HIPPOCAMPAL SUBFIELD CA1-3 SHOWS DIFFERENTIAL STRUCTURAL AND FUNCTIONAL NETWORK PLASTICITY AFTER STRESS-REDUCING SOCIO-AFFECTIVE MENTAL TRAINING

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Abstract

The hippocampus forms a central modulator of the HPA-axis, impacting the regulation of stress on brain structure, function, and behavior. The current study assessed whether three different types of 3-months mental training modules geared towards nurturing a) attention-based mindfulness, b) socio-affective skills, or c) socio-cognitive abilities may impact hippocampal integrity by reducing stress. We evaluated mental training-induced changes in hippocampal subfield volume and intrinsic functional connectivity, based on resting-state fMRI connectivity analysis in a group of healthy adults (N=332). We then related these changes to changes in diurnal and chronic cortisol levels. We observed increases in bilateral cornu ammonis volume (CA1-3) following the 3-months compassion-based module targeting socio-affective skills (Affect module), as compared to socio-cognitive skills (Perspective module) or a waitlist cohort that did not undergo an intervention. Structural changes were paralleled by increases in functional connectivity of CA1-3 when fostering socio-affective as compared to socio-cognitive skills. Moreover, training-related changes in CA1-3 structure and function consistently correlated with reduction in cortisol output. In sum, we provide a link between socio-emotional behavioral intervention, CA1-3 structure and function, and cortisol reductions in healthy adults.

Introduction

Stress-related disorders rank among the leading causes for disease burden world-wide (1). It is therefore essential to find ways to efficiently prevent or reduce stress (2). In recent years, research has shown that contemplative mental training programs can be efficient in stress reduction (e.g. (3-5); for a meta-analysis see (6)), while simultaneously inducing brain plasticity (7-9). It is, however, still unclear which types of mental practices most effectively reduce stress and induce stress-related brain plasticity. Stress is a multi-layered construct (10), and most studies have focused on stress-related self-reports and questionnaires (6). A less investigated marker in the stress reduction context through contemplative mental training is diurnal cortisol, from which summary indices such as the cortisol awakening response (CAR), the total diurnal output, and the diurnal cortisol slope are frequently investigated (11). The steroid hormone and glucocorticoid cortisol acts as the end-product of the hypothalamic-pituitary-adrenal (HPA) axis, and is key to stress regulation (for reviews, see (12, 13)). Cortisol is considered an important mediator of the relation between chronic stress and stress-related disease (14, 15). Previous research suggests an important association between hippocampal integrity and stress related cortisol activity (16, 17), although findings are inconclusive. To close these gaps, we investigated the differential efficiency of three types of mental training (attention-based, socio-affective and socio-cognitive) on their ability to induce structural as well as functional plasticity of hippocampal subfields and reduce diurnal cortisol levels.

The hippocampus has a high glucocorticoid receptor density (18-21) making this region a target of investigations into stress-related brain changes. Being three layered allocortex, the hippocampal formation consists of multiple subfields, or zones, starting at the subiculum (SUB) and moving inward to the hippocampus proper; the cornu ammonis (CA1-3), and dentate gyrus (CA4/DG)(22-25). These subfields have unique microstructure (22-26) and participate differently in the hippocampal circuitry (27), likely implicating different functions (28-33). Indeed, intrinsic functional MRI analyses during wakeful rest have shown that the hippocampal subfields show functional signal correlations with a broad range of cortical regions, part of visual, control, and default functional networks (26, 33-36). Hippocampal subfield volumes and associated intrinsic functional connectivity have been shown to be heritable (34, 37), indicating that individual variation in subfield structure and function is, in part, under genetic control. Other lines of research have reported hippocampal structure and function to be highly sensitive to contextual factors such as stress (21). Mediated through its dense network of glucocorticoid receptors, the hippocampus transmits the negative feedback signals of

a wide range of glucocorticoid levels on HPA axis activity (20). Through this inhibitory role on HPA axis dynamics, it is linked to emotional reactivity (38), stress sensitivity (17, 39-41), and causally involved in a variety of stress-related disorders (42).

Previous brain imaging research has examined the relationship between cortisol activity and hippocampal morphology. Most of this research measured saliva cortisol levels to gauge the diurnal cortisol profile. Thus, a reduced cortisol awakening response, the response to the anticipated demands of the upcoming day (43), has been associated with smaller hippocampal volume in healthy individuals (44-46) and different psychiatric (47, 48) and metabolic (46, 49) conditions. In fact, the examination of patients with temporal lobe damage suggested that hippocampal integrity may be a necessary condition for the proper mounting of the CAR (50, 51). Next, to changes in hippocampal structure, alterations in hippocampal functional connectivity have been reported to be associated with changes in cortisol levels (52, 53). There is also contrary work showing associations between elevated awakening, evening, diurnal, or 24-hour cortisol levels in healthy elderly with age-related hippocampal atrophy (54-57) and, again, samples with psychiatric conditions (58, 59). While such inconsistencies in previous neuroimaging work may reflect the fact that different indices of diurnal cortisol tap into different facets of HPA axis regulation, studied samples were diverse in terms of health status, only small in size, and largely cross-sectional. Also, associations between stress and hippocampal structure and function over time are incompletely understood. Thus, longitudinal investigations, such as mental training studies aiming at stress reduction and repeatedly assessing both brain and cortisol release can help to better understand the dynamic associations between stress, cortisol and hippocampal structure and function.

In recent years, contemplative mental training interventions, such as the mindfulness-based stress reduction (MBSR) program (60) or compassion-focused therapy (61), have gained in popularity as potential therapeutic tools to improve mental and physical health (62) and at reducing stress (6). The fact that these mental training interventions can have a positive impact on the practitioner's stress sensitivity makes them a suitable model to investigate the interrelationship between training-related changes in hippocampal structure, function, and cortisol output. Next to reductions in reactive measures following acute psychosocial stress induction in the laboratory (5), reduced subjective-psychological stress load is the most widely reported outcome (for a review, see (6)). Evidence for lower diurnal cortisol output stems mainly from mindfulness-based interventions, notably MBSR, for which reductions in CAR and

afternoon/evening cortisol levels have been reported in healthy and diseased individuals (63-65). Moreover, work in the current sample has shown that hair cortisol and cortisone are reduced through mental practice (3). Hair cortisol measurements have suggested to provide a window into long-term impact of cortisol exposure (66). These findings are contrasted by numerous null results (for meta-analyses, see (67, 68)), possibly due to modest samples sizes and mixed effects of different training contents on stress-related processes. Furthermore, 8-weeks mindfulness programs such as MBSR and others typically cultivate different types of mental practices, making it difficult to understand which type of mental practice is most efficient in reducing different types of outcomes, including various stress-markers (see also (3-5)).

The current study, therefore, investigated differential effects of distinct mental training practices onto the association between changes in hippocampal subfields and underlying stress-related diurnal cortisol profiles changes over training in the context of a large-scale 9-month mental training study, the *ReSource Project* (69). In addition, we sought to explore the effects of long-term exposure to stress onto hippocampal subfields as a function of mental training in a subset of individuals (3). Healthy participants attended three 3-months training modules termed *Presence* (cultivating attention and interoceptive awareness), *Affect* (cultivating compassion, prosocial motivation and dealing with difficult emotions) and *Perspective* (cultivating metacognition and perspective-taking on self and others) (**Figure 1**). *Presence* resembles typical mindfulness-based interventions, but excludes socio-emotional or socio-cognitive practices (60, 70). By contrast, *Affect* and *Perspective* target social skills through the training of either socio-emotional and motivational skills such as empathy, compassion and care (*Affect*) or socio-cognitive skills such as perspective taking on self and others (*Perspective*). In previous work, stemming from the same participant sample as examined here, we found a reduction in CAR specifically after the training of socio-affective capacities (4), and of acute stress reactivity after the training of socio-affective or socio-cognitive capacities (5). Conversely, but also in the current sample, levels of hair cortisol, a systemic marker of long-term stress exposure, were reduced equally after the tree mental practice types targeting either attention and interoception, socio-affective or socio-cognitive skills (3), suggesting a domain-specific effect of mental training content on day-to-day cortisol fluctuations, but not on long-term stress. Furthermore, our group could also show differentiable training-related changes in cortical structure and intrinsic functional organization following the three ReSource project training modules, illustrating the existence of training-related structural plasticity of the social

brain (7, 71). Domain-specific changes in hippocampal subfield structure and intrinsic functional connectivity, and how these relate to mental training specific changes in stress-related diurnal cortisol output, have not yet been studied. We, therefore, examined whether module-specific changes in diurnal cortisol levels may relate to specific structural and intrinsic functional changes in different hippocampal subfields and functional resting state data.

We evaluated the longitudinal relationship between hippocampal subfield volumetry, a quantitative index of hippocampal grey matter, and subfields' resting-state functional connectivity in a large sample of healthy adults participating in the *ReSource Project* (69). We contrasted training effects on hippocampal structure, function, and their associations with cortisol across the different types of mental training (i.e., *Presence*, *Affect*, *Perspective*). To resolve hippocampal structure, we employed a surface-based multi-template algorithm that has been shown to perform with excellent accuracy in healthy and diseased populations of a comparable age range as the currently evaluated cohort (72). Such a model is good to represent different subfields *in vivo*, which have a differentiable structure and function (73, 74), and thus may show differentiable changes as a function of mental training. Such targeted assessment of hippocampal sub-regions may map circuit plasticity secondary to potential stress reduction, and reveal whether changes in hippocampal structure parallel changes in hippocampal subfield functional networks. To model the interplay between individual-level correspondence in hippocampal and stress markers, we evaluated the association of changes in hippocampal structure and function with changes in different indices of diurnal cortisol release.

Results

We analyzed structural, resting-state as well as cortisol-based stress markers from the large-scale *ReSource Project* (69). For details, see http://resource-project.org and the preregistered trial https://clinicaltrials.gov/ct2/show/NCT01833104.

In brief, participants were randomly assigned to two training cohorts (TC1, N=80; TC2, N=81) and underwent a 9-months training consisting of three sequential training modules (*Presence*, *Affect*, and *Perspective*) with weekly group sessions and daily exercises, completed via cell-phone and internet platforms (**Figure 1, Table 1-3,** see *Materials and Methods* and *Supplementary Materials* for details). TC1 and TC2 started their training regimen with the *Presence* module, then underwent the latter two modules in different orders (TC1: *Affect-Perspective*; TC2 *Perspective-Affect*) to serve as active control groups for each other (**Figure 1C**). Another active control group (TC3; N=81) completed three months of *Affect* training only. Additionally, a matched test-retest control cohort did not undergo any training (RCC, N=90). All participants were examined at the end of each 3-months module (T_1, T_2, T_3) using 3T MRI, behavioral and peripheral physiological measures, all of which were identical to the baseline (T_0) measures**.**

Change in bilateral CA1-3 volume following Affect mental training.

Our design allowed us to examine whether the volume of hippocampal subfields shows increases or decreases following the distinct training modules. We tracked longitudinal changes in hippocampal subfield volumes using mixed-effects models (*74*). Excluding participants with missing or low quality structural and functional data, the sample included 86 individuals for *Presence*, 92 individuals for *Affect*, 83 individuals for *Perspective*, and 61 *active controls (Affect)* with hippocampal change scores. We included 164 change scores of *retest controls* over T_1, T_2, T_3. We observed relative increases in bilateral Cornu Ammonis 1-3 (CA1-3), but not in subiculum (SUB) nor CA4 and dentate gyrus (CA4/DG) subfields, following *Affect* versus *Perspective* training (left: t=2.360, p=0.019, FDRq>0.1, Cohens D =0.282; right: t=2.930, p=0.004, FDRq=0.048, Cohens D =0.350), *Affect* (left: t=2.495, p=0.013, M: 25.511, SD: 130.470, CI [-1.509 52.531; right: t=2.374, p=0.018, M: 40.120, SD: 181.300, CI [2.573 77.666]), *Perspective* (left: t=-1.143, p>0.1, M:-23.048, SD: 137.810, CI [-53.139 7.043; right: t=-2.118, p=0.035, M:-39.602, SD: 208.470, CI [-85.122 5.917]). We did not observe differences between *Presence* and Active control cohort, *Affect* TC3. Overall, for all hippocampal subfields, findings associated with volume increases in CA1-3 following the *Affect*

training were most consistent across timepoints and contrasts (**Supplementary Table 1-6**). We observed no overall change in hippocampal subfield volume following mental training (**Supplementary Table 8**).

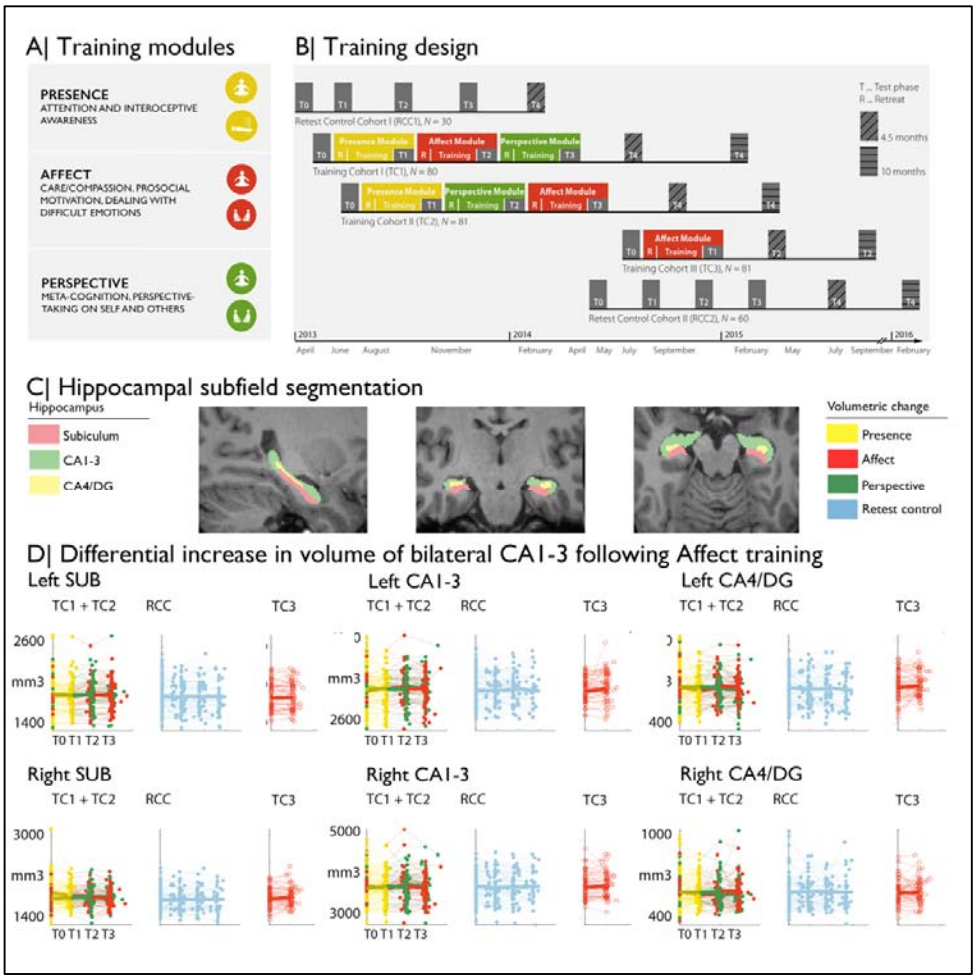

Fig. 1 Training induced plasticity of hippocampal subfield volume. A) Training modules; B) Training design; C) Subfield volumes in left and right hemispheres across individuals and timepoints; D) Scatterplot of subfield volumes as a function of timepoints and groups.

Increased functional connectivity of CA1-3 following socio-affective versus socio-cognitive mental training.

Subsequently, we studied whether hippocampal CA1-3 would show corresponding changes in intrinsic function following mental training. To do so, we first mapped the top 10% of normalized functional connections at baseline to probe the CA1-3 functional connectivity network with equal number of parcels across subfields. Functional connectivity was strong to medial prefrontal regions, precuneus extending to posterior cingulate, anterior temporal regions and angular gyrus (CA1-3: **Figure 2**; see *Supplementary Materials* for other subfields).

Evaluating functional connectivity changes, we found that connectivity of the right CA1-3 functional network showed differential changes when comparing *Affect* training to *Perspective* training (2.420, p=0.016, FDRq=0.032, Cohens D =0.289), but not versus retest control (**Table 1** and **Supplementary Table 8-14**). Comparing *Affect* TC3 relative to *Presence* training, we did not observe changes (**Table 1**). No other subfield showed differential changes in main contrasts within its functional network.

Table 1. Changes in mean hippocampal subfield functional network between training and active control cohorts [T0-T1] and [T1-T3]

Affect TC3 vs Presence	**LSUB**	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
t-value	0,058	0,366	0,541	-0,230	-0,411	0,151
p-value	0,953	0,715	0,589	0,818	0,682	0,880
Cohens D	0,008	0,052	0,077	-0,033	-0,058	0,021
Affect vs Perspective						
t-value	0,644	0,137	0,272	1,674	2,420	1,088
p-value	0,520	0,891	0,786	0,095	0,016	0,278
Cohens D	0,077	0,016	0,032	0,200	0,289	0,130

Left CA1-3 showed decreases in connectivity to left posterior insula when comparing *Affect* to *Perspective* training (FDRq<0.05; t=-3.097, p=0.003, Cohens D=-0.370). On the other hand, we observed connectivity increases between right CA1-3 and right mPFC for the same contrast (FDRq<0.05; t=3.262, p=0.002, Cohens D =0.389). No other subfields showed alterations in functional connectivity when comparing *Affect* to *Perspective* or *Presence* to *Affect TC3*. These analyses indicate an overlap between volumetric increases and functional alterations when comparing changes following socio-affective mental training versus socio-cognitive training in CA1-3. Yet, despite volumetric changes showing moderate consistent change following socio-affective mental training, this pattern was not present for functional change, where we predominantly observed differential effects for socio-affective mental training relatively to socio-cognitive mental training.

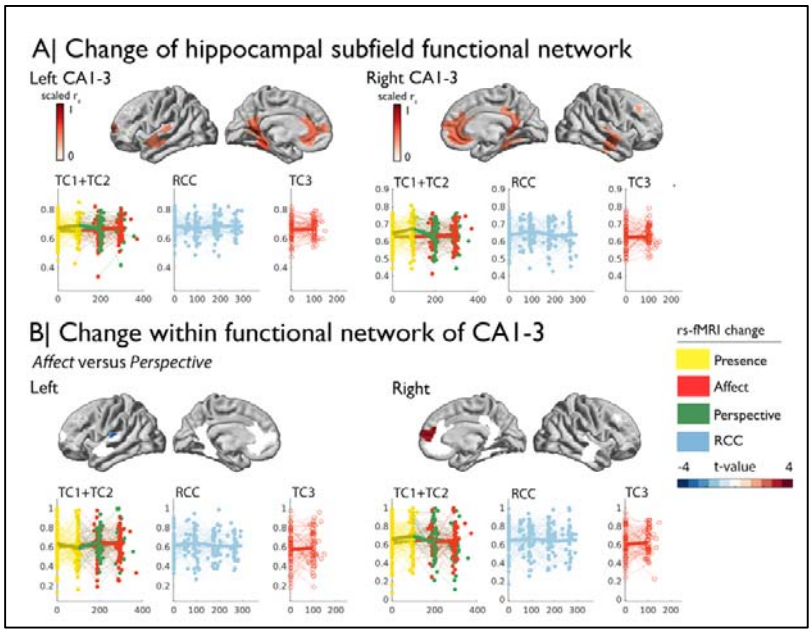

Fig. 2 Training induced plasticity of CA1-3 functional connectivity. A) *upper:* CA1-3 functional connectivity at baseline, top 10% of regions representing the CA1-3 functional network; *lower:* scatter plot visualizing change within the CA1-3 network across timepoints and groups; networks and scatters of SUB and CA4/DG are available in the supplements; B) Regional change within CA1-3 functional network Affect versus Perspective (FDRq<0.05); *right:* scatter plot visualizing mean change within the CA1-3, FDRq<0.05 regions across timepoints and groups.

Association between change in subfield volume, function, and stress markers

Last, we probed whether group-level changes in hippocampal subfield CA1-3 volume observed following the *Affect* module would correlate with changes in diurnal cortisol indices (n=92), based on the notion that the hippocampal formation is a key nexus within the HPA-axis (17). Volume changes in bilateral CA1-3 showed a negative association with change in total diurnal cortisol output (operationalized as the area under the curve with respect to ground; AUC_g) (left: t= -2.237, p=0.028, uncorrected; right: t=-2.283, p=0.025, uncorrected), indicating that with a reduction in stress-levels as measured by AUC_g, there were increases in CA1-3 volume. No other subfield showed an association with AUC_g, or with any of the other cortisol indices, below p<0.05 uncorrected (**Table 2**). Assessing the associations between cortisol indices and the CA1-3 functional connectivity in *Affect* (n=92), we could not observe individual level modulation of diurnal cortisol markers and group-level effects (**Table 3** and **Supplementary Table 15**). Yet, we observed positive associations between mean functional network of *left* CA1-3 and diurnal slope (t=2.653, p=0.01, uncorrected) and AUC_g (t=2.261, p=0.027, uncorrected). When assessing whether particular regions within the CA1-3 network showed alterations in intrinsic functional connectivity, we observed that AUC_g modulated increases in connectivity between left CA1-3 and parietal occipital area (FDRq<0.05). Overall

these analyses extend group-level observations regarding the link between socio-affective mental training and CA1-3 structure to the individual-level. Again, we observed some consistency in structure and function in case of CA1-3. When evaluating associations between diurnal cortisol change across modules, (*Presence*, *Affect*, and *Perspective*), we observed comparable patterns as for *Affect* only, underscoring the association between cortisol and CA1-3 (**Supplementary table 16 and 17, Supplementary Figure 2 and 3**). Last, we explored associations of subfield volume and hair cortisol, a long-term marker of systemic cortisol exposure, in a sub-sample of N=44 participants repeatedly tested across modules (*Presence*, *Affect*, and *Perspective*), based on previous observations of domain-general effects of mental training on cortisol and cortisone (3). Increases in LCA1-3 volume and intrinsic function were correlated to cortisol decreases (volume: t=-2.574, p=0.011, function: t=-2.700, p=0.008), and so were right CA4/DG volume (t=-3.138, p=0.002) and left SUB function (t=-2.890, p=0.005) (**Supplementary Table 18 and 19**).

Table 2. Correlating change in subfield volume and diurnal cortisol indices in *Affect*.

	LSUB	LCA1-3	LCA4/DG	RSUB	RCA1-3	RCA4/DG
CAR	1,007, p>0.1	-0,355, p>0.1	0,166, p>0.1	-1,364, p>0.1	-1,543, p>0.1	-0,404, p>0.1
Slope	-0,283, p>0.1	-0,878, p>0.1	0,728, p>0.1	0,634, p>0.1	-1,245, p>0.1	-1,716, p<0.1
AUC_g	-0,945, p>0.1	-2,237, p=0.028	0,636, p>0.1	-0,222, p>0.1	-2,283, p=0.025	-1,446, p>0.1

Table 3. Correlating change in subfield functional network and diurnal cortisol indices in *Affect*.

	LSUB	LCA1-3	LCA4/DG	RSUB	RCA1-3	RCA4/DG
CAR	0,066, p>0.1	-0,476, p>0.1	-0,535, p>0.1	-0,764, p>0.1	-0,425, p>0.1	-0,534, p>0.1
Slope	0,800, p>0.1	2,653, p=0.01	1,662, p>0.1	1,385, p>0.1	0,773, p>0.1	1,102, p>0.1
AUC_g	0,914, p>0.1	2,261, p=0.027	1,638, p>0.1	-0,697, p>0.1	0,024, p>0.1	-0,447, p>0.1

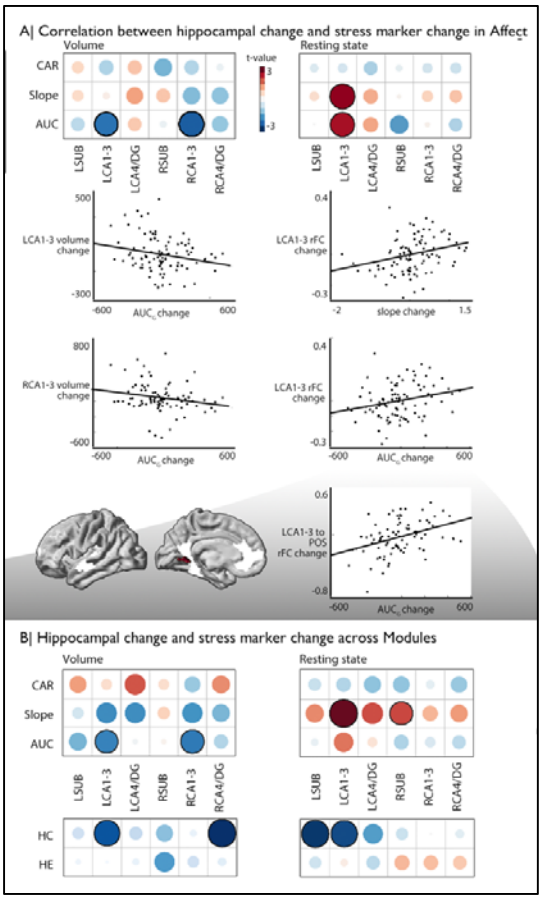

Fig. 3. Associations between changes in structure and function of hippocampal subfield volume and markers of stress change in Affect. A). *Upper left:* Correlation between hippocampal subfield volume change in Affect and CAR, slope, and AUC markers of stress change, *Upper right*: Correlation between hippocampal subfield intrinsic functional change in Affect and CAR, slope, and AUC markers of stress change, *middle:* Scatter plots visualize the correlation between volume change and cortisol marker change (below $p<0.05$), *bottom*: region level change within left CA1-3, FDRq<0.05; B). *Upper*: Overall impact of diurnal cortisol markers on hippocampal subfield volume and function over *Presence*, *Affect* and *Perspective*; *Lower*: Overall impact of hair cortisol markers on hippocampal subfield volume and function over *Presence*, *Affect* and *Perspective*

DISCUSSION

We investigated the effects of different types of mental training formats on stress-related changes in the human hippocampus in a large healthy sample of a 9-month longitudinal mental training study, the ReSource project (69). The hippocampal formation is a highly plastic allocortical region implicated in stress and emotional reactivity (12, 13, 17). Here, we automatically segmented hippocampal subfields SUB, CA1-3, and CA4/DG, to evaluate whether subfield volume change as a function of different types of meditation-based mental trainings modules, and whether observed changes correspond to intrinsic functional as well as stress-related peripheral-physiological alterations as probed by training-related changes in levels of diurnal cortisol.

When comparing the effect of the mental training modules *Presence*, *Affect*, and *Perspective* against each other and to test-retest retest effects on hippocampal subfield structure, we observed consistent increases in bilateral CA1-3 volume following socio-emotional *Affect* training relative to socio-cognitive *Perspective* training and no training in retest controls. Moreover, alterations in structure were mirrored by changes in functional connectivity of right CA1-3 following *Affect* versus *Perspective* training. In particular, we observed relative increases of functional connectivity of right CA1-3 towards mPFC, and decreases between left CA1-3 towards PI, mainly driven by changes in connectivity following *Perspective* training. Evaluating training-related changes in diurnal cortisol output (cortisol awakening response, total diurnal output and diurnal slope), bilateral CA1-3 volume increases correlated with decreases in total diurnal cortisol output (assessed as the area under the curve with respect to ground, AUC_g, sampled on 10 occasions over two consecutive days). Intrinsic connectivity of CA1-3 following *Affect* showed a positive association with left CA1-3 network change and diurnal slope and total diurnal cortisol output, where the latter associated with increased connectivity between left CA1-3 and parietal-occipital area. Interestingly, these associations were similar when combining the trainings, suggesting the association between CA1-3 and diurnal cortisol markers is present irrespective of training content. Moreover, we observed consistent associations between left CA1-3 and hair cortisol, a chronic stress marker, across trainings in a sub-sample of the current study.

Our longitudinal, multi-modal approach could thus show that CA1-3 structure changes following compassion-based mental training. Training-based increases in CA1-3 volume also related to decreases in total diurnal cortisol release, indicating a link between mental training, CA1-3 volume, and cortisol release. Functional connectivity findings were less clear, yet

again showed a difference between socio-affective and socio-cognitive mental training in CA1-3, and associated with CA1-3 intrinsic functional change with changes in diurnal cortisol markers, and long-term cortisol exposure. While the experimental nature of our training study allows concluding that CA1-3 structure changed as a function of *Affect* training, and that individual differences in CA1-3 structural change corresponded to cortisol release change, we cannot make any claims about which training-induced change caused the other. Thus, it is possible that, owing to the *Affect* module, the activation of emotion/motivation-related functional processes is key to reducing the daily stress load and associated cortisol release (75, 76). Such reduction in cortisol levels may then explain downstream brain alterations. According to this interpretation, changes in CA1-3 volume may come secondary to stress reduction and consequently alterations in cortisol release following compassion-based training. Alternatively, it may be that emotion/compassion-based training specifically targets CA1-3 volume and function, and, as per its role as the central break of the HPA axis (16, 17), improves its capacity to inhibit cortisol release. This explanation could explain the lack of *average* diurnal cortisol (i.e., AUC_g) change following *Affect* training per se (4), as it may be relevant for individual variations in brain change and thus be more difficult to detect based only on average change per module. In sum, it is likely that observed alterations in hippocampal structure and function, as well as their associations with diurnal cortisol change, are not explained by a single mechanism, but rather result from a combination of factors.

The observed increases in CA1-3 volumes following *Affect* training had small effects. However, findings were consistent when independently assessing the left and right hippocampus subfields, and seen despite an implicit correction for total brain volume through the use of a stereotaxic reference frame. In particular, we observed that increases in CA1-3 volume after *Affect* training corresponded to a decrease in total diurnal cortisol as well as hair cortisol output. These results can be interpreted in line with the mainly inhibitory role of the hippocampus in stress regulation (18-20, 77). Specifically, the hippocampus is involved in the negative feedback inhibition of the HPA axis. Mineral- and glucocorticoid receptors are present in abundance in hippocampal neurons, from where they transmit the negative feedback signals of a wide range of glucocorticoid levels on HPA axis activity (20). The extremely high numbers of mineral- and glucocorticoid receptors make the hippocampus a prominent target for the neurotoxic effects of glucocorticoids (78-80). In particular the CA1 may be susceptive to stress-based environmental effects due to synaptogenesis associated with NR2B subunits of glutamate receptors (NMDAR)(81). Along these lines, sustained exposure to high glucocorti-

coid levels was shown to relate to calcium influx, and may produce CA3 pyramidal neuronal damage, which has been reported in rodents and tree shrews (82-84). Next to demonstrating a consistent relationship between total daily cortisol output and hippocampal structure, the absence of findings for cortisol awakening response (CAR), diurnal slope or hair cortisone levels may a divergence in the sensitivity of alternative cortisol-based stress markers to structural neuroimaging markers.

Structural MRI findings were complemented by the separate assessment of task-free ("resting-state") functional connectivity networks. In the current cohort, we could demonstrate widespread patterns of hippocampal functional connectivity to mesiotemporal, lateral temporal, together with anterior as well as posterior midline regions, lateral temporo-parietal, and dorsolateral prefrontal cortices - a pattern in excellent accordance to previous studies probing hippocampal functional connectivity at rest in healthy populations (26, 33, 36, 85, 86), and outlining "mesiotemporal" components of default-mode networks (87, 88). Assessing modulations of connectivity by mental training, we could provide independent, yet weak, support for a specific relationship of the compassion-based socio-affective *Affect* training, relative to socio-cognitive *(Perspective*) training modules, on hippocampal network embedding. In particular, we observed an increased functional integration of the right CA1-3 with medial prefrontal cortical regions (mPFC) in individuals following socio-affective mental training relative to socio-cognitive training. Studies in rats and non-human primates have demonstrated a high density of glucocorticoid receptors in the mPFC (89, 90). Accordingly, the mPFC, like the hippocampus, was shown to play a key role in HPA-axis regulation (48, 77, 91, 92). In a previous positron emission tomography study, glucose metabolism in the mPFC was negatively associated with acute stress-induced salivary cortisol increases; notably, the authors observed a negative metabolic coupling between mPFC areas and the mesiotemporal lobe (93). In related work on iso-cortical changes in structure and intrinsic function following the ReSource training, we have observed structural changes in insular, opercular and orbitofrontal regions following socio-affective mental training (7, 71). At the same time, we observed little change in large-scale functional organization following this training, relative to changes observed following attention-based mindfulness and socio-cognitive training. Previous work has implicated the hippocampal formation at the nexus of multiple large-scale networks and cortical organization (26, 94). Indeed, it may be that particular changes in the CA1-3 are central in coordinating the signal flow within the hippocampal complex, ultimately coordinating the balance between large-scale association networks in the iso-cortex (26). Integrating this with

our empirical observation of socio-affective training taking up a regulatory or stabilizing functional role, relative to socio-cognitive and attention-mindfulness training, it is possible that such alterations are orchestrated by adaptive processes (95). Future work may be able to further disentangle the causal relationship between iso- and allo-cortical structure and function, and the role of specific hippocampal subfields.

Our finding of training-induced HC volume increases following socio-affective mental training overlapped with reductions in cumulative diurnal cortisol release. Additionally, we observed functional connectivity decrease between left CA1-3 and parietal-occipital area in individuals showing reduced diurnal cortisol release and overall connectivity decreases of left CA1-3, relating to reductions in diurnal cortisol slope. Importantly, these associations could be found also when including *Presence* and *Perspective* in our analysis, suggesting of a domain-general relationship between diurnal cortisol alterations and CA1-3 volume and function. Other work based on the same cohort showed mixed specificity of stress-reducing effects as a function of mental training. For example, both social modules, that is *Affect* and *Perspective* training, reduced acute cortisol reactivity to a psychosocial stressor (96), which is considered a dynamic state of HPA axis activity (5). Regarding the CAR, only *Affect* training was able to reduce this dynamic proxy of anticipatory stress (4). Considering hair cortisol, a longer-term proxy of systemic stress, all training modules were shown to be equally effective in stress reduction over a training period of three to nine months (3). Indeed, in our work we observed a consistent association between left CA1-3 volume and functional increases and hair cortisol decreases, hinting at a relationship between CA1-3 and both short-term and long-term stress level changes. Thus, different types of mental training result in stress reduction (e.g., (3-5)). In a recent paper, we argued that the variable pattern of mental training effects on different cortisol indices may be explained by the functional roles of these indices (4). Thus, indices reflecting dynamic HPA axis properties, such as acute stress reactivity and the CAR, were suggested to change with socio-affective (*Affect*) and socio-cognitive practice (*Perspective*) (also see (5)). Hair cortisol as a marker of cumulative stress load likely reflecting the low-grade and continuous strain inherent to daily hassles (97-99), was contrarily suggested to change independent of training type (also see (3)). The current findings do not necessarily contradict this reasoning, due to differences in interpretation of group-level and individual-level changes. Indeed, while we observed that CA1-3 volume was selectively increased by socio-affective mental training at the group-level and that individual variation in CA1-3 volume increase within the *Affect* module correlated with reduced diurnal cortisol release de-

crease, the pattern linking bilateral CA1-3 volume increases to reduced diurnal cortisol release was also present when combining all modules. Similarly, in follow-up analysis on functional alterations of hippocampal subfields, we could observe group-level increases in connectivity to mPFC for right, but not left, CA1-3, when comparing socio-affective and socio-cognitive training. While right CA1-3 group-level changes did not link to individual level change in cortisol markers following socio-affective mental training, individual level changes in left CA1-3 corresponded to changes in cortisol markers, again following *Affect* but also across all practices combined. Thus, we cannot at this point derive a consistent pattern of how mental training influences different indices of cortisol activity, yet we do find a consistent change in CA1-3 following social-affective mental training, and observe domain-general patterns of change associations between CA1-3 and cortisol markers. From a mechanistic viewpoint, we hypothesize that *Affect* training stimulates emotion-motivational (reward) systems associated with positive affect (75, 76), and regulated by oxytocin and opiates (100, 101). Since these neuropeptides are also involved in stress regulation (102, 103), they could be considered to provide a double hit, and prime candidates to mediate hippocampal volume increase and stress reduction in particular following compassion-based practice, yet also present following other practices.

It is of note that non-adherence to saliva sampling in ambulatory settings has been shown to exert a significant impact on the resulting cortisol data (104, 105) and that the present data does not fully conform to the recently provided consensus guidelines on the assessment of the CAR (106, 107), which were published after the conception of our study. Most importantly, we did not employ objective measures for the verification of participants' sampling times. Hence, diurnal cortisol data have to be treated with some caution since the possibility of non-adherence-related confounding cannot be excluded (104-107). We nevertheless addressed the issue of non-adherence through an experience sampling approach based on mobile phones handed out to our participants. As shown by the relatively low proportion of missing data, these devices may have boosted adherence by reminding participants of a forthcoming sampling time-point.

To conclude, our longitudinal study investigated how different types of mental training affect changes in hippocampal subfield volume, intrinsic functional networks, and stress-related markers of diurnal and hair cortisol. We find that 3-months socio-affective mental training module cultivating compassion and care resulted in volume increase of the hippocampal sub-

field CA1-3, with corresponding alterations in functional connectivity. Volumetric increases correlated with a reduction in total diurnal cortisol output. Across analyses we observed consistent alterations between cortisol change and CA1-3 volume and function, pinpointing this region as a potential candidate for further investigations on stress and the human brain. Our results may be informative for the development of targeted interventions to reduce stress, and inspire the update of models on the role of different hippocampal formations for human socio-emotional and stress-related processes.

Methods

Participants

We recruited a total of 332 healthy adults (197 women, mean±SD=40.7±9.2 years, 20-55 years), in the winters of 2012/2013 and 2013/2014. Participant eligibility was determined through a multi-stage procedure that involved several screening and mental health questionnaires, together with a phone interview [for details, see (69)]. Subsequently, a face-to-face mental health diagnostic interview with a trained clinical psychologist was carried out. The interview included a computer-assisted German version of the Structured Clinical Interview for DSM-IV Axis-I disorders, SCID-I DIA-X (108), and a personal interview, SCID-II, for Axis-II disorders (109, 110). Participants were excluded if they fulfilled criteria for: i) an Axis-I disorder within the past two years, ii) schizophrenia, psychotic disorders, bipolar disorder, or substance dependency, or iii) an Axis-II disorder at any time in their life. Participants taking medication influencing the HPA axis were also excluded. None of the participants had a history of suffering from neurological disorders or head trauma, based on an in-house self-report questionnaire completed prior to the neuroimaging investigations. Included participants furthermore underwent a diagnostic radiological evaluation to rule out the presence of mass lesions (e.g., tumors, vascular malformations). The study was approved by the Research Ethics Committees of University of Leipzig (#376/12-ff) and Humboldt University in Berlin (#2013-02, 2013-29, 2014-10), and all participants provided written informed consent prior to participation. The study was registered with the Protocol Registration System of ClinicalTrials.gov under the title “Plasticity of the Compassionate Brain” with the Identifier: NCT01833104. For more details on recruiting and sample selection, please see (69).

ReSource training program

In the *ReSource Project*, we investigated the specific effects of commonly used mental training techniques by parceling the training program into three separate modules (*Presence*, *Affect* and *Perspective*). Participants were selected from a larger pool of potential volunteers by bootstrapping without replacement, creating cohorts not differing significantly with respect to several demographic and self-report traits (69). Each cultivated distinct cognitive and socio-affective capacities (*69*). Participants were divided in two 9-month training cohorts experiencing the modules in different orders, one 3-month *Affect* training cohort and one retest control cohort. In detail, two training cohorts (TC1, TC2) started their training with the mindfulness-based *Presence* module. They then underwent *Affect* and *Perspective* modules in different orders thereby acting as mutual active control groups. To isolate the specific effects

of the *Presence* module, a third training cohort (TC3) underwent the 3-month *Affect* module only (**Fig. 1B**).

As illustrated in **Fig 1A**, the core psychological processes targeted in the *Presence* module are attention and interoceptive awareness, which are trained through the two meditation-based core exercises Breathing Meditation and Body Scan. The *Affect* module targets the cultivation of social emotions such as compassion, loving kindness and gratitude. It also aims to enhance prosocial motivation and dealing with difficult emotions. The two core exercises of the *Affect* module are Loving-kindness Meditation and Affect Dyad. In the *Perspective* module participants train meta-cognition and perspective-taking on self and others through the two core exercises Observing-thoughts Meditation and Perspective Dyad. The distinction between *Affect* and *Perspective* modules reflects research identifying distinct neural routes to social understanding: One socio-affective route including emotions such as empathy and compassion, and one socio-cognitive route including the capacity to mentalize and take perspective on self and others (further details on the motivation of this division can be found in previous work (69)).

The two contemplative dyads are partner exercises that were developed for the *ReSource* training (111). They address different skills such as perspective taking on self and others (*Perspective* dyad) or gratitude, acceptance of difficult emotions and empathic listening (*Affect* dyad), but are similar in structure (for details see: (69)). In each 10-min dyadic practice, two randomly paired participants share their experiences with alternating roles of speaker and listener. The dyadic format is designed to foster interconnectedness by providing opportunities for self-disclosure and non-judgmental listening (69, 111). Our recommendation was to train for a minimum of 30 minutes (e.g. 10 minutes contemplative dyad, 20 minutes classic meditation) on five days per week.

MRI acquisition

MRI data were acquired on a 3T Siemens Magnetom Verio (Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil. Structural images were acquired using a T1-weighted 3D-MPRAGE sequence (repetition time [TR]=2300 ms, echo time [TE]=2.98 ms, inversion time [TI]=900 ms, flip angle=7°; 176 sagittal slices with 1mm slice thickness, field of view [FOV]=240×256 mm^2, matrix=240×256, 1×1×1 mm^3 voxels). We recorded task-free functional MRI using a T2*-weighted gradient EPI sequence (TR=2000ms, TE=27ms, flip angle=90°; 37 slices tilted at approximately 30° with 3 mm slice thickness, FOV=210×210mm^2, ma-

trix=70×70, 3×3×3 mm^3 voxels, 1 mm gap; 210 volumes per session). During the functional session, participants were instructed to lie still in the scanner, think of nothing in particular, and fixate a white cross in the center of a black screen.

Structural MRI analysis: Hippocampal subfield volumetry

Based on the available high-resolution T1-weighted images, the subiculum (SUB), CA1-3, and CA4/DG were segmented using a patch-based algorithm in all participants individually (72). This procedure uses a population-based patch normalization relative to a template library (112), providing reasonable time and space complexity. In previous validations, this algorithm has shown high segmentation accuracy of hippocampal subfields (72), and in detecting hippocampal subfield pathology in patients with epilepsy (113). It was furthermore demonstrated that these representations can be used to probe sub-regional functional organization of the hippocampus (33, 34). Hippocampal volumes were estimated based on T1w data that were linearly registered to MNI152, such that intracranial volume was implicitly controlled for.

As previously reported (114), an initial quality check of automated hippocampus segmentations was conducted by two independent raters, RL and LP. Both raters were blind to participant characteristics including age, sex, and training or control group. In short, each segmentation was rated for quality on a scale of 1–10, with points being subtracted depending on the severity of detected flaws. One point was subtracted for minor flaws, e.g. part of a segmentation extends slightly beyond the hippocampal boundary, or does not cover a small aspect of the hippocampal formation. Two points were subtracted for medium flaws, e.g. gaps between subfield segmentations. Finally, major flaws immediately qualified for resampling, and included e.g. one or more subfield segmentations being clearly misplaced. Given a minimum of 70% inter-rater reliability, segmentation ratings were then averaged and evaluated, with scores of 5 and lower qualifying for reprocessing with the algorithm. Following this second round of processing, segmentations were rated again. Any remaining segmentations with average scores lower than 5 were excluded from the analysis.

Task-free functional MRI analysis: Hippocampal connectivity

Processing was based on DPARSF/REST for Matlab [http://www.restfmri.net (115)]. We discarded the first 5 volumes to ensure steady-state magnetization, performed slice-time correction, motion correction and realignment, and co-registered functional time series of a given subject to the corresponding T1-weighted MRI. Images underwent unified segmentation and

registration to MNI152, followed by nuisance covariate regression to remove effects of average WM and CSF signal, as well as 6 motion parameters (3 translations, 3 rotations). We included a *scrubbing* (116) that modeled time points with a frame-wise displacement of ≥0.5 mm, together with the preceding and subsequent time points as separate regressors during nuisance covariate correction.

We linearly co-registered extracted hippocampal subfield volumes with the functional MRI data for each individual using FSL flirt (http://www.fmrib.ox.ac.uk/fsl/), followed by nearest neighbour interpolation. Following, we generated functional connectivity maps from both the left and right hippocampal subfields in each individual. Functional connectivity was calculated as the correlation between the mean time series of the seed region and the time series of all cortical parcels based on the Schaefer 400 parcellation. To render them normally distributed and scale the profiles across participants, correlation coefficients underwent a Fisher r-to-z transformation and were rescaled, resulting in connectivity profiles between 0 and 1 for each participant and timepoint. Functional networks were defined as the top 10% regions based on mean connectivity profile of the respective subfield in the ipsilateral hemisphere at baseline. Individuals with a framewise-displacement of >0.3mm (<5%) were excluded.

Diurnal cortisol assessments

For cortisol assessment, 14 saliva samples (7 per day) were obtained over the course of two consecutive weekdays (Mondays/Tuesdays, Wednesdays/Thursdays or Thursdays/Fridays, depending on participant availability). In detail, samples were taken upon free awakening (while still in bed; S1) and at 30 minutes, 60 minutes, 4, 6, 8 and 10 hours after awakening. Saliva was collected using Salivette collection devices (Sarstedt, Nuembrecht, Germany). Participants were instructed to place collection swabs in their mouths and to refrain from chewing for 2 minutes. They were asked to not eat, drink (except water), or brush their teeth during the 10 minutes before sampling, and to not smoke during the 30 minutes before sampling. If deviating from this guideline, they were asked to thoroughly rinse their mouth with water before taking a sample. Participants otherwise followed their normal daily routine. To maximize adherence to the sampling protocol, participants were given pre-programmed mobile devices using an in-house application that reminded them to take each (except the first) Salivette at the designated time. Sampling times of the non-morning probes were jittered (+/- 15 min) to avoid complete predictability. Samples were kept in the freezer until returned to the laboratory, where they were stored at -30 ºC until assay (at the Department of Biological

and Clinical Psychology, University of Trier, Germany). Cortisol levels (expressed in nmol/l) were determined using a time-resolved fluorescence immunoassay (117) with intra-/inter-assay variability of 10/12%.

Raw cortisol data were each treated with a natural log transformation to remedy skewed distributions. Across the full sample, any values diverging more than 3 SD from the mean were labeled outliers and winsorized to the respective upper or lower 3 SD boundary to avoid influential cases. Logged and winsorized cortisol data was then averaged across the two sampling days, and the most commonly used summary indices of diurnal cortisol activity were calculated (11). The CAR was quantified as a change score from S1 to either the 30- or 60-minute post-awakening sample, depending on the individual peak in hormone levels. If participants peaked at S1 rather than at 30 or 60 minutes thereafter, the 30-minute data point was used to operationalize the (inverse) CAR, given that it was always closer in magnitude to S1 than the 60-minute data point. The cortisol decline over the course of the day (diurnal slope) was operationalized as a change score from baseline to the final sample of the day (at 600 minutes after awakening). Total daily cortisol output was operationalized as the area under the curve with respect to ground, AUC_g (118), which considers the difference between the measurements from each other (i.e., the change over time) and the distance of these measures from zero (i.e., the level at which the change over time occurs). Awakening, 240, 360, 480, and 600 minutes post-awakening cortisol values were included in the calculation of the AUC_g. To prevent it from having an undue influence, the CAR samples at 30 and 60 minutes were excluded from the total output score calculation. On each sampling day, awakening time and sleep duration were registered using the pre-programmed mobile device immediately upon awakening in parallel to taking the first Salivette. These measures were averaged across the two sampling days to minimize situational influences.

Assay of Steroid Hormone Concentration in Hair

Details on sample and dropout have been reported previously (3). To evaluate cortisol and cortisone, hair strands were taken as close as possible to the scalp from a posterior vertex position at T0 and after each following timepoint (T0-T3). Hair samples were enfolded in aluminum foil and stored in the dark at room temperature until assay at the Department of Psychology, TU Dresden, Germany. We evaluated the proximal 3-cm segment of hair to study accumulation of cortisol and cortisone over each 3-month period, based on the assumption of an average hair growth rate of 1 cm/month (119). Hormone concentrations were captured us-

ing liquid chromatography–tandem mass spectrometry, the current criterion standard approach for hair steroid analysis (120). All hormone concentrations were reported in picograms per milligram. For the current longitudinal research aim, all samples of one participant were always run with the same reagent batch to avoid intraindividual variance due to batch effects.

Quality control and case selection

Structural MRI data without artifacts and acceptable automated segmentations were available in 943 participant-timepoints. Functional MRI data were available in 849 participant-timepoints. We opted to have consistent sample sizes in structure and function and therefor including only people that had both structural and functional data available. Please see **Table 4.** for participant numbers across timepoints and measures for structural and functional data.

Table 4. Sample size per timepoint.

	Structural MRI data	**Structural and Functional MRI data**
T0	288 (TC3:71)	258 (TC3: 70)
T1	272 (TC3:68)	238 (TC3: 64)
T2	193	172
T3	190	181

Table 5. Reason for missing data across the study duration. *MR incidental findings* are based on T_0 radiological evaluations; participants who did not meet *MRI quality control* criteria refers to movement and/or artefacts in the T1-weighted MRI; dropout details can be found in (69); *no MRT*: due to illness / scheduling issues / discomfort in scanner; *other*: non-disclosed; *functional MRI missing:* no complete functional MRI; *functional MRI quality:* >0.3mm movement (low quality in volume + surface)

Reason for dropout (TC1, TC2, RCC: N=251)	**T_0**	**T_1**	**T_2**	**T_3**
Structural MR incidental finding	5	(5 based on T_0)	(5 based on T_0)	(5 based on T_0)
Structural MRI quality control	7	6	4	2
Dropout	2	7(2 based on T_0)	9(7 based on T_{01})	16(9 based on T_{012})
Medical reasons	1	7(1 based on T_0)	8(7 based on T_{01})	15(8 based on T_{012})
Other	4	10	7	7
Functional MRI missing/low QC	29	30	21	9
Hippocampal QC	15	12	25	16

Table 6. Reason for missing data across the study duration. *MR incidental findings* are based on T_0 radiological evaluations; participants who did not survive *MRI quality control* refers to movement and/or artefacts in

the T1-weighted MRI; dropout details can be found in (69); *no MRT*: due to illness / scheduling issues / discomfort in scanner; *other*: non-disclosed.

Reason for dropout (TC3, N=81)	**T_0**	**T_1**
MR incidental finding	3	(3 based on T_0)
MRI quality control	0	0
Dropout	0	3
Medical reasons	1	2
Other	5	3
Functional MRI missing	1	4
Hippocampal QC	1	2

Among those, salivary cortisol measures were available in *Presence* n= 85 (53 females, age= 40.87 SD 9.69, 20-55), *Affect* n= 89 (50 females, age= 40.11 SD 9.87, 20-55), *Perspective* n= 81 (48 females, age= 40.14 SD 9.78, 20-55). Hair cortisol change scores were available in *Presence* n= 31 (21 females, age= 39.55 SD 10.40, 20-54), *Affect* n= 44 (24 females, age= 37.52 ST 10.78, 20-54), *Perspective* n= 41 (24 females, age= 38.14 SD 10.51, 20-54).

Statistical analyses

Using SurfStat for Matlab (version 2022b) (121, 122), we carried out structural and functional MRI analysis for the left and right hippocampal subfield difference scores between different 3-month timepoints. All models statistically corrected for nuisance effects of age and sex, as well as random effect of subject. Main contrasts considered in the group analyses concern *Presence* versus *Active Control* (T_0-T_1) and *Affect* versus *Perspective* (T_1-T_3). Additionally, investigations include analyses versus Retest Control Cohort as well as subgroups defined by training cohort and timepoint. In case of multiple comparison, we performed Bonferroni correction (123).

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DATA AND CODE AVAILABILITY

Summary data and analysis scripts (Matlab) to reproduce primary analyses and figures are publicly available on GitHub (https://github.com/CNG-LAB/valk_hippocampal_change), and raw data-plots are provided whenever possible. In line with EU data regulations (General Data Protection Regulation, GDPR), we regret that raw data cannot be shared publicly because we did not obtain explicit participant agreement for data-sharing with third parties. Our work is based on personal data (age, sex and neuroimaging data) that could be matched to individuals. The data is therefore pseudonominized rather than anonymized and falls under the GDPR. Data are available upon request (contact via valk@cbs.mpg.de).

SUPPLEMENTARY ANALYSES

Table S1. Descriptive statistics T0-T1

Presence	**LSUB**	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
t-values	1,335	0,836	-0,452	-0,623	0,788	-0,751
p-value	0,183	0,404	0,652	0,534	0,432	0,454
Mean	4,616	30,930	-4,686	-7,279	13,244	-2,419
std	83,141	205,390	51,976	98,493	166,340	64,548
CI min	-13,209	-13,105	-15,830	-28,396	-22,419	-16,258
CI max	22,442	74,965	6,458	13,838	48,907	11,421
Affect TC3						
t-values	1,195	1,456	1,739	1,528	1,334	0,060
p-value	0,234	0,147	0,084	0,128	0,184	0,952
Mean	4,295	46,443	7,312	19,426	23,344	3,705
std	90,258	206,540	43,280	121,990	187,470	63,729
CI min	-18,821	-6,454	-3,773	-11,816	-24,670	-12,617
CI max	27,411	99,340	18,396	50,669	71,358	20,027
RCC						
t-values	-0,955	-0,497	-1,698	-0,126	-2,526	0,778
p-value	0,341	0,620	0,091	0,900	0,012	0,437
Mean	-14,000	6,259	-12,111	-0,870	-50,259	10,407
std	66,176	156,220	41,762	91,759	139,760	79,943
CI min	-32,063	-36,381	-23,510	-25,916	-88,406	-11,413
CI max	4,063	48,900	-0,712	24,175	-12,112	32,228

Table S2. Descriptive statistics T1-T3

Perspective	**LSUB**	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
t-values	0,456	-1,143	-0,463	0,573	-2,118	1,291
p-value	0,649	0,254	0,644	0,567	0,035	0,198
Mean	4,434	-23,048	-1,398	2,108	-39,602	12,024
std	71,215	137,810	45,224	99,892	208,470	76,355
CI min	-11,116	-53,139	-11,273	-19,704	-85,122	-4,649
CI max	19,984	7,043	8,477	23,921	5,917	28,697
Affect						
t-values	1,121	2,495	0,235	0,210	2,374	0,394
p-value	0,263	0,013	0,814	0,833	0,018	0,694
Mean	8,424	25,511	1,489	-2,098	40,120	5,087
std	63,328	130,470	36,293	112,520	181,300	76,124
CI min	-4,691	-1,509	-6,027	-25,399	2,573	-10,678
CI max	21,539	52,531	9,005	21,204	77,666	20,852
RCC						
t-values	-1,102	-1,118	-1,052	-0,409	1,052	-0,557
p-value	0,271	0,264	0,294	0,683	0,294	0,578

Mean	-6,864	-21,845	-3,700	-8,591	15,673	-1,827
std	75,284	137,630	45,632	104,680	155,170	71,276
CI min	-21,090	-47,853	-12,323	-28,372	-13,650	-15,297
CI max	7,363	4,162	4,923	11,190	44,995	11,642

Table S3. T0-T1 change statistics

Affect TC3 vs Presence	**LSUB**	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
t-value	-0,065	0,454	1,519	1,487	0,401	0,548
p-value	0,948	0,650	0,130	0,139	0,689	0,584
Cohens D	-0,009	0,065	0,217	0,212	0,057	0,078
Affect TC3 vs RCC						
t-value	1,359	1,228	2,175	1,036	2,452	-0,461
p-value	0,176	0,221	0,031	0,302	0,015	0,645
Cohens D	0,194	0,175	0,311	0,148	0,350	-0,066
Presence vs RCC						
t-value	1,522	0,883	0,875	-0,317	2,248	-1,021
p-value	0,130	0,379	0,383	0,752	0,026	0,308
Cohens D	0,217	0,126	0,125	-0,045	0,321	-0,146

Table S4. T1-T3 change statistics

Affect vs Perspective	**LSUB**	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
t-value	0,417	2,360	0,458	-0,245	2,930	-0,604
p-value	0,677	0,019	0,647	0,807	0,004	0,547
Cohens D	0,050	0,282	0,055	-0,029	0,350	-0,072
Affect vs RCC						
t-value	1,504	2,460	0,861	0,417	0,935	0,641
p-value	0,134	0,014	0,390	0,677	0,351	0,522
Cohens D	0,180	0,294	0,103	0,050	0,112	0,077
Perspective vs RCC						
t-value	1,025	-0,067	0,359	0,659	-2,139	1,250
p-value	0,306	0,947	0,720	0,510	0,033	0,212
Cohens D	0,123	-0,008	0,043	0,079	-0,256	0,149

Table S4. T1-T3 change statistics – Training cohort 1 and 2 *Affect* versus *Perspective*

TC1	**LSUB**	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
t-value	1,557	2,549	1,263	0,214	4,243	-0,224
p-value	0,122	0,012	0,209	0,831	0,000	0,823
Cohens D	0,273	0,447	0,222	0,038	0,744	-0,039

TC2						
t-value	-0,819	0,447	-0,300	-0,757	0,102	-0,681
p-value	0,414	0,656	0,765	0,451	0,919	0,497
Cohens D	-0,149	0,081	-0,055	-0,138	0,019	-0,124

Table S5. T1-T2 change

T1-T2	**LSUB**	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
Affect vs Perspective						
t-value	0,612	1,751	0,944	0,404	3,743	-0,174
p-value	0,541	0,082	0,347	0,687	0,000	0,862
Cohens D	0,108	0,308	0,166	0,071	0,659	-0,031
Affect vs RCC						
t-value	1,995	0,967	0,582	0,974	2,637	0,622
p-value	0,048	0,335	0,562	0,332	0,009	0,535
Cohens D	0,351	0,170	0,102	0,171	0,464	0,110
Perspective vs RCC						
t-value	1,271	-0,938	-0,448	0,508	-1,454	0,786
p-value	0,206	0,350	0,655	0,613	0,148	0,433
Cohens D	0,224	-0,165	-0,079	0,089	-0,256	0,138

Table S6. T2-T3 change

T2-T3	**LSUB**	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
Affect vs Perspective						
t-value	-0,033	1,768	-0,176	-0,582	0,641	-0,748
p-value	0,974	0,079	0,860	0,561	0,523	0,456
Cohens D	-0,005	0,293	-0,029	-0,096	0,106	-0,124
Affect vs RCC						
t-value	0,212	2,691	0,832	-0,302	-1,006	0,326
p-value	0,832	0,008	0,407	0,763	0,316	0,745
Cohens D	0,035	0,445	0,138	-0,050	-0,167	0,054
Perspective vs RCC						
t-value	0,239	0,828	0,988	0,296	-1,628	1,075
p-value	0,811	0,409	0,325	0,768	0,106	0,284
Cohens D	0,040	0,137	0,164	0,049	-0,269	0,178

Table S7. Overall change in subfield volume.

Training vs RCC	**LSUB**	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
t-value	1,033	0,702	1,035	-1,348	0,774	0,017
p-value	0,303	0,484	0,302	0,180	0,440	0,986

Cohens D	0,172	0,117	0,172	-0,225	0,129	0,003

Table S8. Descriptive statistics mean subfield functional network change T0-T1

Presence						
t-values	-1,223	-0,803	-0,915	-0,757	-0,507	0,387
p-value	0,223	0,423	0,361	0,450	0,613	0,699
Mean	-0,004	-0,001	-0,008	0,000	0,009	0,004
std	0,091	0,089	0,093	0,089	0,099	0,087
CI min	-0,023	-0,020	-0,028	-0,018	-0,012	-0,014
CI max	0,015	0,018	0,011	0,019	0,029	0,023
Affect TC3						
t-values	-1,089	-0,247	-0,105	-1,053	-1,071	0,587
p-value	0,278	0,805	0,917	0,294	0,285	0,558
Mean	-0,004	0,003	0,000	-0,004	0,002	0,007
std	0,078	0,091	0,082	0,085	0,081	0,096
CI min	-0,024	-0,021	-0,021	-0,026	-0,019	-0,018
CI max	0,016	0,026	0,021	0,018	0,022	0,032
RCC						
t-values	-0,521	-1,462	0,023	0,198	1,384	0,296
p-value	0,603	0,145	0,981	0,843	0,168	0,767
Mean	-0,001	-0,011	0,000	0,009	0,029	0,004
std	0,107	0,095	0,100	0,094	0,097	0,080
CI min	-0,030	-0,036	-0,028	-0,017	0,002	-0,017
CI max	0,028	0,015	0,027	0,034	0,055	0,026

Table S9. Descriptive statistics mean subfield functional network change T1-T3

Perspective						
t-values	0,046	-0,071	0,461	-1,443	-2,012	-1,089
p-value	0,963	0,943	0,645	0,150	0,045	0,277
Mean	-0,003	-0,007	0,003	-0,012	-0,024	-0,006
std	0,088	0,100	0,092	0,089	0,081	0,099
CI min	-0,022	-0,029	-0,017	-0,032	-0,041	-0,028
CI max	0,017	0,015	0,023	0,007	-0,006	0,016
Affect						
t-values	1,050	0,139	0,899	1,116	1,691	0,569
p-value	0,295	0,889	0,369	0,265	0,092	0,570
Mean	0,007	-0,005	0,007	0,011	0,010	0,010
std	0,103	0,110	0,100	0,092	0,098	0,098
CI min	-0,015	-0,028	-0,013	-0,008	-0,010	-0,010
CI max	0,028	0,018	0,028	0,030	0,031	0,030
RCC						
t-values	0,225	1,206	-0,608	-0,839	-0,701	-0,436

p-value	0,822	0,229	0,544	0,402	0,484	0,663
Mean	0,000	0,005	-0,005	-0,006	-0,010	0,001
std	0,079	0,079	0,071	0,089	0,092	0,092
CI min	-0,015	-0,010	-0,019	-0,023	-0,028	-0,017
CI max	0,014	0,020	0,008	0,011	0,007	0,018

Table S10. Functional connectivity network change T0-T1

Affect TC3 vs Presence						
t-value	0,058	0,366	0,541	-0,230	-0,411	0,151
p-value	0,953	0,715	0,589	0,818	0,682	0,880
Cohens D	0,008	0,052	0,077	-0,033	-0,058	0,021
Affect TC3 vs RCC						
t-value	-0,347	0,782	-0,080	-0,785	-1,556	0,177
p-value	0,729	0,435	0,936	0,433	0,121	0,860
Cohens D	-0,049	0,111	-0,011	-0,112	-0,221	0,025
Presence vs RCC						
t-value	-0,430	0,491	-0,607	-0,626	-1,283	0,046
p-value	0,668	0,624	0,545	0,532	0,201	0,964
Cohens D	-0,061	0,070	-0,086	-0,089	-0,182	0,006

Table S11. Functional connectivity network change T1-T3

Affect vs Perspective						
t-value	0,644	0,137	0,272	1,674	2,420	1,088
p-value	0,520	0,891	0,786	0,095	0,016	0,278
Cohens D	0,077	0,016	0,032	0,200	0,289	0,130
Affect vs RCC						
t-value	0,575	-0,703	1,023	1,326	1,631	0,681
p-value	0,566	0,483	0,307	0,186	0,104	0,496
Cohens D	-0,049	0,111	-0,011	-0,112	-0,221	0,025
Perspective vs RCC						
t-value	-0,113	-0,824	0,709	-0,458	-0,939	-0,472
p-value	0,910	0,410	0,479	0,648	0,348	0,637
Cohens D	-0,061	0,070	-0,086	-0,089	-0,182	0,006

Table S12. Functional connectivity network change T1-T3: Training cohort 1 and 2 *Affect* versus *Perspective*

TC1						
t-value	-0,362	-0,985	-0,339	-0,254	-0,417	-0,085
p-value	0,718	0,326	0,735	0,800	0,677	0,933
Cohens D	-0,063	-0,172	-0,059	-0,044	-0,073	-0,015
TC2						
t-value	1,189	1,171	0,669	2,873	3,815	1,683
p-value	0,237	0,244	0,505	0,005	0,000	0,095

Cohens D	0,215	0,212	0,121	0,520	0,691	0,305

Table S13. Functional connectivity network change T1-T2

Affect vs Perspective						
t-value	-0,423	0,055	-0,713	0,810	2,121	0,737
p-value	0,673	0,956	0,477	0,419	0,036	0,463
Cohens D	-0,074	0,010	-0,126	0,143	0,373	0,130
Affect vs RCC						
t-value	-0,766	-1,978	-0,285	0,088	0,923	-0,061
p-value	0,445	0,051	0,776	0,930	0,358	0,952
Cohens D	-0,049	0,111	-0,011	-0,112	-0,221	0,025
Perspective vs RCC						
t-value	-0,287	-1,967	0,487	-0,780	-1,375	-0,846
p-value	0,775	0,052	0,627	0,437	0,172	0,399
Cohens D	-0,061	0,070	-0,086	-0,089	-0,182	0,006

Table S14. Functional connectivity network change T2-T3

Affect vs Perspective						
t-value	1,378	0,202	1,037	1,678	1,501	0,911
p-value	0,170	0,840	0,301	0,096	0,136	0,364
Cohens D	0,227	0,033	0,171	0,277	0,248	0,150
Affect vs RCC						
t-value	1,488	0,760	1,598	1,630	1,192	0,996
p-value	0,139	0,449	0,112	0,105	0,235	0,321
Cohens D	-0,049	0,111	-0,011	-0,112	-0,221	0,025
Perspective vs RCC						
t-value	0,045	0,533	0,499	-0,121	-0,367	0,043
p-value	0,964	0,595	0,619	0,904	0,714	0,966
Cohens D	-0,061	0,070	-0,086	-0,089	-0,182	0,006

Table S15. Association between stress-markers and within functional network sub-regions.

	LCA1-3 - PI	**RCA1-3 - mPFC**
CAR	-0.939, p>0.1	-0.137, p>0.1
Slope	0.652, p>0.1	0.385, p>0.1
AUC_g	-0.625, p>0.1	-0.484, p>0.1

Table S16. Overall effects of cortisol markers on hippocampal volume in *Presence*, *Affect*, and *Perspective*.

	LSUB	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
CAR	1,260, p>0.1	0,491, p>0.1	1,882, p<0.1	0,487, p>0.1	-1,116, p>0.1	1,383, p>0.1
Slope	-0,561, p>0.1	-1,861, p<0.1	-1,836, p<0.1	0,667, p>0.1	-1,788, p<0.1	-1,361, p>0.1

AUC_g	-1,383, p>0.1	-2,008, p<0.05	-0,117, p>0.1	0,113, p>0.1	-2,117, p<0.03	-0,872, p>0.1

Table S17. Overall effects of cortisol markers on hippocampal function in *Presence*, *Affect*, and *Perspective*.

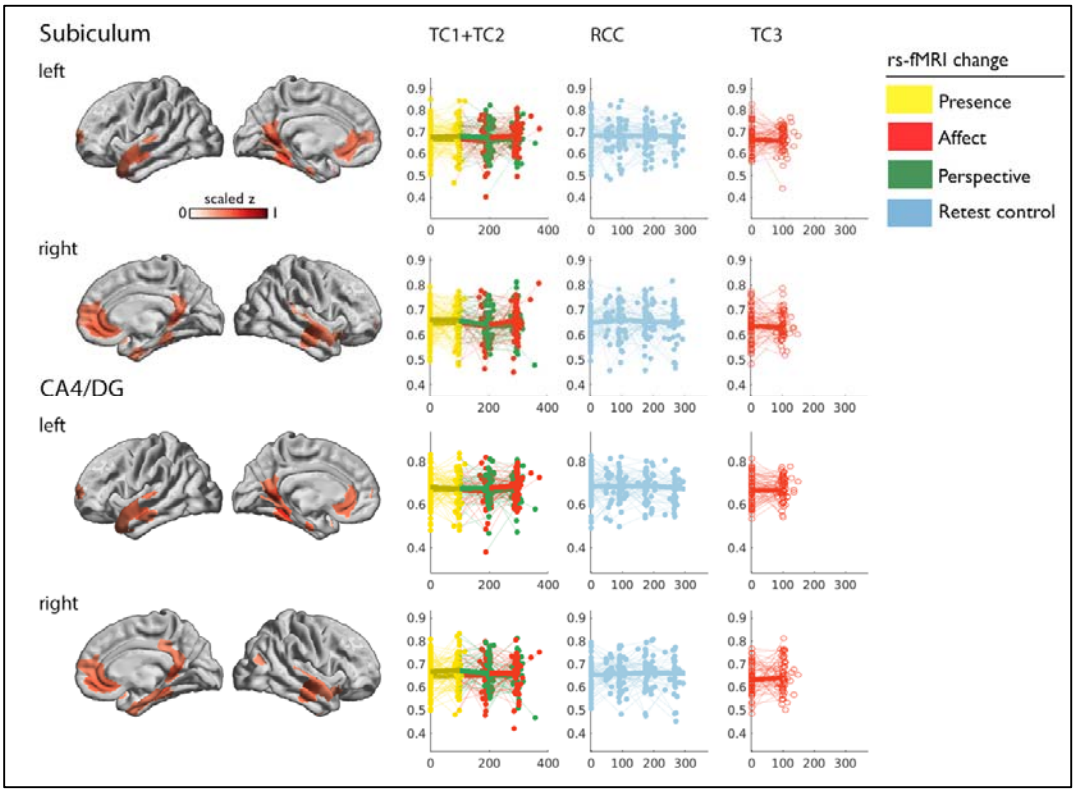
	LSUB	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
CAR	-0,666, p>0.1	-0,896, p>0.1	-1,221, p>0.1	-1,173, p>0.1	-0,290, p>0.1	-1,131, p>0.1
Slope	1,416, p>0.1	3,024, p<0.001	1,949, p<0.1	1,984, p<0.05	0,991, p>0.1	1,284, p>0.1
AUC_g	-0,232, p>0.1	1,614, p>0.1	0,405, p>0.1	-0,919, p>0.1	-0,463, p>0.1	-0,787, p>0.1

Table S18. Effects of hair cortisol markers on hippocampal subfield volume in *Presence*, *Affect*, and *Perspective* (cortisol (HC) and cortisone (HE))

	LSUB	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
HC	-0,595, p>0.1	-2,574, p=0.011	-0,750, p>0.1	-1,251, p>0.1	-0,199, p>0.1	-3,138, p=0.002
HE	-0,127, p>0.1	-0,040, p>0.1	-0,204, p>0.1	-1,765, p<0.1	-0,589, p>0.1	-0,311, p>0.1

Table S19. Effects of hair cortisol markers on hippocampal subfield function in *Presence*, *Affect*, and *Perspective* (cortisol (HC) and cortisone (HE))

	LSUB	**LCA1-3**	**LCA4/DG**	**RSUB**	**RCA1-3**	**RCA4/DG**
HC	-2,890, p=0.005	-2,700, p=0.008	-1,675, p>0.1	-0,638, p>0.1	-0,019, p>0.1	-0,329, p>0.1
HE	-0,627, p>0.1	0,237, p>0.1	-0,791, p>0.1	0,983, p<0.1	0,916, p>0.1	0,798, p>0.1



Supplementary Figure 1. Mean change in functional network of subiculum and CA4/DG.

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