The Association between Sleep Quality and Cognitive Function in Patients with Non-functioning Pituitary Adenoma's

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COMPULSORY DECLARATION

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

Signature: Signed by candidate Date: 11 February 2023

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Abstract

Existing research indicates that (a) cortisol and growth hormone are important for sleep regulation and cognition, (b) sleep is important for overall cognitive functioning (and for memory consolidation, in particular), and (c) patients with pituitary disease (PD) experience hormonal dysregulation, impaired quality of sleep, and particular patterns of cognitive dysfunction. However, the current study is the first to examine (using objective measures of sleep quality) whether there are relations among sleep disruption, cognitive impairment, and the presence of PD. Participants were 10 patients with non-functioning pituitary adenomas (NFPA) and 10 case-matched healthy controls. Using a crossover design, each participant was administered standardized neuropsychological tests (Rey Auditory Verbal Learning Test [RAVLT], Wechsler Logical Memory Test [LM test], Finger Tapping Task [FTT]) assessing declarative and procedural memory performance after a period of sleep and after an equivalent period of wakefulness. Fitbit Alta HR devices recorded objective sleep data and the Pittsburgh Sleep Diary captured self-reported sleep data. Consistent with previous literature, analyses detected significant between-group differences in cognitive performance: Controls performed better than NFPA patients in certain aspects of cognition, particularly in Retention on the LM test $p = .027$ and Recognition on the RAVLT $p = .011$. With regards to objective sleep quality, analyses detected no significant between group differences on any of the variables measured, however, controls reported to have better subjective sleep quality than patients, $p = .016$, and they reported to be more alert when awakening than patients $p = .015$. Although the priori hypotheses were only partially confirmed, the current findings contribute to the existing body of psychological research on PD patients and may provide an impetus for further research in the field. For example, potential clinical and practical implications are that patients' relatively poor performance on certain memory tasks cognition can guide researchers and clinicians toward a deeper understanding of cognitive function in patients with PD and may, for instance, lead to a focus on specific memory rehabilitation interventions designed for this patient group. Such interventions may assist in improving their adherence to daily treatment regimens and their capacity to successfully complete other important daily activities.

Keywords: Pituitary Disease, non-functioning pituitary adenomas, cortisol, growth hormone, sleep, memory.

Abbreviations

ACTH	Adrenocorticotrophic hormone
ANOVA	Analysis of variance
BDI-II	Beck Depression Inventory II
CAR	Cortisol awakening response
CRH	Corticotropin-releasing hormone
EEG	Electroencephalograph
ESE	Effect size estimate
FTT	Finger Tapping Task
GC	Glucocorticoid
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GR	Glucocorticoid receptor
HPA	Hypothalamic-pituitary-adrenal
LM	Logical Memory
MINI	Mini International Neuropsychiatric Interview
MR	Mineralocorticoid receptor
NFMA	Non-functioning pituitary adenoma
NFMA	Non-functioning pituitary macroadenoma
NREM	Non-rapid eye movement
PD	Pituitary Disease
PFC	Pre-frontal cortex
PSG	Polysomnography

RAVLT	Rey Auditory-Verbal Learning Test
REM	Rapid eye movement
SWS	Slow-wave sleep
TST	Total sleep time
WASO	Wake after sleep onset

Chapter 1:
Introduction and Literature Review

Sleep is a normal physiological function that is of vital importance to overall health and well-being (Walker, 2017). Specifically, sleep plays crucial roles in promoting cognitive functioning (particularly in the domain of memory consolidation), mental health, and physical health (including, but not limited to, cardiovascular, cerebrovascular, and metabolic health; Ramar et al., 2021; Vyazovskiy, 2015; Worley, 2018).

Healthy sleep is a period of sleep that is free from disruption / disorder, adequate in duration, and appropriate in timing and regularity (Buysse, 2014; Chaput & Shiau, 2019; Watson et al., 2015). Although the amount of sleep that is deemed adequate differs from person to person (Chaput et al., 2018), there is a general consensus among sleep researchers that the average adult needs approximately 7 or more hours of sleep per night (Carskadon & Dement, 2005; Watson et al., 2015).

However, the amount of sleep attained per night is not the only important factor in determining sleep health: the organisation of sleep stages is as important (Altevogt & Colten, 2006). Irregularities in one's sleep schedule and sleep structure can have major consequences. For example, several studies have shown that irregular cycling through sleep stages is linked to sleep disorders such as narcolepsy, delayed sleep phase disorder, advamced sleep phase disorder, free-running disorder, and irregular sleep-wake rhythm (Carskadon & Rechtschaffen, 2011; Sack et al., 2007; Zepelin et al., 2005) and that sleep disruption leads to an array of physical and psychological problems (including compromised immunity, accelerated progression of medical diseases, increased risk of depression, and impaired attention, memory consolidation, reasoning, and judgement; Anothaisintawee et al., 2016; Furihata et al., 2015; Hung et al., 2014; Irwin, 2015; Irwin et al., 2017; Itani et al., 2017).

Of particular interest to the current research are associations between disrupted sleep and cognitive impairment. Recent neuroscience literature suggests there are significant associations between sleep disruption and memory processing, and that these associations may be mediated by the hormone cortisol. Because patients with pituitary disease (PD) experience fluctuations in hormone secretion (due to endogenous imbalances caused by a tumour of the pituitary gland, or by exogenous supplementation of hormones), and because they often report poor sleep patterns and poor memory, these patients provide a rare opportunity for investigation of possible associations between sleep quality and cognitive function.

In this Master's research project, I describe sleep quality and memory function in a sample of patients with non-functioning pituitary adenomas, and investigate whether sleep enhances memory consolidation in patients as it does in controls.

Literature Review

This literature review is structured as follows. After a brief description of normal human sleep, I discuss the role that hypothalamic-pituitary-adrenal (HPA) axis-controlled hormones play in sleep regulation and in memory. Then, I outline the pivotal role of sleep in memory processing. Thereafter, I describe the aetiology of PD and introduce the characteristics of patients with PD, with particular emphasis on features that allow critical investigation of relations between sleep and cognition. Finally, I review previously published studies investigating sleep disruption and cognitive dysfunction in PD patients, highlighting aspects of the work that leave significant questions unanswered.

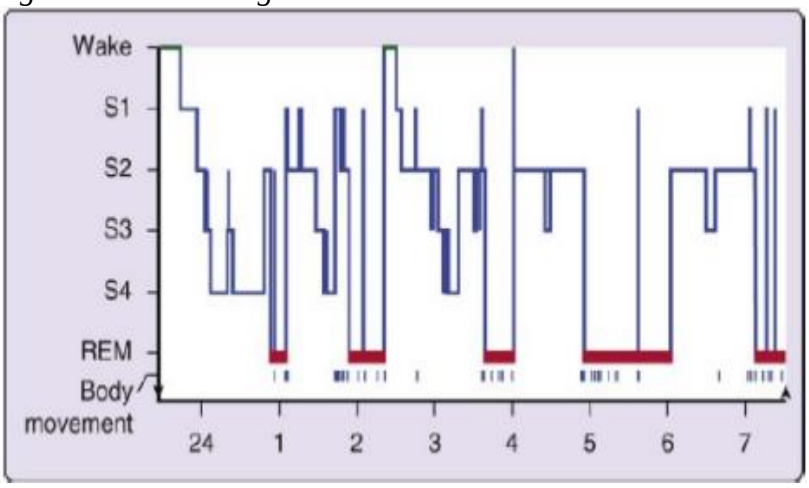
Staged Components of Normal Human Sleep

Normal human sleep is divided into two major components: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Each of these is accompanied by distinct levels of arousal and neuronal synchronicity (Chokroverty, 2017; Stickgold 2005). NREM sleep is a combination of four separate stages (stage 1, stage 2, stage 3, and stage 4). Depending on sleep duration, the average person experiences 4–6 sleep cycles (i.e., stage 1 $\rightarrow$ stage 2 $\rightarrow$ stage 3 $\rightarrow$ stage 4 $\rightarrow$ REM sleep) per night (Chokroverty, 2017; Lockely & Foster, 2012). Each sleep cycle lasts approximately 90–100 minutes. Stage 1 typically lasts for 1–7 minutes after sleep onset. Stage 2 tpyically lasts for 10–25 minutes. Only a few minutes are spent in stage 3 before the transitioning into stage 4, which lasts for 20–40 minutes. The body may re-enter Stage 2 for approximately 5 minutes before crossing over into REM sleep, which lasts for about 5–10 minutes (Patel et al., 2022). The percentage of NREM and REM sleep within each cycle changes through the night: During the first few cycles NREM sleep dominates while in the last few cycles an increasingly higher level of REM sleep is observed (Lockely & Foster, 2012; Markov & Goldman, 2006).

A visual summary of these typical nightly sleep patterns is often presented by a hypnogram (see Figure 1).

Figure 1

Hypnogram (a Graph Displaying Sleep as a Function of Time) Showing the Progression of Sleep Stages Across One Night in a Normal Volunteer



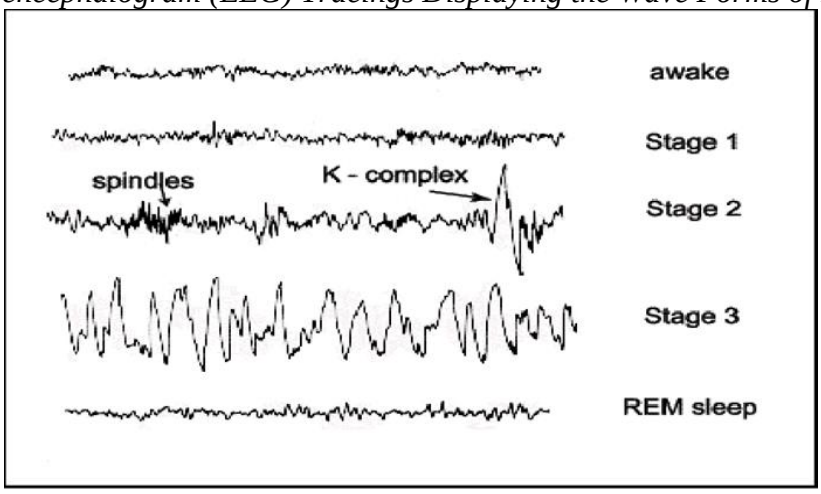
Note. Figure taken from Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep, 27*(7), 1255–1273.

Stage 1, which occurs at the onset of sleep, is the phase marking the transition from wakefulness to sleep. Electroencephalogram (EEG) recordings during this stage tend to show the disappearance of alpha waves and the appearance of theta waves. During this stage, breathing occurs at a regular rate and appropriate tone is present in the skeletal muscles. Stage 2 is a light form of sleep (i.e., one can easily be awoken during it). Electrophysiologically, it is characterised by sleep spindles and K complexes. Stages 3 and 4 together constitute slow-wave sleep (SWS), which is the deepest form of sleep. SWS is characterised by slow brainwaves as well as slow heart rate and respiration. EEG recordings of SWS typically show the occurrence of delta waves (Fogel & Smith, 2011; Steriade, 2006). REM sleep is characterised by physiological similarities with states of wakefulness: increased mental activity, a reduced arousal threshold, low muscle tone, an increased pulse and breathing rate, and an activated central nervous system. EEG recordings during REM sleep show mixed frequencies, including theta and sawtooth waves, and are almost identical to the EEG recordings of a person who is fully awake (Lockely & Foster, 2012; Nielsen, 2000; Ravassard et al., 2015).

Figure 2 presents typical EEG recordings of human sleep and waking activity.

Figure 2

Electroencephalogram (EEG) Tracings Displaying the Wave Forms of Different Sleep Stages



Note. On the third tracing (stage 2) the arrows point to sleep spindles and K-complexes. This image is taken from: Susmakova, K. (2004). Human sleep and sleep EEG. *Measurement Science Review*, *4*(2), 59–74.

The Role of HPA Axis-Controlled Hormones in Sleep

The HPA axis plays an important role in modulating the complex processes that determine need, timing, and organisation of sleep (Borbely et al., 2016; Buckley & Schatzberg, 2005; Chorous et al., 2016; Hirotsu et al., 2015). For instance, the inhibition and secretion of HPA axis-controlled hormones (including corticotrophin-releasing hormone [CRH], adrenocorticotrophic-releasing hormone [ACTH], and growth hormone releasing hormone [GHRH]) are responsible for changes in sleep patterns. Specifically, the hypothalamic release of CRH enhances ACTH levels, which in turn stimulates the release of cortisol from the adrenal glands (Balbo et al., 2010; Steiger, 2007). ACTH and cortisol levels reach their peak around 09h00 (i.e., relatively shortly after waking). As the day goes on, these concentrations gradually decrease, reaching their lowest point around midnight. Approximately 2–3 hours after the onset of sleep, cortisol concentrations start to rise again, reaching their morning peak at 08h00 (Buckley, & Schatzberg, 2005). In contrast, GHRH stimulation of growth hormone (GH) occurs most prominently during the first half of the night (corresponding with the most SWS-rich period of sleep), with much less such stimulation occurring during the second half of the night (i.e., during the most REM-rich period of sleep). This apparently reciprocal interaction of GH and cortisol seems to play a major role in sleep regulation (Angelousi et al., 2018; Chennaoui et al., 2021; Steiger, 2007; Steiger et al., 2013).

The Role of Growth Hormone, an HPA Axis-Controlled Hormone, in Sleep

As noted above, GH secretion is closely linked to the sleep-wake cycle (Collop et al., 2008; Rowley & Badr, 2022). In one of the earliest studies describing this relationship, Davidson and colleagues (1991) examined the secretory patterns of GH and cortisol in relation to sleep and wakefulness in young men during baseline wake and sleep periods, during 40 hours of staying awake, and during post-deprivation recovery sleep. During sleep deprivation, GH surge disappeared, whereas during recovery sleep GH excursions were greater and the secretion was prolonged, displaying that the GH surge shifts with the sleep-wake cycle. This pattern of data shows clearly that the nocturnal GH surge is largely sleep-dependent.

Many studies have shown that dysfunction in the concentrations of circulating endocrine hormones, such as GH, leads to sleep disturbances (see, e.g., Kotronoulas et al., 2009; Van Cauter et al., 1998). Several of these studies have been conducted using samples of patients with GH deficiency (a condition characterised by a profound decrease in GH secretion from the pituitary gland; Hayashi et al., 1992; Ismailogullari et al., 2009; Richard & Thorpy, 1988; Yeun et al., 2019). For example, Copinschi et al. (2010) used both subjective and objective methods to measure sleep quality in a group of such patients and found that GH deficiency was associated with objectively disordered sleep, poor subjective sleep quality, and daytime sleepiness.

Associations between GH and sleep have also been demonstrated in patients with acromegaly (a disease characterised by the overproduction of GH; Chanson & Salenave, 2008; Melmed, 2022). These patients present with sleep problems (including sleep apnoea and reduced self-perceived and subjective sleep quality; Kim et al., 2020; Melmed, 2022; Romjin et al., 2016; Watson & Vitiello, 2007; Wennberg et al., 2019; Zhang et al., 2019).

The Role of GH, an HPA Axis-Controlled Hormone, in Cognition

GH interacts with particular brain structures and thereby affects cognitive functioning (Nyberg & Hallberg, 2013). This interaction occurs at the level of GH receptors that, although present throughout the brain, are concentrated in the hippocampus, choroid plexus, putamen, hypothalamus, thalamus, and pituitary gland (Lai et al., 1993; Nyberg & Hallberg, 2013). Of particular importance here is that compared to the other aforementioned brain structures, GH receptors are expressed up to four times more in the hippocampus, a brain structure central to many aspects of learning and memory (Bird & Burgess, 2008; Davachi & DuBrow, 2015; Eldridge et al., 2000; Fortin et al., 2002; Lai et al., 1993; Maguire et., 2016; Postle, 2016; Tulving & Markowitsch, 1998; Webb et al., 2012).

Hence, it is not surprising that numerous studies observe the presence of cognitive deficits in patients with abnormally high levels of GH (see e.g., Gagliardi et al., 2021; Sievers et al., 2008; Sievers et al., 2012). In one particularly notable example from this subsection of the literature, Leon-Carrion et al. (2010) compared performance on tests of attention, visuoconstructive ability, visual and verbal memory, verbal fluency, and executive function, as well as recordings of EEG and electromagnetic tomography outputs, in patients with acromegaly (n = 16) and age-, education, and gender-matched healthy controls n = 16. They found, in patients relative to controls, evidence of memory impairment and decreased neural activity in specific brain areas, and hence suggested that abnormally high concentrations of GH were a prime factor underlying significant between-group differences.

It is also not surprising that cognitive impairments in patients with GH deficiencies improve with replacement therapy (Deijen et al., 1998; Falleti et al., 2006). GH replacement therapy has been shown to have positive effects on performance in many cognitive domains, including, mental alertness, attention, motivation, and memory (Aberg et al., 2006; Almqvist, et al., 1986; Chaplin et al., 2015; Deijen et al., 1998; Dykens et al., 2017; Loche et al., 2014; Nyberg, 2000). For example, Oertel et al. (2004) conducted a double-blind controlled trial over 6 months, during which adult GH deficient patients n = 18 were randomized into either a placebo group or a group in which they were treated with recombinant human growth hormone. They found that attention performance improved in GH deficient hypopituitary patients following atleast 3 months of GH therapy, but no such improvements were observed in the placebo group.

The Role of Cortisol, an HPA Axis-Controlled Hormone, in Sleep

The secretion and inhibition of cortisol play key roles in regulating sleep onset and terminating sleep, respectively. At sleep onset, cortisol is at its lowest daily concentration. Night-time awakenings are accompanied by an initial release of CRH and cortisol and subsequently by the temporary inhibition of those hormones. The first morning awakening is accompanied by a surge in cortisol secretion; this is known as the cortisol awakening response (CAR; Bush & Hudson, 2010; Henry et al., 2021). Hence, the relationship between HPA axis-controlled hormones and sleep is bidirectional: cortisol directly impacts sleep, and sleep directly impacts the hormone's production (Balbo et al., 2010; Chorous et al., 2016; van Dalfsen & Markus, 2018).

Impact of Cortisol on Sleep. Many studies have shown that a dysfunction in HPA axis activity may play a role in disordered sleep (Buckley & Schatzberg, 2005; Han et al., 2012; Steiger, 2002; Vgontzas et al., 2003). For instance, D'Angelo et al. (2015) found, using

objective sleep measures, that patients with Cushing's Syndrome (a disorder characterised by an overproduction of cortisol) frequently experienced poor sleep quality characterized by nocturnal fragmentation, higher frequency of wrist movements, and longer time spent awake after sleep onset. Two earlier studies had documented that patients with Cushing's Syndrome experience reduced SWS (Krieger et al., 1972; Shipley 1992). Similarly, patients with Addison's disease (an endocrinological disorder characterized by adrenal insufficiency that requires lifelong hormone replacement therapy; this therapy often does not restore concentrations to normal physiological levels; Barthel et al., 2019; Lovas et al., 2003) frequently experience sleep disruptions, poor sleep quality, sleep architectural aberrations, and daytime fatigue (García-Borreguero et al., 2000; Henry, 2019; Henry et al., 2015, 2017, 2018; Lovas et al., 2003).

The effects of cortisol on sleep are also demonstrated in major depressive disorder (MDD) and in normal aging. Dysfunctional HPA axis activity, leading to abnormally high cortisol concentrations, is a key feature of the pathophysiology of MDD (Brown et al., 2004; Holsboer & Ising, 2010; Nandam et al., 2020; Pandi – Perumal et al., 2020; Pariante, 2017; Steiger et al., 1989). In this context, hypercortisolism appears to lead to sleep disturbances that include decreased sleep efficiency, decreased SWS, reduced REM latency, and increased REM intensity (Adrien, 2002; Benca et al., 1997; Berk et al., 2009; Riemann et al., 2001; Thase et al., 1997; Tsuno et al., 2005).

In older adults, the circadian mechanism of cortisol becomes less efficient and a decrease in sleep quality is experienced (Akerstedt et al., 2016; Carrier et al., 1996; Czeisler et al., 1992; Edwards et al., 2010; Espirito, 2008; Gulia & Kumar, 2018; Spiegel et al., 1999; Steiger, 2002, 2003; Steiger et al., 1998; Yiallouris et al., 2019). As age increases, there are progressive decreases in total time asleep, in sleep efficiency, and in SWS, as well as progressive increases in the number of night-time awakenings (Li et al., 2018; Naifeh et al., 1987; Ohayon et al., 2004; Rao et al., 1999; Van Cauter, 2000; Vitiello, 2006; Williams et al., 1972).

Impact of Sleep on Cortisol. There are instances in which HPA axis dysfunction is the result of disordered sleep or a change in the sleep-wake cycle (Bush & Hudson, 2010). For example, people with insomnia (a condition characterized by difficulty falling/staying asleep; Krystal et al., 2019) or obstructive sleep apnoea (a disorder in which breathing repeatedly stops and starts while sleeping; Chaiard & Weaver, 2019) have been shown to experience irregular HPA axis activity that leads directly to an increase in cortisol

concentrations (Bratel et al., 1999; Edwards et al., 2014; Henley et al., 2009; Kritikou et al., 2015; Vgontzas et al., 2001, 2007).

Researchers studying the sleep patterns of shift workers (Cannizzaro et al., 2020; James et al., 2017; Sachdeva & Goldstein, 2020), and more specifically Shift Work Sleep Disorder (SWSD – a sleep disorder associated with shift work and characterised by difficulty sleeping and/or excessive sleepiness resulting from a misalignment of the sleep-wake cycle with the internal circadian rhythm; Drake et al., 2004; Schwartz & Roth, 2012; Wickwire et al., 2017), have made contributions to the literature showing the impact of sleep variability on cortisol concentrations. For instance, Li et al (2018) used a sample of 70 physicians and found that shift work altered the diurnal cortisol pattern and was particularly predictive of increased cortisol secretion.

A similar series of studies has described the consequences for cortisol concentrations of daytime napping (Vgontzas et al., 2007; Vgontzas et al., 2003). For instance, Ward et al (2008) found that, in a sample of children aged 3 to 5 years, disruptive napping patterns were associated with higher afternoon cortisol concentrations and a smaller reduction in cortisol from morning to afternoon. Disruptive napping patterns were also associated with longer night-time sleep, shorter nap durations, and later rise times, illustrating again the close links between sleep-wake cycles and HPA axis activity. Similarly, Woods and colleagues (2011) found associations between excessive daytime napping and elevated evening cortisol levels in 12 nursing home residents with dementia.

However, it is not only disrupted sleep timing that can dysregulate HPA axis activity; disrupted sleep quality can have similar effects. Several studies have found that poor sleep quality is associated with elevated basal cortisol concentrations. Such elevations suppress sleepiness by stimulating arousal, which (again illustrating the bidirectional nature of this relationship) result in an increase in sleep disruptions (e.g., spending more time awake and less time in REM sleep; Hirotsu et al., 2015; Vgontzas et al., 2002).

A related strand of work in the literature reports that an increase in cortisol concentrations is observed during periods of night-time sleep deprivation, and that this increase persists during the following day (Chapotot et al., 2001; Leproult et al., 1997; Meerlo et al., 2002; Minkel et al., 2014; Steiger, 2002; Von Treuer et al., 1996; Wright et al., 2015). One account of this observation suggests that sleep deprivation is perceived by the body as a stressor, and that consequently the routine physiological stress response is triggered. Part of this stress response is activation of the HPA axis and diminution of the usual negative feedback regulation of the axis (Buckley & Schatzberg, 2005; Hirotsu et al.,

2015; Lee et al., 2013; McEwen, 2006). After a prolonged period of wakefulness, the need for sleep increases, which leads to feelings of fatigue and sleepiness, resulting in suppression of HPA-axis activity (Balbo et al., 2010).

Jetlag (specifically due to its effects on sleep) has been found to affect cortisol secretion (Doan et al., 2010 Lemmer et al., 2002; Paragliola et al., 2021; Zhang et al., 2020). For instance, Cho and colleagues (2000) assessed the cortisol concentrations of airline cabin crews and compared their values to the cortisol concentrations of ground crews. They reported that cabin crew members who had frequently experienced jetlag had higher cortisol excursions.

The Role of Cortisol, an HPA Axis-Controlled Hormone, in Cognition

Cortisol plays a vital role in modulating various internal functions. It helps to regulate metabolic and immune systems, to redistribute blood flow, to control blood glucose, and to reduce inflammation (Fries et al., 2009; Janicki-Deverts et al., 2016; Lightman et al., 2020; Reynolds & Walker, 2003; Scheer et al., 2009). However, prolonged exposure to excessive cortisol concentrations can be detrimental to health. For instance, stress-related cortisol elevations have been linked to diabetes, hypertension, and immunosuppression (Liu & Doan, 2019; Liu et al., 2017; Vivian et al., 2013).

In a similar way, the relationship between cortisol and cognitive performance follows an inverted-U shape (Andreano & Cahill, 2006; Henry et al., 2017). To achieve optimal cognitive function, a moderate amount of cortisol is needed; concentrations that are too low or too high have negative effects on cognition. Numerous studies have shown, for instance, that cognitive impairment in otherwise healthy adults and in patients with Alzheimer's disease, major depressive disorder, and Cushing's syndrome is associated with elevated cortisol concentrations (Beluche et al., 2010; Franz et al., 2011; Hinkelmann et al., 2009; Lee et al., 2007; McEwen, 2002). To examine the effects of low cortisol levels on cognition, Lupien et al. (2002) employed pharmacological manipulation by administering metyrapone to decrease cortisol levels in healthy young adults. They found that decreased levels of the hormone significantly impaired delayed recall of previously learned material.

Cortisol affects cognition through the interaction of the hormone with particular brain structures (Jentsch et al., 2022; Kim & Diamond, 2002; Lupien et al., 2005; McEwen et al., 2015; Wingenfeld & Wolf, 2014). This interaction is made possible by glucocorticoid receptors (GR) and mineralcorticoid receptors (MR), which are distributed throughout the brain. When glucocorticoids are secreted into the bloodstream they easily pass through the blood-brain barrier and enter the brain, where they alter gene expression by binding to GRs

(which has a low affinity for cortisol) and MRs (which has a high affinity for cortisol). This difference in affinity results in a difference in occupation of the two receptor types under different physiological conditions and at different times of day. For instance, when cortisol reaches its nadir (i.e., in the evening around midnight), the hormone occupies more than 90% of MRs, but only 10% of GRs. However, when cortisol levels reach their peak around 09h00 (i.e., relatively shortly after waking) or during a stressful event, MRs are saturated and there is occupation of approximately 70% of GRs (Lupien et al., 2007; Newcomer et al., 1999; Wingenfeld & Wolf, 2015; Wolf, 2003; Wolf et al., 2016)

Outside of the roles that MRs and GRs play in various adaptation processes (e.g., neuronal differentiation, excitability, behavioural reactivity, mood; de Kloet et al., 2005; Fritzsimons et al., 2013; Joels, 2006; Reul & Kloet, 1985), together these receptors play a critical role in memory function (de Kloet, 2014; de Kloet et al., 1999; Lupien et al., 2007: Vogel et al., 2016). Specifically, and especially when exposed to acute stress, MR activation is important in appraisal of incoming material, encoding of information, and memory retrieval. GR activation complements this by promoting memory consolidation and behavioural reactivity (Koning et al., 2019). These twin roles of MRs and GRs in memory processing were described in an elegant study by Tytherleigh et al. (2004). They examined the effects of MRs in isolation, GRs in isolation, and a combination of MRs and GRs on working memory and two separable components of declarative memory (episodic memory and semantic memory). Their participants were 9 people with Addison's disease; their experimental manipulations was the activation of receptors using exogenous steroids (9-alpha fluorohydrocortisone to activate MRs, dexamethasone to activate GRs). They found that participants performed better on a working memory task when both receptors were activated compared to when GRs only were activated. Participants also performed better on an episodic memory task when both receptors were activated compared to when either the MRs or the GRs only in isolation were activated.

The synaptic mechanism underlying these effects of MR and GR activation on memory processing is long-term potentiation (LTP; the continuous reinforcement of synaptic connections required for information storage; Lynch, 2004). Illustrating this point, de Kloet (1999) showed that LTP was enhanced when all MRs, but only some GRs, were activated, but that LTP was impaired when GRs were over-activated and MR occupation was low.

MRs are highly expressed in the prefrontal cortex (PFC) and in limbic areas (particularly the hippocampus and amygdala), whereas GRs are distributed widely throughout the brain (de Kloet, 2014; McEwen, 2022; Senft et al., 2016; Vogel et al., 2016). Hence, it is

unsurprising that cortisol elevations have dramatic effects on the PFC, a brain structure crucial for a variety of executive functions, including attention, impulse control, an scrutinizing environmental stimuli, as well as a variety of memory functions (Domenech & Koechlin, 2015; Donoso et al., 2014; Euston et al., 2012; Kane & Engle, 2002; Stokes, 2015), and on the hippocampus, which as mentioned before is crucial for learning and memory (Bird & Burgess, 2008; Davachi & DuBrow, 2015; Eldridge et al., 2000; Fortin et al., 2002; Maguire et., 2016; Postle, 2016; Tulving & Markowitsch, 1998).

Cortisol, the Prefrontal Cortex, and Cognition. The PFC plays vital roles in encoding and delayed recall of declarative memory (i.e., memory for facts and events that can be consciously recalled; Squire, 2004) material (Nyberg et al., 2000), post-retrieval selection of that retrieval, and working memory. During post-retrieval selection processes, the PFC facilitates the accurate reconstruction of memories by suppressing irrelevant and enhancing relevant information (Burgess, 1996; Eichenbaum, 2017). To facilitate working memory capabilities, the PFC promotes cognitive flexibility and goal-directed behaviour (Arnsten, 2009; Arnsten et al., 2015) by allowing the storage of a mental "sketch" of information and protecting it from internal and external interferences (e.g., by inhibiting inappropriate behavioural reactivity and by regulating attention).

An overwhelming body of evidence indicates that both persistent and short-term cortisol elevations of cortisol have negative effects on PFC functioning (Arnsten, 2009; Barsegyan et al., 2010; Cornelisse et al., 2011; De Quervain et al., 2000; Elzinga & Roelofs, 2005; Lupien et al., 1999; McCormick et al., 2007; Schoofs et al., 2009; Wolf et al., 2001). In particular, persistently elevated cortisol concentrations cause the atrophy of PFC dendrites (Stomby et al., 2016) while enhancing the noradrenalin system, resulting in diminution of neuronal firing in the PFC (Arnsten et al., 2015; Liston et al., 2006). Short-term cortisol elevations (e.g., those that might be stress induced) strengthen dopaminergic activity, which raises glutamate levels in the PFC (Moghaddam, 2002; Yuen et al., 2009). Short-term elevations of glutamate can enhance working memory, while excessive elevations can diminish it. Hence the relationship between noradrenalin, dopamine, and glutamate and working memory follows an inverted-U shape: too little or too much of those hormones impairs the functioning of the PFC (Arnsten et al., 2015).

Cortisol, the Hippocampus, and Cognition. Accumulating evidence suggests that both exogenously supplemented and endogenous secretions of cortisol have marked effects on hippocampal-dependent cognition (especially learning, encoding, and recall of declarative memory material; Davachi & Wagner, 2002; Reber et al., 2002; Squire et al., 1992;

Wingenfeld & Wolf, 2014; Wolf et al., 2016). Of note here is that, with regard to acute cortisol elevations, a number of factors (e.g., dose, time of administration, type of memory task evaluated, whether the stressor was applied at encoding, consolidation, or retrieval, whether the material being studied was neutral or emotionally arousing) influence whether memory performance is enhanced (Abercrombie et al., 2003; Benion et al., 2015; de Kloet et al., 1999; Lupien & McEwen, 1997; Smeets et al., 2007; Wolf, 2003) or diminished (Het et al., 2005; Shields et al., 2017). Chronic glucocorticoid elevations appear, overwhelmingly, to diminishes memory performance (Belanoff et al., 2001; Gold et al., 2002; Judd et al., 2014).

The hippocampus spans both cerebral hemispheres, and there is marked lateralization of functioning. The left cerebral hippocampus is responsible for the processing of verbal declarative memory whereas the right cerebral hippocampus is responsible for the processing of visual-spatial memory (Besson et al., 2014; Frisk & Milner, 1990; Maguire et al., 1999; Roche et al., 2005). High concentrations of cortisol have a negative impact on both the left and right hippocampus, thus leading to poor performance on, respectively, tests assessing verbal declarative memory and spatial cognition (Baddeley et al., 2003).

With regard to spatial cognition, several empirical studies confirm that increased cortisol concentrations impair performance on tasks assessing visuospatial memory and navigation tasks (Duncko et al., 2007; Elzinga & Roelofs, 2005; Guenzel et al., 2014; Kirschbaum et al., 1996; Luine et al., 1994; Lupien et al., 2005; Schwabe et al., 2007; Taverniers et al., 2010; Thomas et al, 2010; but see also Driscoll et al., 2005; Klopp et al., 2012; McCormick & Teillon, 2001; Newcomer et al., 1999; van Gerven et al., 2016).

The data on cortisol and verbal declarative memory is more robust. For instance, both laboratory-based (i.e., stress-induced) cortisol increases (Elzinga & Roelofs, 2005; Kuhlmann et al., 2005; Payne et al., 2007; Smeets, 2011; Wolf et al., 2001) and similar increases via pharmacological manipulation (Buss et al., 2004; De Quervain et al., 2002; Monk & Nelson, 2002; Newcomer et al., 1999; Rimmele et al., 2003; Tops et al., 2003; Wolf et al., 2001) have been found to impact verbal declarative memory negatively. In one particularly notable early study, Kirschbaum and colleagues (1996) showed that verbal declarative memory was impaired following cortisol increase by stress induction (using a brief psychosocial laboratory-based stressor) as well as following oral administration of 10 mg hydrocortisone. They also noted that procedural memory (i.e., memory for the particular sequential procedures, such as riding a bicycle; Squire, 2004; which is not hippocampal-dependent; Marshal & Born, 2007) remained intact. Several other studies confirm that increased cortisol

concentrations have no effect on procedural memory (Newcomer et al., 1994; Schwabe et al., 2009; Schwabe & Wolf, 2012).

Relationships between cortisol and memory consolidation are especially important. The term *memory consolidation* refers to a largely offline, time-dependent process, in which recently acquired information is strengthened and transferred into long-term memory, where it remains accessible for retrieval (Diekelmann et al., 2009; Stickgold, 2005). Numerous studies confirm that increases in cortisol concentrations support memory consolidation for emotionally arousing material (see, e.g., Buchanan & Lovallo 2001; Cahill & Alkire 2003; Cahill et al. 2003; Cunningham et al., 2021; Kuhlmann & Wolf, 2006; McCullough et al., 2015; Payne et al., 2007; Smeets et al., 2008; Wolf, 2009). The data are, however, less consistent with regard to the effects of cortisol on the consolidation of neutral material: Some studies report an enhancing effect (Abercrombie et al. 2003; Maheu et al. 2005; Andreano & Cahill 2006; Beckner et al. 2006), others reports a diminishing effect (Kirschbaum et al. 1996; Payne et al. 2006, 2007), and still others report no significant effects in either direction (Buchanan & Lovallo 2001; Cahill et al. 2003).

Of particular interest here is that at least one study shows that elevated pre-learning cortisol levels enhance memory consolidation for negatively arousing stimuli only when learning is followed by a period of sleep, rather than a period of wakefulness (Bennion et al., 2015). This finding suggests that it is the interaction between cortisol concentrations while learning and post-learning sleep that benefits memory consolidation.

Associations between Sleep Processes and Memory Processing

Broadly speaking, memory processing may be divided into three general steps: encoding (learning new information and transforming it into a form that can be stored as a memory trace), storage (retaining the information), and retrieval (gaining access to the information from memory stores in the brain; AuBuchon et al., 2019; Bennion et al., 2015; Payne & Kensinger, 2010). The processes of encoding and retrieval occur during waking hours, but consolidation into long-term storage is not compatible with being awake (Diekelman & Born, 2010). Hence, one of the greatest contributions of sleep to cognition is that it promotes memory consolidation (Scullin & Bliwise, 2015; Spencer et al., 2017; Stickgold, 2005).

Several studies provide evidence for sleep-dependent memory consolidation (see, e.g., Dang-Vu et al., 2006; Diekelmann et al., 2009; Marshall & Born, 2007; Marshall et al., 2006). For instance, some show that people who experience impaired sleep perform more poorly on memory tests than those whose sleep is uninterrupted (Griessenberger et al., 2012;

Paavonen et al., 2010). A separate set of studies indicates that memory recall is enhanced when a period of sleep, compared to a period of waking, follows learning of emotional material (Nishida et al., 2008; Payne et al., 2008; Wagner et al., 2001), performance of procedural tasks (Fischer et al., 2002; Gais et al., 2002; Huber et al., 2004; Korman et al., 2007; Mednick et al., 2003; Smith, 1995; Stickgold et al., 2000; Stickgold et al., 2000; Walker et al., 2002; Walker et al., 2003), and encoding of declarative memory information (Lahl et al., 2008; Plihal & Born, 1997; Rasch et al., 2007; Tucker et al., 2006). Henry et al. (2017) found that healthy controls performed better on tasks assessing declarative memory when recall was separated by a period of sleep compared to a period of waking. However, patients with Addison's disease (who as a consequence of their endocrinological condition experienced disrupted sleep) derived no such benefit from a period of sleep.

Related strands of this literature suggest that different stages of sleep are responsible for consolidating different types of memory (Ackerman, 2014; Born et al., 2006; Stickgold, 2005) and that specific physiological features of sleep stages (e.g., brain oscillatory activity or spindles) support different functions in the memory consolidation process (Antony et al., 2019; Astori et al., 2013; Gandhi & Emaddy, 2022; Luthi, 2014; Mednick et al., 2013; Patel et al., 2022; Peyrache & Seibt, 2020; Schabus et al., 2004; Tamminen et al., 2013; Ulrich, 2016). For instance, with regard to procedural memory most studies indicate that consolidation of motor skills occurs primarily during NREM sleep (either stage 2 or SWS; Stickgold & Walker 2007; Walker et al., 2002).

The consolidation of declarative memories, which are relatively more complex, may be dependent on more than one sleep stage (Stickgold, James, et al., 2000; Stickgold et al., 2000). This, at least partly, explains why findings regarding sleep-dependent consolidation of declarative memory are somewhat mixed. Whereas some studies suggests that consolidation of declarative memory is seen after SWS-rich sleep periods, and that there seems to be little-to-no benefit from REM-rich periods of sleep (Diekelmann et al., 2010; Farhadian et al., 2021; Gais & Born, 2004; Marshall & Born, 2007; Plihal & Born, 1997; Rasch & Born, 2013; Smith, 2001; Tucker et al., 2006; Wagner & Born, 2008), other studies indicate that uninterrupted REM sleep enhances memory for declarative material (Empson & Clark, 1970; Fogel et al., 2007; Rauchs et al., 2004; Tilley & Empson, 1978).

Several theoretical frameworks and models attempt to account for the processes underlying memory consolidation (see, e.g., Paller, 2009; Squire et al., 2015; Sutherland & Lehman, 2011; Yonelinas et al., 2019). Among the most prominent in the current literature are the synaptic homeostasis hypothesis, the sequential hypothesis, and the Active Systems

Consolidation (ASC) theory (Hoedlmoes et al., 2022). According to the synaptic homeostasis hypothesis, while the organism is awake learning occurs alongside synaptic potentiation, which leads to an accumulation of synaptic strength (Dash et al., 2009; Vyazovskiy et al., 2008). Subsequently, when the organism is asleep, a down-scaling of synaptic strength ensues as the body attempts to return to synaptic homeostasis. This means that neural systems require less energy and that synapses are allowedd to be replenished and readily available for further daytime encoding (Dash et al., 2009; Tononi & Cirelli, 2006, 2014; Vyazovskiy et al., 2008). This model further proposes that down-scaling (a negative feedback response to an increase in network activity, designed to ultimately lessen the firing rate of neuron) is supported by SWS (Tononi & Cirelli, 2006, 2014).

The sequential hypothesis also suggests that SWS supports memory processing. However, it goes further than the synaptic homeostasis hypothesis by proposing that the sequence in which REM sleep follows SWS during healthy sleep, and not simply SWS in isolation, that benefits memory consolidation processes (Giuditta, 2014; Giuditta et al., 1995). Specifically, this hypothesis proposes, first, that SWS supports system consolidation—memory traces from the waking day are reactivated and redistributed to long-term storage during that stage of sleep. It further proposes that REM sleep supports synaptic consolidation (i.e., a process that allow new memories to stabilise over a period of time, typically over 4–8 hours; Clopath, 2012)—during that stage of sleep there is extra strengthening of redistributed memory traces (i.e., those traces previously moved to long-term storage; Diekelmann & Born, 2010).

Strauss et al. (2022) reported on an experimental test of the sequential hypothesis. They recruited 37 participants with central hypersomnolence disorder, a condition characterized by the individual falling asleep in the REM stage before entering NREM stages (i.e., the reverse of the usual sleep physiological order, where NREM sleep precedes REM sleep). Participants were asked to perform a visual perceptual learning task before and after daytime naps. The naps were stopped after one sleep cycle, which started in either NREM or REM sleep and was followed by the other stage (i.e., the comparison was NREM-REM vs. REM-NREM sleep). They compared changes in performance after naps and tracked the sequence of the sleep changes during naps. They found that the presence of sleep spindles was associated with memory consolidation, but only when NREM sleep was followed by REM sleep.

The ASC theory suggests that sensory information encoded in the hippocampus and the neocortex during waking hours is continuously reactivated during sleep. During this

reactivation process the information is slowly redistributed, eventually resulting in strengthening of synaptic connections between the hippocampal regions where the information was encoded and the neocortical regions where it is being stored. These synaptic connections form the basis of long-term memories (Born & Wilhelm, 2012). To prevent a system overload, the process of reactivation is highly selective. Only information that is critical to guiding future behaviour and decisions is reactivated and subsequently transferred into long-term memory (Wilhelm et al., 2011).

The ASC theory also proposes that the interaction between the brain regions concerned with memory consolidation is largely dependent on certain features of NREM sleep (Buzsaki, 1998; Diekelman & Born, 2010). These features include the interaction between slow oscillations (<1 Hz), sleep spindles (~12–16 Hz), and hippocampal ripple activity (Born & Wilhelm, 2012; Ellenbogen et al., 2006; Fogel & Smith, 2011; Helfrich et al., 2021; Stickgold & Walker, 2007).

Perhaps because of its electrophysiological specificity, the ASC theory has become increasingly popular, with a large body of research demonstrating that coordination between slow oscillations and sleep spindles mediates sleep-associated memory consolidation (Hahn et al., 2020; Helfrich et al., 2018; Joechneret al., 2021; Mikutta et al., 2019; Molle et al., 2011; Muehlroth et al., 2019). For instance, Mikutta et al. (2019) explored whether the interaction between slow oscillations and spindle activity (phase-amplitude coupling) support memory consolidation. They linked the interaction between slow oscillatory (0.16–1.25 Hz) and spindle activity (12–16 Hz) during NREM sleep (strength [modulation index] and phase degree of coupling) in healthy adults (n = 20) with parameters of overnight memory consolidation, using declarative and procedural memory tasks. They found that the interaction between oscillations facilitates memory consolidation. Specifically, the co-occurrence of the spindle amplitude maximum with the up-state of the slow oscillation (phase degree) was correlated with declarative memory consolidation and the overall strength of coupling (modulation index) correlated with procedural memory consolidation.

Related to this electrophysiological specificity is a separate set of studies showing that sleep spindles and k complexes (which are characteristic of stage 2 sleep) are important for memory consolidation (Astori et al., 2013; Luthi, 2014; Mednick et al., 2013; Patel et al., 2022; Peyrache & Seibt, 2020; Schabus et al., 2004; Tamminen et al., 2013; Ulrich, 2016). Sleep spindles appear to play a particularly functional role in memory consolidation and have been linked to the consolidation of both procedural and declarative memory (Antony et al.,

2019), whereas k complexes maintain sleep and create a ‘down state’ that facilitates memory consolidation (Gandhi & Emaddy, 2022).

The literature reviewed above, which of course is only a small part of the massive library of work on sleep, makes it clear that this physiological state is more than just a type of passive unconsciousness. Instead, it facilitates protection of memories from interference and forgetting, thus providing ideal physiological conditions for memory consolidation, and actively facilitates storage and easy retrieval of previously acquired knowledge and experiences (Diekelmann & Born, 2010; Sattari et al., 2019). This clear and physiologically supported link between sleep and memory is at least partly why neuroscience researchers are interested in psychiatric, neurological, and endocrinological conditions in which sleep is disrupted and memory is impaired.

Pituitary Disease

Pituitary disease (PD) is commonly caused by a tumour on the pituitary gland. These tumours can be designated as functional or non-functional (Jaffe, 2006). Little is known about the prevalence of pituitary adenomas in South Africa. Globally, however, prevalence is 80–100 cases per 100,000 of the population. Of these, *non-functioning pituitary adenomas* (*NFPA*) account for approximately 15–30% of cases (Chanson et al., 2015).

NFPAs are not usually hormonally active, and therefore symptoms that patients experience result from the pressure that the tumour exerts on the gland. Larger tumours (macroadenomas; > 1 cm in size) exert greater pressure and hence can cause headaches, peripheral vision loss, and hypopituitarism (a condition in which the pituitary gland fails to produce, or does not produce sufficient, hormones; Greenman & Stern, 2009; Jaffe, 2006; Lopes, 2017). Hence, alhough NFPAs are not hormonally active they can impair hormone production; consequently, patients with these tumours may require lifelong hormone replacement therapy.

Patients with *functional pituitary tumours,* by comparison, experience excessive hormone release (and, consequently, aberrant affect, behaviour, and cognition). For example, Cushing’s disease is accompanied by elevated cortisol concentrations, and patients with the disorder may experience an array of physical and psychological symptoms (medical diseases, central obesity, anxiety, irritability, and depression; Bertagna et al., 2009; Colao et al., 2012; Zhang et al., 2020), sleep disturbances (Hirotsu et al., 2015; Romjin, 2016), and cognitive difficulties (Wamsley & Stickgold, 2011; Lonser et al., 2017). Other functional pituitary tumours include prolactinoma, acromegaly, and thyroid stimulating hormone (TSH)-secreting adenomas (Biermasz, 2019; Chanson et al., 2015).

Prolactinomas are the most common functional tumours, and are characterised by an overproduction of the hormone prolactin. This hormone causes testosterone concentrations to diminish in males and oestrogen concentrations to decline in females. These decreases can result in a variety of physical symptoms including impotence, infertility, loss of libido, and absence of menstrual periods. In children it may also cause growth arrest and pubertal delay (Samperi et al., 2019; Yatavelli & Bhusal, 2017). These patients do not experience sleep problems (Barbados et al., 2014; Frieboes et al., 1998; Romjin et al., 2016), but are known to experience cognitive difficulties (Bukowczan et al., 2016; Yao et al., 2018).

Acromegaly is characterised by an overproduction of GH (Chanson & Salenave, 2008; Melmed, 2022). Patients with this disorder experience a variety of clinical dysfunctions (peeling skin, soft tissue swelling, diabetes, arthritis, hypertension, heart failure, and enlargement of the face, hands and feet; Giustina et al., 2020; Melmed, 2007; Vila et al., 2019), sleep problems (sleep apnoea and reduced self-perceived sleep quality; Kim et al., 2020; Romjin et al., 2016; Watson & Vitiello, 2007; Wennberg et al., 2019; Zhang et al., 2019), and cognitive difficulties (Sievers et al., 2012; Wennberg et al., 2019).

TSH-secreting adenomas are a rare form of pituitary disease characterised by an overproduction of TSH (Beck-Peccoz et al., 2019). Patients with these tumours experience a range of physical, psychological, and sleep problems (including hyperthyroidism, fatigue, insomnia, heat intolerance, irritability, anxiety, palpitations, hair loss, increased sweating, diarrhea, and irregular menses; Beck-Peccoz et al., 2019; Clark et al., 2008; Popli & Endo, 2021).

Generally, in patients with functional pituitary tumours, longer duration of disease is associated with an increased risk of cardiovascular and cerebrovascular comorbidities (Oh et al., 2021: Pivonello et al., 2017; Toulis et al., 2018). Both these comorbidities can play a role in the manifestation of cognitive deficits and sleep quality impairments in patients with PD (Wennberg et al., 2019).

Treatment of pituitary tumours. Typically, pituitary tumours are treated with (1) transphenoidal resection, (2) hormone replacement therapy, (3) radiotherapy, (4) pharmacotherapy (e.g., somatostatin analogues, cabergoline and, ketoconazole), or (5) some combination of the four. The course of treatment is dependent on the size of the tumour and the symptoms experienced (Hayhurst et al., 2020; Vance, 2004). For instance, macroadenomas are treated with surgery to relieve the mass effect on closely associated anatomical structures, whereas macroprolactinomas are treated with dopamine agonist

therapy, which aims to shrink the tumour, and to relieve symptoms such as infertility or abnormal sexual function (Greenman & Stern; 2009; Yatavelli & Bhusal, 2017).

Post-surgery, approximately 80–90% of cases report improvement of clinical symptoms. In cases where full resection is not possible, radiotherapy is used postoperatively to prevent residual tumour growth (Dekkers et al., 2008; Greenman et al., 2016).

Although radiotherapy can be effective in controlling tumour growth, it is not a recommended first-line treatment at least partially because it can also have significant side effects, including cognitive difficulties and hypopituitarism (Becker et al., 2002; Chanson et al., 2015; Noad et al., 2004; Ramírez-Guerrero et al., 2021).

At the time of diagnosis, 60–85% of patients with NFPA present with at least one pituitary deficiency (Chanson et al., 2015). The nature of subsequent treatment for hypopituitarism depends on the hormone that is deficient. For example, if an individual experiences a deficiency in cortisol or growth hormone, they will be treated with hydrocortisone or growth hormone replacement, respectively. Of note here is that, in most countries, growth hormone is restricted in adults and is usually used only in to children and adolescents.

Treatment of pituitary diseases is a long- term process and it usually does not promote complete restoration of quality of life (Webb, 2017). Numerous studies suggest that patients with pituitary disease experience a decreased quality of life even after biomedical treatment (Andela et al., 2018; Chanson & Salenave, 2008; Dekkers et al., 2006; Johnson et al., 2003; Page et al., 1997; Rowels et al., 2005; Van Aken et al., 2005). For instance, Van Aken and colleagues (2005) explored self-percieved quality of life in patients who had been in longterm recovery of Cushing's Disease (n= 58). They compared patient data with a healthy control group (n= 98) with the same age and sex distribution and with age-adjusted reference values taken from the literature. They found that patients who had been cured of Cushing's Disease experienced considerably poorer quality of life, with physical and psychosocial difficulties.

A small body of literature indicates that the poor quality of life experienced by patients with pituitary adenomas is associated with poor sleep quality (Biermasz et al., 2011; Leister et al., 2015; Lin et al., 2021; Sagan et al., 2021; Waddle et al., 2019; Zhang et al., 2022).

Sleep Disruption in NFPA. Several independent studies have concluded that patients with PD secondary to non-functioning tumours experience significantly compromised sleep quality. For instance, after collecting polysomnographic and actigraphy data from patients with non-functioning pituitary macroadenomas (NFMA; n = 17) Biermasz et al. (2011)

reported reduced sleep efficiency, less REM sleep, more night-time awakenings, longer sleep duration, and less daytime activity relative to healthy controls (n = 17). Patients also self-reported excessive fatigue, a significant amount of sleep disturbance, and behavioural patterns suggesting a higher risk of developing sleep apnoea.

Joustra and colleagues (2014) replicated this study in a larger sample. Using actigraphy and four subjective sleep quality questionnaires (the Epworth Sleepiness Scale [ESS; Johns, 1991]; the Clinical Symptom Score [Venmans et al.,1999]; the Berlin Questionnaire [Netzer et al.,1999]; and the Pittsburgh Sleep Quality Index [PSQI; Buysse et al., 1989]), they assessed the sleep quality of 69 patients with NFMA. Their data indicated that patients with NFMA experience severely impaired sleep quality, including alterations in sleep-wake patterns as well as decreased daytime functioning, compared to case-matched healthy controls (n = 58).

In a similar study, Leistner et al. (2015) assessed subjective sleep quality in a sample of 247 patients with a pituitary adenoma (including 56 with NFPA). PSQI data indicated that patients with PD experienced decreased sleep quality compared to 757 age- and gender-matched controls.

Consistent with the findings described in the above paragraphs, Van der Klaauw and colleagues (2007) found, using two standardised sleep questionnaires (the ESS and the Munchener Chronotype Questionnaire [Roenneberg et al., 2003]), that patients with NFMA reported significant daytime sleepiness even though they experienced normal sleep patterns in terms of sleep onset, timing, and duration, as well as rise time.

A separate set of studies showed that patients with pituitary tumours (including NFPAs) are prone to experiencing clinical sleep disorders, including sleep-disordered breathing and obstructive sleep apnoea (Romjin, 2016; Ventre et al., 2021). For instance, Ventre et al. (2021) investigated sleep disordered breathing in 6 patients with a pituitary adenoma (including n = 3 NFPA, n = 2 functional pituitary adenomas and n = 1 acromegalic) using the ESS, Berlin questionnaire, and overnight polysomnography. Sleep disordered breathing was observed in all 6 of the patients, however a worsening of the sleep parameters was seen in the patient with acromegaly.

As previous sections of this review make clear, healthy sleep promotes optimal cognitive function; therefore, it is unsurprising that patients with PD are often observed to experience significant cognitive dysfunction.

Cognitive Dysfunction in NFPA. Cognitive dysfunction is a major complication of PD (Bulow et al., 2002; Cespo & Webb, 2014; Grattan-Smith et al., 1992; Noad et al., 2004;

Peace et al., 1998; Peace et al., 1997). Yedinak and Fleseriu (2014) assessed self-perception of cognitive function among patients with acromegaly and NFPA, using the Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog; Wagner et al., 2013). Patients with acromegaly self-reported poor learning and concentration ability and showed difficulty maintaining focus on imminent tasks, whereas patients with NFPA self-reported cognitive dysfunction with regards to mental agility and verbal memory recall.

Bulow and colleagues (2002) assessed mental well-being and cognitive function in a cohort of female patients with hypopituitarism who had undergone surgery for a pituitary tumour (n = 33). Cognitive function was assessed using standardised neuropsychological tests of vocabulary (SRB:1 [Dureman et al., 1971]), perceptual speed (WAIS-R Digit Symbol [Wechsler, 1992]), visuospatial ability (WAIS-R Block Design [Wechsler, 1992]), verbal memory (Cronholm–Molander verbal memory test [Cronholm & Molander, 1957]), spatial learning (Austin Maze Test [Milner, 1965; Walsh, 1985]), and reaction time (Automated Physiological Test Two-way Reaction Time and Inhibition [Levander & Elithorn, 1987]). Patients scored significantly worse than matched controls on tests assessing vocabulary and perceptual speed; they also made more errors and had a longer total performance time on the spatial learning assessment, and their reaction time on the inhibition test was longer and more inconsistent.

Noad et al. (2004) explored whether cognitive impairments experienced by patients with pituitary tumours (including NFPA's) are linked to the type of treatments they received. They recruited patients with pituitary tumours who had undergone either both radiotherapy and surgery (n = 38) or who had undergone surgery alone (n = 33). They assessed various aspects of cognitive function, including intellectual ability, immediate and delayed recall of verbal material and of visual material, visuospatial ability, speed and capacity of language processing, and executive function. Their analyses detected no significant between-group differences on any of the measured constructs except for executive function, where patients who had undergone radiotherapy performed worse than the surgery-alone patients. As expected, all PD patients (regardless of treatment group) demonstrated significant levels of cognitive impairment when their performance was compared to age-standardized test norms. This piece of data suggests that both radiotherapy and surgery may have a negative impact on cognitive function or that the cognitive impairments experienced may be due to the disease itself and not a consequence of treatment intervention.

In a study of similar design, Peace and colleagues (1998) used a range of standardized neuropsychological tests to evaluate the cognitive performance of patients with a pituitary

tumour (including NFPA) against that of healthy controls (*n* = 23). Their patient sample was divided into three subgroups: those who had been treated with trans-frontal surgery (*n* = 23), those who had been treated with transsphenoidal surgery (*n* = 23), and those who had experienced non-surgical treatment (*n* = 23). Their analyses indicated that, compared to healthy controls, patients treated for a pituitary tumour (regardless of treatment type) performed more poorly on neurological tests assessing memory and executive function. Moreover, patients treated surgically were more likely to experience greater cognitive impairment compared to those treated non-surgically. Importantly, the data suggested that cognitive dysfunction could not be attributed to the treatment alone: More than 40% of patients who were not surgically treated showed evidence of cognitive impairment (i.e., they performed more poorly than controls on tasks that require higher levels of cognitive processing), suggesting that disease presence or hormonal irregularities (secondary to the tumour) may be responsible for the observed dysfunction.

Tiemensma et al. (2010) used a battery of standardized neuropsychological tests to compare cognitive function in patients who had long-term cured Cushing's disease (*n* = 74), patients receiving treatment for NFMA (*n* = 54), and case-matched healthy controls (*n* = 74). Compared to healthy controls, patients with cured Cushing's disease and NFMA patients scored significantly lower on tasks assessing memory and executive functioning. Compared to patients with NFMA, those with cured Cushing's disease scored significantly lower on tests assessing memory and executive function. These data suggest that the observed cognitive impairments were likely due to the underlying disease (and, more specifically, perhaps to potentially irreversible effects of prolonged elevated cortisol concentrations on cognitive function).

The studies reviewed above make it clear that sleep processes are critical for cognitive function and that patients with PD experience poor sleep quality as well as cognitive impairments. Hence, it is surprising that only one study (Wennberg et al., 2019) has explored the relationship between sleep and cognitive function in this patient group. Those researchers examined the relationship between sleep disturbances and cognitive dysfunction in a group of 67 patients with acromegaly. The ESS and the PSQI were used to assess sleep quality. Major cognitive domains were assessed using an array of neuropsychological tests: verbal long-term memory (The Short Story Recall Test [Mondi et al., 2011]), visuospatial short-term and working memory (Corsi Block-Tapping Test [Monaco et al., 2013] and the Rey-Osterrieth Complex Figure Test [Rey & Osterrieth, 1941]), selective attention, cognitive flexibility, and sensitivity to interference (the short version of the Stroop Colour-Word Test [Stroop, 1938]),

conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy (the Frontal Assessment Battery [Appollonio et al., 2005]), attentional speed and executive control and attention (Trail Making Test [Reitan,1956]), phonological and semantic fluency (verbal fluency test [Novelli et al., 1986]). They found that 6–10% of patients displayed poor cognitive function, and that there was a significant association (*B* = -.03, 95% *CI* .06, -.002, *p* = .037) between cognitive performance and sleep (i.e., poor cognitive function was associated with poor subjective sleep quality).

Chapter 2:
Rationale, Aims, and Hypotheses

A strong body of evidence indicates that (a) cortisol and growth hormone are important for sleep regulation and cognition, (b) sleep is important for overall cognitive functioning (and for memory consolidation, in particular), and (c) patients with pituitary disease experience hormonal dysregulation, impaired quality of sleep, and patterns of cognitive dysfunction. However, no published study has examined (using objective sleep measures) whether there are relations among sleep disruption, cognitive impairment, and the presence of pituitary disease. Hence, the aim of this project was to describe sleep quality and memory functioning in a sample of patients with non-functioning pituitary adenomas, and to investigate whether sleep enhances memory consolidation in patients as it does in controls.

The study set out to test the following hypotheses: (1) Compared to matched healthy controls, patients with pituitary disease will have poorer sleep quality and will perform more poorly on standard tests of memory; (2) both patients and controls will have better memory performance when a period of sleep, rather than a period of wakefulness, precedes testing of recall for information learned immediately prior to that intervening period; (3) a preceding period of sleep will be significantly more beneficial for memory consolidation in controls than in patients; (4) poorer sleep quality will be associated with poor cognitive function for both patients and controls.

Chapter 3:
Method

Design and Setting

The current study used a quasi-experimental within-subjects repeated-measures design. The independent variables (IVs) were group (two levels of variation: patients with pituitary disease, healthy controls) and experimental condition (two levels of variation: Sleep, Wake).

Regarding the first IV, the study recruited 10 patients with NFPAs and 10 healthy controls case-matched for age (within 3 years), sex, and level of education (within 2 years). The rationale for age matching was to adjust for well-established age-related effects on cognition and sleep architecture (see, e.g., Deary et al., 2009; Gui et al., 2017; Kuo et al., 2016; Miner et al., 2018; Murman, 2015; Salthouse, 2009; Skeldon et al., 2016). Moreover, there are notable sex differences in sleep architecture: Women generally tend to experience more SWS and less stage 1 sleep than men, whereas men are likely to function better than women on fewer than 7 hours of sleep (Aakash et al., 2021; Krishnan & Collop, 2006; Meers et al., 2019; Mehta et al., 2015; Pengo et al., 2018). In terms of education, those who have completed more years successfully (i.e., attained higher levels) are likely to perform better on standard cognitive tests (see, e.g., Alley et al., 2007; Crowe et al., 2013; Guerra-Carrillo et al., 2017; Kiernan et al., 2008; Lee et al., 2006; Wilson et al., 2009).

Regarding the second IV, each participant experienced a Sleep condition (learning and recall of material were separated by 12 hours of sleep) and a Wake condition (learning and recall were separated by 12 hours of daytime wakefulness), with a crossover design. Administration of the two protocols was separated by 1 week, during which participants were required to wear a lightweight wristband (Fitbit, Inc.; San Francisco, CA, USA) to track sleep patterns and to keep a daily sleep diary.

The dependent variables were (a) objectively measured memory performance and (b) objectively measured sleep quality.

All screening and testing took place in the participants' homes.

Participants

Power Analysis

G*Power software (Erdfelder et al., 1996) indicated that to achieve statistical power > .90 using a repeated-measures ANOVA investigating between- and within-group differences and parameters set at correlation among repeated measures = .50 and effect size (Cohen's *f*) = .25, a sample of $N = 18$ ($n = 9$ per group) would be required. Although no published study

has directly investigated the relationship between sleep and memory consolidation in patients with pituitary disease, the estimated effect size is reasonable due to the well-known association between sleep and memory consolidation (Ackerman, 2014; Dang-Vu et al., 2006; Diekelmann et al., 2009; Marshall & Born, 2007; Marshall et al., 2006).

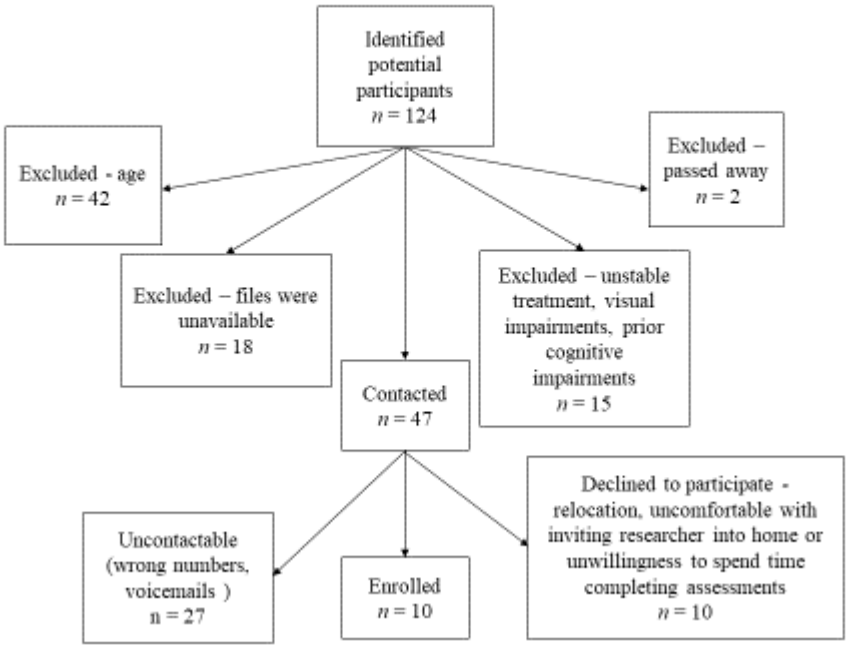
Recruitment

I recruited 10 adult patients (7 women, 3 men) diagnosed with an NFPA from Groote Schuur Hospital's Pituitary Clinic. Doctors and administrators at the clinic provided me with a list of patients and their contact details. I filtered through the list and identified 47 patients who fit the study's eligibility criteria (see next subsection). Eligible patients were called, informed about the nature of the study, and invited to participate. Because the study was conducted during the COVID-19 pandemic and related lockdowns, many patients declined to participate. Some of the other reasons for declining to participate included: relocation, discomfort with inviting a researcher into their home, or unwillingness to spend time completing assessments. If they declined the invitation, I thanked them for their time and assured them that declining to participate would not impact on treatment they were currently receiving or may need in the future from their physicians. If they accepted the invitation, I took verbal consent and set up an in-person meeting at their homes at a time that best suited their schedule.

Figure 3 is a flowchart depicting in detail the steps taken in this recruitment process.

I enrolled 10 healthy controls who were case-matched for age (within 3 years), level of education (within 2 years), and sex. To recruit this sample, I placed advertisements (see Appendix A) on social media platforms such as Facebook and Instagram and informed family members and friends about the study and participant eligibility criteria. Individuals interested in participating were asked to contact the research team to receive more information about the nature of the study. If after considering that information they decided to participate, verbal consent was taken and a home visit was scheduled at a time that best suited their schedule.

Figure 3
Flowchart Depicting the Patient Recruitment Process



Note. The initial list of 124 patients was provided by doctors and administrators at Groote Schuur Hospital's Pituitary Clinic.

Eligibility Criteria

Because, as mentioned above, sleep architecture and cognitive function show age-related variability (with particularly strong variation in children and the elderly; Crowley, 2011; Skeldon et al., 2016), only individuals older than 18 years and younger than 65 years were eligible to participate. Individuals prescribed any medication known to have sedative properties (e.g., sleeping medication, anxiolytics) were ineligible to participate. Individuals with a measured IQ lower than 85 (i.e., 1 standard deviation below average), as per the Shipley IQ test, were excluded. All participants were required to have a basic level of English fluency as all study instruments were presented in English. Pregnant women were excluded as they are likely experience variations in sleep patterns, particularly in advanced stages of gestation (Hall et al., 2009; Ko et al., 2010). Also excluded from participation were individuals with a history of (a) neurological disorders (other than PD) that could negatively affect cognitive function (e.g., dementia, epilepsy, severe head injury, stroke) or (b) psychiatric illness associated with disrupted sleep (Ivanenko et al., 2005; Sateia, 2009).

Patients were required to have been on stable replacement therapy for at least 3 months prior to study enrolment. Healthy controls were required to be free of chronic disease and to not be using any chronic medication.

Measures

Screening Measures

A study-specific *Sociodemographic and Medical Questionnaire* (see Appendix B) determined study eligibility by capturing biographical and medical information (e.g., age, sex, level of education, clinical history, treatment regimen) from potential participants.

The *Mini International Neuropsychiatric Interview* (English version 5.0.0; *MINI*; Sheehan et al., 1998; see Appendix C) is a brief (approximately 20-min) interview-based diagnostic instrument that enquires about the presence of major DSM-IV (American Psychiatric Association, 2013) Axis I psychiatric disorders. The MINI can be administered by trained lay persons. Because it has good validity compared to other clinical interviews, as well as good inter-rater and test-retest reliability (Buer Christensen et al., 2020; Kaminer et al., 2001; Marra et al.,2020), the MINI has been used in psychological and psychiatric research in many countries, including South Africa (see, e.g., Henry et al., 2017; Joska et al., 2010). In the current study, it was used to exclude from participation individuals with major psychiatric disorders (e.g., Major Deppressive Episodes, Panic Disorder, Social Phobia, and Post Traumatic Stress Disorder).

The *Beck Depression Inventory-Second Edition* (*BDI-II*; Beck et al., 1996; see Appendix D) is a brief (approximately 10-min) instrument that measures the intensity and depth of depression in adolescents and adults. It is the most popular reported measure of depression in both research and clinical domains (Gjengedal et al., 2021; Arnason et al., 2008; Votaw et al., 2020). Each of its 21 items is rated on a 4-point scale, with score ranges from 0–3. Hence, the total possible score ranges from 0–63. Individuals who scored >29 (an indication of severe depressive symptoms) were excluded from participation. The BDI-II has been proven to be a reliable and valid measure for identifying depression in South African clinical and non-clinical samples (Kagee et al., 2014; Makhubela & Mashegoane, 2016; Ward et al., 2003).

The *Shipley-2 Intelligence Test* (Shipley et al., 2009) is a brief (approximately 20-min) measure of general intellectual functioning. Participants are required to complete two multiple-choice subtests: The Vocabulary scale requires the test taker to provide the correct definition (taken from a list of five options) for each of a list of 40 words, and the Block Patterns scale requires identification of a missing piece in each of a series of 12 visual designs. An overall IQ score is derived from aggregating scores on the two subtests. Each subtest has good internal consistency and reliability (Shipley et al., 2009). The Shipley-2 has been used frequently in both clinical and non-clinical samples (Dotterer et al., 2021; Henry et

al., 2017; Zelko et al., 2018). In the current study, it was used to exclude individuals with a measured IQ lower than 85 (i.e., one standard deviation below the normative average).

Memory Tests

The *Rey Auditory Verbal Learning Test* (*RAVLT*; Lezak et al., 2004; see Appendix E) is a widely used standardized measure of verbal learning and memory. The test administrator reads a 15-item word list to the test taker at a rate of 1 word per second, and at the end asks the test taker to recall as many words from the list as possible. This process is repeated 5 times. The test taker is then presented with a second list (representing an interference) of 15 words and is asked to recall as many of those words as possible. Immediately thereafter, the test taker is asked to recall as many words as possible from the original list. In this study, an additional recall trial was administered after a 12-hour delay.

The RAVLT is suitable for use with young and old adults and with clinical and nonclinical samples (Schoenberg et al., 2006; Vogel et al., 2012). Furthermore, it is used frequently in South African clinical and research settings (see, e.g., Blumenau & Broom, 2011; Chipps et al., 2014; Koopowitz et al., 2021; Skuy et al, 2001).

The *Logical Memory (LM)* subtest of the Wechsler Memory Scale-Third Revision (WMS-III; Wechsler, 1997; see Appendix F) measures narrative episodic memory. The test administrator presents a short story to the test taker, and then asks them to repeat it as accurately as possible. This procedure is repeated for a second story. In this study, an additional set of recall trials (one for each of the two stories) were administered after a 12-hour delay. Logical Memory is one of the most frequently used WMS subtests (Ahn et al., 2019), is the most internally consistent of the primary WMS subtests, and has test-retest reliability ranging from .58 to .79 (Iverson, 2001). This subtest has been used successfully in several South African research studies (see, e.g., Breen et al., 2019; Henry et al., 2017).

The *Finger Tapping Task* (*FTT*; Walker et al., 2002) is a computerised task that assesses procedural memory. Participants are required to use the non-dominant hand to repeatedly type, for 30 seconds, a 5-element number sequence. The sequence appears at the top of the screen at all times to avoid reliance on working memory. This procedure is repeated for 12 trials, with each trial (a) presenting a sequence and (b) separated from the next by a 30-second break. Performance is scored as the number of correctly repeated sequences on each trial. In this study, the participants were asked to complete three more 30-second trials after a 12-hour delay. This procedural memory test is used frequently in studies assessing relations between sleep and memory (see, e.g., Page et al., 2021; Rasch et al., 2007; Wilhelm et al., 2008).

To eliminate the possibility that practice may enhance the successful completion of these tests, parallel forms of the RAVLT, Logical Memory subtest, and the FTT were used in the *Sleep* and *Wake* conditions.

Assessments of Sleep Quality

A commercially available *Fitbit* Alta HR (Fitbit, Inc.; San Francisco, CA, USA) recorded activity and sleep patterns in everyday environments during the *Sleep* and *Wake* conditions, and during the week between the two conditions. The Fitbit Alta HR is a small, lightweight wristband that records detailed motion data (e.g., number of steps taken, calories burnt, heart rate, body position, body temperature, and sleep).

Of particular importance for the present study was that this device provides information about whether the participant is asleep or awake. Independent studies report that new-generation sleep-staging Fitbit models such as the Alta HR are valid measures for tracking sleep duration and can differentiate between sleep and wake as well as an actigraph can. Hence, these wearable devices can be used as alternatives to actigraphs to assess sleep-wake cycles (Haghayegh et al., 2019; Kawasaki et al., 2022; Lee et al., 2019).

The *Pittsburgh Sleep Diary* (Monk et al., 1994; see Appendix G) collected self-reported data on sleep patterns (e.g., time of onset of sleep and time of awakening) over the night of the *Sleep* condition and during the week between the *Sleep* and *Wake* conditions. Data recorded from sleep diaries correlate strongly with those from objective measures, including polysomnographs and actigraphs (Asaka & Takada, 2011). Studies that add subjective to objective measures of sleep can draw robust conclusions relating to sleeping habits (see, e.g., Kushida et al., 2001; Schokman et al., 2018).

Procedure

After participants read and signed informed consent documents (see Appendix H), eligibility was confirmed by having them complete the screening measures described above. Each patient and their matching control were then randomly assigned to either the Sleep-Wake or the Wake-Sleep administration order. Hence, half of the participants (Wake-Sleep order) experienced the Wake condition first and the other half (Sleep-Wake grouporder) experienced the Sleep condition first. In the *Wake* condition, participants were instructed not to sleep between the morning and evening memory testing sessions. In the *Sleep* condition, participants were instructed not to sleep during the day ahead of the evening testing session. All participants were encouraged to maintain their usual daily routines (e.g., to refrain from drinking caffeinated beverages or exercise excessively if they would not ordinarily do so).

Investigators arrived at the participant's home at either 19h00 (*Sleep* condition; see Figure 4) or 07h00 (*Wake* condition; see Figure 5). The participant was given a Covid-19 safety pack (containing a mask, sanitizer and, gloves), Covid-19 safety protocol sheet (see Appendix I), sleep diary, and Fitbit, along with instructions about how to use each. The participant subsequently completed the RAVLT and Logical Memory learning and immediate recall trials and the initial set of FTT trials. They completed the delayed recall and re-test trials 12 hours later (i.e., the next morning if they were in the *Sleep* condition, or the same day in the evening if they were in the *Wake* condition). After a week the counterbalanced procedure was administered.

Figure 4
Study Protocol: Sleep-Wake administration order

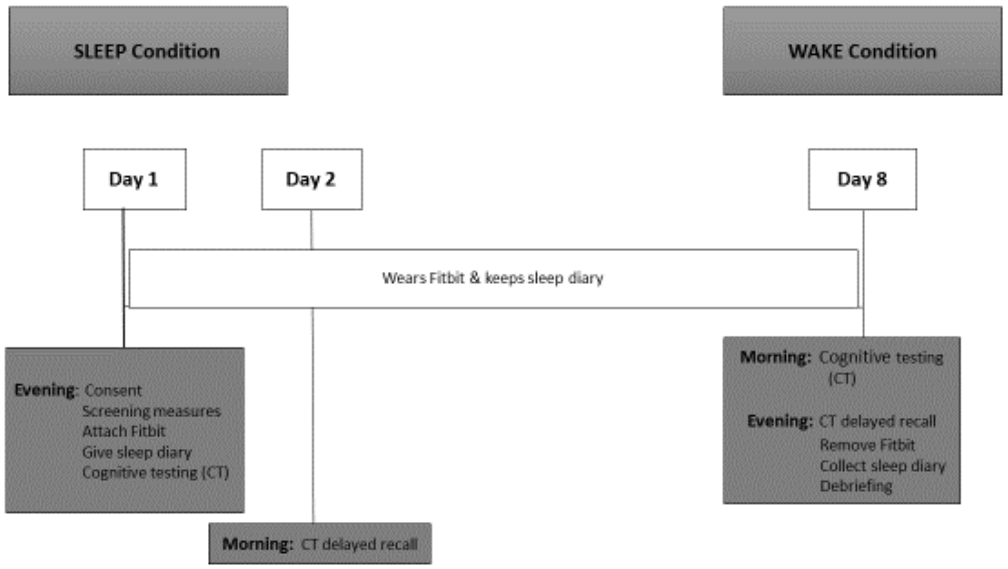
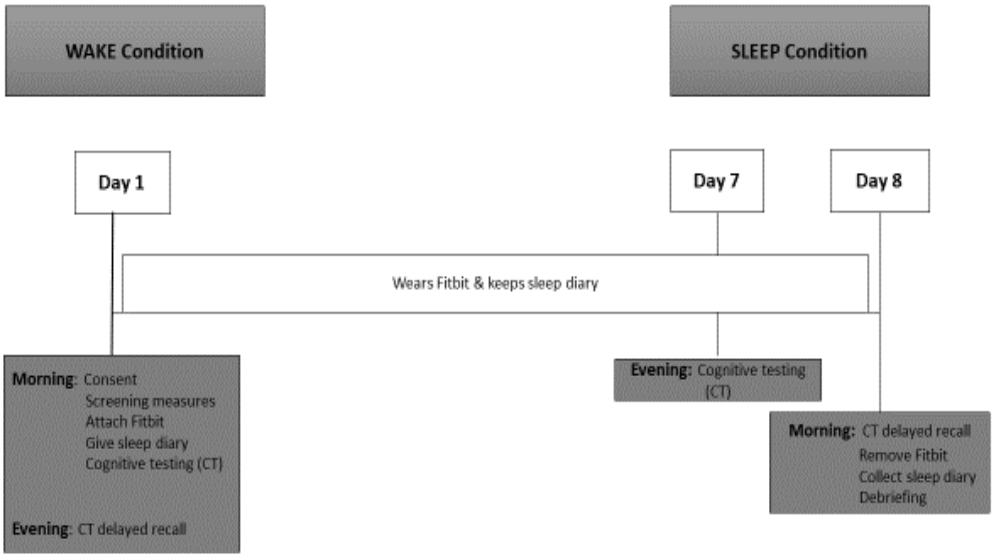


Figure 5
Study Protocol: Wake-Sleep Administration Order



Ethical Considerations

Ethical approval was obtained from the University of Cape Town (UCT) Department of Psychology Research Ethics Committee (see Appendix J), from the UCT Faculty of Health Sciences Human Research Ethics Committee (see Appendix K), and from Groote Schuur Hospital's Research Ethics Committee (see Appendix L).

Consent and Confidentiality

Informed consent was taken in two parts. First, during the initial telephone contact I asked patients to provide verbal consent to ensure that they were comfortable with the researcher visiting them at home. Second, in-person consent was taken using standard informed consent procedures and the documents presented in Appendix H. Hence, participants were informed of the relevant procedures, including data collection, permission to use data generated during the study, and anonymous publication of the results. Voluntary withdrawal at any stage during the study was permissible without any consequence. The collected data were delinked and anonymized from the database and stored in a password-protected laptop repository, which was only accessible to investigators. A duplicate repository of the data are kept on a password-protected external hard drive.

Risks and Benefits

Participants received no direct benefits from their involvement in the study. Participation did not pose any foreseeable social, psychological, or physical risks. If, during scoring of the psychiatric interview or intelligence test a previously unknown disorder

became apparent, they were encouraged to contact their doctor at the Pituitary Clinic, who would refer them to a psychologist or psychiatrist close to their residence.

Debriefing

I debriefed each participant immediately following the end of their involvement in the study. In addition, I sent them an email or a hard-copy debriefing letter (see Appendix M) and a summary of the study results when those were available.

Data Management and Statistical Analyses

I used SPSS (v. 26.0) to complete all analyses. The threshold for statistical significance was set at $\alpha = .05$, unless otherwise noted. For each of the analyses described below, I calculated the appropriate effect size estimate, and I interpreted these estimates following convention (e.g., for Cohen's *d*, 0.20–0.30 = small; ≈ 0.50 = medium; > 0.80 = large; Cohen, 1992).

Examination of q-q plots and other representations of the data distributions indicated there were no significant outliers in the data and that none of the assumptions underlying any of the inferential statistical analyses described below were violated. Hence, I could proceed safely with parametric tests.

Deriving Outcome Variables

I scored the three memory tests following standard procedures (Lezak et al., 2004; Walker et al., 2002; Wechsler, 1997). The RAVLT outcome variables of interest were (1) *Learning*, the sum of all words recalled correctly across learning trials 1–5; (2) *Percent Retention*, the number of words recalled correctly on the delayed recall trial divided by number of words recalled on learning trial 5, expressed as a percentage; and (3) *Recognition*, the number of correctly identified words divided by the number of correct words present in the table (see recognition table in Appendix E) minus the number of incorrectly identified words divided by the number of incorrect words in the table (see recognition table in Appendix E). The Logical Memory outcome variables were (1) *Learning*, the sum of all elements recalled correctly across Story A and Story B; and (2) *Percent Retention*, the number of story elements recalled correctly in the delayed recall trials of Story A and Story B, divided by number of story elements recalled during Learning, expressed as a percentage. The FTT outcome variables were (1) *Post-training Performance*, the average number of completed sequences across the last three trials of the training session; (2) *Post-training Error Rate*, the average number of errors across the last three trials of the training session; (3) *Percent Retention*, the average number of completed sequences across the three retest trials divided by Post-Training Performance, expressed as a percentage; and (4) *Change in Error Rate*, the average number of errors across the three re-test trials minus Post-Training Error Rate.

Data from the sleep diaries helped determine, grossly, when participants were sleeping, when they got into bed at night, when they woke up in the morning, and subjective sleep quality. The Fitbit provided higher resolution data about their actual sleep in that it

measured how much sleep they obtained during the night-time periods. From those two sources of data, I derived these outcome variables, for all the nights over the Sleep condition (one variable per night): (1) *Sleep Latency*, the number of minutes between when the participant turned out the lights at night and when they fell asleep (sleep onset); (2) *Total Sleep Time* (*TST*), the number of minutes spent sleeping in the period between sleep onset and morning waking; (3) *Wake After Sleep Onset* (*WASO*), the number of minutes spent awake in the period between sleep onset and morning waking; (4) *Sleep Efficiency*, TST divided by time in bed multiplied by 100; and (5) *Number of Awakenings*, the number of times the participant woke up for more than 1 minute in the period between sleep onset and morning waking. The subjective sleep variables were derived from the sleep diary, in which they were asked to rate aspects of their sleep on a scale from 1 to 10: (1) *Sleep Quality*, 1 being very bad and 10 being very good; (2) *Mood upon Awakening*, 1 being very tense and 10 being very calm; and (3) *Alertness upon Awakening,* 1 being very sleepy and 10 being very alert.

Inferential Analyses

Primary analyses proceeded across five discrete steps. First, independent sample *t*-tests (for continuous variables) and chi-squared tests (for categorical variables) assessed the magnitude of between-group differences with regard to sociodemographic, depression, and IQ characteristics. Second, a series of independent sample *t*-tests assessed the magnitude of between-group differences with regard to variables indexing objective sleep quality (i.e., Sleep Latency, TST, WASO, Sleep Efficiency, Number of Awakenings) and subjective sleep quality (i.e., sleep quality, mood upon awakening, and alertness upon awakening) on the night of the Sleep condition. Third, separate series of paired-samples *t*-tests for patients and controls assessed whether the participants' sleep patterns on the night of the Sleep condition were representative of their usual sleep patterns. Specifically, analyses compared their average objective sleep data recorded over the 6 nights prior to the Sleep condition night (if they experienced the Wake condition first) or the 6 nights after the Sleep condition night (if they experienced the Sleep condition first) and compared it to the data recorded over the night of the Sleep Condition. The outcome variables here were; Sleep Latency, TST, WASO, Sleep Efficiency, Number of Awakenings. Fourth, a series of 2x2 (Group [NFPA Patients, Healthy Controls] x Condition [Sleep, Wake]) repeated-measures ANOVAs assessed between- and within-group differences on the RAVLT, Logical Memory, and FTT outcome variables (10 in total). Fifth, a series of bivariate correlational analyses using Pearson's

coefficient assessed whether within each group, sleep outcome variables were associated with cognitive outcome variables.

Secondary analyses investigated whether, and to what degree, participants' sociodemographic and clinical characteristics affected the outcomes of interest. Specifically, a series of bivariate correlational analyses using Pearson's coefficient (for continuous variables) and independent-sample *t*-tests (for categorical variables) assessed whether (a) within each group, sociodemographic variables (age, education, sex), IQ score, and BDI-II score were significantly associated with the sleep outcome variables, and (b) within each group, sociodemographic variables (age, education, sex), IQ score, and BDI-II score were significantly associated with the cognitive outcome variables. These latter analyses were conducted separately for cognitive data from the Sleep and Wake conditions. Finally, for the patient group only similar bivariate correlational analyses (for continuous variables) and independent-sample *t*-tests (for categorical variables) assessed the magnitude of association between NFPA disease characteristics (e.g., time since diagnosis, whether they were treated with hydrocortisone medication or not, and whether they were treated with radiotherapy or not) and the set of sleep and cognitive outcome variables.

Chapter 4:

Results

Sample Characteristics

The overall age range of the sample was 29–65 years (*M* = 50.55, *SD* = 11.84). Participants had completed between 8 and 13 years of formal education (*M* = 11.10, *SD* = 1.46). Most participants (14 of 20, 70%) were women.

As expected given the case-control design and recruitment method, analyses detected no significant between-group differences with regard to age or education, or with regard to gender distribution (see Table 1).

Regarding measures of depression and general intellectual functioning, analyses detected no significant between-group differences on either the BDI-II or the Shipley-2. On the BDI-II, all participants scored within the range conventionally defined as "minimally depressed" (0–13 points; Beck et al., 1996).

Table 1

Sample Sociodemographic Characteristics (N = 20)

	Group				
Variable	NFPA Patients (*n* = 10)	Healthy Controls (*n* = 10)	t / χ^2	*P*	ESE
Age (years)			-0.20	.838	-0.09
M (SD)	51.10 (11.29)	50.00 (12.39)			
Range	29–65	31–65			
Education (years)			0.60	.551	0.27
M (SD)	10.90 (1.37)	11.30 (1.56)			
Range	8–12	8–13			
Sex			0.00	1.00	.00
Male (*f*, %)	3 (30.00)	3 (30.00)			
Female (*f*, %)	7 (70.00)	7 (70.00)			
BDI-II total score					
M (SD)	3.60 (1.77)	2.50 (2.75)	1.06	.303	0.47
Range	1–6	0–9			
Shipley-2 IQ score			0.42	.674	0.19
M (SD)	93.60 (13.84)	91.50 (7.02)			
Range	73–123	86–104			

Note. NFPA = non-functioning pituitary adenoma; ESE = effect size estimate (Cohen's *d* for *t*-tests and Cramer's *V* for chi-square tests); *M* = mean; *SD* = standard deviation; *f* = frequency; BDI-II = Beck Depression Inventory-II.

Patient Clinical Characteristics

On average, the sample of 10 patients with NFPA had been diagnosed at 42 years of age, with the average disease duration being a little over 9 years. Eighty percent of patients

had received both radiotherapy and surgery; the others had only undergone transphenoidal surgery (see Table 2). At the time of the study no patient was receiving radiotherapy and it had been at least 1 year since their last radiotherapy session.

As stipulated by the study's eligibility criteria, all patients had been on a stable treatment regimen for at least 3 months prior to enrolment. The following hormone replacement treatments were used: hydrocortisone (n = 3), L- thyroxine (n = 3), or both hydrocortisone and L-thyroxine (n = 4). One female patient had also received letrozole and one male patient a testosterone injection. One patient reported having developed diabetes post-operatively; another reported current diagnoses of both diabetes and hypertension.

Table 2
NFPA Patient Characteristics (N = 10)

Variable	Statistic
Age at diagnosis (years)	
M (SD)	41.90 (9.58)
Range	24–50
Duration of disease (years)	
M (SD)	9.20 (5.61)
Range	3–20
Treatment	
Surgery only (*f*, %)	2 (20%)
Surgery and radiotherapy (*f*, %)	8 (75%)
Medical comorbidities (*f*, %)	
Diabetes mellitus	2 (20%)
Hypertension	1 (10%)

Note. NFPA = non-functioning pituitary adenoma. *M* = mean; *SD* = standard deviation; *f* = frequency.

Sleep Quality on the Sleep Night: Between-Group Comparisons

Table 3 presents descriptive data and the results of statistical analyses for participants' sleep quality over the night of the Sleep Condition. Inferential analyses detected no significant between-group differences on any of the objectively measured outcome variables (all *ps* > .114). However, the descriptive statistics indicate that, on average and as compared to patients, controls had longer sleep latency (unexpectedly, given that one would predict this effect would be in the opposite direction) and longer TST, that they spent more minutes awake after sleep onset (again, unexpectedly), and that they experienced fewer night-time awakenings. For both groups, sleep efficiency was excellent at 91%.

Regarding the subjective measures, analyses detected significant between-group differences with regard to sleep quality and alertness upon awakening, as well as a strong

trend toward significance with regard to mood upon awakening (see Table 3). On average and as compared to patients, controls rated their sleep quality more highly and reported greater alertness and better mood upon awakening. All of these between-group differences were associated with large effect size estimates.

Table 3

Sleep Quality Over the Night of the Sleep Condition: Descriptive Statistics and Between-Group Comparisons (N = 20)

	Group				
Variable	NFPA Patients (n = 10)	Healthy Controls (n = 10)	T	P	ESE
Objective Measures					
Sleep Latency (min)	22.50 (28.98)	27.40 (21.75)	0.42	.674	0.16
TST (min)	371.20 (93.30)	384.30 (62.20)	0.36	.716	0.19
WASO (min)	34.10 (17.95)	36.80 (23.39)	0.28	.776	0.12
Sleep Efficiency (%)	0.91 (0.04)	0.91 (0.05)	-0.11	.911	-0.05
Number of Awakenings	2.10 (1.44)	1.30 (0.48)	-1.65	.115	-0.74
Subjective Measures					
Sleep Quality	7.01 (2.23)	8.90 (1.11)	-2.38	**.016***	-1.06
Alertness Upon Waking	7.30 (2.29)	9.27 (1.35)	-2.36	**.015***	-1.05
Mood Upon Waking	7.92 (2.26)	9.28 (1.20)	-1.67	.056	-0.74

Note. In the second and third columns, means are presented with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; TST = total sleep time; WASO = waking after sleep onset; ESE = effect size estimate (in this case, Cohen's d).
*p < .05. **p < .01. ***p < .001. All p-values are one-tailed, given that analyses were testing the hypothesis (based on previous literature) that sleep quality would be better in controls than in patients. Statistically significant p-values are denoted in boldface font.

Objective Sleep Data Over the 7-Day Study Period: Within-Group Analyses

To confirm that participants' sleep patterns on the night of the Sleep condition were representative of their usual sleep patterns, within-group analyses compared their average sleep data recorded over either the 6 nights prior to the Sleep condition night (if they experienced the Wake condition first) or the 6 nights after the Sleep condition night (if they experienced the Sleep condition first) and compared it to their sleep data recorded on the night of the Sleep Condition.

As Table 4 shows, for both patient and control data analyses detected no significant differences between the Sleep condition night and the 6-night average, for any of the outcome variables (for patients, all *ps* > .052; for controls, all *ps* > .185). Only the Sleep Latency for patients trended toward statistical significance (note also the large effect size here), with participants taking longer to fall asleep on the night of the Sleep condition than on average

across the surrounding nights. Overall, then, these data suggest that participants' sleep on the night of the Sleep condition was representative of their regular sleep patterns.

Table 4

Sleep on the Night of the Sleep Condition versus 6-night Average Before/After that Night: Descriptive Statistics and Within-Group Comparisons (N = 20)

Variable	Sleep Condition	6-Night Average	*t*	*p*	ESE
NFPA Patients (*n* = 10)					
Sleep Latency (min)	16.30 (12.02)	22.21 (14.38)	-2.23	.052	-0.70
TST (min)	389.80 (82.95)	347.47 (136.63)	1.28	.232	-0.40
WASO (min)	32.80 (16.37)	33.80 (21.77)	-0.21	.835	-0.06
Sleep efficiency (%)	.92 (.04)	.91 (.04)	1.00	.341	0.03
Awakening (# of times)	2.20 (1.54)	2.11 (0.95)	.263	.798	0.08
Healthy Controls (*n* = 10)					
Sleep Latency (min)	43.50 (90.27)	28.75 (15.81)	0.53	.610	0.16
TST (min)	421.20 (48.10)	391.83 (52.08)	1.43	.185	0.45
WASO (min)	35.10 (27.91)	32.03 (10.14)	0.42	.684	0.13
Sleep efficiency (%)	.92 (.06)	.92 (.02)	-0.01	.990	< 0.001
Awakening (# of times)	1.30 (0.82)	1.25 (0.21)	0.17	.868	0.05

Note. In the second and third columns, means are presented with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; TST = total sleep time; WASO = waking after sleep onset; ESE = effect size estimate (in this case, Cohen's *d*).
**p* < .05. ***p* < .01. ****p* < .001.

Cognitive Data: Effects of Group, Condition, and The Group x Condition Interaction

Table 5 presents descriptive data and statistical analyses regarding RAVLT, Logical Memory, and FTT performance for both patients and controls within the Sleep and Wake conditions.

Declarative Memory: RAVLT. Regarding the Learning variable, the analysis detected no significant main effects of Group, $F(1, 18) = 3.11$, $p = .095$, $\eta^2 = .10$, or of Condition, $F(1, 18) = 1.77$, $p = .200$, $\eta^2 = .02$, and no significant Group x Condition interaction, $F(1, 18) = .197$, $p = .662$, $\eta^2 < .001$. Regarding the Percent Retention outcome variable, the analysis also detected no significant main effects of Group, $F(1,18) = 1.50$, $p = .235$, $\eta^2 = .04$, or of Condition, $F(1, 18) = .616$, $p = .443$, $\eta^2 = .01$, and no significant Group x Condition interaction, $F(1,18) = 1.44$, $p = .245$, $\eta^2 = .03$.

Regarding the Recognition outcome variable, the analysis detected significant main effects of Group, $F(1, 18) = 23.33$, $p < .001$, $\eta^2 = .56$, and of Condition, $F(1, 18) = 13.77$, $p = .002$, $\eta^2 = .44$, and a significant Group x Condition interaction, $F(1, 18) = 6.85$, $p = .017$, $\eta^2 = .27$. Interpreting these findings given the directions of means presented in Table 5 suggests that (a) regardless of condition, controls had significantly better recognition for previously

learned material than patients, (b) regardless of group, participants had significantly better recognition when a period of sleep, rather than a period of waking, separated learning and recall, and (c) patients' performance benefitted more than that of controls when a period of sleep, rather than a period of waking, separated learning and recall.

Declarative Memory: Logical Memory test. Regarding the Learning variable, the analysis detected no significant main effect of Condition, $F(1,18) = 0.22$, $p = .644$, $\eta^2 < .001$, or of Group, $F(1,18) = .018$, $p = .895$, $\eta^2 < .01$. It did, however, detect a trend toward a significant Group x Condition interaction, $F(1,18) = 3.53$, $p = .076$, $\eta^2 = .03$. Because one of the main aims of this study was to describe memory consolidation for NFMA patients and Healthy Controls under the two conditions (Sleep and Wakefulness), I explored the Group x Condition interaction further by conducting within-group post-hoc pairwise comparisons. These analyses found a trend toward a significant between-condition difference for the patient group ($p = .057$; better performance in the Wake than in Sleep condition, as shown in Table 5), but no such trend within the control group ($p = .166$; relatively equivalent performance in the two conditions, as shown in Table 5).

Regarding the Percent Retention outcome variable, the analysis detected a significant main effect of Group, $F(1,18) = 5.80$, $p = .027$, $\eta^2 = .16$, but no significant main effect of Condition, $F(1,18) = 1.35$, $p = .260$, $\eta^2 = .02$, and no significant Group x Condition interaction, $F(1,18) = 8.20$, $p = .977$, $\eta^2 < .01$. The significant effect of Group indicates that, regardless of experimental condition, controls retained more information over the delay between learning and recall than patients (see descriptive data in Table 5). A further note of interest with regard to these data is that, although this difference did not reach the threshold for statistical significance, both patients and controls retained more information when a period of sleep, rather than a period of waking, separated learning and recall.

Procedural memory: FTT. The analyses detected no significant main effect of Group, no significant main effects of Condition, and no significant Group x Condition interactions for most FTT variables, all *p*s > .120. The only exception was for the Change in Error Rate variable, where analyses detected a significant main effect of Group, $F(1,18) = 4.50$, $p = .049$, $\eta^2 = .07$. This significant effect indicates that, regardless of experimental condition, patients had a significantly smaller increase in errors than controls (see descriptive data in Table 5).

Table 5

Cognitive Data: Performance by Patients and Controls in the Sleep and Wake Conditions (N = 20)

	Group			
	NFPA Patients (n = 10)		Healthy Control (n = 10)	
Variable	Sleep	Wake	Sleep	Wake
RAVLT				
Learning	39.70 (8.16)	41.60 (8.59)	44.80 (8.50)	48.60 (10.66)
Percent Retention	63.54 (20.06)	60.76 (24.41)	65.39 (21.50)	78.62 (26.68)
Recognition	.78 (.17)	.51 (.27)	.99 (.04)	.94 (.13)
Logical Memory				
Learning	22.20 (4.44)	24.70 (5.41)	24.50 (4.19)	23.00 (7.51)
Percent Retention	72.66 (21.09)	66.73 (18.46)	88.44 (14.80)	82.22 (19.58)
Finger Tapping Task				
Post-training Performance	20.44 (12.83) [a]	22.00 (13.49) [a]	28.90 (10.57)	30.70 (10.30)
Post-training Error Rate	0.01 (0.02) [a]	0.06 (0.12) [a]	0.01 (0.01)	0.02 (0.01)
Percent Retention	91.01 (20.39) [a]	86.23 (25.23) [a]	94.81 (48.61)	89.74 (17.55)
Change in Error Rate	< 0.01 (0.03) [a]	-0.06 (0.12) [a]	0.005 (0.02)	0.01 (0.04)

Note. Means are presented, with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; RAVLT = Rey Auditory-Verbal Learning Test.

[a] Data based on 9 participants (1 patient did not complete the Finger Tapping Task).

Within-group Associations between Sleep and Cognitive Variables

Within the NFPA patient group, analyses detected no significant correlations between most of the sleep and cognitive variables, all *ps* > .070. The only significant associations were between sleep efficiency and FTT post-training error rate, $r = -.817$, $p = .007$; between awakening and RAVLT recognition, $r = .647$ $p = .043$; and between alertness and LM retention, $r = -.776$, $p = .008$ (see Table 6). These correlations indicate that better sleep efficiency was associated with a smaller change in FTT error rate, more awakenings were associated with better recognition, and those patients who rated themselves as being more alert upon awakening learnt less information.

Within the healthy control group, analyses detected no significant correlations between most of the sleep and cognitive variables all *ps* >.074. The only significant correlation was between awakening and FTT post-training performance, $r = -.798$, $p = .006$. (see Table 6). This correlation indicated that fewer awakenings were associated with better post-training performance on the FTT.

Table 6

Bivariate Correlations for the NFPA patient group and Healthy Control groups: Associations between Sleep Outcome Variables and Cognitive Outcome Variables (N = 20)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Sleep Latency	1.00	-.070	.463	**-.**529	-.139	-.282	-.454	-.370	-.506	-.011	-.168	-.513	.564	-.293	.149	.052	-.083
2. TST	-.455	1.00	.125	.295	.407	-.030	.221	.373	.378	-.445	-.094	.470	-.309	-.388	-.563	-.025	.613
3. WASO	.505	-.167	1.00	**.900**	-.171	.325	.337	.341	.086	.148	-.004	.114	.205	-.355	.621	.168	-.385
4. Sleep Efficiency	-.594	.404	**-.965**	1.00	.374	-.379	-.234	-.125	.180	-.268	.021	.110	-.400	.242	**-.817**	-.182	.588
5. Awakening	.135	-.188	-.142	.047	1.00	-.270	-.138	-.005	.303	.214	**.647**	.359	-.257	.205	-.312	-.362	.364
6. Sleep Quality	**.729**	-.581	.555	**-.652**	-.166	1.00	**.829**	.535	-.134	-.148	-.174	.070	-.185	-.418	.502	.251	-.284
7. Mood	.463	-.449	.370	-.440	-.428	**.829**	1.00	**.816**	.157	-.164	.025	.336	-.479	-.563	.209	.558	.019
8. Alertness	.090	-.094	.389	-.337	**-.703**	.535	**.816**	1.00	.350	-.339	-.050	.147	**-.776**	-.574	-.082	.489	.060
9. RAVLT Learning	.281	-.416	.216	-.318	.043	-.029	-.309	-.432	1.00	.037	.395	**.654**	-.383	.185	-.036	-.135	-.234
10. RAVLT Retention	.053	-.047	.078	-.046	-226	-.128	-.338	-.140	.618	1.00	.474	.273	.214	.614	.591	-.266	-.310
11. RAVLT Recognition	-.565	-.097	**-.**507	**.**431	-.245	-.174	.025	-.050	-024	-.128	1.00	.430	-.024	.116	.174	.124	-.100
12. LM Learning	.369	-.321	.567	-.619	-.356	.298	.336	.242	.538	.346	.017	1.00	-.037	.184	.109	-.110	.174
13. LM Retention	-.222	.046	-.324	.283	-.070	.125	.457	.310	**-.701**	**-.861**	.424	-.304	1.00	.184	.456	-.222	-.254
14. FTT PT Performance	-.588	.292	-.077	.189	**-.798**	-.239	.122	.518	-.127	.237	.482	.229	.036	1.00	.192	**-.786**	-.246
15. FTT PT ER	-.233	.170	.208	-.105	-.360	.226	.178	.391	-.287	-.095	.161	-.305	.042	.417	1.00	-.095	**-.792**
16. FTT Retention	.266	-.393	-.542	.367	.540	.134	.041	-.460	-.020	-.350	.276	-.313	.342	-.562	-.280	1.00	.176
17. FTT Change in ER	.121	.319	-.298	.333	.075	-.363	-.106	-.117	-.147	-.085	-.318	.061	.132	-.156	**-.750**	.101	1.00

Note. Data presented are Pearson's *r* correlation coefficients. Patient data are presented in the top right cells of the table, shaded light grey; control data are presented in the bottom left cells of the table, not shaded.

TST = Total Sleep Time; WASO = Wake after Sleep Onset; RAVLT = Rey Auditory Verbal Learning Test; LM = Weschler Logical Memory subtest; FTT= Finger Tapping Task; PT = Post-Training; ER= Error Rate. Statistically significant associations (one-tailed) are highlighted in boldface font.

Secondary Analyses: Associations between Sociodemographic / Clinical Variables and the Major Outcome Variables

Within-group Associations between Sociodemographic / Clinical Variables and Sleep Outcome Variables. For the NFPA patient group, analyses detected no significant correlations between age and any of the sleep outcome variables, or between BDI-II score and any of the sleep outcome variables, all *p*s > .075 (see Table 7). The strongest associations here were between age and (a) WASO, $r = -.59$, $p = .075$, and (b) sleep efficiency, $r = .58$, $p = .079$ (i.e., there were mild trends toward suggesting that older age was associated with fewer night-time awakenings and better sleep efficiency).

For the healthy control group, analyses detected no significant correlations between age and any of the sleep variables, all *ps* > .149 (see Table 7). With one exception, depressive symptomatology also bore a non-significant relationship to sleep. Higher BDI-II scores (i.e., greater levels of depressive symptomatology) were significantly associated with shorter total sleep times, $r = -.79$, $p = .006$.

Table 7

Bivariate Correlations for the NFPA Patient and Healthy Control Groups: Associations between Sociodemographic / Clinical Variables and Sleep Outcome Variables (N = 20)

	1	2	3	4	5	6	7	8	9	10	11	12
1. Sleep Latency	1.00	-.070	.463	-.529	-.139	-.282	-.454	-.370	-.340	-.259	-.143	.043
2. TST	-.455	1.00	.125	.295	.407	-.303	.221	.373	.148	.046	.583	.243
3. WASO	.505	-.167	1.00	**-.900**	-.171	.325	.337	.341	-.587	.122	-.302	.082
4. Sleep Efficiency	-.594	.404	**-.965**	1.00	.374	-.379	-.234	-.125	580	-.054	.486	-.010
5. Awakenings	.135	-.188	-.142	.047	1.00	-.270	-.138	-.005	-.102	.453	.318	-.199
6. Sleep Quality	-.085	.361	.399	-.254	-.527	1.00	**.829**	.535	.270	.192	-.136	.065
7. Mood	-.276	.402	.328	-.191	-.410	**.910**	1.00	**.816**	.197	.355	-.140	.083
8. Alertness	-.238	.304	.338	-.288	-.234	**.853**	**.978**	1.00	.208	.518	-.202	-.236
9. Age	.260	.432	.022	.099	-.148	.455	.144	.073	1.00	-.250	.168	.157
10. Education	.508	-.501	.475	-.558	-.279	-.099	-.025	-.020	-.492	1.00	-.002	**-.794**
11. IQ	-.129	.179	.010	.002	-.475	.114	.316	.233	-.396	.449	1.00	.133
12. BDI-II	.176	**-.794**	-.102	-.143	.375	-.629	-.585	-.502	-.488	.193	-.072	1.00

Note. Data presented are Pearson's *r* correlation coefficients. Patient data are presented in the top right cells of the table, shaded light grey; control data are presented in the bottom left cells of the table, not shaded. NFPA = non-functioning pituitary adenoma; TST = total sleep time; WASO = waking after sleep onset; IQ = overall cognitive functioning, as measured by Shipley IQ test; BDI-II = Beck Depression Inventory-II total score. Statistically significant associations (one-tailed) are highlighted in boldface font.

Regarding within-group sex differences in sleep quality, as Table 8 shows the only statistically significant observation was with regard to subjectively rated sleep quality within the patient group: male patients provided higher sleep quality ratings than did female patients. Within the control group, there was a minor non-significant trend toward objectively measured sleep latency being longer in men than in women.

Table 8

Sex Differences in Objective and Subjective Sleep Quality: Within-Group Descriptive Statistics and Mean Comparisons (N = 20)

	Group				
Variable	Men	Women	*t*	*p*	ESE
NFPA Patients (*n* = 10)					
Latency (min)	21.67 (7.63)	22.86 (5.22)	0.56	.478	0.03
TST (min)	395.33 (142.69)	360.86 (76.51)	-0.51	.311	-0.32
WASO (min)	35.67 (4.50)	33.43 (21.79)	-0.17	.434	-0.11
Sleep efficiency (%)	.91 (.03)	.91 (.05)	0.20	.420	0.14
Awakening (# of times)	2.33 (1.52)	2.00 (1.52)	-0.31	.380	-0.21
Sleep Quality	9.00 (0.89)	6.16 (2.10)	-2.18	**.030***	-1.51
Mood	9.19 (0.70)	7.38 (2.52)	-1.17	.136	-0.81
Alertness	7.38 (1.66)	7.26 (2.59)	-0.07	.473	-0.04
Healthy Controls (*n* = 10)					
Latency (min)	41.67 (31.75)	21.29 (15.10)	-1.43	.095	-0.99
TST (min)	347.33 (64.37)	400.14 (58.70)	1.27	.120	0.87
WASO (min)	30.00 (11.35)	39.71 (27.29)	0.57	.289	0.40
Sleep efficiency (%)	.91 (.03)	0.90 (0.05)	-0.21	.416	-0.15
Awakening (# of times)	1.33 (0.57)	1.29 (0.48)	-0.13	.448	-0.09
Sleep Quality	9.00 (1.73)	8.85 (0.92)	-1.75	.433	-0.12
Mood	9.00 (1.73)	9.40 (1.05)	0.47	.325	0.32
Alertness	9.00 (1.73)	9.38 (1.31)	0.39	.352	0.27

Note. In the second and third columns, means are presented with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; TST = total sleep time; WASO = waking after sleep onset; ESE = effect size estimate (in this case, Cohen's *d*).
Sleep Quality, Mood, and Alertness = subjective sleep data.
*$p < .05$. **$p < .01$. ***$p < .001$. Statistically significant *p*-values (one-tailed) are denoted in boldface font.

Within-group Associations between Sociodemographic / Clinical Variables and Cognitive Outcome Variables.

Analyses involving cognitive data from the Sleep condition detected the following. For the NFPA patient group, there were no significant associations between any of the sociodemographic / clinical variables (i.e., age, education, IQ, BDI-II score) and any of the cognitive outcome variables, all *p*s > .112 (see Table 8). For the Healthy Control group, there were significant positive correlations between education and (a) RAVLT Learning, $p = .028$, (b) RAVLT Retention, $p = .036$, (c) RAVLT Recognition, $p = .014$, and (d) Logical Memory Learning, $p = .002$ (see Table 9).

Analyses involving cognitive data from the Wake condition detected the following. For the NFPA patient group, there were no significant associations between any of the sociodemographic / clinical variables (i.e., age, education, IQ, BDI-II score) and any of the cognitive outcome variables, all *p*s > .113 (see Table 10). For the Healthy Control group, there were significant positive correlations between (a) education and Logical Memory Learning, $p = .005$, (b) education and RAVLT Recognition, $p = .003$, and (c) IQ and Logical Memory Retention, $p = .049$ (see Table 9).

Table 9

Bivariate Correlations for the NFPA Patient and Healthy Control Groups: Associations between Sociodemographic / Clinical Variables and Cognitive Outcome Variables, Sleep Condition (N = 20)

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. RAVLT Learning	1.00	.037	.395	**.654**	-.383	.185	-0.36	-.135	-234	-.163	.285	.343	-.032
2. RAVLT Retention	.618	1.00	.474	.273	.214	.614	.591	-.266	-.310	-.449	-.167	-.487	.287
3. RAVLT Recognition	.529	.524	1.00	.430	-.024	.116	.174	.124	-.100	-.404	.533	.109	-.178
4. LM Learning	.538	.346	.544	1.00	-0.37	.184	.109	-.110	.174	-.321	.113	.386	.377
5. LM Retention	**-.701**	**-.861**	-.274	-.304	1.00	.184	.456	-.222	-.254	-.532	-.376	.158	.237
6. FTT PT Performance	-.127	.237	.395	.229	.036	1.00	.192	**-.786**	-.246	-.211	-.210	-.131	-.021
7. FTT PT Error Rate	-.287	-.095	.026	-.305	.042	.417	1.00	-.095	**-.792**	-.524	-.025	-.510	.134
8. FTT Retention	-.020	-.350	.005	-.313	.342	-.562	-.280	1.00	.176	.101	.187	-.231	.045
9. FTT Error Rate Change	-.147	-.085	-.264	.061	.132	-.156	**-.750**	.101	1.00	.276	-.021	.325	.168
10. Age	-.491	-.402	-.397	-.485	.266	-.142	.430	.080	.110	1.00	-.250	**.**168	.157
11. Education	**.688**	**.664**	**.740**	**.853**	-.567	.089	-.238	-.175	-.122	-.492	1.00	-.002	**-.794**
12. IQ	.398	.338	.275	.582	-.069	.324	-.400	-.294	.246	-.396	.449	1.00	.133
13. BDI-II	.281	-.336	.318	.226	.335	-.307	-.299	**.635**	-.180	-.488	.193	-.072	1.00

Note. Data presented are Pearson's *r* correlation coefficients. Patient data are presented in the top right cells of the table, shaded light grey; control data are presented in the bottom left cells of the table, not shaded. NFPA = non-functioning pituitary adenoma; RAVLT = Rey Auditory Verbal Learning Test; LM = Wechsler Logical Memory subtest; FTT= Finger Tapping Task; PT = Post-Training; IQ = overall cognitive functioning, as measured by Shipley IQ test; BDI-II = Beck Depression Inventory-II total score. Statistically significant associations (one-tailed) are highlighted in boldface font.

Table 10

Bivariate Correlations for the NFPA Patient and Healthy Control Groups: Associations between Sociodemographic / Clinical Variables and Cognitive Outcome Variables, Wake Condition (N = 20)

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. RAVLT Learning	1.00	.201	.034	.019	**.914**	.209	-.254	.617	.274	.289	-.221	.435	.338
2. RAVLT Retention	.131	1.00	-.324	.447	.276	.471	-.227	.268	.215	-.012	.285	.079	-.220
3. RAVLT Recognition	.336	.031	1.00	-.554	.050	-.432	.285	.018	-.283	-.433	.565	.212	-.389
4. LM Learning	.219	.568	**.635**	1.00	.240	**.834**	-.038	-.292	.045	-.096	-.229	-.104	.252
5. LM Retention	.072	-.014	.497	.444	1.00	.339	-.064	.389	.089	.077	-.247	.531	.489
6. FTT PT Performance	-.175	.060	.369	.049	-.153	1.00	-.087	-.064	.079	-.263	-.140	-.298	.109
7. FTT PT Error Rate	.539	-.370	.176	.000	.369	-.368	1.00	**-.797**	**.998**	.223	.039	-.334	.306
8. FTT Retention	.253	-.615	.180	.101	.245	.295	.339	1.00	**.786**	.200	.034	.347	-.236
9. FTT Error Rate Change	.104	.334	.269	.042	-.012	.363	-.402	**-.676**	1.00	.261	-.052	.389	-.292
10. Age	-.299	-.371	-.465	-.402	-.159	-.441	.428	.146	-.321	1.00	-.250	.168	.157
11. Education	.300	.200	**.830**	**.802**	.224	.261	-.024	.227	.074	-.492	1.00	-.002	**-.794**
12. IQ	.182	.212	.387	.558	**.634**	.067	.231	.218	-.353	-.396	.449	1.00	.133
13. BDI-II	.547	-.124	.328	.070	.281	-.178	.043	.191	.453	-.488	.193	-.072	1.00

Note. Data presented are Pearson's *r* correlation coefficients. Patient data are presented in the top right cells of the table, shaded light grey; control data are presented in the bottom left cells of the table, not shaded. NFPA = non-functioning pituitary adenoma; RAVLT = Rey Auditory Verbal Learning Test; LM = Wechsler Logical Memory subtest; FTT= Finger Tapping Task; PT = Post-Training; IQ = overall cognitive functioning, as measured by Shipley IQ test; BDI-II = Beck Depression Inventory-II total score. Statistically significant associations (one-tailed) are highlighted in boldface font.

Regarding within-group sex differences in cognitive performance, for the NFPA patient group there were no statistically significant observations: Sleep condition, all *p*s > .173 (see Table 11); Wake Condition, all *p*s > .126 (see Table 12).

For the healthy control group, analyses of data from the Sleep condition detected no significant sex differences for most cognitive outcome variables. There was a significant sex difference on the FTT Percent Retention variable, with men retaining more information than women, and a trend toward a significant sex different on the FTT post-training performance variable, with women performing better than men (see Table 11).

For the healthy control group, analyses of data from the Wake condition detected no significant sex differences with regard to the RAVLT Learning, RAVLT Recognition, Logical Memory Learning, Logical Memory Retention, and FTT Change in Error Rate variables, all *p*s > .131. Analyses did, however, detect significant sex differences on the RAVLT Retention and FTT Percent Retention variables, as well as trends towards significant sex differences on the FTT Post-Training Performance, with women retaining more information on the RAVLT and displaying a better post-training performance on the FTT than men, but men retained more information on the FTT than women (see Table 12).

Table 11

Cognitive Data: Sex Differences in Performance by Patients and Controls in the Sleep Condition (N = 20)

Variable	Group		*t*	*P*	ESE
	Men	Women			
NFPA Patients (n = 10)					
RAVLT					
Learning	38.33 (6.42)	40.29 (9.21)	0.329	.375	0.227
Percent Retention	61.14 (31.97)	64.57 (16.10)	0.234	.410	0.162
Recognition	.80 (.23)	.76 (.16)	-0.304	.385	-0.210
Logical Memory					
Learning	23.00 (2.64)	21.86 (5.17)	-0.354	.366	-0.244
Percent Retention	75.00 (25.00)	71.65 (21.33)	-0.217	.417	-0.150
Finger Tapping Task					
Post-training Performance	14.33 (4.50) [a]	23.50 (14.89) [a]	1.011	.173	0.715
Post-training Error Rate	0.02 (0.02) [a]	0.01 (0.02) [a]	-0.570	.293	-1.791
Percent Retention	92.70 (12.63) [a]	90.17 (24.48) [a]	-0.165	.437	-0.116
Change in Error Rate	-0.00 (0.02) [a]	0.00 (0.04) [a]	0.260	.401	0.184
Healthy Controls (n = 10)					
RAVLT					
Learning	44.00 (7.81)	45.14 (9.37)	0.184	.429	0.127
Percent Retention	60.64 (18.12)	67.42 (23.83)	0.436	.337	0.301
Recognition	1.00 (.00)	.98 (.05)	-0.632	.272	-0.436
Logical Memory					
Learning	22.67 (4.16)	25.29 (4.27)	0.894	.199	0.617
Percent Retention	94.44 (9.62)	85.88 (16.50)	-0.823	.217	-0.568
Finger Tapping Task					
Post-training Performance	22.33 (13.31)	34.17 (6.55)	1.855	.053	1.312
Post-training Error Rate	0.01 (0.02)	0.01 (0.01)	-0.318	.379	-0.219
Percent Retention	139.06 (60.77)	75.85 (30.25)	-2.283	**.026***	-1.575
Change in Error Rate	-0.00 (0.03)	0.00 (0.02)	0.684	.257	0.472

Note. Means are presented, with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; RAVLT = Rey Auditory-Verbal Learning Test.

[a] Data based on 9 participants (1 patient did not complete the Finger Tapping Task).

*p < .05. **p < .01. ***p < .001.

Table 12

Cognitive Data: Sex Differences in Performance by Patients and Controls in the Wake Condition (N = 20)

Variable	Group		*t*	*P*	ESE
	Men	Women			
NFPA Patients (n = 10)					
RAVLT					
Learning	44.67 (12.34)	40.29 (7.29)	-0.719	.246	-0.496
Percent Retention	47.16 (16.92)	66.59 (25.81)	1.178	.136	0.813
Recognition	0.93 (0.11)	0.94 (0.15)	0.096	.463	0.067
Logical Memory					
Learning	22.67 (2.30)	25.57 (6.26)	-0.354	.366	0.523
Percent Retention	71.66 (26.19)	64.62 (16.29)	-.460	.329	-0.366
Finger Tapping Task					
Post-training Performance	14.33 (6.02)[a]	25.83 (14.95)[a]	1.247	.126	0.881
Post-training Error Rate	0.03 (0.03)[a]	0.08 (0.15)[a]	0.572	.293	0.405
Percent Retention	92. 50 (15.61)[a]	83.10 (29.77)[a]	-0.501	.316	-0.355
Change in Error Rate	-0.02 (0.04)[a]	-0.07 (0.14)[a]	-0.617	.278	-0.436
Healthy Controls (n = 10)					
RAVLT					
Learning	54.67 (8.08)	46.00 (11.07)	-1.207	.131	-0.833
Percent Retention	52.19 (18.60)	89.94 (21.31)	2.646	**.015***	1.826
Recognition	0.93 (0.11)	0.94 (0.15)	0.096	.463	0.067
Logical Memory					
Learning	19.33 (9.86)	24.57 (6.52)	1.012	.171	0.698
Percent Retention	77.99 (24.24)	84.03 (19.14)	0.427	.340	0.294
Finger Tapping Task					
Post-training Performance	23.00 (12.16)	34.00 (8.22)	1.702	.064	1.174
Post-training Error Rate	0.04 (0.01)	0.01 (0.01)	-1.823	.053	-1.258
Percent Retention	106.40 (6.68)	82.59 (15.77)	-2.453	**.020***	-1.69
Change in Error Rate	-0.01 (0.04)	0.01 (0.04)	1.163	.139	0.803

Note. Means are presented, with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; RAVLT = Rey Auditory-Verbal Learning Test.

[a] Data based on 9 participants (1 patient did not complete the Finger Tapping Task).

*p < .05. **p < .01. ***p < .001.

Associations between NFPA Patient Clinical Characteristics and Sleep/Cognitive Outcome Variables.

Time since Diagnosis. Analyses detected no significant correlations between time since diagnosis and any of the sleep variables, all *p*s > .092 (see Table 13). The strongest association here was a negative correlation with WASO (r = -.56, p = .92; patients diagnosed more recently tended to have longer periods of waking after sleep onset).

With regard to cognitive measures, analyses of the Sleep condition data detected no significant correlations between time since diagnoses and any of the outcome variables, all *p*s > .078 (see Table 14). The strongest association here was a negative correlation with Logical Memory Retention (r = -.58, p = .78; patients diagnosed more recently tended to perform better on the task).

Analyses of the Wake condition cognitive data also detected no significant correlations, all *p*s > .052 (see Table 14). The strongest association here was a negative correlation with RAVLT Recognition (r = -.63, p = .052; patients diagnosed more recently tended to perform better on the task).

Table 13

Bivariate Correlations: Associations between NFPA Patient Time Since Diagnosis and Sleep Quality Outcome Variables (N = 10)

	1	2	3	4	5	6	7	8	9
1. Sleep Latency (min)	1.00								
2. TST (min)	-.070	1.00							
3. WASO (min)	.463	.125	1.00						
4. Sleep Efficiency (%)	-.529	.295	**-.900**	1.00					
5. Awakenings	-.139	.407	-.171	.374	1.00				
6. Sleep Quality	-.282	-.030	.325	-.379	-.270	1.00			
7. Mood	-.454	.221	.337	-.234	-.138	**.829**	1.00		
8. Alertness	-.370	.373	.341	-.125	-.005	.535	**.816**	1.00	
9. Time Since Diagnosis	-.502	-.321	-.560	.470	-.194	-.118	-.086	.145	1.00

Note. Data presented are Pearson's *r* correlation coefficients. NFPA = non-functioning pituitary adenoma; TST = total sleep time; WASO = waking after sleep onset. Sleep Quality, Mood, and Alertness = subjective sleep data.
Statistically significant associations (one-tailed) are highlighted in boldface font.

Table 14

Bivariate Correlations: Associations between NFPA Patient Time Since Diagnosis and Cognitive Outcome Variables (Sleep and Wake Conditions) (N = 10)

	1	2	3	4	5	6	7	8	9	10
1. RAVLT Learning	1.00	.037	.395	**.654**	-.383	.185	-.036	-.135	-.234	.106
2. RAVLT Retention	.201	1.00	.474	.273	.214	.614	.591	.266	-.310	.024
3. RAVLT Recognition	.034	-.324	1.00	.430	-.024	.116	.174	.124	-.100	-.288
4. LM Learning	.019	.447	-.544	1.00	-.037	.184	.109	-.110	.174	-.309
5. LM Retention	**.914**	.276	.050	.240	1.00	.184	.456	-.222	-.245	-.581
6. FTT PT Performance	.209	.471	-.432	**.834**	.339	1.00	.192	**-.786**	-.246	.483
7. FTT PT Error Rate	-.254	-.227	.285	-.038	-.064	-.087	1.00	-.095	**-.792**	.288
8. FTT Retention	.617	.268	.018	-.292	.389	-.064	**-.797**	1.00	.176	-.157
9. FTT Change in Error Rate	.274	.215	-.283	.045	.089	.079	**-.998**	**.786**	1.00	-.094
10.Time Since Diagnosis	.133	.504	-.628	.411	-.034	.524	-.312	.209	.314	1.00

Note. Data presented are Pearson's *r* correlation coefficients. Sleep condition data are presented in the top right cells of the table, shaded light grey; Wake condition data are presented in the bottom left cells of the table, not shaded. NFPA = non-functioning pituitary adenoma; RAVLT = Rey Auditory Verbal Learning Test; LM = Wechsler Logical Memory subtest; FTT = Finger Tapping Task; PT = Post-Training.

Statistically significant associations (one-tailed) are highlighted in boldface font.

Hydrocortisone Treatment. Broadly speaking, analyses detected no significant differences between the sleep quality of NFPA patients who had and had not been treated with hydrocortisone (see Table 15). Among the group of objective and subjective sleep variables, only WASO was significantly different across the two groups (patients who had been treated with hydrocortisone spent more time awake after sleep onset; this difference was associated with a larger effect size estimate). These treated patients also tended, non-significantly, to have longer sleep latencies and longer total sleep times.

Regarding cognitive outcomes, analyses of the Sleep condition data detected no significant between-group differences, all *p*s > .213 (see Table 16 for descriptive statistics). Analyses of the Wake condition data detected no significant between-group differences for the RAVLT Retention, RAVLT Recognition, Logical Memory Retention, and most of the FTT variables, all *p*s > .211. Analyses of the Wake condition data did, however, detect significant between-group differences for RAVLT Learning $t(1,18) = 1.94$, $p = .044$, Cohen's $d = 1.25$ and FTT Percent Retention, $t(1,18) = 2.59$, $p = .018$, $d = 1.83$ (see Table 16 for descriptive statistics).

Table 15

Sleep Quality Data, Sleep Condition Night: Between-Group Comparisons, NFPA Patients Treated with Hydrocortisone versus Those Not Treated with Hydrocortisone (N = 10)

	Group				
Variable	Hydrocortisone (n = 6)	No Hydrocortisone (n = 4)	T	p	ESE
Objective Measures					
Sleep Latency (min)	32.50 (34.60)	7.50 (5.00)	-1.40	.099	-0.90
TST (min)	406.00 (102.90)	319.00 (49.11)	-1.55	.079	-1.00
WASO (min)	41.83 (17.29)	22.50 (13.02)	-1.89	**.048***	-1.22
Sleep Efficiency (%)	.90 (.04)	.93 (.04)	0.91	.193	0.59
Awakenings (# of times)	2.17 (1.16)	2.00 (2.00)	-0.68	.435	-0.10
Subjective Measures					
Sleep Quality	6.76 (1.81)	7.39 (3.04)	.416	.344	.268
Mood	7.71 (2.33)	8.25 (2.46)	.348	.368	.255
Alertness	7.47 (2.27)	7.03 (2.55)	-.286	.391	-.185

Note. In the second and third columns, means are presented with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; TST = total sleep time; WASO = waking after sleep onset; ESE = effect size estimate (in this case, Cohen's *d*).
*p < .05. **p < .01. ***p < .001. Statistically significant p-values are denoted in boldface font.

Table 16

Cognitive Performance Data, Sleep and Wake Conditions: Between-Group Comparisons, NFPA Patients Treated with Hydrocortisone versus Those Not Treated with Hydrocortisone (N = 10)

	Condition			
	Sleep		Wake	
	Hydrocortisone	No Hydrocortisone	Hydrocortisone	No Hydrocortisone
Variable	(*n* = 6)	(*n* = 4)	(*n* = 6)	(*n* = 4)
RAVLT				
Learning	41.50 (8.59)	37.00 (7.78)	37.83 (8.03)	47.25 (6.55)
Percent Retention	64.54 (20.66)	62.05 (22.17)	58.12 (23.86)	64.72 (28.34)
Recognition	.74 (.17)	.81 (.19)	.90 (.16)	1.00 (.00)
Logical Memory				
Learning	22.50 (4.93)	21.75 (4.27)	26.67 (6.05)	21.75 (2.75)
Percent Retention	72.45 (22.68)	72.97 (21.83)	62.64 (19.21)	72.87 (18.00)
Finger Tapping Task				
Post-training Performance	19.50 (12.43) [a]	22.33 (16.25) [a]	22.16 (14.74) [a]	21.66 (13.57) [a]
Post-training Error Rate	0.02 (0.01) [a]	0.01 (0.02) [a]	0.08 (0.15) [a]	0.03 (0.03) [a]
Percent Retention	87.73 (14.78) [a]	97.58 (31.94) [a]	74.44 (21.36) [a]	109.81 (12.50) [a]
Change in Error Rate	-0.00 (0.04) [a]	0.00 (0.02) [a]	-0.07 (0.14) [a]	-0.02 (0.04) [a]

Note. Means are presented, with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; RAVLT = Rey Auditory-Verbal Learning Test.

[a] Data based on 9 participants (1 patient did not complete the Finger Tapping Task).

Radiotherapy Treatment. Analyses detected no significant differences between the sleep quality (both objectively and subjectively measured) of NFPA patients who had and had not been treated with radiotherapy (see Table 17). The largest between-group difference here was for Sleep Latency, where analyses observed a trend toward those who had received radiotherapy treatment spending significantly less time between going to bed and falling asleep, $p = .051$ and a large effect size estimate.

Regarding cognitive outcomes, analyses of the Sleep condition data detected no significant between-group differences on the RALVT Learning, RALVT Retention, RAVLT Recognition, Logical Memory Retention, and all of the FTT variables, all *ps* > .122 (see Table 18 for descriptive statistics). The analyses did detect a trend toward a significant between-group difference with regard to Logical Memory Learning, $t(1,18) = -1.57$, $p = .071$, Cohen's $d = -1.28$, with patients who have received radiotherapy learning less information on this subtest.

Analyses of the Wake condition data detected no significant between-group differences for the RAVLT Learning, RAVLT Retention, RAVLT recognition, and Logical Memory Retention, and most of the FTT variables all *p*s > .178. The analyses did detect a significant difference on LM Learning $t(1,18) = -0.50$, $p = .048$, Cohen's $d = -0.77$, and a trend towards significance on the post training performance variable of the FTT $t(1,18) = -1.63$, $p = .073$, Cohen's $d = -1.31$. Showing that patients who were treated with radiotherapy learnt more information on the LM subtest and performed better on the FTT when learning and recall was separated by a period of being awake (see Table 18 for descriptive statistics).

Table 17

Sleep Quality Data, Sleep Condition Night: Between-Group Comparisons, NFPA Patients Treated with Radiotherapy versus Those Not Treated with Radiotherapy (N = 10)

	Group				
Variable	Radiotherapy (n = 8)	No Radiotherapy (n = 2)	t	p	ESE
Objective Measures					
Sleep Latency (min)	15.00 (10.69)	52.50 (67.17)	1.84	.051	1.45
TST (min)	383.88 (100.82)	320.50 (27.57)	-0.84	.211	-0.66
WASO (min)	33.63 (18.18)	36.00 (24.04)	0.15	.439	0.12
Sleep efficiency (%)	.91 (.04)	.89 .06)	-0.55	.297	-0.43
Awakening (# of times)	2.38 (1.50)	1.00 (0.00)	-1.23	.126	-0.97
Subjective Measures					
Sleep Quality	7.44 (2.29)	5.28 (0.80)	-1.26	.122	-0.99
Mood	8.33 (2.07)	6.28 (3.03)	-1.16	.138	-0.92
Alertness	7.55 (2.20)	6.28 (3.03)	-0.68	.255	-0.54

Note. In the second and third columns, means are presented with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; TST = total sleep time; WASO = waking after sleep onset; ESE = effect size estimate (in this case, Cohen's *d*).

*p < .05. **p < .01. ***p < .001. Statistically significant p-values are denoted in boldface font.

Table 18

Cognitive Performance Data, Sleep and Wake Conditions: Between-Group Comparisons, NFPA Patients Treated with Radiotherapy versus Those Not Treated with Radiotherapy (N = 10)

	Condition			
	Sleep		Wake	
Variable	Radiotherapy (n = 8)	No Radiotherapy (n = 2)	Radiotherapy (n = 8)	No Radiotherapy (n = 2)
RAVLT				
Learning	40.38 (7.74)	37.00 (12.72)	42.63 (7.94)	37.50 (13.43)
Percent Retention	66.93 (20.19)	50.00 (17.67)	60.33 (19.05)	62.50 (53.03)
Recognition	.77 (.19)	.76 (.14)	.92 (.14)	1.00 (.00)
Logical Memory				
Learning	23.25 (4.06)	18.00 (4.24)	26.13 (5.11)	19.00 (0.00)
Percent Retention	68.92 (17.41)	87.61 (36.36)	69.60 (17.16)	55.26 (26.05)
Finger Tapping Task				
Post-training Performance	22.71 (13.63) [a]	12.50 (6.36) [a]	25.57 (13.25) [a]	9.50 (0.70) [a]
Post-training Error Rate	0.02 (0.02) [a]	0.01 (0.02) [a]	0.08 (0.14) [a]	0.02 (0.03) [a]
Percent Retention	86.56 (18.37) [a]	106.61 (25.99) [a]	81.98 (24.61) [a]	101.11 (29.85) [a]
Change in Error Rate	0.00 (0.03) [a]	-0.00 (0.01) [a]	-0.07 (0.13) [a]	-0.02 (0.03) [a]

Note. Means are presented, with standard deviations in parentheses. NFPA = non-functioning pituitary adenoma; RAVLT = Rey Auditory-Verbal Learning Test.

[a] Data based on 9 participants (1 patient did not complete the Finger Tapping Task).

Discussion

This project aimed to describe sleep quality and memory functioning, and the relations between them, in patients with pituitary disease (PD). To accomplish this aim, I recruited a sample of 10 patients with non-functioning pituitary adenomas (NFPA) and 10 healthy matched controls. Objective assessments of cognitive functioning and sleep quality were performed via face-to-face interviews, which were conducted at participants' homes. Using a crossover design, each participant was administered standardized neuropsychological tests (Rey Auditory Verbal Learning Test [RAVLT], Wechsler Logical Memory Test [LM test], Finger Tapping Task [FTT]) assessing declarative and procedural memory performance after a period of sleep and after an equivalent period of wakefulness. This design allowed the study to undertake the specific examination of whether sleep enhances memory consolidation in patients as it does in healthy controls. Analyses detected significant between-group differences with regard to certain aspects of cognition (e.g., retention of verbal declarative materials, recognition memory): In all cases, controls performed better than patients. However, analyses detected no significant between-group differences with regard to sleep quality. Furthermore, both patients' and controls' recognition memory benefited significantly more from a period of sleep compared to a period of wakefulness.

This chapter discusses the status of each of the study's hypotheses, and outlines how the current findings relate to existing literature. It concludes by exploring some possible limitations of the study and providing recommendations for future research.

Hypothesis 1: Between-Group differences in Sleep Quality and Cognitive Functioning

The first part of Hypothesis 1 stated that, compared to matched healthy controls, patients with NFPA will have poorer sleep quality (as indexed by, for example, more nighttime awakenings after sleep onset, longer sleep latency, a shorter total sleep time, and worse sleep efficiency). This prediction was not confirmed: Analyses detected no significant between-group differences on any of the objective sleep variables monitored. However, there were non-significant trends suggesting that patients had shorter total sleep time and more night-time awakenings.

The current non-significant findings with regard to the sleep quality of pituitary disease patients in comparison to that of controls stands in contrast to existing literature on the topic (see, e.g., Biermasz et al., 2011; Joustra et al., 2014; Leistner et al., 2015; Shipley et al., 1992). These previously published studies report that patients with non-functioning pituitary macroadenomas

(NFMA) experience significantly compromised sleep quality (including reduced sleep efficiency, more nighttime awakenings, alterations in sleep-wake patterns, decreased daytime functioning and less daytime activity, as well as sleep-disordered breathing and obstructive sleep apnea).

One possible reason for discrepancies between the current study's findings and those from previous studies is that the device used to record objective sleep quality in the current study (*Fitbit Alta HR*) was not sensitive enough to detect subtle changes in sleep patterns that might be detected by other, more sophisticated devices. The aforementioned previously published studies assessed sleep in patients with PD (including NFPA) using polysomnography (PSG) and actigraphy (Biermasz et al., 2011; Joustra et al., 2014; Leistner et al., 2015).

However, the Fitbit Alta HR has been shown to be a viable alternative to actigraphy in that it can reliably differentiate between sleep and wake states and provide gross estimates of sleep parameters (Haghayegh et al., 2019; Kawasaki et al., 2022; Lee et al., 2019; Zhang et al., 2022). Thus, one must acknowledge that the current findings could be a true reflection of the lack of significant between-group differences in sleep quality. Consistent with this speculation and with the current findings, Van der Klaauw and colleagues (2007) found that patients with NFMA experienced normal sleep patterns (onset, sleep timing, duration, and rise time). They also reported that even though NFMA patients experience normal sleep patterns, they still self-report significant daytime sleepiness. Similarly, the current sample of NFPA patients' self-reports of sleep quality, alertness upon awakening, and mood upon awakening contrasted significantly with controls' reports. Specifically, patients reported significantly poorer sleep quality, decreased levels of alertness upon awakening, and lower mood upon awakening.

Lipinska and Thomas (2017) found a mismatch between laboratory-based objective sleep measures and everyday subjective sleep quality in individuals diagnosed with post-traumatic stress disorder. Hence, there are open questions of why in these samples subjective reports do not match objective measures, and whether there are relatively small but clinically significant impairments in PD patients' sleep architecture. Although Biermasz et al. (2011) showed that NFMA patients experience decreased REM sleep and increased stage 1 sleep, these results have not been replicated. Such replication must be explored using laboratory-based PSG; wearable devices such as the Fitbit Alta HR cannot replicate the robust data regarding density of sleep stages that PSG provides (Zhang et al., 2022).

The second part of Hypothesis 1 stated that patients with NFPA will have worse cognitive function than matched healthy controls. This prediction was partially confirmed: Patients performed significantly more poorly on some (but not all) tasks assessing verbal declarative memory and some (but not all) aspects of procedural memory.

Specifically, on a story memory task controls recalled significantly more information than patients. On a list-learning task, controls performed significantly better than patients on a delayed recognition task, and analyses detected a trend towards significance (controls > patients) with regard to performance on the learning trials of the task. Regarding procedural memory, controls made significantly fewer errors on a computerized task which required participants to use the non-dominant hand to repeatedly type, for 30 seconds, a 5-element number sequence.

The current findings are consistent with those presented in previous studies and support the inference that patients with PD experience difficulties in certain cognitive domains, including the consolidation of declarative memories and procedural memory (Bulow et al., 2002; Cespo & Webb, 2014; Grattan-Smith et al., 1992; Noad et al., 2004; Peace et al., 1998; Peace et al., 1997; Tiemensma et al., 2010).

Because patients in the current sample had been treated for a NFPA and had been in recovery or on stable treatment for at least 1 year prior to study enrolment, this finding with regard to their memory performance suggests that cognitive dysfunction may be present even when hormone dysregulation is no longer a problem. One reason for this persistent dysfunction even in the absence of hormone dyregulation might be gleaned from results presented by Yedinak and Fleseriu (2014). They found that perceived cognitive dysfunction was higher among patients with NFPA than among patients with acromegaly. They went on to infer that, because their NFPA patients were not experiencing any apparent biochemical issues, their cognitive impairment might be traced to electrophysiological or neurovascular change due to a tumour and that they may have suffered from growth hormone deficiency. It is certainly possible that the current sample of NFPA patients may have been growth hormone deficient. Treatment for this deficiency is rare in South Africa because of the exorbitant costs constraints of appropriate therapy. In summary, then, the cognitive problems experienced by the current patients may be due to structural or neurovascular changes as a result of a tumour.

Hypothesis 2: Within-group Comparisons on Sleep Quality and Cognitive Function

Hypothesis 2 stated that both patients and controls will have better memory performance when a period of sleep, rather than a period of wakefulness, separates learning of information from recall testing of that information. Analyses only partially confirmed this hypothesis. In both groups there was a significant between-condition difference for the RAVLT recognition task, with patients and controls both recognizing more words when learning and recognition was separated by a period of sleep rather than a period of normal waking activity. This finding is consistent with existing literature showing that a period of sleep after learning improves performance on a delayed recognition task (Drosopoulos et al., 2005; Maurer et al., 2015; Payne et al., 2008; Sheth et al., 2009; Van Der Helm et al., 2010; Wagner et al., 2007).

However, analyses of the healthy control data detected no other significant between-condition differences in cognitive performance. For most cognitive outcome variables (i.e., all except the ones mentioned in the previous paragraph), healthy controls had equivalent improvement in memory performance under both conditions. This finding contrasts with a large body of literature showing that a period of sleep, more than a period of normal waking, benefits the retention of previously learned declarative material (Henry et al., 2017; Lahl et al., 2008; Nishida et al., 2008; Payne et al., 2008; Plihal & Born, 1997; Rasch et al., 2007; Tucker et al., 2006; Wagner et al., 2001) and previously learned procedural tasks (Fischer et al., 2002; Gais et al., 2002; Huber et al., 2004; Korman et al., 2007; Mednick et al., 2003; Smith, 1995; Stickgold et al., 2000; Stickgold et al., 2000; Walker et al., 2002; Walker et al., 2003).

Similarly, in the NFPA patient group, analyses detected no significant between-condition differences in cognitive performance other than those mentioned above. Although this finding was contrary to expectations, it is consistent with what Henry et al. (2017) found in their study of cognitive function in patients with Addison's disease. They reported that memory performance in a sample of these patients did not benefit from a period of sleep, and inferred that it may be because these patients experience an abnormal circadian rhythm of cortisol, in addition to an abnormal sleep cycle (i.e., their physiological conditions were not favourable for sleep-dependent memory consolidation).

Pituitary tumours stimulate hormonal release, which results in fluctuations in hormone secretion. Because patients with PD may require exogenous supplementation of hormones, which

increases HPA-axis activity (Buckley & Schatzberg, 2005), and are not subject to the same negative feedback inhibition that exists among healthy individuals, one might expect that these patients will experience similar circadian rhythm abnormalities (as experienced by patients with Addison's disease in the Henry et al. [2017] study). Thus, it is unsurprising that previous studies report that patients with NFMA experience decreased REM sleep, increased stage 1 sleep, more nighttime awakenings, increased daytime sleepiness (Biermasz et al., 2011; Joustra et al., 2014) and are prone to experiencing sleep-disordered breathing and obstructive sleep apnoea (Romjin, 2016; Ventre et al., 2021).

A large body of literature has established that sleep is crucial for memory consolidation (Diekelmann et al., 2009; Marshall & Born, 2007; Marshall et al., 2006). Within that literature are a few prominent theories attempting to explain the process of sleep-dependent memory consolidation. Some of these theories suggest that the consolidation of particular types of memory is reliant on the characteristics of particular sleep stages (Ackerman, 2014; Antony et al., 2019; Astori et al., 2013; Born et al., 2006; Born & Wilhelm, 2012; Buzsaki, 1998; Diekelman & Born, 2010; Ellenbogen et al., 2006; Fogel & Smith, 2011; Gandhi & Emaddy, 2022; Hahn et al., 2020; Helfrich et al., 2021; Helfrich et al., 2018; Joechner et al., 2021; Luthi, 2014; Mednick et al., 2013; Mikutta et al., 2019; Molle et al., 2011; Muehlroth et al., 2019; Patel et al., 2022; Peyrache & Seibt, 2020; Schabus et al., 2004; Stickgold, 2005; Stickgold & Walker, 2007; Tamminen et al., 2013; Tononi & Cirelli, 2006, 2014; Ulrich, 2016) and that the sequence in which one sleep stage follows the other throughout the night is particularly important (Clopath, 2012; Giuditta, 2014; Giuditta et al., 1995). This latter point was highlighted by Strauss et al. (2022), who found that sleep spindles were associated with memory consolidation only when NREM sleep was followed by REM sleep.

One might speculate that patients in the current study (and the patients with Addison's disease in the Henry et al. [2017] study) may have experienced sleep in a manner that did not facilitate memory consolidation (e.g., they might not have spent adequate time in the appropriate sleep stages, and their transitions between sleep stages may not have been have been ideal). However, as noted previously, detailed investigation of the length, depth, and duration of sleep stages were beyond the scope of this study.

Hypothesis 3: Between-group Comparisons on Cognitive Tests

Hypothesis 3 stated that a preceding period of sleep will be significantly more beneficial for memory consolidation in healthy controls than in patients. This prediction was only partially confirmed: Analyses indicated that, at post-sleep testing, controls retained significantly more information from the story memory subtest and recognized more words from the list learning subtest than patients did. Controls also had better post-training FTT performance post-sleep than patients did. Of note among the analyses of these cognitive data is that even for variables where no significant differences were found, the means were still in the predicted direction (i.e., controls benefitting more than patients from the intervening period of sleep). Failure to detect significant differences may therefore be attributable to small sample sizes.

According to some sleep researchers, sleep efficiency (i.e., the ratio of time spent in bed to time sleeping) should be kept above 85% to yield optimum health benefits (Ohayon et al., 2017; Reed & Sacco, 2016). In the current study, both patients and controls recorded an average of 91% sleep efficiency, with no significant between-group differences. Despite this similarity, these overnight periods of sleep were more beneficial for the cognitive performance of controls than patients. One possible explanation for this finding may be that gross measures of sleep quality (e.g., total sleep time, number of minutes of waking after sleep onset, number of awakenings after sleep onset) do not capture the sleep disruptions that affect cognitive performance in patients. More specifically, the disruptions may be at the level of sleep architecture, specifically the amount of time spent in the relevant sleep stages. For instance, previous studies showed evidence of altered sleep architecture in PD patients (particularly, reduced time in REM sleep and an increase in Stage 1 sleep; Biermasz et al., 2011; Romjin, 2016). This is relevant particularly because numerous studies suggest that uninterrupted REM sleep enhances memory for declarative material (Empson & Clark, 1970; Fogel, et al., 2007; Rauchs et al., 2004; Tilley & Empson, 1978).

Hypothesis 4: Within-group associations between sleep and cognitive variables

Another overall aim of the current study was to assess whether there are relations between sleep and cognition in PD patients. To accomplish this aim, I examined associations between sleep outcome variables and cognitive outcome variables for both groups of participants separately. In the NFPA patient group, analyses suggested that better sleep efficiency was

associated with a smaller post-training error rate on the FTT. Similarly, in the healthy control group analyses suggested that fewer awakenings were associated with better post-training performance on the FTT.

However, analyses detected no other significant associations between the two sets of outcome variables in the healthy control group, meaning the current findings are only partially consistent with the wealth of research showing that sleep plays a vital role in overall cognitive function (Dang-Vu et al., 2006; Diekelmann et al., 2009; Marshall & Born, 2007; Marshall et al., 2006; Scullin & Bliwise, 2015; Spencer et al., 2017; Stickgold, 2005).

In one of the few previous studies that measured both sleep and cognition in PD patients, Wennberg and colleagues (2019) found that in patients with acromegaly poor cognitive function was associated with poor subjective sleep quality. In the current study, however, analyses suggested that *more* night time awakenings were associated with *better* recognition memory, and that patients who rated themselves as being *less* alert upon awakening scored *better* on learning trials. The unconventional direction of these associations might be explained as follows. First, the patient with the highest number of nighttime awakenings also had a perfect RAVLT recognition score, and this data point may have influenced the results unduly (particularly given the small sample size). Second, with regard to the association between alertness upon awakening and learning, it is important to note that learning always took place the evening before participants were asked to rate their level of morning alertness, and therefore it is quite possible that this is a spurious association.

Secondary Analyses

Analyses of data from the healthy control group indicated that more years of education levels and higher IQ scores were significantly associated with better learning and retention on the declarative memory tasks, and better performance on the procedural memory task. This set of results is expected given the well-documented positive association between education, IQ, and performance on standardized cognitive tests (Alley et al., 2007; Crowe et al., 2013; Guerra-Carrillo et al., 2017; Guez et al., 2018; Lee et al., 2006; Parisi et al., 2012; Tucker-Drob et al., 2009; Van Hooren et al., 2007; Wilson et al., 2009).

Interestingly, however, these relationships were not observed in the patient group. Within that group, analyses indicated that younger age was associated with spending more time awake after sleep onset and with lower sleep efficiency levels. These findings is not consistent with

those from previous studies, which suggest that healthy aging is characterized by a decline in sleep efficiency and a tendency to spend more time awake after sleep onset (Akerstedt et al., 2016; Desjardins et al., 2019; Ohayon et al., 2004; Pace- Schott & Spencer, 2011; Unruh et al., 2008). There were no such any age-related associations in the control group. It might be that, for NFPA patients, the circadian and homeostatic sleep-regulatory processes that are usually affected by aging are also impacted by disease presence and treatment type, thus impacting the sleep efficiency of each patient differently.

Separate analyses of data from the healthy control group indicated that greater depressive symptomatology (i.e., a higher BDI score) was associated with shorter total sleep time. This result is compatible with previous studies showing shorter sleep duration is associated with higher levels of depression (Kay et al., 2018; Shim & Kang, 2017; Toffol et al., 2014). Again, however, these associations were not observed in the patient group. This between-group discrepancy might be accounted for the by the fact that the participant in the control group who had the highest BDI score also had a relatively short sleep duration. This case might have been particularly influential given the small samples sizes.

Finally with regard to depression scores, it is important to note that for both patients and controls the average BDI-II score fell within the range conventionally described as “not depressed” or “minimally depressed” (Beck et al., 1996). Hence, it is important not to over-interpret the significant association described above.

Another analysis of data from the healthy control group detected a trend toward a significant sex difference with regard to sleep latency (i.e., men took longer to fall asleep than women). This is at odds with previous research, which suggests that women typically have longer sleep latencies than men (Middelkoop et al., 1996; Silva et al., 2008; Vagiakis et al., 2006). Of note here is that there were only 3 men in the control group, and that one of them recorded relatively high sleep latency times. Again, the small sample size might mean that this outlier might have been unusually influential.

Further analyses of control-group data indicated that, in the Sleep condition, women performed better than men on the FTT, but men retained more information than women on the same task. A similar pattern was found in the Wake condition: Women performed better and made fewer errors than men on the FTT, but men retained more information than females on the same task.

At least one previous study has shown that there may be a male advantage in motor learning, rather than in motor performance (Dorfberger et al., 2009). Hence the current data patterns may be explained by the fact that even though females performed better on the FTT task, males may have learned better in the learning session and thus had a better percent retention.

Furthermore, on the RAVLT women in the control group retained more information than their male counterparts. This finding is consistent with a large literature indicating that women excel at verbal learning tasks (see, e.g., Hirnstein et al., 2023; Kramer et al., 1997; Li & Singh, 2014; Smith et al., 2009).

All of the sex difference results must be interpreted with extreme caution, however, given that (1) as noted before, the sample size was quite small, and (2) gender distribution in this study was not equal – there were 3 men and 7 women per group.

Correlational analysis suggested that, among patients, longer disease duration was associated with spending less time awake after sleep onset (i.e., better sleep quality). One explanation for this finding is that, perhaps, a longer disease duration means that physicians have had more time to find which treatment works best for the patient (e.g., regulates hormones more effectively), and hence were able to adjust treatments in such a way that they (directly or indirectly) improved sleep quality.

Patients treated with hydrocortisone spent, relative to those not treated this way, significantly more time (a) trying to fall asleep after going to bed at night, and (b) awake after sleep onset. These findings are consistent with numerous previous studies showing that elevated cortisol levels cause sleep disturbances (Buckley & Schatzberg, 2005; GarcÍa-Borreguero et al., 2000; Han et al., 2012; Henry, 2019; Henry et al., 2018; Henry et al., 2017; Henry et al., 2015; Lovas et al., 2003; Steiger, 2002; Vgontzas et al., 2003). Moreover, at least one previous study (Andela et al., 2018) shows that sleep problems experienced by patients with PD may be linked to the experience of hydrocortisone replacement therapy.

With regards to verbal declarative memory, results showed that patients who were treated with hydrocortisone learned significantly fewer words on the RAVLT task. This finding is consistent with research that showed the hormone cortisol diminishes the consolidation of neutral material (Kirschbaum et al. 1996; Payne et al., 2007). Previous research shows that the effect of hydrocortisone on memory follows an inverted-u shape, while moderate amounts can enhance memory performance, too little or too much can hinder it (Herbert et al., 2006; Lupien et al.,

1997; Young et al., 2013). Perhaps in this patient group the cortisol concentration level was not ideal for memory performance.

With regards to procedural memory, results showed that those who received hydrocortisone treatment retained significantly less information on the FTT. This finding is not consistent with research, which documented that elevated cortisol levels have no effect on procedural memory (Newcomer et al., 1994; Schwabe et al., 2009; Schwabe & Wolf, 2012), as it is not hippocampal-dependent. However, these results should be interpreted with caution, as cortisol levels were not measured in this study, thus we cannot be sure of what the patient cortisol concentration was at the time of testing. Furthermore, given the small numbers of participants who had received hydrocortisone therapy (N= 6), the current study was not powered to detect the effects of hydrocortisone therapy on sleep quality or cognitive function.

The effect of radiotherapy on sleep quality is not well-documented in the context of PD, in the current study analyses detected no significant differences on any of the sleep domains examined. Furthermore, at the time of the study no patients were undergoing radiotherapy and it had been at least 1 year since their last radiotherapy treatment. And at least one study showed that the negative effects of radiotherapy on sleep improves with time (McQuade et al., 2017).

With regards to radiotherapy and cognition, analyses detected that patients who had received radiotherapy learned less information on the LM subtest. This finding is in line with research documenting that radiotherapy negatively affects verbal declarative memory (Brummelman et al., 2011; Noad et al., 2004). However, given the small number of participants who had undergone radiotherapy (N= 8), the current study was not powered to detect the effects of radiotherapy on sleep quality and cognitive function.

An earlier study recruited patients with pituitary tumours, either who had undergone both radiotherapy and surgery or who had undergone surgery alone They found that patients who had undergone radiotherapy performed more poorly than the surgery only group on tests assessing executive function (Noad et al., 2004). In the current study we could not corroborate this as only 2 patients underwent surgery only.

Limitations and Directions for Future Research

Given the time-restricted nature of my degree registration, data for this study had to be collected during the height of the COVID-19 pandemic (2020 - 2022). To slow the spread of the novel coronavirus, the government of the Republic of South Africa imposed extensive restrictions on the movement of people within the country. Some of these restrictions included requirements

for most of the population to stay home and to limit the amount of social contact. People with pre-existing chronic health conditions were identified as being among those at high risk for COVID-19 infection and subsequent serious illness.

Because patients who have been treated for PD are at risk for multisystem morbidities (Bertagna et al., 2009; Colao et al., 2012; Zhang et al., 2020), all of the above-described circumstances affected participant recruitment negatively. Potential patient participants were, understandably, cautious about socializing. Moreover, the study employed strict eligibility criteria to ensure that the current data were free of confounders (e.g., age variability, education variability, IQ variability, and effects of hormone supplementation on sleep and cognition).

Hence, the sample size is small and the statistical power limited. I was therefore not able to conduct in-depth investigations of, for instance, the associations between demographic/clinical variables and the sleep/memory outcome variables. Clearly, future studies should aim to recruit larger sample sizes. However, given the rarity of PD (global estimates suggest a prevalence of 80–100 cases per 100,000 population; Chanson et al., 2015) this may be challenging.

A second limitation is related to the device used to record objective sleep data. As mentioned previously, the Fitbit Alta HR may not have been sensitive enough to detect subtle changes in sleep patterns. It is also limited in its ability to track sleep architecture (i.e., the structural organization of sleep patterns). Because memory consolidation is supported by particular characteristics of specific sleep stages (Ackerman, 2014; Born et al., 2006; Stickgold, 2005) and by the way the body transitions between sleep stages throughout the night, future studies may benefit from using polysomnography to investigate sleep in this patient group.

A third limitation is related to the fact that the patient group only consisted of NFPA patients. Studies show variability in sleep quality and cognitive function between patients with different kinds of pituitary tumours (see, e.g., Romijn, 2016; Tiemensma et al., 2010; Yedinak & Fleseriu, 2014). Perhaps the associations between clinical variables and sleep/memory outcome variables, or interactions between clinical variables and the experimental conditions, may be different in different patient groups. Hence, future studies may benefit from, for instance, enrolling patients that are representative of both non-functional and functional pituitary tumours.

A fourth limitation relates to the fact that the study did not measure cortisol concentrations. If future studies wish to determine the effect of cortisol on sleep or cognition in

pituitary disease patients, objective measurement of cortisol concentrations at the time of testing is warranted.

Summary and Conclusion

The current study aimed, generally, to advance the understanding of psychological functioning in patients with PD. More specifically, this investigation sought to expand the body of knowledge focused on understanding the influence of sleep on memory in the context of non-functioning pituitary adenomas and to investigate whether sleep enhances memory consolidation in pituitary disease patients as it does in healthy controls.

Analyses detected significantly poorer cognitive performance in patients than in matched healthy controls but no significant between-group differences in sleep quality. Despite this latter non-significant result, the analyses did find that a period of sleep (rather than a period of normal waking) between learning and recall was more beneficial for performance on certain cognitive tasks (e.g., Rey Auditory Verbal Learning Test [RAVLT], Wechsler Logical Memory Test [LM test], Finger Tapping Task [FTT) in healthy controls than in NFPA patients.

This finding raised the question of whether NFPA patients experience cognitive difficulties as a result of disrupted sleep architecture (e.g., the amount of time spent in the particular sleep stages) rather than with more gross measures of sleep quality (e.g., amount of time spent asleep, number of minutes of waking after sleep onset, number of nighttime awakenings after sleep onset). To investigate this question, future studies should make use polysomnographic techniques to investigate sleep in pituitary disease patients.

Although the priori hypotheses were only partially confirmed, the current findings contribute to the existing body of psychological research on PD patients and may provide an impetus for further research in the field. For example, potential clinical and practical implications are that patients' relatively poor performance on certain memory tasks cognition can guide researchers and clinicians toward a deeper understanding of cognitive function in patients with PD and may, for instance, lead to a focus on specific memory rehabilitation interventions designed for this patient group. Such interventions may assist in improving their adherence to daily treatment regimens and their capacity to successfully complete other important daily activities.

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Appendix A:

Advertisement for controls

ARE YOU INTERESTED PARTICIPATING IN A SLEEP STUDY?

The Department of Psychology at the University of Cape Town is currently running a study on sleep and cognition**.**

What does participation entail?

. This study will take place over a period of 1 week. During which, you will be required to wear a fitbit monitor and document your sleep patterns in a sleep diary. You will also be

required to complete two morning sessions and two evening sessions of memory testing. These testing sessions will take place prior to the week, and again at the end of the week. After the final session of memory testing you will be debriefed about the nature, design and purpose of the study.

The study will be arranged well in advance (at least 1 week) and at your convenience.

How do I know if I qualify to take part?

If you are between the ages of 18 and 65 years, fluent in English, free of chronic illnesses, neurological disorders, and psychiatric illnesses, are not pregnant, are not currently using medication known to have sedative properties, you qualify to take part in this study.

What are the benefits and risks of taking part?

By participating in this study you will be afforded the opportunity to learn about sleep and cognition from a psychological perspective, and ask the researcher any questions you might have about sleep and cognition.

Participation in this study does not pose any foreseeable psychological or physical risks.

If you are interested in participating or if you have any questions you want to ask before deciding to participate, please contact Musaddiqah Brown via email at brwmus001@myuct.ac.za, or via telephone at 0216964116.

Appendix B:
Sociodemographic Questionnaire

Section A. (for all participants)

Participant Number……

Age…….

Sex……

Email
address……

Postal
address……

Highest level of education obtained…….

How well do you speak and Understand English?

1□ Very well 2□ Well 3□ Basic 4□Not well 5□ Not at all

Medical Information

Do you have a history of psychiatric illness (e.g., mood or psychotic disorders)?

……

Do you have a history of neurological disorders that could negatively affect memory, attention, learning, judgement, and reasoning (e.g., dementia, epilepsy, severe head injury, stroke)?

……

……

Are you currently on any sleep medication?

……

Are you currently pregnant?

……

Section B. (for patients only)

When were you first diagnosed with pituitary disease? ……..

What forms of treatment are you currently on? .....
How long have you been on this treatment? ……...

Are you receiving Radiotherapy/ or have you received Radiotherapy in the past?

……..

Are you on any medication?

If yes, please specify which medication

……
……
……

Section C. (for controls only)

Do you suffer from any chronic illnesses? 1□ Yes 2□ No 3□ I don't know

If yes, please specify

……

Are you on any medication/ treatment? 1□ Yes 2□ No

If yes, please specify

……
……

Appendix C:

MINI

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSMIII-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for
ICD-10). The results of these studies show that the
M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ±
11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category. •At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them ({) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that <u>each dimension</u> of the question is taken into account by the patient (for example, timeframe, frequency, severity, and/or alternatives).

<u>Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded</u> <u>positive in the</u>

<u>M.I.N.I.</u> The M.I.N.I. Plus has questions that investigate these issues.

Appendix D:

BDI-II

1.

0 I do not feel sad.

1 I feel sad

2 I am sad all the time and I can't snap out of it.

3 I am so sad and unhappy that I can't stand it.

2.

0 I am not particularly discouraged about the future.

1 I feel discouraged about the future.

2 I feel I have nothing to look forward to.

3 I feel the future is hopeless and that things cannot improve.

3.

0 I do not feel like a failure.

1 I feel I have failed more than the average person.

2 As I look back on my life, all I can see is a lot of failures.

3 I feel I am a complete failure as a person.

4.

0 I get as much satisfaction out of things as I used to.

1 I don't enjoy things the way I used to.

2 I don't get real satisfaction out of anything anymore.

3 I am dissatisfied or bored with everything.

5.

0 I don't feel particularly guilty

1 I feel guilty a good part of the time.

2 I feel quite guilty most of the time.

3 I feel guilty all of the time.

6.

0 I don't feel I am being punished.

1 I feel I may be punished.

2 I expect to be punished.

3 I feel I am being punished.

7.

0 I don't feel disappointed in myself.

1 I am disappointed in myself.

2 I am disgusted with myself.

3 I hate myself.

8.

0 I don't feel I am any worse than anybody else.

1 I am critical of myself for my weaknesses or mistakes.

2 I blame myself all the time for my faults.

3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.

1 I have thoughts of killing myself, but I would not carry them out.

2 I would like to kill myself.

3 I would kill myself if I had the chance.

10.

0 I don't cry any more than usual.

1 I cry more now than I used to.

2 I cry all the time now.

3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.

1 I am slightly more irritated now than usual.

2 I am quite annoyed or irritated a good deal of the time. 3 I feel irritated all the time.

12.

0 I have not lost interest in other people.

1 I am less interested in other people than I used to be.

2 I have lost most of my interest in other people.

3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.

1 I put off making decisions more than I used to.

2 I have greater difficulty in making decisions more than I used to. 3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.

1 I am worried that I am looking old or unattractive.

2 I feel there are permanent changes in my appearance that make me look unattractive

3 I believe that I look ugly.

15.

0 I can work about as well as before.

1 It takes an extra effort to get started at doing something.

2 I have to push myself very hard to do anything.

3 I can't do any work at all.

16.

0 I can sleep as well as usual.

1 I don't sleep as well as I used to.

2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.

1 I get tired more easily than I used to.

2 I get tired from doing almost anything.

3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.

1 My appetite is not as good as it used to be.

2 My appetite is much worse now.

3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.

1 I have lost more than five pounds.

2 I have lost more than ten pounds.

3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.

1 I am worried about physical problems like aches, pains, upset stomach, or constipation.

2 I am very worried about physical problems and it's hard to think of much else.

3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I have almost no interest in sex.

3 I have lost interest in sex completely.

Appendix E:

RAVLT

RAVLT 1

List A	A1	A2	A3	A4	A5	List B	B1	A6	A7	LIST A
Drum						Desk				Drum
Curtain						Ranger				Curtain
Bell						Bird				Bell
Coffee						Shoe				Coffee
School						Stove				School
Parent						Mountain				Parent
Moon						Glasses				Moon
Garden						Towel				Garden
Hat						Cloud				Hat
Farmer						Boat				Farmer
Nose						Lamb				Nose
Turkey						Gun				Turkey
Colour						Pencil				Colour
House						Church				House
River						Fish				River
# Correct										# Correct

Recognition Task 1

Bell (A)	Home (SA)	Towel (B)	Boat (B)	Glasses (B)
Window (SA)	Fish (B)	Curtain (A)	Hot (PA)	Stocking (SB)
Hat (A)	Moon (A)	Flower (SA)	Parent (A)	Shoe (B)
Barn (SA)	Tree (PA)	Colour (A)	Water (SA)	Teacher (SA)
Ranger (B)	Balloon (PA)	Desk (B)	Farmer (A)	Stove (B)
Nose (A)	Bird (B)	Gun (B)	Rose (SPA)	Nest (SPB)
Weather (SB)	Mountain (B)	Crayon (SA)	Cloud (B)	Children (SA)
School (A)	Coffee (A)	Church (B)	House (A)	Drum (A)
Hand (PA)	Mouse (PA)	Turkey (A)	Stranger (PB)	Toffee (PA)
Pencil (B)	River (A)	Fountain (PB)	Garden (A)	Lamb (B)

RAVLT 2

List A	A1	A2	A3	A4	A5	List B	B1	A6	A7	LIST A
Pipe						Bench				Pipe
Wall						Officer				Wall
fhAlarm						Cage				Alarm
Sugar						Sock				Sugar
Student						Fridge				Student
Mother						Cliff				Mother
Star						Bottle				Star
Painting						Soap				Painting
Bag						Sky				Bag
Wheat						Ship				Wheat
Mouth						Goat				Mouth
Chicken						Bullet				Chicken
Sound						Paper				Sound
Door						Chapel				Door
Stream						Crab				Stream
# Correct										# Correct

Recognition Task 2

alarm (A)	Eye (SA)	Soap (B)	Ship (B)	Bottle (B)
Aunt (SA)	Crab (B)	Wall (A)	Car (PA)	Seat (SB)
Bag (A)	Star (A)	Clock (SA)	Mother (A)	Sock (B)
Creek (SA)	Rag (PA)	Sound (A)	Duck (SA)	Tone (SA)
Officer (B)	Bun (PA)	Bench (B)	Wheat (A)	Fridge (B)
Mouth (A)	cage (B)	bullet (B)	Floor (SPA)	Rock (SPB)
Arrow (SB)	Cliff (B)	Night (SA)	Sky (B)	Bread (SA)
Student (A)	Sugar (A)	Chapel (B)	Door (A)	Pipe (A)
Hail (PA)	Cream (PA)	Chicken (A)	Bridge (PB)	Ball (PA)
Paper (B)	Stream (A)	Coat (PB)	Painting (A)	Goat (B)

Appendix F:

Logical Memory Test

LM 1

	Score 0 or 1		
Story A	Story Unit	Thematic Unit	Scoring criteria
Michael			Michael" is required
Simpson			"Simpson" is required
has earned			A word or phrase meaning "has earned"
a reputation			"Reputation" is required
for being stubborn			"Stubborn" or some form of the word is required
after refusing			A word or phrase meaning "refusing"
to accept			"Accept" is required
his pay cheques			"Pay cheques" is required
Instead of the cheques			A phrase or expression indicating an alternative to the cheque**s**
he wanted his wages			An expression indicating that "he wanted **his** wages" or "money" or "pay"
to be paid			"To be paid" required
in cash			"Cash" in any context
He eventually			An expression indicating that "he eventually"
won the battle			"Won" is required
and collected			“Collected" or a similar word or phrase is required
ten thousand dollars			"Ten thousand dollars" is required
in back pay			A phrase indicating "in back pay" is required

His wife			"Wife" is required plus an indication that it was his wife
was pleased			A word or phrase meaning to be pleased, but not ecstatic
because she had been forced			"Forced" is required
to cook			"Cook" or some form of the word is required
on a camping stove			"Camping stove" is required
after services to their home			"Services" is required plus an indication that it was at their home
were cut off			An expression meaning disconnected
18 months ago			“18 months ago is required”

	Score 0 or 1		
Story B	Story Unit	Thematic Unit	Scoring criteria 72
A recent			A word or phrase meaning recently
Survey			"Survey(s)" is required
of supermarket shoppers			"Supermarket" is required together with an indication that those involved were shoppers
revealed that			A word or phrase meaning "revealed that"
eight out of ten			"Eight out of ten" is required
Trolleys			"Trolleys" or a synonym is required
have faulty wheels			"Wheels" is required plus any word or phrase meaning "faulty"
or are difficult to steer			"Steer" or some form of the word is required
More than half			A phrase or word signifying "more that half" is required
of the people surveyed			An expression meaning "the people **surveyed**"
Reported			A word or phrase meaning "reported"
having had accidents			"Accidents" (in any context)
with their shopping carts			An indication that the trolleys were involved in the accidents
These ranged from			Word or phrase indicating a range
collisions			"Collisions" (in any context)
with other shoppers			A phrase signifying that other shoppers were involved
to knocking			"Knocking" or some synonym is required
into stacks			"Stacks" or a synonym is required
of groceries			"Groceries" or a synonym is required
on display.			"Display" (in any context)
Retailers			"Retailers" is required

claim			"Claim" or a synonym is required
that the problem is not with the trolleys			"Problem" is required plus an indication that the trolleys are not the cause of the difficulties
but that shoppers			"Shoppers" or a synonym is required
are not using them carefully			"Care" or some form of the word is required

LM 2

	Score 0 or 1		
Story A	Story Unit	Thematic Unit	Scoring criteria 72
Anna			Anna or variant of the name
Thompson			Thompson is required
of South			South (in any context)
London			London in any context
Employed			Indication that she held a job
As a cook			Cook or some form of the word is required
In a school			"School" is required
Canteen,			"canteen" is required
Reported			Indication that a formal statement was made to someone in authority (in any context)
At the police			"police" in any context
Station			"station" (in any context)
That she had been held up			An indication that she had been held up
On the High Street			"the High street" in any context
The night before			indication that it took place the previous night
And robbed			Indication that a robbery took place.
Of fifty six pounds			An indication that an amount of money greater than 49 pounds but less than 60 pounds was taken from her.
She had four			Four is required together with an indication that the children were hers
Small children			"Children" or a synonym is required
The rent was due,			A phrase indicating that the rent was due

And they had not eaten			An indication that they were without food
For 2 days			"2 days" is required
The police,			A word or phrase signifying more than one member of the police
Touched by the woman's story			Indication that her story evoked sympathy
Made up a collection			A phrase indicating that money was collected
For her			A phrase indicating that the money that was collected was for her or her children.

	Score 0 or 1		
Story B	Story Unit	Thematic Unit	Scoring criteria
At 6:00			6:00 is required
On Monday			"Monday" is required
evening			Evening (in any context)
Joe			Joe or variant of the name
Grant			"Grant" is required
Of Liverpool			"Liverpool" is required
Was watching television			Indication that he was watching/listening to television
As he dressed			Indication that he was getting dressed
To go out			Indication that he was going out
A weather report			Indication that there was an announcement about weather
Interrupted the programme			Indication that there was a break in regular scheduling
To warn that thunderstorms			Indication that there was a warning about a storm
Would move into the area			Indication that a storm was coming
Within the next 2 to 3 hours			A phrase meaning about 2 to 3 hours
And remain until morning			Indication that it would stay until morning
The announcer said			Indication that someone was reporting about a storm
The storm could bring hail			Indication that hail is possible
And up to 4 inches			“4 inches” is required
And cause the temperature to drop			"rain" is required

By 15 degrees			"a decrease by 15 degrees" is required
Joe decided to stay home			Indication that he decided to stay home
He took off his coat			Indication that he took off outer clothing
And sat down			Indication that he was sitting down
To watch old films			Indication that he was viewing a film

Appendix G:

Pittsburgh Sleep Diary

Fill out this part first thing in the morning

Time: Date:

Went to bed last night at:	
Lights out at:	
Minutes till you fell asleep:	
Finally awoke at:	
Awakened by (circle one):	Alarm clock Asked someone to wake me Noises Just woke
Number times you woke up during the night (circle one)	0 1 2 3 4 5 6 7 8 9 10
Total number of minutes awake:	0 1 2 3 4 5 or more
Woke to use bathroom (circle # times)	0 1 2 3 4 5 or more
Awakened by noises/children/bedpartner (circle # times)	0 1 2 3 4 5 or more
Awakened due to pain or discomfort (circle # times)	0 1 2 3 4 5 or more
Just woke (circle # times)	0 1 2 3 4 5 or more

Sleep Quality	0 (very bad) 1 2 3 4 5 6 7 8 9 10 (very good)
Mood upon awakening	0 (very tense) 1 2 3 4 5 6 7 8 9 10 (very calm)
Alertness upon awakening	0 (very sleepy) 1 2 3 4 5 6 7 8 9 10 (very alert)

Fill out this part last thing at night

When did you have these meals…	Breakfast		
	Lunch		
	Dinner		
How many caffeinated drinks did you have today?			
How many cigarettes?			
How many alcoholic drinks?			
Which medications did you take today?	Name	Dose	Time Taken
What exercise did you do today? If nothing tick here:	Start time	End time	Type of exercise
How many daytime naps did you take and when? If none tick here:	Start time	End time	
Did you take the fitbit off today at all?	Time off	Time back on	

Appendix H:

Consent Form

DEPARTMENT OF PSYCHOLOGY

UNIVERSITY OF CAPE TOWN

Study Title: Associations between Sleep Quality and Cognitive Function in Patients with a Non-Functioning Pituitary Adenoma

Purpose

You are invited to participate in a study that will measure sleep and memory functioning in patients with a non-functioning pituitary adenoma and in healthy adults.

Researcher

Principal Investigator: *Professor Kevin G. F. Thomas*

Student Investigator: *Musaddiqah Brown*

Email: *Brwmus001@myuct.ac.za*

Contact Number: *021 6964116*

I am a Psychology Master's student at the University of Cape Town. The information obtained from this study will be used for my Master's thesis project.

Study Procedures

How long will you be required to participate in the study?

- The study will take place over a period of 1 week. During this week, you will be required to wear a *fitbit monitor* (a lightweight device that is strapped onto the waist so that it can record your physical movements) and to fill out a *sleep diary* each day. You will also be required to complete two morning sessions and two evening sessions of memory testing.

What will be done if you decide to participate in the study?

- The study will be arranged at your convenience and well in advance.

- You will be placed into one of two groups (Sleep-Wake or Wake-Sleep) before the research process begins.
- You are encouraged to maintain your usual sleep and wake-up routine.
- One week ahead of the study, you will be required to keep a sleep diary, which will be emailed to you or sent to you via WhatsApp.
- On Day 1 of the study, the researcher will arrive at your house either at 7am (Sleep-Wake group) or 7pm (Wake-Sleep group). After you have signed the consent forms the study will begin with the administration of a cognitive test and a questionnaire that will require you to answer questions about your mood and mental health.
- You will then complete a series of memory and attention tasks. These will take approximately 1 hour.
- Thereafter, the researcher will provide you with a fitbit monitor and a sleep diary, as well explain to you how you are supposed to use each of the tools. You will record information in the sleep diary and wear the fitbit on your waist for the following week.
- The researcher will leave and then return 12 hours later. If you are in the Sleep-Wake group, that means the researcher will return the same evening. If you are in the Wake-Sleep group, that means the researcher will return the next day. You will then be required to complete more memory and attention tasks. These will take approximately 1 hour.
- After a week has passed (during which you will have monitored your sleep via the fitbit on your waist and by filling in the sleep diary), the researcher will arrive at your house at either 7am (if you are in the Wake-Sleep group) or at 7pm (if you are in the Sleep-Wake group). You will then complete a series of memory and attention tasks. The researcher will leave and return 12 hours later, on either the same day (Wake-Sleep group) or on the next day (Sleep-Wake group). You will then be required to perform the final memory and attention tasks, after which you will remove the fitbit and return it, along with your sleep diary, to the researcher.
- You will then have reached the end of the study. The researcher will then provide detailed information about the design of the study and the research questions we are

seeking to address. You will also be given the opportunity to ask questions and to have them be answered as completely as possible

Participation in this study is voluntary and you may withdraw at any stage without any penalties.

Privacy and Confidentiality

- All the data obtained in this study will form part of a Psychology Master's research thesis.
- No names will be mentioned in the write up of the study. To ensure anonymity, we will assign each participant a unique identifying number.

Risks

Participation in this study does not pose any foreseeable physical or psychological risks. If the results of your psychiatric interview or intelligence test suggest that there may be some form of mental or behavioural disorder, you will be encouraged to contact your doctor at the Pituitary Clinic, who will refer you to a psychologist or psychiatrist close to your residence.

The fitbit is a small lightweight monitor. It should not cause any discomfort if worn for a 1-week period. If you experience discomfort at any point, you may contact the researcher to discuss removing it.

Benefits

You will receive no direct benefits for participating in this study. But, you will be advancing knowledge on sleep and cognition in pituitary disorders which may help future treatment initiatives.

Would you like to receive a summary of your results? Yes □ No □

Signatures

Researcher

The participant has been made aware of the nature and purpose of the study. They have been informed about the procedures, confidentiality agreement, risks and benefits.

Researcher's Signature ……. Date……

Participant

I have been informed about the nature of this study. I agree to participate and consent to have my answers be used for purpose of the research. I know that I am free to withdraw from this study at any given time should I feel the need to do so, and in doing so I will not encounter any penalties.

Participant's Signature ……. Date……

Appendix I:

Covid-19 Safety Protocol

In order to limit the spread of the coronavirus, and to ensure your safety, we have implemented the following safety protocols:

ALL PARTICIPANTS WILL RECEIVE A SAFETY PACK CONTAINING A MASK, SANITIZER AND, GLOVES.

7. **WEAR A MASK** – The researcher and participant will be required to wear a mask throughout the research process.
8. **HAND HYGEINE** – The researcher and participant will be required to sanitize upon arrival and as needed throughout the research process.
9. **AVOID CLOSE CONTACT** – The researcher and participant are to maintain a distance of 1.5 meters (about 2 arms' length from each other) at all times.
10. **COUGH ETIQUETTE-** Always cover your mouth and nose with a tissue when you cough or sneeze/ use the inside of your elbow to shield your face. Immediately discard the tissue, wash your hands with soap/ sanitize your hands after.
11. **GLOVES-** The gloves will be used when completing the memory task on the laptop. Before putting the gloves on, sanitize your hands. After the task has been completed, you may discard the gloves.
12. **RESCHEDULE IF YOU ARE FEELING UNWELL OR IF YOU HAVE BEEN IN CONTACT WITH PEOPLE WHO ARE POSITIVE-** you may reschedule at **ANYTIME**.

Should you experience symptoms suggestive of Covid-19, please do not hesitate to contact the researcher (021 696 4116 or email: brwmus001@myuct.ac.za). Other available helplines include; The National Coronavirus hotline (0800 029 999), The Provincial hotline (021 928 4102), or WhatsApp 'Hi' to (060 012 3456).

Thank you for complying with our safety protocol.

Appendix J:

Psychology Department Ethical Clearance

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 December 2020

Musaddiqah Brown
Department of Psychology
University of Cape Town
Rondebosch 7701

Dear Musaddiqah

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, "Associations between cognitive function and sleep quality in patients with a non-functioning pituitary adenoma. The reference number is PSY202-049.

I wish you all the best for your study.

Yours sincerely

Catherine Ward
Professor
Chair: Ethics Review Committee

Appendix K:

Faculty of Health Science Ethical Clearance

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

18 June 2021

HREC REF: 033/2021

Prof K Thomas
Department of Psychology
Upper Campus
Email: kevin.thomas@uct.ac.za
Student: Brwmus001@myuct.ac.za

Dear Prof Thomas

PROJECT TITLE: ASSOCIATIONS BETWEEN SLEEP QUALITY AND COGNITIVE FUNCTION IN PATIENTS WITH A NON-FUNCTIONING PITUITARY ADENOMA-MASTERS CANDIDATE-MISS MUSADDIQAH BROWN

Thank you for your response letter, the HREC apologise for the very delayed response.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 June 2022.

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)

The HREC acknowledge that the student: Miss Musaddiqah Brown will also be involved in this study.

Please quote the HREC REF 033/2021 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.

HREC/REF 033/2021sa

Appendix L:

Groote Schuur Hospital Ethical Clearance

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHResearch.Request@westerncape.gov.za

PROFESSOR IAN ROSS

E-mail: ian.ross@uct.ac.za/ kevin.thomas@uct.ac.za / mhmish@gmail.com

Dear Professor Ross

RESEARCH PROJECT: Associations between Sleep Quality and Cognitive Function in Patients with a Non-Functioning Pituitary Adenoma

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 June 2022.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab. consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) **Kindly submit a copy of the publication or report to this office on completion of the research.**
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.
o) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 20 July 2021

C.C. Mr. L. Naidoo, Prof. N. Ntusi, Dr. H. Aziz

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Observatory 7925
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www.westerncape.gov.za/health

Apendix M:

Study Debriefing Letter

Previous studies have found that (a) sleep is important for memory functioning and (b) patients with pituitary disease experience disrupted sleep and problems with memory processing. Despite the existence of a large body of research examining the harmful effects of poor sleep on memory processing, no published study has examined the relationship between sleep and memory function in patients with pituitary disease. The aim of this project is to describe sleep quality and memory functioning in a sample of patients with a non-functioning pituitary adenoma and healthy controls, and to investigate whether sleep benefits memory processing in patients as it does in controls.

How was this tested?

In this study, you were asked to keep a sleep diary and wear an actigraph monitor for 1 week, this kept track of your sleep patterns. You also completed a series of memory and attention tasks under 2 conditions. A *Sleep* condition, where learning of memory materials was separated by 12 hours of sleep, and a *Wake* condition where learning of memory materials was separated by 12 hours of being awake, which tested memory processing.

We expect to find that:

(1) Compared to matched healthy controls, patients with pituitary disease will have poorer sleep quality, and will perform more poorly on memory tests.

(2) Both patients and controls will have better memory performance when a period of sleep rather than wake separates learning from recall.

(3) A period of sleep will be significantly more beneficial for memory consolidation in healthy controls than in patients.

Why is this important to study?

It is hoped that this body of psychological research will serve to further understand patients with pituitary disease, particularly in resource-poor settings where access to full hormone supplementation, in particular growth hormone is not available. By confirming our hypotheses, the study will lay the ground work for future studies of pituitary disease patients with a view to developing interventions targeted at directly improving sleep patterns and thereby indirectly improving memory functioning.

What if I want to know more?

You will receive a summary of the findings when the research is completed, however if you have any concerns or questions regarding this research, please contact Musaddiqah Brown at 0798613947/ Brwmus001@myuct.ac.za