive functions. In addition, unlike the Grattan-Smith et al. (1992) paper but in line with the more recent publications, the surgical groups were found to be more impaired than the non-surgical patients. Furthermore, whereas Peace et al. (1997) observed no difference in neuropsychological profile between transfrontal and transsphenoidal patients, this investigation reports that transfrontal patients were more severely impaired than transsphenoidal. Finally, unlike Guinan et al. (1998), but supporting the findings of the first two publications, there was no significant difference between those who had radiotherapy and those who had not. Methodologically, the same battery of tests was used as in the Peace et al. (1997) study; consequently the same criticism applies. The important executive function of abstraction was not investigated in the assessment. As with that study, it would have

been valuable to add a standard test of abstraction such as the Twenty Questions Task to the executive battery.

In sum then, the four central studies implicate pituitary adenomas and their treatment in cognitive dysfunction. Aside from this general idea, the articles are divided on much of the specifics, principally the nature of the deficits involved and their cause. The mechanism(s) behind these supposed deficits have not yet been identified, largely because of problematic research designs and sampling. Whether impairment is due to compression of adjacent structures, disruption of pathways and/ or hormonal imbalance resulting from the tumour itself, or whether surgical, radiological and/ or medical intervention is responsible, is still unclear.

Of substantial consequence is the fact that in no study were adenoma patients set up as an independent sample group prior to treatment. Instead, they formed part of various composite groups. The reason for this design fault is the persistent focus on the effects of adenoma treatment, without regard for a systematic investigation into those of the adenoma itself. The result of this error of attention is that where cognitive dysfunction was found, at the stage of interpretation the articles have been powerless to attribute the deficits to any specific mechanism. In all likelihood, the rationale behind this intervention-focussed research is that it allowed for patients to be assessed post rather than prior to intervention. This is in the context of the relative speed with which intervention is carried out in first world countries, where the research has been conducted and published. Sadly in a country like South Africa where poverty is rife and state hospitals are under-resourced, patients may wait as long as six months before being treated.

This allows sufficient opportunity for full neuropsychological assessment prior to intervention, meaning that the effects of the tumour itself can be separated from those of its treatment.

PITUITARY AND COGNITION

Aside from the four specific investigations into the cognitive effects of the treatment of pituitary tumours, there are three broad areas of work also related to the topic of adenomas: a) theses on the cognitive effects of adenomas, based on theory rather than systematic investigation, b) research into the effects of surgical, radiological and medical intervention in which the dependent measures do not include neuropsychological variables and c) investigations into individual hormonal changes and neuropsychological effects.

Theory-based Theses on the Cognitive Effects of Adenomas

To date, there has been no study published that systematically investigated the cognitive effects of a range of pituitary adenomas prior to treatment. What has been disseminated are a small number of academic texts, alleging a link between adenomas and neuropsychological deficits, with no explanation as to the neural basis for or mechanism behind these assertions. Luria (1976), for instance, explains that gross changes of consciousness, severe changes in memory and disorders of interest or emotions can occur with pituitary tumours. Randall (1982:16) reports "changes in intellect and personality". Lishman (1987) lists the following disturbances: amnesic states, emotional instability, apathy, paranoia, and general deterioration of personality. Aside from the fact that they are conceptual rather than investigative, what these texts have in common is that they offer a particularly nebulous account of cognitive presentation.

The Effects of Surgical, Radiological and Medical Intervention

As discussed, there is no shortage of publications focussing on surgical, radiological and medical treatment of adenomas. Despite this, and the reason for the deliberation about the new studies, is that one would be hard-pressed to find evidence of research in which cognition and/ or mood was investigated in relation to pituitary intervention. Hence, interest in possible neuropsychological effects of adenoma treatment requires a certain level of awareness of the various associations between neuroanatomical systems and cognition, and an application of this knowledge to texts with an exclusively neurophysiological focus.

With respect to the effects of pituitary surgery, Ciric et al. (1997) surveyed 958 neurosurgeons regarding the frequency and type of complications associated with the transsphenoidal procedure. The five most common complications were related to anesthesia, carotid artery injury, central nervous system injury, hemorrhage/ swelling of residual tumour and loss of vision. Of relevance to cognition, are the carotid artery injuries and hypothalamic injuries, occurring with an incidence of 1 to 2%. Due to the fact that the carotid arteries supply most of the cerebral hemispheres, through the anterior cerebral and middle cerebral arteries, carotid injury could potentially lead to any form of cognitive dysfunction, with the exception of the agnosias. In that the hypothalamus is implicated in behaviour patterns relating to physical protection, such as rage and fear reactions, mood states may be affected by hypothalamic lesions (Lezak, 1995).

In a follow-up study of 19 patients five to ten years after transfrontal surgery for an adenoma, Muhr et al. (1980) noted postoperative atrophic changes in three patients. The changes were in the frontal lobes, manifesting as a combination of reduced attenuation in the parenchyma and a

widened horn of the lateral ventricle on the ipsilateral side as that on which the craniotomy had been performed. Frontal lobe atrophy can lead to executive dysfunction, with characteristic deficits in such functions as attention, planning, inhibition and abstraction.

As to the effects of radiotherapy as treatment for brain tumours, Victor and Ropper (2001) outline three identifiable syndromes, differentiated from one another by time of onset and symptomatology: acute, early delayed and late delayed reactions. Of significance to cognition is late delayed injury. The processes involved are necrosis, spongiform changes in white matter, atrophy and demyelination. Symptoms tend to surface three months to several years following radiotherapy and can resemble those of either an enlarging mass or a progressive dementia.

Patients are described as mentally slowed and slightly disinhibited. Focal or generalized seizures can occur.

Kramer (1968) reviewed the literature of published cases of necrosis following radiotherapy to the pituitary region and concluded that injury tends to occur with administration of excessively high doses (between 7,700 and 43,200 rads). "(Brain necrosis) must be considered quite rare when an acceptable dose is given in a single course of treatment spread over an adequate amount of time" (1968: 310).

As regards the effects of dopamine agonists on cognition, McDowell, Whyte and D'esposito (1998) maintain that dopamine is an important neurotransmitter in terms of executive functioning. Patients with Parkinson's disease, characterized by depleted dopamine levels, exhibit cognitive impairment attributable to executive dysfunction. When treated with

dopaminergic medication, these patients have been shown to improve on a range of executive function tasks, such as the Wisconsin Card Sorting Task, a verbal fluency task and the Tower of London task. The authors examined the effects of low-dose bromocriptine on cognitive processes in 24 traumatic brain injury patients. Each patient was assessed twice: once on 2.5 mg bromocriptine and once on a placebo. The authors found bromocriptine to improve performance on tasks of executive function, specifically dual-task performance, inhibition, verbal fluency and perseveration. There was no improvement in tasks measuring cognitive processes outside of executive functions. The authors concluded that bromocriptine has a positive effect on specific executive processes. The fact that only executive tasks were improved relative to other functions was taken to mean that the effect was not attributable to increased arousal, attention or response speed. As to the neural basis of the improvement, McDowell and colleagues postulated that direct prefrontal D₂ receptor activity (some studies have shown stratification of D₂ receptors to layer V of the prefrontal cortex) or the activity of D₂ receptors in the striatum (where most D₂ receptors are situated) which activate the prefrontal cortex through mesocortical dopaminergic loops might be responsible.

Administration of bromocriptine has been associated with psychotic reactions, namely hallucinations and delusions, but the reported incidence is low. These reactions are said to occur with relatively low doses and remit with cessation of medication (Meyers, 1998).

Investigations into Individual Hormonal Changes and their Neuropsychological Effects

Pituitary adenoma symptomatology has been so well documented that there is near consensus regarding the list of associated features. The high incidence of these tumours has meant that even

introductory neurology, neurosurgery and endocrinology texts have included a section on presentation of adenomas. Throughout the countless medical texts, both introductory and advanced, the manifestations of pituitary adenomas have almost always been profiled as almost entirely corporeal. The biggest exception has been the attention given to the psychiatric manifestations of Cushing's syndrome specifically. Conventionally, prolactinomas are reported to present with amenorrhea and galactorrhea in women and loss of libido and sexual impotence in men, growth hormone-secreting adenomas with morphological features and ACTH-secreting adenomas with obesity, hypertension, diabetes mellitus, osteoporosis, amenorrhea, psychosis and depression. Non-functioning adenomas are associated with visual field defects and headaches. These are the established presentations, available on the pages of every standard textbook on the subject. The absence of neuropsychological data in most pituitary texts reflects the prevailing opinion amongst medical professionals that pituitary tumours do not affect cognition or mood.

That said, if we look to the individual hormonal changes associated with pituitary tumours, there have been some publications reporting associations between excess and/ or deficient hormone production and cognitive dysfunction. It is to these specific papers that we now turn.

Neuropsychological Effects of Prolactin

Based on a review of pretreatment physician notes of 16 men with prolactinomas, Cohen, Greenberg and Murray (1984) describe the emergence of a specific symptom constellation, one aspect of which they term 'apathy'. For the purposes of the study, the authors define apathy as 'fatigue, lethargy and/ or loss of interest in daily activities' (1984: 926). While it is clear from the objectives and conclusion of the paper that the intent of the study was to identify and

communicate psychiatric manifestations of hyperprolactinemia, the fact that such a broad definition of apathy was used, meant that non-psychiatric causes of fatigue and lethargy would also have been categorized as 'apathy'. A further methodological point is that data was accumulated from patient charts that had been completed over a ten year period prior to the outset of the study. The disadvantage of this research design is its reliance on numerous clinicians who may or may not have been equipped to assess - or been mindful of - psychiatric functioning.

Neuropsychological Effects of Growth Hormone

Margo (1981) reports a case of psychiatric complications associated with acromegaly. The patient in question had a pituitary tumour with elevated growth hormone levels. She also suffered from chronic depressive illness. Following radiation therapy for the adenoma, she became significantly less depressed. The paper reasons that while the precise relationship between the two diseases for the patient is unresolved, the possibility exists that the growth hormone abnormality may have been responsible for the patient's depression.

Several articles have been published with reference to quality of life in patients with GH deficiency (Deijen, de Boer, Blok and van der Veen, 1996; McGauley, 1989; Peace, Orme, Sebastian et al., 1997; Rosen, Wiren, Wilhelmsen, Wiklund and Bengtssen, 1994). Growth hormone deficient children have been reported to be psychologically immature and to display deviant personality development while deficient adults have been reported to be more likely to be unemployed and single (Deijen et al., 1996). Using self-report measures, some authors have found that those with deficient GH tend to report poorer quality of life than control subjects

(McGauley, 1989; Rosen et al., 1994). Meyers (1998) notes that patients with affective disorders often have abnormal growth hormone secretion, thereby implicating the hormone in mental illness processes. In contrast to these reports, Deijen et al. (1996) administered three questionnaires exploring various aspects of mood and psychological state to 17 patients with isolated growth hormone deficiency as well as 41 healthy participants and found no differences with respect to depression or anxiety.

There is evidence associating GH deficiency with memory loss. Deijen et al. (1996) evaluated the cognitive performance of 31 men with multiple pituitary hormone deficiencies (including GH deficiency) as well as 17 men with isolated growth hormone deficiency and found both to exhibit subnormal memory performance compared with healthy controls on tests of list-learning and paired associates. The authors concluded that poor memory in both groups was related to growth hormone deficiency. Although no specific mechanism has been identified for memory loss in growth hormone deficient adults, it is worth noting that high density growth hormone binding sites have been demonstrated in brain regions implicated in learning, specifically, the hippocampus (Burman et al., 1998).

Neuropsychological Effects of ACTH

The primary topic that has received attention in the literature is the link between ACTH-producing adenomas and psychiatric disturbances, most notably depression (Dorn, Burgess, Dubbert et al., 1995). In addition, Tran and Elias (2003) report that generalized anxiety disorder occurs in 79% of Cushing's patients. Finally, emotional lability and even frank psychosis can

occur (Yeh & Chen, 1997). Weitzner (1998) notes that psychopathology may even predate the onset of the physiological changes associated with Cushing's disease.

Dorn et al. (1995) examined 33 patients with Cushing's syndrome, the majority of which ($n = 29$) had pituitary adenomas. These patients had higher levels of depression and anxiety compared with healthy controls. 66.7% of patients met criteria for a psychiatric diagnosis. The most common diagnosis was major depressive disorder, with other diagnoses including hypomania, panic and alcohol or drug abuse. The authors concluded that patients with Cushing's syndrome exhibit significant psychopathology.

Starkman and Scheingart (1981) examined 35 patients with Cushing's syndrome prior to treatment. Of the group, 26 had a pituitary tumour, while the rest were made up of thymomas, adrenal adenomas and adrenal carcinomas. Based on semi-structured interviews, 86% of the sample was identified as experiencing increased irritability and anger, 77% depressed mood (ranging from short periods of sadness to suicide attempts), and 66% generalized anxiety. With regard to cognition, 83% of the sample was described as subjectively experiencing memory difficulties: these patients forgot appointments, lost objects and had difficulty remembering names. On testing, 31% of patients could not recall three cities after 15 minutes. 66% reported impaired concentration, manifesting as distractibility. In accordance with this, 51% of participants were classified as abnormal on the Mental Status Examination's Serial 7 subtraction task. These cognitive dysfunctions were in the context of normal orientation and consciousness. There was an association between both ACTH and cortisol levels and the severity of neuropsychological deficits.

As far as the neurophysiological process relating to these cognitive deficits is concerned, the adrenal cortex secretes hormones collectively known as corticosteroids in response to the release of ACTH by the anterior pituitary. Hypersecretion of ACTH due to a pituitary adenoma leads to increased corticosteroid secretion (Erlanger, Kutner, and Jacobs, 1999). Prolonged exposure to high levels of corticosteroids has been reported to adversely affect memory (Keenan, Jacobson, Soleymani, Mayes, Stress and Yaldoo, 1996) and the mechanism responsible has been identified as the remodeling of hippocampal physiology (Brown, Rush & McEwen, 1999). Excess corticosteroids are said to accelerate pathologic changes in the hippocampus, a site essential to memory processes (Keenan et al., 1996).

As far as exogenously administered cortisol (such as cortisone or prednisone) is concerned, the link between high doses (more than 40mg per day) and acute psychiatric reactions has been well established. Episodes generally involve psychoses and or euphoria (Starkman & Schteingart, 1981). Burman et al. (1995) explain that many patients with hypoadrenalism secondary to pituitary disease are given a standard dose of corticosteroids despite the fact that a lower dose would normally be sufficient. They reason that there is inter-individual sensitivity to corticosteroids and that the administration of conventionally high doses might have negative emotional effects.

In a paper examining the effects of both acute and chronic prednisone treatment on memory, Keenan et al. (1996) assessed memory functions in 25 patients with systemic disease (without CNS involvement) and compared the results with matched controls. Patients were receiving

doses of between 5 and 40 mg daily (mean 16.4mg) and had been on stable treatment for at least one year. Memory performance in the prednisone patients was significantly worse than that of controls. In a second investigation published within the same article, the authors examined the acute effects of prednisone on memory across three months of therapy. Prednisone dosage ranged from 5 to 80mg. This prospective design entailed the assessment of seven patients three times: one week prior to, one week after and twelve weeks after prednisone treatment. There was a consistent decrease in memory performance across time. The authors concluded that both acute and chronic prednisone treatment can adversely affect memory.

As to whether these findings relating to exogenous steroids are relevant to patients with spontaneously high cortisol levels, Starkman and Schteingart (1981) caution that the level of circulating cortisol in Cushing's patients is not as high as the equivalent amount of steroids administered with hormone replacement therapy. Moreover, Cushing's patients are exposed to sustained elevated cortisol levels rather than acute changes associated with steroid administration.

With respect to the effects of reduced ACTH on cognition, in Deijen et al. (1996)'s assessment of 31 men with multiple pituitary hormone deficiencies subnormal perceptual-motors performance was found. Since a substantial number of the patients were ACTH deficient, the authors attributed the low scores to ACTH deficiency. In addition, Meyers (1998) reports that patients with reduced cortisol levels, states such as those with Addison's disease, can present with cognitive impairments, particularly memory loss (Meyers, 1998).

Neuropsychological Effects of Thyroid Hormones

TSH, which is released by the anterior pituitary, stimulates the release of thyroid hormones like triiodothyronine and thyroxine by the thyroid gland (Beckwith, 2001). Abnormalities in TSH levels - such as those caused by a pituitary tumour or its treatment - can lead to abnormal thyroid hormone levels, inducing hypo- or hyperthyroidism.

Hyperthyroidism - the secretion of excess thyroid hormones - has been indicated to play a role in affective and anxiety disorders, most notably emotional lability and irritability (Beckwith, 2001). In a review of the effects of hormones on mood and cognition, Erlanger et al. (1999) report that patients with Grave's disease – hyperthyroidism in the context of diffuse goiter, ophthalmopathy and dermopathy due to an autoimmune disorder – often meet the criteria for multiple psychiatric diagnoses including major depression, generalized anxiety disorder, panic disorder, hypomania, agoraphobia, obsessive-compulsive disorder and obsessive-compulsive personality disorder. The authors maintain that the persistent psychiatric feature across numerous studies is the presence of anxiety.

In terms of cognition, it has been proposed that hyperthyroidism increases the sensitivity of tissue to catecholamine, a neurotransmitter of profound importance in models of memory and attention (Beckwith, 2001). MacCrimmon, Wallace, Goldberg and Streiner (1979) and Wallace, MacCrimmon and Goldberg (1980) report that serum T₄ levels of thyrotoxic patients correlated with impaired concentration and memory, as measured by the Stroop Test and Wechsler Memory Scale. Alvarez, Gomez, Alvarez and Navarro (1983) report that thyrotoxic patients performed worse than healthy controls on the Toulouse-Pieron Concentration Attention Test. Trzepacz,

McCue, Klein, Levey and Greenhouse (1988b) report that ten thyrotoxic patients showed mild deficits in attention, memory and complex problem-solving.

Hypothyroidism too has been associated with neuropsychological dysfunction in both the psychiatric and cognitive arenas. Psychiatric symptoms associated with hypothyroidism include depression, emotional lability and less often, psychoses (Beckwith, 2001) like paranoia and psychotic ideation (Erlanger et al., 1999). Whybrow, Prange and Treadway (1969) reported that patients with hypothyroidism performed worse than patients who were thyrotoxic on the Trail Making and Porteus Mazes tests, demonstrating impaired attention and problem-solving. An important criticism of the study is that hypothyroid patients' performance was not compared with that of healthy controls, meaning that no standard baseline was ever set up. In a large-scale study, Osterweil, Syndulko, Cohen et al. (1992) compared 54 hypothyroid patients with 30 age-matched euthyroid controls and found that they performed significantly more poorly on the Mini Mental State Exam, copying a cube, the Inglis Paired Associates Learning Test, the Animal Naming Test and Trails Part A. Monzani, Guerra, Caraccio et al. (1993) found that patients with subclinical hypothyroidism performed worse than healthy controls on Logical Memory, Digit Span, Visual Memory, Associative Memory and overall Memory Quotient.

As to whether cognitive deficits remain once patient is euthyroid, Whybrow et al. (1969) found that the hypothyroid deficits they uncovered (attention and problem-solving) persisted after patients had returned to a euthyroid state. Osterweil et al. (1992) report that a five month course of replacement therapy significantly improved performance on Trails Part A and the Inglis Paired Associates Learning Test but did not improve performance on the Mini Mental State

Exam, copying a cube and the Animal Naming Test in previously hypothyroid patients. Mennemeier, Garner and Heilman (1993) report significant ongoing memory impairment in a 63 year old female patient with primary hypothyroidism following seven months of thyroid replacement therapy. The patient's performance was compared with that of healthy controls on various memory tests including the Weschler Memory Scale and found abnormal. In another single case study, Leentjens and Kappers (1995) report that poor concentration and memory remained after treatment in a 43 year old female with primary hypothyroidism. The patient continued to perform poorly on neuropsychological tests and complained of difficulty with various tasks of daily living after treatment.

In sum, it may be concluded that hypo- and hyperthyroid states have been associated with psychiatric disorders as well as impaired cognitive performance, specifically within the spheres of memory, attention and problem-solving. Moreover, there have been reports of these impairments persisting even after the patient has returned to a euthyroid state.

Neuropsychological Effects of Gonadotropins and Gonadal Hormones

The anterior pituitary's two gonadotropic hormones - LH and FSH - stimulate the production of gonadal hormones: androgens, estrogens and progestins (Erlanger et al., 1999). There is evidence that gonadotropins have a role in certain cognitive processes. Gordon and Lee (1986) administered tests of both visuospatial and verbal functioning to healthy adults and measured their FSH, LH and gonadal hormone levels. In both men and women, high levels of FSH were associated with poorer performance on visuospatial tasks and improved performance on verbal tasks. Higher LH levels were associated with improved performance on both the visuospatial and

verbal tasks. These results suggest that FSH and LH have independent properties that affect cognitive performance in specific ways, although more research is needed in this area.

Testosterone, the most abundant of the androgens, has been associated with both psychiatric and cognitive functioning. Excess testosterone has been linked to dominant and aggressive behaviour, disinhibition, attention-seeking, enterprise, resourcefulness and impulsivity. Conversely, low testosterone levels have been associated with passive and dependent behaviour (Burman et al., 1998). In line with these findings, testosterone receptors have been localized to regions associated with emotion, particularly the amygdala (Deijen et al., 1996).

As regards cognition, androgens are thought to influence optimal spatial functioning. Janowsky, Oviatt and Orwoll (1994) administered testosterone supplements to older men experiencing age-related decline in androgen levels and measured their performance on a wide range of neuropsychological tests. The supplement significantly improved performance on the Block Design subtest of the WAIS-R (Wechsler, 1981) compared with controls.

Estradiol – the primary estrogen - has been the subject of several studies investigating cognition. Normal estrogen levels have been alleged to account in part for intact memory processes. Studies of postmenopausal women, when estradiol levels decline naturally, report that those receiving hormone replacement therapy show significant improvement on memory batteries such as the Wechsler Memory Scale, with a definite increase on the Logical Memory subtest (Erlanger et al., 1999). However, it has been proposed that this menopausal memory cognitive decline is secondary to executive dysfunction. For instance, postmenopausal women not receiving hormone

replacement are reported to exhibit perseverative errors as well as experience difficulty inhibiting incorrect responses (Keenan & Soleymani, 2001).

OBJECTIVES

As discussed, ineffective research designs and sampling in the latest pituitary studies has meant that adenoma patients have not been assessed as an independent sample group prior to treatment. The consequence is that the mechanism(s) behind the supposed cognitive deficits have not been identified. The South African context is such that the protracted interval between diagnosis and treatment provides a unique opportunity for neuropsychological assessment prior to intervention, meaning that the effects of the tumour itself can be separated from those of its treatment.

Moreover, in no previous study have macroadenoma patients been the focus of investigations. As mentioned before, the South African context is unusual in that the proportion of macroadenomas encountered within the adenoma patient population is greater than in developed countries. It is true that macroadenoma patients have been included in prior neuropsychological research, but as with the pre-treatment patients discussed above, these patients have been subsumed in larger adenoma sub-groups, and macroadenomas have never been utilized as a means of investigating exaggerated adenoma effects, where any potential dysfunction has the best chance to declare itself. This is a particularly worthwhile venture in light of the incongruity between prior assumptions about adenomas and the new contentious claims.

Aside from the necessity for theoretical confirmation, it is important that adenoma symptomatology be clearly delineated for the sake of earliest possible diagnosis. Pituitary tumours are notoriously insidious; particularly the GH-secreting variant with its very gradual

course, as well as prolactinomas in men, which do not lead to suggestive amenorrhoea. Also, should new knowledge determine that pituitary adenomas lead to cognitive dysfunction, it would be beneficial to formalize the particular aspects of the diagnostic and treatment processes to which the discipline of neuropsychology could contribute. For instance, cognitive assessment might become part of diagnosis so as to document impairment and its functional implications. Likewise, cognitive rehabilitation could form part of intervention in order to assist in the development of residual cognitive skills. Further to these aspects of clinical utility, the interface of neuropsychology and endocrinology is a fascinating, complex domain, which has the potential to yield insights into the nature of cognition itself. Research in the area takes a step in the direction of increased understanding of the interaction between the hormonal system and cognitive functioning.

The present study was designed to answer firstly the question of whether pituitary macroadenomas produce neuropsychological effects, and secondly, whether there is a difference in the neuropsychological effects of the two primary modes of treatment for pituitary adenomas, namely: 1) transsphenoidal surgery supplemented with radiotherapy and 2) dopamine agonist therapy.

METHOD

Sample

Four groups of patients were examined. A diagrammatic breakdown of participant groupings appears in Figure 1. Patients ranged from 20 to 67 years of age (mean 49 years). 21 were female

and 19 male. In order to rule out confounding effects of other medical conditions on cognition, the following exclusion criteria were set up: previous strokes, additional brain tumours, dementia, head trauma with loss of consciousness, primary epilepsy, history of alcohol abuse and history of narcotic use. Macroadenomas have been known to cause hydrocephalus by obstructing CSF outflow at the third ventricle (Hirsch and Jewkes, 1996). Because the cognitive effects of hydrocephalus are well documented (Ogden, 1986) and not the object of investigation here, those patients currently presenting with, or having previously been diagnosed with, hydrocephalus were excluded from the study.

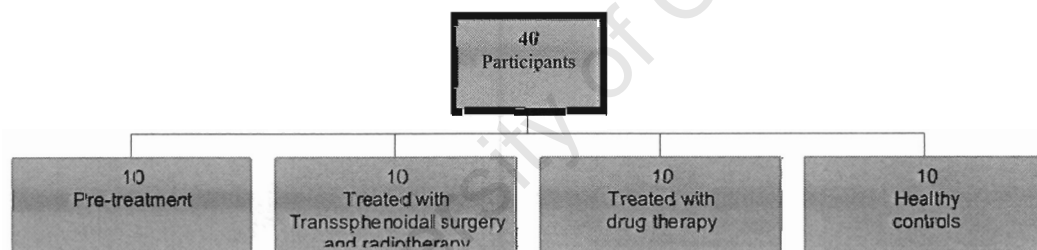


Figure 1 Breakdown of Participant Groupings

A total of 54 patients were interviewed and assessed in full. Of these, 14 were systematically excluded prior to the data analysis stage. Four patients were excluded because, despite having had a full history taken on assessment, certain medical information came to light with the examination of the hospital file that suggested possible compromised cognitive functioning for

reasons other than a pituitary tumour. Two of these patients had a history of trauma with loss of consciousness, one an additional brain tumour and the last, stroke. Two more patients were excluded because independent examination of patient scans with the aid of a radiologist revealed - despite macroadenoma diagnoses - a meningioma in the first case and a microadenoma in the second. Another patient was excluded when it was decided to extend the time-since-treatment criterion to six months for the surgery group, in order to further minimize acute treatment effects. An additional six patients were excluded because, despite identifiable as post-treatment, they did not qualify for inclusion in either of the two treatment groups. Their intervention schedules were unique (for instance, having received both transphenoidal and transfrontal surgical procedures), and so poor representations of standard pituitary treatment. Finally, a single patient was excluded since he was over 70 years of age at the time of assessment, and may ostensibly have been affected by natural, age-related cognitive decline. These rigorous exclusions, while undoubtedly leading to a smaller study sample, successfully eliminated possible confounding variables that may have been mistaken for a relationship between adenomas and cognitive dysfunction.

Both the Pre-treatment and Surgery/ Radiotherapy Groups consisted entirely of non-functioning adenomas. The Medication Group included eight prolactinomas, one dual-secreting adenoma and one non-functioning adenoma. The three treatment groups are subdivided according to tumour type in Table 1. The groups were not matched according to disease type on account of previous findings that tumour aetiology does not impact on cognitive functioning. Guinan et al. (1998) regrouped patients in terms of tumour type, rather than treatment type, and reanalyzed neuropsychological test data. Analysis of Variance was carried out and revealed no significant

difference between the new groupings. Likewise, Grattan-Smith et al. (1992) found that tumour type had no statistically significant effect on the neuropsychological tests carried out.

<i>Tumour Type</i>	<i>Pre-treatment</i>	<i>Surgery/ Radiotherapy</i>	<i>Medication</i>
Prolactinoma	0	0	8
Dual-Secreting	0	0	1
Non-functioning	10	10	1

Table 1 Tumour type by treatment group

At the onset of the study, it was decided that only those patients whose first language was English would be interviewed, but it soon became apparent that this would result in far too small a sample size. For one, South Africa has 11 official languages and the fact that the study was conducted at state hospitals meant that a true cross-section of the population was involved. Moreover, because only macroadenoma patients were included (in other words, patients who had been diagnosed relatively late in the disease process), participants tended to be the more disadvantaged of state patients. Many were from rural areas where English is seldom used and had had little education. For these reasons the criterion of English as a first language was relaxed to the principle of English fluency. In other words, patients who were proficient enough in English to be tested - despite having a mother tongue other than English - were included as well.

The study did not undertake endocrine testing on the day of assessment due to unavailability of resources. Moreover, it was felt that venous sampling would dramatically reduce consent to participate. However, the fact that participants were recruited from hospital settings meant that

they were being seen regularly by endocrinologists, and that their most recent endocrine levels were available for perusal. For each participant, results were obtained of the endocrine test performed closest to the neuropsychological testing (either prior to or just following the session). 17 participants were receiving hormonal replacement therapy. Five patients in each of Pre-treatment and Surgery/ Radiotherapy Groups and three patients in the Medication Group were receiving hydrocortisone for adrenal insufficiency. Of the Pre-treatment, Surgery/ Radiotherapy and Medication Groups, five, seven and three patients were receiving thyroxine due to thyroid deficiencies. Two patients from each of the Pre-treatment and Medication Groups, and five from the Surgery/ Radiotherapy Group were receiving either oestrogens, progestogens or androgens for sex hormone insufficiency. Treatment groups are subdivided according to hormone replacements in Table 2.

<i>Hormone Replacement</i>	<i>Pre-treatment</i>	<i>Surgery/ Radiotherapy</i>	<i>Medication</i>
Hydrocortisone	5	5	3
Thyroxine	5	7	3
Oestrogens/ Progestogens	1	5	1
Androgens	1	1	1

Table 2 Hormone replacements by treatment group

Since, of the three new studies dealing with pituitary irradiation, two convincingly found no cognitive effects (Grattan-Smith et al., 1992; Peace et al., 1997), the third producing results which could reasonably be attributed to the tumour itself (Guinan et al., 1998), for the purposes of this study it was decided that there was little theoretical necessity to include an independent

irradiation-only sample. This decision was also bred by neurological practice in that radiotherapy very rarely acts as a single modality treatment for adenomas, and this is even more factual in the case of the larger macroadenomas. What is most commonly the case is combined therapy, with an irradiation follow-up to surgical intervention.

Likewise, recruiting an adequate surgery-only sample would have proven near impossible considering that the majority of surgical interventions for macroadenomas aim to debulk the mass and/ or decompress local structures, before supplementation with radiation therapy. It is for this reason that this study includes a single group made up of cases where both surgery and radiotherapy have been performed.

The original intention was to assess two surgical groups: one transsphenoidal and one transfrontal. After careful analysis of Groote Schuur Hospital operation files and interviews with the primary pituitary surgeon, it became clear that transcranial surgery is more obscure a procedure in practice than it appears in the literature. In fact, since 1994 only six transfrontal operations were performed for the removal of pituitary adenomas at Groote Schuur, as compared with approximately 100 transsphenoidal procedures. Not only would the sample of transcranial patients have been too small for adequate population representation, but it was deemed futile to investigate the effects of a treatment that is utilized so infrequently vis-à-vis transsphenoidal surgery. Taking into account that the other most commonly used treatment for pituitary tumours is medication, the grouping schema used in this study is accurate and authentic, mimicking real treatment applications, and therefore of practical value for practitioners and patients in today's medical setting.

1) Pre-treatment Group

Ten patients, recently diagnosed with a pituitary macroadenoma and not yet having undergone primary treatment were recruited from the neurosurgery wards of Groote Schuur Hospital and Tygerberg Hospital in the Western Cape and Baragwanath Hospital in Gauteng. Five patients were on hormone replacement therapy for hypofunction of the pituitary's target glands: the adrenals, thyroid and gonads. Five of these were receiving cortisol replacement, five thyroxine, one testosterone and one estrogen.

In order for there to be the adequate opportunity for patients to be referred and assessed, a sufficient time interval between diagnosis and treatment was required. It is in the nature of medical treatment to be administered far more promptly than surgery post diagnosis. Surgical intervention is limited by time and space on an under-resourced surgery ward's waiting list. Moreover, while patients are accustomed to taking medication, surgery - and brain surgery in particular - is often weighed and considered for a certain time before it is consented to. It is for these reasons that although both the endocrine and neurosurgery departments of the two Western Cape hospitals agreed to refer macroadenoma patients post diagnosis and before treatment, it was only the surgery departments that managed to generate patients that fit the requirement for sufficient time gap for assessment. This is significant because, as outlined earlier, the type of adenoma at presentation in large part influences the type of treatment offered. What this has meant for this study is that the pre-treatment group, restricted by the requisite time lapse between diagnosis and treatment, consists entirely of patients chosen for surgery rather than the non-invasive medication option, which is generally the non-functional adenoma.

2) Surgery/Radiotherapy Group

Ten patients, having undergone transsphenoidal surgery to remove a pituitary macroadenoma were selected through a review of Groote Schuur Hospital neurosurgery operation files. Three patients had undergone repeat transsphenoidal procedures. All surgical patients recruited had been treated postoperatively with radiotherapy. Only cases in which the patient's most recent surgery and/ or radiotherapy took place at least six months prior were selected, so as not to contaminate the data with any acute post-treatment effects. The mean time since most recent surgery was five years (with a range of nine months to 18 years). The mean time since radiotherapy was four years (with a range of ten months to 11 years).

3) Medication Group

Ten patients who had been treated medically for a pituitary macroadenoma were recruited from Groote Schuur Hospital's joint pituitary clinic. All patients were currently being treated with/ or had been treated with a dopamine agonist. In seven cases, the agonist involved was bromocriptine with dosage ranging from 1.25mg per day to 2.5mg per day (mean 2.25mg per day). In two cases, the medication was cabergoline with twice-weekly dosages of 1mg and 3mg. The final participant was receiving pergolide in a daily dose of 200mg. The length of treatment to completion or to date of assessment ranged from seven months to 13 years (mean four years).

4) *Control Group*

In order to match any possible circumstantial stress or depression resulting from medical diagnoses and hospital admissions - psychological factors which might impact upon test performance - Groote Schuur Hospital inpatients were chosen as a control group. Nine patients were enlisted from Groote Schuur Hospital's neurology ward, all of which cases in which the cerebrum was not implicated, and one case from the orthopedics ward. A list of these patients' diagnoses appears in Table 3 below.

-
1. Neurofibromatosis
 2. Peripheral Neuropathy
 3. Peripheral Neuropathy
 4. Peripheral Neuropathy
 5. Cervical Spondylotic Myelopathy
 6. Motor Neurone Disease
 7. Motor Neurone Disease
 8. Rheumatoid Arthritis
 9. Spinal Injury
 10. Chronic Osteitis
-

Table 3 Confirmed Diagnoses of Control Group Patients

Materials

General Information

A basic questionnaire was given to all participants surveying date of birth, gender, handedness, first language, years of education, nature of most recent employment, subjective estimation of own vision, audition and motor functioning, past medical history and current medications.

Premorbid Functioning

- Weschler Adult Reading Test (WART)

Participants were required to read aloud a list of 50 irregular English words. The number of words pronounced correctly yielded an estimate of premorbid intelligence.

Memory and Executive Functions

The focus was on neuropsychological tests of memory and executive functions, because these functions had been alleged to be impaired in patients with pituitary tumours (Grattan-Smith et al., 1992; Guinan et al., 1998; Peace et al., 1997; Peace et al., 1998). The second factor which influenced the selection of the two primary domains of testing was a series of consultations with neurologists leading to a thorough understanding of the growth patterns of pituitary tumours as well as consultations with neurosurgeons and radiologists regarding the surgical and radiotherapeutic procedures used in treatment. Normal memory processing and executive functioning are dependent on intact frontal and temporal lobes, and these structures are adjacent to the pituitary gland, putting them at risk of incidental damage from the adenoma itself, as well as from surgical and radiotherapeutic interventions targeting the gland.

The first stage in the process of test choice was the selection of comprehensive standardized memory and executive functions batteries, from which individual subtests would be selected. To this end, the Wechsler Memory Scale - Third Edition (UK adaptation) (WMS-III^{UK}) and the Delis-Kaplan Executive Function System (D-KEFS) were chosen for their confirmed reliability and validity. These batteries are the gold standards of memory and executive functions tests for both neuropsychological research and clinical utility.

Multiple measures were selected within the domains of memory and executive functions so as to add accuracy to the interpretation of possible findings. Within the area of memory both verbal and visuospatial recollection were assessed, as were immediate and delayed memory and capacity for recognition vis-à-vis capacity for recall. Verbal immediate recall was assessed using WMS Logical Memory I and WMS Verbal Paired Associates I. Verbal delayed recall was established with WMS Logical Memory II and WMS Verbal Paired Associates II. Verbal delayed recognition was examined in Logical Memory II. Visual immediate recall was assessed using WMS Family Pictures I, and visual delayed recall using WMS Family Pictures II. Visual immediate recognition was established with WMS Faces I and visual delayed recognition with Faces II. Executive functions were assessed in both the verbal and visual modalities, assessing the full range of higher-level functions. The primary verbal executive functions test utilized was the D-KEFS Verbal Fluency Test, while the main non-verbal tests were the D-KEFS Trail Making Test and the D-KEFS Tower Test. The D-KEFS Colour-Word Interference Test and the D-KEFS Twenty Questions Test are unique in that they provide measures of both verbal and non-verbal problem-solving skills within the same task.

Once the tests had been chosen, the next stage of the materials process involved the scrutiny of all test materials for cultural specificity. Where necessary, test items were adapted for the South African population so as to minimize cultural bias. This involved simple substitutions rather than fundamental changes to the material. These adaptations are listed in Table 4 below.

Subtest	Modifications
WMS Logical Memory I and II	<i>South London to East London High Street to Main Road Pounds to Rands Liverpool to Durban</i>
WMS Verbal Paired Associates I and II	<i>Badger to Squirrel</i>

Table 4 Adaptations to Standardized Tests for the South African Population

The following tests were employed:

Memory

- Logical Memory I and II

Two short stories are presented orally by the examiner. The participant is required to recall the stories immediately and after a 25 - 35 minute delay, as well as answer key questions in a true/false format. The test measures immediate and delayed verbal recall as well as delayed verbal recognition. Six scores were computed: 1st Recall Total Score, LM I Recall Total Score, LM II Recall Total Score, Recognition Total Score, Learning Slope Calculation and Percent Retention Calculation.

- Faces I and II

A series of faces is presented visually by the examiner. The participant is required to recognize the faces from two further series immediately and after a 25 - 35 minute delay. The test measures immediate and delayed visual recognition. Two scores were computed: F I Recognition Total Score and F II Recognition Total Score.

- Family Pictures I and II

A series of family photographs is presented visually by the examiner. The participant is required to recall information pertaining to the photographs immediately and after a 25 - 35 minute delay. The test measures immediate and delayed visual recall. Three scores were computed: FP I Recall Total Score, FP II Recall Total Score and Percent Retention Calculation.

- Verbal Paired Associates I and II

A series of novel word associations is presented orally by the examiner. The participant is then prompted with the first word of each pair, and is required to recall the corresponding word immediately and after a 25 - 35 minute delay. The test measures immediate and delayed verbal recall. Five scores were computed: 1st Recall Total Score, VPA I Recall Total Score, VPA II Recall Total Score, Learning Slope Calculation and Percent Retention Calculation.

Executive Functions

- Trail-Making Test

The participant is required to connect numbers and letters in an alternating, ascending sequence. The test measures cognitive flexibility, as well as rule observance. Two scores were computed: Completion Time and Total Errors.

- Verbal Fluency Test

The participant is required to generate as many words as possible that begin with a series of designated letters. The test measures spontaneous verbal generation. One score was computed: Total Correct.

- Colour-Word Interference Test

The participant is required to name dissonant ink colours in which colour names are printed. The test measures inhibition of overlearned responses, as well as rule observance. Two scores were computed: Completion Time and Total Errors.

- Twenty Questions Test

The participant is presented with a stimulus page depicting pictures of 30 common objects. The participant is required to ask the fewest number of yes/no questions possible in order to identify the unknown target object. The test measures abstract thinking. Three scores were computed: Initial Abstraction Score, Total Questions Asked and Total Weighted Achievement Score.

- Tower Test

The participant is required to move disks across three pegs in order to build a designated tower.

The test measures planning as well as rule observance. Three scores were computed:

Completion Time, Total Achievement Score and Total Rule Violations.

Procedure

Each patient's hospital file was examined for the following information: previous medical history, endocrine status, MRI report, tumour dimensions, tumour type, any postoperative complications and current medication.

Participants were interviewed at outpatient clinics, in neurosurgery wards at the bedside, at special appointments in various hospital offices, or in their homes. In each case, care was taken to ensure as quiet and undisturbed an environment as possible. Each assessment session lasted approximately three hours. The sequence of tests was the same for all participants. Not all participants completed all tests, chiefly because of time constraints on the part of these patients. The controls group was assessed on the same battery of neuropsychological tests as used in the patient groups. Testing was carried out in a standardized manner, as defined by the administrations manuals accompanying test materials. Assessments were conducted and marked by the author.

Ethics

The study protocol was approved by the University of Cape Town's department of Psychology, Groote Schuur Hospital's Ethics Board, Groote Schuur Hospital's Medical Records department, the department head of neurosurgery at Tygerberg Hospital, Tygerberg Hospital's Medical Records department, and the department head of neurosurgery at Baragwanath Hospital. All participants were handed a consent form prior to testing, which was simultaneously elucidated by the assessor. Following this, any participant questions were answered. Written consent was then obtained from each participant.

RESULTS

All analyses were carried out using the STATISTICA package. Conventional significance levels were adopted ($p < 0.05$). According to one-way analysis of variance (ANOVA), the four groups did not differ in terms of age, years of education or estimated premorbid IQ, as determined by the WART. These results are shown in Tables 5 - 7.

	df	SS	MS	F	P
GROUP	3	1314.20	438.07	2.8282	0.052141
Error	36	5576.20	154.89		
Total	39	6890.40			

Table 5 Results for age across groups

	df	SS	MS	F	P
GROUP	3	591.075	197.025	0.87471	0.463223
Error	36	8108.900	225.247		
Total	39	8699.975			

Table 6 Results for years of education across groups

	Df	SS	MS	F	P
GROUP	3	516.07	172.02	1.6497	0.196817
Error	33	3441.01	104.27		
Total	36	3957.08			

Table 7 Results for estimated premorbid IQ across groups

One-way ANOVA was used to determine group differences on the 27 measures of the nine neuropsychological tests. The four groups did not differ significantly on the following 26 measures of memory and executive functions at the 5% level: *LMI 1st Recall Total Score, LMI Recall Total Score, LMII Recall Total Score, LMII Recognition Total Score, LMII Learning Slope Calculation, LMII Percent Retention Calculation, FI Recognition Total Score, FII Recognition Total Score, FPI Recall Total Score, FPII Recall Total Score, FPII Percent Retention Calculation, VPAI 1st Recall Total Score, VPAI Recall Total Score, VPAIL Recall Total Score, VPAIL Learning Slope Calculation, VPAIL Percent Retention Calculation, Trail Making Completion Time, Trail Making Total Errors, Verbal Fluency Total Correct, Colour-Word Interference Completion Time, Colour-Word Interference Total Errors, Twenty Questions Initial Abstraction Score, Twenty Questions Total Questions Asked, Twenty Questions Total Weighted Achievement Score, Tower Total Achievement Score and Tower Total Rule Violations.*

The sole test that yielded a significant difference was the *Tower Total Item Completion Time* ($F(3.7276) p = 0.019713$).

	df	SS	MS	F	P
Group	3	285338	95113	3.7276	0.019713
Error	36	918573	25516		
Total	39	1203911			

Table 8 Tower Total Item Completion Time test results

To examine more closely the significant finding, Tukey's Honestly Significant Differences was carried out as a post-hoc inter-item test. Table 10 shows a difference was found between the Pre-treatment and Medication Groups. The performance favoured that of the Medication Group.

	Group	{1}	{2}	{3}	{4}
1	Pre-treat		0.860690	0.014744	0.692573
2	Surgery	0.860690		0.092934	0.989209
3	Meds	0.014744	0.092934		0.173115
4	Control	0.692573	0.989209	0.173115	

Table 9 Tukey's Honestly Significance Differences results

In summary, no significant difference was found between the performance of the Pre-treatment, Surgery/ Radiotherapy, Medication or Control Groups on twenty-six of the twenty-seven neuropsychological measures. The single significant difference favoured the Medication group over the Pre-treatment Group in the Tower Item Completion Time test.

GENERAL DISCUSSION

This study involved a neuropsychological investigation of 30 patients with pituitary macroadenomas with two important questions in mind:

1) Do discrepancies in memory and executive performance exist between pituitary macroadenoma patients and healthy controls?

and

2) Do discrepancies in memory and executive performance exist between transsphenoidal/ radiotherapy patients and bromocriptine agonist patients in relation to healthy controls?

Although a significant difference was found between the Pre-treatment and Medication Groups on a single executive test, it is most critical that a further fundamental question be posed:

3) If differences are found, are these discrepancies of practical significance?

To answer the two original questions, it is evident from the statistical analyses that in all but one of the neuropsychological measures, there were no significant differences between the performances of the four groups. A single discrepancy did arise in the form of the Tower Item Completion Time measure between the Pre-Treatment and Medication Groups. It is clear then, in answer to the first question that there is no difference in memory and executive performance between pituitary macroadenoma patients and healthy controls. In order to satisfy the second original question, we must return to the further fundamental question as to the practical significance of the single significant finding.

It is the interests of sound research to interpret statistical findings within meaningful theoretical frameworks. Conceptually, from what we understand about the brain, it is a somewhat anomalous result if only a single executive function is impaired in the context of otherwise intact executive functioning.

According to the D-KEFS Administration Manual:

“One sign of a well-trained, experienced examiner is that he or she is not quick to interpret low test scores as indicating cognitive deficits. Rather, the experienced clinician first comprehensively evaluates whether a cognitive deficit is consistently revealed by several test measures that also are designed primarily for evaluating the ability area or are highly dependent on that ability for successful performance.”

(p.32)

The point is that the single discrepancy did not persist across the 11 tests assessing executive functions in their entirety. Executive functions are a complex conglomeration of functions, and executive performance is based upon a host of complex and multifactorial processes. Each of the 11 executive tests, including the Tower Item Completion Time taps a host of fundamental higher-level cognitive skills, and there is considerable overlap between them. Given this actuality, it is extremely unlikely that the significant finding reflects a broad population difference between pre-treatment and medicated pituitary patients, and so another explanation is in order.

This explanation we find in the form of statistical probability. Because the study was primarily exploratory in nature, in order to maximize the chance of detecting group differences and therefore minimize type II errors, the conventional alpha level of 0.05 was not adjusted using Holm's (1979) conservative Bonferoni procedure. The flip-side of this preference for discovery is that the probability of type 1 error is increased, with its likelihood of false positive findings.

Taken together, these two factors are sufficient to discredit the significant finding and conclude that in answer to the second original question, neither of the two primary treatment schedules for pituitary adenomas appear to be responsible for, or associated with impaired memory or executive functioning.

Cognitive deficits have been previously reported in pituitary patients (Grattan-Smith et al., 1992; Peace et al., 1997; Guinan et al., 1998; Peace et al., 1998) but these studies need to be interpreted with caution due to three factors discussed at length, namely 1) their incongruity with all

previous work in the genre of pituitary symptomatology, 2) substantial methodological shortcomings, some of which violate the validity of the findings, and 3) their discord on basic issues such as the nature of and mechanisms responsible for the very cognitive deficits they describe. Furthermore, the present study was set up in the South African context, which granted two very advantageous research conditions. The first was the time lapse between diagnosis and treatment, which allowed sufficient opportunity for full neuropsychological assessment prior to intervention, and therefore the investigation of adenoma patients prior to treatment. The second was the relatively large proportion of macroadenomas at diagnosis, allowing the study a full macroadenoma-only sample and the opportunity to examine a magnified version of adenoma effects. These conditions created a context for research that was not afforded to the previous pituitary studies.

Relevant to the question of the applicability of these macroadenoma-specific findings to microadenoma patients, the most important consideration is the fact that macroadenomas are so designated solely because of their size; their histological features differ in no way from those of their smaller counterparts. Moreover, previous work has shown that size of pituitary tumour does not impact on memory or executive impairment performance (Grattan-Smith et al., 1998).

As has been discussed, the treatment schedule for pituitary adenomas varies depending on numerous factors such as endocrine functioning, tumour size, patient age, patient's visual symptoms, and so forth. The present study does not support the conception of surgical, radiotherapeutic or medical pituitary treatment as a determinant of cognitive functioning, and so

cognitive functioning need not be considered a significant variable in the already-complex choice of treatment.

This is not to say that there do not exist any nonspecific psychosocial consequences of dealing with a chronic illness like pituitary disease. Counseling for patients and families should be kept in mind as possible recommendations to pituitary patients who are experiencing anxiety or depression. Issues of adjustment to illness are general and apply to many chronic conditions, as do the emotional struggles a family may experience in dealing with a member who has a chronic condition. In light of this, neuropsychologists seem well qualified to play an important part in the management of pituitary adenomas.

It must be acknowledged at this point that this was a retrospective study, meaning that patients were not interviewed prior to the development of the adenoma. In other words, there is no documented assessment measure available, no mark of baseline functioning, with which to compare the current pre-treatment assessments. Using a control group of normally functioning individuals does its best to establish a measure of expected scores, as do years of education and Wart scores, but these are limited in that they are only estimations of patient norms.

In the same vein, post-treatment groups were not assessed post diagnosis and prior to treatment. Time was the most crucial factor contributing to this limitation of study design, so: The gap between surgery and radiotherapy stands at approximately six months. The radiotherapy process itself takes roughly two months. In addition, in order not to contaminate cognitive performance with acute effects of surgery or radiotherapy, a time lapse of six months since most recent

surgery and/ or radiotherapy was set. If a surgery/ radiotherapy group was to be assessed both prior to surgery and following radiotherapy, the data gathering process for a single patient in this group would have been no less than fourteen months. Including a discrete group of pre-treatment macroadenoma patients acted to establish a measure of expected functioning prior to treatment, but once again, these are limited in that they are only estimations of expected pre-treatment functioning for the treatment groups.

The final limitation is relevant to the question of the external validity of these findings. Pituitary patients were enrolled on the basis of the absence of confounding cerebral pathologies, namely: previous strokes, additional brain tumours, dementia, head trauma with loss of consciousness, primary epilepsy, history of alcohol abuse and history of narcotic use. These exclusion criteria may well have led to the construction of an 'ultra healthy' group, not accurately reflecting the general population of pituitary patients.

The present study was conducted as an exploration of the findings of a recent series of articles associating pituitary tumours and/ or their treatment with cognitive dysfunction. These new texts were published at the end of a long line of scientific literature that demarcates adenoma symptomatology and treatment effects to the realm of the physical. The present study demonstrated clearly that pituitary macroadenomas do not lead to cognitive impairment when compared with controls. Moreover, neither of the two primary modes of treatment for adenomas was associated with cognitive dysfunction relative to controls. These findings support the original assumption of the many published pituitary articles and case reports, and corroborate

with the prevailing opinion amongst medical professionals, that pituitary tumours do not affect cognition or mood. This study provides reassurance for clinicians and pituitary patients.

University of Cape Town

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