

Age Related Cortisol Circadian Changes & Cognition

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LIST OF ABBREVIATIONS

DHEA	Dehydroepiandrosterone
CAR	Cortisol Awakening Response
SCN	Suprachiasmatic Nucleus
HPA	Hypothalamic-Pituitary-Adrenal
CRF	Corticotrophin Releasing Factor
ACTH	Adrenocorticotropic Hormone
CRD	Circadian Rhythm Disorder
PTSD	Post-Traumatic Stress Disorder
aMCI	amnesic Mild Cognitive Impairment
PND	Peak-Nadir Difference
LC	Locus Coeruleus

SUMMARY

Cortisol, a corticosteroid, is a hormone recognized for its role in acute and chronic stress responses and has been linked to Alzheimer's disease risk and cognitive decline. The circadian rhythm of cortisol has been widely studied in young people and its daily fluctuations have been well-characterized across repeated studies. However, conclusions regarding cortisol's age-related circadian rhythm changes and their cognitive implications vary, and this may be due to participant pool or methodological differences across studies. In this study using archival data, participants ($M_{\text{age}} = 53.6$ years, $SD = 16.99$, range = 23-71, $N = 54$, 28 females) provided saliva samples seven times a day for 10 consecutive days. The relationship between the difference between the daily Peak and Nadir cortisol measure (PND) and Age suggested no age-related decline in PND. This study also investigated the relationship between PND and cognitive outcomes. Results indicated that PND was not a significant predictor of Overall Cognitive Performance, Processing Speed, or Episodic Memory, but was a significant predictor of Working Memory. Potential explanations for this outcome are proposed based on previous empirical findings and theoretical models.

INTRODUCTION

Aging is characterized by physiological changes in body systems, including the endocrine system, which lead to a decline of biological functions. The worldwide demographic shift towards an older population places aging research, particularly cognitive aging, at the forefront of quality-of-life enhancement and extension. The neuroendocrinological system provides insight into a prevailing cause of age-related decline in biological functions.

Neuroendocrinological Systems

The hypothalamus and pituitary gland of the brain interact with the ovaries, testes, adrenal glands, thyroid, liver, and mammary glands via different pathways that culminate in the synthesis of hormones which regulate growth, metabolism, reproduction, lactation, and stress. These hormones travel via the bloodstream to a target organ where they bind with specific receptors causing an end organ physiological effect. The endocrine system is largely responsible for maintaining homeostasis in the body and regulating organs (De Kloet, 1992).

Aging is a known risk-factor for the degradation of the endocrine systems. Sex steroid levels generally decline with age during menopause in women and ‘andropause’ in men (Lamberts et al., 1997). Likewise, there is a marked age-related decline in the secretion of the steroid hormone dehydroepiandrosterone (DHEA) by the adrenal gland (Zhao et al., 2003). In contrast, cortisol, another adrenal gland steroid, shows no decline in older adulthood and, in fact, may increase with age (Moffat et al., 2020; Nater et al., 2013). Endocrine aging has also been causally linked to other age-related changes including reproductive senescence and bone weakening (i.e. osteoporosis) (De Kloet, 1992). As a well-known target of numerous hormones with receptors for adrenal and sex

steroids, thyroid hormones, and others, the brain has been the subject of a substantial body of research investigating how age-related changes in the hormonal milieu may affect age-related brain processes. In fact, considerable research has linked these age-related changes *in average hormone levels* to age-related changes in brain function, particularly changes in cognitive performance and dementia risk (Saelzler et al., 2021). Many of these hormones display patterns of daily fluctuations in synthesis and/or secretion known as the hormonal circadian rhythm. Recent research suggests that hormone level, as well as the pattern of hormonal circadian rhythm, may also be age sensitive with negative effects on brain health (Wilcox et al., 2014).

Circadian Rhythms

Many of the body's daily physiological processes occur on a 24-hour cycle. This 24-hour long oscillation period known as the circadian rhythm can be observed in sleep/wake cycles, daily variations in blood pressure, and the rising and falling core body temperature throughout the day. Animals, plants, and bacteria have been found to demonstrate 24-hour cyclical bodily and behavioral processes, and circadian rhythms are even observable within individual cells of the body (Johnson et al., 2008). When these rhythms are specifically informed by *zeitgebers* (from the German for "time givers"), they are known as diurnal rhythms. External cues, such as light and dark retinal inputs, are used to approximate the time of day. Other cues, though less robust than the light/dark cycle, can include social events, exercise, and food intake (Lewis et al., 2018, 2020).

Cortisol

Cortisol is a corticosteroid found in the human body and is commonly referred to as the "stress hormone." It is also involved in the metabolism of proteins, carbohydrates, and fats and has anti-inflammatory effects (Thau et al., 2023). In healthy individuals, cortisol secretion follows a prominent diurnal rhythm which peaks in the morning, about 30 minutes after waking, and

gradually decreases throughout the day until a trough (i.e., its nadir) at night. Importantly, cortisol secretion occurs in bursts, known as pulsatile release; therefore, cortisol's true diurnal rhythm is never a smooth oscillation, rather it has spurts of sudden secretion that together mimic an oscillatory shape (Lightman et al., 2020). The morning peak is a robust characteristic of the cortisol diurnal rhythm known as the Cortisol Awakening Response (CAR). Specifically, free cortisol levels measured in saliva increase by 50-75% in the first 30 minutes of waking (Pruessner et al., 1997). Although the precise function of the CAR is unknown, several hypotheses exist to explain it. These hypotheses generally reason that the CAR is a result of anticipation of daily demands (Adam et al., 2017; Fries et al., 2009). A second cortisol dynamic of note is the decrease following the CAR, referred to as the diurnal decline by Edwards and colleagues (2001). This characteristic of the cortisol diurnal profile is similarly robust; after the awakening peak and until nighttime, cortisol steadily decreases in the saliva and bloodstream to below the amount at waking before once again rising upon waking (Pruessner et al., 1997). Less is known about the purpose of the diurnal decline or how this feature interacts with peripheral organs.

Biological Mechanisms of the Cortisol Diurnal Rhythm

Suprachiasmatic Nucleus

Zeitgebers are processed at the Suprachiasmatic Nucleus (SCN) of the anterior hypothalamus. The SCN is often referred to as the “master pacemaker” due to its role in regulating biological diurnal rhythms that maintain the homeostasis of the body. The SCN receives *zeitgeber signals*, for example, light via the retino-hypothalamic tract and sends output to other brain areas and ultimately to the peripheral organ systems to inform time of day which can regulate various time-dependent physiological and behavioral systems (Moore & Lenn, 1972; Ralph et al., 1990). Thus, the SCN regulates endocrine systems and hormonal output throughout the day with a diurnal

rhythm. Cortisol, and other hormones such as growth hormone, melatonin, and vasopressin, follow a distinct diurnal rhythm due to the regulatory influence of the SCN (Gnocchi & Bruscalupi, 2017).

The literature generally agrees that aging does not directly impair the SCN, rather that aging impacts peripheral cells' receptivity to signals from the SCN (Yamazaki et al., 2002). Regardless, diurnal rhythms in older adults are typically less stable than in young adults. Older adults are more prone to interrupted and poorer quality sleep, more daytime napping, and more daytime drowsiness (Carskadon et al., 1982; Huang et al., 2002). Numerous age-related neurological diseases are associated with disordered circadian rhythms, for example, insomnia. Poor sleep is strongly correlated with hippocampal atrophy which raises the question of whether age-related hippocampal atrophy mediates the relationship between age and poor sleep and whether the SCN may be implicated in this relationship (Yang et al., 2022).

Hypothalamic-Pituitary-Adrenal Axis

The Hypothalamus and Pituitary Gland work together with the adrenal glands in a system referred to as the Hypothalamic-Pituitary-Adrenal (HPA) axis. The HPA axis works to synthesize cortisol and control its levels throughout the body (W. L. Miller, 2018). Before cortisol can be released into the bloodstream, the paraventricular nucleus of the hypothalamus synthesizes and releases the peptide Corticotrophin Releasing Factor (CRF) along the pituitary portal to the pituitary gland. In response, the anterior pituitary gland releases the peptide Adrenocorticotrophic Hormone (ACTH) into the bloodstream reaching the adrenal glands where cortisol is synthesized in the *zona fasciculata* of the adrenal cortex. Cortisol is released into the blood stream where its rising level is detected by glucocorticoid receptors on the hypothalamus which then inhibits further release of CRF and ACTH from the hypothalamus and pituitary gland, respectively (Spencer & Deak, 2017). Furthermore, the hippocampus plays an inhibitory role in the diurnal production of

cortisol and the HPA axis' response to acute stress (Jankord & Herman, 2008). This occurs when cortisol binds with glucocorticoid receptors in the hippocampus (De Kloet, 1992). Other brain structures with glucocorticoid receptors include the amygdala, prefrontal cortex, locus coeruleus, and the anterior cingulate cortex (Ebner et al., 2014).

The hypothalamus plays a major role in the regulation of endocrinological systems, including appetite and metabolism, the stress response, reproduction, and non-endocrinological functions including thermoregulation and the cardiovascular system (Frolkis et al., 1972; Shahid et al., 2023). It is a region within the forebrain, situated anterior to the optic chiasm, superior of the midbrain, and inferior of the thalamus (Daniel, 1976; Dudás, 2021). Broadly, the hypothalamus receives input stimuli from sensory and autonomic systems and responds by adjusting the output of highly specialized neurotransmitters and neuropeptides into the blood stream or to other brain regions. These neurosecretory output signals subsequently communicate with the rest of the body via the central nervous system, the pituitary gland, or the bloodstream to produce essential behavioral and physiological responses (Shahid et al., 2023).

The production of many hormones is regulated by the hypothalamus, in tandem with the pituitary gland, which has been coined the “master gland” (Lin et al., 2015). The pituitary gland is positioned inferior to the hypothalamus; there it receives input stimuli from the hypothalamus via the pituitary portal system to either stimulate or inhibit the release of hormones into the bloodstream for downstream travel to their target site (Lin et al., 2015; Spencer & Deak, 2017). Accumulating evidence shows that the pituitary gland also has an endogenous circadian clock that may be implicated in the timeliness of hormonal production and secretion into circulation (Guillaumond et al., 2012; Hughes et al., 2007). Together, the hypothalamus and pituitary gland

regulate the production of hormones which elicit physiological and behavioral functions necessary for survival (Shahid et al., 2023).

Adrenal glands are situated just superior to the kidneys and are composed of two tissue types: the outer cortex and the inner medulla. Together, these tissues have three layers, an outer layer known as the *zona glomerulosa*, the middle layer, known as the *zona fasciculata*, and the inner layer, the *zona reticularis*. These three layers are each responsible for the synthesis of different types of hormones and within the *zona fasciculata* of the adrenal cortex is where cortisol is synthesized (Megha et al., 2023). Because of cortisol's fat-soluble properties, it must bind to a corticosteroid-binding globulin to travel through the bloodstream. Without the corticosteroid-binding globulin, cortisol can easily pass through the phospholipid bilayers of cell membranes at which point, cortisol can bind with glucocorticoid receptors in a cell (Thau et al., 2023).

Although not formally a member of the HPA axis, the hippocampus plays a vital role in the regulation of cortisol production. The hippocampus is located in the medial temporal lobe, and operates within the limbic system (Carlesimo, 2022; ten Donkelaar et al., 2020). It is understood in rodents and non-human primates that the hippocampus has defined projections to the hypothalamus via the fornix system and the same is believed to be true in humans (Dudás, 2021; Swanson & Cowan, 1975). The hippocampus works in tandem with the hypothalamus as an inhibitor to the HPA axis. Specifically, the hippocampus acts in a negative feedback loop on the HPA axis. Due to abundant glucocorticoid receptors within the hippocampus, it detects cortisol levels in the blood stream which then allows the hippocampus to signal to the HPA axis to reduce ACTH release (Herman & Cullinan, 1997; Jacobson & Sapolsky, 1991; Sapolsky et al., 1986). Though the inhibitory relationship between the hippocampus and the HPA axis has been studied extensively, its precise nature is still not well understood (Herman et al., 2005). Other than being

an intermediary of HPA axis activity, the hippocampus is a brain system largely responsible for learning as well as the encoding and retrieval of memory and navigation (Goto, 2022; Thomas, 2015). Studies have found that hypothalamic neurons communicate new or updated memories and learning to the hippocampus by reinforcing synaptic strength (Burdakov & Peleg-Raibstein, 2020). The exact neural network of the hippocampus and its downstream relationship with other memory centers is still debated; regardless, the hippocampus is well known to be highly implicated in the regulation, formation, retrieval and update of memories and knowledge (Carlesimo, 2022).

Aging Effects on the Hypothalamic-Pituitary-Adrenal Axis

For decades, researchers have observed neuroendocrinological changes across the lifespan and speculated widely about the causes, effects, related processes, and explanations (Davies, 1993; Guidi et al., 2021; Hayflick, 1985; Meites, 1988). Older adults are prone to changes in energy consumption, increases in abdominal fat storage, and decreases in lean muscle mass (Barzilai et al., 2012). These changes have been linked to impairments in hypothalamic receptors for leptin, a hormone implicated in appetite, satiety, and metabolism and thus is a vital regulator of food consumption and energy use (Campfield et al., 1995; Pelleymounter et al., 1995; Scarpace et al., 2001). Regarding energy expenditure, aging is correlated with a steady decline in core body temperature. Body temperature is fueled by available energy resources and regulated by thermoregulatory neurons of the hypothalamus. Temperature regulation is thus believed to be a secondary side effect of reduced hypothalamic function (Rothhaas & Chung, 2021; Yu et al., 2018). Older adults notoriously have decreased basal body temperatures and variability within the circadian fluctuation is diminished (Geneva et al., 2019; Vitiello et al., 1986). These findings suggest age-related changes in normal hypothalamic function and their far-reaching effects illustrate the interconnectedness of these neural and peripheral systems.

The hippocampus endures remarkable pathological effects of aging as it is susceptible to atrophy and dysfunction in older age (Braak & Braak, 1995; Jack et al., 2000). The subgranular zone of the hippocampal dentate gyrus is one of only two brain regions known to perform neurogenesis in adulthood, making it a vital region for continued memory and learning (Ming & Song, 2011). However, the hippocampus presents impaired performance and volume reduction in light of chronic stress, as seen in depressed patients (Malykhin & Coupland, 2015; McKinnon et al., 2009), and similarly, due to a lifetime of daily stress, that is, allostatic load (Ming & Song, 2011). Specifically, age interacts with the hippocampus via a reduction of long-term potentiation and neurogenesis which also are linked to hippocampal atrophy (Lister & Barnes, 2009; Olariu et al., 2007). In normal aging, these biological changes impair behavior and cognitive performance (Lister & Barnes, 2009).

Several studies have linked hippocampal function with navigation ability in older adults and expansive research on the topic has promoted the inclusion of navigational ability in the clinical diagnosis of Alzheimer's Disease (Gallagher et al., 1993; Moffat, 2009; Techentin et al., 2014). Secondly, the hippocampus' role in episodic memory, and specifically recollection, has sparked interest as an indicator of cognitive performance (Squire et al., 2007). Interestingly, Wolk and colleagues found that hippocampal volume mediated the relationship between age and recollection (2011). A third cognitive ability performed by the hippocampus is pattern discrimination – the ability to distinguish differences in highly similar patterns of neural activation, e.g., differentiating between two similar but not identical images (Kirwan & Stark, 2007; Marr, 1971). This ability is noticeably impaired in healthy older adults compared to their healthy younger counterparts (Holden et al., 2012).

Circadian Rhythm Disorder (CRD) can occur as a comorbidity of other psychological disorders or merely as a side-effect of normal, healthy aging. CRD is characterized as the loss of synchronicity in one's circadian rhythms, typically identified by irregular sleep patterns and daytime drowsiness. In rodent models, CRD has been linked to impaired memory function as it is believed to cause poor blood flow to the hippocampus which might lead to neuronal death (Wang et al., 2020). The disorder is also believed to simultaneously lead to inflammation which damages the hippocampus and may lead to hippocampal atrophy (Wang et al., 2020). Alzheimer's Disease, a well-known, age-related disease, is widely believed to be caused by an agglomeration of amyloid beta proteins, and in a study by Adler and colleagues, the discovery of these amyloid beta proteins was highly correlated with irregular circadian rhythms. The study argued that because healthy circadian rhythms enforce a stable metabolism, those with circadian disruptions lack enough energy to perform memory consolidation and long-term potentiation; thus, circadian rhythm disruptions may be a pre-cursor to or an indicator of Alzheimer's Disease (Adler et al., 2019). Others have discovered links between circadian rhythm disruptions and neurodegenerative disorders such as Parkinson's Disease, multiple systems atrophy, and progressive supranuclear palsy (Ferini-Strambi & Marelli, 2012; Gros & Videnovic, 2020; Stamelou et al., 2019; Swaab et al., 2021). The accumulation of these findings indicate that irregular circadian rhythms may precede memory function deficits and severe neurodegeneration. These findings also suggest that dynamic deviations from a typical circadian rhythm may provoke cognitive decline, separate from the belief that abnormal yet static deviations of healthy metabolic levels can provoke cognitive decline. For the specific purposes of this discussion, it is suggested that dynamic deviations from the regular cortisol diurnal rhythm, rather than just a change to mean/total levels of cortisol, may be associated with impaired cognition.

Age induced atrophy and degeneration of the hippocampus also seems linked to a reduced inhibitory effect on the HPA axis (De Kloet, 1992). This can be observed in increases to basal activity of the HPA (possibly characterized by heightened daily mean levels of cortisol or ACTH), the dampening of the HPA rhythm (characterized by flattened rhythms of cortisol secretion), and the HPA system's heightened stress response (De Kloet, 1992; Issa et al., 1990; Lorens et al., 1990). However, it is difficult to determine the directionality of this relationship given that prolonged cortisol exposure was found to contribute to hippocampal atrophy in primates (R. Sapolsky et al., 1990) and that there is a known reduction in the negative feedback loop of the hippocampus in older adults (Pavlov et al., 1986; R. M. Sapolsky et al., 1986).

It is necessary to deliberate beyond correlational results and search for the mechanistic bond that ties age-related cortisol dynamic changes with cognitive function. The hippocampus, as noted, seems a likely candidate as the mediator between the functionality of the HPA axis and cognitive performance. Several researchers have investigated the link the hippocampus plays in the relationship, but more work is necessary to understand whether there is an age-induced deterioration of the hippocampus which casts downstream effects on the HPA axis, cognitive performance, or both (G. E. Miller et al., 2007). It should also be recognized that there may be other brain regions within the limbic system that are implicated in the effect. The amygdala and anterior cingulate cortex, regions known to be saturated with glucocorticoid receptors like the hippocampus (Q. Wang et al., 2013), have shown volumetric changes related to cortisol output, but not the hippocampus (Ennis et al., 2019). In identifying cognitive metrics that vary with cortisol mean output as well as variable diurnal dynamics, we are able to further deduce the neurological mechanistic link.

Aging Cortisol Rhythms

Several age-related changes to cortisol synthesis are cited in the literature which include higher mean level outputs of cortisol in older adults than young adults (Deuschle et al., 1997; S.Lupien et al., 2005; Nater et al., 2013; Moffat et al., 2020), attenuated CAR rhythms in older adults (Ennis et al., 2016; Fries et al., 2009; Nater et al., 2013), and attenuation in the diurnal decline in older adults (Deuschle et al., 1997; P. D. Evans et al., 2011). While there is some disagreement in the literature regarding the certainty or degree to which mean cortisol levels and diurnal slope change across the lifespan, attenuation of the CAR is repeatedly seen with increased age in humans.

A disordered CAR has been associated with major depressive disorder and various cognitive impairments attributed to major depressive disorder (Dedovic et al., 2010). Other studies focusing on abnormal cortisol diurnal slopes have found associations with major depressive disorder (Doane et al., 2013), chronic fatigue (Bower et al., 2005; Kumari et al., 2009), and cardiovascular disease (Matthews et al., 2006). Some hypothesize that the flattening of the cortisol diurnal slope may occur as a function of the severity of one's depression (Hsiao et al., 2010) and it may likewise be supposed that the age-related flattening of the cortisol diurnal slope may occur as a function of allostatic load (Karlmanngla et al., 2022). Given that these findings suggest a link between HPA axis dysregulation and complications for other vital bodily systems, researchers have become interested in the relationship between age related changes to cortisol's diurnal rhythm, rather than just total or average daily cortisol output, and the possible related health effects, both physical and cognitive.

Circadian Factors and Cognition

In older adults, chronic and acute higher mean cortisol levels are found to correlate with poorer overall cognition compared to younger adults, specifically in the memory and attention cognitive domains (for review, see Lupien et al., 2005). Lupien and colleagues began exploring this phenomenon decades ago when they looked into varying trends in basal cortisol levels among older adults. Based on longitudinal data that had been collected by the team, participants were identified as either having (1) a positive daily slope and a basal cortisol level that increased over the year prior, (2) a positive daily slope but their basal cortisol levels stayed the same, or (3) a negative daily slope. The older adults who had a positive slope and increasing basal levels performed significantly worse on explicit memory tasks (i.e. a cued recall test) than the participants from the other two groups, but all three groups' results were similar on the implicit memory recall tasks (Lupien et al., 1994). These results are reminiscent of amnesic patients with hippocampal damage (Penfield & Milner, 1958; Scoville & Milner, 2000).

Mean cortisol level is a common measurement in the field, and it serves as the basis for many relevant discoveries. One team performed a longitudinal study evaluating healthy older adults and found that an increased mean cortisol level in the earlier years of the study predicted worsened performance on verbal recall in the latter years of the study (Li et al., 2006); this finding is consistent with other reports and upholds former findings that high basal cortisol is associated with worsened declarative memory in healthy older adults (Greendale et al., 2000; S. Lupien et al., 1994; Seeman et al., 1997). Similar results are also observable when manipulating acute cortisol levels via the use of intranasal dexamethasone (Newcomer et al., 1994; Wolkowitz et al., 1990). Further, risk of developing Alzheimer's disease increased for older adults who showed heightened basal cortisol levels (Ennis et al., 2017).

Another characteristic of the cortisol diurnal rhythm that has been heavily studied is the CAR and its relationship with cognitive performance (Buchanan et al., 2004; Ennis et al., 2016; P. Evans et al., 2012; Law et al., 2015, 2020; Wolf et al., 2005; Zhang et al., 2015). The consistent finding with these studies remains that healthy participants' CAR serves as a same-day index of cognitive ability, often specific to executive function. In an analysis performed by Ennis and colleagues, CAR measures taken 8-38 months prior to the cognitive evaluation predicted episodic memory in the older adult population (2016). Specifically, those with a more positive (i.e. healthier) CAR performed better on the episodic memory tests than those with a flatter or more negative CAR. In a study of six amnesic adult males, the CAR was not a significant feature of their otherwise normal cortisol diurnal rhythm (Wolf et al., 2005), and another study identified participants with damage to the hippocampus as lacking a CAR but retaining all other normal features of the cortisol diurnal rhythm (Buchanan et al., 2004). These findings suggest that the hippocampus is heavily implicated in the proper functioning of the CAR.

Finally, the diurnal decline is an interesting component of cortisol's daily rhythm with an apparent acceleration in research interest in the last decade. This dynamic has been evaluated in relation to several health factors including major depressive disorder, anxiety disorder, cancer, cardiovascular disease, obesity, immune health, and various other psychiatric and physical disorders, all pointing to the cortisol diurnal slope as an indicator of general health (Adam et al., 2017; Karlamangla et al., 2022). Aging is a known comorbidity of desynchronization of the cortisol diurnal rhythm and relatedly, the attenuation of cortisol's diurnal slope (P. D. Evans et al., 2011). Due to the observed far-reaching implications of a flattened cortisol slope, researchers have become interested in the mechanisms, drawing comparisons between age related cortisol attenuation and the effects of chronic stress and post-traumatic stress disorder (PTSD) on cortisol

rhythm (Kinney et al., 2023; Starr et al., 2019). Few studies have explored the relationship between cortisol daily slope and cognition, but thus far, the findings have reported that a greater variance between the maximum cortisol daily level and the minimum cortisol daily level is related to better overall cognitive performance and some specific cognitive domains (Beluche et al., 2010; Dijckmans et al., 2017; P. D. Evans et al., 2011).

Evans and colleagues explored the relationship between cortisol dynamics and cognitive performance in an older adult sample (2011). This group sampled salivary cortisol eight times per day for two days, totaling 16 cortisol measurements, and used nine cognitive tasks to inform several cognitive domains. The cognitive assessments were used to develop a principal component which was used as the overall cognitive performance outcome measure. The results showed an apparent correlation between poor overall cognitive performance and a less steep diurnal decline, a correlation that existed independent of age. This study also analyzed their cortisol metrics against the specific cognitive assessments and discovered a link between older age and cortisol diurnal decline and poorer performance on tests of declarative memory and executive functioning. Although Evans and colleagues found verbal fluency to be a non-significant loading in their overall cognitive performance principal components analysis, Beluche and colleagues identified a relationship between impaired verbal fluency in women with more shallow diurnal declines (2010). This longitudinal study recorded salivary cortisol samples three times a day for two consecutive days, totaling six measurements for time point one, and six measurements for time point two which was four years later. The longitudinal analysis found a relationship between flatter diurnal slope and worsened visuospatial performance and visual memory in men and worsened verbal fluency in women.

Another longitudinal study, performed by Karlamangla et al., evaluated key indicators of allostatic load, identifying compression of cortisol diurnal dynamic range as a likely indicator (2022). They evaluated this metric in the context of cognitive decline and all-cause mortality. Their study design sampled salivary cortisol four times per day for four consecutive days; they also measured change in executive function and episodic memory over the span of about 10 years. Attenuation of diurnal decline, as determined by the difference between the peak and nadir, was associated with decreased executive function performance over time. Although episodic memory was shown to decline with age, cortisol diurnal decline was not a predictor of this trend.

Dijkmans and colleagues (2017) utilized a mini-mental state examination and Trail Making Tests A and B to evaluate general cognitive performance in healthy older adults and older adults diagnosed with amnesic Mild Cognitive Impairment (aMCI). They compared general cognitive performance with cortisol dynamics and overall physical performance, which measured functional mobility, walking speed, lower body strength, and balance. They measured salivary cortisol at five timepoints for one day only. As expected, aMCI patients showed worse performance on cognitive and physical tasks than the healthy older adult participants. In turn, greater diurnal decline in cortisol from morning to night was associated with better performance on the cognitive assessments in both healthy and aMCI participants. Contrary to previous findings (Csernansky et al., 2006; Lara et al., 2013; Lind et al., 2007), the study reported insignificant differences in cortisol indices between the healthy and aMCI groups. This incongruency illustrates a fairly common problem encountered in this field of research, which is that some highly supported trends are not always upheld by other research. One likely cause is inconsistency in cortisol sampling methods.

Cortisol rhythm studies frequently suffer from under sampling due to either too few samples in a day (Beluche et al., 2010; Dijckmans et al., 2017; Karlamangla et al., 2022) or too few days of sampling (Beluche et al., 2010; Dijckmans et al., 2017; P. D. Evans et al., 2011b; Karlamangla et al., 2022). These shortcomings can severely detract from the power of the analysis and may skew results. Hellhammer and colleagues have suggested that cortisol samples be measured over a period of six days to ensure the individual's rhythm is clearly captured to minimize the possibility that within-individual inferences are based on atypical, random or unnatural fluctuations (2007). Few studies meet these strict criteria, and it may be for this reason that findings contradict each other.

This Study

Though previous studies have investigated correlations between cortisol's diurnal slope and cognitive ability, whether this is consistent with age-related diurnal slope changes is not well established. The extant literature has produced somewhat inconsistent results, possibly due to inadequate frequency and duration of cortisol sampling. Specifically, some studies have found that steeper cortisol diurnal decline predicts better overall cognitive performance in older adults (Beluche et al., 2010; P. Evans et al., 2012). Attenuated diurnal decline has also been associated with poor declarative memory and executive functioning (P. Evans et al., 2012; Karlamangla et al., 2022). This study investigates the use of cortisol's diurnal variability as a predictor of cognitive performance in younger and older adults. This study expands the cortisol sampling frequency and duration by measuring cortisol at seven time-points daily, for 10 consecutive days. To our knowledge, 70 cortisol measures per individual allows for the most comprehensive assessment of cortisol dynamics in the literature. Moreover, we measure episodic memory and expand the cognitive assessment to include working memory and processing speed, two domains which have

not been evaluated against cortisol diurnal rhythmicity, as far as we know. This study will attempt to replicate previous findings as well as apply the same analytical methods to two novel cognitive domains.

Specific Aims

Review of the scientific literature shows that there are age-related diurnal dynamic changes in cortisol and that there is some suggestion that this age-related diurnal rhythm change may modulate cognitive function in older age. Specific Aim 1 will investigate diurnal variability of cortisol across the adult lifespan. Specifically, we hypothesize (H1) that the difference between the peak and the nadir of cortisol's diurnal measurements will be greater for young adults than for older adults. Specific Aim 2 will investigate whether there is a relationship between cortisol diurnal attenuation and cognitive performance. Specifically, we hypothesize (H2.1) that the difference between the peak and nadir of the cortisol rhythm will be a significant predictor of overall cognitive performance. That is, participants who have a smaller difference between the peak and nadir cortisol rhythm measures will also score lower on the overall cognitive performance about two years later. We expect this relationship to exist independent of age. Specific Aim 2 will also investigate the relationship between the peak and nadir difference of cortisol and specific cognitive domains at about two years post saliva sampling. Specifically, we hypothesize (H2.2) that the difference between the peak and nadir of the cortisol rhythm will be significant predictors of the specific cognitive domains of working memory and processing speed. However, based on the previously cited literature (Karlamanla et al., 2022), we hypothesize that the difference between the peak and nadir of cortisol's rhythm will not be a significant predictor of episodic memory.

METHODOLOGY

Participants

Participants from the metro-Atlanta area were previously recruited for a study investigating everyday life stressors (Nater et al., 2013). Fifty-four participants ($M_{\text{age}} = 53.6$ years, $SD = 16.99$, range = 23-71, $N = 54$, 28 females) were recruited and provided saliva samples and received cognitive assessments. Participants were excluded if they had any of the following diagnoses: PTSD, bipolar disorder, psychosis, eating disorders, alcohol/substance abuse, Parkinson's Disease, Alzheimer's Disease, Thyroid Dysfunction, Cushing's or Addison's disease, hormone producing cancer, or a body mass index greater than 35. Participants were also excluded if they had a history of alcohol abuse, were pregnant at the time of the study, or indicated that their job involves shift work. Lastly, participants were excluded if they had recently (in the prior six months) experienced a major life event such as death of a family member or a major surgery.

Materials

The saliva samples from the archival data set were collected with the use of Starstedt Salivettes. Cortisol was assayed from the saliva using commercial chemiluminescence immunoassay (IBL, Hamburg, Germany). The collection process is outlined in greater detail in Nater et al. (2013). The study also measured the following cognitive domains: Episodic Memory, Working Memory, and Processing Speed. The Associative Memory Task (Paired Associates) was the assessment used to quantify episodic memory (Hines et al., 2009). Letter Comparison and Pattern Comparison comprised the processing speed assessments (Kane et al., 2004; Mackworth,

1959; Schmiedek et al., 2014). Finally, working memory was measured with the NBack and Reading Span (R Span) Task (Salthouse & Babcock, 1991).

Method

Participants collected saliva samples seven times a day for 10 consecutive days: immediately after waking, 30 minutes after waking, then at approximately 09:00, 12:00, 15:00, 18:00, and 21:00 (see Figure 1). Each saliva sample was assayed for cortisol levels. Participants returned between 8-38 months later to complete episodic memory, working memory, and processing speed assessments using the Yes–No Associative Recognition Task (Hines et al., 2009), N-back (Mackworth, 1959) and Reading Span (Kane et al., 2004), and Letter Comparison and Pattern Comparison (Salthouse & Babcock, 1991), respectively. This study utilizes this highly unique and well-suited archival data to answer the hypotheses; unusually, this study sampled 70 measurements per person, allowing the assessment of within-participant cyclicality over 10 consecutive days which optimizes the ability to study the phenomenon of circadian rhythms.

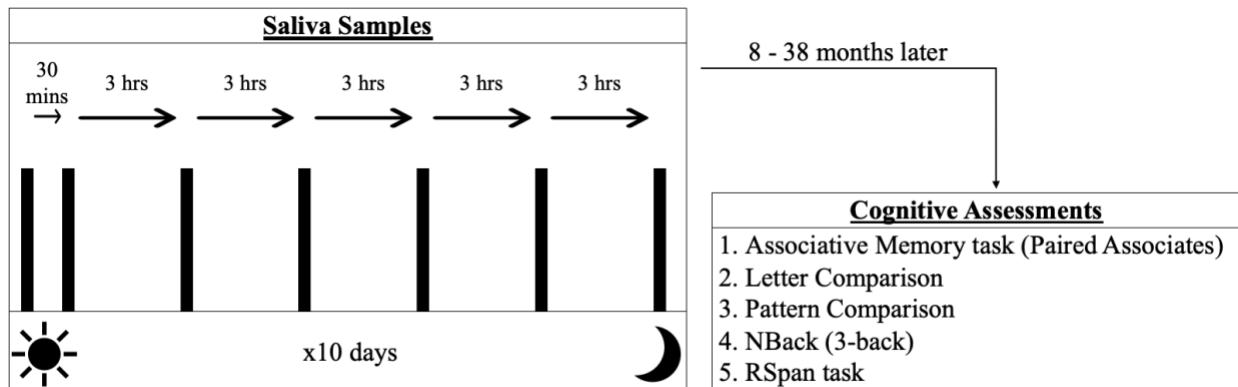


Figure 1: The study began with participants taking seven saliva samples per day for ten days. Eight to 38 months later, participants returned to complete a battery of cognitive assessments.

RESULTS

Pre-Processing

To address the hypotheses, I derived a diurnal rhythm change score from the cortisol biomarker in this dataset and named it the Peak-Nadir Difference (PND) score. The PND is calculated by subtracting the highest cortisol measurement in a given day by the respective lowest cortisol measurement and dividing by the mean of all seven data points in that day. The PND is calculated for each participant, for each day, and then averaged across all 10 days which provides an overall PND score for each participant. Hierarchical regression was used to analyze this score and its relationship with age, Overall Cognitive Performance, the three dimensions of cognitions, and relevant covariates. The process of determining inclusion of covariates will be described later. Figure 2 illustrates how each individual's data appears when plotted horizontally on a line graph. Figure 3 illustrates the PND that was collected from each day, for each participant; the averaged daily PND was used in the analyses.

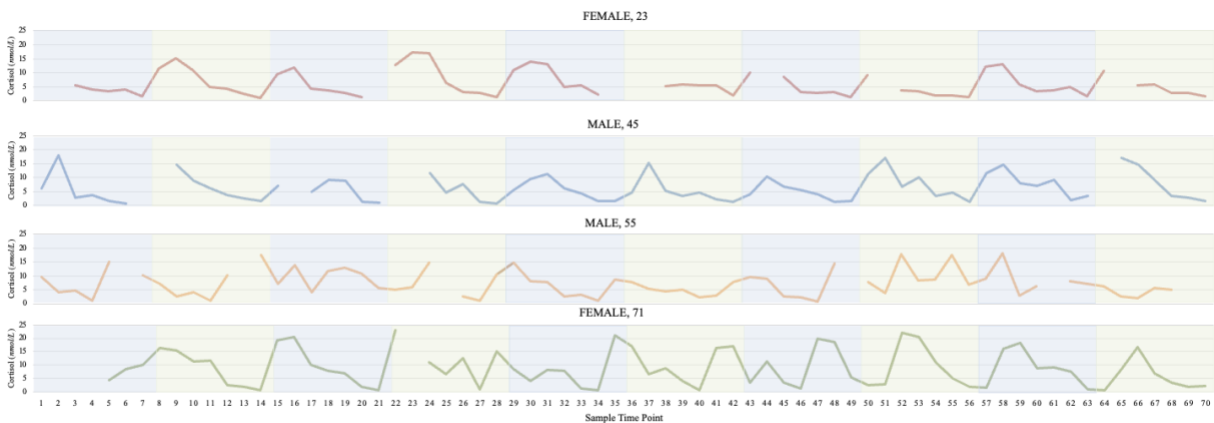


Figure 2: Pre-view of the cortisol data in this dataset. Each color block indicates one day, and the line indicates cortisol levels (nmol/L). Gaps in the line are indicative of missing data at that time point for that participant.

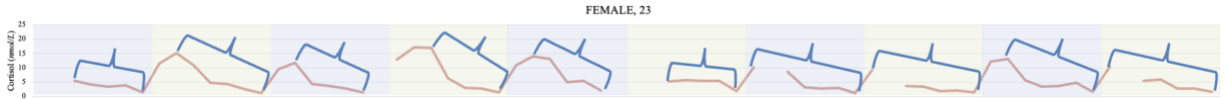
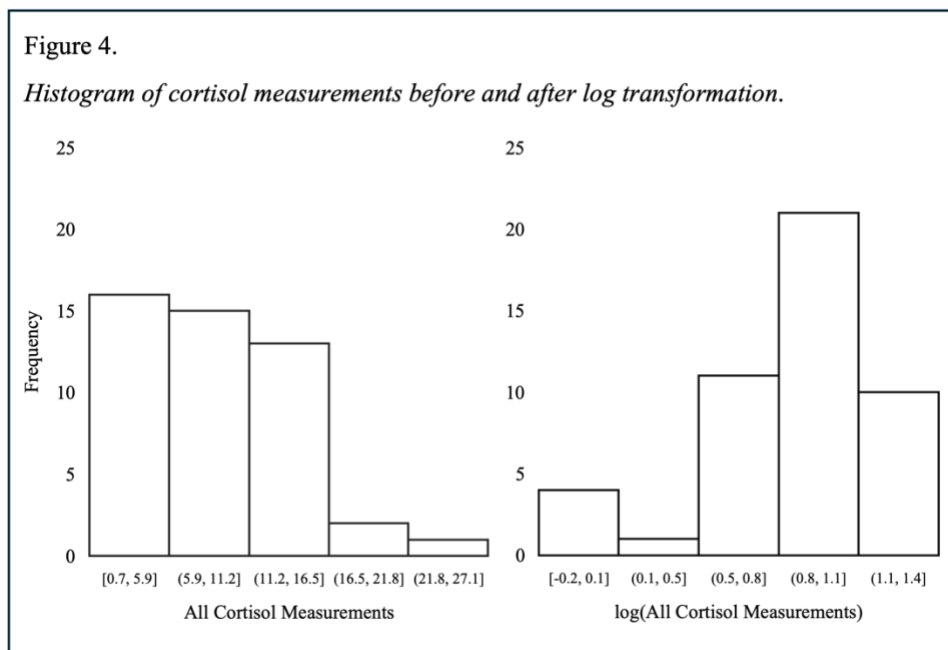


Figure 3: The leftmost end of the bracket indicates the Peak of the diurnal rhythm and the right most end of the bracket indicates the Nadir measurement of the diurnal rhythm. $(\text{Peak} - \text{Nadir}) \div \text{Daily Mean} = \text{Daily PND Score}$.

Prior to beginning the statistical analyses, all variables underwent pre-processing. The five cognitive assessments (i.e. Associate Memory Task, Letter & Pattern Comparison, NBack, and R Span Task) were used to compose the three cognitive domains. Scores on each test were standardized as z-scores to create composite variables. NBack and R Span z-scores were summed to produce a Working Memory measure; Letter and Pattern Comparison Tests were summed to produce the Processing Speed measure; and the Associative Recognition Task was standardized to produce Episodic Memory. All five standardized assessments were summed to produce the Overall Cognitive Performance score. Cortisol measures were log transformed (Nater et al., 2013) to normalize positive skew. Prior to log transformation, skewness = 1.42, and following transformation, skewness was reduced to -0.29, which is within the recommended range (See Figure 4).



PND was calculated by selecting the higher of either the first or second cortisol measurement and subtracting the lowest cortisol measurement to follow it and dividing this difference by the mean of all seven data points in that day. The same was repeated for all 10 days and averaged to produce the Mean PND for each participant. Lastly, the Mean PND was standardized to allow for between subject analysis.

Days in which participants were missing the first and second, or only the second, measurement were excluded as the calculation would not accurately capture the diurnal decline. Additionally, days in which participants had less than 4 samples were excluded from the analysis. Because the PND was averaged across days, a cut off of at least five days of viable cortisol data was set, and no participants fell below this cut off. Therefore, all 54 participants were included in the analysis.

We computed zero-order correlations between the selected outcome variables and potential covariates and next, evaluated the relationship between PND and age using linear regression and Likelihood Ratio Analyses. Following this, hierarchical regression was used to determine the predictive ability of PND for the following outcome variables: Overall Cognitive Performance, Working Memory, Processing Speed, and Episodic Memory. Covariates were entered into an initial model (Model 1) and PND was entered into a second model (Model 2) to predict the cognitive outcomes. Two-step models were utilized to predict the domain-specific outcome variables, which included Working Memory, Processing Speed, and Episodic Memory.

Participant Descriptions

Descriptive statistics of the study sample can be seen in Table 1. Participant demographics were collected during the first visit. Education was classified as a categorical item, with the options being 1) Less than 12 years, 2) GED, 3) High school diploma, 4) Technical/

Vocational/ Trade school diploma or certificate, 5) College Freshman, 6) College Sophomore, 7) College Junior, 8) Bachelor's degree, 9) Master's degree, or 10) J.D., M.D., or Ph.D.. Health was a self-report Likert scale item, in which 1 was “poor health” and 5 was “excellent health.” SES was determined based on yearly income; participants reported which range their yearly income fell into with the options being: 1) \$0 -\$29,999; 2) \$30,000 –\$44,999, 3) \$45,000 -\$59,999, 4) \$60,000 -\$89,999, or 5) \$90,000 +. Menstrual status was based on a multiple-choice question about the current state of participant’s menstrual period. Participants were categorized into three options: 1) Premenopausal, 2) Perimenopausal, or 3) Menopausal or Post-Menopausal. No participants reported being on hormone replacement therapy. The Perceived Stress Scale is a one-time measure of how stressful an individual appraises life events, and responses are recorded on a five-point likert scale (Cohen & Williamson 1988). Because the time between the initial lab visits (which initiated the saliva sampling) and the second lab visit (which administered the cognitive assessments) varied for each individual, this was calculated and included in analyses. Relatedly, the time at which the cognitive assessments were taken also varied between participants, as did average wake time. Therefore, these variables were also investigated as potential covariates. The average number of total cortisol measurements, out of 70 total possible measurements is reported in Table 1. Finally, mean cortisol level was also calculated and included as a potential covariate; it can be seen in Table 2.

Table 1*Descriptive statistics of study variables (N = 54).*

	<i>N (%)</i>	<i>M (SD)</i>	<i>Range</i>
1. Sex (female)	28 (51.9%)		
2. Age		53.64 (16.99)	(22.3, 80.9)
3. Race (white)	45 (83%)		
4. Education (completed bachelor's degree)	21 (39%)		
5. Health		3.91 (0.85)	(2, 5)
6. Socio Economic Status		2.90 (1.37)	(1, 5)
7. Menstrual status (menopausal; N = 28 Females)	14 (50%)		
8. Perceived Stress Scale		38.78 (4.68)	(30, 54)
9. Days between lab visits		958.59 (118.13)	(711, 1160)
10. Time of cognitive assessment		13:13 (2:25)	(09:05, 19:52)
11. Average wake time		06:56 (00:59)	(04:36, 08:51)
12. Average number of cortisol measures		61.24 (4.64)	(43, 67)
12. Episodic Memory		0.00 (1.0)	(-1.78, 1.92)
13. Working Memory		0.02 (1.72)	(-4.07, 3.63)
14. Processing Speed		-0.00 (1.85)	(-3.09, 5.68)
15. Overall Cognitive Performance		0.01 (3.61)	(-7.04, 11.12)
16. Peak-Nadir Difference		-1.62 (0.11)	(-1.88, -1.4)

Zero Order Correlation

The correlations between variables are reported in Table 2. Notable correlations include the positive correlation between Age and Days between lab visits in which older participants tended to have fewer days between visits. Older participants tended to have lower PSS and an earlier waking time. Those with fewer years of education tended to have lower SES. Participants who reported higher SES were more likely to score lower on the PSS and complete the cognitive assessments at an earlier time in the day. Covariates for the following models were determined if their correlation with the outcome variables (specified in later sections) had an alpha of less than 0.20 (Ennis et al., 2016).

Table 2

Zero-order correlation coefficients between age, covariates, cognitive outcomes, and Peak-Nadir Difference.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Sex															
2. Age	-.26.														
3. Education	.02	-.23.													
4. Health	-.06	-.05	.1												
5. Socio Economic Status	-.01	.13	.32*	.25.											
6. Menstrual Status (females only)	N/A	0.36*	-.41*	.07	.04										
7. Perceived Stress Score	.14	-.3*	-.13	-.23.	-.37**	-.04									
8. Days between lab visits	.27.	-.33*	.18	-.06	.14	-.35	.2.								
9. Time of cognitive assessment	-.04	-.19.	-.15	-.08	-.5**	0.08	.2.	-.23.							
10. Average Wake Time	.02	-.33*	-.05	-.04	-.44**	-.4	.24.	.13	.38**						
11. Overall Average Cortisol	-0.01	-.06	-.01	-.11	-.12	-.11	-.07	-.25.	.02	.11					
12. Episodic Memory	.15	-.32*	.27.	-.08	-.03	-.38	.16	.13	-.16	.14	-.03				
13. Working Memory	-.17	-.41**	.19.	.24.	-.1	-.31	-.01	.12	-.12	.15	.05	.38**			
14. Processing Speed	.17	-.69**	.18.	-.02	-.25.	-.41*	.19.	.16	.11	.38**	-.03	.49**	.55**		
15. Overall Cognitive Performance	.05	-.60**	.25.	.08	-.18	-.43*	.14	.16	-.04	.28*	0.0	.69**	.83**	.87**	
16. Peak-Nadir Difference	-.14	.28*	-.16	0.06	-.06	0.04	-.1	-.33*	.02	-.08	-.27*	.00	.14	-.12	-.01

. $p < .2$, * $p < .05$, ** $p < .01$.

H1: Peak-Nadir Difference

Because Days between lab visits and average overall cortisol were correlated with PND, they were included as covariates in the model using Age to predict PND. In this case, older participants were quicker to return for the second lab visit, while younger participants were slower to return. There is no indication that this was an intentional methodological choice. In this study sample, participants with lower overall average cortisol levels were likely to have a higher PND and vice versa. Two regression models were created to evaluate whether prediction ability improved with the inclusion of Age when PND is the outcome variable.

Table 3a

Summary of linear regression analysis where PND is the dependent variable.

	Peak-Nadir Difference			
	B	SE	<i>t</i>	<i>p</i>
<i>Model 1</i>				
Days between lab visits	-0.000	0.000	-3.554***	0.000
Average Overall Cortisol	-.38	.115	-3.311**	0.002
<i>Model 2</i>				
Days between lab visits	-0.000	0.000	-2.948**	0.005
Average Overall Cortisol	-.361	.116	-3.103**	.003
Age	0.001	0.001	0.998	0.323
<i>Model 1</i>				
R ²	0.241			
F(2, 51)	9.411***			
<i>p</i>	0.000			
<i>Model 2</i>				
Delta-R ²	0.00			
F(1, 50; change)	1.00			
<i>p</i>	0.323			

Table 3b

Summary of the Likelihood Ratio Test comparing Models 1 & 2 referenced in Table 3a.

	Peak-Nadir Difference		
	<i>df</i>	Log Likelihood	Chi-Square <i>p</i>

<i>Model 2</i>	5	52.330	1.065	.302
<i>Model 1</i>	4	51.797		

* $p < .05$, ** $p < .01$, *** $p < .001$.

The first model (Model 1) included days between lab visits and overall average cortisol; the second model (model 2) included days between lab visits, overall average cortisol, and age. PND was the outcome measure in both models. The second model did not account for any more variance of PND and did not predict the outcome variable, PND (Table 3a). The Likelihood Ratio Test further indicated that the second model is not an improvement of model fit (Table 3b). Therefore, model comparison showed that Age was not a significant predictor, and the Likelihood Ratio Test suggested that Age did not significantly improve model fit, thus, we conclude that Age was not a strong predictor of PND in the sample. The interaction between Age and overall average cortisol was evaluated and there are no significant results to report.

H2.1: Overall Cognitive Performance

Hierarchical regression analysis was utilized in predicting Overall Cognitive Performance with PND (Table 4). The covariates selected for the Overall Cognitive Performance hierarchical regression were Age, Sex, Education, and Average Wake Time. The first step (Model 1) included the above covariates and predicted the outcome measure, Overall Cognitive Performance (see Table 4). In the second step, PND was added as a predictor. This did not increase Adjusted R^2 , and model comparison approach revealed that the inclusion of PND did not significantly improve model fit. The interactions between Age and PND, Age and Sex, and Sex and PND were evaluated and there are no significant results to report

Table 4

Summary of hierarchical regression analyses where Overall Cognitive Performance is the

dependent variable.

	Overall Cognitive Performance			
	B	SE	<i>t</i>	<i>p</i>
<i>Model 1</i>				
Age	-0.122	0.278	-4.4***	<0.001
Sex	-0.760	0.849	-0.895	0.375
Education	0.301	0.279	1.08	0.286
Average Wake Time	0.000	0.000	0.779	0.44
<i>Model 2</i>				
Age	-0.134	0.003	-4.793***	<0.001
Sex	-0.713	0.832	-0.858	0.395
Education	0.346	0.274	1.264	0.213
Average Wake Time	0.000	0.000	0.766	0.447
PND	6.784	3.87	1.751	0.087
<i>Model 1</i>				
R ²	0.346			
F(4, 48)	7.904***			
<i>p</i>	< 0.001			
<i>Model 2</i>				
Delta-R ²	0.037			
F(1, 47; change)	2.96			
<i>p</i>	0.092			

* $p < .05$, ** $p < .01$, *** $p < .001$.

H2.2 Specific Cognitive Domains

Working Memory

Hierarchical regression analysis was also used to investigate the predictive ability of PND for Working Memory. The covariates selected for the Working Memory hierarchical regression were Age, Education, and Health. The first step (Model 1) included the covariates and predicted the outcome measure, Working Memory (see Table 5). This model accounted for a significant amount of variance $F(3, 43) = 4.441, p < 0.05$. In the second step, PND was added as a predictor in Model 2, and according to the model comparison between Model 1 and 2, increased the amount

of variance accounted for $F(1, 47) = 3.07, p < 0.05$. Furthermore, this analysis reiterates the positive correlation between PND and Working Memory, that is, the individuals with a greater difference between their peak and nadir cortisol measure tended to score higher on the Working Memory assessments recorded about eight to 38 months later. The interaction between Age and PND was evaluated and there are no significant results to report.

Table 5

Summary of hierarchical regression analyses where Working Memory is the dependent variable.

		Working Memory			
		<i>B</i>	SE	<i>T</i>	<i>p</i>
<i>Model 1</i>					
Age		-0.043	0.015	-2.896**	0.006
Education		0.075	0.155	0.481	0.633
Health	0.39	0.254	1.572	0.123	
<i>Model 2</i>					
Age		-0.05	0.015	-3.463**	0.001
Education		0.120	0.149	0.802	0.427
Health		0.377	0.244	1.544	0.130
PND		4.900	2.232	2.195*	0.034
<i>Model 1</i>					
R ²		0.183			
F(3, 43)		4.441**			
<i>p</i>		0.008			
<i>Model 2</i>					
Delta-R ²		0.07			
F(1, 42; change)		4.82*			
<i>p</i>		0.034			

* $p < .05$, ** $p < .01$, *** $p < .001$.

Processing Speed

To evaluate the predictive ability of PND on Processing Speed, a hierarchical design was

once again employed. The covariates used to predict Processing Speed were Age, Education, SES, PSS, and Average Wake Time as they all correlated with Processing Speed at an alpha of less than 0.2. Model 1 included these covariates and predicted the outcome measure, Processing Speed. This model accounted for a significant amount of variance $F(6, 43) = 8.336, p < 0.001$ (see Table 6). When PND was added into the second step (Model 2), the model comparison approach showed no improvement of model fit and indicated that PND is not a strong predictor of Processing Speed when recorded about eight to 38 months later, $F(1, 42) = 0.129, p > 0.05$. The interactions between Age and Sex, Age and PND, and Sex and PND were evaluated and there are no significant results to report.

Table 6

Summary of hierarchical regression analyses where Processing Speed is the dependent variable.

	Processing Speed			
	<i>B</i>	SE	<i>t</i>	<i>p</i>
<i>Model 1</i>				
Age	-0.072	0.014	-5.275***	<0.001
Sex	0.012	0.409	0.03	0.976
Education	0.093	0.142	0.654	0.517
SES	-0.239	0.177	-1.349	0.184
PSS	-0.031	0.046	0.679	0.501
Average Wake Time	0.000	0.000	1.3	0.2
<i>Model 2</i>				
Age	-0.073	0.014	-5.21***	<0.001
Sex	0.027	0.415	0.064	0.949
Education	0.097	0.144	0.672	0.505
SES	0.229	0.181	-1.267	0.212
PSS	-0.029	0.047	-0.612	0.544
Average Wake Time	0.000	0.000	1.273	0.210
PND	0.71	1.98	0.359	0.772
<i>Model 1</i>				
R ²	0.473			

F(6, 43) 8.336***
 p < 0.001

Model 2
 Delta-R² -0.012
 F(1, 42; change) 0.129
 p 0.722

* $p < .05$, ** $p < .01$, *** $p < .001$.

Episodic Memory

The last domain-specific regression also utilized a hierarchical approach to measure whether PND is a significant predictor of Episodic Memory. The covariates Age and Education were included in Model 1 to predict Episodic Memory. This model accounted for a significant amount of variance, $F(2, 48) = 4.092, p < 0.05$ (see Table 7). When PND was added into the second step (Model 2), the model comparison approach showed no improvement of model fit and indicated that PND is not a strong predictor of Episodic Memory when recorded about eight to 38 months later, $F(1, 47) = 1.058, p > 0.05$. The interaction between Age and PND was evaluated and there are no significant results to report.

Table 7

Summary of hierarchical regression analyses where Episodic Memory is the dependent variable.

	Episodic Memory			
	<i>B</i>	SE	<i>T</i>	<i>p</i>
<i>Model 1</i>				
Age	-0.016	0.009	-2.013*	0.049
Education	0.145	0.091	1.587	0.119
<i>Model 2</i>				
Age	-0.019	0.009	-2.243*	0.029
Education	0.157	0.092	01.702	0.095

PND	1.373	1.334	1.029	0.309
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Model 1

R ²	0.110
F(2, 48)	4.092*
<i>p</i>	0.023

Model 2

Delta-R ²	0.34
F(1, 47; change)	1.058
<i>p</i>	0.309

* $p < .05$, ** $p < .01$, *** $p < .001$.

In all regression models, scatter plots were visually inspected to rule out potential non-linear relationships. Although Menstrual Status was correlated with some cognitive measures, it was not included in the models as it was likely a duplicative effect of age. Furthermore, Menstrual Status was neither correlated with PND ($r = -0.05$) or total/average cortisol ($r = -0.11$), and this is consistent with previous literature (Woods et al, 2009).

DISCUSSION

This study was grounded in the literature linking cortisol dynamics with cognitive performance, especially in the context of aging. The design of this study was intended to probe cortisol diurnal decline and potential relationships with age and specific cognitive outcomes. Specifically, the study hypothesized that PND would decrease with age, similar to the known age-effects on the CAR, however this hypothesis was not supported. Additionally, the study investigated whether the PND may be a predictor of cognitive performance, both broadly and within specific domains. The findings indicated that while the PND was a predictor of Working Memory performance, it was not a predictor Overall Cognitive Performance, Processing Speed, or Episodic Memory.

H1: Peak-Nadir Difference

Previous studies cite an association between age and attenuated cortisol diurnal decline, a finding that was not replicated in this study (Karlmanjla et al 2020, Nater et al 2013, Evans et al 2011). Cortisol rhythm dysregulation is a frequently reported finding in both pathological diagnoses and age, and this empirical finding is what informed the hypotheses of this study. However, an important distinction to make when comparing results is the variation in acquiring the diurnal decline value. In this study, the PND was calculated as the difference between the morning peak measure and the subsequent nadir, divided by the mean of the respective day. However, other studies calculate this decline differently, whether as a linear slope (difference in the post CAR cortisol level and a specific cortisol measure recorded later in the day, divided by time between the two measurement points) (Nater et al., 2013, Ennis et al., 2016), or as a

quadratic slope (Ennis et al., 2016). The purpose of our PND calculation was to measure the greatest possible range of cortisol levels from waking to evening, rather than restricting the metric to a predetermined shape. This method is believed to capture to full breadth of cortisol dynamics in a given day. Post-hoc analyses also revealed that this sample did not have a strong correlation or linear relationship between daily linear slope and age, $r = .151$; $F(1, 52) = 1.369$, $p > .05$.

H2.1: Overall Cognitive Performance

Results from this study regarding overall cognition did not support previous findings (Beluche et al., 2010; P. Evans et al., 2012). When accounting for Age, Sex, Education, and Average Wake Time, PND was not a significant predictor of Overall Cognitive Performance at the eight to 38 month later checkup. It is noteworthy that there was no relationship between PND and Overall Cognitive performance, as well as no relationship between PND and Age. Thus, the likely link driving this relationship in previous reports is the relationship observed in this data, that is, Age and Overall Cognitive Performance ($r = 0.6$, $p < 0.01$). This may be added evidence against the previously cited PND and Overall Cognitive Performance relationship. Although Evans and colleagues (2011) found a correlation between diurnal decline and cognitive performance while holding age constant, the null finding in the current data was not due to the inclusion of several covariates as our sample showed a zero-order correlation between Overall Cognitive Performance and PND of $r = .00$. It is plausible that the delay in saliva sampling and cognitive assessments led to the weak correlation and absent predictive ability in this data set. These results suggest a need for a more rigorous evaluation of the relationship between cortisol diurnal decline and its associations with overall cognition.

H2.2: Processing Speed and Episodic Memory

An important element of this study was to identify the association between PND and specific cognitive domains, namely, Processing Speed, Episodic Memory, and Working Memory. Our hypothesis that Processing Speed would be predicted by PND was not supported, but the hypothesis that PND would not be a predictor of Episodic Memory was supported. Although much of the previous literature has not discussed the relationship between processing speed and PND, findings regarding Episodic Memory are fairly consistent with previous results. Namely, Karlamangla and colleagues (2022) investigated this precise relationship. They concluded that Episodic Memory is not related to PND. This is consistent with the findings discussed in this study and provides additional evidence that Episodic Memory is unrelated to the PND dynamic of cortisol's diurnal rhythm. On the contrary, it may be the delay between saliva sampling and cognitive assessments which led to these findings. Perhaps the results would differ if the cortisol was sampled at the same time as the assessments.

Some theoretical models would predict an association between Episodic Memory and PND because of previous literature identifying links between Episodic Memory and other cortisol metric as well as the known biological relationship between the Hippocampus and the HPA Axis (Buchanan et al., 2004; Ennis et al., 2016; P. Evans et al., 2012; Law et al., 2015, 2020; Wolf et al., 2005; Zhang et al., 2015). Importantly, studies investigating the CAR dynamic find strong support for the relationship between cortisol CAR and Episodic Memory, and this association provides support for the Hippocampus-HPA Axis relationship framework. However, little evidence exists to suggest that the Hippocampus is involved in cortisol dynamics beyond the CAR (i.e. diurnal decline; Karlamangla et al., 2022). Thus, it may be plausible that the

Hippocampus in some way moderates the CAR, but one or multiple other brain systems moderate cortisol diurnal decline.

H2.2: Working Memory

Previous literature has investigated the relationship between PND and cognitive domains of attention, Working Memory, and Executive Function (P. Evans et al., 2012; Karlamangla et al., 2022) and served as the basis for the hypothesis that PND would be a predictor of Working Memory. The significant findings and replication from the present data adds valuable evidence to the proposition that cortisol diurnal decline may predict Working Memory/Executive Function control systems. In tandem with the repeated finding that diurnal decline has little to no association with Episodic Memory, potential explanations should be considered. Just as the Hippocampus has historically been proposed as a moderator/mediator for cortisol circadian rhythmicity, other brain regions associated with the HPA axis and Working Memory/Executive Function should be investigated. Potential brain regions may include the Locus Coeruleus (LC), a node with a well understood relationship with the HPA axis or the Prefrontal Cortex.

The LC is related to the hypothalamic and cortisol milieu in many ways. CRF, once believed to only be necessary for the production of cortisol in the HPA axis, is now known to be a more globally involved neurotransmitter with neuromodulatory effects on the LC (Valentino, 1988). In healthy, normal humans, then, LC-norepinephrine activity and CRF act in a positive feed forward loop. Perhaps this relationship influences the daytime patterns of cortisol and serves as the link between PND and Working Memory.

Likewise, the Prefrontal Cortex in humans is known to have a wide distribution of GC receptors and is a brain region involved in both Working Memory and Executive Function (Funahashi & Kubota, 1994; Nyberg, 2018). The Prefrontal Cortex has long been studied as a

control center for Executive Function and Working Memory, and in the last decade or so, researchers have begun to investigate the three-way relationship between cortisol, Working Memory/Executive Function, and the Prefrontal Cortex (Bogdanov et al. 2016; Woodcock et al. 2019; Hernaus et al. 2018; Farooqi et al. 2018). There is a known inhibitory relationship between stress-related cortisol and Working Memory within the Prefrontal Cortex, and considering the results of this study, it may be worth investigating whether the PND-Working Memory effect is related to the Prefrontal Cortex's role in Working Memory. Specifically, does greater attenuation of cortisol promote healthy functioning of the Prefrontal Cortex and thus bolster Working Memory performance?

Implications and Future Directions

Completion of this study has advanced our knowledge and understanding of the basic mechanistic features of neuroendocrinology, aging, and possible associations with cognitive decline. Given the inability to reproduce findings linking diurnal decline and age, as well as overall cognitive performance reinforce the need for further studies which aim to dissect this relationship. As well, limitations discussed below may have influenced this null finding. Furthermore, the significant relationship between PND and Working Memory offers new insight into the biological nature between the HPA-Axis and neighboring brain regions. Future studies may explore the roles the SCN, HPA Axis, Locus Coeruleus, and Prefrontal Cortex play in this interaction, which may point to a more conclusive link between hormone diurnal dynamics and cognitive performance.

Limitations

The limitations of this study are shared by all diurnal rhythm studies. It is challenging to capture perfect diurnal rhythms without severely limiting the participants' daily lifestyle. Thus, our diurnal rhythm markers lack in completeness, however, efforts were made to extract as much

granularity out of the multiple days of saliva samples. The lag between lab visits one and two limits our ability to definitively link cortisol rhythmicity and cognition and may have contributed to null findings. However, these results may serve as evidence that cortisol dynamics can predict cognitive performance months or years later. As well, our sample size was quite small given the age-range of our participants. In general, there is a tradeoff between the frequency of cortisol sampling ($N = 70$, in our case) and the sample size due to the very high participant burden. Ideally, future studies will combine high-frequency sampling with a large sample size to more definitively study age, cortisol dynamics and cognition. Our data analysis was also restricted due to the archival nature of the study. Our inability to measure other hormones of interest and our inability to choose cognitive assessments limits interpretation. Likewise, the inclusion of other cognitive assessments may benefit our findings and arguments. Specifically, a global cognitive performance assessment would aid in the investigation of an Overall Cognitive Performance-PND relationship (i.e. H2.1). Nevertheless, the findings from this study will direct future attempts to fill the gaps in an important knowledge domain.

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