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Day differences in CAR predict plasticity

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Abstract

The cortisol awakening response (CAR) is the most prominent, dynamic and variable part of the circadian pattern of cortisol secretion. Despite this its precise purpose is unknown. Aberrant patterns of the CAR are associated with impaired physical and mental health and reduced cognitive function, suggesting that it may have a pervasive role or roles. It has been suggested that the CAR primes the brain for the expected demands of the day but the mechanisms underlying this process are unknown. We examined temporal covariation of the CAR and rapid transcranial magnetic stimulation (rTMS)-induced long term depression (LTD)-like responses in the motor cortex. Plasticity was evaluated across 180 measures from 5 time points on 4 sessions across 9 researcher participants, mean age 25 ± 2.5 years. Plasticity estimates were obtained in the afternoon after measurement of the CAR on 4 days, at least 3 days apart. As both CAR magnitude and rTMS-induced responses are variable across days we hypothesised that days with larger than individual average CARs would be associated with a greater than individual average plasticity response. This was confirmed by mixed regression modelling where variation in the CAR predicted variation in rTMS-induced responses (Df: 1, 148.24; F: 10.41; p=0.002). As the magnitude of the CAR is regulated by the 'master' circadian CLOCK, and synaptic plasticity is known to be modulated by peripheral 'slave' CLOCK genes, we suggest that the CAR may be a mediator between the master and peripheral circadian systems to entrain daily levels of synaptic plasticity.

Introduction

There is good evidence that sustained exposure to high levels of glucocorticoids evokes neuronal cell damage and impairs synaptic plasticity (Sapolsky et al., 1990; Joels, 2008; Suro 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; Gibson et al., 2010; Evans et al., 2011) as well as a wide range of neuropsychiatric diseases (Wulff et al., 2010; Menet and Rosbash, 2011; Jagannath et al., 2013).

In healthy animals, including humans, glucocorticoid hormones have a marked underlying circadian pattern with characteristically low levels during sleep, peak levels soon after awakening, followed by a gradual decline (Edwards et al., 2001). This circadian pattern is regulated by the central master CLOCK: the hypothalamic suprachiasmatic nucleus (SCN) (Perreau-Lenz et al., 2003). Furthermore, it has increasingly become recognised that glucocorticoids adjust the circadian rhythm and function of the ubiquitous *peripheral* CLOCKs. Dysfunction or dysregulation in either circadian system alters internal homeostasis and causes pathologic changes virtually in all tissues, including the brain (Nader et al., 2010).

In healthy humans, the initial burst of cortisol secretion that occurs on awakening (cortisol awakening response: CAR) is a distinct aspect of the circadian pattern of cortisol secretion (Pruessner et al., 1997; Edwards et al., 2001; Fries et al., 2009;

Clow et al., 2010) and exhibits notable day-to-day variability (Hellhamer et al., 2007; Law et al., 2013). A study in one healthy young male revealed that daily CAR magnitude varied tenfold and was associated with anticipated obligations in the coming day (Stalder et al., 2009). Although this was consistent with the idea that the CAR may prime the brain for the expected demands of the day ahead (Fries et al., 2009), the mechanisms underlying this process have not been elucidated.

We set out to examine the CAR in relation to levels of synaptic plasticity measured in motor cortex some 6-7 hours after awakening. We chose to use a model of synaptic plasticity previously used to explore associations with levels of cortisol in healthy intact participants: rapid transcranial magnetic stimulation (rTMS)-induced long term depression (LTD)-like responses in the motor cortex (Sale et al., 2008; Pitcher et al., 2012). We used this measure as a representative indicator of effects caused by any factor that affects the whole brain. We hypothesised that one function of the CAR is to regulate the sensitivity of synaptic plasticity, known to be modulated by peripheral CLOCK genes (Wang et al., 2009) during the coming day and that this could be one mechanism whereby the CAR could influence a wide range of behaviours. We predicted that day-to-day variation in the CAR would correlate with day-to-day variation in rTMS-induced synaptic plasticity of the motor cortex.

Material and Methods

Design and Participants

In this study we sought to relate temporal variation within a large sample (N=180) of plasticity estimates to temporal variation of the magnitude of the CAR. The design was entirely within-participant with estimates collected at 5 fixed time points repeated over 4 sessions and replicated over 9 healthy, normal BMI participant researchers from the Universities of Adelaide and South Australia (78% female; mean age 25 ± 2.5 years), chosen to ensure rigorous adherence to the demanding protocol.

Procedure

The protocol was in accordance with the Declaration of Helsinki and was approved by the University of Adelaide Human Ethics Committee. Participants gave written informed consent prior to testing and were screened for any conditions that would contraindicate TMS (Rossi et al., 2009). Testing sessions were never less than 3 days apart to minimise carry over effects from the rTMS protocols (Goldsworthy et al., 2012; Hamada et al., 2013). On each study day, a CAR was determined upon awakening and plasticity estimates were assessed on the same afternoon.

Estimation of the cortisol awakening response

Saliva samples were collected using Salivettes (Sarstedt Ltd.), immediately on awakening and at 15, 30, and 45 min post-awakening (samples 1-4, respectively) on each study day. Sampling accuracy was recorded by electronic monitoring. Awakening times were determined using wrist-worn Actiwatches (Actiwatch-Score, Cambridge UK).These are piezoelectric motion sensors that distinguish sleep and awakening periods by reduced and increased activity respectively. Saliva sampling times were verified using Medical Event Monitoring (MEMS) caps as described by Smyth et al. (2013). During the saliva collection period protocol instructions were to

take nil by mouth other than water, and to refrain from brushing teeth to avoid abrasion and micro-vascular leakage. Cortisol analyses were carried out using a standard enzyme-linked immunosorbent assay protocol (Salimetrics, USA). The limit of detection of the assay was 0.33nmol/L.

Adherence to the saliva sampling protocol was excellent. No sampling time deviated more than 5 minutes from the requested saliva collection times relative to verified awakening (Smyth et al., 2013). Four of the 144 saliva samples were below the limit of detection of the assay: three awakening samples, and one 30 min sample. Undetectable samples were treated as missing data, and all other cortisol measures were included in the final analysis. CAR magnitude was calculated as the mean cortisol increase (MnInc) from 0-45mins: sample 2+sample 3+sample 4)/3-sample 1.

Transcranial magnetic stimulation

All TMS sessions were completed in the afternoon (at 2 or 3pm) in order to minimise time of day influences (Sale et al., 2007). Muscle contractions in the hand in response to TMS stimulation of the motor cortex were recorded as electromyographic (EMG) activity in the right first dorsal interosseous (FDI) using surface electrodes placed in a belly-tendon configuration. The EMG signal was amplified (x1000; CED 1902 amplifier, CED, UK), band pass filtered (20-1000 Hz) and digitized at a sampling rate of 2 kHz (CED 1401 interface, CED, UK). A Magstim-200 stimulator (Magstim Co., Whitland, UK) generated single-pulse stimuli, delivered through a figure-of-eight coil (90 mm diameter) placed tangentially to the scalp with the handle pointing backward at a 45° angle away from the midline. Suprathreshold pulses were delivered over the left M1 at numerous sites in order to

identify the optimal site for consistently evoking motor evoked potential (MEPs) in the relaxed right FDI and this site was marked on the scalp. The TMS intensity that elicited MEPs of approximately 1mV (SI_{1mV}) in the relaxed FDI was determined (for each testing session) at baseline and was used to examine changes in MEP amplitude after each protocol. Although we did not use individual neuronavigation to place the coil, it is likely that there was little change in its position from day to day since the baseline intensity and amplitude of the 1mV was the same on each occasion. Any minor change in position or angle would have been random and could not contribute to the effects we observed. Two blocks of 15 single-pulse TMS trials, with an inter-trial interval of 7 seconds (± 10%), were delivered at baseline and one block of 15 single-pulse TMS trials was then delivered 0, 5, 10, 20, and 30 minutes after rTMS. Individual MEP data trials were excluded if EMG activity was present in the 100 ms immediately prior to TMS. The peak-to-peak MEP amplitude (in mV) was measured for each trial to give an index of the size of the muscle twitch and the mean amplitude at each post-rTMS time point was expressed as a ratio of the mean of the two baseline samples. This provided and index of the change in the size of the muscle response to the same brain stimulus after rTMS relative to baseline prior to rTMS: the MEP ratio or neuroplasticity index.

The rTMS protocol adopted was continuous theta burst stimulation (cTBS) which was delivered using a figure of eight shaped Double-Cooled-Coil-System coil (70mm, Magstim, UK). Bursts of three pulses were delivered at 50 Hz every 200 ms continuously for 40 seconds (Huang et al., 2005). TBS intensity was set to 80% of active motor threshold (AMT); AMT was defined as the minimum intensity required to elicit a MEP in FDI of at least 200 µV in at least five out of 10 consecutive trials when

performing a low-level voluntary contraction of FDI (10% of maximal voluntary contraction) and was determined for each testing session. This paradigm is known to induce long term depression (LTD)-like effects resulting in a smaller muscle response (hence a reduced MEP ratio) post rTMS.

Data Analysis

Data were analysed using mixed regression modelling (Blackwell et al., 2006) of variation in the 180 MEP-ratio estimates. CAR magnitude was included as the principal covariate, and was participant-centred since absolute differences in participants' average CAR magnitude was not the focus of this study. Participant centring expresses exclusively within-participant variation (i.e. participants' deviations from their own study means). We modelled time-point within session (at 0, 5, 10, 20, and 30 minutes) and session number (1-4) as fixed factors. Intercept effects were modelled as both fixed and random effects. Finally, further modelling was undertaken to check that any findings from initial modelling were not confounded by associations with awakening time and level of cortisol.

Results

Table 1 presents descriptive data for the study. As expected, following rTMS the average MEP ratio was less than 1 (0.9±0.29). In other words, as expected, the peak-to-peak MEP amplitude (in mV) post-rTMS was less than at base, indicating the induction of LTD-like synaptic plasticity. The average CAR across days showed a mean increase of 2.72 nmol/l cortisol in the 45 minutes after waking.

Insert Table 1 here

Table 2 shows F-ratios and significances for the parameters in the modelled data. There was no significant difference between the MEP ratios measured at the 5 post-rTMS time points (sample numbers 1-5), allowing us summarise the effect of rTMS as a single overall mean ratio (as shown in Table 1). Similarly there were no differences in the mean MEP ratios on each of the 4 days (session numbers 1-4), suggesting that there was no adaptation to the procedure over the period of testing.

Insert Table 2 here

The magnitude of the CAR was significantly associated with their mean MEP ratios collected on the same day. Calculation of the estimate coefficient (-.013) suggests that for each single nmol/l above their own average CAR on any testing day, the predicted MEP ratio would be .013 points (approximately 1.4%) lower than average. Since lower MEP ratios reflect a larger response to the rTMS protocol, the finding suggests that larger than average CARs in the morning predict greater neuroplasticity measured later in the afternoon.

Figure 1 plots the relationship between morning CAR and afternoon rTMS response. Data are expressed relative to mean responses for both measures over the 4 days. The data show that if the CAR magnitude was larger than individual means, then there was a greater chance that the response to rTMS indicated greater neuroplasticity i.e. an MEP ratio lower than the expected mean.

Further modelling examined whether CAR magnitude was confounded by the covariates of awakening time and / or awakening level of cortisol. The effect was robust to such statistical control, remaining independently significant with a similar effect size.

Insert Figure 1 here

Discussion

This study of temporal variation with multiple sampling across days shows a highly significant relationship between cortisol awakening response and the capacity to induce synaptic plasticity in the motor cortex on that same day. Specifically, on days when individuals' CARs were bigger than their own individual averages there were greater changes in the size of the muscle response following the rTMS protocol, measured that afternoon, indicating greater neuroplasticity. Likewise lower than average CARs predicted smaller changes in the size of the muscle response after rTMS.

The rTMS protocol used here (continuous theta bust, cTBS) is thought to provide a measure of the responsiveness of early long term depression (LTD)-like processes in the motor cortex (Huang et al*., 2005*; Huang et al., 2007). The measure varies considerably between individuals as it is affected by factors such as age and genetics (Ridding and Ziemann, 2010; Hamada et al., 2012). However, there are also large variations in an individual's response measured on different days (Sale et al., 2007). The present results suggest for the first time that the daily magnitude of the CAR may be responsible for some daily variation in synaptic plasticity.

We have studied a specific index of plasticity in the motor cortex, but evidence suggests this measure can serve as a representative marker of effects caused by any factor that affects the whole brain (e.g. secretion of glucocorticoids). For example administration of an NMDA antagonist in humans can be detected by reduced rTMS-induced plasticity in motor cortex (Wolters et al., 2003; Stefan et al., 2002). Similarly the human Huntington's disease gene in mice reduces synaptic plasticity in many cortical regions; in humans this is reflected in reduced plasticity in the motor cortex (Crupi et al., 2008). This TMS paradigm also has the advantage of being non-invasive and appropriate for use in healthy intact volunteers. Our hypothesis here is that the changes we see in motor cortex synaptic plasticity will reflect changes in other brain areas, all of which could be affected by the CAR. The relationship between individual day to day changes in cortical plasticity to relevant day to day differences in behaviour have yet to be examined, so the functional implications of such changes in plasticity are not yet fully described. However we know that plasticity interacts with learning, speeding it up or slowing it down (ref for this from John), which suggests some commonality.

Aberrant patterns of the CAR have been consistently linked with indices of impaired physical and mental health (Kudielka and Kirschbaum 2003; Fries et al., 2009). In particular the CAR has been associated with cognitive function, an attenuated CAR has been associated with lower hippocampal volume (Buchanan et al., 2004; Pruessner et al., 2007), amnesia (Wolf et al., 2005), deficits in verbal memory and processing speed (Aas et al., 2011; Evans et al., 2011), and worse executive function (Evans et al., 2012). Furthermore inhibition of the CAR using the cortisol

synthesis inhibitor metyrapone impaired memory retrieval in healthy young participants (Rimmele et al., 2010).

The CAR is the most prominent and dynamic element of the circadian pattern of cortisol secretion. Despite this its precise purpose is unknown. Evidence suggests causal pathways linking circadian cortisol disruption to sub-optimal brain function and brain disorder (Wulff et al., 2010; Jagannat et al., 2013). One putative pathway involves dysregulation of the circadian CLOCK system (Menet and Roshbash, 2011). In this scheme the SCN acts as the light-activated 'master' CLOCK, which synchronises the peripheral 'slave' CLOCKs through neural and humoral pathways (Nader et al., 2010). It has been proposed that one of these pathways may involve the CAR (Law et al., 2013), which is regulated by dual inputs from the SCN: via the hypothalamic pituitary adrenal axis as well as a direct neural pathway to the adrenal cortex (Clow et al., 2010). These dual pathways mean it can fine tune sensitivity of the adrenal cortex to adrenocorticotrophic hormone (the secretagogue for cortisol) and make it ideally suited to relay messages to the periphery from the master CLOCK. Glucocorticoids are known to affect peripheral CLOCKs in almost all organs and tissues by influencing the expression of several clock-related genes, which in turn have been shown to modify synaptic plasticity (Wang et al., 2009). This means that the circadian pattern of glucocorticoid secretion (and as indicated by this study the CAR in particular) can affect function in a sustained way over the day, not just by the influence of ambient levels e.g. direct inhibition of NMDA receptor function. Although peripheral clock function was not directly examined in this study circulating leukocytes provide an ideal tissue source for further work investigating the CAR and the circadian clock system in humans (see Kusangi et al, 2008). Day differences in

mRNA expression of Per1, Per2, Per3 mRNA, in particular, at a set time in the afternoon relative to morning CAR would be of particular interest.

Conclusions

This study has demonstrated for the first time significant covariation between the cortisol awakening response and rTMS-induced synaptic plasticity of the motor cortex, measured 6-7 hours later the same day. These findings may indicate a pivotal role for the CAR in priming the brain for the day ahead (Fries et al., 2009; Clow et al., 2010) possibly by entrainment of peripheral CLOCKs in the brain that can influence the sensitivity of synaptic plasticity. As well as shedding light on a possible role for the CAR and informing the marked state variation in this measure of neuroplasticity it offers a plausible mechanism by which state factors which affect the CAR (such as stress) can affect brain plasticity.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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