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Research article

Intrinsic functional connectivity between amygdala and hippocampus during rest predicts enhanced memory under stress

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ABSTRACT

Declarative memories of stressful events are less prone to forgetting than mundane events. Animal research has demonstrated that such stress effects on consolidation of hippocampal-dependent memories require the amygdala. In humans, it has been shown that during learning, increased amygdala-hippocampal interactions are related to more efficient memory encoding. Animal models predict that following learning, amygdala-hippocampal interactions are instrumental to strengthening the consolidation of such declarative memories. Whether this is the case in humans is unknown and remains to be empirically verified. To test this, we analyzed data from a sample of 120 healthy male participants who performed an incidental encoding task and subsequently underwent resting-state functional MRI in a stressful and a neutral context. Stress was assessed by measures of salivary cortisol, blood pressure, heart rate, and subjective ratings. Memory was tested afterwards outside of the scanner. Our data show that memory was stronger in the stress context compared to the neutral context and that stress-induced cortisol responses were associated with this memory enhancement. Interestingly, amygdala-hippocampal connectivity during post-encoding awake rest regardless of context (stress or neutral) was associated with the enhanced memory performance under stress. Thus, our findings are in line with a role for intrinsic functional connectivity during rest between the amygdala and the hippocampus in the state effects of stress on strengthening memory.

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1. Introduction

Stressful events are typically well remembered (Gold et al., 1975; McGaugh, 2002). Due to consolidation processes, the enhanced memory retention found for these events increases over time (LaBar and Phelps, 1998). Animal data indicate that during consolidation, the amygdala can modulate hippocampal-dependent memories (McGaugh, 2002) which presumably underlies the increased retention for stressful events. Evidence for the involvement of the amygdala and hippocampus in memory for emotional material in humans is, however, limited to the time of encoding (Dolcos et al., 2005; Fastenrath et al., 2014; Richardson et al., 2004). Whether amygdala-hippocampal interactions continue playing a role in the effects of stress on declarative memory in humans *after* learning is unknown.

The amygdala and hippocampus are both anatomical and functional connected. Anatomical studies in rodents have indicated there are reciprocal connections between the amygdala and hippocampus (Pitkänen et al., 2000). With BOLD-fMRI in humans, it has been shown that the amygdala and hippocampus are functionally connected during awake rest (Roy et al., 2009). Changes in these connectivity patterns due to state changes have also been observed. Electrophysiology studies in rodents, for instance, demonstrated that amygdala-hippocampal theta coherence increases during the expression of conditioned fear in mice (Seidenbecher et al., 2003). Furthermore, after chronic immobilization stress in rats, beta and gamma synchrony was enhanced between the lateral amygdala and the CA1 region of the hippocampus, which lasted up to 10 days (Ghosh et al., 2013). In humans, increased connectivity between the amygdala and hippocampus has been observed following fear learning (de Voogd et al., 2016a; Hermans et al., 2016). We therefore first hypothesized that functional connectivity between the amygdala and hippocampus would be elevated during post-encoding rest within a stressful context compared to a neutral context.

Amygdala-hippocampal interactions have furthermore been shown to be relevant for later memory in animals and humans. In

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rodents, it was shown that increases in theta coherence between amygdala and hippocampus during sleep after fear learning was predictive for later fear retention (Popa et al., 2010). Indeed, the amygdala is critically involved in the consolidation of long-term memories by regulating memory processes in regions elsewhere in the brain, such as the hippocampus (McGaugh, 2002; Roozendaal et al., 2009). For example, early studies have shown that stimulation of the amygdala after learning enhances retention for avoidance training (Gold et al., 1975), and injections of *d*-amphetamine in the amygdala enhances hippocampal-dependent memory in a spatial water-maze task (Packard et al., 1994). A recent study showed that electrical stimulation of the basolateral complex of the amygdala (BLA) after rodents have seen novel objects leads to enhanced memory for those objects, as well as enhanced synchrony in the gamma frequency range in the hippocampus (Bass and Manns, 2015). Indeed, the amygdala can influence hippocampal neural plasticity (Abe, 2001) indicating that the amygdala might still be involved in memory formation after the learning event has taken place by strengthening synaptic consolidation in the hippocampus.

Evidence for the involvement of the amygdala and hippocampus in declarative memory in humans mostly comes from studies that have investigated encoding processes. With BOLD-fMRI it was shown that during encoding, amygdala-hippocampal connectivity is stronger for emotionally arousing stimuli that were successfully encoded compared to neutral stimuli (Dolcos et al., 2005), with a directionality from the amygdala to the hippocampus (Fastenrath et al., 2014). The critical importance of interactions between amygdala and hippocampus during encoding of emotional material has furthermore been shown in patients with damage to either of these two regions (Richardson et al., 2004). Also, when β-adrenergic activation is blocked via systemic administration of propranolol, the emotional enhancement effect for arousing material (Van Stegeren et al., 1998) as well as the subsequent memory effect in the amygdala (Strange et al., 2004) is diminished. Amygdala-hippocampal interactions might continue playing a role after learning. For instance, it was shown that when stress is induced after learning, memory for the learned material is enhanced as well (Smeets et al., 2008). Moreover, systemic administration of cortisol shortly before learning enhanced recall for emotional material not immediately but 24 h later (Kuhlmann and Wolf, 2006). These data together indicate that amygdala-hippocampal interactions are crucial for the enhancing effects of stress on memory, but whether interactions between these regions continue to play a role after learning in humans is unknown. Therefore, the main aim of this study was to test the hypothesis that enhanced functional connectivity between the amygdala and hippocampus during post-encoding rest due to stress would predict enhanced subsequent declarative memory under stress.

To test our hypotheses, we analyzed an existing data set from a functional MRI study investigating the effects of stress on cognition (Berkers et al., 2016; Everaerd et al., 2015; Henckens et al., 2016; Klumpers et al., 2015). A large sample of 120 healthy men came to the lab twice and performed the same tasks once interleaved with aversive movie clips in the stressful context and once interleaved with neutral movie clips in the neutral context. The order of the sessions was counterbalanced. During each session, participants performed an incidental encoding task, which was followed by a final movie clip, and subsequently underwent a resting-state scan (6 min 30 s). Within this time frame it is possible to probe early consolidation processes as has been shown in previous studies (de Voogd et al., 2016a; Hermans et al., 2016; Tambini et al., 2010). The encoding task included 32 neutral faces which were paired with either a neutral (*e.g.*, driver) or a negative (*e.g.*, murderer) identity. Participants were instructed to judge whether the face matched the identity. Memory for the association was tested at the end of the experiment outside of the scanner. Our first prediction was that amygdala-hippocampal connectivity would be increased in the stressful context compared to the neutral context and that this enhancement would be predicted by acute stress (assessed with stress-induced cortisol levels). Secondly and more importantly, we predicted that amygdala-hippocampal connectivity during post-encoding awake rest in a stressful context would predict enhanced memory performance as compared to the neutral context. Additionally, we explored the effect of individual differences in trait anxiety and depression on memory performance and amygdala-hippocampal connectivity, because individual differences in these personality traits were shown to underlie memory dysfunction as well as functional alterations in regions such as the amygdala and hippocampus (Sandi and Richter-Levin, 2009).

2. Material and methods

2.1. Participants

One-hundred-twenty right-handed healthy male volunteers (range: 18.1–30.8 years [M = 21.9 SD = 2.6]) completed the study. Exclusion criteria for participation were a current or past psychiatric or neurological disorder, history of somatic disease potentially affecting the brain, regular use of psychoactive drugs during the preceding 6 months, history of substance abuse, current or past alcohol dependence, or MRI contraindications. Only male participants were included in this study because of the difficulty in controlling for the effects of menstrual cycle on the stress response (Kirschbaum et al., 1999). We excluded 5 participants from the analyses due to movement during the anatomical scan leading to inaccurate segmentation (n = 1), sleeping (n = 2), and excessive movement (>4 SD above the mean displacement) during one of the resting-state sessions (n = 2). Participants gave written informed consent and were paid for their participation. This study was approved by the local ethical review board (CMO region Arnhem-Nijmegen, The Netherlands).

2.2. Design and procedure

The data presented here were acquired as part of a large study which involved two lab visits (see Fig. 1A). Participants underwent a neutral and a stress induction session in the afternoon of which the order was counterbalanced and separated by an average of 2 weeks (minimum of 5 days). All test sessions took place between noon and 8 pm to control for diurnal variation in cortisol levels. The stress and neutral sessions included three and four experimental tasks, respectively. The first task (t = 90 min) was a dynamic facial expression task (Everaerd et al., 2015; Henckens et al., 2016), the second task (t = 105 min) was an emotional conflict task, the third task (t = 120 min) was the face-identity association task (Berkers et al., 2016 and current study). After this, a resting-state scan (t = 127 min) was obtained (current study). Lastly (t = 150 min), the neutral session included a fear conditioning task (Klumpers et al., 2015) and the stress session a T1 and DTI scan (t = 140 min). Here, we test an independent hypothesis on previously unreported data (resting-state functional MRI).

To induce a stressful state, highly aversive movie clips were shown in the MRI scanner during the stress session (Hermans et al., 2011). These clips consisted of scenes of a movie (*Irréversible*, 2002, by Gaspar Noé) containing extreme physical and sexual aggression and violence against men and women. As a control condition, neutral, non-arousing scenes of another movie (*Comment j'ai tué mon père*, 2001, by Anne Fontaine) were shown in the scanner during the neutral session. The stressful and the neutral movie clips were similar in the amount of speech, human (face) presence, luminance,

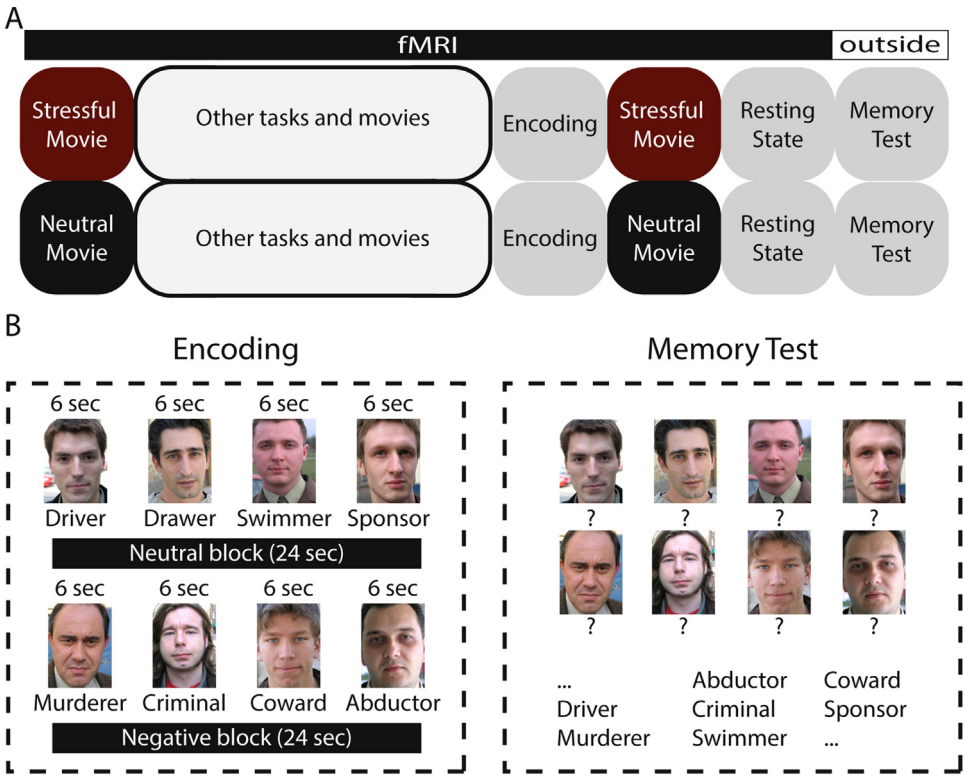

Fig. 1. A) Overview of the experimental design. Within-subject design with a stress and neutral session. In the stressful context, participants performed tasks which were interleaved with aversive movie clips. In the neutral context, the tasks were interleaved by neutral movie clips that were matched to the stress movies. Participants performed a face-identity association paradigm and underwent a resting-state scan (6 min 30 s). During the resting-state scan participants were instructed to keep their eyes closed. Saliva cortisol samples, blood pressure and mood state was assessed at three time points; before the start of the scanning procedure (t = 45 min), following the first task (t = 95 min) and at the end of the scanning session (t = 130 min). Heart rate frequency and heart rate variability was assessed during the resting-state scan. B) Face-identity association paradigm. During encoding, participants were instructed to indicate whether they thought the identity would fit the face via a button press. During recall, participants were instructed to pair the identities with the faces, and to do so only in case they would remember the association with high confidence.

environment, and language. The participants were asked to watch the movie clips from an eye-witness perspective.

The face-identity association encoding task (Berkers et al., 2016) was the 3rd task in both sessions (see Fig. 1A). It was followed by a final movie clip (2 min 11 s), after which the resting-state scan was conducted. Only the neutral session additionally included a fear conditioning task. Therefore, the memory tests in the two sessions, which were conducted at the end of each session outside of the scanner, were not performed at the exact same time point relative to the encoding task. The memory test in the stress session (range: 18–46 min after encoding) was performed on average 15 min earlier than the neutral session (range: 12–60 min after encoding). There was, however, substantial between-subject variation in the test delay difference between sessions [neutral minus stress range: −24 min to +34 min]. This allowed us to use regression analyses (of memory performance onto test delay) to test whether the test delay may have affected our findings independent of the stress manipulation.

Finally, a structural scan was obtained at the end of the stressful session. The total duration of scanning was approximately 105 min per session.

2.3. Face-identity association task

The encoding task contained 32 neutral faces that were associated with an identity (see Fig. 1B). There were 16 neutral (*e.g.,* driver) and 16 negative (*e.g.,* murder) identities which were presented in writing simultaneously with the face. The face-identity associations were presented in a block design. There were eight blocks (24 s per block) and each block contained 4 associations (6 s per association), which were either all neutral or all negative. Participants were instructed to indicate whether they thought the identity would fit the face via a button press. Additionally, the task contained three baseline blocks during which participants had to make a perceptual judgment (*i.e.,* indicating whether the left or right ear was higher). The association pairs as well as the block order were counterbalanced across participants. See also (Berkers et al., 2016).

2.4. Resting-state scan

The resting-state scan (6 min 30 s) was performed after the encoding task and the final movie clip. During the resting-state scan participants were instructed to remain alert and awake and keep their eyes closed.

2.5. Memory recall test

Participants were tested for their memory of the associations after leaving the scanner room. The memory test consisted of a list of all faces and a list of all identities that were presented during encoding. Participants were instructed to pair the identities with the faces, and to do so only in case they would remember the association with high confidence. As a memory measure, we took the total percentage correct (see: Berkers et al., 2016). Theoretical chance level was 1/32 (3.125%), but participants were instructed to only fill in the associations of which they were certain.

2.6. Stress measurements

During the course of the experiment, saliva samples, blood pressure, and mood state was assessed at three time points. The first assessment was before the start of the scanning procedure (t = 45 min), a second following the first task (t = 95 min), and the final assessment at the end of the session (t = 130 min). Saliva samples were obtained using Salivette cotton swabs (Sarstedt, Rommelsdorf, Germany). Additionally, participants collected two extra samples at home on the day before the visit for the second session. The participants were instructed to take one saliva sample just prior to lunch (early afternoon) and one just prior to dinner (late afternoon). These time points were chosen because cortisol levels are reasonably stable at these time points (Henckens et al., 2010, 2009; Hermans et al., 2011; Qin et al., 2009) and correspond to the time of testing of the experiment. The average of the samples taken at home was used as a baseline to scale the samples from the experimental day. Participants had to place a cotton swab in their mouth and chewed gently on it for 1 min to produce saliva. All samples were stored at −20 °C until assaying. Laboratory analyses were performed at the Department of Biopsychology, Technical University of Dresden (Dresden, Germany). Biochemical analysis of free cortisol in saliva was performed using a commercially available chemiluminescence immunoassay (IBL Inc.). Stress-induced cortisol responses were calculated in the following way: (cortisol level (T2) stress session minus cortisol level (T2) neutral session)/Basal cortisol level (average of the two samples measured at home; see Everaerd et al., 2015; Henckens et al., 2016). Mood state was assessed using the Positive and Negative Affect Schedule (PANAS) questionnaire (Watson et al., 1988). Resting blood pressure measurements were obtained using a standard automatic blood pressure device, and during the experiment in the MRI scanner using a Ambulo™ 2400 device. The stress induction effects reported in this study have already been reported elsewhere (see: Everaerd et al., 2015; Henckens et al., 2016).

Finger pulse was recorded using a 50 Hz pulse oximeter and was continuously assessed during scanning. The average heart rate frequency (HRF) and heart rate variability (HRV) during the resting-state scan were used to test for a difference between the stress and neutral session. Additionally, pulse measures were used for retrospective image-based correction (RETROICOR) of physiological noise artifacts in BOLD-fMRI data (Glover et al., 2000). Raw pulse was processed offline using in-house software for interactive visual artifact correction and peak detection, and were used to specify fifth-order Fourier models of the cardiac phase-related modulation of the BOLD signal (Van Buuren et al., 2009), yielding 10 nuisance regressors for cardiac noise. Additional regressors were calculated for HRF and HRV, yielding a total of 12 regressors.

2.7. Anxiety and depression questionnaires

Participants filled in the Dutch versions of the Beck Depression Inventory (BDI; Beck et al., 1996) and the State-Trait Anxiety Inventory (STAI-t; Van der Ploeg, 1980). The average BDI score was 4.3 (range: 0–18) and for the STAI-t it was 35.5 (range: 21–60). In total five participants had a BDI score within the range of "mild depression" (14–19). Additional analyses showed that excluding these participants did not influence the results and conclusions of this study. We therefore included all participants in the final sample.

2.8. MRI data acquisition

MRI scans were acquired using a Siemens (Erlangen, Germany) 1.5 T Avanto MR scanner. A series of 265 T2*-weighted blood oxygenation level-dependent (BOLD) images were recorded using gradient echo-planar imaging (EPI) with ascending slice acquisition (27 axial slices; TR, 1.49 s; TE, 35 ms; flip angle, 80°; slice thickness, 3.5 mm; slice matrix size, 64 × 64; slice gap, 0.7 mm; FOV, 224 × 224 mm; bandwidth, 1906 Hz/px; echo spacing, 0.59 ms). We discarded the first five volumes to allow for T1 equilibration. A high-resolution structural image (1 mm isotropic) was acquired using a T1-weighted 3D magnetization-prepared rapid gradient-echo sequence (MP-RAGE; TR, 2730 ms; TE, 2.95 ms; flip angle, 7°; FOV, 256 × 256 × 176 mm).

2.9. MRI data preprocessing in native space and group analyses in standard stereotactic space

All resting-state EPI images were preprocessed in native space (*i.e.*, without stereotactic normalization) to optimally accommodate interindividual structural variability of the hippocampus. Mutual information maximization-based rigid body registration was used to register structural and (motion-corrected) functional images. The bilateral hippocampus was individually defined in native space using automated anatomical segmentation of T1-weighted images using FSL FIRST (see http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST).

First-level models were applied to the realigned and co-registered functional images in native space and contained the mean (de-noised and de-trended) time course of the hippocampus (left, right) as a regressor of interest and 37 additional nuisance regressors. These included six motion parameter regressors (3 translations, 3 rotations), the zero-centered squares of the six motion parameters, the first derivatives of the six motion parameters, the zero-centered squares of the derivatives of the six motion parameters. The derivatives of the realignment parameters were added to model effects due to scan-to-scan motion (Chang et al., 2015; Woo et al., 2015). To correct for physiological motion or noise artifacts due to the cardiac cycle, 10 RETROICOR cardiac phase regressors, HRF and HRV were added (see also Section 2.6). High pass filtering (1/128 Hz cut-off) and AR(1) serial correlations correction was also included. Heart rate recording failed for ten participants. Therefore, the model did not include the 10 RETROICOR, HRF, and HRV regressors for these participants. Excluding these participants from analyses did not change the results and conclusions. We therefore included these participants in all analyses.

For the purpose of a whole-brain group analyses we first segmented the structural images into grey matter, white matter, and CSF images using a unified probabilistic template registration and tissue classification method (Ashburner and Friston, 2005). Tissue images were then registered with in-house site-specific tissue templates using DARTEL (Ashburner, 2007), and registered (using an affine transformation) with the MNI152 template included in SPM8. Next, the beta images, obtained at the first level analyses in native space, of the whole-brain connectivity maps with the hippocampus (left, right) were transformed into standard stereotactic (MNI152) space using DARTEL, resliced into 2 mm isotropic voxels, and smoothed with a 6 mm FWHM Gaussian kernel.

We conducted two second-level models including single-subject normalized beta maps for the regressor containing the hippocampal time course in the first-level analyses. These maps were entered into a hemisphere (left, right) by session (stress, neutral) repeated-measures ANOVA. The first model was conducted to investigate the relationship between our connectivity measures and memory performance and included the following covariates: (1) the difference in memory performance between stress and neutral conditions, (2) the interaction term of this difference and session (stress vs. neutral), and (3) session order. The second model was conducted to investigate the relationship between our connectivity measures and cortisol responses and included the following covariates: (1) the difference in baseline-corrected cortisol responses between stress and neutral conditions, (2) the interac-

Table 1
Descriptive statistics of stress measures, mean (standard deviation).

	Basal Cortisol (nmol/L)		Cortisol (nmol/L)			Systolic Blood pressure			Self-report negative affect			During resting-state scan	
	S1	S2	T1	T2	T3	T1	T2	T3	T1	T2	T3	HRF	HRV
Stress	10.83 (7.18)	7.25 (7.16)	8.45 (4.44)	7.12 (3.46)	7.16 (4.23)	123.93 (11.47)	109.05 (8.09)	110.32 (8.17)	13.67 (4.10)	17.06 (7.38)	19.03 (7.60)	62.05 (10.05)	88.17 (42.75)
Neutral			7.58 (4.38)	6.11 (3.64)	6.66 (3.81)	124.46 (11.93)	106.71 (7.77)	108.15 (7.39)	13.68 (4.41)	13.56 (4.36)	13.55 (4.55)	59.47 (10.66)	103.47 (57.69)

tion term of this difference and session (stress vs. neutral), and (3) session order. We used a cluster-forming voxel-level threshold of $p < 0.001$ (uncorrected). Alpha was set at 0.05, whole-brain family-wise error (FWE) corrected at the cluster level using Gaussian Random Field Theory based methods (Friston et al., 1996). Based on a priori hypotheses, results for amygdala were corrected for a reduced search volume using small volume corrections (SVC) based on an anatomical mask of the amygdala (Automated Anatomical Labeling atlas; Tzourio-Mazoyer et al., 2002).

2.10. Time course extraction and ROI segmentation

Additionally, we extracted the averaged (de-noised and detrended) BOLD-fMRI voxel time courses for amygdala and hippocampus for both the left and right hemisphere, from the functional images in native space (described in Section 2.9). This was done to investigate the correlation between the amygdala-hippocampal connectivity between sessions. Functional connectivity was calculated using (Fisher's z transformed) pairwise Pearson's correlations between the mean time course of the amygdala and hippocampus for both left and right hemisphere. A repeated-measures ANOVA was performed with hemisphere (left, right) and session (stress, neutral) as within-subject factors and session order as between-subject factor to compare the connectivity between the sessions. Additionally, across-subject partial (*i.e.,* controlling for the order of the session) Pearson's correlations were performed to investigate the association between these native-space functional connectivity measures and memory performance. The latter was merely done to confirm our whole-brain analyses. Similar to the hippocampus, the amygdala was individually defined in native space using automated anatomical segmentation of T1-weighted images using FSL FIRST (see http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST).

2.11. Statistical testing

Partial eta squared ($P\eta^2$) effect size estimates are reported for all relevant tests. Pearson's correlations were used for correlations across participants. Alpha was set at 0.05 throughout.

3. Results

3.1. Stress measures

Successful stress induction in this dataset has also been reported elsewhere (see: Everaerd et al., 2015; Henckens et al., 2016). To confirm successful stress induction in the current sample we tested the same salivary hormone measures, physiological measures, and self-reports. Baseline-corrected salivary cortisol levels [$F(1,112) = 10.526$, $p = 0.002$, $P\eta^2 = 0.09$], baseline-corrected systolic blood pressure [$F(1,113) = 8.020$, $p = 0.005$, $P\eta^2 = 0.07$], as well as baseline-corrected self-report of negative affect (PANAS questionnaire) [$F(1,112) = 35.535$, $p = 2.97E\text{-}8$, $P\eta^2 = 0.24$] were higher for the stress session compared to the neutral session. Furthermore, *during* the resting-state session heart rate frequency (expressed in beats per minutes) was higher for the stress session compared to neutral [$F(1,103) = 17.439$, $p = 6.22E\text{-}5$, $P\eta^2 = 0.15$], and heart rate variability was decreased [$F(1,103) = 9.539$, $p = 0.003$, $P\eta^2 = 0.09$]. Lastly, cortisol responses were shown to interact with session order [$F(1,112) = 5.596$, $p = 0.02$, $P\eta^2 = 0.05$] as well as the heart rate frequency [$F(1,103) = 11.595$, $p = 0.001$, $P\eta^2 = 0.10$]. When stress was the first session, cortisol responses [$t(55) = 4.125$, $p = 1.27E\text{-}4$, $D = 1.11$] and heart rate frequency [$t(51) = 4.882$, $p = 1.08E\text{-}5$, $D = 1.37$] were higher in the stress session compared to the neutral session. There was no difference between the sessions when neutral was the first session for the cortisol responses [$t(57) = 0.601$,

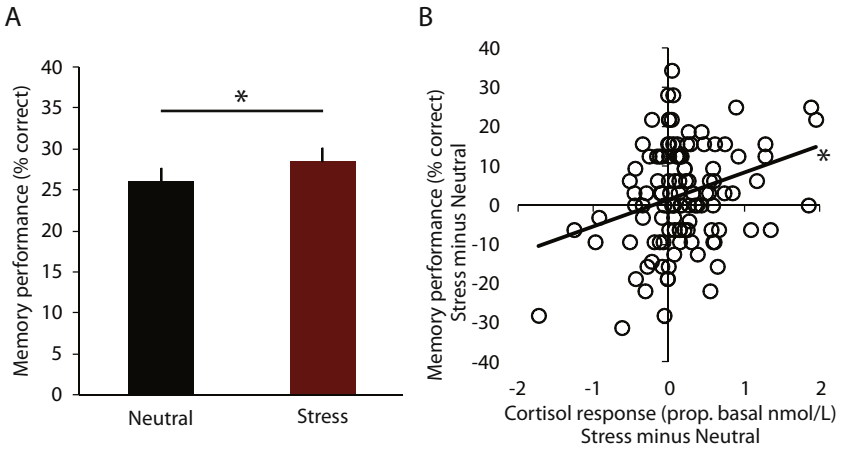

Fig. 2. A) Average memory performance (percentage correct) for both sessions. B) Across-subject correlation between baseline-corrected, stress induced cortisol responses (nmol/L) and difference in memory performance (percentage correct) under stress. *p < 0.05.

$p = 0.55$, $D = 0.16$] and heart rate frequency [$t(52) = 0.609$, $p = 0.55$, $D = 0.17$]. Cortisol levels and heart rate frequency were the lowest when the neutral session was the second session. The other stress measures did not interact with session order.

In conclusion, these data show that our manipulation was successful in inducing mild stress: cortisol, blood pressure, heart rate frequency, and heart rate variability were altered as intended during the stress context as compared to the neutral context. For the descriptive statistics see Table 1.

3.2. Behavioral data

On average, 27.28% (SD = 16.56) of the 32 associations were remembered which was above what could be expected based on chance (1/32) [$t(114) = 15.642$, $p = 3.79E\text{-}30$, $D = 2.93$]. We next compared memory performance between the stress and neutral context. The memory tests in the two sessions, however, were not performed at the exact same time point relative to the encoding task (see Section 2.2.). Therefore, we investigated first the effect of the test delay on memory performance. There was no indication that the test delays correlated with memory performance in either the neutral [$r(112) = 0.08$, $p = 0.38$] or the stress [$r(112) = 0.05$, $p = 0.63$] condition. The difference in test delay between the sessions was also not associated with a difference in memory performance between the sessions [$F(1,112) = 0.122$, $p = 0.73$, $P\eta^2 = 0.001$]. Thus, despite this difference in time of testing, there was no indication this influenced performance across or within subjects.

Next, we therefore investigated the effect of session (stress vs. neutral) on memory performance. We found a main effect of session [$F(1,113) = 4.903$, $p = 0.029$, $P\eta^2 = 0.042$], meaning that the associations in the stress session (M = 28.53, SD = 17.13) were better remembered than the associations in the neutral session (M = 26.03, SD = 18.41). When we controlled for the test delay, the difference between the sessions remained significant [$F(1,112) = 4.869$, $p = 0.029$, $P\eta^2 = 0.042$]. The order of the sessions interacted with the effect of stress [$F(1,113) = 13.57$, $p = 3.54E\text{-}4$, $P\eta^2 = 0.11$]. Only when the stress session was first, memory was enhanced for this session (M = 28.83%, SD = 15.35) compared to the neutral (M = 22.07%, SD = 17.58) session [$t(56) = 4.431$, $p = 4.41E\text{-}5$, $D = 1.18$]. When the neutral session was first, memory in the stress (M = 28.23%, SD = 18.84) session did not differ from the neutral (M = 29.92%, SD = 18.54) session [$t(57) = 0.987$, $p = 0.33$, $D = 0.26$]. Lastly, when comparing the negative and the neutral associations, we found that overall the neutral associations were remembered better than the negative associations [$F(1,113) = 37.88$, $p = 1.18E\text{-}8$, $P\eta^2 = 0.25$], but there was no interaction with session [$F(1,113) = 2.34$, $p = 0.13$, $P\eta^2 = 0.02$]. For the functional MRI analyses, we therefore collapsed the valence categories, and added overall performance as well as the order of the sessions as covariates.

Finally, we tested whether individual differences in cortisol responses to stress correlated with memory enhancement under stress. Indeed, we found that the stronger the stress-induced cortisol response was, the greater the memory was enhanced due to stress [$r(112) = 0.24$, $p = 0.01$]. See Fig. 2. In summary, stress indeed enhanced memory performance, and the stress-induced cortisol response was associated with this memory enhancement.

Table 2
Peak voxel coordinates and cluster statistics and size for post-encoding resting-state with hippocampus (left, right) as seeds.

Region	Side	x(mm)	y(mm)	z(mm)	Z-score	Cluster p	Size (mm^3)
Neutral > Stress							
Precuneus/Post central gyrus/Superior parietal lobule	L/R	−6	−48	58	5.54	p < 0.001	90904
Lingual/Calcarine sulcus/Cuneus	L/R	−20	−82	−12	5.60	p < 0.001	72048
Inferior occipital gyrus	R	36	−92	−6	4.67	P < 0.001	4176
Main effect memory [stress − neutral]							
Amygdala	L	−20	−6	−16	4.14	p = 0.004 (SVC)	256
Main effect memory [stress − neutral] − Left hippocampus							
Amygdala	L	−20	−6	−16	3.72	p = 0.009 (SVC)	152
Amygdala	L	−30	−6	−14	4.43	p = 0.016 (SVC)	72
Main effect memory [stress − neutral] − Right hippocampus							
Amygdala	L	−20	−6	−18	3.78	p = 0.008 (SVC)	176

Notes: All coordinates are defined in MNI152 space. All reported statistics are significant at $p < 0.05$, cluster-level corrected for the whole brain unless indicated otherwise (SVC).

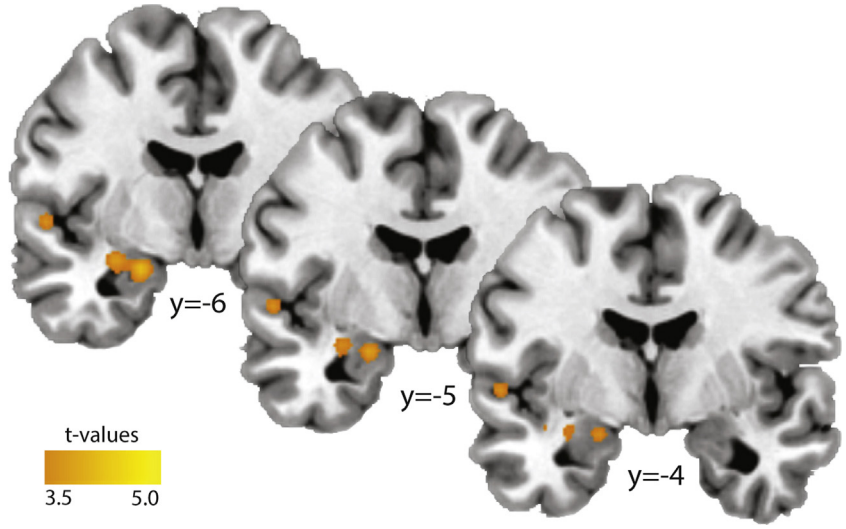

Fig. 3. Whole brain connectivity with hippocampal seeds (left, right) during post-encoding rest predicting memory enhancement under stress. A significant cluster was found in the amygdala (FWE-SVC). Statistical parametric maps are thresholded at p < 0.001, uncorrected, for visualization purposes. Whole-brain cluster-level corrected inferential statistics are reported in Table 2. For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.

3.3. Whole-brain functional connectivity with the hippocampus during post-encoding rest

We then tested the hypothesis that amygdala-hippocampal connectivity as a function of stress was associated with the enhanced memory under stress. We performed a whole-brain connectivity analysis with the time course of the hippocampus as a seed for each participant. We subsequently performed a second-level ANOVA with hemisphere (left, right) and session (stress, neutral) as within-subject factors, the difference in memory performance between stress and neutral conditions, the interaction term of this difference and session (stress vs. neutral), and session order as covariates. There were no significant differences in amygdala-hippocampal connectivity between the sessions (no voxels exceeded the clustering threshold, even at a more liberal threshold of $p < 0.005$, uncorrected). When further comparing the two sessions, we did find weaker connectivity between hippocampus and regions in the occipital and parietal cortex in the stress session compared with the neutral session. For all whole-brain connectivity results see Table 2.

Next, we did not find any significant connectivity increases across the brain or within the amygdala (no voxels exceeded the clustering threshold, even at a more liberal threshold of $p < 0.005$, uncorrected) associated with enhanced memory performance. Interestingly, we did find that the *average* connectivity (*i.e.,* the averaged connectivity across both sessions) between the hippocampal seed (left and right combined) and a cluster in the left amygdala was associated with memory enhancement under stress (cluster size = 256 mm3, cluster $p = 0.004$, FWE-SVC).

To ensure these results are not driven solely by the neutral session, we investigated both sessions separately. Within the stress session alone, the connectivity between the hippocampal seed and a cluster in the left amygdala predicted the memory enhancement under stress (cluster size = 208 mm3, cluster $p = 0.006$, FWE-SVC). Also within the neutral session alone, the connectivity between the hippocampal seed and a cluster in the left amygdala predicted the memory enhancement under stress (cluster size = 8 mm3, cluster $p = 0.03$, FWE-SVC).

Lastly, since the effect was only on the left, we conducted an additional check to test whether the effects on the left were also driven by the connectivity with the left hippocampus. We found that the connectivity between both hippocampal seeds (left: cluster 1 size = 152 mm3, cluster p = 0.009, FWE-SVC; cluster 2 size = 72 mm3, cluster p = 0.02, FWE-SVC; right: cluster size = 176 mm3, cluster p=0.008, FWE-SVC) and the left amygdala predicted memory enhancement under stress. Furthermore, if we lower the cluster defining threshold to $p < 0.005$, we see a (near significant) cluster in the right amygdala as well (cluster size = 48 mm3, cluster p = 0.097, FWE-SVC).

We did not find any significant clusters associated with stress-induced cortisol responses (cluster defining threshold of $p < 0.001$, cluster significance $p = 0.05$ FWE whole-brain corrected).

In conclusion, our data indicate that hippocampal connectivity with the (left) amygdala was associated with memory enhancement under stress and this was regardless of state (*i.e.*, acquired in stress or neutral sessions). See Fig. 3 and Table 2.

3.4. Region of interest analyses

We then reasoned that amygdala-hippocampal connectivity, in relation to memory enhancement under stress, may constitute a *trait* rather than a *state* factor. If this is the case, then the connectivity measures between sessions would be correlated with each other. We therefore extracted the average time courses from the anatomically defined amygdala and hippocampus in a native-space analysis. This allowed us to compute amygdala-hippocampal functional connectivity measures for each session, which we could then correlate between the two sessions. Indeed, the average time-course connectivity between the amygdala and hippocampus was correlated between the two sessions across subjects [$r(112) = 0.35$, $p = 1.41E\text{-}4$]. See Fig. 3. Confirming our results obtained using the whole-brain voxel-wise approach described above, the mean amygdala-hippocampal connectivity did not differ significantly between the sessions [$F(1,113) = 0.21$, $p = 0.65$, $P\eta^2 = 0.002$]. Furthermore, we found a significant correlation between the mean amygdala-hippocampal connectivity and memory enhancement under stress [left: $r(112) = 0.22$, $p = 0.02$; right $r(112) = 0.11$, $p = 0.26$; see Fig. 4].

We next tested whether individual differences in cortisol responses to stress would be associated with functional connectivity between the amygdala and hippocampus. Cortisol responses did not correlate with the average functional connectivity [$r(112) = 0.07$, $p = 0.48$]. There was a non-significant trend

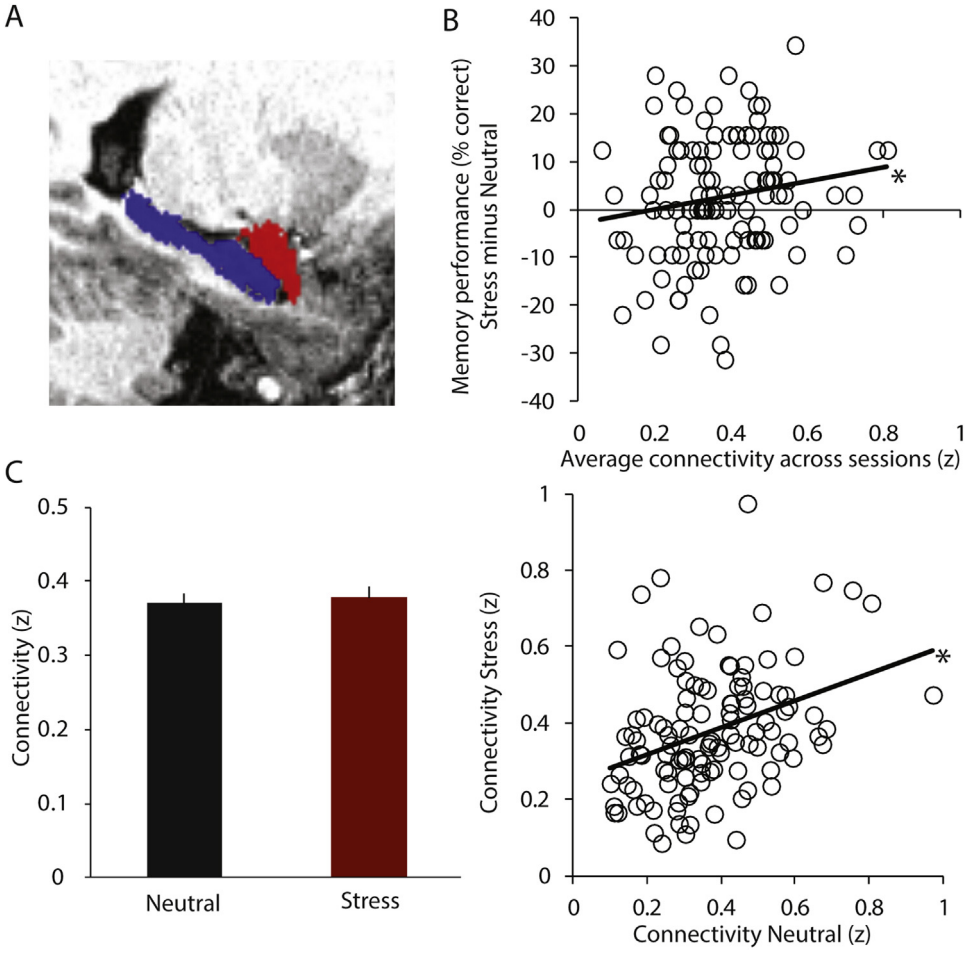

Fig. 4. A) Single subject example of amygdala and hippocampus segmentation. B) Across-subject correlation between average left amygdala-hippocampal connectivity across sessions (Fisher z-transformed) and enhanced memory performance under stress. C) Bar graph represents the average amygdala-hippocampal connectivity (Fisher z-transformed) for stress and neutral. D) Across subject correlation of the amygdala-hippocampal connectivity (Fisher z-transformed) between the sessions. *, $p < 0.05$.

towards a positive correlation between cortisol responses to stress and a difference in functional connectivity between the amygdala and hippocampus [$r(112) = 0.16$, $p = 0.09$].

In conclusion, our ROI analyses confirmed the whole-brain analyses by showing that amygdala-hippocampal connectivity during rest regardless of state was associated with a state effect on memory (*i.e.*, enhancement due to stress).

3.5. Correlations between psychological traits and functional connectivity/memory performance

Finally, because the functional connectivity between the amygdala and hippocampus did not differ between sessions, we investigated whether individual differences in amygdala-hippocampal connectivity would be correlated with individual differences in measures of depression and anxiety. We therefore correlated the average amygdala-hippocampal connectivity with the outcome of the STAI-t (range: 21–60) and BDI (range: 0–18) questionnaires. However, this did not yield any significant correlation [STAI-t: $r(112) = 0.07$, $p = 0.46$ and BDI: $r(112) = 0.08$, $p = 0.40$]. There was also no correlation between the questionnaires and the enhanced memory under stress [STAI-t: $r(112) = -0.08$, $p = 0.43$ and BDI: $r(112) = 0.07$, $p = 0.48$]. It is important to note that there is little variance in BDI questionnaire scores within a healthy population, potentially reducing the possibility to find a correlation. Moreover, the BDI scores are strongly positively skewed (skewness z-score = 5.33). In conclusion, individual differences in amygdala-hippocampal connectivity and enhanced memory under stress were not explained by individual differences in trait characteristics of depression and anxiety.

4. Discussion

The aim of this study was to investigate the role of post-encoding amygdala-hippocampal connectivity in the consolidation of memories encoded under stress. For this, we used an existing dataset from a large study (n = 115) investigating the influence of stress on cognition. We found that memory performance was enhanced under stress, and that stress-induced cortisol responses were associated with this memory enhancement. Critically, amygdala-hippocampal connectivity was also associated with stress-induced memory enhancement, but did so *regardless* of context (stress, neutral). Amygdala-hippocampal connectivity during post-encoding awake rest did not differ between the sessions, and positively correlated across participants. Thus, our data indicate that amygdala-hippocampal connectivity during rest facilitates memory enhancement under stress as *trait* rather than a *state* factor.

We found that memory performance was increased under stress. It is important to note that this finding is possibly confounded by a difference in test delay between the encoding and retention test between sessions. There was, however, no indication that individual differences in test delay accounted for the difference in memory performance, either within or between the sessions.

Despite this potential confound, this finding is in line with many previous studies in both animals (McGaugh, 2002; Roozendaal et al., 2009) and humans (Henckens et al., 2009; Smeets et al., 2008; Wiemers et al., 2013). Moreover, the stress-induced cortisol responses correlated positively with the enhancement under stress, indicating further that the difference in memory retention is more likely to be induced by stress.

Differences in memory retention between stressful and mundane events are partly due to immediate effects of stress on attentional, sensory, and mnemonic processes (de Voogd et al., 2016b; Dolcos et al., 2005). Indeed, human studies have shown that memory is enhanced for material that is encoded under stress compared to when it is encoded in a non-stressful context (Henckens et al., 2009; Wiemers et al., 2013). Critically, however, this difference in memory retention is further increased via preferential consolidation (LaBar and Phelps, 1998; McGaugh, 2002). Memory for the learned material was also shown to be enhanced when stress is induced *after* learning (Smeets et al., 2008). Additional evidence for the importance of post-encoding processes for later memory comes from pharmacological administration studies. Post-encoding intravenous infusion of epinephrine in humans was shown to enhance memory performance (Cahill and Alkire, 2003). Administration of cortisol before learning, furthermore, did not affect immediate recall but did enhance recall for emotional material tested 24 h later (Kuhlmann and Wolf, 2006). Thus, our data are in line with a large body of literature showing that stress and stress-sensitive hormones can improve memory performance by enhancing consolidation.

We found that post-encoding amygdala-hippocampal connectivity during rest was associated with memory enhancement under stress regardless of context (stress or neutral). Animal studies have implicated a role for the amygdala in modulating memory after learning (McGaugh, 2002; Roozendaal et al., 2009). Specifically, it was shown that the amygdala mediates arousal-related neuromodulators' effects on memory processes elsewhere in the brain (Roozendaal et al., 2009), such as in the hippocampus (Packard et al., 1994). Additional studies have shown that when the amygdala is lesioned, the effect of arousal on memory is diminished (Cahill and McGaugh, 1991; Liang et al., 1982). Human patient studies have also found support for the involvement of the amygdala in mediating stress effects on hippocampal-dependent memory. For example, patients with lesions to the amygdala, resulting from Urbach-Wiethe disease, do not show an emotional enhancement of episodic memory consolidation (LaBar and Phelps, 1998). Furthermore, data from patients with damage to either the amygdala or hippocampus indicated that there are reciprocal interactions between these regions during encoding of emotional material (Richardson et al., 2004). Based on these findings, we expected that stress would increase the connectivity between amygdala and hippocampus, which would subsequently predict enhanced memory under stress. However, we did not find an increase in amygdala-hippocampal connectivity between the two sessions and found that amygdala-hippocampal connectivity as a *trait* was associated with memory enhancement under stress.

In the current study memory performance was assessed immediately and not after a longer period (that would include sleep for example). How are the processes we observed related to consolidation? It has been suggested that, even though systems-level consolidation can continue for up to years after learning (Frankland and Bontempi, 2005), it most likely starts immediately after learning (Dupret et al., 2010). Neuroimaging studies in humans that have investigated consolidation processes supported this notion by showing that these early processes are predictive of immediate memory. For example, hippocampal-cortical interactions (Tambini et al., 2010) as well as hippocampal multivoxel correlation structures (Tambini and Davachi, 2013) during post-encoding rest were predictive of immediate memory performance. Another study showed that reactivation of encoding patterns during post-encoding rest was higher for remembered versus forgotten items in an immediate test (Staresina et al., 2013). Previous studies found that these early consolidation processes are also related to memory assessed 24 h later (de Voogd et al., 2016a; Hermans et al., 2016). Together, these findings indicate that early consolidation processes are relevant for memory performance tested at different delays. However, our findings of a trait-like effect of amygdala-hippocampal connectivity associated with stress-induced memory enhancement does not indicate reactivation of newly learned information.

What could be a possible explanation for this finding? First, amygdala-hippocampal connectivity between resting-state sessions did not differ. Previous human imaging studies using BOLD-fMRI have shown that the amygdala and hippocampus are indeed functionally connected during awake rest (Roy et al., 2009), but our findings are not in line with previous studies showing this connectivity is increased following fear learning (de Voogd et al., 2016a; Hermans et al., 2016). Although there was a trend towards a correlation between stress-induced cortisol responses and increased amygdala-hippocampal connectivity under stress, our data did not indicate that stress influenced connectivity between these regions. Second, across participants the functional connectivity between the sessions was highly correlated, even though the sessions were on different days and on average two weeks apart. Our data therefore indicate that functional connectivity between the amygdala and hippocampus during rest is, at least, also a trait characteristic.

This finding is in line with previous findings on resting-state connectivity that have indicated that functional connectivity is a stable and strong trait characteristic despite additional influences of mental states (Geerligs et al., 2015). Furthermore, individual differences in intrinsic functional connectivity have been shown to be relevant for cognitive processes, because these were shown to predict state-independent individual differences in intellectual performance (van den Heuvel et al., 2009b) and learning (Gerraty et al., 2014). Importantly, there is a close link between functional connectivity and structural connectivity (van den Heuvel et al., 2009a) suggesting that the relationship between trait differences in functional connectivity could be related to underlying anatomical connections. With regards to the amygdala and hippocampus, studies in animals have indeed indicated these regions are structurally connected (Pitkänen et al., 2000). Thus, our data extend these previous studies by showing that resting-state functional connectivity between the amygdala and the hippocampus as a trait factor can account for state effects of stress on memory performance. A previous finding indeed showed that the amygdala to hippocampal volume ratio was predictive of interindividual differences in negative memory bias (Gerritsen et al., 2012). Thus, although stress might trigger state-dependent amygdala-hippocampal interactions during post-encoding rest, as has been shown in animals (McGaugh, 2002; Roozendaal et al., 2009) and humans (de Voogd et al., 2016a; Hermans et al., 2016), there are additional trait characteristics that play an important role in the effects of stress on memory. In particular, trait factors such as amygdala-hippocampal volume ratio (Gerritsen et al., 2012) or intrinsic connectivity between these regions (the present study), but also genetics (Li et al., 2013) may determine the degree to which hormones and neurotransmitters released during stress are able to engage the amygdala to modulate mnemonic processes in the hippocampus.

Finally, we asked whether this trait connectivity between the amygdala and hippocampus was related to individual differences in anxiety and depression. However, we did not find a correlation between amygdala-hippocampal connectivity and individual dif-

ferences in our measures for trait anxiety (STAI-t) and depression (BDI). Previous studies have indicated that structural characteristics of the amygdala and hippocampus, such as volume ratio, are related to pathological anxiety and depression (MacMillan et al., 2003). Furthermore, depressed (Irwin et al., 2004) and social anxiety disorder patients (Liao et al., 2010) were found to have a different functional connectivity pattern between the amygdala and other parts of the brain compared to healthy controls. Since we did not find a relationship between amygdala-hippocampal connectivity and trait anxiety or depression in healthy volunteers, our results cannot be explained by underlying differences in anxiety and depression predispositions. This is, however, a healthy population with limited variance in these measures.

Lastly, we found that the stress-enhanced memory performance was only present when stress induction took place in the first session. We found the same pattern in some of the stress induction measures, namely the cortisol responses and heart rate frequency. In line with previous studies (Hermans et al., 2011), the effect size of the stress induction was low to moderate (range $P\eta^2 = 0.07–0.24$). Moreover, cortisol as well as blood pressure measures decreased over the course of the experiment, although less so for the stress session, which is in line with previous observations with the same stress induction procedure (Qin et al., 2012, 2009). The order effect in the memory performance might therefore be related to the impact of the stress induction. Although a within-subjects design has limitations, for example participants had already been exposed to the entire set-up which is known to be stressful by itself (Lueken et al., 2012; Muehlhan et al., 2011), the overarching aim of the entire study was to investigate inter-individual variance in stress responsivity for which a within-subject design is most adequate. Whether similar effects can be observed using stronger stress induction procedures, remain unknown.

In conclusion, our data show that amygdala-hippocampal connectivity during rest is associated with the strengthening of memory under stress, but constitutes a *trait* rather than a *state* characteristic. This finding implicates a role for intrinsic functional connectivity between these regions in determining the degree to which stress-sensitive hormones and neurotransmitters are able modulate memory formation.

Conflict of interest

The authors declare no conflict of interests.

Contributors

All authors contributed to the development of the research question. Ldv analyzed the data. Ldv and EH wrote the manuscript. All authors discussed and commented on the results and manuscript.

Role of the funding source

The funding source had no role in study design, data analysis, or writing of the manuscript.

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