



Impaired quality and efficiency of sleep impairs cognitive functioning in Addison's disease



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ABSTRACT

Background: Standard replacement therapy for Addison's disease (AD) does not restore a normal circadian rhythm. Periods of sub- and supra- physiological cortisol levels experienced by patients with AD likely induce disrupted sleep. Given that healthy sleep plays an important role in memory consolidation, the novelty of the current study was to characterise, using objective measures, the relationship between sleep and memory in patients with AD, and to examine the hypothesis that poor sleep is a biological mechanism underlying memory impairment in those patients.

Methods: We used a within-subjects design. Ten patients with AD and 10 matched healthy controls completed standardised neuropsychological tests assessing declarative memory (Rey Auditory Verbal Learning Test) and procedural memory (Finger Tapping Task) before and after a period of actigraphy-measured sleep, and before and after a period of waking.

Results: Relative to healthy controls, patients with AD experienced disrupted sleep characterised by poorer sleep efficiency and more time spent awake. Patients also showed impaired verbal learning and memory relative to healthy controls ($p=0.007$). Furthermore, whereas healthy controls' declarative memory performance benefited from a period of sleep compared to waking ($p=0.032$), patients with AD derived no such benefit from sleep ($p=0.448$). Regarding the procedural memory task, analyses detected no significant between-group differences (all p 's < 0.065), and neither group showed significant sleep-enhanced performance.

Conclusions: We demonstrated, using actigraphy and standardized measures of memory performance, an association between sleep disturbances and cognitive deficits in patients with AD. These results suggest that, in patients with AD, the source of memory deficits is, at least to some extent, disrupted sleep patterns that interfere with optimal consolidation of previously-learned declarative information. Hence, treating the sleep disturbances that are frequently experienced by patients with AD may improve their cognitive functioning.

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1. Introduction

We aimed to quantify and describe sleep quality and memory functioning in a sample of patients with Addison's disease (AD) and healthy controls, and to explore whether, in both groups, a period of sleep benefits memory consolidation as much as a period of waking does. AD is a rare endocrine disorder, characterized by decreased production of glucocorticoids and mineralocorticoids, typically resulting from destruction of the adrenal cortex. Even

when using standard replacement-medication regimens (e.g., oral hydrocortisone and fludrocortisone), patients with AD experience cognitive impairments (e.g., poor memory) and behavioral irregularities (e.g., sleep disturbances) that impact negatively on their quality of life (Ten et al., 2001; Tytherleigh et al., 2004). Although there is a strong relationship between healthy sleep and optimal memory performance (Dudai et al., 2015), only one previous study explored the association between sleep quality and cognitive functioning in patients with AD (Henry et al., 2015). In that study, data from self-report questionnaires and latent variable modeling suggested that poor quality of life, depressed mood, and memory impairment may be mediated by sleep disruption in Addison's disease. Although that study was limited in that it used only self-report measures, and in that it focused on general cognition rather

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than on theoretically-specified cognitive domains (e.g., memory), it nonetheless provided impetus for the current investigation. The novelty of the current study is that it uses objective measures of both sleep and memory to characterize the relationship between the two, and to examine the suggestion that poor sleep is a biological mechanism underlying memory impairment in patients with AD.

Under normal physiological circumstances, the orderly night-time sequencing of, and transitions between, slow-wave sleep (SWS) and rapid eye movement (REM) sleep, provide optimal conditions for memory consolidation (Diekelmann and Born, 2010). This process of consolidation begins during SWS, when favorable physiological conditions (e.g., slow oscillations in neocortical networks, hypothalamic-pituitary-adrenal (HPA) axis suppression) allow the replay and reactivation of memory traces encoded during waking (Born et al., 2006). Then, during REM sleep, similarly favorable physiological conditions (e.g., suppression of norepinephrine, increased levels of acetylcholine and serotonin, ponto-geniculo-occipital and theta waves, potentiation of expression of Immunoglobulin E) allow these reactivated memory traces to be integrated with pre-existing knowledge networks, thereby facilitating long-term potentiation (Walker and Stickgold, 2010). Cortisol plays a key role in initiating and maintaining these different sleep stages, accounting for its influence on the success of memory consolidation during healthy sleep (Bennion et al., 2015).

Patients with AD, even when on replacement therapy, report disrupted sleep and experience altered sleep architecture (Gillin et al., 1974). For instance, Lovas et al. (2003) found that one-third of their sample of patients with AD reported weekly sleep disturbances, while just over 10% reported repeated awakenings and difficulty falling asleep. In a polysomnographic study, García-Borreguero et al. (2000) found that patients with AD who took a dose of hydrocortisone just before bedtime had fewer night-time awakenings and reduced REM latency, and spent more time in REM sleep, compared to patients whose medication had been withheld for 1.5 days.

These disrupted sleep patterns may arise because patients with AD, despite hydrocortisone replacement, do not exhibit normal diurnal cortisol variation. These patients have extremely low cortisol levels before their morning dose of hydrocortisone (with lower-than-normal levels between midnight and the early hours of the morning). After taking the medication, cortisol concentrations increase rapidly at first, but then decline quickly due to a short half-life of approximately 2 h (Harbeck et al., 2009). This pattern contrasts with that of healthy individuals, whose cortisol release is in a pulsatile, but circadian, rhythm (Young et al., 2004).

The relationship between cognition and circulating glucocorticoids typically follows an inverted U-shaped pattern. Specifically, a certain level of cortisol is needed to enhance cognitive functioning; decreases below or increases beyond the threshold of optimal functioning impair cognition (McEwen, 1997). Numerous studies have shown that, in healthy adults, elevated cortisol levels are associated with impaired memory performance (Smeets, 2011). In neurobiologically similar fashion, variable sub- and supra-physiological concentrations of cortisol could also play an important role in the impaired cognitive functioning that is often characteristic of patients with AD. Recent literature suggests that patients with AD experience particular difficulties on verbal learning and memory tests (e.g., Henry et al., 2014; Schultebrucks et al., 2015; Tiemensma et al., 2016). Due to this known association between altered cortisol and impaired performance on standardized memory tests, objective assessment of other factors (e.g., disrupted sleep) that might contribute to deficient memory performance in patients with AD is especially pertinent.

1.1. The current study

Patients with AD frequently experience sleep complaints and memory deficits. However, no published study has used objective measures to investigate disrupted sleep as a possible mechanism underlying the memory deficits observed in these patients. We thus aimed to quantify and describe sleep quality and memory functioning in a sample of patients with AD and healthy controls, and to explore whether sleep augments memory consolidation in patients as it does in controls. Based on literature suggesting that (a) cortisol plays a key role in maintaining the integrity of sleep architecture, (b) sleep plays an important role in cognitive functioning, and (c) hydrocortisone replacement medication used by patients with AD does not restore the natural circadian rhythm and has direct effects on sleep architecture, we hypothesised that:

- (1) Patients with AD may report and experience disrupted, poor-quality sleep compared to healthy controls;
- (2) Healthy controls' memory performance may be enhanced by sleep, whereas patients' performance will derive no such benefit.

2. Methods and materials

2.1. Study design

This was a repeated-measures quasi-experimental study, featuring two groups of participants: Patients with AD and healthy controls. Each participant experienced two experimental protocols: a *Sleep* condition, where a period of sleep separated learning and recall of memory material, and a *Wake* condition, where a period of wakefulness separated learning and recall. Presentation of the conditions was counterbalanced across participants. Administration of the two protocols was separated by 1 week, during which participants wore an actigraph and kept sleep diaries.

The independent variables were group, with two levels of variation (patients with AD versus healthy controls), and memory consolidation condition, with two levels of variation (*Sleep* versus *Wake*). The two broad classes of dependent variables were (a) objectively-measured memory performance, and (b) objectively-measured sleep quality.

2.2. Participants

Participants were 10 adult patients with AD and 10 community-dwelling adults who were free of any chronic illness. We matched the groups on age, education (within 1–3 years), as well as sex and race distribution (each group included 2 men and 8 women, and 8 white and 2 mixed-ancestry individuals). We recruited patients from the South African Addison's Disease database (SAAD; Ross et al., 2010). The diagnosis of AD was made on the basis of suggestive clinical presentation, low basal cortisol level and simultaneously elevated ACTH concentration, or, where indicated, a peak cortisol following 250 µg ACTH stimulation of less than 550 nmol/L associated with a basal raised plasma ACTH exceeding 10.1 pmol/L (Ross et al., 2010). We recruited healthy controls using posters placed on noticeboards around the university community and in the nearby offices of large corporations.

Exclusion criteria applied to all participants were (1) age (we excluded individuals younger than 18 and older than 55 years because there are age-related effects on sleep architecture); (2) the presence of severe depressive symptomatology (HPA-axis hypersecretion and disrupted sleep are frequently-encountered symptoms of depression; Palagini et al., 2013; Steiger, 2002); (3) measured IQ at 1 standard deviation below average (lower IQ

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