Neurobiology of Learning and Memory 147 (2018) 65–73

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Reward anticipation modulates the effect of stress-related increases in cortisol on episodic memory

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ARTICLE INFO

Keywords:
Reward anticipation
Post-encoding stress
Recognition memory
Recollection
Familiarity
Tag-and-capture

ABSTRACT

When acute stress is experienced shortly after an event is encoded into memory, this can slow the forgetting of the study event, which is thought to reflect the effect of cortisol on consolidation. In addition, when events are encoded under conditions of high reward they tend to be remembered better than those encoded under non-rewarding conditions, and these effects are thought to reflect the operation of the dopaminergic reward system. Although both modulatory systems are believed to impact the medial temporal lobe regions critical for episodic memory, the manner, and even the extent, to which these two systems interact is currently unknown. To address this question in the current study, participants encoded words under reward or non-reward conditions, then one half of the participants were stressed using the social evaluation cold pressor task and the other half completed a non-stress control task. After a two-hour delay, all participants received a free recall and recognition memory test. There were no significant effects of stress or reward on overall memory performance. However, for the non-reward items, increases in stress-related cortisol in stressed participants were related to increases in recall and increases in recollection-based recognition responses. In contrast, for the reward items, increases in stress-related cortisol were not related to increases in memory performance. The results indicate that the stress and the reward systems interact in the way they impact episodic memory. The results are consistent with tag and capture models in the sense that cortisol reactivity can only affect non-reward items because plasticity-related products are already provided by reward anticipation.

1. Introduction

A growing body of research has indicated that one's memory for events can be influenced by various factors that are extrinsic to the encoding event itself such as the level of physical or social stress experienced by the participant. The effects of acute stress on memory are complex and vary according to the timing and intensity of the stressor (Cadle & Zoladz, 2015; Diamond, Campbell, Park, Halonen, & Zoladz, 2007; Joëls, Fernandez, & Roozendaal, 2011; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012), but one common finding is that acute stress can protect recently learned information from forgetting (Andreano & Cahill, 2006; Cahill, Gorski, & Le, 2003; McCullough & Yonelinas, 2013). For example, after encoding a series of photographs, if participants are then required to hold their arm in ice water or in warm water for three minutes, subsequent memory is greater for the group that was stressed by the ice-water compared to the group that was not stressed (Cahill et al., 2003; McCullough & Yonelinas, 2013; Smeets, Otgaar, Candel, & Wolf, 2008). In addition, a number of studies have measured salivary cortisol to index the stress response and found that participants who showed larger stress-induced cortisol increases showed better memory if stress is experienced after learning (e.g. Cahill et al., 2003; McCullough, Ritchey, Ranganath, & Yonelinas, 2015). In rodent models of stress and memory, the interplay of cortisol and noradrenaline following learning has been shown to modulate hippocampal plasticity, thereby increasing the likelihood that recent experiences will be preserved or consolidated in long-term memory (McGaugh & Roozendaal, 2002). Many of these models posit that arousal during encoding is a critical factor that interacts with post-encoding stress, leading researchers of human memory to investigate memory for emotional information.

Aside from emotion, however, little is known about which recent experiences will be remembered better when stress follows encoding. One possibility, which we set out to test in this study, is that the effects of post-encoding stress may depend on the extent to which other modulatory systems such as the reward system are engaged during encoding. Recent work has indicated that if one is expecting to be

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https://doi.org/10.1016/j.nlm.2017.11.007
Received 4 July 2017; Received in revised form 15 October 2017; Accepted 15 November 2017
Available online 21 November 2017
1074-7427/

rewarded that this can enhance memory, even for aspects of the event that are not directly rewarded. For example, Wittmann, Dolan, and Düzel (2011) presented participants with a speeded number comparison task in which participants indicated whether a given number was smaller or larger than five. On reward trials, participants gained a monetary reward if the response was both correct and within a specified time window, but they lost a small amount of their money if the response was either incorrect or too slow. Importantly, prior to each trial they were presented with a word that indicated whether the trial could be rewarded or not. For example, if the word was a 'living' thing then the following number trial could be rewarded, whereas if the word was a 'non-living' thing then the number task would not be rewarded (or vice versa). In a subsequent recognition memory test, participants were better able to recognize the words that were encountered in reward trials, than those presented in the non-reward trials, despite the number comparison task being the actual determinant of reward. In a similar study, fMRI results indicated that the reward effects were related to an increase in activity in SN/VTA (Wittmann et al., 2005), activity which is thought to be involved in producing an increase in dopamine.

Whether post encoding stress differentially impacts memory for reward and non-reward materials has not yet been examined, but a consideration of recent 'tag-and-capture' models of memory consolidation (Ballarini, Moncada, Martinez, Alen, & Viola, 2009; Frey & Morris, 1997; Moncada & Viola, 2007; Redondo & Morris, 2011; Viola, Ballarini, Martínez, & Moncada, 2014; Wang, Redondo, & Morris, 2010), suggests that they may interact. In these models, memory traces are "tagged" during initial encoding, but these tags are expected to decay quite rapidly, unless the memory trace is able to capture plasticity-related products (PRPs) that become available around the time of encoding or shortly after it. Important PRPs are activity regulated cytoskeleton-associated protein (ArC), Homer1a and the AMPAR (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor) subunit Glur1 but also dendritic mRNA (Redondo & Morris, 2011). Importantly, these products may arise from the target event itself or from other events occurring around the same time. Both tag and capture are necessary for consolidation into long-term memory, in that without capture, tagged memories would be quickly forgotten. Thus, one possible account of post-encoding stress is that stress provides the plasticity related products that are captured by the items that were tagged during encoding. However, if the items were encoded under conditions in which the items were already tagged and captured then the stress effects may no longer be observed. Presumably, items that are encoded both under the reward and non-reward conditions would be tagged. The subsequent release of dopamine in the reward condition may be sufficient to induce increased PRPs that can be captured by those tags, resulting in enhanced memory. In this way, reward may mask any effects produced by increases in cortisol associated with the post-encoding stressor. Thus, we expected that stress would selectively enhance memory for items that were tagged but not yet captured (i.e., the non-reward items) but would not enhance memory for the items that were tagged and captured during encoding (i.e., the reward items). In addition, we expected to see that increased stress-related cortisol would be correlated with increases in memory for the non-reward items, whereas for reward items, we expected this relationship to be absent or less pronounced.

In order to determine whether post-encoding stress and reward interacted to promote enhanced memory, we investigated the effects of post-encoding stress and reward anticipation in a single experiment. Participants completed alternating trials of a categorical judgment task and a numerical comparison task, in which the former indicated whether the subsequent trial could be rewarded or not. After these tasks, half of the participants completed a stress-induction task, and we later tested memory for the words in the categorical judgment task. Prior work has indicated that stress can impact both recollection and familiarity based memory processes (e.g. McCullough et al., 2015), and so we measured recollection and familiarity using the receiver operating characteristic (ROC) method and the Remember/Know (R/K) method. The ROC method derives parameter estimates for recollection and familiarity on the basis of the shape of confidence-based receiver operating characteristics, whereas the R/K procedure measures recollection and familiarity on the basis of subjective reports. These two methods generally lead to similar measures of recollection and familiarity, as they did in the current experiment. In addition, we included a measure of source memory and a measure of free recall as they are often used to index recollection (Yonelinas, 2002).

2. Method

2.1. Participants

Students enrolled in psychology courses at the University of California, Davis were recruited from an online pool and received course credit as compensation for their participation. In total 75 participants participated, but one participant was excluded because of memory performance at chance. The final sample included 44 females and 30 males. Of the 74 in the final sample, 34 were in the stress and 40 were in the control group. The mean age of the included participants was 19.78 (SD = 1.64) years. Exclusion criteria for the current study were, participation in similar studies, age under eighteen years, left-handedness, uncorrected impairment of vision as well as impaired color vision, smoking, usage of oral contraceptives, high blood pressure or any other heart condition. Even though the participants were specifically told that they could only participate if they do not use oral contraceptives, a review of the questionnaires revealed that two nevertheless reported such. In order to preserve our statistical power, we decided not to exclude those participants after the experiment. The study was approved by the Institutional Review Board at the University of California, Davis.

2.2. Apparatus and material

2.2.1. Hormonal assessment

The participants were asked to abstain from eating one hour and caffeine four hours prior to the study as well as to avoid strenuous exercise on the day of the study. Analysis was done at the local laboratory of the Ruhr-University Bochum with the DEMEDITECs Cortisol Free in Saliva enzyme-linked immunosorbent assay (ELISA) Kit. Cortisol intra- and inter-assay coefficients of variation (CV) were below 10.6%. CNP-G3 was the substrate for the measurement of the enzymatic action of α-amylase at 405 nm. The intra- and inter-assay CV for this analysis were both below 8%.

Several studies showed that even when overall stress group difference is not significant that individual differences in stress related increases in cortisol are related to memory (e.g. Andreano & Cahill, 2006; McCullough et al., 2015; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001), therefore we additionally analyzed the quantitative relationships between changes in these stress markers and the memory measures. To do this, Δ-cortisol and Δ-α-amylase was calculated:

$$\Delta\ cortisol = sample_2 - sample_1$$

$$\Delta\ \alpha\ amylase = sample_2 - sample_1$$

2.2.2. Stress manipulation

2.2.2.1. Socially evaluated cold pressor test (SECPT) and the control task. Submerging ones hand or arm in ice water paired with social evaluation is perceived as stressful and engages the HPA axis (Schwabe, Haddad, & Schachinger, 2008). For the present study the protocol of the SECPT was adjusted so that four people at a time could undergo the test (see Minkley, Schröder, Wolf, & Kirchner, 2014). The participants were asked to submerge their arm in a bucket filled with ice water (0–3 °C) as long as they could stand, up to a maximum of three minutes. Social

evaluation was implemented by telling the participants that they have to face the experimenter and their facial expressions during the task were being analyzed by the experimenter, who took notes and reminded the participants to look at him. All sessions were led by a male experimenter.

The procedure of the non-stressful control condition differed from the SECPT only to that respect that the water had room temperature (20–24 °C) and the participants were not told that their facial expressions during the task were analyzed.

2.2.3. Computer tasks

For the tasks outlined below Matlab and Psychtoolbox 3 (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007) installed on Windows 7 environments were used for presentation.

2.2.3.1. Stimuli. The words used in the study were taken from the MRC Psycho-linguistic Database (Wilson, 1988). The pool of words (i.e., 90 living and 90 non-living) was constrained to words with four to nine letters and with range of concreteness (CONC) values was between 600 and 670. Words were eliminated that had than one meaning or for which it was difficult to decide to which category they belong. The living category contained fruits, animals or humans, while the non-living category was mainly made up of objects. The words presented during encoding (i.e., 60 living and 60 non-living) were chosen at random for each participant, and the test list contained a mixture of the studied and non-studied words.

2.3. Procedure

At each session, three to four participants were tested sitting next to each other (see Fig. 1 for illustration of a session). Moveable walls prevented participants from seeing any PC screen but his/her own. All test sessions began between 9 and 11 am and started with obtaining informed consent from the participants. Then the participants were asked to fill out questionnaires about their demographics and information about the day (e.g. time they woke up). They were also asked to answer the question “How nervous, tense, and/or wired do you feel right now?” on a scale from one to seven. After this, they completed the encoding task.

At the beginning of each encoding trial (Fig. 2), a fixation cross was presented for 1600 ms, followed by the presentation of a word either printed in orange cursive font (source A) or in blue Old English font (source B). The participant had a maximum of 1500 ms to decide whether the word was living or non-living, but a response initiated the subsequent fixation period. The participants were informed that the changes in font were not important for their decisions and they were kept naive about the subsequent memory test. Participants used the left and right arrow keys to indicate their response (with the keys for living/non-living counterbalanced across participants). Each categorical decision was followed by a fixation cross for 1600 ms before a randomly chosen number (1, 4, 6 or 9) was presented for 100 ms, after which the participant had to decide if it was greater or less than 5 by pressing the left or right arrow. Depending on the word presented and number comparison response, feedback was presented for 1600 ms.

Prior to the task, each participant was informed that either living words or non-living words indicated number comparison trials that could yield monetary reward. Whether living or non-living trials indicated rewarded trials remained constant throughout the experiment for each person, but was counterbalanced across participants. On reward trials, $ 0.3 could be earned if the number comparison response was correct and within a certain time limit, and $ 0.1 would be lost if the response was incorrect or late. Participants were informed that the response time window would be adjusted to their performance. The algorithm used a staircase procedure aimed at limiting the actual reward rate to 75%. At the end of each trial, the participants received feedback on the trial and their overall performance/earnings. Participants were not informed that memory for the words would be tested later.

When each of the participants finished this task, the first saliva sample was taken. This was followed either by the SECPT or the non-stressful control task. Subsequently, the participants were asked to indicate how stressful the previous experience was for them and which strategies they used to deal with it. After this, the participants were free to occupy themselves for the next two hours with anything they liked, as long as it did not disturb the other participants. After 30 min, they were asked to provide the second saliva sample. Then they were left undisturbed for the remaining time. Five minutes before the two hours elapsed, the participants were asked to provide the third saliva sample. This was followed by a free recall task in which participants were given ten minutes to write down as many words as they remembered from the earlier part of the experiment. Subsequently, the participants' recognition and source memory was tested with the computer retrieval task. We choose a two-hour delay period between encoding and retrieval because our previous work (McCullough & Yonelinas, 2013) has shown that two hours are enough for cortisol levels to return to baseline and for significant effects of stress on memory.

Recognition memory was tested by presenting the previously encoded words as well as the 60 remaining words (30 from each category; see Fig. 3 for an illustration of a trial). Each word was preceded by fixation cross presented for 1600 ms and presented in plain black font. The participant was asked to rate their recognition confidence as from 1 (sure new) to 5 (sure old) or *recollected*. Participants were instructed to choose *recollected* if they remembered any specific detail about the word being presented in the earlier task. Examples of specific details were any thought about or reactions to the word as well as the response given but also the fact the participants remembered noise heard from the hallway when the word was presented. The test word stayed on screen until the participants gave their response. After providing a recognition judgment, the participant was asked to indicate if the word was printed in orange cursive font (source A) or in blue Old English font (source B) by pressing the left and right arrow key, respectively. If the word was new or they were unsure of the source, they were asked to randomly press a key.

At the end of the experiment the participant received the money earned during encoding, rounded up to the next dollar value.

2.4. Data preparation & analysis

All steps of the data analysis were completed within R (https://www.r-project.org/). The package *nlme* was used for Linear Mixed-

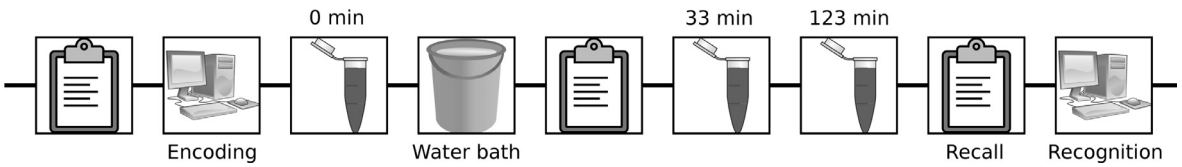

Fig. 1. Illustration of the procedure. The time points are referenced to the first saliva sample (i.e. 0 min). On average, the participants arrived at −36 min, when they completed demographic and questionnaire forms. The encoding task started at −30 min. The first saliva sample was collected as soon as each participant completed the encoding task. At 7 min, the 3-min water bath was completed. The participants then filled out the stress questionnaire. After 33 min and 123 min the second and the third saliva samples were collected, respectively. The 10-min free recall task started at 126 min, followed by the recognition task, which ended at 154 min.

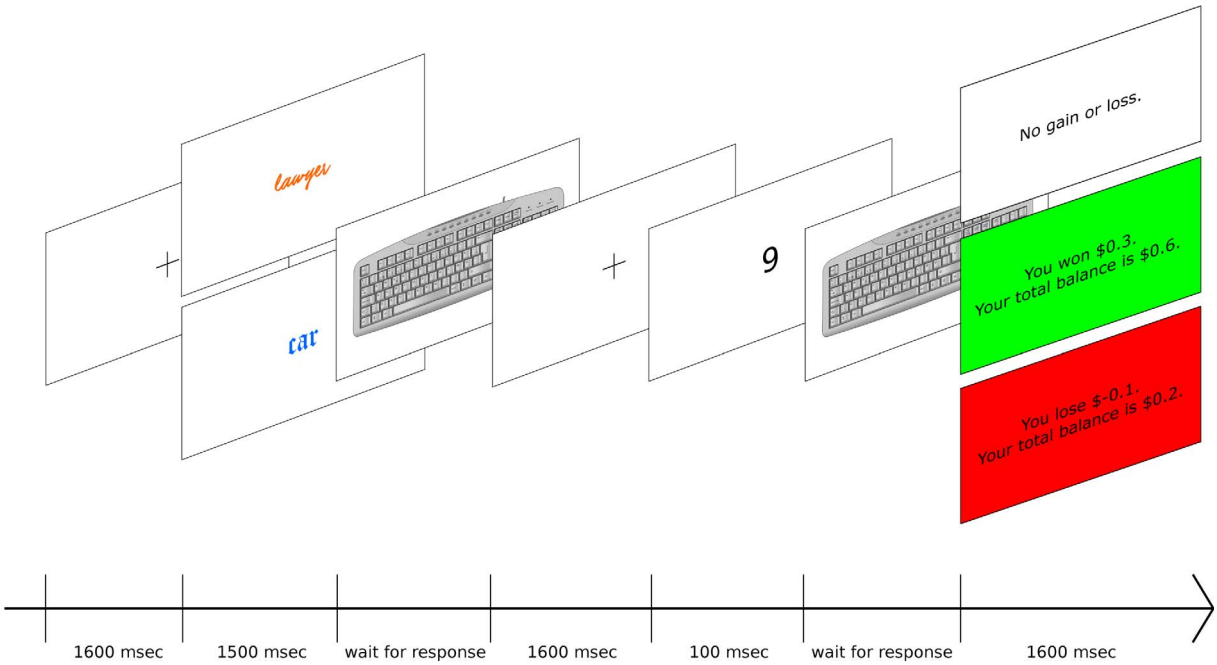

Fig. 2. Each encoding trial started a fixation cross followed by the 1500 ms presentation of a word printed in orange cursive font or in blue Old English font. Participants had as long as needed to decide if the word was living or non-living, which initiated a fixation interval before a random number was presented for 100 ms. Participants decided whether this number was smaller or greater than five. After the response was given, feedback was presented for gain trials, loss trials, and non-reward trials, and the next trial began. If the trial was a non-reward trial, the feedback display was white and "No gain or loss" was shown. On reward trials in which the participant was correct and fast enough, the background color was green and the display said "You won $0.3. Your total balance is $ X." On reward trials in which the participant was either too slow or incorrect or both, then the background color was red and the display said "You lost $0.1. Your total balance is $ X." (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Effects Model, while the function *lm* was used for standard linear regression. The package *ez* was used for ANOVAs. The RT data was subjected to an outlier removal procedure based on the median absolute deviation method (see Leys, Ley, Klein, Bernard, & Licata, 2013). We used five absolute median deviations from the median, in order to only remove responses, in which the participant actively paused. Data from the recognition memory task were analyzed with the R package memoryROC (https://github.com/JAQuent/memoryROC). Recollection and familiarity were estimated according to both the ROC and the R/K procedures (Yonelinas, 1994; Yonelinas, 2001). The ROC procedure of dual process signal detection (DPSD) model which postulates that recognition memory is driven by two separate and dissociable processes: recollection and familiarity (Yonelinas, 1994). Individually, models are fitted to participants' data in each condition. This contrasts the approach of the R/K procedure, where a particular response option (e.g. 1 or) is taken as evidence of recollection or familiarity, respectively, across all participants. In the ROC procedure, participants' data were fit to a dual process signal detection (model) model separately for reward and non-reward words by minimizing the sum squared errors (for a more details see the description of *fitDPSD* function in memoryROC package). For the ROC procedure, R and 5 responses are typically collapsed when examining ROCs in this paradigm because R responses are most often associated with the highest levels of confidence (Yonelinas, 2001), so they were combined with the high confidence familiarity-

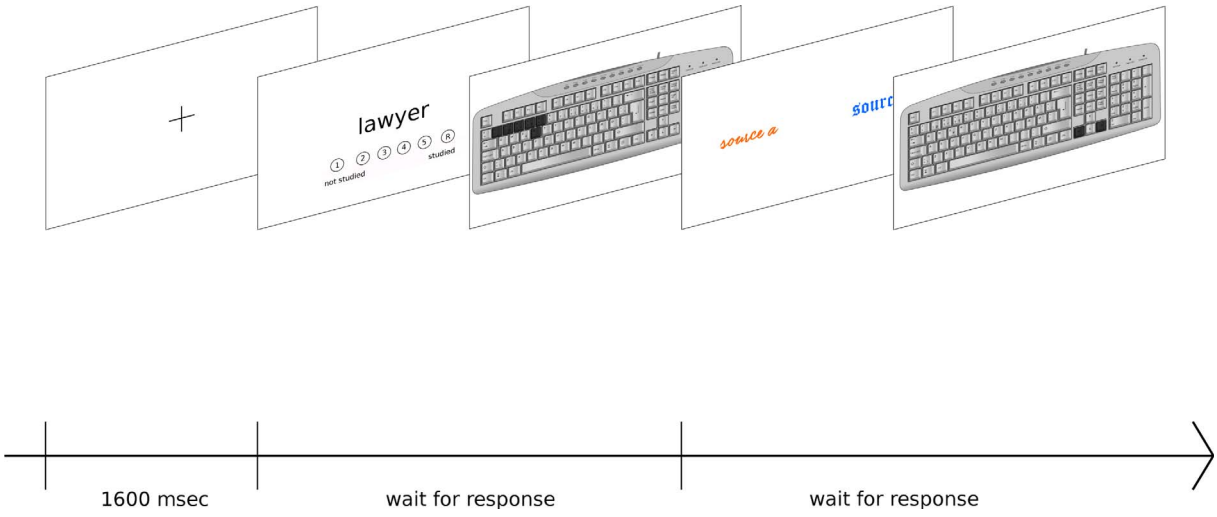

Fig. 3. Each retrieval trial began with a fixation cross that was followed by presentation of a studied or a new word along with a scale from not studied (1) to studied (5) plus R (i.e. recollected). The test word and response scale was presented until the participants gave their response by pressing a number key or the letter "R". Then participants provided a source discrimination judgment by pressing the left or right arrow key, and the next trial began.

based responses. Log-linear transformed d' served as a general index of memory performance. For the R/K procedure, the proportion of remember responses served as the estimates for recollection and the proportion of items rated as familiar but not as remembered served as the estimate for familiarity. In equations,

$$recollection = P(R|old) - R(new)$$

$$familiarity = (P(5 \cup 4 \cup 3|old)/(1 - P(R|old))) - F(new)$$

where

$$R(new) = P(R|new)$$

$$F(new) = P(5 \cup 4 \cup 3|new)/(1 - R(new)).$$

Source memory performance was measured by the hit rate of source discrimination.

3. Results

3.1. Encoding

On average, participants gained reward in 75.27% (SD = 4.57%) of the rewarded trials yielding $ 12.06 (SD = $ 1.1), which corresponds well with our target values (75% and $ 12). Furthermore on the number comparison task, RT were faster on reward predicting trials (370 ms; SD = 89 ms), than on non-reward predicting trials (383 ms; SD = 87 ms), $t(73) = 3.26$, $p = .002$. However in the living/non-living categorization task, RT were not faster on reward predicting trials (1058 ms; SD = 360 ms), than on non-reward trials (1065 ms; SD = 335 ms), $t(74) = 0.43$, $p = .671$. In contrast, RT significantly differed depending on the color and font the word was presented in (i.e. the source), source A (1093 ms; SD = 365 ms) versus source B (1030 ms; SD = 330 ms), $t(74) = 4.48$, $p < .001$.

3.2. Stress manipulation

3.2.1. Self-report

Before the start of the experiment, the stress group did not differ from the control group in terms of nervousness, $t(72) = 0.01$, $p = .989$. After the water bath, however, participants in the stress group reported being more nervous, $t(72) = -3.48$, $p < .001$, experiencing the previous task as more stressful, $t(72) = -8.91$, $p < .001$, and more painful, $t(72) = -8.82$, $p < .001$, than participants in the control group. Participants in the stress group removed their arms after 2 min and 23 s (SD = 53 s) on average, while no participant in the control group removed his/her arm early.

3.2.2. Cortisol response

A conditional growth model with intercept and slope as random factors was used to model the cortisol responses (see Fig. 4(A)). The multilvevel approach indicated a significant main effect of sample (0 min vs. 33 min vs. 123 min), $\chi^2(7) = 177.23$, $p < .001$, and a non-significant main effect of group (stress vs. control), $\chi^2(1) = 2.39$, $p = .122$. However, there was a significant interaction between the samples and group $\chi^2(2) = 13.27$, $p = .001$. This indicates that the change between samples was different for participants in the stress and control groups. Post-hoc t-tests were used to break this interaction down (FDR-corrected for multiple testing). The two groups did not differ at the first time point, $p = .422$. However, after 33 min the cortisol concentration was significantly higher in the stress group, $p = .002$. This difference was still observable after approximately 120 min, $p = .019$.

3.2.3. α-Amylase response

The same model structure was used to analyze the α-amylase response (see Fig. 4(B)). One sample could not be analyzed because the sample did not contain enough saliva; therefore the respective participant was excluded from this analysis. Similar to the previous analysis, there was a significant main effect of sample (0 min vs. 33 min vs. 123 min) $\chi^2(7) = 125.18$, $p < .001$, and a non-significant main effect of group (stress vs. control), $\chi^2(1) = 0.24$, $p = .625$. However, there was a significant interaction between the samples and group $\chi^2(2) = 6.75$, $p = .034$. Post-hoc t-tests were used to break this interaction down (FDR-corrected for multiple testing). The groups did not differ at the first time point, $p = .714$, nor at the second time point, $p = .288$. After approximately 123 min the α-amylase concentrations were higher in the stress group, but the difference did not survive the correction, $p = .09$.

3.3. Categorical analysis

All memory measures were analyzed in a 2 × 2 × 2 mixed ANOVA with reward (non-reward vs. reward) as a within participants factor, gender (male vs. female) and stress (stress vs. control) as between factors. Note that we included gender as a variable because previous studies found larger stress effects in males (but see Shields, Sazma, McCullough, & Yonelinas, 2017).

Overall, there were no significant effects on the measures of recollection or familiarity (see Table 1). Similarly, for overall recognition measured using d' there were no main effects or interactions, all $ps > .663$. For estimates of recollection as indexed by the ROC analysis, recollection was slightly higher in the reward compared to the non-reward condition, but this difference was not significant, $t(73) = -1.48$, $p = .072$ (one-tailed). There were non-significant trends for main effects of reward (with higher recollection for reward predicting words, $F(1, 70) = 2.8$, $p = .099$) and gender (with higher recollection for male participants, $F(1, 70) = 3.49$, $p = .066$). Similarly, there were no significant effects in the ANOVA with familiarity estimates or with source memory or free recall as the dependent variables, all $ps > .133$, $ps > .172$ and $ps > .155$, respectively. Estimating recollection and familiarity using the R/K procedure led to results similar to those of the ROC analysis.

3.4. Quantitative relationships with Delta-cortisol

Prior studies of post-encoding stress have indicated that even when overall stress group difference is not significant that individual differences in stress related increases in cortisol are related to memory (e.g. Andreano & Cahill, 2006; McCullough et al., 2015; Wolf et al., 2001). To examine the associations of stress-induced increases in cortisol on memory we examined the quantitative relationship between Δ-cortisol and the memory measures in the stress group. Two participants were excluded due to extremely low and high values for Δ-cortisol (more than four median absolute deviation (MAD) difference). Only the regression models for recollection (ROC) and free recall provided a significant fit and are therefore reported here.

Increases in stress-related cortisol (i.e., Δ-cortisol) were directly related to increases in ROC recollection estimates for the non-rewarded items, but no such relationship was observed for the reward items (see Fig. 5). That is, a linear model (i.e., Model 1) for recollection significantly fit the data, $F(3, 72) = 6.04$, $p < .001$, $r^2 = .201$, and accounted for 20.1% of the variance in the data. Model 2 which included a quadratic component did not fit the data better than Model 1, $F(2, 70) = 0.82$, $p = .447$. In Model 1, Δ-cortisol, $b = 0.011$, $SE = 0.003$, $p < .001$, and reward, $b = 0.135$, $SE = 0.052$, $p = .01$, were significant predictors. The interaction term between Δ-cortisol and reward was also significant, $b = -0.01$, $SE = 0.004$, $p = .009$. This interaction was broken down by looking at the bivariate correlation coefficients between Δ-cortisol and recollection for reward and non-reward words separately. Among the stressed participant, the correlation between Δ-cortisol and recollection for non-reward words was significant, $r = .623$, $p < .001$, while the correlation between Δ-cortisol and recollection was not significant for reward words, $r = .036$, $p = .83$.

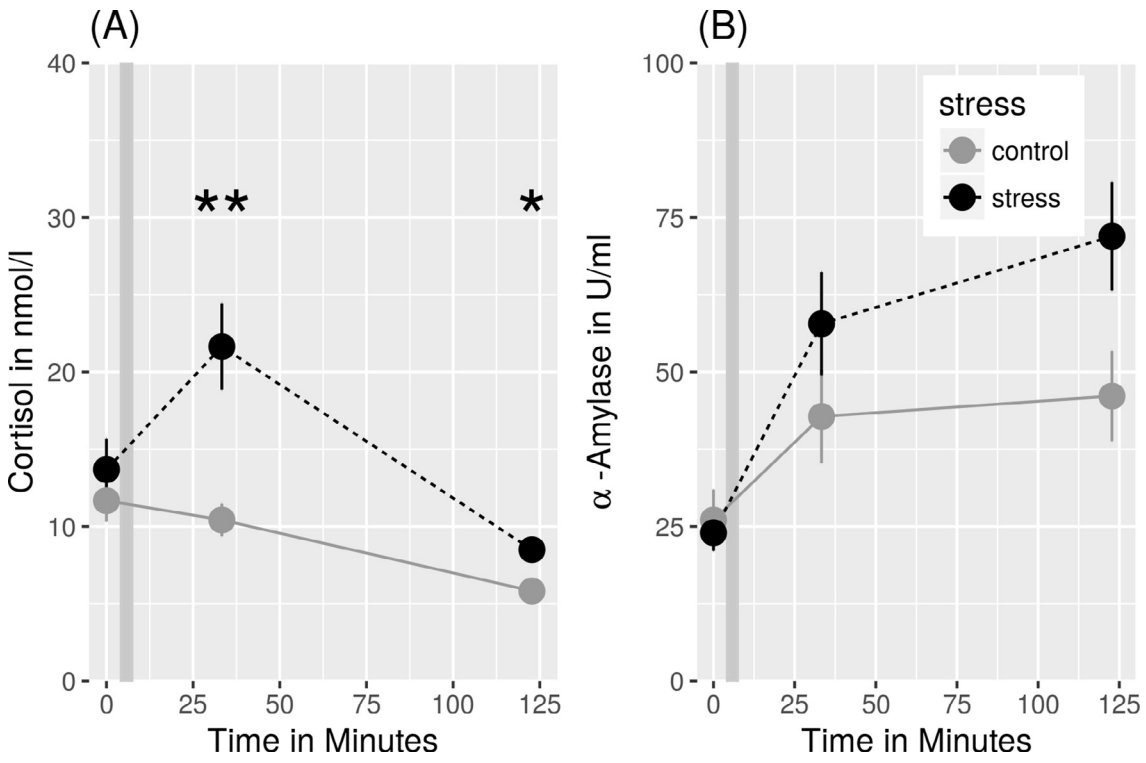

Fig. 4. (A) Salivary cortisol. Mean values (error bars represent standard error of mean) of salivary cortisol concentrations in nmol/l of participants of the control (grey) and stress group (black). The first sample was taken just before the water bath, represented by the vertical grey bar. On average, the second and third samples were taken at 33 min and 123 min after the first sample. Participants of the stress group did not differ from the control group at the baseline, but showed significantly increased values at 33 min and 123 min. (B) Salivary α-amylase. Mean values (error bars represent standard error of mean) of salivary α-amylase concentrations in U/ml of participants of the control (grey) and stress group (black). The samples were taken at the times described above. Participants of the stress group did not significantly differ from the control group at any time point. * $p < .05$, ** $p < .01$ (FDR-corrected).

Note that although when the RK estimates of recollection were modeled, Model 1 did not reach significance, the overall pattern of results were similar to that of the ROCs estimates That is, among stress participants, the correlation between Δ-cortisol and recollection (R/K) for non-reward words was significant, $r = .37$, $p = .022$, but the correlation between Δ-cortisol and recollection (R/K) was not significant for reward words, $r = .115$, $p = .492$.

Consistent with the recollection analysis, an examination of free recall scores indicated that increases in stress-related cortisol (i.e., Δ-cortisol) were related to increases in recall for the non-reward items, but no such relationship was observed for the reward items (see Fig. 6). That is, the linear model (i.e., Model 1) significantly fit the data, $F(3, 72) = 4.84$, $p = .004$, $r^2 = .168$, and accounted for 16.78% of the variance in the data. Model 2 which included a quadratic component did not fit the data better than Model 1, $F(2, 70) = 0.32$, $p = .727$. In model 1, Δ-cortisol, $b = 0.003$, $SE = 0.001$, $p = .001$, and reward, $b = 0.056$, $SE = 0.018$, $p = .003$, were significant predictors. The interaction term between Δ-cortisol and reward was also significant, $b = -0.004$, $SE = 0.001$, $p = .005$. This interaction was broken down by looking at the bivariate correlation coefficients between Δ-cortisol and free recall for reward and non-reward words separately. Among stressed participants, the correlation between Δ-cortisol and free recall for non-reward words was significant, $r = .554$, $p < .001$, while the correlation between Δ-cortisol and free recall was not significant for reward words, $r = -.108$, $p = .519$.

4. Discussion

Our aim was to examine the effects of reward and post-encoding stress on episodic memory, to determine whether these two factors interacted when influencing memory. Based on tag-and-capture models (Ballarini et al., 2009; Frey & Morris, 1997; Moncada & Viola, 2007; Redondo & Morris, 2011; Viola et al., 2014; Wang et al., 2010), we predicted that stress would benefit memory for the non-reward items, but would have less of a beneficial effect for reward items. The current results indicated that there were no main effects or interactions between either the stress or the reward manipulations on memory, thus these results did not provide strong support for the predictions. However, there were significant interactive effects of reward and stress-related changes in cortisol on both recollection and free recall. Namely, for non-reward items, recollection and recall were found to increase linearly with stress-related changes in cortisol, but no such relationship was observed for reward items. Importantly, the interactions between stress-related cortisol and reward were significant, indicating that the different patterns of results could not be attributed to statistical thresholding effects whereby one effect simply failed to reach the statistical threshold for significance. Thus, the results provide partial support for our hypotheses in showing that memory is related to stress-

Table 1
Aggregated data for free recall, recognition d′, recollection & familiarity (ROC & R/K), and source memory with standard deviation in parentheses.

Stress	Reward	Recall	d′	Rec (ROC)	Fam (ROC)	Rec (R/K)	Fam (R/K)	Source
Control	Non-reward	0.11 (0.06)	0.95 (0.43)	0.25 (0.16)	0.68 (0.44)	0.17 (0.16)	0.23 (0.18)	0.52 (0.05)
Control	Reward	0.11 (0.06)	0.96 (0.4)	0.29 (0.22)	0.61 (0.39)	0.19 (0.19)	0.23 (0.17)	0.52 (0.06)
Stress	Non-reward	0.11 (0.06)	0.94 (0.39)	0.24 (0.19)	0.69 (0.44)	0.2 (0.16)	0.23 (0.18)	0.51 (0.05)
Stress	Reward	0.13 (0.07)	0.95 (0.32)	0.29 (0.2)	0.62 (0.36)	0.22 (0.16)	0.23 (0.16)	0.53 (0.06)

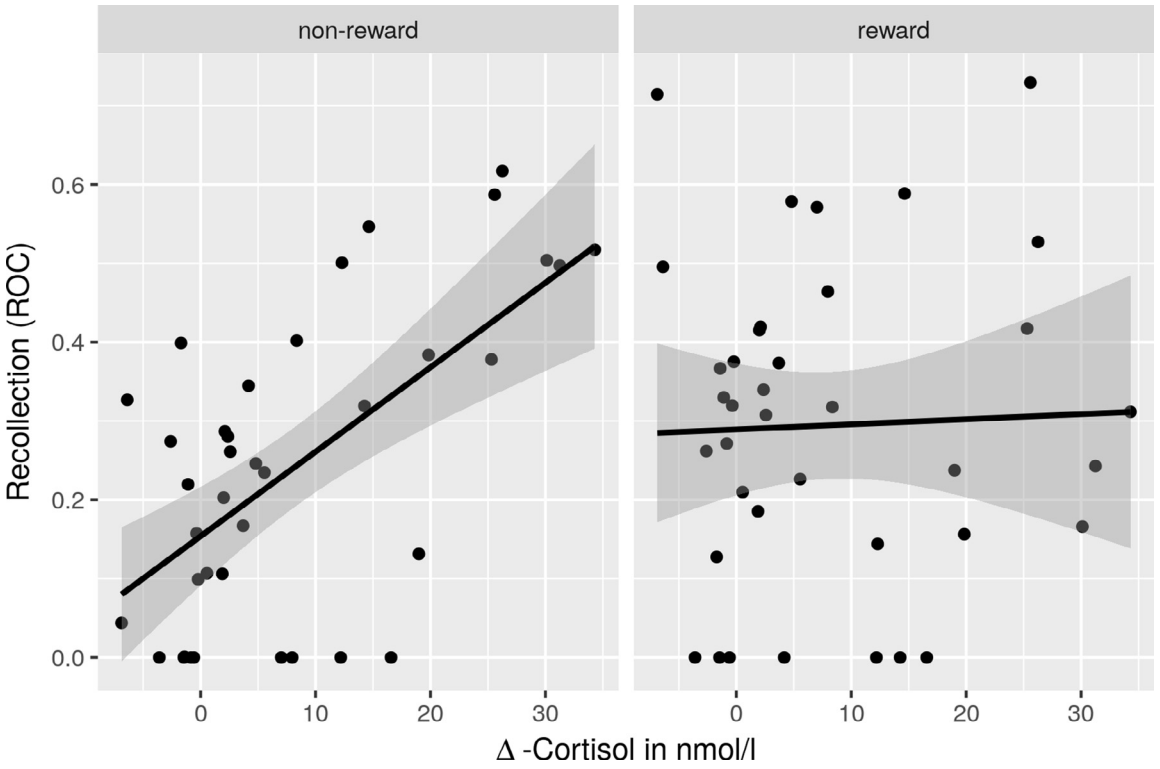

Fig. 5. Relationship between Δ-cortisol and recollection (ROC). There was a significant correlation between Δ-cortisol and recollection (ROC), $r = .623$, $p < .001$ for non-reward words, such that estimates of recollection (ROC) linearly increased with Δ-cortisol. Such a relationship was absent for reward words, $r = .036$, $p = .83$.

related increases in cortisol when the study materials were not associated with a reward trial, but not when the materials were associated with reward trials.

Numerous prior studies have indicated that reward (e.g. Wittmann et al., 2011, 2005), and post-encoding stress (Shields et al., 2017) generally improve episodic memory, and so the current failure to find significant main effects of either manipulation was a surprise. Though, we have to admit that the reward studies used longer delays then we

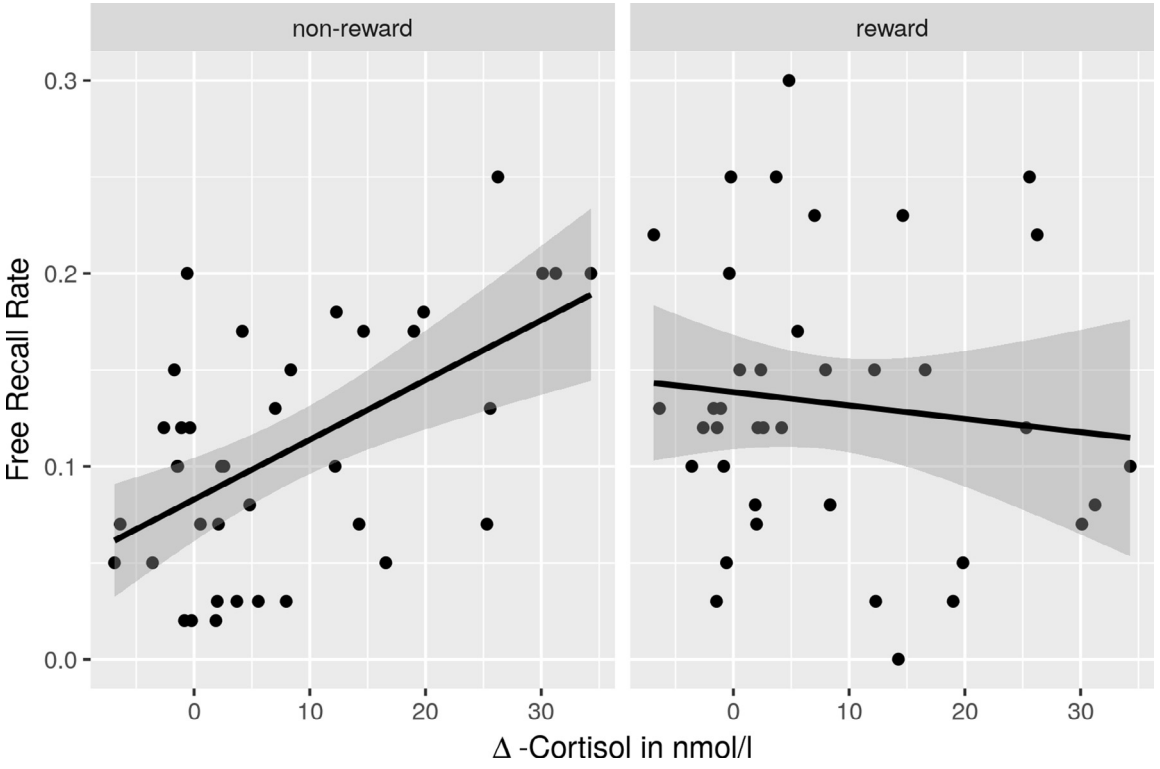

Fig. 6. Relationship between Δ-cortisol and free recall. There was a significant correlation between Δ-cortisol and free recall, $r = .554$, $p < .001$ for non-reward words, such that free recall rates linearly increased with Δ-cortisol. Such a relationship was absent for reward words, $r = -.108$, $p = .519$.

did, which could be one factor why we did not observe reward effects. We can only provide post hoc accounts of this discrepancy, and further work will need to be conducted to evaluate these suggestions. For the stress effects, the current paradigm was based on previous studies in terms of the stressor, materials, procedures, and participants. However, one unusual aspect of the current results was that the stress-related increase in cortisol was found to last somewhat longer than what was observed in prior studies (see McCullough & Yonelinas, 2013). That is, by the time of the two-hour delayed memory test, stressed participants' cortisol levels were still significantly higher than those of the control participants, whereas in previous studies cortisol levels have usually returned to baseline by this time. It is well established that increased cortisol can impair the ability to retrieve information from memory (Wolf, 2017), and so any post-encoding stress benefit in the current study may have been masked by a retrieval impairment. Another possible factor is we did not control for menstrual phase; a factos that the meta-analysis from Shields et al. (2017) suggests can reduce observed effects of stress. However, arguing against this account would be the fact that we did not find any evidence for gender effects in the current study. Another factor that may have been important was that the current study was conducted earlier in the day (9:00 am) than in many studies; another factor that can reduce the effects of stress (Shields et al., 2017).

One factor that may have led to a reduction in the magnitude of the reward effects in the current study is the relatively short delay between study and test. Several previous studies of reward have used test delays of at least 24 h (e.g. Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Loh et al., 2015; Wittmann, Schiltz, Boehler, & Düzel, 2008; Wittmann et al., 2005). However, significant reward effects have been observed with a delay that is less than two hours (Gruber, Ritchey, Wang, Doss, & Ranganath, 2016; Shigemune, Tsukiura, Kambara, & Kawashima, 2014), and this was the reason we designed the study using the short delay. Importantly however, the current reward manipulation was effective in the sense that it was critical in determining whether the stress-induced cortisol relationships with memory were or were not observed.

The central finding of this work is that memory performance (recollection and free recall) for non-reward stimuli increased linearly with cortisol reactivity in participants, who were stressed after encoding, whereas cortisol reactivity did not predict memory performance for reward stimuli in the same individuals. We interpret this finding as being consistent with tag-and-capture theories of consolidation (Frey & Morris, 1997; Redondo & Morris, 2011). By this account, some portion of the non-reward study items were tagged during the encoding phase but would be forgotten unless they captured plasticity-related products (PRPs). For participants who exhibited a large stress response, the increase in cortisol may have provided the PRPs necessary to rescue those memories from forgetting. In contrast, the reward items had presumably already captured the PRPs produced by the reward-related increase in dopamine, and so effects of post-encoding cortisol release may have been effectively masked by the effects of reward.

Viewed through the tag-and-capture framework, both glucocorticoids secreted in response to stress and dopaminergic innervation from the SN/VTA circuitry engaged during reward anticipation might affect the capturing mechanism by increasing the availability of PRPs in the hippocampus or the efficiency with which these are captured by the synaptic tags. How does this framework fit with existing models explaining the effects of stress on memory? The integrative model of stress and memory (Schwabe et al., 2012) integrates the view that effects of stress on memory need concurrent activity of glucocorticoid and noradrenergic systems (Roozendaal, Okuda, de Quervain, & McGaugh, 2006) with the view that stress effects differ depending on whether stress is experienced within or outside of the context of encoding (Joëls, 2006). According to this model, the interaction of catecholamines and rapid and non-genomic glucocorticoid actions in the basolateral part of the amygdala is central for the effect of stress on memory. This interaction switches the system to "memory formation mode" (e.g. involving interactions of the prefrontal cortex and hippocampus). During "memory formation mode" early consolidation is enhanced. Catecholamine levels return to baseline very fast, while glucocorticoid, which now mainly exert their influence through genomic pathways, remain high. This initiates a "memory storage mode", during which activity is reduced, and the threshold for processing and consolidating new experiences is raised, which is supposed to aid long-term storage. The model predicts that stress experienced shortly before or during learning enhances memory, while stress has impairing effects if it occurs longer before learning. During the memory formation mode stress could provide PRPs. For this process, mainly rapid and non-genomic glucocorticoid actions and concurrent (nor-) adrenergic actions have been identified as important (Joëls et al., 2011; Schwabe et al., 2012). In contrast, during memory storage mode, high glucocorticoid levels from stress would result in occupation of both GR and MR sites, leading to reduced excitability of the hippocampus (de Kloet, Vreugdenhil, Oitzl, & Joëls, 1998). This could prevent tagged memory traces from capturing PRPs, or prevent the tagging process in the first place. Thus, the tag-and-capture hypothesis provides a mechanistic explanation why stress in close proximity to encoding can enhance memory as predicted by the integrative model.

On the molecular level, there are striking similarities between the effects of stress and the tag-and-capture theory. Noradrenergic effects are primarily associated with the rapidly-acting G-coupled pathway (large proteins embedded the cell membrane activating signal transduction; Joëls et al., 2011). Noradrenaline triggers a cascade on the AMPAR pathway (Joëls et al., 2011). Glucocorticoids can also act on G-coupled receptors and both the glucocorticoid receptor (GR) and the mineralcorticoid receptor (MR) are implicated in the rapid effects of glucocorticoids after stress (Joëls et al., 2011). Glucocorticoids binding to GR lead to slowly enhanced AMPAR surface expression in the amygdala and the hippocampus, but the major role for the rapid effects on the AMPAR is played by MR (Joëls et al., 2011). Interestingly, the AMPAR also plays a role in the tag-and-capture hypothesis. Specifically, the AMPAR is also a target of PRPs. For instance, Glur1, one candidate PRP, targets this receptor (Redondo & Morris, 2011). While tag setting is associated with the actin network and CaMKII activity, which both lead to structural changes such as increased AMPAR expression, the maintenance of these alterations require the presence of PRPs (Redondo & Morris, 2011). Thus, stress models and tag-and-capture processes can be viewed as converging on the same molecular targets.

In sum, stress and reward anticipation might have different physiological underpinnings, but the effects triggered by these manipulations can appear very similar at the behavioral level. We suggest a common link, which could lay in their efficiency to induce the late LTP that is necessary for LTM. We argue that one common link is that all these manipulation rely on tag-and-capture mechanisms.

5. Funding

JAQ received travel funds from the Hans Böckler Foundation. The contribution of OTW was supported by the German Research Foundation (DFG) project B4 of the Collaborative Research Centre (SFB) 874 "Integration and Representation of Sensory Processes". This research was also supported by NEI R01EY025999 to APY.

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