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Short Communication

The stress hormone cortisol blocks perceptual learning in humans

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ABSTRACT

Cortisol, the primary glucocorticoid (GC) in humans, influences neuronal excitability and plasticity by acting on mineralocorticoid and glucocorticoid receptors. Cellular studies demonstrated that elevated GC levels affect neuronal plasticity, for example through a reduction of hippocampal long-term potentiation (LTP). At the behavioural level, after treatment with GCs, numerous studies have reported impaired hippocampal function, such as impaired memory retrieval. In contrast, relatively little is known about the impact of GCs on cortical plasticity and perceptual learning in adult humans. Therefore, in this study, we explored the impact of elevated GC levels on human perceptual learning. To this aim, we used a training-independent learning approach, where lasting changes in human perception can be induced by applying passive repetitive sensory stimulation (rss), the timing of which was determined from cellular LTP studies. In our placebo-controlled double-blind study, we used tactile LTP-like stimulation to induce improvements in tactile acuity (spatial two-point discrimination). Our results show that a single administration of hydrocortisone (30 mg) completely blocked rss-induced changes in two-point discrimination. In contrast, the placebo group showed the expected rss-induced increase in two-point discrimination of over 14%. Our data demonstrate that high GC levels inhibit rss-induced perceptual learning. We suggest that the suppression of LTP, as previously reported in cellular studies, may explain the perceptual learning impairments observed here.

1. Introduction

Cortisol, the primary glucocorticoid (GC) in humans, influences neuronal excitability and plasticity by acting on mineralocorticoid and glucocorticoid receptors (De Kloet et al., 2005). Cellular studies have shown that increased GC levels, due to activation of the glucocorticoid receptor (GR), can inhibit neuronal plasticity by reducing hippocampal long-term potentiation (LTP) (Diamond et al., 2007; Pavlides et al., 1993). This in turn is thought to affect learning processes.

Indeed, at a behavioural level, numerous studies have reported impaired hippocampal function after treatment with GCs (Wolf, 2009). With respect to episodic memory, a detrimental effect of GCs on memory retrieval has been shown repeatedly (e.g. de Quervain et al., 2000). In contrast, memory consolidation is enhanced by GC administration post-training (Wolf, 2009). The formation of implicit memories, such as priming, are thought to be relatively insensitive to the effects of pharmacological cortisol (e.g. Kirschbaum et al., 1996). In addition to its effects on the limbic system, cortisol has also been shown to influence the prefrontal cortex (PFC) and elicit negative effects on working memory (for a recent meta-analysis see (Shields et al., 2015)).

However, little is known about the impact of GCs on adult cortical plasticity and on human perceptual learning. Several years ago, Daw et al. reported reduced plasticity in the developing visual cortex in kittens, following long-term treatment with cortisol, implicating a role for cortisol in ocular dominance plasticity (Daw et al., 1991). Oral administration of hydrocortisone has also been shown to modify plasticity in the human motor cortex (Sale et al., 2008).

Thus, the aim of this study was to determine how elevated GC levels might affect human perceptual learning. To this aim, we used a training-independent learning approach, which can induce lasting changes in perception by applying passive repetitive sensory stimulation (rss). Regarding the timing of the stimulations, the parameters were adapted from cellular LTP studies (Dinse

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et al., 2003; Beste and Dinse 2013). Numerous studies have shown that LTP-like tactile rss induces improvements in tactile perception, which parallels major reorganization in the cortex (Dinse et al., 2003; Pleger et al., 2003; Ragert et al., 2008). Therefore, training-independent learning offers the unique possibility of linking cellular plasticity to human perceptual learning. Owing to suppression of LTP caused by elevated GC levels previous cellular studies (Diamond et al., 2007; Pavlides et al., 1993), we predicted that the administration of hydrocortisone in humans would also affect stimulation-induced learning.

2. Material and methods

2.1. Participants and procedure

This study was approved by the Ethics Committee of the Ruhr-University of Bochum, and all participants provided written informed consent. We conducted a placebo-controlled double-blind study. In total, 30 right-handed male participants were randomised into two groups: 1) cortisol group and 2) control group. The cortisol group received a single 30-mg dose of hydrocortisone, while the control group were treated with a placebo drug. The dose of hydrocortisone administered was based on previous studies showing that a dose of 30 mg can impair hippocampus-dependent memory retrieval (e.g. Kuhlmann et al., 2005). Tests were carried out late in the morning throughout the entire experiment. Participants and experimenter were blinded against drug treatment. Tactile acuity was assessed on the tip of the index-finger by measuring spatial two-point discrimination thresholds, as a marker of tactile perceptual ability. To induce tactile plasticity, we applied tactile LTP-like rss. Discrimination thresholds were measured before and after rss. Saliva samples were obtained at baseline, 80 min, and 120 min after the administration of hydrocortisone or placebo to assess salivary cortisol concentrations (see Fig. 1 for the timeline of the experiment). Participants had no history of neurological or psychiatric illness, drug abuse, or use of medication affecting the nervous system. Upon completion of all experiments, subjects were asked to report their subjective experiences and feelings following the administration of the drug and rss.

2.2. Tactile acuity assessment

Tactile acuity of the right index-finger was assessed by measuring two-point discrimination thresholds using the method of constant stimuli as described previously (Dinse et al., 2003; Pleger et al., 2003; Ragert et al., 2008). The stimuli consisted of seven pairs of needles with different distances, ranging from 0.7 to 2.5 mm, and a single needle of zero distance which served as a control. Tactile stimuli were applied for ~1 s, with an application force of 150–200 mN. Participants had to determine if they had the sensation of one or two needles immediately after the application of the stimulus, and report their perception of a single needle or a doubtful stimulus as 'one', while the perception of two distinct stimuli was reported as 'two'. The stimuli were presented 10 times in a random order resulting in 80 trials per session. The percentage of presentations identified as 'two' for each distance was plotted against the needle distances. This resulted in the generation of a psychometric function which was fitted by a binary logistic regression. The threshold was determined as 50% of correct responses. All participants were required to complete one training session prior to testing to become familiar with the procedure.

2.3. Statistical analysis

Statistical comparisons of effects of cortisol administration and of rss effects were performed in IBM SPSS Statistics for Windows using multivariate ANOVAs with Group as a between-subjects factor and Time as a within-subjects factor. Group data are presented as mean ± standard error of the mean (SEM) unless otherwise specified.

2.4. Repetitive sensory stimulation

Rss was applied for 30 min to the right index-finger. The stimulation sequence was the same as that described previously (Ragert et al., 2008) and consisted of 20-Hz bursts for 1.4 s with 5 s inter-train intervals, a ramp fall-time of 0.3 s and a 0.2-ms pulse width. The pulses were transmitted via adhesive surface electrodes (1 × 4 cm) fixed on the first and third finger segments (cathode proximal). The stimulation intensity was adjusted individually with an average stimulation intensity of 5.57 ± 0.41 mA in the cortisol group, and 5.33 ± 0.30 mA in the placebo group.

3. Results

3.1. Cortisol concentrations

The mean age of the cortisol group was 26.6 years ± 0.91and that of the control group was 27.1 years ± 0.99. In the cortisol group, cortisol levels were increased from a baseline (pre-rss) level of 18.3 ± 2.7 nmol/l to a post-rss level of 199.8 ± 20.2 nmol/l $p < 0.001$ for GROUP and TIME). In the placebo group, the cortisol levels remained unchanged (pre-rss: 15.5 ± 1.8 nmol/l; post-rss: 10.1 ± 1.6 nmol/l; $p > 0.1$).

3.2. Tactile learning

As expected, the placebo group showed a stimulation-induced improvement in two-point discrimination as indicated by a 14.6% reduction in the threshold level, which corresponds to an effect size of 0.70 (Cohen's d). In this group, the threshold decreased from 1.69 mm ± 0.07 at baseline to 1.46 mm ± 0.10 post-stimulation. In contrast, in the cortisol group, a single dose of hydrocortisone (30 mg) completely blocked the stimulation-induced improvement in tactile acuity. Instead, we observed a slight, non-significant increase in the threshold of 1.9% (Fig. 1; 0.04 Cohen's d; $p = 0.006$ for GROUP and TIME). We also observed a significant GROUP x TIME interaction ($p = 0.014$). The discrimination thresholds in the cortisol group were 1.92 mm ± 0.11 pre-rss and 1.94 mm ± 0.10 post-rss. There was no significant difference in the baseline performance between the two groups ($p = 0.09$).

4. Discussion

Our data show that high GC levels affect implicit/cortical learning by blocking the increase in tactile perceptual abilities typically observed following rss. Numerous lines of evidence indicate that intensive training may not be necessary for the induction of implicit/procedural learning. It has been suggested that the effectiveness of rss stems from the fact that the stimulation protocols used are optimized to alter synaptic transmission and efficacy, thus providing novel ways to investigate the relationship between learning processes and their underlying cellular and molecular mechanisms in humans. In the tactile domain, rss leads to improved tactile perceptual abilities, which is associated with increased cortical activation and representational map changes (Pleger et al., 2003), and enhanced cortical excitability and is NMDA-receptor

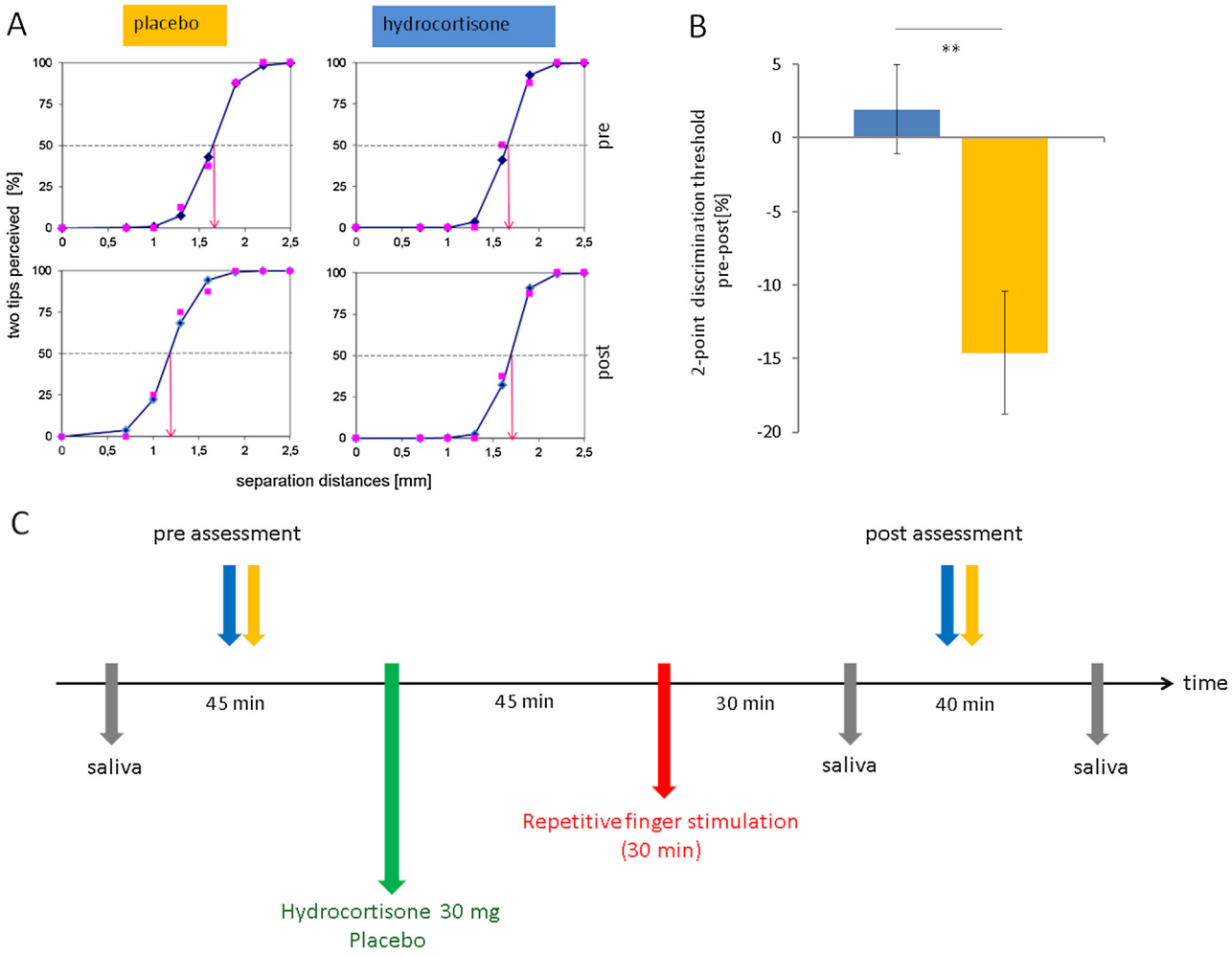

Fig. 1. (A) Psychometric functions (top: pre; bottom: post) illustrating the effects of repetitive sensory stimulation on the threshold of two-point discrimination in a representative participant from each group. Two perceived presentations are shown as percentages (x-axis) for different tip separation distances (y-axis). The pink data points indicate the decisions of participants regarding the differences in distance between tips, and the blue curve/data points show the fitted binary logistic regression. The two-point discrimination threshold was determined on the basis of a 50% criterion (see red arrows) (B) Percentage change (±SEM) in the two-point discrimination threshold compared pre-/post–30 min of repetitive sensory stimulation in the hydrocortisone (blue) and placebo groups (yellow, N = 15 each). Asterisks indicate significant group differences $^{**}p < 0.01$. (C) Experimental schedule showing the time points for saliva collection, drug administration, application of repetitive sensory stimuli, and time of assessment pre-/post-tactile acuity measures.

dependent and subject to modification through neuromodulators (Dinse et al., 2003). The effects induced by a single rss session typically last ~8 h (Pleger et al., 2003); however, daily repeated rss sessions over 2 weeks lead to persistent changes.

The discovery that a single dose of hydrocortisone substantially affects rss-induced perceptual improvement suggests that high GC levels not only impair hippocampal plasticity (Diamond et al., 2007; Wolf, 2009) but also neuronal plasticity in the sensory cortex. Human neuroimaging studies have shown that cortisol reduces the task-induced blood oxygenation level-dependent (BOLD) signal response during memory retrieval in the hippocampus (Oei et al., 2007). Similar observations have been made in the dorsolateral PFC during a working memory task (Qin et al., 2009). It remains to be determined whether the cortisol-induced impairment in tactile learning is also associated with a reduction in the BOLD response during the training session.

Studies investigating the administration of GCs or behaviour-induced stress responses report a significant attenuation of episodic memory retrieval, while in parallel, memory consolidation is enhanced (Wolf, 2009). The data from our study reveal even more severe effects of GCs in the perceptual learning domain, where the effect of learning was completely eliminated. Since previous studies have shown that the effect of learning induced by rss is NMDA-receptor dependent (Dinse et al., 2003), we suggest that the suppression in LTP observed following GC administration reported in electrophysiological studies (Diamond et al., 2007; Pavlides et al., 1993) may explain the perceptual learning impairments observed here. As such, the effects of GC administration described here suggest that cortisol could be a powerful modulator of rss-induced learning. This is in contrast to a recent unpublished study which demonstrated that reward or attention lack any modulatory influence on this form of training-independent sensory learning (Dinse unpublished observations). Furthermore, rss-induced changes have been shown to correlate with cortical changes such as excitability, BOLD signal intensity and electroencephalogram (EEG)-measured dipole localization (Pleger et al., 2003, 2001). In all cases, little or no perceptual improvement were linked to little or no changes in the cortex. Therefore, it seems reasonable to assume that the lack of effects of rss after hydrocortisone administration might be due to the inhibition of cellular plasticity mechanisms such as LTP.

In the motor domain, paired associative stimulation (PAS), consisting of electrical stimulation of the left median nerve, coupled with transcranial magnetic stimulation over the right motor cortex

is often used to study excitability of the human motor system. Following PAS, motor-evoked potentials (MEPs) increase as a function of time of day, which can be explained by the daily variation in cortisol levels (Sale et al., 2008). These levels are much lower than the cortisol levels found in our study following GC administration. In another study, oral administration of hydrocortisone (24 mg) prevented PAS-induced facilitation of MEPs, indicating that circulating levels of cortisol can modify plasticity of the motor cortex (Sale et al., 2008) which is in line with our observations in the tactile learning domain.

Recent evidence indicates that GCs enhance early visual sensory processing (Weckesser et al., 2016). In contrast, more complex hippocampal-based scene perception seems impaired by stress (Paul et al., 2016). Whether similar effects occur in the tactile domain still needs to be determined by future studies investigating the impact of GCs on two-point discrimination.

Comments received from participants upon completion of the study that addressed subjective experiences and feelings following drug application and rss, revealed no peculiarities. To determine if the administration of hydrocortisone had an effect on the decision process associated with the two-point discrimination we examined in detail the statistics of the single responses. In both groups at baseline, the number of wrong detections of a single stimulus was zero, a response pattern which we also observed post-treatment (i.e. under the influence of hydrocortisone). This pattern was also observed for the first separation distance of 0.7 mm (see Fig. 1 for examples of individual psychometric curves). However, it should be noted that previous studies have indicated that GCs can affect decision making processes (Putman et al., 2010; Starcke and Brand, 2012; Vinkers et al., 2013). Therefore further studies are needed to investigate in how far task instructions and thus affected decision making could confound the observed effects on altered discrimination performance.

The dose of hydrocortisone used in the present study leads to substantial elevations in cortisol concentrations; therefore, it remains to be determined whether moderate psychosocial stress-induced increases in cortisol have similar effects on tactile learning. In addition, stress leads to a rapid activation of the sympathetic nervous system, an alteration which was not mimicked in our current study.

GCs can act via rapid non-genomic mechanisms by influencing membrane bound receptors. After a time delay of 60–90 min, genomic effects, mediated by intracellular receptors, predominate (Joels et al., 2008). Owing to the design of our current study, we were unable to differentiate between these two modes of action. Previous studies have attempted to unravel the different contributions of genomic and non-genomic effects by varying the interval period between administration of cortisol and subsequent performance in a memory encoding task (e.g. see (Henckens et al., 2012)).

From a clinical perspective, corticosteroids are an essential cornerstone in the treatment of immunological and neurological diseases. Therefore, it is possible that the inhibition of procedural learning following the administration of hydrocortisone described here may also affect rehabilitation outcomes. Further studies are required to explore the possible side-effects of clinical corticosteroid treatment on cortical learning. Moreover, the possible effects of hydrocortisone administration in female participants and the possible time-course effects of GCs require further clarification.

Overall, our data reveal that GCs substantially influence cortical learning processes. These findings demonstrate that learning-induced tactile improvement is controlled by GCs, suggesting that stress-related mechanisms inhibit perceptual learning in a similar manner to that already reported with regard to episodic memory retrieval (Wolf, 2009).

Contributors

HRD, JCK, MT & OTW designed the study, wrote the protocol, and conducted literature searches. JCK conducted the study. HRD, JCK & ML analyzed the data. HRD, JCK, ML, MT & OTW interpreted the data. MP, HRD, MT & OTW wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest regarding this manuscript.

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