

**Single dose hydrocortisone administration does not enhance motor
sequence learning or reward learning in humans**

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Abstract

Despite its physiological and clinical relevance, the influence of hydrocortisone on
20 specific kinds of learning remains relatively unexplored. We measured the effect of
hydrocortisone on motor sequence and reward learning under non-stress
conditions. 54 healthy young volunteers were randomly assigned to a dose of
20mg hydrocortisone versus placebo. Participants performed two well-defined
learning tasks. Hydrocortisone did not affect motor sequence or reward learning.

25 **Introduction**

Cortisol is involved in a broad range of physiological processes, especially under stress conditions (Schwabe and Wolf, 2012). Nevertheless, only little is reliably known about how cortisol affects specific kinds of learning. Findings in previous studies have been complex and partly contradictory. For instance, memory
30 consolidation, a mechanism underlying Cognitive-Behavioural Therapy (CBT), can be both enhanced and impaired through hydrocortisone administration (de Quervain et al., 2017). Low-dose administration has been suggested to improve CBT, potentially by enhancing extinction learning (Bentz et al., 2010). This is based on the suggestion that hydrocortisone acts on glucocorticoid receptors in brain
35 areas that are involved in learning and memory processes, such as hippocampus, amygdala and frontal lobe. Potentially related effects on other types of learning, however, remain underexplored. Exploring such effects will help reduce ambiguity in the interpretation of psychological and clinical results that might be linked to hydrocortisone administration. We hypothesise that – in line with its enhancing
40 effects on exposure-based CBT – a single dose of hydrocortisone will improve motor and reward learning.

Experimental studies with well-defined learning paradigms and homogeneous samples of healthy individuals are needed to further restrict hypotheses of how hydrocortisone affects learning.

45 In this study, we used two well-defined learning tasks that deliberately differed in their complexity and cognitive demands. The first task measured motor sequence learning. This repetitive/procedural task relied on simple parameters such as reaction time (RT), with low cognitive demands. The second task measured reward learning based on complex decision-making, requiring cognitive adaptation in a
50 high-demand situation.

Methods

54 volunteers were tested one hour after receiving 20mg hydrocortisone (low
55 dose) or placebo orally, in a double-blind design. Dosing and timing of administration was chosen in accordance with previous studies assessing the effects on psychological treatment (de Quervain et al., 2017). Standard power calculations based on previous research into the effects of a single dose of hydrocortisone on working memory in healthy volunteers (Miller et al., 2015)
60 suggest sample sizes of 20 per drug group to achieve effect sizes of at least 0.95 at

an α -level of 0.05, with observed iconic memory indices of $M=12/SD=8$ in the placebo group and $M=30/SD=22$ in the hydrocortisone group (relation to memory as closest available alternative to learning for the dose used). Participants gave written informed consent. The study was approved by the South-Central-Oxford
65 National-Research-Ethics-Committee (REC-reference:13/SC/0144; IRAS-ID:125610), as part of a larger study (see Günthner et al. (2016) and Scholl et al. (2014) for detailed methods).

The motor task measured learning as decrease in RT over time as participants repeatedly responded with button presses to a fixed 10-digit-sequence (shown on-
70 screen), that was repeated three times in each of 15 “learning blocks”. On each trial, participants had to react to a cue appearing in one of four on-screen positions. Cue presentation was independent of participants’ responses.

Consolidation tasks (3 learning blocks) were conducted 2 and 24 hours after initial testing.

75 The reward task required participants to repeatedly choose between two options, taking into account the following features per option: reward and loss magnitudes (shown on-screen), and probabilities of reward or loss occurring if they chose an option (had to be learnt). Learning was assessed using a computational reinforcement learning model (see Scholl et al. (2014)) that derived separate
80 measures (learning rate, α) for learning about reward and loss. The model

contained probability estimates regarding the outcome of both options, which were continuously updated based on previous trial outcomes:

$$Prediction_t = Prediction_{t-1} + \alpha * (Outcome_{t-1} - Prediction_{t-1})$$

The estimates were integrated with the explicitly cued magnitudes to calculate

85 how valuable each option was (option utility). Utility was calculated as a weighted sum of probability and magnitude, as we previously found strong support for this model in the same placebo group reported here (Scholl et al., 2014).

$Utility_{Reward} = \mu * Prediction_{Reward} + Magnitude_{Reward}$, with μ indicating the importance of the learnt probability. The utility for loss was computed in the same

90 way. Reward and loss utilities were then added together to create the overall utility. A standard soft-max decision rule was used to predict probabilities for choosing an option based on the utilities:

$$P_{Option A} = \frac{e^{Utility(A) \times \beta}}{e^{Utility(A) \times \beta} + e^{Utility(B) \times \beta}}, \text{ with } \beta \text{ describing a participant's tendency to choose the option with higher utility.}$$

95 The model was fit for each participant separately using Matlab's `fminsearch` algorithm.

Three participants did not participate in this task, seven were excluded from analysis (failure to follow instructions).

Sociodemographic, personality and mood (VAS) parameters were measured to

100 assure that different task behaviour would not be due to respective group

differences. Analyses were done in Matlab, SPSS and JASP. Bayes Factors (BF) were computed to quantify the evidence for the null hypothesis relative to the experimental hypothesis ($BF_{01} > 1$ providing anecdotal, > 3.2 providing substantial evidence that the null model is true). We used a default cauchy prior with scale

105 0.707.

Results

The groups were well-matched in terms of sociodemographic, personality and mood parameters (Table 1).

110 In the motor task, learning (RT improvement) occurred in both groups (Figure 1(a); ANOVA, effect-of-block(15): $F(2.2, 114.5) = 15.93$, $p < 0.001$), but did not differ between them (ANOVA, block(15)-group(2)-interaction: $F(2.0, 114.5) = 0.82$, $p = 0.45$, $BF_{01} = 82.2$ [substantial]). Neither did average RT (ANOVA, effect-of-group(15): $F(1, 52) = 0.001$, $p = 0.97$, $BF_{01} = 2.8$) or overall amount learnt (first versus

115 last learning block; $t(52) = -1.03$, $p = 0.31$, $BF_{01} = 2.3$, CI: $-0.75/0.26$). Accuracy was high throughout the task (both groups $> 90\%$, all learning blocks).

Consolidation tasks found no differences between groups (2h: ANOVA, effect-of-group: $F(1, 52) = 0.08$, $p = 0.78$, $BF_{01} = 1.9$, block-group-interaction: $F(1.7, 89.7) = 0.01$,

p=0.99, $BF_{01}=9.2$; 24h: ANOVA, effect-of-group: $F(1,52)=0.08$, $p=0.78$, $BF_{01}=1.6$,

120 block-group-interaction: $F(1.8,93.8)=0.29$, $p=0.73$, $BF_{01}=8.4$).

In the reward task, both groups did similarly well overall (i.e. money won, points won/lost, all $p>0.40$). Using a computational learning model, we found no differences in learning rates (figure 1B), for either reward ($t(42)=-0.16$, $p=0.88$, $BF_{01}=3.3$ [substantial]) or loss ($t(42)=0.74$, $p=0.46$, $BF_{01}=2.6$ [anecdotal]). There

125 was also no difference in any other model parameter (all $p>0.32$).

Table 1. Sociodemographic parameters and questionnaire measurements.

	Placebo		Hydrocortisone		
Age	22.15 ± 0.51		22.10 ± 0.73		
Gender, F:M	17:17		10:10		
BDI	1.68 ± 0.44		2.00 ± 0.51		
Education years	16.56 ± 0.36		16.15 ± 0.52		
Trait anxiety	30.53 ± 1.31		30.55 ± 1.65		
Weight	66.19 ± 1.82		65.41 ± 2.32		
Neuroticism	5.18 ± 0.76		5.10 ± 1.25		
ACS	60.74 ± 0.87		60.05 ± 1.60		
BIS	15.62 ± 0.55		15.95 ± 0.97		
BAS	24.94 ± 1.00		26.30 ± 0.96		
ASI	16.44 ± 2.39		16.90 ± 2.46		
	Placebo		Hydrocortisone		Logistic Regression
VAS item	before	after	before	after	regression weight
Anxious	7.4 ± 1.4	4.8 ± 1.2	10.7±2.2	5.5 ±1.5	-0.7(-1.4;0.0)
Sleepy	27.7 ± 3.6	21.9 ±3.6	23.0±3.5	19.6±3.5	-0.2(-0.5;0.0)
Flushed	8.5 ± 1.7	3.3 ± 0.6	11.0±2.3	4.2 ±1.0	1.1(-0.6;2.7)
Tearful	3.0 ± 0.7	2.5 ± 0.4	3.5 ±0.6	2.8 ±0.4	-2.8(-7.1;1.5)
Nauseous	3.1 ± 0.7	3.0 ± 0.7	3.6 ±0.7	5.0 ±1.5	-1.6(-3.2;0.1)
Hopeless	3.2 ± 0.6	2.2 ± 0.3	2.8 ±0.4	2.6 ±0.3	1.8(-0.9;4.5)
Tremor	3.3 ± 0.7	2.7 ± 0.6	3.7 ±0.6	3.2 ±0.5	2.4(-0.5;5.4)
Sad	4.5 ± 0.8	2.2 ± 0.3	4.7 ±0.9	2.7 ±0.4	-2.2(-5.0;0.5)
Dizzy	2.7 ± 0.6	3.1 ± 0.6	5.0 ±1.3	7.1 ±2.0	1.3(0.0;2.5)
Depressed	2.6 ± 0.4	2.5 ± 0.4	3.2 ±0.6	2.7 ±0.4	1.0(-0.7;2.6)
Tachycardia	4.7 ± 1.2	3.7 ± 0.9	5.1 ±1.0	3.6 ±0.6	-2.2(-4.6;0.1)
Alert	49.8 ± 4.3	45.3 ±4.7	55.4±4.9	54.3±6.0	0.3(0.0;0.6)

Sociodemographic, personality and mood parameters (VAS=visual analogue scale) for the placebo and the hydrocortisone groups. Values are mean and standard error of the mean.

Regression weights for each VAS item are shown with 95% confidence intervals, following a logistic regression predicting group assignment based on the VAS items after drug administration (controlling for baseline VAS scores by also including them in the regression). Model comparison of the regression including the VAS items at drug peak-level suggests that the VAS items overall are not different between the groups (BIC: null model (including baseline VAS scores): 112.6, model including all VAS items: 131.8). Abbreviations for the baseline questionnaires: BDI [Beck Depression Inventory], Trait anxiety, Neuroticism [Eysenck Personality Questionnaire], ACS [Attention Control Scale], BIS /BAS [Behavioral

Inhibition/Behavioral Activation Scale], ASI [Anxiety Sensitivity Index]. Visual analogue scale measurements [VAS] data was acquired before the administration of hydrocortisone and after and indicated by participants by placing a tick on a line of length 100mm.

Figure 1. Motor task (reaction time) and reward task (learning rates) results.

[insert Figure 1.]

(a) Motor task: Reaction time. Log-transformed reaction time (ms) across all learning blocks, including consolidation after 2 (C1) and after 24 hours (C2). Blocks 1 and 15 were no learning blocks, but random sequence blocks, to familiarise participants with the task pre-testing (block 1) and to assure that improvements in reaction times were due to sequence learning, not non-specific motor skill improvement (block 15; reaction time for both groups higher than in preceding block, $p < .001$) (b) Reward Task: Learning rates (α) did not differ between the two groups for reward ($p = 0.88$) or loss ($p = 0.46$). Error bars are standard error of the mean.

Discussion

Hydrocortisone did not affect motor sequence learning. In contrast, Römer et al.

155 (2011) found hydrocortisone to actually delay learning. The differing results might
be due to the different experimental paradigms, as they used higher-order
sequential regularities (colour combinations predicting future colours) that could
be detected by subjects. That delayed learning at the very beginning of the task
accounted for the learning impairment is in line with this hypothesis, as attentional
160 control and strategy learning are especially relevant in the beginning of learning a
repetitive sequence.

Hydrocortisone did not affect reward learning. Stress has been found to affect
valuation of rewarding stimuli (Pego et al., 2010), and hydrocortisone has been
suggested to influence reward perception and processing (Kinner et al., 2016). Yet,
165 previous studies did not focus on learning specifically.

Stress-induced cortisol-release, which was not the focus of this study, also varies
individually and is accompanied by responses in other systems. This difference to
exogenous hydrocortisone administration as used in this study could be relevant
to our results.

170 In sum, we found no evidence that motor and reward learning are impacted by
hydrocortisone. Dosing, time dependency and design particulars may have
influenced our results.

Strategic exploration is needed to further assess how hydrocortisone affects
learning. Using comparable learning paradigms with healthy individuals and
175 patients suffering from a disease, cognitive impairment, emotional disturbance or
stress, might help to better understand the influence of hydrocortisone on
cognitive mechanisms in dependency of health status or psychological state.

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Conflict of Interest

We declare no potential conflict of interest.

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Data available on request.

References

- 190 Bentz D, Michael T, de Quervain DJ, et al. (2010) Enhancing exposure therapy for anxiety disorders with glucocorticoids: from basic mechanisms of emotional learning to clinical applications. *J Anxiety Disord* 24: 223-230.
- de Quervain D, Schwabe L and Roozendaal B. (2017) Stress, glucocorticoids and memory: implications for treating fear-related disorders. *Nat Rev Neurosci* 18: 7-19.
- 195 Günthner J, Scholl J, Favaron E, et al. (2016) The NMDA receptor partial agonist d-cycloserine does not enhance motor learning. *J Psychopharmacol* 30: 994-999.
- Kinner VL, Wolf OT and Merz CJ. (2016) Cortisol alters reward processing in the human brain. *Horm Behav* 84: 75-83.
- 200 Miller R, Weckesser LJ, Smolka MN, et al. (2015) Hydrocortisone accelerates the decay of iconic memory traces: on the modulation of executive and stimulus-driven constituents of sensory information maintenance. *Psychoneuroendocrinology* 53: 148-158.
- Pego JM, Sousa JC, Almeida OF, et al. (2010) Stress and the neuroendocrinology of anxiety disorders. *Curr Top Behav Neurosci* 2: 97-117.
- 205 Römer S, Schulz A, Richter S, et al. (2011) Oral cortisol impairs implicit sequence learning. *Psychopharmacology (Berl)* 215: 33-40.
- Scholl J, Günthner J, Kolling N, et al. (2014) A role beyond learning for NMDA receptors in reward-based decision-making-a pharmacological study using d-cycloserine. *Neuropsychopharmacology* 39: 2900-2909.
- 210 Schwabe L and Wolf OT. (2012) Stress modulates the engagement of multiple memory systems in classification learning. *J Neurosci* 32: 11042-11049.