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Abstract

There is evidence that stress-induced disruption of the circadian rhythm of cortisol secretion, has negative consequences for brain health. The cortisol awakening response (CAR) is the most prominent and dynamic aspect of this rhythm. It has complex regulatory mechanisms making it distinct from the rest of the cortisol circadian rhythm, and is frequently investigated as a biomarker of stress and potential intermediary between stress and impaired brain function. Despite this, the precise function of the CAR within the healthy cortisol circadian rhythm remains poorly understood. Cortisol is a powerful hormone known to influence cognition in multiple and complex ways. Studies of the CAR and cognitive function have used varied methodological approaches which have produced similarly varied findings. The present review considers the accumulating evidence linking stress, attenuation of the CAR and reduced cognitive function, and seeks to contextualise the many findings to study populations, cognitive measures, and CAR methodologies employed. Associations between the CAR and both memory and executive functions are discussed in relation to its potential role as a

neuroendocrine time of day signal that synchronises peripheral clocks throughout the brain to enable optimum function, and recommendations for future research are provided.

Keywords

Cortisol; Stress; Cortisol Awakening Response; Cognition; Memory; Executive Function; Hippocampus; Pre-Frontal Cortex; Circadian Rhythm; Human.

1. Stress, cortisol and cognition

Stress is known to have marked and varied effects on cognitive function (McEwen and Sapolsky, 1995; McEwen and Gianaros, 2011; McEwen, 2012) and these effects are largely attributed to the actions of the hormone cortisol on brain function. Cortisol is a powerful steroid hormone released from the adrenal cortex into the circulation following activation of the hypothalamic-pituitary-adrenal (HPA) axis by stress and the hypothalamic suprachiasmatic nucleus (SCN).

The effects of cortisol on cognitive functions in humans are seen in response to both acute and chronic elevated secretion (see Lupien et al., 1994 Vedhara et al., 2000; Buchanan and Lovallo, 2001; Mizoguchi et al., 2004). These can be either enhancing or impairing effects depending upon the specific cognitive function, and the timing and quantity of cortisol exposure (Kirschbaum et al., 1996; Domes et al., 2005; Schilling et al., 2013; Yehuda et al., 2007). The extent to which cortisol influences different functions is, in part, a reflection of the number and type of cortisol receptors found in the associated brain regions. Two separate intracellular receptors are expressed within the body that bind with cortisol: Glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). GR are found in most tissues, whereas MR are found in the brain, kidney, colon, heart and sweat glands (Joëls et al., 2008). The MR shows a similar intrinsic affinity for aldosterone, cortisol and corticosterone, while the GR has reduced intrinsic affinity for glucocorticoids in comparison (Gomez-Sanchez, 2010). Within the cell, MR and GR activation interacts in either a complementary or

opposing fashion depending on the cell type, and this interaction is crucial in determining cell function (Gomez-Sanchez, 2014).

An important moderator of acute cortisol and cognition associations is the timing of the cognitive measure relative to cortisol secretion. Cortisol exerts effects on neuronal activity via both rapid-acting, nongenomic (independent of alterations in gene expression) and slow-acting, genomic (mediated by alterations in gene expression) effects (Joëls et al., 2011). This is an adaptive feature as, in the context of a stress-response, it facilitates both immediate enhancement of cognitive functions required to respond to the immediate challenge, and slower effects to influence cognition when different demands may be faced. For example, a meta-analysis of acute cortisol administration and executive functions conducted by Shields et al. (2015) showed that rapid, nongenomic effects of cortisol enhanced inhibition, while slower, genomic effects impaired inhibition. As such, the time-dependent nature of this relationship may contribute substantially to the variability in results of studies of cortisol effects on cognition.

The hippocampus, pre-frontal cortex, and amygdala all show high levels of both MR and GR receptors compared to other brain regions (De Kloet et al., 2000; Herbert et al., 2006). The effects of cortisol on the functioning of these regions is determined by the balance of the MR binding relative to GR binding. For example, basal levels of cortisol binding to MR receptors in the hippocampus (HC) in the temporal lobe has been shown to enhance excitability, and elevated levels of cortisol binding to the GR during stress responding have the opposite effect (De Kloet, Oitzl, & Joëls, 1999; Herbert et al., 2006). Longer-term regulation of brain structure and function by prolonged exposure to cortisol is also achieved by alteration of the density of neurons through apoptosis and inhibited neurogenesis (Pittenger and Duman, 2008), and by influencing dendritic complexity (McEwen, 2008). Glucocorticoids play an important role in mediating the remodelling of neurons in the hippocampus and frontal cortex during repeated stress exposure, likely due to regulatory effects on glutamate (McEwen, 1999, 2008; Vyas et al., 2002). Such actions make cortisol, along with other mediators

such as serotonin, GABA, and excitatory amino acids, an important modulator of brain plasticity and cognitive functions (McEwen, 1999; 2008).

2. The cortisol awakening response

Cortisol secretion in healthy humans shows a marked circadian rhythm, characterised by a gradual increase during the late part of sleep to peak after morning awakening, then declining throughout the day to the nadir in the late evening and early part of sleep (Weitzman et al., 1971; Linkowski et al., 1985). The cortisol awakening response (CAR) is the dynamic increase in cortisol concentrations within the first hour after awakening from night-time sleep, peaking around 30- to 40-min post-awakening (Clow et al., 2004; Pruessner et al., 1997). The CAR is seen from early infancy to older adulthood (Fries et al., 2009; Stalder et al., 2013), and initial studies indicated that it is observed in around 77% of the healthy adult population (Wüst et al., 2000b), though this figure appears far higher when appropriate study methodology is employed (e.g. Oskis et el., 2009; Smyth et al., 2016). Within the circadian rhythm of cortisol secretion the CAR is a relatively discrete aspect, since it is initiated by morning awakening and is superimposed upon the circadian rhythm (Clow et al., 2004, 2010b; Wilhelm et al., 2007). This has been demonstrated by investigation of measures of pre- and post-awakening levels of cortisol and ACTH in blood and saliva showing that steep increases are seen in secretion of both hormones in response to awakening, and that these are distinct from baseline circadian secretion (Wilhelm et al., 2007). The CAR is also relatively independent of cortisol secretion across the rest of the day (Edwards et al., 2001; Schmidt-Reinwald et al., 1999; Maina et al., 2009). This is thought to be because regulation of the CAR involves additional direct modulation of the adrenal cortex by the SCN (via the pathway described previously), which enhances adrenal sensitivity in the immediate post-awakening period (Clow et al., 2010b).

The CAR is a dynamic post-awakening increase in cortisol secretion and therefore its measurement requires two components: cortisol levels immediately post-awakening, and the post-awakening rise (Stalder et al., 2016). For example, it can be calculated as the ‘area under the curve with respect to

increase' (AUCi), 'mean increase' (MnInc), and simple delta measures (i.e. peak value minus that upon awakening). But measures of total cortisol levels in the post-awakening period, such as the 'area under the curve with respect to ground' (AUCg), should not be considered as CAR measures as they lack sensitivity to this dynamic increase (for detailed description of CAR measures, see Stalder et al., 2016).

The CAR is considered a key link between mind and body due to its sensitivity to psychosocial factors such as negative affect and anticipation of workload in the day ahead (Clow et al., 2010b; Fries et al., 2009). Since first identification of the CAR in humans by Pruessner et al. (1997), it has been researched extensively in the context of understanding its regulation and its implications as a biomarker of health status (Clow et al., 2004; 2010a; Fries et al., 2009). From this research it has been established that the magnitude of the CAR is associated with a range of physiological and psychological factors, at both an inter- and intra-individual level. Although it was initially thought that the CAR was heightened in chronic stress (Chida and Steptoe, 2009) more reliable methodologies consistently report attenuation with chronic stress (e.g. O'Connor et al, 2009; Juster et al., 2011; Lovell et al., 2011; Saban et al, 2012; Duan et al, 2013). This observation is consistent with reports of a flattened cortisol diurnal decline in a range of negative physical and psychological health outcomes (Adam et al., 2017). In other words, chronic stress leads to a reduced dynamic range in the circadian rhythm of cortisol secretion, including the CAR.

Regarding physiological factors, it has been established that CAR magnitude shows a negative association with age (Heaney et al., 2010; Knoops et al., 2010) and varies by sex (Wüst et al., 2000b; Wright & Steptoe, 2005; Oskis et al., 2009). Notably sex differences have been observed in the timing of the CAR peak, with average peak concentrations seen at 30-min post-awakening in males and at 45-min post-awakening in females (Oskis et al., 2009). Females also typically show a delayed decline in cortisol post-CAR peak resulting in greater overall cortisol secretion in the post-awakening hour (Wüst et al., 2000b). Genetic factors also appear to play an important role in determining interindividual differences in the CAR; Wüst et al. (2000a) reported results from a twin study

revealing a heritiability index estimate of .40 for dynamic increase in cortisol levels post-awakening. While, with regard to psychosocial factors, it has been shown that in healthy participants a greater CAR magnitude is seen both in response to negative prior-day experiences and increased anticipations of challenge in the coming day (Adam et al., 2006; Clow et al., 2010a; Doane & Adam, 2010; Stalder et al., 2010a,b).

CAR research to date has primarily focused on its application as a biomarker in association with a range of psychosocial and physical variables including health outcomes (Chida & Steptoe, 2009). In addition to attenuation in chronic stress cross-sectional studies have reported blunted CAR profiles in cardiovascular, autoimmune, allergic, and psychiatric disorders (Wüst et al., 2000b; Clow et al., 2004; Fries et al., 2009). As for stress research results of such studies in clinical populations have often been inconsistent, perhaps due to participant inaccuracy in CAR sampling (i.e. delays in collecting the first waking sample result in erroneous CAR estimates), differences in experimental design, and differences in sample demographics such as age, gender and genotype (Clow et al., 2010a; Smyth et al., 2016; Stalder et al., 2016). The CAR is also typically used as a trait (inter-individual) measure, despite being subject to substantial state (within-individual) variation, which presents another potentially challenge for interpretation of results from between-subjects studies (for review, see Law et al., 2013).

Most CAR studies rely upon participants' self-collection of saliva samples within the domestic setting, and validity of results therefore depend upon accuracy of sampling. However, inaccurate reporting of awakening and/or sampling times is relatively common, and failure to effectively monitor such inaccuracy has been recognised as a serious confound in this area (for review, see Stalder et al., 2016). This is particularly the case if sampling delay exceeds the beginning of the dynamic increase in cortisol section, which occurs ~8-min post-awakening (Clow et al., 2004; Smyth et al., 2016). The recent consensus guidelines for CAR research (Stalder et al., 2016) propose objective assessment of sampling accuracy using electronic monitoring of both awakening and sampling times. While detailed assessment of the effects of sampling inaccuracy is not the focus of the present paper, it is important

to consider that many of the studies of stress, the CAR, and cognition were conducted prior to there being detailed knowledge of these methodological issues. Given the importance of this potential confound, the present review accounts for whether electronic monitoring of awakening was included in the studies described (see Table 1).

Another factor associated with within-subject, day-to-day variation in CAR magnitude is pre- and post-awakening light exposure (e.g. Scheer & Buijs, 1999, Thorn et al., 2004, Petrowski et al., 2019). In two recent and well-controlled sleep laboratory experiments in males, Petrowski et al. (2019) explored the differential effects of immediate post-awakening light exposure on the CAR and found consistent stimulatory effects of both blue and green wavelength light. The positive association between CAR magnitude and light exposure is indicative of the modulatory influence of the SCN on the CAR, and may have implications for a role of the CAR within healthy function as a potential time-of-day marker for peripheral clocks of the circadian system, under the influence of the SCN (Clow et al., 2010b; Menet and Rosbash, 2011; Law et al., 2013; Karatsoreos, 2014).

The SCN regulates the CAR via two separate pathways; the previously described input to the Paraventricular Nucleus PVN and the HPA axis cascade (corticotropin-releasing hormone and adrenocorticotropic hormone), and also a direct autonomic input to the adrenal cortex via the splanchnic nerve (Clow et al., 2010a). This dual-pathway SCN input plays an important role in determining CAR magnitude by a combination of pre- and post-awakening influences. While the HPA axis encourages cortisol secretion by increasing circulating ACTH in anticipation of awakening, the direct SCN-adrenal pathway is implicated in the fine-tuning of the CAR (Buijs et al., 2003). It achieves this by encouraging reduced adrenal sensitivity to ACTH in the immediate pre-awakening period, and then reversing this upon awakening such that adrenal sensitivity to ACTH is increased in the immediate post-awakening period (Fehm et al., 1984; Buijs et al., 1997, 2003; Bornstein et al., 2008). Direct innervation from SCN to adrenal gland is also implicated in CAR regulation due to the increased adrenal sensitivity to light in this period, as in rats this has been demonstrated to be both independent of circulating ACTH and dependent upon SCN integrity (Buijs et al., 1999).

Despite considerable research interest in the CAR for over twenty years, a precise role for the CAR within the healthy function has yet to be elucidated. The most prominent theory for the function of the CAR is that it provides an allostatic 'boost' upon awakening, to help the individual deal with the anticipated demands of the coming day (Adam et al., 2006; Clow et al., 2010; 2014; Fries et al., 2009; Law et al., 2013). It is thought that a morning 'boost' provided by the CAR may involve modulation of cognition (see Fries et al., 2009; Clow et al., 2010b). This is in part due to correlational evidence of blunted or absent CARs in various disorders involving cognitive impairment. However, a causal relationship is feasible due to the many associations between cortisol secretion and cognition that are described within the present review. If true, this would mean that the CAR may not just be a biomarker of stress but play a role in the pathway from chronic stress to cognitive dysfunction.

3. The Suprachiasmatic nucleus

The circadian rhythm of cortisol secretion plays a major role in synchronising biological functions to appropriate times of day around the sleep-wake and the light-dark cycles (Oster et al., 2016). The suprachiasmatic nucleus (SCN) of the hypothalamus acts as the circadian pacemaker in humans and synchronises circadian cortisol secretion to exogenous zeitgebers. Importantly, the SCN itself does not express GR and therefore acts as a cortisol output signaller only (Herbert et al., 2006). The SCN receives light information from the eye, though this photic input requires neither rods nor cones (the only previously known retinal photoreceptors), but instead a novel class of intrinsically photoreceptive melanopsin expressing retinal ganglion cells (Berson, Dunn, & Takao, 2002; Berson, 2007). These photosensitive cells project directly to the SCN via the retinohypathalamic tract (Berson, 2007; Herbert et al., 2006).

Exposure to light stimulates a cascade of molecular events in the SCN involving clock gene expression, which facilitates the entrainment of endogenous circadian rhythms to the light-dark cycle and allows for adaptation to seasonal changes in day length (Bunney and Bunney, 2000). Animal

studies have shown that if the SCN is removed, the duration of sleep and wake remain similar, but that these behaviours no longer show a regular cycle (Buijs et al., 2003). As such the SCN does not directly control these behaviours, but simply plays a role in synchronising them with the external environment.

Regarding cortisol secretion, the SCN is connected to the PVN of the hypothalamus both directly by axonal projections from SCN neurons, and indirectly via the SCN output pathway to the dorsomedial hypothalamus (Herbert et al., 2006). The SCN also exerts direct autonomic influence over cortisol secretion via the splanchnic nerve (for review see Clow et al., 2010a,b). This fast-acting, non-HPA dependent pathway is thought to be particularly important with regards to modulation of circadian rhythms as it mediates adrenal sensitivity to ACTH according to the time of day (Bornstein et al., 2008; Buijs et al., 1997; Buijs et al., 2003; Clow et al., 2010b). Thus, the SCN's light-responsive mediation of both the HPA-axis and non-HPA pathways helps to ensure fine-tuning of cortisol secretion that is appropriately synchronised to day-night cycles; stimulating secretion during the daytime and inhibiting it during the night (Benarroch, 2011).

4. Peripheral clocks of the circadian system

While the SCN acts as the central circadian pacemaker, there are 'peripheral clocks' in organs throughout the body, including the brain. These peripheral clocks show 'free-running' circadian rhythms in isolation but are synchronised by indirect signalling from the SCN. It has been established that the SCN entrains endocrine and behavioural rhythms (e.g. glucocorticoids, melatonin; sleep-wake, and body temperature) via a range of signalling methods, which include direct influence by neuronal input and indirect influence via regulation of paracrine signals. In turn, these rhythms act to synchronise peripheral clocks, including those in the brain (Antle & Silver, 2005; Menet and Rosbash, 2011). As the authors have noted previously (Clow et al., 2010b; Law et al., 2013) this suggests a role for the circadian cortisol rhythm, including the CAR, in entrainment of the peripheral circadian clocks in the body and brain. This hypothesis is supported by evidence that human peripheral clocks are

entrained by glucocorticoids (Cuesta, Cermakian, and Boivin, 2015), and that the circadian rhythm of circulating glucocorticoids works to synchronise circadian rhythms of peripheral clocks with the SCN master clock (Oster et al., 2016).

5. The circadian system and psychopathology

The importance of the circadian rhythm of cortisol secretion is highlighted by evidence that disruption to this rhythm is associated with a broad range of both psychological and somatic conditions, including cognitive deficits (Lupien et al., 2009), post-traumatic stress disorder (Yehuda et al., 1996), chronic stress (Miller, Chen, & Zhou, 2007), burnout (Pruessner, Hellhammer, & Kirschbaum, 1999), chronic fatigue syndrome (Nater et al., 2008), major depressive disorder (Linkowski, 2003; Yehuda et al., 1996), and increased incidence and progression of disease (Sephton & Spiegel, 2003).

Dysregulation of circadian rhythms is often observed in patients suffering from psychological disorders, such as depression and schizophrenia. As opposed to just being a symptom of these disorders, it has been proposed that such dysregulation might contribute to their aetiology (Menet and Rosbash, 2011, Karatsoreos, 2014). This is supported by accumulating evidence for SCN and circadian rhythm influence on mood and cognitive performance, including numerous demonstrations that impairment of the SCN in animal models has downstream consequences for various brain regions involved in cognition and emotion (for review, see Menet and Rosbash, 2011). Relevant to cortisol and the CAR, animal studies have shown that alterations to SCN integrity and function cause impairments to hippocampus-dependent memory (Ruby et al., 2008; Stephan & Kovacevic, 1978) and that such effects on memory can be induced by simply changing the pattern of the light/dark cycle (Devan et al., 2001). This potentially implicates the CAR, as a light-sensitive, time-of-day marker modulated by the SCN and HC and associated with HC-dependent memory and other cognitive functions.

An abnormal CAR is most often thought of as a side effect (or “biomarker”) of pathology, but it remains possible the CAR may contribute the relationship between chronic stress and impaired cognition. It is known that glucocorticoids entrain peripheral clocks in humans (Pezük, et al., 2012; Cuesta et al., 2015, Oster et al., 2016), and this suggests that the circadian cortisol rhythm (of which the CAR is the most prominent aspect) may influence the temporal programmes of gene expression in diverse brain regions, complementing their neural regulation by circadian inputs (Herbert et al., 2006). It is also recognised that mismatch between the circadian cortisol and neural patterns may contribute to localised malfunction of these brain regions (Herbert et al., 2006).

In this context, and in light of the direct modulation of the adrenal cortex by the SCN (via the splanchnic nerve) to enhance adrenal sensitivity to ACTH in the immediate post-awakening period, it is reasonable to hypothesise that the CAR may function as a hormonal time-of-day marker and to influence the timing of peripheral clocks (Clow et al., 2010b; Law et al., 2013). Such a hypothesis is currently speculative, but deserves further investigation.

6. The CAR and cognition

There are well established circadian rhythms in cognitive performance in humans, including declarative memory and executive function (Blatter and Cajochen, 2007; Dijk, Duffy & Czeisler, 1992; Schmidt et al., 2007; Valdez et al., 2008), and it is speculated that the CAR may play a role in the modulation of daytime cognition (see Fries et al., 2009; Clow et al., 2010b). One hypothesis, proposed by Clow et al. (2010b), is that the CAR might assist in the recovery of cognitive functions in the post-awakening period; a process known as ‘sleep inertia’ (SI; for review, see Hilditch and Mchill, 2019). Electroencephalograph (EEG) and brain imaging studies indicate that although awakening from sleep comprises rapid reestablishment of consciousness, the attainment of alertness is relatively slow (Ferrara et al., 2006). SI is considered to be the time lag between these two states and has been shown to typically last anywhere between 1- and 30-minutes post-awakening (Ferrara et al., 2006, Ikeda and Hayashi, 2008, Hilditch and Mchill, 2019). SI is therefore temporally associated with the

CAR, as the substantial increase in cortisol has been shown to begin approximately 10 minutes post-awakening (shown in healthy young females; Smyth et al., 2013) and peak at around 30-45 minutes (Clow et al., 2004).

SI is known to be influenced by circadian phase and sleep stage upon awakening (Tassi and Muzet, 2000), and a proposed cause of SI is the delay in blood flow reaching the anterior cortical regions of the brain after awakening (Balkin et al., 2002). Scheer et al. (2008) used body temperature measurements to establish the circadian phase at the time of waking within a forced desynchrony protocol, and found that the worst SI impairment of cognition occurred when participants were woken during their biological 'night' (approximately between 2300 and 0300 hours of the circadian cycle). Notably, it has also been demonstrated that the CAR is blunted in cases of night-time awakening (Dettenborn, Rosenloecher, & Kirschbaum, 2007), again indicating the potential for an association between these two processes. Finally, it has also been shown that exposure to light during this immediate post-waking period is an effective countermeasure for the symptoms of SI (Ferrara, De Gennaro, & Bertini, 2000). This might again implicate the CAR in assisting with the recovery from SI, given that cortisol and the CAR are stimulated by light exposure (Scheer and Buijs, 1999; Thorn et al., 2004).

Numerous studies have indicated relationships between the CAR and indices of cognition beyond the immediate post-awakening period, including declarative memory, prospective memory, working memory, and executive functions. The results of these studies have been inconsistent, likely due to variation in nature and timing of both CAR and cognitive measures, different sample populations, and irregularity in monitoring sampling accuracy (see Stalder et al., 2016). This inconsistency of methodology and results, combined with the lack of reviews or meta-analyses in this area, limits understanding about CAR and cognition associations. It is the aim of the present review to address this limitation and shed some light on the associations between CAR and cognition. A summary of studies exploring the relationship between the CAR and cognition is presented in Table 1.

[Insert Table 1 here]

9. The CAR and memory functions

It is well established that cortisol secretory activity is associated with integrity of the HC (as described in section 1). For example, circulating cortisol influences memory storage and retrieval (Lupien et al., 2009), and elevated circulating cortisol during sleep negatively impacts upon on simultaneous HC-dependent memory consolidation (Born and Wagner, 2009). The HC has been implicated in the regulation of hormonal responses to physical and psychological challenge, primarily in an inhibitory capacity, contributing to the negative feedback cycle (Fries et al., 2009; Herman et al., 2005). The CAR too has been shown to be associated with HC integrity, volume, and associated function (Almela et al., 2012; Bruehl, Wolf, & Convit, 2009; Buchanan et al., 2004; Pruessner et al., 2007; Wolf et al., 2005). For example, neither is the CAR observed in individuals with unilateral and bilateral HC lesions, nor those with severe global amnesia (Buchanan et al., 2004; Wolf et al., 2005). Further, it has been demonstrated that a larger CAR is associated with increased HC volume in healthy young men (Pruessner et al., 2007), and impaired declarative memory performance in older adults (Almela et al., 2012).

Several studies have explored associations between the CAR and HC-dependent memory. For example, CAR magnitude has been shown to be positively associated with episodic memory in healthy adults (Ennis et al., 2016). In a sample of elderly participants without dementia, Geerlings et al. (2015) also demonstrated that higher levels of cortisol at 45-min post-awakening are associated with better processing speed, spatial working memory and executive function (assessed by digits backward test and a variant of the Stroop task). While Geerlings et al. (2015) did not assess the CAR directly, the results implicate a possible role of the CAR due to the timing of the cortisol assessment (i.e. around the same time as the typical CAR peak), and would be in agreement with the accumulating evidence for a relationship between cortisol secretion in the post-awakening period and

HC function. This study also indicated an association with slightly greater white matter volume, although there was no association with general memory performance or with volume of grey matter.

The association between the CAR and HC function may be bi-directional, such that the HC may regulate cortisol secretion during the CAR period, but so too may the increase in cortisol secretion during the CAR period influence hippocampal function. This is because not only does an abnormal CAR occur in the presence of lesions to these brain regions, but also that changes in cortisol secretion and the CAR influence HC-dependent memory functions. For example, Rimmele et al. (2010) demonstrated that pharmacologic suppression of the CAR using metyrapone impaired subsequent free recall of prior day learnt text and imagery.

The importance of HC function upon awakening is apparent; besides its importance for episodic memory function, the HC is also involved in space and time orientation (O'Keefe and Nadel, 1978; Burgess, Maguire, & O'Keefe, 2002). It has therefore been hypothesised that the CAR may play a role in activation of prospective memory function upon-awakening, encouraging the orientation of self in terms of space and time, and dealing with the cognitive demands of the post-awakening period (Bäumler et al., 2014a,b; Fries et al., 2009). This hypothesis was tested by Bäumler et al. (2014a) who demonstrated that, in a sample of young children, performance on a game-like prospective memory task was positively associated with CAR magnitude. This was followed by a study within a (smaller) sample of the same young children which showed that a naturalistic prospective memory intervention (requiring the child to remind their parent of a planned gift upon awakening) resulted in a larger CAR compared to that on control days. As such, these findings not only provide support for the previously discussed CAR and HC-associated memory function relationship, but also for the hypothesis that the CAR is related to anticipation of challenge in the coming day (Clow et al., 2010b Fries et al., 2009).

In addition to declarative and prospective memory, the CAR has also been investigated in relation to working memory. A larger trait CAR (measured across 2 days) has been shown to be associated with increased working memory performance in older adult males in one study, though the same study

failed to find a relationship in females of similar age (Almela et al., 2012). Moriarty et al. (2014) also reported a strong relationship between overall levels of cortisol secretion within the post-awakening period and spatial working memory in healthy older adults. The latter study indicated a U-shaped relationship, such that extreme high or low levels of cortisol were associated with decreased memory performance, which the authors interpreted as consistent with the previously reported positive relationship. However, this study did not employ electronic controls for participant sampling accuracy and the relationship was only observed with total cortisol secretion, as opposed to a (dynamic) CAR measure. Contradicting both of these reports, a recent study by Butler et al. (2017) found there to be no association between the CAR and working memory. In sum, evidence for a relationship between CAR and working memory can be considered tentative and inconsistent. The inconsistency in this area might suggest a need for further research, with appropriate application of electronic measures to monitor sapling accuracy, and careful control for other known confounds in CAR research (Clow et al., 2010a; Stalder et al., 2016).

10. The CAR and executive function

One of the most prominent structures responsible for executive function is the frontal cortex (FC) which, like the HC, both expresses a high density of cortisol receptors and plays a role in regulating the HPA axis (Lupien et al., 2009). This relationship too is bi-directional, such that endogenous glucocorticoids modulate the cognitive functions of the pre-frontal cortex (Mizoguchi et al., 2004). However, relationships between cortisol secretion and executive function are complicated, not least because executive function is a broad and non-unitary concept encompassing many high-level cognitive processes, which depend upon several separate pre-frontal cortex structures. But also because many executive functions are responsible for control and organisation of other cognitive functions (Miyake et al., 2000; Gilbert and Burgess, 2008; Diamond, 2013). While consensus has yet to be reached on an exact definition of executive function (Gilbert and Burgess, 2008), perhaps the best evidence is for there being three separate types: ‘set shifting’ (or ‘cognitive flexibility’) which is the ability to switch between competing task demands, ‘updating’ or working memory functions, and

'inhibition' which includes both cognitive and behavioural inhibitory processes (Miyake et al., 2000; Diamond, 2013).

Outside of the CAR literature, it has been demonstrated that acute increases in exogenous glucocorticoids are positively associated with set shifting and response inhibition measures (Dierolf et al., 2016; Shields et al., 2015; Vaz et al., 2011). A recent study also has demonstrated a positive association between acute increases in endogenous cortisol and immediate, short-term enhancement of cognitive flexibility (Dierolf et al., 2016). However, studies in this field have yielded inconsistent results depending upon the type of executive function assessed and the relative timing of the measures, likely due to the differential effects of rapid (non-genomic), and slower (genomic) effects of cortisol secretion (Shields et al., 2015). For example, both Wingenfeld et al. (2011) and Vaz et al. (2011) have reported that such associations are no longer apparent if set shifting is measured more than one hour after an acute increase in exogenous cortisol. There are good theoretical grounds for expecting rapid, non-genomic effects of cortisol to enhance response inhibition as this would support greater cognitive control over actions when dealing with a stressor (Shields et al., 2015), which would not necessarily be adaptive if experienced long after (at the genomic level). Therefore, the criticality of both type and timing of executive function measures is apparent. This is a major complication for CAR-cognition studies also, and such differences in timing of the relevant measures might explain why there have been similarly inconsistent results in this field (see table 1).

CAR magnitude has been shown to be positively associated with both working memory and attention-switching performance in older adults (Almela et al., 2012; Evans et al., 2012), as well as a measure of response inhibition in the afternoon of the same day in healthy young adults (Shi et al., 2018). Oosterholt et al. (2016) also found that in a sample of patients with clinical burnout, CAR magnitude was associated with better updating performance and fewer cognitive failures. But negative associations with task updating, speed of memory, error monitoring, and serial sequence learning have been reported in other samples (Hodyl et al., 2016, Maldonado et al., 2008; Oosterholt et al., 2016; Zhang et al., 2015), as well as one study reporting no association with task switching in healthy young

adults (Butler et al., 2017). Similar inconsistency has occurred in studies of CAR associations with overall cognitive performance (e.g. Aas et al., 2011; Evans et al., 2011; Labad et al., 2016).

Associations between CAR and cognitive flexibility (set shifting) have been somewhat more consistent, with a positive association between CAR magnitude and cognitive flexibility (Trail Making task performance) found in older adults (Evans et al., 2012), and a positive association with attention-switching performance seen both in a sample of healthy young adults (Law et al., [IN PRESS]) and a single case study of a healthy young male (Law et al., 2015). The positive association between cognitive flexibility and CAR magnitude was not observed in a recent study reporting a negative association between the CAR and emotion and gender task switching (Dierolf et al., 2016). However, as the CAR was defined by Dierolf et al. as mean morning cortisol AUCg across three consecutive days prior to the experiment (therefore not measuring the dynamic CAR per se), this finding might be better understood as a relationship between task switching and total post-awakening cortisol secretion.

A limitation for interpreting the findings of many CAR-EF studies is that they have not accounted for the substantial day-to-day variation in CAR magnitude (for review, see Law et al., 2013). The majority have been correlational between-subjects, or 'trait', studies, often measuring the CAR on just one or two days. This is a limitation since it is thought day-to-day ('state') differences account for around two thirds of the variance in CAR magnitude (Hellhammer et al., 2007; Almeida et al., 2009; Stalder et al., 2009, 2010b), and it has been recommended by Hellhammer et al. (2007) that to achieve a reliable trait measure of the CAR requires sampling over 6 consecutive days. In addition, such state variation is associated with a range of environmental and behavioural factors, such as differences in lighting and awakening times, that can potentially confound trait studies (Law et al., 2013). While the impact of daily variation in the CAR on EF has received less attention, the within-subject positive association between CAR and attention switching at 45 min post awakening (Law et al., 2015), as well as the within-subjects finding of a same-day association between CAR magnitude and an index

of brain plasticity (Clow et al., 2014), offer some indication of the potential for investigating state associations between CAR and EF, even in healthy young participants.

11. Recommendations for Future Research

As described above, the CAR is the most prominent, dynamic and variable part of the circadian pattern of cortisol secretion, is under the modulatory influence of the SCN masterclock, and is timed to mark the significant circadian event of morning awakening. As such, there is good reason to hypothesise that one role for the CAR may be to act as a time-of-day marker for synchronisation of circadian rhythms. Such a role for the CAR could potentially explain associations between CAR magnitude and the function of brain regions with a high affinity for cortisol, including memory and executive functions of the hippocampus and pre-frontal cortex, respectively. Future research exploring associations between the CAR and other cognitive functions related to these brain regions could further elucidate this relationship, while studies of clock gene function (using clock gene knockout mice, for example) might have potential to provide insight into the underlying mechanisms.

To ensure clarity and comparability of research findings, it will be important for future studies in this area to include careful controls for the many potentially confounding factors described here. For example, clear consideration and recording of the timing of cognitive measures in relation to the CAR is of critical importance in order to differentiate between rapid, non-genomic effects (for example, within 15-30 mins of the CAR) and slower acting, genomic effects observed later in the day (Joëls et al., 2011). Of perhaps principle significance for valid CAR measurement is the inclusion of measures to ensure sampling accuracy, as laid out in the consensus guidelines of Stalder et al. (2016). While further consideration should also be given to day-to-day (‘state’) differences in the CAR (as described in Law et al., 2013) as study of such variation has considerable potential to provide insight into CAR function, for example, by within-subject measurement of the CAR over several days along with same-day cognitive measures. Moreover, such state variation must be taken into account in future between-

subject (‘trait’) studies of the CAR by sampling over several days to achieve a reliable trait measure (Hellhammer et al., 2007). Implementing controls for potentially confounding state factors such as differences in awakening times and ambient light exposure might also allow for greater precision in determining associations between CAR and cognition (Law et al., 2013). Indeed, recent evidence indicates that blue/green wavelength light exposure is a more significant potential confounding factor than had previously been appreciated, though this also may have potential for investigation as an intervention for CAR manipulation (Petrowski et al., 2019).

If the CAR does support the re-establishment of cognitive functions (Fries et al., 2009; Clow et al., 2010b; Law et al., 2013) then in theory, the light-responsive nature of the CAR would allow for optimally enhanced cognitive function when awakening at dawn, in preparation for the day ahead. A recent, detailed assessment of the implications of differing ambient light levels between CAR observations has indicated that post-awakening blue or green wavelength light influences CAR magnitude (Petrowski et al., 2019). This is a factor which can be easily controlled for either by direct measurement of light levels or, in ambulatory studies, simply by controlling for season, time of awakening and type of lighting (e.g. LED vs. fluorescent bulb; Petrowski et al., 2019). This, too, may present a direction for future research, as the recovery of executive functions such as cognitive flexibility may be assessed within the context of differences in ambient light at awakening. Indeed, preliminary support for such a relationship is provided by studies using functional magnetic resonance imaging techniques which indicate that exposure to light during the morning period results in increased activation of the subcortical regions associated with alertness and working memory (Vandewalle et al., 2006, 2010). Variation of light exposure therefore presents a potential method for manipulating CAR magnitude in order to examine effects on cognition or the activation of associated brain regions. Moving beyond correlational studies, experiments involving light-based intervention or other means for CAR manipulation might have considerable potential for further advancing understanding of the relationship between the CAR and cognition.

12. Conclusion

In summary, there is a growing body of research exploring relationships between stress, the CAR, and cognition. Within this literature, much of the focus has been on HC function, though there has been increasing interest in associations with frontal functions in recent years. Given the methodological difficulties within the area there have been relatively consistent demonstrations of correlational relationships in older adults: a larger average CAR being associated with better average memory and executive function. Day-to-day variation in the CAR has also been associated with day-to-day variation in executive function in healthy young populations However, there has been no dedicated effort to explore the mechanisms that might underpin a causal relationship between the CAR and cognition. It is suggested here that the CAR, which is regulated by two distinct pathways from the central body clock (SCN), might be a powerful time-of-day marker, synchronising peripheral clocks in the brain to optimise brain function appropriate for the demands of the upcoming day. Chronic stress and aging lead to attenuation of the CAR and this may provide a route by which these factors impact cognition. If shown to be the case this provides a valuable target for intervention in cognitive decline. It is exciting to speculate that behavioural strategies that optimise the CAR (e.g. light, stress management, physical activity, early awakening, not smoking) might prove beneficial in a range of conditions not typically thought to be associated with neuroendocrine function. As such, there are many important questions in this field that remained unanswered and which present promising directions for further research.

13. References

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Table 1: Summary of CAR-cognition studies

Memory Only

Author	Sample	CAR Measure	Cognitive Test	Findings	Notes
Pruessner et al. (2007)	13 healthy males (age 19-32, mean =23.85)	AUC of 0-30-60 (4 days, at weekly intervals)	DM (cued recall) before and after a stressor	No significant relationship	Unclear if AUCg or AUCi used. No electronic monitoring of sampling accuracy
Bäumler et al. (2014a)	97 children (ages 3-6)	0-30 delta (3 days)	Prospective memory (ball sorting)	CAR (+) prospective memory	Electronically monitored sampling accuracy
Bäumler et al. (2014b)	35 children (ages 3-6)	0-30 delta (2 days)	Naturalistic prospective memory (remembering to perform an action)	CAR (+) when prospective memory performance required	Electronically monitored sampling accuracy
Almela et al. (2012)	88 healthy middle aged adults (ages 55-77)	AUCi & AUCg (2 days)	DM and WM	AUCi, AUCg (-) DM *in men only,* CAR (+) WM	Those with negative CAR also showed poorer DM. Did not electronically monitor sampling accuracy
Rimmele et al. (2010)	16 healthy males (mean age 22.3, SD 3.89)	'Morning cortisol' 7:00-8:30 am at 15 min intervals (1 day)	DM (free recall)	Inverted U-shaped relationship: extreme high or low CAR (-) DM	Experiment conducted within a laboratory

Moriarty et al. (2014)	19 males age 30-60 (mean 40.6, SD 5.8)	AUCg & AUCi (1 day)	Spatial working memory (Newcastle 2D SM test) and Attention networks (broadly EF).	U-shaped relationship, extreme high or low AUCg (-) SWM	No relationship with AUCi (CAR). Did not electronically monitor sampling accuracy
Hinkelmann et al. (2013)	41 depressed patients, 41 controls (ages 18-70)	AUCg & AUCi (2 days)	Verbal learning & visuospatial memory	In depressives, AUCi & AUCg (-) both mem scores. In controls, CAR (+) verbal mem	Broad age range. Did not electronically monitor sampling accuracy
Hodyl et al. (2016)	39 healthy adults (mean age 22, SD 4)	AUCi (2 days)	Serial sequence reaction time task	CAR (-) learning and speed of performance	Electronically monitored awakening, but not sampling times

Executive Function Only

Author	**Sample**	**CAR Measure**	**Cognitive Test**	**Findings**	**Notes**
Evans et al. (2012)	50 older adults (ages 60-91)	MnInc, and average peak time (2 days)	Trail making	Early peak + CAR (+) EF	Electronically monitored sampling accuracy
Law et al. (2015)	Case study of healthy young adult male	0-30 min rise (50 days)	Attention switching task	Within-subject CAR (+) attention switching performance	Single participant case study. Electronically monitored

					sampling accuracy
Zhang et al. (2015)	63 healthy young Males	AUCi (sum of 2 dayss)	Go/no go task	CAR (+) error-related negativity latency and post-error miss rate	No electronic monitoring of sampling accuracy
Dierolf et al. (2016)	40 healthy males, ages 18-28 (mean age 23, SD 2.9)	Mean AUCg (3 days)	Emotion vs. gender task switching	AUCg (-) task switching performance	Did not examine dynamic (CAR) measure. No monitoring of sampling accuracy
Butler et al. (2017)	109 healthy males, ages 21-63 (mean age 34.2, SD 10.6)	0-30 delta (2 days)	Accuracy of planning/problem solving (Tower of London- type task and set shifting)	CAR (-) problem solving. No significant association with task switching or WM	12% of awakening times were electronically monitored
Shi et al. (2018)	47 healthy males, ages 18-26 (mean age 22.4, SD 1.9)	Peak concentration minus that on awakening (1 day)	Go/no go task	CAR (+) response inhibition	Measured CAR on one day only. Electronically monitored sampling accuracy
Law et al. [IN PRESS]	55 healthy young adults (mean age 20.2, SD 3.0)	MnInc (2 days)	Attention switching task	CAR (+) attention switching performance	Electronically monitored sampling accuracy
Various Cognitive Measures					

Author	Sample	CAR Measure	Cognitive Test	Findings	Notes
Maldonado et al. (2008)	116 children, ages 9-12, defined as either low or high stress	0-30 delta (1 day)	Cognitive drug research assessment system	CAR (-) speed of memory	Sampling supervised by participants' parents, without electronic monitoring of accuracy
Stawski et al. (2011)	1,500 midlife adults (mean age 57, SD 12)	0-30 min 'Morning rise' (4 days)	Overall measure inc. word recall, working mem, reasoning & proc speed	No relationship with dynamic measure, but overall cortisol levels (+) overall cog	No age differences in observed relationship. Electronically monitored approximately 25% of sampling, but not awakening times
Evans et al. (2011)	50 older adults, ages 60-91 (mean 74)	Mean 0-45, and 0-30 delta (2 days)	Overall cog perf (OCP)	CAR (+) overall cog	Electronic monitoring of sampling accuracy
Franz et al. (2011)	795 male twins ages 51-60 (mean 55.9, SD 2.6)	0-30 delta (3 days, non-consecutive)	Range including spatial abilities, short- and long-term mem, EF, verbal fluency, reasoning, & processing speed	CAR (-) visual-spatial memory	Reported that the effect was entirely driven by overall diurnal cortisol. Participants received electronic sampling time

					reminders, but no electronic monitoring of accuracy
Aas et al. (2011)	30 Patients with first episode psychosis, 26 controls (ages 18-65)	AUCi (1 day)	Range including OCP, verbal mem, spatial abilities, processing speed, EF WM	In patients, CAR (+) Verbal memory and processing speed	No relationship between CAR and cog in healthy controls. Did not monitor sampling accuracy
Cullen et al. (2014)	Children at risk for psychosis, & healthy control group (age range 11-14)	AUCi (2 days)	Broad range of memory and EF tests	In at risk groups, CAR (+) letter fluency and verbal memory	No relationship in healthy controls. Did not monitor sampling accuracy
Oosterholt et al. (2016)	85 adults (31 with clinical burnout, 27 non-clinical burnout, 27 healthy controls)	AUCg & 0-30 delta (2 days)	EF (prepotent response inhibition, irrelevant information inhibition, & task switching), verbal mem, cognitive failures (self-report)	Burnout patients (-) CAR, also worse updating (measured by 2-back task), and more cognitive failures	Did not directly compare cortisol & cognition measures, and did not monitor CAR sampling accuracy
Ennis et al. (2016)	56 healthy adults, ages 23-79 (mean = 53, SD = 16.9)	0-30 delta divided by 0-30 sample-time delta (10 days)	Episodic mem, Working mem, processing speed. All measured 8-38 months after	CAR (+) episodic memory, but no association with working mem	Did not electronically monitor sampling accuracy

			CAR	or processing speed	
Hidalgo et al. (2016)	64 healthy adults, ages 57-76 (mean = 64.7, SD = 4.1)	AUCi (2 days)	Logical mem, verbal paired associates, family pictures test, letter-number sequencing, digit span, spatial span	CAR (-) immediate verbal and visual recall, but no association with any other measures	No significant effects with appropriate controls applied. Electronically monitored sampling but not awakening time
Labad et al. (2016)	60 patients with early psychosis, ages 18-35	AUCi (1 day)	Range including OCP, WM, verbal & visual mem, reasoning & problem solving, social cognition	CAR magnitude (-) OCP, and flatness of CAR (-) spatial memory	Did not monitor sampling accuracy, and measured CAR on one day only (different day to cognitive test)
Salvat-Pujol et al. (2017)	97 medicated patients with MDD (mean age = 59.8, SD = 11.7), 97 healthy controls (mean age = 56.6, SD = 11.9)	AUCi (1 day)	Range of tests, including Hopkins verbal learning test, trail making, Rey complex figure test, Stroop, WM span	CAR (+) trail making, processing speed and Rey complex figure for MDD in remission	Did not monitor sampling accuracy, and measured CAR on one day only. No relationship with any measure in overall sample

AUCi = Area under the curve with respect to increase, AUCg = Area under the curve with respect to ground, OCP = Overall cognitive performance, WM = Working memory, DM = Declarative memory, EF = Executive function, Mem = Memory, MDD = Major depressive disorder, SD = Standard

deviation, (+) = Associated increase, (-) = Associated decrease