PLAGIARISM DECLARATION

PLAGIARISM

This means that you present substantial portions or elements of another's work, ideas or data as your own, even if the original author is cited occasionally. A signed photocopy or other copy of the Declaration below must accompany every piece of work that you hand in.

DECLARATION

1. I know that plagiarism is wrong. Plagiarism is to use another's work and pretend that it is one's own.

2. I have used the American Psychological Association formatting for citation and referencing. Each significant contribution to, and quotation in, this essay/report/project from the work or works, of other people has been attributed, cited and referenced.

3. This essay/report/project is my own work.

4. I have not allowed and will not allow anyone to copy my work with the intention of passing it off as his or her own work.

NAME: Olivia de Villiers and Claudia Elliot-Wilson

STUDENT NUMBER: DVLOLI001 and ELLCLA004

SIGNATURE: O. de Villiers and C. Elliot-Wilson

TOPIC: Research Project

Cognition, but not Sleep, is Disrupted in Patients with Non-Functioning Pituitary Adenomas

Olivia de Villiers and Claudia Elliot-Wilson

ACSENT Laboratory
Department of Psychology
University of Cape Town

Supervisor: Dr Kevin G. F. Thomas
Co-supervisors: Dr Michelle Henry, Dr Ian Ross, Dr Thurandrie Naiker, and Dr Patrick Semple
Word count: 7997

The financial assistance of the National Research Foundation (NRF) towards this study is hereby acknowledged. Opinions, findings and conclusions or recommendations expressed in any publication generated by the NRF supported study, is that of the author(s) alone, and the NRF accepts no liability whatsoever in this regard.

Abstract

A robust neuroscience literature indicates that healthy sleep supports cognition and that sleep disruption is associated with cognitive dysfunction. Moreover, separate strands of the literature on patients with pituitary disease indicate that they often (a) demonstrate cognitive dysfunction and (b) experience disrupted sleep. The current study is, however, the first to explore directly whether sleep disruption mediates relations between pituitary disease and cognitive dysfunction. We recruited 20 patients with non-functioning pituitary adenomas (NFPA) and 19 sociodemographically matched healthy controls. We obtained self-report information regarding sleep disruption from the Global Sleep Assessment Questionnaire, and objective data regarding cognitive functioning across various domains (including processing speed, working memory, episodic memory, and executive functioning) from the Brief Test of Adult Cognition by Telephone battery. Analyses detected significantly poorer cognitive performance in patients than in controls (p = .007; a finding consistent with previous studies), but detected no significant between-group differences in sleep disturbance (p = .55) and no significant association between sleep disturbance and cognitive performance (p = .57; findings inconsistent with previous studies). We concluded that, in this sample, sleep disruption did not mediate relations between NFPA and cognitive dysfunction. Nonetheless, an important clinical implication of our data is that cognitive remediation alongside usual treatment may benefit NFPA patients. Moreover, we demonstrated that physically distanced administration of a cognitive test battery is effective in pituitary disease patients and can replicate results obtained from in-person administration. To explore the mediation question further, future research should use objective measures to characterize sleep disruption more accurately.

Sleep is a universal behavioural and biological phenomenon that supports crucial aspects of human health (Irwin, 2015; Mukherjee et al., 2015). Healthy sleep is associated with lower risk for a range of medical illnesses and psychiatric disorders, and with better concentration and memory (Irwin et al., 2017; Tantawy et al., 2013). Hence, disrupted sleep duration or quality can have detrimental consequences for physical, mental, and cognitive health. Of particular interest to neuroscientists is the role sleep plays in memory consolidation (Peter-Derex, 2019; Wamsley & Stickgold, 2011).

The purpose of this study was to explore whether sleep disruption mediates cognitive dysfunction in patients with pituitary disease (specifically, non-functioning pituitary adenomas [NFPA]). These patients provide an opportunity to investigate relations between sleep and cognition because the pituitary gland is a central component of a neuroendocrine system (the hypothalamic-pituitary-adrenal [HPA] axis) that regulates sleep-wake cycles and that plays a critical role in learning and memory processing. Hence, organic damage to the pituitary gland may result in HPA-axis dysregulation and, consequently, sleep disruption and cognitive dysfunction (Emerald, 2016).

Below, we describe commonly occurring pituitary diseases and outline ways in which sleep patterns tend to be disturbed in patients with pituitary disease. Thereafter, we examine studies investigating cognitive dysfunction in these patients before reviewing literature on how sleep disruption and cognitive dysfunction may be related in their clinical presentation.

Pituitary Diseases

The term *pituitary disease* refers to a generic group of disorders in which the pituitary gland functions abnormally, leading to hyper- or hypo-secretion of pituitary hormones. The pituitary gland's normal functioning can be altered by organic damage (e.g., by a tumour/neoplasm). Pituitary tumours can be classified by size (i.e., microadenomas [diameter <1 cm] or macroadenomas [diameter >1 cm; Machado et al., 2016; Shirvani et al., 2016) or by functionality (i.e., functioning or non-functioning adenomas). Functioning adenomas directly affect hormone release from the pituitary gland, and consequently influence physiology and cognition. Although non-functioning pituitary adenomas (NFPA) can be relatively benign in comparison, they do still affect both physiology and cognition (Dekkers et al., 2007; Øytese et al., 2016).

Cushing's disease and acromegaly can both result from functioning pituitary adenomas. Cushing's disease is characterised by the pituitary gland's overproduction of adrenocorticotropic hormone (ACTH), which stimulates an excessive concentration of cortisol from the adrenal glands which is associated with increased risk of cognitive

dysfunction and reduced sleep quality (Balbo et al., 2010; Bertagna et al., 2009; Forget et al., 2016; Ly et al., 2015). Acromegaly is a consequence of the overproduction of growth hormone (GH) by the pituitary gland. This overproduction causes excessive deposition of glycosaminoglycan (i.e., complex carbohydrates) and collagen, resulting in tissue overgrowth in the upper airways and respiratory apparatus. This structural remodelling can cause obstructive sleep apnea (Romijn, 2016).

Sleep Disruption in Pituitary Diseases

Sleep consists of two main stages: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. NREM sleep is subdivided into three stages: stage 1 (light sleep), stage 2, and stage 3 (deep sleep, in which slow-wave sleep [SWS] occurs). Neuroscience research has investigated the occurrence of disrupted sleep, across these stages, in patients with pituitary disease because of the bidirectional relationship between sleep and HPA-axis functioning (Balbo et al., 2010). For instance, HPA-axis activity (and consequent release of ACTH and cortisol) is inhibited during SWS (Van Cauter et al., 2008). In turn, sleep is disrupted when the HPA axis is highly active because this level of activity (which consequently increases cortisol release) inhibits SWS. HPA-axis activity has also been associated with changes in REM sleep, though these findings are less clear. Corticotropin releasing hormone (CRH) is thought to reduce REM sleep, with increases in CRH levels promoting wakefulness (Buckley & Schatzberg, 2005). CRH stimulates release of ACTH and subsequent release of cortisol, though associations between raised cortisol levels and REM sleep appear to be dichotomous. García-Borreguero et al. (2000) suggest that contradicting results may indicate that some cortisol is needed for REM sleep, but an excess of cortisol decreases REM sleep.

Pituitary tumours alter HPA-axis activity by affecting hormone release from the gland itself. When this alteration increases HPA-axis activity, one would expect (following the reasoning outlined above) that patients with pituitary disease would experience consequences such as reduced SWS, fragmented sleep, or altered REM sleep duration. Such disrupted sleep can exacerbate HPA-axis hyperactivity, continuing a problematic feedback loop (Buckley & Schatzberg, 2005).

Broadly speaking, empirical literature confirms these expectations. Patients with NFPA often present with decreased REM sleep, increased stage 1 sleep, more night-time awakenings, and increased daytime sleepiness (Biermasz et al., 2011; Joustra et al., 2014; although see van der Klaauw et al., 2007, for contrasting data). Biermasz et al. (2011) suggest that these sleep disturbances could be attributed to damage sustained to the

retinohypothalamic tract or to the suprachiasmatic nucleus by the presence of the NFPA or by the treatment thereof. Damage to either of these brain structures can interfere with regular circadian rhythms and thereby disrupt sleep (Astiz et al., 2019).

Patients with Cushing's disease often complain of sleep disturbances (Romijn, 2016). Compared to non-diseased controls, these patients have lighter, more fragmented sleep periods, more night-time awakenings, greater REM sleep density, and a significantly longer stage 1 sleep duration (Shipley et al., 1992). Patients with acromegaly commonly suffer from sleep apnea (37–54% prevalence; Hernández-Gordillo et al., 2012; Vouzouneraki et al., 2018) often leading to excessive sleepiness, which worsens with the severity of the condition (Bjorvatn et al., 2015; Zhou et al., 2016).

Cognitive Dysfunction in Pituitary Disease

Patients with pituitary disease often demonstrate cognitive dysfunction, with the specific nature of the impairment varying dependent on the nature of the organic damage (Yedinak & Fleseriu, 2014). Patients with Cushing's disease frequently display impaired performance on tests assessing learning, memory, and executive functioning (Tiemensma et al., 2010), whereas patients with acromegaly present with impaired attention, visuoconstructional abilities, visual/verbal memory, verbal fluency, and executive functioning (Leon-Carrion et al., 2010). In a study comparing patients with acromegaly to patients with NFPA, Yedinak and Fleseriu (2014) reported that the former group self-reported poor learning and concentration abilities and showed difficulty maintaining focus on imminent tasks, while the latter group self-reported more cognitive dysfunction in the domains of mental agility and verbal memory recall.

As noted above, Cushing's disease is characterised by excess secretion of cortisol. Therefore, brain structures with heavy concentrations of glucocorticoid receptors are especially sensitive to these excesses (Fan et al., 2019; Harbeck et al., 2009). One such structure is the hippocampus, which plays a crucial role in declarative memory processing (Antony & Paller, 2017). Hence, structural and functional Cushing's disease-related changes in the hippocampus contribute to the irreversible impairment in performance on declarative memory tasks seen in these patients.

Leon-Carrion et al. (2010) suggest that the excess secretion of GH and insulin-like growth factor 1 (IGF-1) that characterises acromegaly might explain decreased electroencephalographic activity in the prefrontal and middle temporal cortices in these patients. They suggested that these electrophysiological alterations may be the underlying cause behind the cognitive impairment displayed by these patients.

Patients with pituitary disease are often treated with radiotherapy and it is thus important to ascertain whether their cognitive impairments are due to disease presence, the radiotherapy treatment, or some combination of the two (Crouzeix et al., 2019). Noad et al. (2004) compared patients who had received both surgery and radiotherapy to those who had received only surgery for the removal of the pituitary tumours. Their analyses detected impaired performance in both groups, and no between-group differences, on a standard assessment of executive functioning (the Stroop Color-Word Test; Stroop, 1938). This finding suggests that the cognitive dysfunction present in patients with pituitary disease should not differ on the basis of treatment.

Does Sleep Disruption Mediate the Association Between Cognitive Dysfunction and Pituitary Disease?

The review above indicates that patients with pituitary disease experience disrupted sleep quality and duration as well as specific patterns of cognitive dysfunction. However, only one published article (Wennberg et al., 2019) investigates a possible relationship between sleep disruption and cognitive dysfunction in pituitary disease. This fact is surprising because a large and well-established body of literature suggests that sleep quality, by itself, has significant effects on cognitive performance.

Healthy, uninterrupted sleep supports numerous cognitive processes, including memory consolidation (i.e., the integration of newly acquired information into existing neural networks; Cellini, 2017; Krause et al., 2017; Peter-Derex, 2019; Wamsley & Stickgold, 2011). Sleep-dependent memory consolidation involves the movement of information encoded during the waking day into permanent memory traces. A key mechanism underlying this process occurs during SWS, when newly encoded information is transferred between hippocampal and neocortical regions in a reiterative process, thus making uninterrupted sleep after learning an important part of memory consolidation (McDevitt et al., 2017; Tantawy et al., 2013). Studies also suggest that an uninterrupted night of sleep *before* learning allows for more efficient retrieval of that information on subsequent days (Cordeira et al., 2018; Walker, 2008). This enhanced efficiency is facilitated by sleep-dependent memory reorganisation that stores existing memories more economically so as to prepare brain structures for subsequent storage and recall of newly encoded material (Wamsley & Stickgold, 2011). More specifically, processes of neuroplastic memory trace reorganisation involve strengthening of synaptic connections for more efficient storage of new memories within existing neural networks (Peter-Derex, 2019). By negatively impacting these processes, sleep disruption

may, for instance, cause individuals to experience relative difficulty recalling information learned on previous days.

In other words, sleep disruption may in fact mediate the association between the presence of pituitary disease and cognitive dysfunction. However, as noted above, only one published study reports on an investigation that approaches this possibility. Wennberg et al. (2019) administered self-report questionnaires assessing sleep quality and overall quality of life to 67 acromegalic patients. The same patients were administered a comprehensive neuropsychological test battery that assessed the various cognitive domains. The researchers found a weak association (B = -.03, 95% CI .06, -.002, p = .037) between sleep quality and cognitive performance, and a stronger association (B = -.03, 95% CI -.05, -.006, p = .015) between sleep quality and overall quality of life. On that basis, they concluded that the link between sleep disruption and cognitive dysfunction in patients with pituitary disease is firm and warrants further investigation.

Rationale, Aims, and Hypothesis

Numerous studies report that patients with pituitary disease experience reduced sleep duration and quality. A separate strand of the literature reports specific patterns of cognitive dysfunction in these patients. However, despite a wealth of scientific literature confirming that disrupted sleep has predictable negative effects on cognitive functioning, only one study has addressed the possibility of sleep disruption mediating the association between cognitive dysfunction and pituitary disease. That study (Wennberg et al., 2019) found associations between sleep quality and cognitive performance, and between sleep quality and overall quality of life, in a group of patients with acromegaly. Although it appears to have established a firm link between the constructs of interest, it (a) sampled patients from only from one type of pituitary disease, (b) did not include comparison with a matched healthy control group, and (c) could not, by design, undertake direct investigation of the mediational relationship. Hence, further research is required to expand upon the findings presented by Wennberg et al. (2019).

The current study sought to provide some of that expansion. We investigated sleep quality and cognitive performance in a different group of patients with pituitary disease (viz., those with NFPA), included a group of sociodemographically matched healthy controls, and undertook direct investigation of whether sleep disruption mediates the relationship between pituitary disease and cognitive dysfunction. We tested these specific hypotheses: (1) patient performance on an objective test of cognitive performance will be significantly worse than that of controls; (2) patients will self-report significantly more disrupted sleep than controls;

and (3) sleep disturbance will mediate the relationship between the presence of pituitary disease and cognitive performance.

Method

Design and Setting

The study used a correlational case-controlled design. All data were collected telephonically. The presence or absence of NFPA served as the predictor variable. The outcome variable was score on a cognitive test battery. The mediating variable was score on a self-report sleep quality questionnaire.

Participants

Recruitment

We recruited 20 patients with NFPA (10 women; Figure 1 is a flowchart describing how we arrived at this number). To obtain this sample, we inspected the Groote Schuur Hospital (GSH) Radiotherapy Clinic patient database to identify individuals who met the study's eligibility criteria. We identified 51 patients with NFPA (surgery only, or surgery and radiotherapy) and obtained their contact details from their GSH files. We attempted to make telephonic contact with each of them. For those with whom contact was successful (n = 24), we presented a verbal recruitment script that indicated how we obtained their contact details, gave a brief description of the study, and asked if they would be willing to participate (see Appendix A). If they replied in the affirmative we scheduled the telephonic interview for a time that suited them.

We recruited 19 healthy control participants (10 women). Each member of this group matched a member of the patient group on these key sociodemographic variables: age (within 5 years), sex, level of education (within 2 years), and socioeconomic status (SES). Controls were matched accordingly as there are well-established literatures describing age-related declines in cognition and in sleep patterns (Crowley et al., 2018; Kuo et al., 2016; Miner & Kryger, 2018). There are also well-established sex differences in sleep patterns and sleep disorders (Meers et al., 2019). Additionally, higher levels of education act as a protective factor against cognitive dysfunction later in life (Guerra-Carrillo et al., 2017; Liu & Lachman, 2019). Finally, a large literature describes the impact of SES on cognitive performance across the lifespan (Hackman & Farah, 2009; Huang et al., 2019).

To obtain the control sample, we gathered contact details of friends, family members, or spouses of patients and of our own family and friends who might have matched patient demographics. We then called them to enquire about their interest in participating.

Eligibility Criteria

We required that all participants be aged between 18 and 65 years. This criterion was put in place due to the extensively described age-related variability in sleep architecture and cognitive functioning (Kuo et al., 2016). Sleep architecture changes with age and is particularly variable in children, adolescents, and older adults (Crowley et al., 2018; Miner & Kryger, 2018). Similarly, there are well-documented cognitive declines in otherwise healthy older adults, and cognitive functioning is much more variable in children and adolescents than in young- and middle-aged adults (Mella et al., 2016; Whitley et al., 2016).

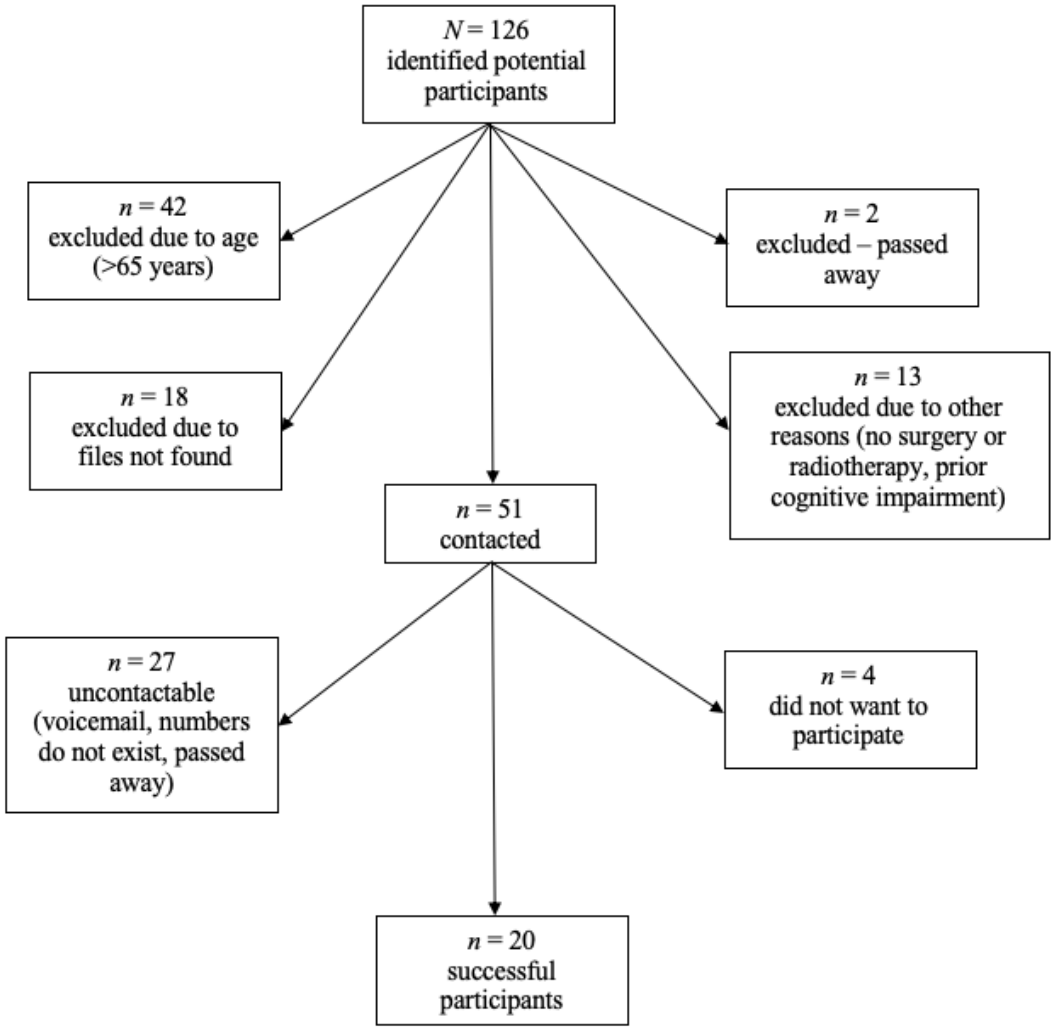
Regarding specific criteria that were applied in constituting the patient group, all these participants were required to have an NFPA, with diagnosis confirmed by medical records and Radiotherapy Clinic doctors. They were required to have been on a stable treatment regimen for at least 3 months prior to study enrolment, and to have received either radiotherapy treatment and surgery or only surgery.

Regarding specific criteria that were applied in constituting the healthy control group, all these participants were required to be free from pituitary disease.

All participants in both groups were required to be free from any neurological, medical, or other illness/disease that may negatively impact cognitive functioning or alter sleep (Krystal, 2012; Teodoro et al., 2018; Wennberg et al., 2019).

Figure 1

Flowchart Showing Attrition During NFPA Patient Recruitment



Measures

Sociodemographic and Medical Questionnaire

This study-specific instrument (see Appendix B) collected data regarding age, sex, education, SES, medical history, and, for patients, diagnosis, duration of illness, treatment type, and duration of treatment. Collection of sociodemographic data ensured that all participants met the study's eligibility criteria and that there was adequate matching of patients and controls. Collection of medical data ensured that patients' clinical characteristics were described adequately and could be used in secondary analyses if necessary.

Global Sleep Assessment Questionnaire (GSAQ)

This 11-item instrument (Roth et al., 2002; see Appendix C) is designed to screen for the presence of sleep disorders and to distinguish between several possible such disorders.

Each item asks about a symptom the respondent may have experienced in the previous 4 weeks, and is answered using a 4-point scale (the response options are *always*, *usually*, *sometimes* and *never*). Hence, the possible score range is 1–4 per question, with higher values indicating greater possibility of the presence of a sleep disorder.

Regarding psychometric properties, the GSAQ has good internal consistency (α = .76), a test-retest reliability range of .51 to .92 over a period of 7–14 days, and good convergent and divergent validity (Petrov et al., 2014; Roth et al., 2002).

Regarding cross-cultural validity, in a diverse sample of participants (e.g., across ages, genders, ethnicities and education levels), the GSAQ was able to detect possible sleep disorders efficiently (Roth et al., 2002). Although the instrument has been used successfully in many cultural contexts (see, e.g., Flo et al., 2012; Seo et al., 2017), there have been no published studies reporting its use in South Africa.

Although the GSAQ is normally a self-administered questionnaire, its length and layout lend themselves to telephonic administration.

Brief Test of Adult Cognition by Telephone (BTACT)

This test battery (Tun & Lachman, 2006; see Appendix D) is designed to assess a number of different cognitive domains in adults. It comprises the six subtests listed below, all derived from valid and reliable in-person psychometric tests that have been adapted for telephone administration (Castanho et al., 2014).

The *Rey Auditory-Verbal Learning Test* assesses episodic memory using a 15-word list. The researcher reads the list then asks the participant to repeat as many of the words as possible. This trial assesses learning and immediate recall. After a delay of approximately 15 minutes (during which the other BTACT subtests are administered), the participant is asked to recall as many words as they remember. This trial assesses delayed recall. The outcome measure for each trial is the number of words correctly recalled.

The *Digits Backwards* test assesses working memory. The researcher reads a string of numbers (starting with a 2-digit sequence) and the participant is required to repeat the numbers in reverse order. If the repetition is correct, the researcher reads a new string that is one digit longer (up to an 8-digit sequence). After two incorrect repetitions, the test is discontinued. The outcome measure is how many digit sequences are repeated correctly.

The *Category Fluency* test assesses verbal generativity. The participant is required to name as many different animals as they can within 60 seconds. The outcome measure is how many unique animals they name.

The *Stop and Go Task* assesses the ability to inhibit automatic responses. On the first round of 20 trials, the participant must say ‘go’ when the researcher says ‘green’ and ‘stop’ when the researcher says ‘red’ (this is the normal order). The second round of 20 trials reverses this order where the participant must say ‘stop’ when the researcher says ‘green’ and ‘go’ when the researcher says ‘red’ (this is the reverse order). The third round of 32 trials mixes the normal and reverse orders, requiring the participant to alternate between the normal order and reverse order responses to green and red as the researcher indicates. The outcome measure is the number of correct responses in the third round.

The *Number Series* test measures reasoning. The researcher reads a sequence of numbers to the participant and asks them to state what the next number should be. This process is repeated five times using different number sequences. The outcome measure is the number of correct answers.

The *Backward Counting Task* measures processing speed. The participant is given 45 seconds to count backwards in 1’s from 100. The outcome measure is how many numbers they count backwards minus the number of errors made.

The BTACT is suitable for assessment of cognitively impaired and cognitively intact individuals and can be applied across a wide range of ages and educational backgrounds (Castanho et al., 2014; Gurnani et al., 2015; Lachman et al., 2014). Moreover, the use of a telephonic test battery in research has many advantages. Assessment over the telephone rather than in person is more cost-effective and efficient and facilitates access to larger and more diverse samples. Telephonic assessment also allows data collection even when in-person testing is not possible (Gavett et al., 2013; Tun & Lachman, 2006).

The performance of individuals administered the BTACT is not significantly different to the performance of individuals administered similar tests in person, with correlations from .55 to .95 (Tun & Lachman, 2006). The battery has good psychometric properties, with good test-retest reliability, convergent validity, and discriminant validity (Lachman et al., 2014). It has been used successfully in many cultural contexts, including South Africa (Gurnani et al., 2015; Henry et al., 2014).

Procedure

We called potential participants and invited them to enroll in the study. If they accepted, we gave them full details of the protocol (see Appendix E) and asked for their verbal consent. If they provided consent, we asked if we could begin administration of the study instruments within that call. If an individual was willing to participate but could not complete the questionnaires at the time of the initial call, we scheduled an alternative time.

We administered the sociodemographic questionnaire, GSAQ, and BTACT, in that order. The standardized administration of these tests took approximately 45 minutes. At the conclusion of test administration, we thanked the participant for their involvement, invited them to ask any questions, and debriefed them completely following a standard verbal script (see Appendix F).

Data Management and Statistical Analysis

Deriving Outcome Variables

The major outcome variables in this study were participants' scores on the GSAQ and on the BTACT. We scored the GSAQ following standard methods (Roth et al., 2002). The conventional method of scoring the BTACT involves calculating a *z*-score for each subtest, followed by calculating an average of these *z*-scores to obtain a composite *z*-score, which serves as an indication of global intellectual functioning. This method is potentially problematic in that it makes many assumptions about how individual subtest performance is related to the overall construct of cognition (Gurnani et al., 2015; Tun & Lachman, 2006). These assumptions are often violated, and so Gavett et al. (2013) proposed an alternative scoring method. Their bi-factor model generates both a general factor (i.e., one representing overall cognitive ability as measured by all the test items) and a secondary factor (i.e., one representing other cognitive factors assessed by the different subtests). The bi-factor model incorporates sociodemographic variables, and uses regressions to predict cognition. This method produces an unadjusted overall *z*-score, in addition to *z*-scores adjusted for participants' age, sex, education, and combinations of the three. Gavett and colleagues present strong psychometric evidence suggesting that the use of this bi-factor BTACT scoring method may be highly advantageous in interpreting performance on the test. Hence, we used both scoring methods.

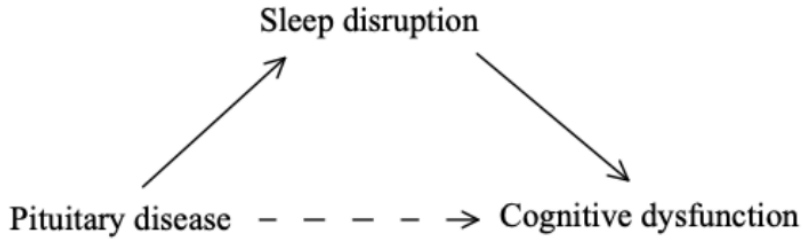
Inferential Analyses

We used RStudio (v. 1.1.456) for all statistical analyses, with the threshold for statistical significance (α) set at .05. First, we generated a complete set of descriptive statistics that gave us an overall picture of the data to identify outlying data points (i.e., those more than 3 standard deviations from the group mean) and to test assumptions underlying subsequent inferential analyses. Second, a series of independent-sample *t*-tests (for continuous variables) and chi-square tests (for categorical variables) assessed between-group differences in key sociodemographic characteristics. Third, a series of independent-sample *t*-tests assessed between-group differences in sleep disturbances (as measured by GSAQ total score) and cognitive performance (as measured by BTACT total score as well as scores on each of the

BTACT subtests). Fourth, we used regression modelling to investigate the possible mediating effect of sleep disruption on the relationship between presence of NFPA and cognitive dysfunction. Following Baron and Kenny (1986), we planned to run three separate regression models: the first describing the relationship between group status (patients versus controls) and cognitive performance, the second describing the relationship between group status and sleep disruption, and the third evaluating whether sleep disruption mediates the relationship between pituitary disease and cognitive dysfunction (see Figure 2). Then, we planned to run a Sobel test (Sobel, 1982) to determine whether the model involving both pituitary disease and sleep disruption in predicting cognitive dysfunction is significantly stronger than that involving only pituitary disease as a predictor. Finally, using Pearson's product-moment correlation tests, secondary analyses explored within-group associations between sleep disturbance and cognitive performance.

Figure 2

Model Showing the Proposed Mediating Effect of Sleep Disruption on the Relationship between Pituitary Disease and Cognitive Dysfunction



Ethical Considerations

Ethical approval for the study procedures was granted by the Research Ethics Committees of the Department of Psychology (PSY2020-029; see Appendix G) and Faculty of Health Sciences (HREC REF: 462/2019; see Appendix H) of the University of Cape Town. The Health Sciences ethical approval was obtained for the larger project last year and was renewed this year (see Appendix I).

Consent and Confidentiality

All participants were given full details of the study protocol. They were told that their participation would involve us collecting data from them via telephonic administration of a set of tests and questionnaires, that we would be using and analysing their data in our research, and that we intended on publishing the results of the study. They were told that their participation was completely voluntary and that they were free to withdraw from the study at

any point should they feel uncomfortable. They were assured that they would not be required to provide any explanation for withdrawal and would not be penalised, or have their treatment compromised in any way, for such withdrawal. We outlined the measures put in place to maintain confidentiality of the data and informed them that all results and data would be reported and published anonymously. These consent procedures were all performed telephonically, and participants were asked to provide verbal consent. This consent needed to be in place before any tests or questionnaires were administered.

Risks and Benefits

There were no foreseeable physical, psychological, or social risks associated with participation. Participants received no compensation or benefits in exchange for their involvement.

Debriefing

Each participant was verbally debriefed (see Appendix F) after they had completed all tests and questionnaires. We followed this up by emailing a formal debriefing letter (see Appendix J). In the verbal debriefing participants were also offered the option to have access to a summary of the study results.

Results

Sample Characteristics

The overall age range of the sample was 34–65 years (M = 52.33, SD = 9.15). The education range was 4–16 years (M = 10.95, SD = 2.78). As expected given our case-control design and recruitment strategies, analyses detected no significant between-group differences with regards to age, education, or sex distribution (see Table 1).

Patient Characteristics

Average time since NFPA diagnosis was 8.37 years (SD = 4.29). Patients had either received both radiotherapy and surgery (n = 15; 75% of the sample) or had only undergone surgery (n = 5; 25%) for the treatment of their pituitary tumour (see Table 2). No patient was receiving radiotherapy at the time of the study and at least 1 year had passed since their last radiotherapy treatment.

Eighteen patients had been on a stable hormone replacement treatment regimen for at least 3 months prior to study enrolment, whereas two patient participants did not require replacement therapy.. Prescribed hormone replacement medication included: hydrocortisone (n = 2; 10%), L-thyroxine (n = 6; 30%), or both hydrocortisone and L-thyroxine (n = 10; 50%). Two male patients had also received a Depo-Testosterone injection.

Table 1

Sample Sociodemographic Characteristics (N = 39)

	Study Group			
Variable	NFPA Patients (n = 20)	Healthy Controls (n = 19)	t / χ^2	p
Age (years)				
M (SD)	52.90 (9.22)	51.74 (9.29)	0.39	.70
Range	35–63	34–65		
Education (years)				
M (SD)	10.25 (2.43)	11.68 (3.00)	-1.65	.11
Range	4–15	5–16		
Sex			0.03	.62
Male (*f*, %)	10 (50.00)	11 (57.89)		
Female (*f*, %)	10 (50.00)	8 (42.11)		

Note. NFPA = non-functioning pituitary adenoma, *M* = mean, *SD* = standard deviation

Table 2

NFPA Patient Characteristics (N = 20)

Variable	Statistic
Age at diagnosis (years)	
M (SD)	44.26 (7.53)
Range	29 – 57
Duration of disease (years)	
M (SD)	8.37 (4.29)
Range	1.5 – 16
Received surgery only (# of participants, %)	5 (25%)
Received surgery and radiotherapy (# of participants, %)	15 (75%)
Additional comorbidities (# of participants, %)	
HIV+	1 (5%)
Smoking	2 (10%)
Diabetes mellitus	4 (20%)
Diabetes insipidus	1 (5%)
Hypertension	2 (10%)
BMI > 25	1 (5%)
Epilepsy	1 (5%)

Note. NFPA = non-functioning pituitary adenoma; BMI = body mass index.

Between-group Comparisons: Sleep Quality and Cognition

On average, GSAQ scores for patients were slightly lower than those for controls. However, analyses detected no significant between-group difference in this regard (see Table 3).

In contrast, analyses of BTACT outcome measures suggested there were significant between-group differences with regard to cognitive performance on most individual subtests. The order of means indicated that, on average, patients performed significantly more poorly (i.e., demonstrated significantly greater cognitive dysfunction) than controls on the BTACT

composites (adjusted and unadjusted for demographic variables) as well as on subtests assessing episodic memory, executive functioning and reasoning (see Table 3).

Table 3

Between-group Comparisons: Sleep quality and cognitive performance (N = 39)

	Study Group						
	Patients	Controls				95% CI	
Outcome Variable	(*n* = 20)	(*n* = 19)	*t*	*p*	ESE	LL	UL
GSAQ total score	36.40 (4.79)	37.26 (3.97)	-0.61	.55	.20	-0.46	0.85
BTACT							
Composite *z*-score[a]	-0.55 (0.54)	0.00 (0.67)	-2.84	.007**	.91	0.23	1.59
Episodic Memory							
Immediate recall	-0.64 (0.92)	0.00 (1.00)	-2.09	.04*	.67	0.004	1.34
Delayed recall	-0.69 (0.84)	0.00 (1.00)	-2.36	.02*	.75	0.08	1.43
Total memory	-0.34 (0.71)	0.00 (1.00)	-1.24	.22	.40	-0.26	1.05
Working Memory							
Digit Span-Backwards	-0.60 (0.89)	0.00 (1.00)	-1.98	.05	.64	-0.03	1.30
Executive Functioning							
Category fluency	-0.76 (0.63)	0.00 (1.00)	-2.84	.007**	.91	0.23	1.59
Red-Green (total score)	-0.14 (0.73)[b]	0.22 (0.28)[c]	-1.97	.06	.13	-0.54	0.80
Reasoning							
Number Series	-0.74 (0.50)[d]	0.00 (1.00)	-2.88	.007**	.28	-0.38	0.94
Speed of Processing							
Counting Backwards	-0.26 (0.58)	0.00 (1.00)	-0.99	.33	.32	-0.33	0.97
Bi-factor *z*-score[e]							
Unadjusted	-1.04 (1.00)	-0.10 (1.10)	-2.78	.009**	.89	0.21	1.57
Adjusted for:							
Age	-1.48 (1.22)	-0.35 (1.33)	-2.79	.008**	.89	0.21	1.57
Education	-0.21 (1.25)	0.56 (1.31)	-1.86	.07	.60	0.07	1.26
Gender	-1.22 (1.13)	-0.14(1.26)	-2.80	.008**	.90	0.22	1.58
Age, education	-0.57 (1.31)	0.31 (1.38)	-2.06	.05*	.66	-0.01	1.33
Age, gender	-1.48 (1.21)	-0.33 (1.34)	-2.81	.008**	.90	0.22	1.58
Age, education, gender	-0.56 (1.29)	0.35 (1.39)	-2.12	.04*	.68	0.01	1.35

Note. Patients are those with NFPA (non-functioning pituitary adenoma); Controls are sociodemographically matched healthy controls. In columns 2 and 3, means are presented with standard deviations in parentheses. ESE = effect size estimate (Cohen's *d*); GSAQ = Global Sleep Assessment Questionnaire; BTACT = Brief Test of Adult Cognition by Telephone.

[a]Conventional scoring method for the BTACT. [b]*n* = 19; data from one participant in this group were omitted from analysis because they contained outlying values. [c]*n* = 18; data from one participant in this group were omitted from analysis because they contained outlying values. [d]*n* = 19; data from one participant in this group were omitted from analysis because they contained outlying values. [e]Bi-factor scoring method for the BTACT.

*$p < .05$. **$p < .01$.

Mediation Testing: Regression Analyses

Linear regression modelling indicated that group status was a significant predictor of cognitive performance (see Table 4). This significant relationship held for several individual BTACT subtest scores (Immediate Recall, Delayed Recall, Category Fluency, Number Series) and for overall BTACT performance (both adjusted and unadjusted for demographic variables).

However, a similar linear regression model indicated that group status did not significantly predict sleep quality (see Table 4). This result suggests that the potential mediating effect we were investigating was not present, and so we proceeded no farther with this analytic series.

Table 4

Regression Analysis: Strength of group status (NFPA patients versus healthy controls) as a predictor of sleep quality and cognitive performance (N = 39)

Outcome Variable	ß	*B*	*SE*	95% CI LL	95% CI UL	*F*	*p*	R^2
GSAQ total score	-0.10	-0.86	1.41	-3.73	2.00	0.37	.55	-.02
BTACT								
Composite *z*-score[a]	-.42	-0.55	0.19	-0.94	-0.16	8.08	.007**	.16
Episodic Memory								
Immediate recall	-.33	-0.64	0.31	-1.27	-0.02	4.38	.04*	.08
Delayed recall	-.36	-0.69	0.29	-1.29	-0.10	5.54	.02*	.11
Total memory	-.20	-0.34	0.28	-0.90	0.22	1.53	.22	.01
Working Memory								
Digit Span-Backwards	-.31	-0.60	0.30	-1.21	0.01	3.93	.05	.07
Executive Functioning								
Category fluency	-.42	-0.76	0.27	-1.30	-0.22	8.09	.007**	.16
Red-Green (total score)[b]	-.32	-0.36	0.18	-0.73	0.01	3.88	.06	.07
Reasoning								
Number Series[c]	-.43	-0.74	0.26	-1.26	-0.22	8.30	.007**	.16
Speed of Processing								
Counting Backwards	-.16	-0.26	0.26	-0.79	0.27	0.99	.33	-.0003
Bi-factor *z*-score[d]								
Unadjusted	-.42	-0.93	0.34	-1.61	-0.25	7.70	.009**	.15
Adjusted for:								
Age	-.42	-1.14	0.41	-1.97	-0.31	7.76	.008**	.15
Education	-.29	-0.76	0.41	-1.59	-0.07	3.47	.07	.06
Gender	-.42	-1.07	0.38	-1.85	-0.30	7.85	.008**	.15
Age, education	-.32	-0.89	0.43	-1.76	-0.02	4.25	.05*	.08
Age, gender	-.42	-1.15	0.41	-1.97	-0.32	7.89	.008**	.15
Age, education, gender	.33	-0.91	0.43	-1.78	-0.04	4.49	.04*	.08

Note. Degrees of freedom for *F*-statistic are (1, 37). NFPA = non-functioning pituitary adenoma; GSAQ = Global Sleep Assessment Questionnaire; BTACT = Brief Test of Adult Cognition by Telephone; CI = confidence interval; LL = lower limit; UL = upper limit. [a]Conventional scoring method for the BTACT. [b]*N* = 37; data from two participants (one from the control group and one from the patient group) were omitted from analysis because they contained outlying values. [c]*N* = 38; data from one participant in the patient group were omitted from analysis because they contained outlying values. [d]Bi-factor scoring method for the BTACT.

*$p < .05$. **$p < .01$.

Secondary Analyses

Within-Group Bivariate Correlations: Sleep Disturbance and Cognition

Although there were some moderately strong correlations (e.g., between GSAQ score and Red-Green total score in the control group, and between GSAQ score and Immediate Recall score in the control group), analyses detected only one statistically significant association between sleep disturbance and cognitive performance. In the patient group,

GSAQ score and Red-Green total score were significantly positively correlated (i.e. patients who experienced greater sleep disturbances performed worse on this subtest) (see Table 5). The overall lack of statistical significance is consistent with the results reported above showing no significant between-group difference in GSAQ scores and no significant prediction of sleep disturbance by group status.

Despite the overall lack of statistical significance in these secondary analyses, it is worth noting that there are stronger and more positive correlations present in the control group. This pattern suggests that, in healthy adults, less sleep disturbance is more likely to be associated with better cognitive performance.

Table 5

Bivariate Correlational Analyses: Relations between GSAQ scores and BTACT performance within each group (N = 39)

	Study Group			
	NFPA Patients (n = 20)		Healthy Controls (n = 19)	
BTACT Outcome Variable	*r*	*p*	*r*	*p*
Episodic Memory				
Immediate recall	.21	.37	.31	.20
Delayed recall	-.02	.95	.14	.57
Total memory	-.26	.28	-.16	.52
Working Memory				
Digit Span-Backwards	-.20	.38	.14	.56
Executive Functioning				
Category fluency	.07	.75	.29	.24
Red-Green (total score)	.48[a]	.04*	.43[b]	.08
Reasoning				
Number Series	.14[c]	.57	-.13	.59
Speed of Processing				
Counting Backwards	-.06	.78	.05	.83
Composite *z*-score	.14	.57	.11	.65

Note. Data presented are Pearson's correlation coefficients (r) and associated p-values representing magnitude of association (within each study group) between the listed cognitive outcome variable and GSAQ score, which measures sleep quality. BTACT = Brief Test of Adult Cognition by Telephone; GSAQ = Global Sleep Assessment Questionnaire; NFPA = non-functioning pituitary adenoma.

[a]n = 19; data from one participant in this group were omitted from analysis because they contained outlying values. [b]n = 18; data from one participant in this group were omitted from analysis because they contained outlying values. [c]n = 19; data from one participant in this group were omitted from analysis because they contained outlying values.

*$p < .05$.

Discussion

This study investigated associations between sleep quality, cognitive functioning, and the presence of pituitary disease. Its specific focus was on whether sleep disruption mediates cognitive dysfunction in patients with non-functioning pituitary adenomas (NFPA). We recruited 39 participants (20 patients and 19 sociodemographically-matched healthy controls) and gathered objective assessment of their cognitive functioning and subjective assessment of their sleep quality via a telephone call. Below, we discuss the status of our hypotheses and how the current findings relate to the existing literature. We conclude by examining some possible limitations of the study and by providing recommendations for future research.

Hypothesis 1: Between-Group Differences in Cognitive Performance

Our first hypothesis stated that patient performance on an objective test of cognitive performance (the Brief Test of Adult Cognition by Telephone; BTACT) would be significantly worse than that of controls. Analyses confirmed this prediction. Patients scored significantly more poorly on both the global BTACT index and on most BTACT subtests, including those assessing episodic memory, executive functioning, and reasoning. Moreover, a linear regression model indicated that group membership significantly predicted BTACT-measured cognitive performance.

These data patterns are consistent with the vast majority of previously published literature on the topic. Although this is not a particularly large literature, several studies report that pituitary disease patients (including those with NFPA) present with a variety of cognitive difficulties. These difficulties include problems with visuoconstructional abilities, learning, memory, executive functioning (including verbal fluency and mental agility; Leon-Carrion et al., 2010; Tiemensma et al., 2010; Yedinak & Fleseriu, 2014).

Of note is that, where previous studies in this literature collected data on cognitive performance from self-reports or from in-person administration of a test battery, we were the first to use a remote-administered battery with this clinical population. The fact that the BTACT was sensitive to between-group differences in cognitive performance, and thereby assisted in replicating previous findings that used different methods, provides evidence that continued use of this telephone-administered measure can be recommended for the population of NFPA patients (and, perhaps, for all pituitary disease patients). This is especially noteworthy during a time where more research (especially that involving clinical populations) needs to be conducted remotely.

Hypothesis 2: Between-Group Differences in Sleep Quality

Our second hypothesis stated that patients would self-report significantly more disrupted sleep than controls on the Global Sleep Assessment Questionnaire (GSAQ). Analyses did not confirm this prediction. Because participants in both the patient and control groups tended to report few or no major issues with their sleep quality, GSAQ data were fairly homogenous and so simple *t*-tests detected no significant between-group differences. Moreover, a linear regression model found that group membership did not significantly predict sleep disturbance.

These results stand in contrast to previous literature. Patients with pituitary disease (including NFPA) are often reported to have poorer sleep quality and more sleep disturbances (see, e.g., Biermasz et al., 2011; Joustra et al., 2014). Although it is possible that the reason for the currently observed outcome is that there were truly no between-group differences in sleep quality, one must take into account the context established by previous studies and seek alternative reasons for the non-significant finding.

One such reason involves the measure used to assess sleep quality. The GSAQ is a self-report instrument, with questions pertaining to the respondent's subjective experiences of sleep. Hence, it does not provide data on the more objective characteristics of sleep and sleep staging, such as duration or density of each stage. Previous studies investigating the effects of pituitary disease on sleep quality often measure those characteristics, and subsequently report that patients' sleep is objectively disrupted (Biermasz et al., 2011; Joustra et al., 2014; Shipley et al., 1992). Hence, one might speculate that the GSAQ is not an accurate or sensitive enough measure of sleep disturbance in this context.

Such speculation is supported in two ways. First, objective and subjective measures of sleep quality are often weakly related. For instance, certain sleep parameters, such as duration or onset latency, are often overestimated by subjective measures in comparison to objective measures such as actigraphy or polysomnography (PSG; Lauderdale et al., 2008; Matthews et al., 2018; Silva et al., 2007). Lauderdale et al. (2008) argue that self-report measures of sleep are often inaccurate because they ask respondents to integrate information regarding sleep duration and quality from several days (and sometimes several weeks) when, in actuality, sleep varies each night. In one particularly notable study, Girschik and colleagues (2012) found that, in their sample of 56 Western Australian women aged 18–80 years, self-reported sleep data (collected using the Breast Cancer Environment and Employment Study [BCEES] sleep questionnaire) did not correlate closely with actigraphy data (collected over the course of 7 nights). More recently, Lipinska and Thomas (2017) found that, in their sample of 21

women with PTSD, 19 women with trauma exposure but no PTSD, and 20 healthy controls, there were few significant correlations between self-reported sleep quality averaged over the previous 30 days and PSG sleep data collected in the laboratory.

Second, although the GSAQ may be proficient at detecting clinical sleep disorders and distinguishing between them (Roth et al., 2002), it may not be sensitive to milder (i.e., sub-clinical) forms of sleep disruption or to generally poor sleep quality. Patients in this study may have been experiencing mild sleep disruption and/or poor sleep quality rather than a clinically diagnosable sleep disorder, thus explaining why our GSAQ data did not deliver the expected pattern of results and why our findings are not consistent with previous literature.

Hypothesis 3: Does Sleep Disturbance Mediate the Relationship Between Pituitary Disease and Cognitive Dysfunction?

Our third hypothesis stated that sleep disturbance would mediate the relationship between the presence of pituitary disease and poor cognitive performance. Although one linear regression model confirmed a significant predictive relationship between group membership and cognitive performance, a second detected no significant predictive relationship between group membership and sleep disturbance. Furthermore, in the control group GSAQ-measured sleep disturbance was not significantly correlated with performance on any BTACT subtest or with overall BTACT performance, while in the patient group it was only significantly correlated with a measure of executive functioning (Red-Green total score). This overall lack of relationship stands in contrast to a wealth of previous literature suggesting that healthy sleep promotes intact cognitive performance (see, e.g., Peter-Derex, 2019; Walker, 2008; Wamsley & Stickgold, 2011). This discrepancy between our findings and those described by previously published studies may be a result of the GSAQ's limited ability to report accurately on sleep quality and its lack of sensitivity in detecting sub-clinical sleep disturbances.

Regardless of the reasons underlying the lack of association between sleep and group membership, and between sleep and cognitive performance, the fact that sleep in our sample was not significantly associated with either of the other two major variables meant that the predicted mediating effect could not exist, and we pursued no further analyses in this regard (i.e., we accepted that this hypothesis was not confirmed).

Nonetheless, it is still worthwhile to pursue research investigating the potential mediational role sleep may play in the relationship between pituitary disease and cognitive dysfunction. Future research using alternative measures of sleep quality might yet find such a relationship, thus allowing the mediational role of sleep to be explored further.

Limitations and Directions for Future Research

The following limitations should be noted to ensure that caution is exercised when making deductions from the current findings. First, the study's sample size (N = 39) means it may not have had adequate statistical power to achieve its aims. G*Power software (Faul et al., 2009) suggested that a minimum sample size be set at N = 62 (31 per group) to run a mediation analysis with one independent variable and one mediator if the expected effect size was of medium magnitude (Cohen's f^2 = .15) and the desired statistical power was at least .85. Because only one other study (Wennberg et al., 2019) has examined both sleep disruption and cognitive dysfunction in pituitary disease patients, we estimated a medium effect size based on the well-known relationship between the two (Dzierzewski et al., 2018; Fritz et al., 2012; Yedinak & Fleseriu, 2014). Naturally, if the effect size in the population was smaller, an even larger sample would be needed in order to power the investigation adequately. Hence, future studies in this area should aim to recruit substantially larger groups of patients and controls. However, it should be noted that pituitary disease generally (i.e., not necessarily just NFPA) occurs quite rarely, with prevalence rates estimated as being 7–41.3 / 100 000 population (Ntali & Wass, 2018). Given this rarity, the number of people available to act as participants in research is small, making recruiting statistically powerful sample sizes a difficult task.

Second, as noted above it appears the GSAQ may not be able to detect milder forms of sleep disruption. Furthermore, as a self-report instrument it is not able to report on characteristics of sleep architecture as accurately as objective measures (e.g., PSG, actigraphy) can.

A third limitation is that, although this study used both a patient group and a group of healthy matched controls, the patient group consisted only of those with NFPA. These patients are not representative of all pituitary disease patients (and, perhaps, especially not of those with functional pituitary diseases, such as acromegaly or Cushing's disease). Given that there is some variety in the presentation of both sleep dysfunction and cognitive impairment across pituitary diseases (see, e.g., Romijn, 2016; Yedinak & Fleseriu, 2014), it is possible that relationships between disease presence, sleep quality, and cognition may present differently in different patient groups.

To address these limitations and to allow further exploration of the mooted mediating relationship, future research studies should (a) aim to recruit larger sample sizes to ensure adequate statistical power, (b) use actigraphy or PSG to measure sleep architecture and quality as accurately as possible, and (c) recruit patients with both functional and non-

functional pituitary diseases alongside healthy control groups in order to provide more representative and informative results.

Summary and Conclusion

The overall aim of this study was to investigate associations between sleep, cognition, and pituitary disease. Our key question was whether sleep disruption mediates the relationship between cognitive dysfunction and the presence of a non-functioning pituitary adenoma (NFPA). Although analyses detected significantly poorer cognitive performance in patients than in matched healthy controls, they detected no significant between-group differences in sleep disturbance and no significant association between sleep disturbance and cognitive dysfunction. Hence, our logical conclusion was that, in this sample, sleep disruption did not mediate the relationship between the presence of NFPA and cognitive dysfunction.

Although not all our hypotheses were supported (i.e., our finding that cognitive performance was significantly worse in patients is consistent with previous literature, but our finding that sleep disruption was not significantly worse in patients is inconsistent with the literature), our results do contribute to the existing pool of psychological and neurological research on patients with pituitary disease and they encourage further research in the field. For example, our results reinforce our understanding of the relationship between pituitary disease and cognitive impairment within a clinical population of NFPA patients.

The results we present, and the conclusions one might draw from them, have potential clinical implications. For instance, the finding that NFPA patients performed relatively poorly on the BTACT suggests they may benefit from cognitive remediation alongside their usual medical care. Such remediation might assist in improving their memory function, a key component of medication adherence and other instrumental activities of daily living. Although the current study aimed to investigate whether targeting sleep interventions could help relieve the cognitive dysfunction experienced by these patients, our findings suggest that further research needs to be conducted to establish whether this mediational link does in fact exist or whether further lines of inquiry need to be investigated to establish alternative means for alleviating the burden of the cognitive dysfunction experienced by these patients.

Acknowledgements

We would like to express our sincere thanks and gratitude to the following people, without whom this study would not have been possible:

To our supervisor, Dr Kevin Thomas, and our co-supervisors, Dr Michelle Henry, Dr Ian Ross, Dr Thurandrie Naiker, and Dr Patrick Semple, for all their assistance and valuable input throughout the entire research process.

To Dr Patrick Semple, Dr Thurandrie Naiker, and Dr Ian Ross for granting us use of the Radiotherapy Clinic's databases.

To the staff at Groote Schuur Hospital, for allowing us to use their facilities and resources during data collection.

To our participants, for giving us their valuable time and input for the purposes of our research.

Finally, to our loving families, supportive partners and friends, for their continued support and encouragement during this unprecedented year.

References

Antony, J. W., & Paller, K. A. (2017). The hippocampus from cells to systems. In D. E. Hannula & M. C. Duff (Eds.), *Hippocampal contributions to declarative memory consolidation during sleep* (pp. 245-280). Springer International Publishing. https://doi.org/10.1007/978-3-319-50406-3_9

Astiz, M., Heyde, I., & Oster, H. (2019). Mechanisms of communication in the mammalian circadian timing system. *International Journal of Molecular Science, 20*(2), 343. https://doi.org/10.3390/ijms20020343

Balbo, M., Leproult, R., & Van Cauter, E. (2010). Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity. *International Journal of Endocrinology, 2010*, 1-16. https://doi.org/10.1155/2010/759234

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical consideration. *Journal of Personality and Social Psychology, 51*(6), 1173-1182. https://doi.org/10.1037/0022-3514.51.6.1173

Bertagna, X., Guignat, L., Groussin, L., & Bertherat, J. (2009). Cushing's disease. *Best Practice & Research Clinical Endocrinology and Metabolism, 23*(5), 607-623. https://doi.org/10.1016/j.beem.2009.06.001

Biermasz, N. R., Joustra, S. D., Donga, E., Pereira, A. M., van Duinen, N., van Dijk, M., van der Klaauw, A. A., Corssmit, E. P. M., Lammers, G. J., van Kralingen, K. W., van Dijk, J. G., & Romijn, J. A. (2011). Patients previously treated for nonfunctioning pituitary macroadenomas have disturbed sleep characteristics, circadian movement rhythm, and subjective sleep quality. *The Journal of Clinical Endocrinology and Metabolism, 96*(5), 1524-1532. https://doi.org/10.1210/jc.2010-2742

Bjorvatn, B., Lehmann, S., Gulati, S., Aurlien, H., Pallesen, S., & Saxvig, I. W. (2015). Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea. *Sleep & Breathing, 19*(4), 1387-1393. https://doi.org/10.1007/s11325-015-1155-5

Buckley, T. M., & Schatzberg, A. F. (2005). Review: On the interactions of the hypothalamic pituitary-adrenal (HPA) axis and sleep: Normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *The Journal of Clinical Endocrinology & Metabolism, 90*(5), 3106 –3114. https://doi.org/10.1210/jc.2004-1056

Castanho, T., Amorim, L., Zihl, J., Palha, J., Sousa, N., & Santos, N. (2014). Telephone-based screening tools for mild cognitive impairment and dementia in aging studies: A

review of validated instruments. *Frontiers in Aging Neuroscience, 6,* Article 16. https://doi.org/10.3389/fnagi.2014.00016

Cellini, N. (2017). Memory consolidation in sleep disorders. *Sleep Medicine Reviews, 35,* 101-112. https://doi.org/10.1016/j.smrv.2016.09.003

Cordeira, J., Kolluru, S. S., Rosenblatt, H., Kry, J., Strecker, R. E., & McCarley, R. W. (2018). Learning and memory are impaired in the object recognition task during metestrus/diestrus and after sleep deprivation. *Behavioural Brain Research, 26*(339), 124-129. https://doi.org/10.1016/j.bbr.2017.11.033

Crouzeix, G., Morello, R., Thariat, J., Morera, J., Joubert, M., & Reznik, Y. (2019). Quality of life but not cognition is impacted by radiotherapy in patients with non-functioning pituitary adenoma. *Hormone and Metabolic Research, 51*(3), 178-185. https://doi.org/10.1055/a-0850-9448

Crowley, S. J., Wolfson, A. R., Tarokh, L., & Carskadon, M. A. (2018). An update on adolescent sleep: New evidence informing the Perfect Storm Model. *Journal of Adolescence, 67,* 55-65. https://doi.org/10.1016/j.adolescence.2018.06.001

Dekkers, O. M., Hammer, S., de Keizer, R. J. W., Roelfsema, F., Schutte, P. J., Smit, J. W. A., Romijn, J. A., & Pereira, A. M. (2007). The natural course of non-functioning pituitary macroadenomas. *European Journal of Endocrinology, 156*(2), 217-224. https://doi.org/10.1530/eje.1.02334

Dzierzewski, J. M., Dautovich, N., & Ravyts, S. (2018). Sleep and cognition in the older adult. *Sleep Medicine Clinics, 13*(1), 93-106. https://doi.org/10.1016/j.jsmc.2017.09.009

Emerald, M. (2016). Pituitary gland: Pituitary hormones. *The Encyclopedia of Food and Health*, *4*, 392-400. https://doi.org/10.1016/B978-0-12-384947-2.00548-1

Fan, L., Zhuang, Y., Wang, Y., Liu, X., Liu, D., Xiang, B., He, M., Zhang, Z., Li, Y., Wang, Y., Zhu, X., & Ye, H. (2019). Association of hypokalemia with cortisol and ACTH levels in Cushing's disease. *Annals of the New York Academy of Sciences, 1463*(1), 60-66. https://doi.org/10.1111/nyas.14205

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41*(4), 1149-1160. https://doi.org/10.3758/BRM.41.4.1149

Flo, E., Pallesen, S., Magerøy, N., Moens, B. E., Grønli, J., Hilde Nordhus, I., & Bjorvatn, B. (2012). Shift work disorder in nurses – Assessment, prevalence and related health problems. *PLOS One, 7*(4), e33981. https://doi.org/10.1371/journal.pone.003398

Forget, H., Lacroix, A., Bourdeau, I., & Cohen, H. (2016). Long-term cognitive effects of glucocorticoid excess in Cushing's syndrome. *Psychoneuroendocrinology, 65*, 26-33. https://doi.org/10.1016/j.psyneuen.2015.11.020

Fritz, C. O., Morris, P. E., & Richler, J. J. (2012). Effect size estimates: Current use, calculations, and interpretation. *Journal of Experimental Psychology: General, 141*(1), 2-18. https://doi.org/10.1037/a0024338

García-Borreguero, D., Wehr, T. A., Larrosa, O., Granizo, J. J., Hardwick, D., Chrousos, G. P., & Friedman, T. C. (2000). Glucocorticoid replacement is permissive for rapid eye movement sleep and sleep consolidation in patients with adrenal insufficiency. *Journal of Clinical Endocrinology & Metabolism, 85*(11), 4201-4206. https://doi.org/10.1210/jcem.85.11.6965

Gavett, B., Crane, P., & Dams-O'Connor, K. (2013). Bi-factor analyses of the Brief Test of Adult Cognition by Telephone. *Neurorehabilitation, 32*(2), 253-265. https://doi.org/10.3233/nre-130842

Girschik, J., Fritschi, L., Heyworth, J., & Waters, F. (2012). Validation of self-reported sleep against actigraphy. *Journal of Epidemiology, 22*(5), 462-468. https://doi.org/10.2188/jea.JE20120012

Guerra-Carrillo, B., Katovich, K., & Bunge, S. A. (2017). Does higher education hone cognitive functioning and learning efficacy? Findings from a large and diverse sample. *PLOS, 12*(8), e0182276. https://doi.org/10.1371/journal.pone.0182276

Gurnani, A., John, S., & Gavett, B. (2015). Regression-based norms for a bi-factor model for scoring the Brief Test of Adult Cognition by Telephone (BTACT). *Archives of Clinical Neuropsychology, 30*(3), 280-291. https://doi.org/10.1093/arclin/acv005

Hackman, D. A., & Farah, M. J. (2009). Socioeconomic status and the developing brain. *Cell Press, 13*(2), 65-73. https://doi.org/10.1016/j.tics.2008.11.003

Harbeck, B., Kropp, P., & Mönig, H. (2009). Effects of short-term nocturnal cortisol replacement on cognitive function and quality of life in patients with primary or secondary adrenal insufficiency: A pilot study. *Applied Psychophysiology and Biofeedback, 34,* 113-119. https://doi.org/10.1007/s10484-009-9082-5

Henry, M., Thomas, K. G. F., & Ross, I. L. (2014). Episodic memory impairment in Addison's disease: results from a telephonic cognitive assessment. *Metabolic Brain Disease, 29(2),* 421-430. https://doi.org/10.1007/s11011-014-9511-x.

Hernández-Gordillo, D., del Rocío Ortega-Gómez, M., Galicia-Polo, L., Castorena-Maldonado, A., Vergara-López, A., Guillén-González, M. A., & Torre-Bouscoulet, T.

(2012). Sleep apnea in patients with acromegaly. Frequency, characterization and positive pressure titration. *The Open Respiratory Medicine Journal, 6*, 28-33. https://doi.org/10.2174/1874306401206010028

Huang, Y., Siong, Y., Lai, P. S., Yu, R., Chew, S. H., Gwee, X., Nyunt, M. S. Z., Gao, Q., Ng, T. P., Ebstein, R. P., & Gouin, J. P. (2019). Successful aging, cognitive function, socioeconomic status, and leukocyte telomere length. *Psychoneuroendocrinology, 103*, 180-187. https://doi.org/10.1016/j.psyneuen.2019.01.015

Irwin, M. R. (2015). Why sleep is important for health: a psychoneuroimmunology perspective. *Annual Review of Psychology*, *66*(1), 143-172. https://doi.org/10.1146/annurev-psych-010213-115205

Irwin, M. R., Olmstead, R., & Carroll, J. E. (2017). Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biological Psychiatry*, *80*(1), 40-52. https://doi.org/10.1016/j.biopsych.2015.05.014

Joustra, S. D., Kruijssen, E., Verstegen, M. J. T., Pereira, A. M., & Biermasz, N. R. (2014). Determinants of altered sleep-wake rhythmicity in patients treated for nonfunctioning pituitary macroadenomas. *The Journal of Clinical Endocrinology & Metabolism, 99*(12), 4497-4505. https://doi.org/10.1210/jc.2014-2602

Krause, A. J., Simon, E. B., Mander, B. A., Greer, S. M., Saletin, J. M., Goldstein-Piekarski, A. N., & Walker, M. P. (2017). The sleep-deprived human brain. *Nat Rev Neurosci., 18*(7), 404–418. https://doi.org/10.1038/nrn.2017.55

Krystal, A. D. (2012). Psychiatric disorders and sleep. *Neurologic Clinics, 30*(4), 1389-1413. https://doi.org/10.1016/j.ncl.2012.08.018

Kuo, T. B. J., Li, J., Kuo, H., Chern, C., & Yang, C. C. H. (2016). Differential changes and interactions of autonomic functioning and sleep architecture before and after 50 years of age. *Age, 38*(1). https://doi.org/10.1007/s11357-015-9863-0

Lachman, M. E., Agrigoroaei, S., Tun, P. A., & Weaver, S. L. (2014). Monitoring cognitive functioning: Psychometric properties of the Brief Test of Adult Cognition by Telephone. *Assessment, 21*(4), 404–417. https://doi.org/10.1177/1073191113508807

Lauderdale, D. S., Knutson, K. L., Yan, L. L., Liu, K., & Rathouz, P. J. (2008). Sleep duration: how well do self-reports reflect objective measures? The CARDIA Sleep Study. *Epidemiology, 19*(6), 838-845. https://doi.org/1097/EDE.0b013e318187a7b0

Leon-Carrion, J., Martin-Rodriguez, J. F., Madrazo-Atutxa, A., Soto-Moreno, A., Venegas-Moreno, E., Torres-Vela, E., Benito-López, P., Gálvez, M. A., Tinahones, F. J., &

Leal-Cerro, A. (2010). Evidence of cognitive and neurophysiological impairment in patients with untreated naive acromegaly. *Journal of Clinical Endocrinology & Metabolism, 95*(9), 4367–4379. https://doi.org/10.1210/jc.2010-0394

Lipinska, G., & Thomas, K. G. F. (2017). Better sleep in a strange bed? Sleep quality in South African women with posttraumatic stress disorder. *Frontiers in Psychology, 8,* Article 1555. https://doi.org/10.3389/fpsyg.2017.01555

Liu, Y., & Lachman, M. E. (2019). Education and cognition in middle age and later life: The mediating role of physical and cognitive activity. *The Journals of Gerontology, 75*(7), 93-104. https://doi.org/10.1093/geronb/gbz020

Ly, J., McGrath, J. J., & Gouin, J. (2015). Poor sleep as a pathophysiological pathway underlying the association between stressful experiences and the diurnal cortisol profile among children and adolescents. *Psychoneuroendocrinology, 57,* 51-60. https://doi.org/10.1016/j.psyneuen.2015.03.006

Machado, M. C., Alcantara, A. E., Pereira, A. C., Cescato, V. A., Castro Musolino, N. R., de Mendonça, B. B., Bronstein, M. D., & Fragoso, M. C. (2016). Negative correlation between tumour size and cortisol/ACTH ratios in patients with Cushing's disease harbouring microadenomas or macroadenomas. *Journal of Endocrinological Investigation, 39*(12), 1401-1409. https://doi.org/10.1007/s40618-016-0504-y

Matthews, K. A., Patel, S. R., Pantesco, E. J., Buysse, D. J., Kamarck, T. W., Lee, L., & Hall, M. H. (2018). Similarities and differences in estimates of sleep duration by polysomnography, actigraphy, diary, and self-reported habitual sleep in a community sample. *Sleep Health, 4*(1), 96-103. https://doi.org/10.1016/j.sleh.2017.10.011

McDevitt, E. A., Krishnan, G. P., Bazhenov, M., & Mednick, S. C. (2017). The role of sleep spindles in sleep-dependent memory consolidation. In N. Axmacher and B. Rasch (Eds.), *Cognitive neuroscience of memory consolidation* (pp. 209-226) Springer International Publishing. https://doi.org/10.1007/978-3-319-45066-7_13

Meers, J., Stout-Aguilar, J., & Nowakowski, S. (2019). Sex differences in sleep health. In M. A. Grandner (Ed.), *Sleep and Health* (pp. 21-29). Texas, USA: Academic Press.

Mella, N., Fagot, D., & de Ribaupierre, A. (2016). Dispersion in cognitive functioning: Age differences over the lifespan. *Journal of Clinical and Experimental Neuropsychology, 38*(1), 111-126. https://doi.org/10.1080/13803395.2015.1089979

Miner, B., & Kryger, M. H. (2018). Sleep in the aging population. *Sleep Medicine Clinics, 12*(1), 31-38. https://doi.org/10.1016/j.jsmc.2016.10.008

Mukherjee, S., Patel, S., Kales, S., Ayas, N., Strohl, K., Gozal, D., & Malhotra, A. (2015). An official American Thoracic Society statement: The importance of healthy sleep. Recommendations and future priorities. *American Journal of Respiratory and Critical Care Medicine, 191*(12), 1450-1458. https://doi.org/10.1164/rccm.201504-0767st

Noad, R., Narayanan, K. R., Howlett, T., Lincoln, N. B., & Page, R. C. L. (2004). Evaluation of the effect of radiotherapy for pituitary tumours on cognitive function and quality of life. *Clinical Oncology, 16*(4), 233-237. https://doi.org/10.1016/j.clon.2004.01.012

Ntali, G., & Wass, J. A. (2018). Epidemiology, clinical presentation and diagnosis of non-functioning pituitary adenomas. *Pituitary, 21*, 111-118. https://doi.org/10.1007/s11102-018-0869-3

Øytese, K. A., Evang, J. A., & Bollerslev, J. (2016). Non-functioning pituitary adenomas: Growth and aggressiveness. *Endocrine, 53*(1), 28-34. https://doi.org/10.1007/s12020-016-0940-7

Peter-Derex, L. (2019). Sleep and memory consolidation. *Clinical Neurophysiology, 49*(3), 197-198. https://doi.org/10.1016/j.neucli.2019.05.046

Petrov, M. E., Lichstein, K. L., & Baldwin, C. M. (2014). Prevalence of sleep disorders by sex and ethnicity among older adolescents and emerging adults: Relations to daytime functioning, working memory and mental health. *Journal of Adolescence, 37*(5), 587-597. https://doi.org/10.1016/j.adolescence.2014.04.007

Romijn, J. A. (2016). Pituitary diseases and sleep disorders. *Current Opinion in Endocrinology, Diabetes and Obesity, 23*(4), 345-351. https://doi.org/10.1097/MED.0000000000000265

Roth, T., Zammit, G., Kushida, C., Doghramji, K., Mathias, S. D., Wong, J. M., & Buysse, D. J. (2002). A new questionnaire to detect sleep disorders. *Sleep Medicine, 3*(2), 99-108. https://doi.org/10.1016/S1389-9457(01)00131-9

Seo, J., Kim, J. H., Yang, K. I., & Hong, S. B. (2017). Late use of electronic media and its association with sleep, depression, and suicidality among Korean adolescents. *Sleep Medicine, 29*, 76-80. https://doi.org/10.1016/j.sleep.2016.06.022

Shipley, J. E., Schteingart, D. E., Tandon, R., & Starkman, M. N. (1992). Sleep architecture and sleep apnea in patients with Cushing's disease. *Sleep, 15*(6), 514-518. https://doi.org/10.1093/sleep/15.6.514

Shirvani, M., Motiei-Langroudi, R., & Sadeghian, H. (2016). Outcome of microscopic transsphenoidal surgery in Cushing disease: A case series of 96 patients. *World Neurosurgery, 87*, 170-175. https://doi.org/10.1016/j.wneu.2015.11.046

Silva, G. E., Goodwin, J. L., Sherrill, D. L., Arnold, J. L., Bootzin, R. R., Smith, T., Walsleben, J. A., Baldwin, C. M., & Quan, S. F. (2007). Relationship between reported and measured sleep times: The sleep heart health study (SHHS). *Journal of Clinical Sleep Medicine, 3*(6), 622–630. https://doi.org/10.5664/jcsm.26974

Sobel, M. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. *Sociological Methodology, 13*, 290-312. https://doi.org/10.2307/270723

Stroop, J. R. (1938). Factors affecting speed in serial verbal reactions. *Psychological Monographs, 50*(5), 38-48. https://doi.org/10.1037/h0093516

Tantawy, A. O., Tallaway, H. N. E. T., Farghaly, H. R. S., Farghaly, W. M., & Hussein, A. S. (2013). Impact of nocturnal sleep deprivation on declarative memory retrieval in students at an orphanage: A psychoneuroradiological study. *Neuropsychiatric Disease and Treatment, 9*, 403-408. https://doi.org/10.2147/NDT.S38905

Teodoro, T., Edwards, M. J., & Isaacs, J. D. (2018). A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: Systematic review. *Journal of Neurology, Neurosurgery & Psychiatry, 89*, 1308–1319. http://doi.org/10.1136/jnnp-2017-317823

Tiemensma, J., Kokshoorn, N. E., Biermasz, N. R., Keijser, B. J. S., Wassenaar, M. J., Middelkoop, H. A., Pereira, A. M., & Romijn, J. A. (2010). Subtle cognitive impairments in patients with long-term cure of Cushing's disease. *The Journal of Clinical Endocrinology and Metabolism, 95*(6), 2699-2714. https://doi.org/10.1210/jc.2009-2032

Tun, P., & Lachman, M. (2006). Telephone assessment of cognitive function in adulthood: The Brief Test of Adult Cognition by Telephone. *Age and Ageing, 35*(6), 629-632. https://doi.org/10.1093/ageing/afl095

Van Cauter, E., Spiegel, K., Tasali, E., & Leproult, R. (2008). Metabolic consequences of sleep and sleep loss. *Sleep Medicine, 9*, S23-S28. https://doi.org/10.1016/S1389-9457(08)70013-3

van der Klaauw, A. A., Dekkers, O. M., Pereira, A. M., van Kralingen, K. W., & Romijn, J. A. (2007). Increased daytime somnolence despite normal sleep patterns in patients treated for nonfunctioning pituitary macroadenoma. *The Journal of Clinical Endocrinology and Metabolism, 92*(10), 3898-3903. https://doi.org/10.1210/jc.2007-0944

Vouzouneraki, K., Franklin, K. A., Forsgren, M., Wärn, M., Persson, J. T., Wik, H., Dahlgren, C., Nilsson, A., Alkebro, C., Burman, P., Erfurth, E., Wahlberg, J.,

Åkerman, A., Høybye, C., Ragnarsson, O., Engström, B. E., & Dahlqvist, P. (2018). Temporal relationship of sleep apnea and acromegaly: A nationwide study. *Endocrine, 62*(2), 456-463. https://doi.org/10.1007/s12020-018-1694-1

Walker, M. P. (2008). Cognitive consequences of sleep and sleep loss. *Sleep Medicine, 9*, S29-S34. https://doi.org/10.1016/S1389-9457(08)70014-5

Wamsley, E. J., & Stickgold, R. (2011). Memory, sleep, and dreaming: Experiencing consolidation. *Sleep Medicine Clinics, 6*(1), 97-108. https://doi.org/10.1016/j.jsmc.2010.12.008

Wennberg, A., Lorusso, R., Dassie, F., Benavides-Varela, S., Parolin, M., De Carlo, E., Fallo, F., Mioni, R., Vettor, R., Semenza, C., & Maffei, P. (2019). Sleep disorders and cognitive dysfunction in acromegaly. *Endocrine, 66*, 634–641. https://doi.org/10.1007/s12020-019-02061-1

Whitley, E., Deary, I. J., Ritchie, S. J., Batty, G. D., Kumari, M., & Benzeval, M. (2016). Variations in cognitive abilities across the life course: Cross-sectional evidence from Understanding Society: The UK Household Longitudinal Study. *Intelligence, 59,* 39-50. https://doi.org/10.1016/j.intell.2016.07.001

Yedinak, C., & Fleseriu, M. (2014). Self-perception of cognitive function among patients with active acromegaly, controlled acromegaly, and non-functional pituitary adenoma: A pilot study. *Endocrine, 46*(3), 585-593. https://doi.org/10.1007/s12020-013-0106-9

Zhou, J., Camacho, M., Tang, X., & Kushida, C. A. (2016). A review of neurocognitive function and obstructive sleep apnea with or without daytime sleepiness. *Sleep Medicine, 23,* 99-108. https://doi.org/10.1016/j.sleep.2016.02.008 1389-9457

Appendix A

Recruitment Script

Good morning/afternoon (insert name). How are you today? My name is Olivia de Villiers/ Claudia Elliot-Wilson and I am an Honours student in the Psychology department at the University of Cape Town. I am phoning because having spoken to the doctors at the Pituitary Disease Clinic at Groote Schuur it seems that you fit the eligibility criteria for our study. The study is investigating the relationships between sleep and cognition in patients with pituitary disease. Participating in the study will require you to participate in a telephonic survey that will take approximately 45-60 minutes to complete. Would you be interested in participating?

No

That's absolutely fine. Thank you for your time. Have a nice day.

Yes

Wonderful! Thank you so much for agreeing to participate. Are you available now to complete the telephonic survey? It will take about 45 minutes. If not, we can arrange another time that suits you better and I can give you another call then.

Appendix B

Sociodemographic Questionnaire

Section A. (for all participants)

Name…….. Participant Number……

Age…..

Sex……

Email address……..

Highest level of education obtained…….

What is the total monthly income of the household in which you live? If you are a student please take care to put your immediate caregiver's monthly income not your own. (please circle only one option):

R0 – R499	R500 – R999	R1000 – R2499
R2500 – R5499	R5500 – R9999	R10000 – R20000
R20000 – R30000	R30000 +	

Section B. (for patients only)

How long have you had a pituitary disease?.....

What forms of treatment are you currently on? .....

Provide more information about treatment

……..

.....

How long have you been on this treatment? ……..

Do you suffer from any neurological, endocrinological, psychiatric, psychological, medical or other illness or disease? …….

If yes, please specify

……

……

……

Section C. (for controls only)

Do you suffer from any neurological, endocrinological, psychiatric, psychological, medical or other illness or disease? …….

If yes, please specify

……

……

……

Are you on any type of medical treatment? ……

If yes, please provide more information

……

Are you on any medication? …….

If yes, please specify which medication

……

……

……

Appendix C

Global Sleep Assessment Questionnaire (GSAQ)

Each of the items below is presented next to a row of checkbox response options regarding symptom frequency over the last four weeks. The response options are (4) ‘never’ (3) ‘sometimes’ (2) ‘usually’ and (1) ‘always’ (Roth et al., 2002).

1. Did you have difficulty falling asleep, staying asleep, or did you feel poorly rested in the morning?

2. Did you fall asleep unintentionally or did you have to fight to stay awake during the day?

3. Did sleep difficulties or daytime sleepiness interfere with your daily activities?

4. Did work or other activities prevent you from getting enough sleep?

5. Did you snore loudly?

6. Did you hold your breath, have breathing pauses, or stop breathing in your sleep?

7. Did you have restless or "crawling" feelings in your legs at night that went away if you moved your legs?

8. Did you have repeated rhythmic leg jerks or leg twitches during your sleep?

9. Did you have nightmares, or did you scream, walk, punch, or kick in your sleep?

10. Did the following things disturb you in your sleep: pain, other physical symptoms, worries, medications, or other (specify)?

11. Did you feel sad or anxious?

Appendix D

Brief Test of Adult Cognition by Telephone (BTACT)

WORD LIST RECALL (1.5 minutes on average)

Rey Auditory-Verbal Learning Test (Lezak, 1983)

I am going to read a list of words. Listen carefully. When I am finished, you are to repeat as many of the words as you can remember. It doesn't matter in what order you repeat them. Just try to remember as many as you can. I will say each word only one time, and I cannot repeat any words. You will have up to one and a half minutes, and I will not say anything until I tell you that your time is up. Do you have any questions? Are you ready?

(Read with one second interval between each word)

Now tell me as many words as you can remember.

(Record words recalled correctly by entering the one or two letter code, as well as repetitions of same word and intrusions).

Drum	
Curtain	
Bell	
Coffee	
School	
Parent	
Moon	
Garden	
Hat	
Farmer	
Nose	
Turkey	
Colour	
House	
river	

DIGITS BACKWARD (2.5 minutes)

WAIS III (1997)

I am going to say some strings of numbers, and when I am done I would like you to repeat them backwards, in the reverse order from which I said them. So if I said "3, 8", you would say "8, 3". Do you understand? The sets will get larger as we go.

2-4	4-2	
5-7	7-5	
6-2-9	9-2-6	
4-1-5	5-1-4	
3 - 2 - 7 - 9	(9 - 7 - 2 - 3)	
4 - 9 - 6 - 8	(8 - 6 - 9 - 4)	
1 - 5 - 2 - 8 - 6	(6 - 8 - 2 - 5 - 1)	
6 - 1 - 8 - 4 - 3	3 - 4 - 8 - 1 - 6)	
5- 3 - 9 - 4 - 1 - 8	(8 - 1 - 4 - 9 - 3 - 5)	
7 - 2 - 4 - 8 - 5 - 6	(6 - 5 - 8 - 4 - 2 - 7)	
8 - 1 - 2 - 9 - 3 - 6 - 5	5 - 6 - 3 - 9 - 2 - 1 – 8	
4 - 7 - 3 - 9 - 1 - 2 - 8	(8 - 2 - 1 - 9 - 3 - 7 - 4)	
9 - 4 - 3 - 7 - 6 - 2 - 5 - 8	8 - 5 - 2 - 6 - 7 - 3 - 4 – 9	
7 - 2 - 8 - 1 - 9 - 6 - 5 - 3	(3 - 5 - 6 - 9 - 1 - 8 - 2 – 7)	

CATEGORY FLUENCY (1.5 minutes)

Drachman & Leavitt (1972)

Now I am going to name a category and you will name things that belong in that category. Let's practice with the category "fruit". You could say peach, or pear. Can you think of any other fruits? (*wait for 2 correct items*). In a moment I will give you another category. When I

say begin, you will name all the things from this new category you can think of, as fast as you can. You will have one minute to do this. I will let you know when your time is up. Do you have any questions? Ready? Begin.

Category: Animals

STOP AND GO TASK (3-3.5 minutes)

Next I am going to see how quickly you can respond to the words RED and GREEN.Every time I say GREEN you will say GO, and every time I say RED you will say STOP. Try to be accurate, but respond as quickly as you can. So when I say RED you will say…And when I say GREEN you will say…Do you have any questions? Let's begin. This will last about 1 minute.

RED GREEN:

GREEN	GO	
RED	STOP	
GREEN	GO	
RED	STOP	
RED	STOP	
GREEN	GO	
RED	STOP	
GREEN	GO	
RED	STOP	
GREEN	GO	
RED	STOP	
GREEN	GO	
GREEN	GO	
RED	STOP	

RED	STOP	
GREEN	GO	
RED	STOP	
GREEN	GO	
GREEN	GO	
RED	STOP	

RED GREEN REVERSE

Every time I say RED you will say GO, and every time I say GREEN you will say STOP. Try to be accurate, but respond as quickly as you can. So when I say RED you will say…And when I say GREEN you will say…

GREEN	STOP	
RED	GO	
GREE	STOP	
RED	GO	
RED	GO	
GREEN	STOP	
RED	GO	
GREEN	STOP	
RED	GO	
GREEN	STOP	
RED	GO	
GREEN	STOP	
GREEN	STOP	
RED	GO	
RED	GO	
GREEN	STOP	
RED	GO	
GREEN	STOP	
GREEN	STOP	
RED	GO	

Now I will alternate with asking you to say the normal order of GREEN = GO and RED = STOP and the reverse order of RED = GO and GREEN = STOP

NORMAL	GREEN	GO	
	RED	STOP	
	GREEN	GO	
REVERSE	RED	GO	
	RED	GO	
	GREEN	STOP	
	RED	GO	
	RED	GO	
NORMAL	RED	STOP	
	GREEN	GO	
	RED	STOP	
	GREEN	GO	
	GREEN	GO	
	RED	STOP	
REVERSE	GREEN	STOP	
	GREEN	STOP	
	RED	GO	
	GREEN	STOP	
NORMAL	GREEN	GO	
	RED	STOP	
	GREEN	GO	
	GREEN	GO	
	RED	STOP	
REVERSE	GREEN	STOP	
	GREEN	STOP	
	RED	GO	
	GREEN	STOP	
	RED	GO	
NORMAL	RED	STOP	
	GREEN	GO	

	RED	STOP	
	GREEN	GO	

NUMBER SERIES (2.5 minutes)

Salthouse & Prill (1987)

In the next exercise I will read you a series of numbers that may get larger or smaller in value. At the end you will try to figure out what the next number would be. So if the numbers were 2, 4, 6, 8, 10, the next number would be 12. After I say each number I will pause for as long as you need, and then you should say "okay" when you are ready for me to go on to the next number in the group. So if I said 2, you should say "okay" when you are ready for me to go on to the next number, then I say 4, you say okay, 6, okay, 8, okay, 10, and at the end I will ask you what you think the next number would be. In this case the next number would be 12, as each number has increased by 2.

Let's try one for practice: 35 (okay), 30 (okay), 25 (okay), 20 (okay), 15 (okay) AND the next number would be….???? (The answer should be 10 as each number has decreased by 5). There will be different patterns, and some of these will be harder than others, so just do the best you can. *(Pause after each of the first 4 items for okay response; after the last item, say AND the next number is…?).*

18, 20, 24, 30, 38……(48)	
81, 78, 75, 72, 69…….(66)	
7, 12, 16, 19, 21……...(22)	
28, 25, 21, 16, 10…….(3)	
20, 37, 18, 38, 16…….(39)	

BACKWARD COUNTING TASK (45 seconds)

Next, I would like to see how fast you can count backwards from 100. You will have 45 seconds. Do you have any questions? I will let you know when the time is up.

Begin *(Time for 45 seconds)*

Record final number reached, and number of errors.

Number reached –

Number errors –

DELAYED RECALL (40 seconds on average)

Drum	
Curtain	
Bell	
Coffee	
School	
Parent	
Moon	
Garden	
Hat	
Farmer	
Nose	
Turkey	
Colour	
House	
river	

Appendix E

Consent Form

UNIVERSITY OF CAPE TOWN

DEPARTMENT OF PSYCHOLOGY

1) Study title

Sleep and Cognition in Pituitary Disease

2) Investigators

We are Psychology Honours students at the University of Cape Town and the information obtained from this study will be used for our thesis project.

3) Purpose

You are invited to participate in a study that investigates the effects of sleep on memory, attention and learning in patients with pituitary disease. Only people who meet the following criteria are able to take part:

- People who are between the ages of 18 and 65 years.
- If you are a pituitary disease patient, you need to have been on stable treatment for at least 3 months.
- Women who are not pregnant.
- People who do not have a history of neurological disorder that negatively affects memory, attention, learning, judgement, and reasoning.
- People who do not have a history of psychiatric illness, such as mood disorders (e.g. anxiety or depression) or psychotic disorders (e.g. schizophrenia)
- People who do not have any chronic diseases, other than a pituitary condition.

4) Procedures

The telephonic survey will take approximately 60 minutes to complete. We will ask you questions about your sleep, memory, attention, learning and how you feel about life. Participation is completely voluntary and you may withdraw from the study at any time without penalty.

5) Privacy and Confidentiality

All the data obtained in this study will form part of a Psychology Honours research thesis. Your right to anonymity will be respected, which means that no names will be mentioned in the final write up of the study. Each participant will be assigned a unique number to ensure anonymity of their responses.

6) Risks and Benefits

Participation does not pose any foreseeable psychological or physical risks. However, some questions might be considered personal and therefore if at any point in time you feel uncomfortable, you may terminate the interview or choose not to answer a specific question.

7) Questions and answers

You are encouraged to ask questions if you are unsure about certain details.

8) Signatures

The participant is aware of the nature and purpose of the study. They have been informed about the procedures, confidentiality agreement, and risks and benefits, and they are encouraged to ask further questions should they have any.

Researcher's Signature ……. Date……

Do you agree to participate and consent to have your results used for the purpose of the research thesis and publication in an accredited journal? Are you aware that you are free to withdraw from this study at any given time should you feel the need to do so, and in doing so you will not encounter any penalties?

Participant's verbal consent ……. Date……

Appendix F

Verbal Debriefing Script

This study was concerned with the impact of sleep on memory, attention and learning. Patients with pituitary disease often struggle with sleep and things like memory and attention. However, this is the first study that has looked at the connection between sleep and memory, attention and learning in the context of pituitary disease.

How was this tested?

You were asked questions about your sleep and then your memory, attention and learning were tested.

Hypotheses and main questions:

We expect to find that both pituitary disease and sleep problems affect memory, attention and learning.

Why is this important to study?

This study might help to develop treatments for sleep problems in those with pituitary disease.

We encourage you to ask any questions you may have about the study or your role in the study. Do you have any questions?

Shortly after this call you will receive an email with a formal debriefing letter including our contact details should you have any further questions.

Would you like us to also email you a summary of the study results?

Thank you so much for your participation and for giving so generously of your time. We really appreciate your contribution to our research project.

Appendix G

Ethical approval from the Research Ethics Committee of the Department of Psychology

UNIVERSITY OF CAPE TOWN

Department of Psychology

University of Cape Town Rondebosch 7701 South Africa
Telephone (021) 650 3417
Fax No. (021) 650 4104

08 July 2020

Olivia De Villiers and Claudia Elliot-Wilson
Department of Psychology
University of Cape Town
Rondebosch 7701

Dear Olivia and Claudia

I am pleased to inform you that ethical clearance has been given by an Ethics Review Committee of the Faculty of Humanities for your study, *Sleep Disruption and Cognitive Dysfunction in Pituitary Disease.* The reference number is PSY2020-029.

I wish you all the best for your study.

Yours sincerely

Catherine Ward
Professor
Chair: Ethics Review Committee

Appendix H

Ethical Approval from the Research Ethics Committee of the Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arieff@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

19 August 2019

HREC REF: 462/2019

A/Prof K Thomas
Department of Psychology
Room 2.17
Upper Campus, UCT

Dear A/Prof Thomas

PROJECT TITLE: POOR QUALITY OF LIFE, AFFECTIVE DYSREGULATION, AND COGNITIVE DYSFUNCTION MAY BE MEDIATED BY SLEEP DISRUPTION IN PATIENTS WITH PITUITARY DISEASES (HONOURS CANDIDATES: MS M BROWN & MS T PAGE)

Thank you for your response letter, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned stud, subject to adding the HREC contact details to the informed consent document.

Approval is granted for one year until the 30 August 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the students: - Hussadiqah Brown & Tayla Page will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix I

Ethical Approval Renewal from the Research Ethics Committee of the Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS007: Amendment – study staff

HREC office use only (FWA00001637; IRB00001938)			
☐ Approved			
This serves as notification that all changes to the study staff and documentation described below are approved.			
Chairperson of the HREC signature/ Designee		Date	14/7/2020

Note:
Please note that incomplete amendment submissions will not be reviewed.

Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown.

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	7 July 2020
HREC REF Number	462/2019
Protocol title	Poor Quality of Life, Affective Dysregulation, and Cognitive Dysfunction May Be Mediated by Sleep Disruption in Patients with Pituitary Disease
Protocol number (if applicable)	
Principal Investigator	A/Prof Kevin Thomas
Department / Office Internal Mail Address	Department of Psychology Room 2.17 Upper Campus, UCT

1.1 Does this protocol receive US Federal funding?	☐ Yes	√☐ No

2.1 Staff changes (tick ✓)

Are new personnel being added to this research?	√☐ Yes	☐ No
Are current personnel being removed from this research?	☐ Yes	√☐ No
Is the principal investigator for this research being changed? If yes, please attach revised conflict of interest and PI declaration statements. (Refer: sections 7 and 8.3 in the New Protocol Application Form - FHS013)	☐ Yes	√☐ No

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Do the consent and assent forms need modification to reflect these staff changes? If yes, please attach copies of the revised forms, with all changes highlighted or tracked and listed in the documents for approval.	√☐ Yes	☐ No

2.2 Amended study staff details

Title, first name, surname	Department/Division	E-mail	Role of new staff member
Miss Olivia de Villiers	**Department of Psychology (Honours student)**	**livz.devilliers@gmail.com**	**Data collection, data analysis, report write up**

3. List of documentation for approval

Please list below all staff documentation such as CVs, declarations, GCP certificates and revised consent forms which need approval. This information must correspond to all 'yes' answers in 2.1 above. This form will be signed and returned to the PI as notification of approval. Please add extra pages if necessary.

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS007: Amendment – study staff

HREC office use only (FWA00001637; IRB00001938)			
☐ Approved			
This serves as notification that all changes to the study staff and documentation described below are approved.			
Chairperson of the HREC signature/ Designee		Date	14/7/2020

Note:
Please note that incomplete amendment submissions will not be reviewed.

Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown.

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	7 July 2020		
HREC REF Number	462/2019		
Protocol title	Poor Quality of Life, Affective Dysregulation, and Cognitive Dysfunction May Be Mediated by Sleep Disruption in Patients with Pituitary Disease		
Protocol number (if applicable)			
Principal Investigator	A/Prof Kevin Thomas		
Department / Office Internal Mail Address	Department of Psychology Room 2.17 Upper Campus, UCT		
1.1 Does this protocol receive US Federal funding?		☐ Yes	√☐ No

2.1 Staff changes (tick ✓)

Are new personnel being added to this research?	√☐ Yes	☐ No
Are current personnel being removed from this research?	☐ Yes	√☐ No
Is the principal investigator for this research being changed? If yes, please attach revised conflict of interest and PI declaration statements. (Refer: sections 7 and 8.3 in the New Protocol Application Form - FHS013)	☐ Yes	√☐ No

Do the consent and assent forms need modification to reflect these staff changes? If yes, please attach copies of the revised forms, with all changes highlighted or tracked and listed in the documents for approval.	√☐ Yes	☐ No

2.2 Amended study staff details

Title, first name, surname	Department/Division	E-mail	Role of new staff member
Miss Claudia Elliot-Wilson	Department of Psychology (Honours student)	c.elliotwilson@hotmail.com	Data collection, data analysis, report write up

3. List of documentation for approval

Please list below all staff documentation such as CVs, declarations, GCP certificates and revised consent forms which need approval. This information must correspond to all 'yes' answers in 2.1 above. This form will be signed and returned to the PI as notification of approval. Please add extra pages if necessary.

Appendix J

Study Debriefing

This study was concerned with the impact of sleep on memory, attention and learning. Patients with pituitary disease often struggle with sleep and things like memory and attention. However, this is the first study that has looked at the connection between sleep and memory, attention and learning in the context of pituitary disease.

How was this tested?

You were asked questions about your sleep and then your memory, attention and learning were tested.

Hypotheses and main questions:

We expect to find that both pituitary disease and sleep problems affect memory, attention and learning.

Why is this important to study?

This study might help to develop treatments for sleep problems in those with pituitary disease.

If you are concerned about your sleep or your memory, attention and learning, then we can refer you to the UCT/ Groote Schuur Hospital Memory Clinic. The contact number is 0214066211.

What if I want to know more?

You will receive a summary of the findings when the research is completed. If you have any concerns or questions regarding this research, please contact

Olivia de Villiers at DVLOLI001@myuct.ac.za or

Claudia Elliot-Wilson at ELLCLA004@myuct.ac.za