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Research report

Neural correlates of glucocorticoids effects on autobiographical memory retrieval in healthy women

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ABSTRACT

It is well known that elevated cortisol after stress or after exogenous administration impairs episodic memory retrieval including autobiographical memory (AM) retrieval. This impairment might be mediated by deactivation of a neural network associated with memory retrieval including the prefrontal cortex (PFC) and limbic structures. However, the neural underpinnings of these cortisol effects on AM retrieval have not been investigated yet.

In this study, thirty-three healthy women received either placebo or 10 mg hydrocortisone in a double blind cross-over design before completing an AM test during fMRI. In this test, participants are asked to recall specific events from their own past in response to a cue word.

In a first step, we analyzed the neural underpinnings of AM retrieval in the placebo condition. We found an activation pattern consistent with core regions involved in autobiographical memory recall, including the ventromedial PFC, anterior medial (am)PFC, inferior frontal gyrus, the posterior cingulate cortex, the temporoparietal junction, the middle temporal gyrus and the hippocampus. Further, we analyzed brain activation during AM retrieval after hydrocortisone compared to placebo. Region of interest (ROI) analyses revealed a hydrocortisone-induced deactivation during AM retrieval in the right amPFC. Results of the ROI analyses were non-significant in the left and right hippocampus, the left and right vmPFC and the left amPFC

In sum, during AM retrieval hydrocortisone had the most pronounced effects on the amPFC. This might be explained by the strong involvement of this brain region in self-referential behavior, which is essential for recalling autobiographic information.

1. Introduction

Glucocorticoids, which are secreted by the adrenal cortex in response to stress, pass the blood-brain barrier and bind to specific receptors in the brain: the glucocorticoid receptors (GR) and the mineralocorticoid receptors (MR). Both receptor types are expressed with high density in the hippocampus and the prefrontal cortex (PFC). Notably, these brain areas play a crucial role in memory processes [1]. It is also well known that glucocorticoids affect episodic memory processes [2,3]. While there is extensive evidence that cortisol enhances memory consolidation, memory retrieval is impaired after the acute administration of glucocorticoids (such as hydrocortisone) and after psychosocial stress [1].

Most studies on the effects of glucocorticoids on episodic memory retrieval used word list learning paradigms examining verbal learning and verbal memory, whereas autobiographical memory (AM) retrieval did not gain as much attention. One frequently used approach to investigate the specificity of AM retrieval is the autobiographical memory test (AMT) by Williams and Broadbent [4]. In this test, participants are asked to recall an event from their own past in response to an emotional cue word. The first study using this test to investigate cortisol effects on AM retrieval was conducted by Buss and colleagues [5]. After acute

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administration of 10 mg hydrocortisone, they found reduced AM specificity. The participants produced more general memories such as summarizing several different events instead of reporting one single autobiographic episode. This result was replicated by our group [6,7]. In contrast to hydrocortisone treatment, which stimulates both receptor types (GR and MR), we found that administration of fludrocortisone, a MR agonist, did not alter AM retrieval [8]. Thus, one might hypothesize that specifically GR mediate glucocorticoid effects on AM retrieval. In an additional study, we compared the effects of hydrocortisone on retrieval of recent (last week) or remote (one year before) autobiographical events. Our results suggest that cortisol affects remote but not recent memories [9]. Furthermore, in an elegant study Young and colleagues have shown that cortisol affected AM retrieval in a dose-dependent manner [10]. It that study, hydrocortisone was administered according to body weight, which resulted in mean dosages of 31.8 mg in the high cortisol group and 10.9 mg in the low cortisol group [10]. Thus, differences in the used dosage might – in part - explain the discrepancy in results.

As mentioned above, brain areas with high corticosteroid receptor density play a crucial role in memory processes [1]. Importantly, these brain regions are also involved in AM memory retrieval [11]. One study, for example, investigated the neural representation of recent as well as remote AMs and found strong activations in the ventromedial (vm)PFC and the hippocampus [12]. Young and colleagues adopted the AMT for neuroimaging [13–16]. Their findings suggest that AM retrieval during the AMT is associated with a neural network including the vmPFC, the dorsolateral PFC, the anterior cingulate cortex, the posterior cingulate cortex, the superior and middle temporal gyri and limbic structures, like the hippocampus and parahippocampus. These findings are consistent with what is considered to be the core network of AM retrieval [11,17]. In sum, AM has been associated with activation of prefrontal brain regions, which primary mediate self-referential processes, such as the anteriormedial (am)PFC. Furthermore, AM has also been associated with brain systems involved in memory retrieval such as the mediotemporal lobe and the hippocampus [18].

However, only very few studies investigated the effects of high cortisol levels on neural activation pattern and most studies only used resting state imaging. In one study, healthy individuals were randomized to either an intravenous injection of hydrocortisone or placebo before measuring resting state activity with fMRI [19]. After hydrocortisone, the activity of the hippocampus and amygdala declined significantly compared to placebo. Using positron emission tomography (PET), it has been shown that hippocampal [^{18}F]FDG uptake decreased after hydrocortisone compared to placebo in male Vietnam veterans without posttraumatic stress disorder (PTSD) [20]. Similar effects have been shown in response to a psychosocial stressor [21]. In that study, stress was associated with deactivation across a network of limbic structures, including the hippocampus, amygdala, insula, hypothalamus, ventral striatum, medial-orbital-frontal cortex and the posterior cingulate cortex. These deactivations seem to be associated to the cortisol response as they were only seen in those participants that respond with an increase in cortisol to the psychosocial stressor. It has been shown that one of the primary mechanism of fast membrane action of GCs is neural hyperpolarization as reflected by reduced metabolism during imagery in brain regions such as the hippocampus [19]. GCs are known to suppress neural firing and long term potentiation and especially cortisol-induced downregulation of the PFC seems to be due to genomic action [22].

In the last years, the neural underpinnings on the effects of cortisol on memory gained more attention. In line with the mentioned resting state data, associations between cortisol induced deactivation of prefrontal and limbic brain areas and memory encoding [22], working memory [23] as well as fear acquisition [24] and extinction [24,25] have been reported. Concerning declarative memory retrieval, the study by Yehuda and coworkers [20] found that hydrocortisone not only led to impaired memory retrieval (assessed outside the scanner), but that this impairment was associated with a cortisol-induced change in hippocampal activation. There are - to the best of our knowledge - only two studies that investigated cortisol-induced changes in brain activity during declarative memory recall. One study reported reduced memory recall after hydrocortisone compared to placebo, which was accompanied by a reduction of cerebral blood flow in the right posterior medial temporal lobe, especially in the parahippocampal gyrus, the left visual cortex and the cerebellum [26]. These findings fit to another study, which also found reduced brain activity in the prefrontal cortex and the hippocampus during a memory recognition task after hydrocortisone [27]. In both studies, the participants performed a recognition task of previously learned words in the scanner. The neural underpinnings of cortisol effects on AM retrieval have not been investigated yet.

In conclusion, the well-known impairing effect of glucocorticoids on episodic memory retrieval might be mediated through decreased activation of the prefrontal cortex and the limbic areas, which are highly associated with memory retrieval and which contain a high number of corticosteroid receptors. However, surprisingly few studies investigated the neural underpinnings of cortisol effects on episodic memory retrieval, especially AM retrieval. Therefore, the aim of our study was 1) to investigate the neural underpinnings of AM retrieval and 2) to investigate the neural correlates of AM retrieval under high cortisol levels, i.e. after hydrocortisone administration compared to placebo. We hypothesize that the hippocampus as well as prefrontal brain areas such as amPFC are activated during AM retrieval. Furthermore, we assume that these regions are sensitive to glucocorticoid effects and will, therefore, show a deactivation after hydrocortisone compared to placebo.

2. Materials and methods

2.1. Participants

Thirty-three female participants participated in the study. Exclusion criteria were the following: present or history of mental disorders (assessed by the short version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders for DSM-IV Axis I disorders (SCID-I) [28]), medical illness, medication intake including steroids, pregnancy, and nursing. Additionally, all participants underwent fMRI scanning. Therefore any contraindication (e.g. pacemaker or non-removable metals) represented additional exclusion criteria. Participants were right-handed and native German speakers. All participants were recruited through local advertisement. Procedures were carried out with the participants' full understanding and written informed consent was obtained. Each participant received an allowance of 100 €. The study was approved by the Local Ethics Committee.

2.2. Procedures

A placebo-controlled, double blind cross-over design was conducted. The study consisted of three test sessions. During the first session, the SCID-I was performed by a trained clinical psychologist and sociodemographic data were obtained. The remaining two sessions were conducted with an interceding interval of at least one week. At each session, participants underwent an MRI scan. Sessions started at 3.30 pm, in order to benefit from stable salivary cortisol levels in the afternoon. Two salivary cortisol samples were collected at arrival (+0) and after 15 min (+15) for assessment of basal cortisol levels. Directly after the second saliva sample, either placebo or 10 mg hydrocortisone (Hydrocortisone GALEN 10 mg tablets) were administered orally and in randomized order across test sessions. Participants were then seated in a quiet room until the beginning of the MRI scan (45 min later) and completed a practice trial of the task. Immediately before the MRI scan, a third saliva sample (+ 60) was collected. During the MRI scan, participants completed the autobiographical memory test (detailed

description see below), followed by a resting state measurement and a T1-weighted anatomical scan. After the MRI scan, a fourth saliva sample was collected directly after the scan (+120) and a fifth sample 15 min afterwards (+135). Saliva samples were collected using Salivette devices (Sarstedt). After collection, which took place at room temperature, saliva samples were stored at −80 °C until biochemical analysis. Cortisol concentration was determined in the Neurobiology Laboratory of the Dept. of Psychiatry, Charité – Universitätsmedizin Berlin. Free cortisol was analyzed using a commercially available TR-FRET-based, in-house adopted immunoassay (Cisbio International, Codolet, France), which was performed in principle according to the manufacturer's instructions (see [29] for detailed description). Intraassay coefficients of variation were below 8%, interassay coefficients of variation were below 10%.

2.3. Autobiographical memory test

The Autobiographical Memory Test (AMT) was adapted from Young and colleagues [14] and is based on the original AMT [4]. The AMT in the current study consisted of two parallel versions with 25 words each. Both versions were counterbalanced across conditions and stimuli were presented in a randomized order.

All participants completed the AMT during fMRI. Analogous to the above-mentioned study by Young and colleagues [14], participants were instructed to recall a specific event from their past in response to the particular cue word. Each cue word was presented for an interval of 15 s. Participants had to indicate whether they found a fitting memory via button press on the response box. If they pressed a button, a fixation cross was presented for 10 s during which the participants were instructed to recall the autobiographical memory actively. After this recall period, participants rated the retrieved memory regarding valence (neutral, negative and positive), arousal and recency (childhood, adolescence and adulthood). Each question was presented for 5 s and answers were given by pressing the corresponding button on the response box. Subsequently, the participants were presented a simple arithmetic problem as a control task for 12 s. Participants had to subtract a two-digit number from a number of three digits and were given three answers to choose from. Afterwards, a second fixation cross was presented for 8 s to allow the BOLD signal to normalize before the next trial started. If participants could not find a fitting memory, a reminder appeared on the screen for 5 s. If they still did not press a button, the arithmetic problem was presented, followed by the next trial. Stimuli were presented using the software *Presentation* (Neurobehavioral Systems, Inc.) and the audio-visual stimulation technology VisuaStim Digital (Resonance Technology Company, Inc.).

2.4. fMRI data acquisition

FMRI scans were obtained using a Siemens Magnetom TrioTim (3 T) scanner with a 12-channel receiver coil array and an echoplanar imaging (EPI) pulse sequence [3.0 mm slices acquired sagitally, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 70°, matrix = 64r64, field of view (FOV) = 192 mm, voxel size = 3 × 3x3 mm^3]. The actual number of acquired EPI images during the AMT varied depending on the number of recalled memories with a maximum of 900 EPI images. High-resolution T1-weighted anatomical MRI scans were acquired for co-registration at the end of each MRI session.

2.5. fMRI processing and analyses

Image preprocessing and analyses were performed using SPM 12 (Statistical Parametric Mapping 12, Wellcome Trust Centre for Neuroimaging, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MathWorks Matlab R2015a. Image preprocessing consisted of slice-timing, realignment to the mean image, co-registration with anatomical images acquired at the end of the MRI session and normalization. Concerning the statistical analysis, a model for the different conditions convolved with a hemodynamic response function as explanatory variables within the context of the general linear model on a voxel-by-voxel basis was computed. A fixed-effect model at a single-subject level was carried out to create images of parameter estimates, which were entered into second-level analysis. As a first step, we focused on the effect of AM retrieval in comparison to the control condition (simple arithmetic). Analogous to the study of Young and colleagues, we carried out a one sample *t*-test contrasting the autobiographical memory retrieval condition with the control condition for all participants during the placebo condition. This served to identify BOLD activation related to autobiographical memory retrieval [14,18] in our region of interest and did not include the hydrocortisone condition. Since we were most interested in effects in hippocampus and prefrontal regions, we investigated neural activation in hippocampus and amPFC as a priori regions of interest based on previous literature [18]. We applied small volume correction for spherical ROIs in bilateral amPFC and bilateral hippocampus with a radius of 5 mm and report activation above $p < 0.05$. In addition, on a whole brain level, clusters of activation were identified with a global height threshold of $p < 0.05$, FWE corrected and a cluster threshold of more than 25 voxels.

We then performed region of interest (ROI) analyses to evaluate differences in BOLD activation during the retrieval condition between the placebo and the hydrocortisone condition. Previous studies have shown that effects of hydrocortisone on memory retrieval associated brain regions are most pronounced in prefrontal regions and the hippocampus [26,27]. Since previous literature [11,18] described hippocampus and amPFC as autobiographical memory related brain regions and our initial group analysis (see Table 1) showed the highest task effects in vmPFC as prefrontal region, we focused on amPFC, vmPFC and hippocampus as region of interests. On the basis of peak voxels (coordinates in the MNI stereotactic space) obtained in the group analysis (see Table 1) and their contralateral coordinates, we built spherical (radius = 5 mm) ROIs and carried out analyses for left vmPFC (-4 28 -2), right vmPFC (4 28 -2), left amPFC (-12 56 24), right amPFC (12 56 24), left hippocampus (-20 -16 -20) and right hippocampus (20 -16 -20). For each ROI, we extracted beta weights for each of the two conditions (hydrocortisone, placebo) separately. This procedure was applied for each participant. Paired sample t-tests with the respective beta weights were carried out in order to detect differences between the two conditions. Furthermore, we correlated changes in cortisol with changes in brain activity.

In addition, we performed a whole brain paired sample *t*-test in SPM in order to compare the autobiographical memory retrieval of the

Table 1
Autobiographical Memory Test (AMT). BOLD activity during the AMT in the placebo condition (contrast "recall versus calculate").

Region	WB/ROI	Side	Recall > calculate	Clustersize
vmPFC	WB	R	4 28 -2 (Z: 6.74)	874
amPFC	ROI	L	−12 56 24 (Z: 5.99)	81
Angular Gyrus	WB	L	−50 -68 38 (Z: 6.14)	368
PCC	WB	L	−4 -54 28 (Z: 5.84)	310
IFG	WB	L	−48 30 -6 (Z:5.61)	228
Temporal pole	WB	L	−46 8 -34 (Z:5.99)	133
Tempoparietal junction	WB	R	54 -64 34 (Z: 6.47)	63
Middle temporal gyrus	WB	L	−62 -12 -14 (Z: 5.62)	150
Hippocampus	ROI	L	−20 -16 -20 (Z: 3.93)	51

vmPFC = Ventromedial prefrontal cortex, amPFC = Anterior medial prefrontal cortex, PCC = Posterior cingulate cortex, IFG = Inferior frontal gyrus. WB = local maxima derived from whole-brain analyses with $P < 0.05$, FWE corrected, the extent threshold to k = 25 voxels for all contrasts, ROI = local maxima derived from a priori region-of-interest analyses with $p < 0.05$, small volume corrected, R = right, L = left.The global height threshold was set to $p < 0.05$, The values in the table represent z values with peak voxel coordinates in the MNI stereotactic space.

placebo condition with the hydrocortisone condition

Again, hippocampus and prefrontal regions served as a priori regions of interest based on previous literature [18]. We applied small volume correction for spherical ROIs in bilateral amPFC and bilateral hippocampus on the basis of peak voxels (coordinates in the MNI stereotactic space) obtained in the group analysis (see Table 1) and their contralateral coordinates with a radius of 5 mm and report activation above $p < 0.05$. In addition, on a whole brain level, clusters of activation were identified with a global height threshold of $p < 0.05$, FWE corrected and a cluster threshold of more than 25 voxels.

3. Results

3.1. Sample characteristics

We recruited 33 healthy female participants with a mean age of 28.3 years ($SD = 7.1$). On average, participants attended 12.1 school years ($SD = 1.4$). Nine participants were taking oral contraceptives (27.3%), whereas the majority did not (n = 24, 72.7%). 21 women were in the luteal phase of the menstrual cycle. Nine participants (27.3%) reported regular smoking. On average, participants had a body mass index of 21.8 ($SD = 2.6$), which reflects normal weight.

3.2. Effects of hydrocortisone administration on salivary cortisol concentrations

We conducted a rmANOVA with condition (hydrocortisone vs. placebo) and time (five measurement points) as within-subject factors. ANOVA revealed a significant main effect for condition ($F(130) = 87.9$, $p < .001$), time ($F(2.1, 61.6) = 30.00$, $p < .001$) and a significant condition x time interaction effect ($F(2.1, 62.8) = 38.5$, $p < .001$). Post hoc t-tests indicated, that there was no significant difference in saliva cortisol at the two baseline measurements. The intake of hydrocortisone led to a significant increase in saliva cortisol levels at time points +60 + 120 and +135 ($p < .001$, see Fig. 1).

When controlling for smoking status, intake of oral contraceptives and menstrual cycle phase the results did not change (main effect condition, time and condition x time interaction effect: $p < .001$). There was no main effect of smoking status (p = .28), intake of oral contraceptives (p = .65) and menstrual cycle phase (p = .77) nor any significant interaction.

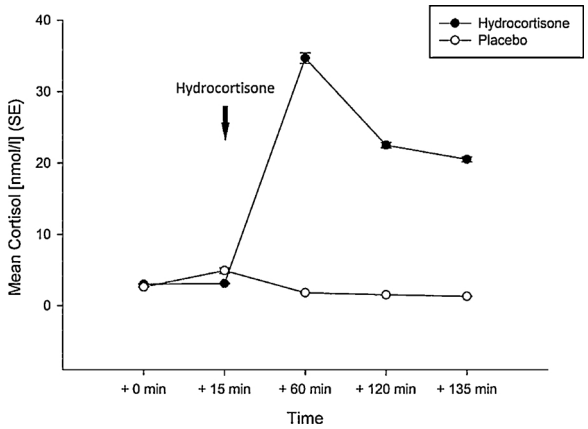

Fig. 1. Salivary cortisol concentrations at beginning (+0) and + 15 min, + 60 min, + 120 min and + 135 min after the first saliva sample. The administration of hydrocortisone or placebo was directly after measurement 2 (+15 m). In the hydrocortisone condition participants showed significant higher salivary cortisol concentrations after drug administration (samples +60, +120, + 135 min).

3.3. Neural correlates of autobiographical memory retrieval

In a first step, we investigated BOLD activity during the AMT in the placebo condition by contrasting the AM retrieval condition with the control condition. This approach was chosen to replicate reported patterns of BOLD activation related to autobiographical memory retrieval.

Since we were most interested in effects in hippocampus and prefrontal regions, we investigated neural activation in hippocampus and amPFC as a priori regions of interest based on previous literature [18]. Analyses revealed AM retrieval related increased BOLD responses in vmPFC, amPFC, IFG, PCC, tempoparietal junction, middle temporal gyrus and hippocampus (see Table 1 and Fig. 2).

3.4. Hydrocortisone-Induced changes in neural activity

We performed ROI analyses to ascertain the effect of hydrocortisone during AM retrieval in our regions of interest. Paired sample t-tests comparing BOLD responses between the hydrocortisone condition and the placebo condition were conducted in the following ROIs: bilateral vmPFC, bilateral amPFC and bilateral hippocampus.

We found a significant difference in the BOLD response of right amPFC between the hydrocortisone condition ($M = -0.3$, $SD = 1.2$) and the placebo condition ($M = .04$, $SD = .13$) ($t(232) = 2.46$, $p < .05$) (Fig. 3), indicating higher activation in the placebo than in the hydrocortisone condition. Results of the ROI analyses were non-significant in left and right hippocampus, left and right vmPFC and left amPFC ($p > .05$), indicating no differences in neural activation during autobiographical memory retrieval between the hydrocortisone and the placebo condition in these regions. Changes in cortisol did not correlate with changes in brain activity ($p > .05$). Order of hydrocortisone and placebo administration did not influence changes in brain activity ($p > .05$)

In addition, we performed a paired sample *t*-test contrasting the hydrocortisone condition with the placebo condition to characterize brain regions influenced by hydrocortisone (see Table 2), with small volume correction for bilateral amPFC and bilateral hippocampus as a priori regions of interest. We found an effect of hydrocortisone on the right amPFC, showing greater activation in the placebo condition compared to hydrocortisone. On a whole-brain level no significant cluster were identified. No significant clusters in grey matter were found for the opposite contrast (hydrocortisone vs placebo).

3.5. Effects of hydrocortisone on ratings on arousal, valence and recency of recalled memories

Frequency of recency, i.e., number of memories recalled from childhood, adolescence and adulthood as well as valence, i.e. how many positive, negative and neutral memories were recalled was analyzed using non-parametric statistics (Wilcoxon Rank Test). There were no differences between the placebo and the hydrocortisone condition for all these dependent variables (all $p > .05$).

Furthermore, we compared arousal ratings between hydrocortisone and placebo condition with a paired sample *t*-test, but found no significant difference (p = .47).

4. Discussion

This is the first study that investigated the neural underpinnings of hydrocortisone effects on AM retrieval in a placebo-controlled crossover design. While one aim of this study was to investigate the neural correlates of baseline AM retrieval during the placebo condition, the primary aim of the study was to identify hydrocortisone-induced changes in neural activity during AM recall.

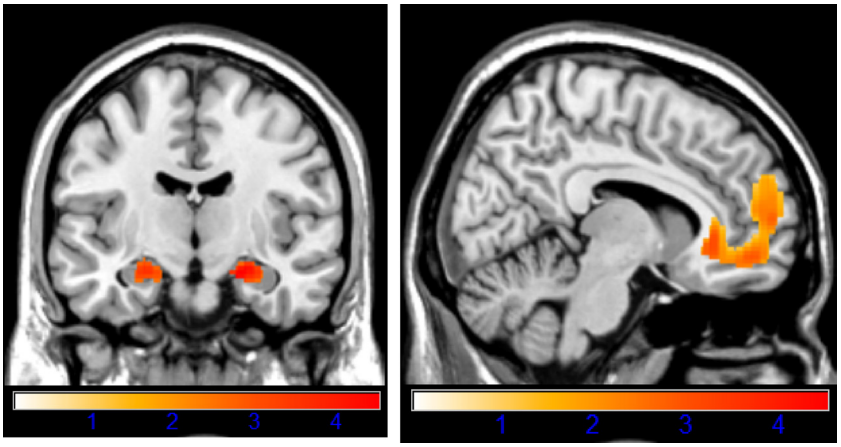

Fig. 2. Autobiographical memory retrieval related brain activation in the hippocampus and the prefrontal cortex (BOLD activity during the AMT in the placebo condition). For depiction, the global height threshold was set to $p < 0.01$, uncorrected, with no minimum cluster size.

4.1. Neural activity during autobiographic memory retrieval (placebo condition)

During AM retrieval we found an activation pattern that included the vmPFC, amPFC, IFG, PCC, tempoparietal junction, middle temporal gyrus and hippocampus. These prefrontal and temporal brain areas are core regions of an AM network because activation pattern in these regions have been consistently found in several AM retrieval paradigms [11,17,30]. Specifically the vmPFC has been associated with AM since its activation was stronger in AM tests compared to (other) episodic memory tasks [31]. In contrast, other prefrontal areas seem to be activated throughout a wide range of memory processes [32]. Accordingly, a meta-analysis of 24 A M retrieval studies provided compelling evidence that prefrontal brain regions, especially in the medial part of the PFC, are strongly involved in AM [17]. Of note, we also found the strongest activation during AM retrieval in prefrontal brain regions, namely vmPFC and amPFC. Both of these brain structures are strongly involved in the processing of self-relevant information [17,18,32]. Self-referential processes are essential for building and constructing AM and for retrieval of specific AMs [11,33]. Further core regions in the AM network are temporal lobe areas [12,17]. The temporal lobe, including the hippocampus, is one of the most important brain regions for episodic memory retrieval, but is also involved in other memory processes such as encoding, learning, working memory and special memory [17,34].

Table 2
Autobiographical Memory Test. Bold activity in the contrast "placebo versus hydrocortisone".

Region	WB/ROI	Side	Recall > calculate	Clustersize
amPFC	ROI	R	8 54 22 (Z: 3.11)	19

amPFC = Anterior medial prefrontal cortex, ROI = local maxima derived from a priori region-of-interest, analyses with $p < 0.05$, small volume corrected, R = right, L = left. The values in the table represent z values with peak voxel coordinates in the MNI stereotactic space.

Our results, in line with the work of Young and coworker [14], provide further evidence that the AMT, which uses a cue driven approach, is a suitable task for imaging studies. Of note, the AMT is frequently used in clinical studies and reduced specificity in AM retrieval, has been reported in several mental disorders such as Major Depressive Disorder (MDD) [35] and PTSD [36–38]. In addition, neuroimaging research suggests that these disorders are not only accompanied by reduced AM specificity but also by alterations in brain regions which are related to AM, for example smaller hippocampal volume [39–42]. In terms of AM retrieval, Young and colleagues reported reduced activity

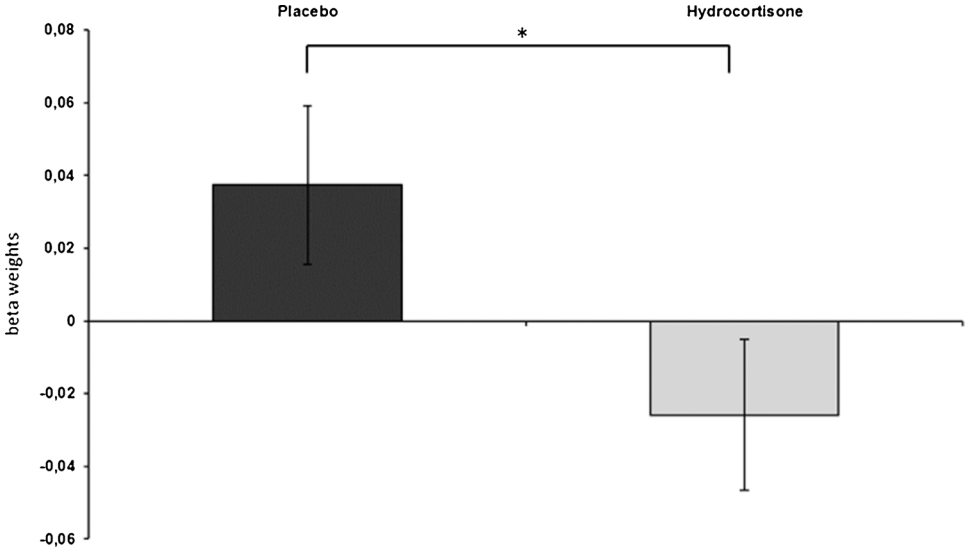

Fig. 3. Region of interest (ROI) in the right amPFC (12, 56, 24): comparison placebo vs hydrocortisone condition. Bar diagrams show differences in the beta weights between the hydrocortisone and placebo condition (*$p < .05$). Error bars indicate standard error of the mean.

in the hippocampus during AM retrieval in MDD, which was accompanied by reduced memory specificity [14]. Of note, the mentioned disorders are also characterized by alterations of the hypothalamic-pituitary adrenal axis, including changes in cortisol activity and corticosteroid receptor function [14,43]. Additionally, effects of exogenous cortisol on memory retrieval seems to be altered compared to healthy individuals [44,45]. MDD patients, for example, did not show the well-described impairing effects of hydrocortisone on AM retrieval [6]. However, as no study so far investigated the neural underpinning of the effects of hydrocortisone on AM retrieval in healthy individuals, this was the main aim of the current study.

4.2. Changes in neural activity during AM retrieval through hydrocortisone

Previous studies have suggested that prefrontal and temporal brain areas are strongly involved in AM retrieval [12,14,18]. Importantly, these brain areas are sensitive for the effects of hydrocortisone on memory retrieval [20,26,27]. Thus, we first performed ROI analyses with amPFC, vmPFC and hippocampus as regions of interest. After hydrocortisone, there was reduced brain activation only in the right amPFC compared to placebo. We did not find significant differences in BOLD signal in the hippocampus, vmPFC and left amPFC after the intake of hydrocortisone compared to placebo during AM retrieval. In addition to our hypothesis-driven ROI analyses, we conducted a whole-brain analysis to further understand acute glucocorticoid effects on neural activity. This analysis also indicated that hydrocortisone leads to a decrease in BOLD signals in right amPFC. Of note, it has been suggested that the PFC is one of the most sensitive brain areas to the effects of stress, including reduced cognitive abilities as well as structural changes [46]. Glucocorticoid receptors are widely distributed in the brain, including limbic as well as prefrontal brain areas [47]. For example, studies in rodents and monkeys demonstrated that the mPFC is rich of GR and a target for negative-feedback effects of GC on HPA activity [48,49]. Furthermore, it has been shown that prefrontal brain areas, including the mPFC, play a crucial role in glucocorticoid-induced memory impairments [50,51]. Thus, it is plausible that we found the most pronounced deactivation of brain activity after hydrocortisone in the mPFC. The high density of glucocorticoid receptors in the PFC might contribute to these changes after hydrocortisone [1].

Our findings extend the understanding of cortisol effects on neural activation on episodic memory to autobiographical memory. Previous studies showed that during memory recall, hydrocortisone reduced brain activity in the PFC and hippocampus [27] as well as in the parahippocampal gyrus and temporal lobe [26]. This fits to our whole brain analysis findings. In contrast to earlier studies, however, we did not find decreased hippocampal activation after hydrocortisone. This might be due to the different tasks that we used. We measured neural activity to autobiographic memories. This is a major difference to the recall of recently learned stimuli in the laboratory such as words pairs a day or a week before retrieval as used in earlier studies [26,27]. A meta-analysis compared neural activation during AM retrieval with other memory tasks such as retrieval of recently learned stimuli during the experiment [18]. The strongest activation in this contrast occurred in the amPFC and other prefrontal areas, while no differences in brain activation could be revealed in hippocampal activity. This is in line with our ROI analyses and fits to the hypothesis, that the amPFC is strongly related to self-referential processes, which is an essential and inevitable aspect in AM retrieval compared to other memory tasks.

Thus, our results suggest that the most specific brain area for AM retrieval, the amPFC, is most sensitive to glucococorticoid effects leading to decreased activity. As mentioned above, the amPFC (and the vmPFC) are strongly related to self-referential processes. It is well known that those stressors which activate the hypothalamus pituitary adrenal axis leading to elevated cortisol include ego-involvement [52]. Therefore, it is biologically plausible that those brain regions involved in the processing of self-relevant stimuli are sensitive to the effects of cortisol. Indeed, cortisol has been shown to reduce the specificity of AM [5,6], which might be seen an indicator for self-referential behavior. Possibly, the individual turns away from dealing with the self to a more global and environmental oriented perception during stress.

4.3. Strength and limitations

To the best of our knowledge this is the largest study on the effects of hydrocortisone on the neuronal underpinnings of episodic memory retrieval so far. Furthermore, it is the first study that investigated a female sample and used an autobiographical memory task.

However, there are also several limitations of our study.

The most limitation is probably the lack of behavioral data on AM performance. As this usually requires verbal or written statements by participants, this poses a major challenge in adapting the AMT for fMRI. We refrained from assessing a description of the retrieved AM during the retrieval phase due to methodological reasons (i.e. movement artefact due to verbal assessment during scanning). Furthermore, we did not conduct an additional post scan AMT because such a second assessment may lack reliability and validity. First, it cannot be ruled out that the participants assign the wrong memory to a cue word. Thus, it is uncertain whether the recalled events are really the same during and post scanning. Furthermore, the participants might be exhausted after the scanning procedure (they are at least 2 h in the lab at that time), which might lead to a less detailed and less specific description of the events in the interview and might lead to errors. Indeed, when comparing the behavioral data reported in the study by Young and colleagues with our former study the rate of specific memories was much lower in the Young study. The behavioral data in the post scan interview revealed 43% specific memories in the healthy control group [14]. In our studies, we found more than 66% specific memories [6,7,44]. Additionally, cortisol levels will begin to fall after the scanning procedure and will differ between fMRI investigation and post scan interview. Thus, effects of cortisol on AM retrieval might differ between scanning and post scan interview. However, it would have been useful to have behavioral data to compare them with the study of Young and colleagues. Furthermore, behavioral data could have served as a link between the changes in brain activity in our study and the impairment of autobiographical memory performance after hydrocortisone observed in other studies [5,6,9,10]. As there is evidence that the glucocorticoid induced decrease in brain activity is accompanied by an impairment in memory performance [20,26,27] one might speculate that the reported reduction in AM specificity after cortisol might also be associated with decreased brain activity, e.g. in the amPFC.

The control task in our autobiographical memory test represents another methodological limitation of our study design. Similar to the study by Young and colleagues [14] we used a simple arithmetic task. Thereby, the comparability between results was enhanced but we are not able to examine whether the observed neural activity is specific for autobiographical memory or represents episodic memory processes in general. However, the observed neural activation during autobiographical memory retrieval in our placebo condition overlaps with the well-documented neural network related to autobiographical memory found in earlier studies [11,17].

Furthermore, our sample consisted of women only and, thus, our results are not transferable to men. However, our results are not in contrast to previous findings in male samples [20,26,27]. Future studies should directly compare females and males, as there is evidence for sex differences in brain connectivity in association with cortisol [53].

The used dosage of 10 mg hydrocortisone was lower compared to other fMRI studies, in which up to 25 mg were used [26]. This might have contributed to differences in brain activation pattern between studies, in addition to effects due to study differences in memory tasks.

Our study included 33 participants and is – compared to previous studies (N = 8 to N = 21 [20,26,27]) - relatively large, but possibly still too small to have sufficient power to detect smaller effects. There is an

intense ongoing discussion on this important issue in imaging research, in which larger samples are proposed [54].

4.4. Conclusion

We provide evidence that hydrocortisone reduces neural activity during AM retrieval, with the largest effect on the amPFC. This might be due to the strong involvement of this brain region in self-referential processes. Furthermore, prefrontal brain areas are rich of corticosteroid receptors, which might contribute to their sensitivity to the effects of stress and stress hormones [46]. In sum, reduced amPFC activity might explain impaired AM retrieval after stress exposure and consecutive cortisol release as previously reported by us and others. Moreover this region might also be involved in the AM impairments observed in stress associated mental disorders.

Declaration of interest

There are no conflicts of interest, financial or otherwise, to declare.

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