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The cortisol awakening response predicts same morning executive function: Results from a 50-day case study

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Running head: Case study of the CAR and EF

Keywords

Cortisol awakening response; CAR; human; executive function; cognition; case study.

Abstract

A relationship between individual differences in trait estimates of the cortisol awakening response (CAR) and indices of executive function (EF) has been reported. However it is difficult to determine causality from such studies. The aim of the present study was to capitalise upon state variation in both variables to seek stronger support for causality by examining daily co-variation. A 50-day researcher-participant case study was employed, ensuring careful adherence to the sampling protocol. A 24-year-old healthy male collected saliva samples and completed an attention switching index of EF on the morning of each study day. Subsidiary control measures included wake time, sleep duration, morning fatigue, and amount of prior day exercise and alcohol consumption. As the CAR preceded daily measurement of EF we hypothesised that, over time, a greater than average CAR would predict better than average EF. This was confirmed by mixed regression modelling of variation in cortisol concentrations, which indicated that the greater the increase in cortisol concentrations from 0-30 min post-awakening (CAR) the better was subsequent EF performance at 45 minutes post-awakening ($t = 2.29$, $p = .024$). This effect was independent of all potential confounding measures. Results are discussed in terms of implications for the understanding of the relationship between the CAR and cognitive function, and the previously suggested role of the CAR in 'boosting' an individual's performance for the day ahead.

1. Introduction

The Cortisol Awakening Response (CAR) is the rapid increase in cortisol concentrations within the first hour after awakening from sleep (Pruessner et al., 1997), and is initiated in response to morning awakening (Wilhelm et al., 2007). The CAR typically peaks around 30 minutes post-awakening in males, and at around 45-min post-awakening in females (Wuest et al., 2000), and is subject to significant state (day-to-day) variation (Hellhammer et al., 2007; Law et al., 2014; Stalder et al., 2009). 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., 2010; Fries et al., 2009). Though the precise function of the CAR remains unknown, numerous studies have indicated relationships between the CAR and indices of cognition including declarative memory (Rimmele et al., 2010; Wolf et al., 2005), prospective memory (Baumler et al., 2014), working memory (Moriarty et al., 2014), and executive function (EF) (Evans et al., 2012). While a relationship between individual differences in CAR magnitude and executive function has been demonstrated in between-subjects studies (e.g. Aas et al., 2011; Cullen et al., 2014; Evans et al., 2012), the impact of *daily* variation in the CAR on EF has not been explored. The aim of the present study was to use an individual case study approach to explore associations between daily variations in the CAR and a measure of EF.

EF can be understood as a range of functions including inhibition and interference control, working memory, and cognitive flexibility (Diamond, 2013; Miyake et al., 2000). One of the aspects of cognitive flexibility is the ability to switch between task demands, often assessed using attention switching paradigms (for review, see Diamond, 2013). Evans et al. (2012) indicated that better performance on one of these tasks, form B of the Trail Making task (Arbuthnott & Frank, 2000), is associated with a larger CAR in older adults.

Current theories for the role of the CAR within the human circadian rhythm suggest that it serves to provide an unspecified physiological or psychological 'boost' upon awakening (Adam et al., 2006; Clow et al., 2010; Fries et al., 2009). These theories are supported by studies reporting state associations between the CAR and both negative prior day psychological experience and anticipation of demand in the day ahead (e.g. Adam et al., 2006; Stalder et al., 2010). Such theories might support the idea of a state association between the CAR and EF, as optimising EF could serve as a homeostatic response suitable for tackling the expected challenges of the waking day.

The aim of the present study was to use a researcher-participant case study design to investigate in detail whether daily variation in the CAR predicted daily variation in EF at the end of the CAR period. The primary hypothesis was that the magnitude of increase in cortisol secretion post-awakening (CAR) would be predictive of subsequently better EF performance in the same morning.

2. Methods

2.1. Design

Ethical approval was provided by the Institutional Ethics Committee. The study employed a 50-day researcher-participant case study design based upon the novel study of Stalder et al. (2009, 2010). The advantages of such a design are two-fold: use of a researcher-participant provides a novel and convenient method for reducing the reliance on participant adherence to the protocol. Non-adherence to the requested saliva sampling protocol, of as little as 5 minutes between awakening and collection of the first sample, can lead to inaccurate CAR assessment (see: Clow et al., 2004; Kudielka et al., 2003; Smyth et al., 2013; Thorn et al., 2006). Intensive testing over 50 days is exceptionally demanding for participants and it has been reported that participant adherence decreases over a period of just 7 days

(Broderick et al, 2004). The researcher-participant design ensures sustained motivation and commitment to the study, maximising adherence (which is checked by electronic monitoring) and reducing data wastage. The possibility of introducing bias was avoided as all data were logged and analysed at the end of the study. The participant could not be aware of daily CAR magnitude, avoiding the possibility of biasing the results, consciously or unconsciously. The researcher-participant (RL) was a 24 year old non-smoking male in postgraduate education, who described himself as healthy and free from medication.

2.2. Materials and measures

While EF and cognitive flexibility can be assessed using a broad range of tasks, many of these are subject to practice effects and therefore unsuitable for repeated assessment (Basso et al., 1999; Rabbitt, 1997). Therefore the Attention Switching Task (AST) was selected from the Cambridge Neuropsychological Test Automated Battery (Cambridge Cognition, Cambridge, UK). The AST was self-administered using a laptop computer with a two-button (left-right) response keypad. The task consisted of repeated presentation of an arrow that can appear on either side of the screen (left or right) and can point in either direction (left of right). The presentation of the arrow is accompanied by a response instruction which can either require the participant to respond to either the spatial location or the direction of the arrow presented. The participant responds by pressing the appropriate key on the response pad (left or right). There are 160 individual arrow presentations in each assessment, with the complete test taking around 6 min to complete. Crucially the presentation sequence in this test is randomised so as to prevent sequence learning. Outcome measures of the AST include both simple reaction time (ms), number of errors, and switch cost. The switch cost measure is an index of mental flexibility (and in turn, executive function), calculated as the difference in mean reaction time for trials following a switch in the task requirement compared to the mean reaction time for non-switched trials. As such, a smaller switch cost score is representative of better EF performance (though note that for

the purposes of presentation, these scores were inverted in the present analysis such that the switch cost variable, ‘EF’, is positively scored).

To alleviate the risk of an AST learning effect the participant completed a short pilot prior to study commencement. A practice effect was observed, such that mean reaction times on the AST task decreased with successive trials. However a relatively consistent level of performance was achieved prior to commencement of the case study reported here.

Prior evening alcohol consumption and prior day exercise duration were both measured by self-report. Alcohol was recorded in estimated 10ml units of alcoholic content, and exercise was recorded in the number of hours of self-assessed high-intensity, sustained aerobic or anaerobic exercise during the day. To objectively assess fatigue, critical flicker frequency (FF) was measured using a flicker fusion system (Lafayette instrumentation, Indiana, USA). This is a measure of the frequency at which rapid flickering light becomes impossible to detect to the human eye. FF is subject to within-individual variation and is a well-validated and widely used, objective measure of central fatigue (e.g. Davranche and Pichon, 2005; Simonson and Brozek, 1952).

To provide an objective measure for validation of self-reported sleep onset and awakening times, actigraphical recordings were collected using a wrist-worn Actiwatch (Philips Respironics, Surrey, UK).

2.3. Procedure

Data were collected on a total of 50 days, at 3-day intervals, so as to match the procedure of a previous CAR case study (Stalder et al., 2009). Fifty study days provided statistical power to test the hypothesis and collection at regular intervals, 3-days apart, standardised the protocol and minimised study fatigue in the participant (which might happen with daily

testing). Data collection took place in the United Kingdom between the months of January and May. Salivary cortisol was assessed at 5 time points across the post-awakening hour: immediately on awakening (0 min), and then at 15, 30, 45 and 60 min post-awakening. The participant took nil-by-mouth apart from water during the post-awakening period to avoid possible confounding effects of abrasion and micro-vascular leakage. Wrist actigraphy was used throughout the study to check self- reported sleep onset and awakening time with an objective measure of awakening time and sleep duration.

On each evening prior to morning cortisol sampling, the participant recorded the duration of exercise and total units of alcohol consumption for the pre-study day. Shortly after awakening, and immediately after collecting the first cortisol sample, the participant completed the flicker fusion task, followed by a short break before taking the second saliva sample at 15 min post-awakening. On each measurement day the AST was completed at approximately 45 minutes post-awakening (after collection of the fourth saliva sample and prior to collecting the 60 min post-awakening sample). On all mornings, though required to be seated for the psychological testing, the participant was otherwise free to move around throughout the sampling period.

On half of the study days (alternating with the protocol described above) the procedure was adapted to incorporate a second AST, completed immediately following the flicker fusion (prior to the 15 minute post-awakening cortisol sample). This additional test was included in order to provide some limited estimates of association between EF performance earlier in the post-awakening period and both subsequent CAR magnitude and later EF performance. This also allowed for exploration of whether inclusion of cognitive testing earlier in the post-awakening period influenced the CAR-EF association at 45 min post-awakening

In-line with the previously published researcher-participant studies (Stalder et al., 2009; 2010), all data handling and analysis was carried out after completion of data collection.

2.4. Cortisol Analysis

Saliva samples were collected with a cotton swab, which was chewed for 1-2 min and stored in a capped 'Salivette' (Sarstedt Inc.). Samples were then frozen at −20 °C within one day of collection and stored at this temperature until analysis. Samples were thawed and centrifuged at 1,500 x g (at 3,000 rpm) for 10 minutes, after which cortisol concentrations were determined by Enzyme Linked Immuno-Sorbent Assay (ELISA; Salimetrics, USA). Intra- and inter-assay variations were below 10% in all cases.

2.5. Treatment of data

Data were analysed using mixed regression modelling (Blackwell et al., 2006) of variation in cortisol concentrations in the first hour after awakening. In healthy males the first 0-30 min period, typically characterises the CAR, and the 30-60 min period is typically characterised by decline in cortisol concentrations. Each period was addressed in independent analyses comprising the running of two consecutive models. In model A (within day), time of sampling (0, 15, and 30 min) was entered as a fixed covariate with day of study (0-50) as the subject variable. In model B (within day + between-day) the covariate of z-scored EF (AST performance) was added to the model together with its interaction with time of sampling. As noted in 2.2, for the purposes of presentation the EF variable was produced by inverting the switch cost variable, such that high scores represent better EF performance. At each modelling point, three ways of modelling residual covariance were compared: random intercept only (equivalent of compound symmetry for repeated measure covariate), random intercept + random time, and finally a first level autoregressive (AR1) covariance structure. In all cases AR1 provided the best fit of the data as indicated by minimizing of the Schwarz's Bayesian Criterion (BIC), and all models presented here adopted an AR1 covariance structure for the repeated measure of cortisol sampling time. Finally, further modelling was

undertaken to check that any findings from the principal model were not compromised by extraneous and potentially confounding variables, including the passage of time (5 months) over the course of the trial.

3. Results

3.1. Descriptives

The cortisol data showed a similar pattern of state variation across the 50 day period to that previously observed in participant TS (Stalder et al., 2009). Table 1 presents descriptive data for all relevant variables. As expected the peak in cortisol is found at 30 min post-awakening, followed by a decline until 60 minutes post awakening.

-- Insert Table 1 here --

3.2. Modelling of data

3.2.1. Cortisol from 0-30mins post-awakening

Model A analysis of the rise in cortisol secretion from 0-30 min post-awakening showed the expected association with sampling time ($t = 13.39$, $p = <.001$). The intercept coefficient (10.15) indicates a predicted concentration of cortisol of 10.15 nmol/l at awakening. The slope coefficient of 0.26 indicates a predicted rise of 0.26 nmol/l per minute over the 30 min period, giving an estimated rise (CAR value) of 7.8 nmol/l.

Model B of the 0-30 min data (introducing main and interactive terms for EF) indicated the same rise in cortisol (i.e. the CAR) as observed in model A with regard to intercept for slope (10.15) and slope coefficient for sample time (.26). Further, in regard to the overall effect on

cortisol of day differences in EF no difference was observed in prevailing starting values (t = -1.66, p = .101). However, the slope interaction between sample time and z-scored EF (ZEF) is significant (t = 2.29, p = .024), indicating that the slope of the mean line varies with EF performance. For every standard deviation above or below mean EF, there is a 1.2 nmol/l increase or decrease in the CAR. Therefore the model predicts that on days when EF is +1 SD, the slope is 9 nmol/l, and on days when EF is -1 SD, the slope is 6.6 nmol/l. Table 2 shows coefficient estimates and significance (p) values for the parameters in the modelled data.

-- Insert Table 2 here --

Further modelling examined whether the effects observed within the 0-30 min period were confounded by the covariates of time (day 1 through day 50), wake time, sleep duration, reaction time scores, prior day exercise, prior day alcohol consumption, fatigue on awakening (FF), or presence of the AST at 15 min post-awakening.

These variables were entered separately into the model, so as to achieve a suitable ratio of variables to cases and conserve degrees of freedom. The results of these analyses indicated that the interaction between CAR-EF proved robust to each of these controls, remaining similarly significant with a similar effect size in all cases. However as a subsidiary finding, a non-hypothesised post hoc finding emerged such that increased prior-day exercise predicted a smaller 0-30 CAR increase (t = -2.03, p = .044), but this was independent of the previously reported CAR-EF association (for which t = 2.55, p = .012 when exercise was included in Model B).

3.2.2. Cortisol from 30-60mins post-awakening

Model A of the cortisol data from the 30-60 min period indicated the expected post-CAR general decline in cortisol secretion ($t = -5.85$, $p = <.001$), but Model B did not indicate any significant interaction with EF in this period ($t = 0.64$, $p = .527$), suggesting that the observed cortisol-EF interaction is unique to the 0-30 min rise (CAR).

3.2.3. Cortisol and earlier AST performance

In addition to these analyses, we also examined the association between the earlier AST measure and CAR (performed on half of the study days). The effect size was substantially lower than for the association between the CAR and EF at 45-min post-awakening (performed on all study days), and did not reach significance (noting the reduced sample size for this analysis) ($t = 1.13$, $p = .26$). Finally there was only a very weak and non-significant relationship between EF functioning measured at 15 min post-awakening and EF measured 45 min post-awakening ($r = .154$, $p = .464$, two-tailed).

4. Discussion

This study explored daily variation in the CAR and an index of executive functioning in a healthy adult male over 50 days. Results indicated that a larger increase in cortisol concentrations from 0-30 min post-awakening predicted better EF (attention switching performance) at 45 minutes post-awakening, independent of day order effects, awakening time, sleep duration, reaction time, prior day exercise, prior day alcohol consumption, earlier cognitive demands (a 15-min post-awakening AST) and level of fatigue on awakening. This observed relationship between the CAR and EF is thus temporally predictive (given the temporal order of CAR and EF measures). The design is nonetheless correlational and the phrase ‘predictive’ should be interpreted with caution in regard to strong inferences of causation.

The results of the present study build on the work of Evans et al. (2012) which showed an association between trait estimates of CAR magnitude and integrity of EF in older adults, with the present data suggesting that the same direction of significant relationship between the CAR and EF also exists in the pattern of daily co-variation for at least one normal healthy young adult male. This accumulating evidence suggests a potentially important relationship between the CAR and pre-frontal functions. It has been suggested (e.g. see Law et al., 2013) that a possible role of the CAR may be to regulate peripheral circadian rhythms under the influence of the suprachiasmatic nucleus (SCN) of the hypothalamus, acting as a time-of-day marker to optimise cognitive function appropriately. This is a feasible explanation of the CAR-EF relationship, as circadian organization of brain functions via the SCN has been suggested to be essential for normal cognitive functioning (Cohen and Albers, 1991; Karatsoreos et al., 2010). Moreover, the recent demonstration of an association between daily variation in CAR magnitude and capacity for neuroplasticity (Clow et al., 2014) provides a possible mechanism which could underpin this relationship. The importance of EF for dealing with challenge in the typical waking day is evident (e.g. Manly et al., 2002), and the direction of this relationship is certainly in line with the prominent theories that the CAR plays a role in preparing or 'boosting' the individual for the day ahead (Adam et al., 2006). Furthermore, if this predictive 'state' relationship between the CAR and EF is in fact causal, then given the known progressive decline in both CAR magnitude and EF performance with advancing age (e.g. Huizinga et al., 2006; Kudielka & Kirschbaum, 2003; Zelazo et al., 2004), this in turn could inform the trait relationship observed in older adults (Evans et al., 2012).

There is good evidence that sustained exposure to high levels of glucocorticoids evokes neuronal cell damage and impairs synaptic plasticity and cognitive function (Joels and Baram, 2008; Sapolsky et al., 1990; Sapolsky et al., 2000; Suri and Vaidya, 2013). However, it has recently become evident that the circadian rhythm of glucocorticoid secretion may *promote* internal homeostasis and optimal brain function (Nader et al., 2010).

For example, animal studies indicate that healthy circadian glucocorticoid oscillations boost learning-dependent synaptic formation and maintenance (Liston et al., 2013). It is clear that disrupted circadian *patterns* (not just sustained high levels) of glucocorticoid secretion are associated with cognitive deficits (Cho et al., 2000; Evans et al., 2011; Gibson et al., 2010) as well as a wide range of neuropsychiatric diseases (Jagannath et al., 2013; Menet and Rosbash, 2011; Wulff et al., 2010). Results from this study are consistent with these findings and, whilst other aspects of the circadian pattern of cortisol were not examined, suggest a role for the CAR in cognitive function.

A limitation of all case study research is generalizability of the results to the wider population; hence the importance of establishing convergence, refinement and replication of effects across studies of differing design, with differing strengths and weaknesses. For instance, sex differences exist in both CAR magnitude and timing of the peak (Pruessner et al., 1997) and the CAR is also associated with menstrual cycle phase (Wolfram et al., 2011); therefore the need for replication of these effects in a female sample is evident. In addition, specific characteristics of the participant might limit generalisability. For example, given the influence of sleep on cortisol secretion the reported average sleep duration of 6:21 hours per night (below the recommended average of 7-9 hours for his age) may have been a factor in the results obtained. While the generalizability of these results might also be limited by the dependence on a single EF measure, these findings of temporal covariation in a single participant-researcher are directionally in agreement with the between-participants covariation findings of Evans et al. (2012), who used a very different EF task (trail-making task B).

The subsidiary finding of increased prior day exercise predicting an attenuated 0-30 min CAR, though novel, was an unexpected and therefore post-hoc finding. Since it may be of interest to some readers, we have reported it here, but caution against over interpretation of

what it might mean. From the perspective of this paper, we would simply emphasise that controlling for exercise did not influence the principal interactive effect of EF on cortisol rise from 0 to 30 mins post-awakening.

5. Conclusions

The results of the present case study are novel and deserving of further research to confirm generalizability. They provide an exciting first indication of a within-subject association between the 0-30 minute CAR and a measure of EF determined after the CAR period. Certainly when combined with the earlier demonstration of a trait-like CAR-EF relationship (Evans et al., 2012), it is apparent that the relationship between the CAR and EF is a highly promising area of investigation, with potentially important implications for the role of the CAR within the healthy circadian rhythm in humans.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Table 1.

Descriptive statistics for cortisol samples (0-60min), sleep variables, reaction time, EF, flicker fusion, prior day alcohol consumption and prior day exercise.

	Mean	SD
Cortisol 1 (0 min)	10.17	4.14
Cortisol 2 (15 min)	13.85	4.81
Cortisol 3 (30 min)	17.86	3.50
Cortisol 4 (45 min)	17.33	4.26
Cortisol 5 (60 min)	14.05	5.27
Wake time (hh:mm)	8:16	1:03
Sleep duration (hh:mm)	6:21	0:52
Overall reaction time (ms)	282.46	20.15
EF (task switching) (ms)	9.18	11.51
Fatigue (flicker frequency) (Hz)	35.22	1.65
Prior day alcohol (units)	0.94	1.91
Prior day exercise (approx. hours)	0.39	0.65

Table 2.

Cortisol increase from 0-30 min associated with better than average Executive Function (EF). Comparison between simple Model A including only sample time and cortisol, with Model B including z-scored EF (ZEF).

	Model A		Model B	
	Coefficent (SE)	*P*	Coefficent (SE)	*P*
Fixed effects				
Intercept	10.15 (.57)	<.001	10.15 (.57)	<.001
Sample time	0.26 (.02)	<.001	0.26 (.02)	<.001
ZEF			–0.95 (.57)	.101
Sample time * ZEF			0.04 (.02)	.024
	Variance (SE)	*P*	Variance (SE)	*P*
AR Diagonal				
AR1 diagonal	16.36 (2.49)	<.001	16.19 (2.50)	<.001
AR1 rho	0.70 (0.05)	<.001	0.71 (0.05)	<.001

SE = standard error