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The cortisol awakening response is associated with performance of a serial sequence reaction time task

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ABSTRACT

There is emerging evidence of a relationship between the cortisol awakening response (CAR) and the neural mechanisms underlying learning and memory. The aim of this study was to determine whether the CAR is associated with acquisition, retention and overnight consolidation or improvement of a serial sequence reaction time task. Salivary samples were collected at 0, 15, 30 and 45 min after awakening in 39 healthy adults on 2 consecutive days. The serial sequence reaction time task was repeated each afternoon. Participants completed the perceived stress scale and provided salivary samples prior to testing for cortisol assessment. While the magnitude of the CAR (Z score) was not associated with either baseline performance or the timed improvement during task acquisition of the serial sequence task, a positive correlation was observed with reaction times during the stable performance phase on day 1 ($r = 0.373$, $p = 0.019$). Residuals derived from the relationship between baseline and stable phase reaction times on day 1 were used as a surrogate for the degree of learning: these residuals were also correlated with the CAR mean increase on day 1 ($r = 0.357$, $p = 0.048$). Task performance on day 2 was not associated with the CAR obtained on this same day. No association was observed between the perceived stress score, cortisol at testing or task performance. These data indicate that a smaller CAR in healthy adults is associated with a greater degree of learning and faster performance of a serial sequence reaction time task. These results support recognition of the CAR as an important factor contributing to cognitive performance throughout the day.

1. Introduction

The morning surge in cortisol that occurs during the first hour after waking is known as the cortisol awakening response (CAR) (Pruessner et al., 1997). This response is a distinct and variable component of the circadian cortisol rhythm, which has characteristics not directly related to the remainder of the diurnal pattern (Clow et al., 2010a; Clow et al., 2004; Fries et al., 2009). The CAR exhibits high intra-individual variability, and appears to have an arousal function on the central nervous system, activating cortical areas that orient an individual to the time, space, and expected events of the day (Fries et al., 2009). There is emerging evidence of a functional relationship between the magnitude of the CAR and cognitive performance, particularly for different types of memory and executive function (Aas et al., 2011; Brosnan et al., 2009; Hinkelmann et al., 2013; Kennedy et al., 2014). This has clear implications for both ageing and clinical conditions, where alterations in the normal diurnal cortisol rhythm, impaired sleep, stress and anxiety are features: all of which affect the magnitude of the CAR (Chida and Steptoe, 2009). It also may have implications for healthy populations, since diurnal cortisol rhythms are known to influence the neural mechanisms underlying learning and memory (Clow et al., 2014).

Historically, studies investigating the CAR and cognitive function appear to have been conducted to identify a biomarker associated with disease or cognitive decline (Law et al., 2013). Much of the current knowledge has therefore been derived from studies of either clinical populations or ageing cohorts. For example, in patients with conditions characterized by either a blunted CAR (including first episode psychosis (Aas et al., 2011), severe autism spectrum disorder (Brosnan et al., 2009), a family history of schizophrenia (Cullen et al., 2014) and irritable bowel disease (Kennedy et al., 2014)), the more abnormally low the CAR, the worse the deficits in working memory and processing speed (i.e. executive function) and hippocampal-mediated visuo-spatial episodic memory. Consistent with the evidence of an inverted U-shaped relationship between cortisol levels and cognitive performance, an

Abbreviations: AUC, area under curve; CANTAB, Cambridge Neurophysiological Test Automated Battery; CAR, cortisol awakening response; LTP, long term potentiation.

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elevated CAR in patients with un-medicated depression has been shown to impair working verbal and non-verbal memory, spatial memory and executive function (Hinkelmann et al., 2013). In neurologically-healthy ageing adults (aged 60–91 years) a larger CAR magnitude was associated with higher scores of executive function in the afternoon (Evans et al., 2012).

A natural extension of this work has been to elucidate the role of the CAR in regulating cognitive capacity in healthy adult populations to delineate biological mechanisms contributing to cognitive function. There are two lines of evidence that suggest the CAR might have an important influence on cognition in this group. Firstly, we have recently shown that the neuroplastic response (i.e. a key neural process underlying learning and memory) induced experimentally with a repetitive transcranial magnetic brain stimulation paradigm is positively associated with the CAR magnitude in healthy young adults (Clow et al., 2014). Moreover, by examining this relationship on multiple days, we demonstrated that day-to-day variations in CAR magnitude correlate positively with day-to-day variations in the magnitude of the neuroplasticity response (Clow et al., 2014). Secondly, while exogenous administration or stress-induced elevations in cortisol are well known to negatively impact encoding, retrieval and consolidation of new information (de Quervain et al., 2009), recent studies using metyrapone to inhibit cortisol synthesis, provide evidence that the CAR also modulates each of these learning processes (Rimmele et al., 2010; Wagner et al., 2005). This pharmacological suppression of the CAR resulted in impaired free recall of previously encoded information (Rimmele et al., 2010), reduced consolidation of neutral texts (Wagner et al., 2005), as well as decreased performance on an attention task (Rimmele et al., 2010).

The aim of the current study was to determine whether the CAR is associated with acquisition, retention and overnight memory consolidation or improvement of a serial sequence reaction time task, which involves neuroplastic (likely long-term potentiation (LTP)-like) changes in neural networks (Pascual-Leone et al., 1995b). In broad terms, LTP describes long-lasting increases in synaptic efficacy induced by neural (usually afferent) stimulation or activity-dependent experience, and is widely accepted to be one of the principal mechanisms underlying learning and memory (Bear, 1996). Further, we conducted a simple reaction time task to assess whether the CAR was related specifically to serial sequence learning or generalized motor reaction time. As high stress-induced cortisol levels can impair learning processes (Campeau et al., 2011), we also assessed perceived stress and measured salivary cortisol at the time of testing to differentiate the independent contributions of the CAR, stress and cortisol on learning processes.

2. Methods

2.1. Participants

Neurologically-healthy young adults (14 male and 25 female, mean age: 22 years, SD = 4) were recruited following provision of written informed consent. Participants attended the laboratories at the University of Adelaide (South Australia) at the same time on two consecutive days, with all testing performed between 1 and 5 pm. The testing duration was approximately 30 min on day 1 and 45–60 min on day 2. All protocols were approved by the University of Adelaide Human Research Ethics Committee, and performed in accordance with the Declaration of Helsinki (2008 version).

2.2. Serial sequence reaction time task

A standard motor serial sequence reaction time task was used to assess memory acquisition (learning) on day 1, and performance was measured 24 h later (i.e. day 2) to assess memory consolidation. This computer based task has been used previously to assess consolidation effects (e.g. Meier and Cock, 2014). Four small grey squares (length: 4.5 cm) were presented horizontally aligned in the centre of a white computer screen, separated by 2 cm. Each square corresponded to a key ("c", "v", "b", "n") aligned on the keyboard. Participants responded by pressing the appropriate key on the keyboard with the index and middle fingers of their dominant hand. Only one square was coloured at any given time, with the sequence progressing only following a response from the participant. Each block comprised of 12 key presses, beginning with the first square turning green, with the subsequent 11 squares turning blue. The order of the 12 key-press sequence was CBNVBCNCVNVB and was repeated in 24 blocks. The sequence was specifically programmed such that there were no direct repetitions (CVCV) and no runs (e.g. CVB) or trills (e.g. CVCV). Each participant was seated directly in front of the computer screen, and was instructed to place their fingers on the corresponding keys prior to task initiation. The participants had explicit knowledge of the task, having been advised that the sequence would repeat and that the first square of each block would be green. Participants were told to respond as quickly and as accurately as possible to the coloured square by pressing the corresponding key. No oral or visual feedback on performance was provided, and participants were not informed that the task would be repeated the following day.

2.3. Simple reaction time task

The CANTAB (Cambridge Neuropsychological Test Automated Battery, Cambridge Cognition Ltd., UK) system utilizing a touch screen computer tablet (Lenovo plus dimensions) and a standard response press pad as an input device was used to assess simple reaction time. Participants were seated at a desk with the touch screen and the response press pad directly in front of them. The participant was instructed to push the press pad button as quickly as possible when a white square appeared on the screen. There was a variable interval between each trial response and the presentation of the stimulus for the next trial. This task was repeated in three phases, which included one practice stage comprising 24 trials and two assessment stages comprising 50 trials. The outcome was mean latency to respond to the stimuli. Trials in which the subject responded before presentation of the stimulus, or failed to respond to the stimulus, were not included in the calculation.

2.4. Saliva sampling and cortisol assessments

To assess the CAR, participants provided saliva samples at awakening, and then 15, 30 and 45 min post-awakening, using Salivettes© (Sarstedt; Numbrecht, Germany) for the two consecutive testing days. Instructions for collection were provided to each participant in oral and written form. These included instructing participants to place the Salivette collection tubes by their bed so that they could provide their first sample without arising. They also requested participants not eat or drink during the 45 minute collection period. Cotton swabs were to be placed in the mouth for approximately two minutes or until saturated and returned to the collection tube. These samples were collected in the participant's own home and stored in the home fridge, and then brought to the laboratory on the second day of testing. The times of collection were recorded in a log completed by each participant. Spot saliva samples were collected each day immediately prior to and after cognitive testing using Salivettes. To extract the saliva, the Salivette cotton swabs were centrifuged at 2500 RPM for 5 min. Saliva was stored at −20 °C prior to analysis. Cortisol was determined using a high sensitivity salivary cortisol enzyme immunoassay kit (Salimetrics, State College, Pennsylvania) as per the manufacturer's instructions. The limit of detection was 0.012 μg/dL. The inter- and intra-assay coefficients were 15% and 3% respectively. Cortisol data was screened for outliers through both visual assessment of histograms and comparison to established norms (Wust et al., 2000).

Participants wore an Actiwatch (Respironics) on their wrist throughout the testing period to record activity, sleep and exposure to