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Human aging reduces the neurobehavioral influence of motivation on episodic memory

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ABSTRACT

The neural circuitry mediating the influence of motivation on long-term declarative or episodic memory formation is delineated in young adults, but its status is unknown in healthy aging. We examined the effect of reward and punishment anticipation on intentional declarative memory formation for words using an event-related functional magnetic resonance imaging (fMRI) monetary incentive encoding task in twenty-one younger and nineteen older adults. At 24-hour memory retrieval testing, younger adults were significantly more likely to remember words associated with motivational cues than neutral cues. Motivational enhancement of memory in younger adults occurred only for recollection ("remember" responses) and not for familiarity ("familiar" responses). Older adults had overall diminished memory and did not show memory gains in association with motivational cues. Memory encoding associated with monetary rewards or punishments activated motivational (substantia nigra/ventral tegmental area) and memory-related (hippocampus) brain regions in younger, but not older, adults during the target word periods. In contrast, older and younger adults showed similar activation of these brain regions during the anticipatory motivational cue interval. In a separate monetary incentive delay task that did not require learning, we found evidence for relatively preserved striatal reward anticipation in older adults. This supports a potential dissociation between incidental and intentional motivational processes in healthy aging. The finding that motivation to obtain rewards and avoid punishments had reduced behavioral and neural influence on intentional episodic memory formation in older compared to younger adults is relevant to life-span theories of cognitive aging including the dopaminergic vulnerability hypothesis.

Introduction

What enables us to learn from motivationally significant events and how does this ability change across the lifespan? Evidence in young adults suggests that the fate of individual memories is influenced by their motivational context. Anticipation of reward or punishment improves declarative memory formation via interaction between motivational and memory-related brain networks (Adcock et al., 2006; Kuhl et al., 2010; Murayama and Kuhbandner, 2011; Murty et al., 2012; Shigemune et al., 2014; Wittmann et al., 2005, 2011; 2013). One behavioral study that did not examine brain function found that high monetary reward anticipation enhanced declarative encoding compared with low-reward on delayed, but not immediate, recognition testing in younger and healthy older adults (Spaniol et al., 2014). An electrophysiology study did not show an effect of reward on immediate recognition memory in either younger or older adults (Steiger and Bunzeck, 2017). A separate neuroimaging study examining value-related modulation of reward and semantic networks during immediate word recall identified an influence of value on memory in younger and healthy older adults (Cohen et al., 2016). However, it is unknown how healthy aging influences the brain

Abbreviations: MIE, monetary incentive encoding; MID, monetary incentive delay; VDR, value directed remembering; fMRI, functional magnetic resonance imaging; SN/VTA, substantia nigra/ ventral tegmental area.

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basis of monetary reward- and punishment-motivated long-term memory formation.

Because dopamine is thought to be a critical neurotransmitter for reward (Schultz, 1998), pre- and post-synaptic age-related dopaminergic vulnerability (Backman et al., 2006; Duzel et al., 2010; Kaasinen and Rinne, 2002; Klostermann et al., 2012; Karrer et al., 2017; Volkow et al., 1998; Wang et al., 1998) could result in an associated reduction in the influence of motivation on memory formation over the lifespan. Dopamine receptors are lost at a rate of 3% per decade from the striatum, and midbrain dopamine transporter expression declines with age (Bannon and Whitty, 1997; Rinne et al., 1990). Although the implications of age-related dopaminergic decline on motivated memory are unknown, fMRI studies suggest that older adults have impaired reward-based learning and decision making (Samanez-Larkin and Knutson, 2015), and dopamine therapy improves the rate at which older adults learn from rewarding outcomes (Chowdhury et al., 2013). Older adults may be particularly susceptible to dopaminergic vulnerability in the context of learning. An fMRI study found age-related reduction in ventral striatal activation during stimulus-reward association learning and preserved ventral striatal response in a learning-free monetary incentive delay (MID) task suggestive of a "dissociation between cognition and motivation with age" (Samaenz-Larkin et al., 2014).

Another line of research on aging raises the possibility that older adults would selectively retain the influence of reward, but exhibit a reduced influence of punishment, on memory formation. Despite declines in dopaminergic neuromodulation, physical health and many cognitive abilities across the lifespan, changes in affective and emotional processing may yield some benefits as adults age. Older adults experience fewer negative emotions, a greater overall sense of wellbeing and emotionally gratifying memory distortion of past choices (Carstensen et al., 2000, 2011; Charles et al., 2001; Kennedy et al., 2004; Labouvie-Vief and Medler, 2002; Mather et al., 2004; Mather and Carstensen, 2005). There is growing evidence for a *positivity effect* in aging; this is an age-related trend that favors positive over negative stimuli in cognitive processing (Brassen et al., 2012; Charles et al., 2003; Leigland et al., 2004; Mather and Carstensen, 2005; Samanez-Larkin et al., 2007). FMRI experiments have shown that older adults are less responsive to potential loss, but equally responsive to potential gain compared to younger adults (Brassen et al., 2012; Samanez-Larkin et al., 2007). In addition, older adults demonstrate an attentional bias toward positive stimuli (Mather and Carstensen, 2003) that is associated with a reduced brain response to negative stimuli and a preserved response to positive stimuli (Mather et al., 2004).

Anticipation of reward or punishment enhances episodic memory via a midbrain-striatal-hippocampal network that is modulated by dopamine (Adcock et al., 2006; Callan and Schweighofer, 2008; Kahn and Shohamy, 2013; Shohamy and Adcock, 2010; Wittmann et al., 2005, 2013; Wolosin et al., 2012). A polysynaptic loop connecting these regions is comprised of direct dopaminergic projections from substantia nigra/-ventral tegmental area (SN/VTA) to hippocampus, and outputs from hippocampus through nucleus accumbens back to SN/VTA (Lisman and Grace, 2005; Shohamy and Adcock, 2010). Dopaminergic neurons in SN/VTA are necessary for hippocampal synaptic plasticity and bias declarative memory formation for motivationally significant events (Bethus et al., 2010; Huang and Kandel, 1995; Lisman et al., 2011; Lisman and Grace, 2005; Otmakhova et al., 2013; Rossato et al., 2009; Shohamy and Adcock, 2010).

Studies of classical conditioning using both primate neurophysiology and fMRI methods suggest that reward- and punishment-related processing, including anticipation of financial rewards and punishments, are critically dependent on the nucleus accumbens and the SN/VTA (Bromberg-Martin et al., 2010; Carter et al., 2009; Delgado et al., 2008; Fiorillo et al., 2003; Jensen et al., 2003; Knutson et al., 2000, 2001; Levita et al., 2012; Matsumoto and Hikosaka, 2009; McClure et al., 2004; Olds and Milner, 1954; Schultz, 1997, 1998; Seymour et al., 2004, 2007; Shigemune et al., 2014; Zaghloul et al., 2009). Functional neuroimaging studies have shown that recruitment of SN/VTA and nucleus accumbens is associated with reward-motivated declarative learning (Adcock et al., 2006; Kuhl et al., 2010; Murayama and Kuhbandner, 2011; Wittmann et al., 2005, 2011). Compared to reward-related memory enhancement, less is known about punishment-related declarative learning. There is, however, evidence that punishment-motivated learning is also dopamine-dependent (Wittmann and D'Esposito, 2015; Wittmann et al., 2013) and involves nucleus accumbens, SN/VTA, and hippocampal regions (Shigemune et al., 2014; Wittmann et al., 2013).

We hypothesized that motivation to obtain monetary rewards and avoid punishments would enhance declarative learning in younger adults and recruit nucleus accumbens, midbrain and hippocampal regions. With respect to older adults, age-related dopaminergic vulnerability and positivity effect raised two alternative hypotheses. Age-related dopaminergic vulnerability suggests that older adults would exhibit reduced influences of both reward and punishment on memory formation. Age-related positivity effect suggests that older adults would exhibit a spared influence of reward (positive) motivation, but a reduced influence of punishment (negative) motivation, on memory formation.

Here, we compared behavior and brain function between healthy younger and older adults during the encoding of individual words that were preceded by motivational cues of receiving money (reward), losing money (punishment), or having no financial consequence (neutral condition) if they were successfully remembered at test 24 h later (monetary incentive encoding (MIE) task). In order to better understand any age-related change in the influence of monetary motivation on memory formation, we also examined brain responses to monetary motivation in the absence of a memory demand. The same participants performed the MID task that has revealed activation in human reward regions (Knutson et al., 2000) that parallels physiological responses in primates (Schultz, 1997). To maximize statistical power, analyses were focused *a priori* on the major components of the reward-declarative memory circuit, namely the nucleus accumbens, SN/VTA region and hippocampus.

Material and methods

Participants

Twenty healthy older and twenty-four healthy younger, right-handed, native English speaking adults participated in this study. All participants provided written, informed consent prior to participation in the study, in accordance with the Declaration of Helsinki. The MIT Committee On the Use of Humans as Experimental Subjects (COUHES) review board approved the study protocol. Eligible participants scored at least 26/30 on the Montreal Cognitive Assessment (Nasreddine et al., 2005), did not take psychoactive medication, and had no history of neurological or psychiatric illness. We excluded four participants: two because of a software malfunction during scanning, and two for use of psychoactive medications disclosed after scanning. The final analysis included 21 Younger Adults (11 women, mean age 21.7 years, range 18–30 years) and 19 Older Adults (8 women, mean age 61.4 years, range 49–84 years). Although there were no significant demographic differences between groups, Older Adults tended to have more years of post-secondary education (Older Adults = mean 4.3 years, SE 0.5; Younger Adults = mean 3.1 years, SE 0.4; $t_{(38)} = 1.8$, $p = .078$) and higher scores on the American version of the National Adult Reading Test (Older Adults = mean 36.9, SE 1.6; Younger Adults = mean 33.3, SE 1.1; $t_{(38)} = 1.8$, $p = .072$). Younger Adults (mean 0.83, SE 0.04) performed significantly better than Older Adults (mean 0.52, SE 0.03) for delayed free recall memory performance on the Rey Auditory Verbal Learning Task ($t_{(38)} = 6.26$, $p < .0001$, $d = 1.98$) (Rey, 1958), a finding that is well documented in healthy aging (Park et al., 2002). Six Older Adults took antihypertensive medications. Exclusion of these participants did not alter our main findings.

Monetary incentive encoding task

Participants studied words under three motivational conditions (reward, punishment and neutral) in an event-related fMRI design and were financially compensated depending on their memory performance. Each encoding block (36 trials total) consisted of 12 trials from each motivational condition. Participants completed six encoding blocks, lasting approximately eight minutes each, with a break after every block. Mnemonic targets were concrete English nouns that were selected from the MRC Psycholinguistic Database (Coltheart, 2007; Wilson, 1988). Words in each condition were matched for word frequency, context frequency, concreteness, and counterbalanced across motivational conditions and participants.

During the encoding phase in the scanner, every trial began with a fixation cross during which participants were asked to remain alert for a cue that followed (Fig. 1). The cue (1 s) signaled the trial type (neutral: "$0" in white; punishment: "-$2" in red; or reward: "+$2" in green) instructing participants on the financial consequence for later remembering or forgetting the target stimulus that followed. After each cue, a temporally jittered fixation cross (2.5–6.5 s) preceded the presentation of a mnemonic target word (2 s). Immediately after the target word, participants completed a visual-motor 'arrows' distractor task to prevent further rehearsal or elaboration of the target word (Stark and Squire, 2001). During the distractor task participants indicated the direction of a right or left-pointing arrowhead (lasting 1 s each, 3–7 arrowheads total) as quickly as possible by pressing a stimulus-response button-box with their index (left arrowhead) or middle finger (right arrowhead). The variable duration of the fixation cross and distractor task increased the design efficiency by reducing the correlation between stimuli on consecutive trials. A similar design has previously been used to investigate MIE for scenes (Adcock et al., 2006). Optseq software was employed to optimize trial onsets, cue and target intervals, and trial order (http://surfer.nmr.mgh.harvard.edu/optseq).

Participants completed a self-timed, computerized 'remember/know' (Tulving, 1985) recognition memory test outside of the scanner twenty-four hours after encoding (mean 23.4 h, range 19–24.5). During retrieval, studied stimuli (216 target words) and lures (216 novel words) were presented in 6 blocks comprised of equal numbers of studied words and novel lures in a random order. Each word was presented in the center of a computer screen in large font. Participants were offered the opportunity to take breaks after each retrieval block.

At test (retrieval phase), participants were asked to decide whether each individually presented word was previously studied (old) or novel (new); if participants were certain they had seen the word during the encoding session but did not recall anything about its occurrence (additional episodic detail) they were asked to make a button press of '2' for 'familiar'. If a participant was certain they had previously studied the word and could also recall anything about the actual event of the word's occurrence at the time of study (e.g., re-experiencing the episode, recollection of the trial type) they responded with button press '1' for 'remember'. If the word was novel or the participant was uncertain if they had studied the word, they were instructed to press '3' for 'new'. Recognition decision prompts remained on the bottom of the screen throughout the test (i.e., '1 = remember, 2 = familiar, 3 = new'). Participants were asked to make recognition judgments as accurately as they could. They were told that 'familiar' or 'remember' ratings would be compensated equally. Prior to the recognition memory task, participants were reminded that new distractors were intermixed with the studied words, and that they would be penalized ($1) for each false alarm (the penalty was included to discourage participants from providing too many positive responses in hopes of making more money; rather, we wanted the most accurate memory judgments possible). Participants received payment upon completion of the recognition memory test depending on their memory performance.

Monetary incentive delay task

Participants completed two runs of a monetary incentive delay (MID) task. On each trial, participants were cued with arrows indicating the reward value of a button press during the upcoming target (a white star). Cues signaled potential reward (up arrow), potential punishment (down arrow) or no monetary outcome (sideways arrow). The amounts at stake were 0, 1 or 5 dollars. Ten trials from each condition (reward, punishment or neutral) were presented in a pseudo-randomized order in each run yielding a total of 20 trials for each condition for each participant. The cue (1 s) and feedback (2 s) appeared after a temporally jittered delay (3–5 s). Difficulty was titrated by performance to a 67% hit rate by adjusting the reaction time window for allowed responses. After target presentation, a feedback screen displayed the reward (for hits) or penalty (for misses) and the cumulative total (Adcock et al., 2006; Knutson et al., 2001).

Procedures

Prior to scanning, participants practiced the MIE task on a practice set of stimuli not shown during scanning. To demonstrate the incentives, participants were told that they could win $144 for perfect memory performance at retrieval. Participants were instructed to try to remember as many of the words as possible. During scanning, participants were asked to stay as still as possible and were reminded during every break between blocks. The use of padding around the head further limited movement and improved comfort. Earplugs were provided to reduce scanner noise. Stimuli were visually presented with a projector and back-projected on to a screen. Participants viewed stimuli via a mirror

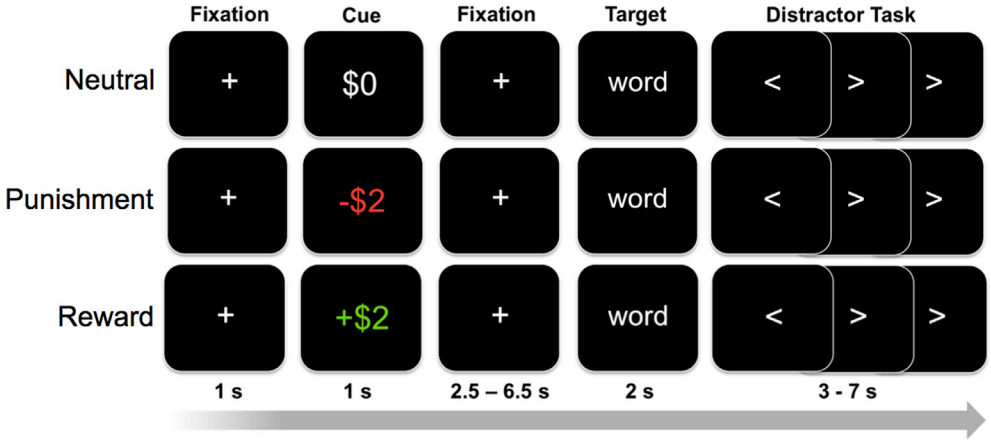

Fig. 1. Monetary incentive encoding task. During this task, participants viewed an equal number of neutral, punishment, and reward trials indicated by a monetary cue ($0, -$2, +$2 respectively). Participants were paid for remembered "+$2" words and penalized for forgotten "-$2" words depending on memory retrieval performance outside the scanner 24 h after encoding.

attached to the head coil. Right index and middle finger behavioral responses to the distractor arrow task were recorded using a four-button fiber optic response box (Current Designs, Inc., Philadelphia, PA, USA).

MRI data acquisition and preprocessing

Imaging was conducted on a 3.0 T Siemens TIM Trio system at the Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research, Massachusetts Institute of Technology. Prior to the fMRI experiment task, one high-resolution T1-weighted structural image was acquired using a magnetization-prepared rapid acquisition with gradient echo sequence (TE 3.39 ms, flip 7°, TR 2530 ms, 176 contiguous slices, voxel size 1 mm isotropic).

Functional brain imaging was collected using a gradient-echo T2*-weighted sequence (TE 30 ms, flip 90°, TR 2 s, 32 contiguous slices ascending, voxel size 3.1 × 3.1 × 3.0 mm). A 32-channel array hexagonal head coil was employed to increase the signal to noise ratio of the fMRI time-series (Triantafyllou et al., 2011). Functional brain images were acquired to maximize coverage of the temporal lobes, midbrain, and striatum, and thus excluded the motor cortex, and dorsal parietal cortex in most participants. Task data were acquired in six runs with 246 vol each (8 min and 12 s). To allow magnetic stabilization, the first 4 vol of each functional run were discarded.

FMRI data preprocessing and statistical analyses were performed with FSL (version 5.0.4), FreeSurfer (version 5.1.0) and ANTs using Nipype and bash scripts for workflow design and execution (Gorgolewski et al., 2011). Functional image preprocessing included simultaneous motion and slice-timing correction using Nipy (Roche, 2011). Functional volumes of each participant were realigned across runs to the first functional volume of the first run, and the mean functional image was coregistered to the anatomical image by employing a rigid-body transformation. High-resolution T_1-weighted structural images were normalized to the Montreal Neurological Institute space using the SyN diffeomorphic algorithm from ANTS (Avants et al., 2006) and the resulting normalization transform was applied to the realigned and coregistered functional images. Data were visually inspected for artifacts. We also employed in-house artifact rejection software *art* (http://www.nitrc.org/projects/artifact_detect/) in Nipype to detect outliers defined as composite volume-to-volume motion 2 mm or intensity threshold greater than 3 standard deviations (SD). Outliers in the functional time-series data were regressed out from the analysis; this resulted in the loss of less than 0.1% of the functional data. The total number of outliers did not significantly differ between groups (Older Adults 3.7, standard error (SE) 0.83; Younger Adults 2.5, SE 0.39; $t_{(38)} = 1.4$, $p = .18$). Functional data were spatially smoothed using an isotropic 8 mm full width at half maximum Gaussian kernel to account for anatomical variability. The time series in each voxel was high-pass filtered with a cutoff of 1/256 Hz.

Analysis of behavioral data

To investigate whether participants employed different memory encoding strategies across trial types, the average reaction time (RT) during the arrow distractor task for all 'hits' ('remember' and 'familiar' response types combined) was examined in hit versus miss trials. Reaction times for the distractor task following target words were submitted to a repeated-measures ANOVA with memory outcome (hit, miss) or trial type (neutral, reward, punishment) as the within-subject factor and group (Younger Adults, Older Adults) as the between-subject factor. To prevent outlier RTs from unduly influencing the means for each participant, outliers (>3 SD from the mean individual RT or under 100 ms) were excluded from the raw data. To test the influence of reward and punishment anticipation on memory, we performed two separate 2 × 3 repeated measures ANOVAs to examine effects of age group and condition on recognition accuracy (defined as hit rate minus false alarm rate), computed separately for 'remember' and 'familiar' responses. Statistical thresholds were set at $p < .05$, two-tailed.

fMRI data analysis

There have been two perspectives on the theoretical framework of recognition memory where it is viewed as a continuum on the one hand and as distinct processes on the other. Dual-process theory posits that recognition memory is supported by two distinct processes, familiarity (the strong sense that an item has previously been encountered without memory of episodic detail) or recollection (retrieval of contextual information of the study event) (Mandler, 1980; Wixted and Mickes, 2010; Yonelinas, 2002). In support of the brain basis of this theory, human lesion and fMRI studies have shown that the neural substrates of recollection are distinct from those of familiarity across cortical and medial temporal lobe regions (Aggleton et al., 2005; Davachi et al., 2003; Eichenbaum et al., 2007; Eldridge et al., 2000; Holdstock et al., 2002; Montaldi et al., 2006; Ranganath et al., 2004; Rugg et al., 2012; Yonelinas et al., 2005). In contrast to dual-process accounts, signal detection theory suggests that recognition judgments result from evaluating a single, continuous memory strength signal (Brezis et al., 2016; Donaldson, 1996; Dunn, 2004; Rotello et al., 2006) or a combination of continuous signals (Ingram et al., 2012; Wixted and Mickes, 2010). According to this view, 'remembered' items exceed a higher memory strength decision criterion whereas 'familiar' items are lower strength memory judgments. Human behavioral and fMRI studies have shown that recollection and familiarity may alternatively be process impure, with 'familiar' judgments associated with a lesser degree of recollection than 'remember' judgments, rather than the absence of recollection (Johnson et al., 2009; Wais et al., 2008).

The present study employed parametric analyses where 'remember' and 'familiar' responses were weighted differently and treated effectively as representing stronger and weaker memories. This approach captures variance related to a memory strength signal congruent with the signal detection theory model. The parametric encoding success analysis also makes the assumption that brain activity in the same regions will contribute to both 'remember' and 'familiar' responses, with greater levels of activation associated with 'remember' responses. Support for this assumption is based on human neuroimaging studies that have shown a graded pattern of brain activity in overlapping cortical and hippocampal/parahippocampal regions for items endorsed as 'remembered' or 'familiar' (Gottlieb and Rugg, 2011; Johnson et al., 2009; Rugg et al., 2012; Smith et al., 2011; Song et al., 2011; Squire et al., 2007; Wais et al., 2010).

The fMRI analysis was conducted on data acquired during memory encoding. Statistical analyses were performed in FSL in three stages: first-level analysis (i.e., within-run) and second-level analysis (i.e., across-run, but within-subject) using a fixed-effects model, and third-level (i.e., across-subjects) mixed-effects analysis that included the main effects of regressors from lower level analyses. First-level, subject-specific analyses were applied using a general linear model. Blood oxygen level-dependent (BOLD) response to each event type was modeled as a double gamma function at target word onsets and convolved with the canonical hemodynamic response function (Friston et al., 1998) within the context of the general linear model. We excluded all trials where participants' reaction times were 2.5 SD greater than the mean for an individual participant. This resulted in a data reduction under 0.002%.

A parametric design was used to test the influence of motivation on recognition accuracy for the cue and target word intervals. Condition regressors weighted all trials, including misses, equally for each event type and were modeled as regressors of no interest. The goal of this step was to regress out activity common to all encoding trials (including misses) before activity related specifically to encoding success was modeled. To investigate parametric modulation of brain activity by recognition accuracy, parametric encoding success modulation (ESM) regressors were included in the design matrix to model the 1-second cue and 2-second target word intervals. The parametric ESM regressors were weighted according to the participant's corrected recognition accuracy (hit rate minus false alarm rate) at retrieval and were used to identify

brain regions in which activation is strongest when forming a memory that will ultimately be recalled with a level of subjective confidence associated with a high level of recognition accuracy ('remember' items), and weaker, but still above baseline, for words that will be recalled as weaker memories ('familiar' items). Thus, the parametric ESM analysis included both response types ('remember', 'familiar') in the model and weighted them differently.

For each participant we calculated the corrected recognition accuracy score separately for targets endorsed as 'familiar' or 'remembered' at retrieval. The values of the parametric ESMs for an individual participant were calculated as follows: Reward Hit Rate $_{(Remembered)}$ − False Alarm Rate$_{(Remembered)}$, Reward Hit Rate $_{(Familiar)}$ − False Alarm Rate$_{(Familiar)}$, Punishment Hit Rate $_{(Remembered)}$ − False Alarm Rate$_{(Remembered)}$, Punishment Hit Rate $_{(Familiar)}$ − False Alarm Rate$_{(Familiar)}$, Neutral Hit Rate $_{(Remembered)}$ − False Alarm Rate$_{(Remembered)}$, Neutral Hit Rate $_{(Familiar)}$ − False Alarm Rate$_{(Familiar)}$. The values of parametric regressors were mean centered across the whole group in order to orthogonalize these values (Poldrack et al., 2011). The parametric ESM was then assigned to all trials for that participant that elicited a particular memory outcome. A similar parametric model was previously used to study motivational memory encoding (Murty et al., 2012). In the previous study participants were explicitly rating memory strength ('very sure', 'pretty sure', 'just guessing') whereas the present study required that participants rate high-confidence memories depending on whether they were recalled with or without episodic detail ('remember' or 'familiar' respectively). Parametric analyses have previously been employed to examine encoding success activations in other human functional imaging studies of memory (Daselaar et al., 2006; Kensinger et al., 2011; Murty et al., 2012; Ritchey et al., 2010; Shigemune et al., 2014; Tsukiura and Cabeza, 2011).

Group-level statistical analyses were performed using a multiple regression model to investigate the difference in encoding modulation by condition between Older Adults and Younger Adults. To examine age-related changes in the neural correlates of motivational memory, estimates for parametric regressors were generated for each participant and then entered into a group-level multiple regression analysis with factors including contrasts of interest (cue/target Reward ESM > Neutral ESM, cue/target Punishment ESM > Neutral ESM) and group (Younger Adults, Older Adults).

ROI analyses

To examine whether activation in reward/punishment and memory-related regions was affected by successful motivated encoding, we performed analyses on anatomically defined *a priori* regions-of-interest (ROIs). Individual participants' anatomy was checked for matching to the template by a trained neurologist. Bilateral hippocampus and nucleus accumbens ROIs were generated by FreeSurfer segmentation of the Montreal Neurological Institute/International Consortium for Brain Mapping (MNI/ICBM) 152 template. A substantia nigra/ventral tegmentum area (SN/VTA) ROI was generated by manual segmentation of the MNI/ICBM 152 template by a trained, expert rater (SN/VTA: lateral boundaries, two parallel anterior-posterior lines intersecting the center of the superior colliculus and the peak curvature of the interpunduncular fossae; posterior boundary, a line intersecting the center of both red nuclei; rostral boundary, delimited by the diencephalic-mesencephalic junction; caudal boundary, defined by the caudal edge of the red nucleus) (as per Murty et al., 2014).

FMRI analysis of the MID task examined activation in the anatomically defined ROIs of SN/VTA and rostral striatum. The rostral striatal ROI was chosen because this region is critical in reward learning (Haber et al., 2006; Seymour et al., 2007) and prior fMRI aging research has shown that dorsomedial caudate is recruited in older adults performing the MID task (Samanez-Larkin et al., 2007). The rostral striatal ROI included nucleus accumbens, rostral caudate and rostral putamen generated by FreeSurfer segmentation of the MNI/ICBM 152 template and included voxels rostral/anterior to a coronal plane at the anterior commissure (Haber et al., 2006).

To characterize the neural correlate of parametric ESM under anticipation of monetary rewards or punishments, we first examined within group BOLD signal across voxels in the anatomically defined *a priori* ROIs in Younger Adults and Older Adults separately. Activation clusters identified within ROIs were small volume cluster-corrected for multiple comparisons with the FSL tool, 'cluster' (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Cluster) by applying an uncorrected voxelwise height threshold $z > 2.33$ (equivalent to $p < .01$, calculated using the fslmaths command '*ptoz*') together with a cluster-corrected threshold of $p < .05$ (Worsley et al., 1996). The analysis used a single pre-threshold mask that included all ROIs. Activation peaks reported are a subset of the local maxima generated for each contrast by 'cluster'. Anatomical labels were determined using the Yale BioImage Suite Package and associated brain atlases (Lacadie et al., 2008).

In order to compare our results to those of Cohen et al. (2016), we performed an analysis that examined the main effect of motivation irrespective of memory performance (Section 3.2.4.). For this analysis, we created a separate GLM that did not contain the parametric ESM regressors. We employed a functional ROI of the reward network that was defined by performance on the MID task, gathered within the same participants who performed the MIE task. The functionally defined ROI included active voxels in all participants (Younger Adults and Older Adults) in the whole-brain contrast of reward greater than neutral anticipatory cue intervals in the MID task (Supplementary Fig. 1). As in other fMRI MID studies, this contrast yielded activation in a large contiguous ROI that included the reward network and visual association cortex (Adcock et al., 2006; Murty et al., 2017; Spaniol et al., 2015). We directly contrasted activation within the functional ROI during motivational (reward and punishment) trials compared to neutral trials during cue and target intervals irrespective of memory outcomes. We also used this functional ROI of the reward network to assess behavioral and neural individual differences in motivation-related memory (detailed below).

Results

Behavioral results

MID task

Total earnings on the MID task were not significantly different between Younger Adults (mean $27.30, SE 1.80) and Older Adults (mean $26.60, SE 1.10) ($t_{(38)} = 0.34$, $p = .74$). Averaging across conditions, there was no difference in mean hit rate between Younger Adults (mean 0.64, SE 0.01) and Older Adults (0.65, SE 0.01) ($t_{(38)} = 0.59$, $p = .56$), suggesting that the algorithm for adaptive adjustment of the target response window was successful. A 2 × 3 repeated measures ANOVA to examine the effect of group (Younger Adults, Older Adults) and condition (reward, punishment, neutral) on hit rate showed a significant effect of condition ($F_{(1,38)} = 5.07$, $p = .009$, $d = 0.51$). *Post hoc* pairwise comparisons across all participants revealed increased hit rates for reward versus neutral trials (mean hit rate ± standard error: reward 65% ± 1%; neutral 62% ± 1%, $t_{(39)} = 2.48$, $p = .018$, $d = 0.56$) and punishment versus neutral trials (punishment 67% ± 2%, $t_{(39)} = 2.78$, $p = .008$, $d = 0.62$). Overall, hit rates did not differ between Younger Adults and Older Adults, suggested by a lack of group effect ($F_{(1,38)} = 0.28$, $p = .6$). There was also no interaction between age group and condition ($F_{(1,38)} = 1.34$, $p = .28$).

Participants responded more slowly on neutral (neutral mean RT in msec ± standard error: Younger Adults 253 ± 6 ms; Older Adults 277 ± 10 ms) than punishment trials (punishment mean RT ± standard error: Younger Adults 239 ± 4 ms; Older Adults 271 ± 12 ms) and more slowly on punishment than reward trials (reward mean RT ± standard error, Younger Adults 229 ± 5 ms; Older Adults 257 ± 10 ms) as revealed by a significant effect of condition ($F_{(1,38)} = 18.48$, $p < .0001$, $d = 0.97$); *post hoc* pairwise comparison punishment versus neutral: Younger Adults $t_{(20)} = 2.82$, $p = .007$, Older Adults $t_{(18)} = 6.3$, $p < .0001$; reward versus

punishment: Younger Adults $t_{(20)} = 6.3$, $p < .0001$, Older Adults $t_{(18)} = 4.29$, $p = .0002$). Although Older Adults responded more slowly overall as shown by a significant effect of group ($F_{(1,38)} = 6.77$, $p = .013$, $d = 0.59$), there was no interaction between condition (reward, punishment, neutral) and age group ($F_{(1,38)} = 0.66$, $p = .52$).

MIE arrow distractor task

Older Adults (mean 465 ms, standard error 16 ms) responded more slowly than Younger Adults (mean 395 ms, SE 8 ms) to the arrow distractor task as indicated by the significant effect of group ($F_{(1,38)} = 15.35$, $p = .0004$, $d = 1.27$) (Table 1). Importantly, there were neither main effects of memory outcome (hits versus misses) ($F_{(1,38)} = 0.38$, $p = .54$) or trial type ($F_{(1,38)} = 1.9$, $p = .15$) on RT, nor an interaction between memory outcome and group ($F_{(1,38)} = 0.32$, $p = .58$) or between trial type and group ($F_{(1,38)} = 1.2$, $p = .3$). Critically, there were no differences across conditions or interactions with age. Inclusion of an individual's mean reaction time as a nuisance covariate in group-level fMRI results did not alter the significance of the main findings. Congruent with these findings, none of the participants reported maintaining a cognitive strategy for preferentially remembering punishment or reward words.

MIE recognition test

The overall hit rate of studied target words was significantly greater than the false alarm rate irrespective of the motivational condition in Younger Adults (mean 'remember' hit rate ± standard error: reward 44% ± 5%, $t_{(20)} = 7.89$, $p < .0001$, $d = 3.53$; punishment 41% ± 5%, $t_{(20)} = 7.63$, $p < .0001$, $d = 3.41$; neutral 23% ± 4%, $t_{(20)} = 5.18$, $p < .0001$, $d = 2.32$, 'remember' false alarm rate 3% ± 1%; mean 'familiar' hit rate ± standard error: reward 31% ± 4%, $t_{(20)} = 2.44$, $p = .02$, $d = 1.09$; punishment 32% ± 3%, $t_{(20)} = 2.8$, $p = .01$, $d = 1.25$; neutral 31% ± 3%, $t_{(20)} = 2.86$, $p = .01$, $d = 1.28$, 'familiar' false alarm rate 24% ± 5%) and Older Adults (mean 'remember' hit rate ± standard error: reward 17% ± 4%, $t_{(18)} = 3.8$, $p = .001$, $d = 1.79$; punishment 16% ± 4%, $t_{(18)} = 3.34$, $p = .004$, $d = 1.57$; neutral 15% ± 4%, $t_{(18)} = 3.26$, $p = .004$, $d = 1.54$, 'remember' false alarm rate 6% ± 2%; mean 'familiar' hit rate ± standard error: reward 39% ± 6%, $t_{(18)} = 3.03$, $p = .007$, $d = 1.43$; punishment 40% ± 6%, $t_{(18)} = 3.68$, $p = .002$, $d = 1.73$; neutral 39% ± 6%, $t_{(18)} = 3.44$, $p = .003$, $d = 1.62$, 'familiar' false alarm rate 31% ± 5%). There was no significant between-group difference in the 'familiar' false alarm rate ($t_{(38)} = 0.97$, $p = .34$) and there was a trend difference in 'remember' false alarm rate ($t_{(38)} = 1.69$, $p = .1$).

To test the influence of reward and punishment anticipation on memory within and across groups, corrected recognition accuracy (defined as hit rate minus false alarm rate) was calculated separately for response types ('remember' and 'familiar') and calculated separately for reward, punishment, and neutral trials. For 'remember' responses, Older Adults (mean 10%, SE 2%) had lower recognition accuracy than Younger Adults (mean 33%, SE 3%), demonstrated by a significant main effect of group ($F_{(1,38)} = 21.7$, $p < .0001$, $d = 1.51$). 'Remember' recognition accuracy was higher for reward and punishment trials than neutral trials, as shown by a significant main effect of condition ($F_{(2,76)} = 14.3$, $p < .0001$, $d = 1.23$). Critically, punishment and reward motivational cues enhanced 'remember' recognition accuracy in the Younger Adults but not the Older Adults, revealed by a significant interaction between group and condition (reward, punishment, neutral) ($F_{(2,76)} = 9.4$, $p = .002$, $d = 0.99$) (Fig. 2).

Table 1
Mean reaction time by memory outcome (hits, misses) and trial type (neutral, reward, punishment) during the arrow distractor task (mean ± SE).

Trial Type	Younger Adults	Older Adults
Hits	395 ± 8 ms	465 ± 16 ms
Misses	395 ± 8 ms	464 ± 16 ms
Neutral	394 ± 8 ms	464 ± 16 ms
Reward	395 ± 8 ms	463 ± 16 ms
Punishment	395 ± 8 ms	468 ± 17 ms

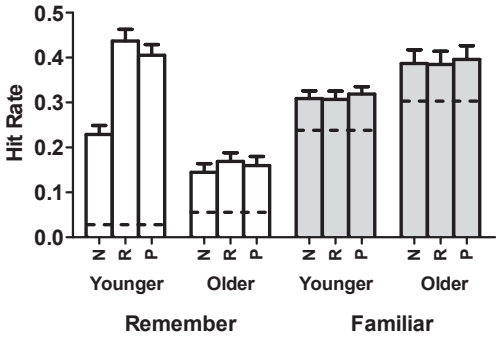

Fig. 2. Monetary reward and punishment improved memory in Younger Adults, but not Older Adults, for words that were correctly endorsed as 'remember', but not 'familiar', at retrieval. Hit rates are shown parsed by condition (N: neutral, R: reward, P: punishment), response type ('remember', 'familiar') and age group. The dashed line indicates the false alarm rate. Error bars represent the standard error of the mean.

Post hoc 2 × 2 ANOVAs with a Bonferroni correction applied showed enhanced 'remember' recognition accuracy for punishment versus neutral trials ($F_{(1,38)} = 9.2$, $p = .004$, $d = 0.98$) and reward versus neutral trials ($F_{(1,38)} = 11.0$, $p = .002$, $d = 1.07$) among Younger Adults compared to Older Adults.

In contrast, there was no significant difference in 'familiar' recognition accuracy between Younger Adults and Older Adults as shown by an absence of group effect ($F_{(1,38)} = 0.1$, $p = .7$). There was no main effect of condition (reward, punishment, neutral) on 'familiar' recognition accuracy ($F_{(2,76)} = 0.5$, $p = .61$) and no interaction between age group and condition ($F_{(1,38)} = 0.001$, $p = 1.0$) (Fig. 2).

FMRI results

Monetary incentive delay task

Younger Adults showed enhanced activation in rostral striatum and midbrain in response to reward compared to neutral cues and Older Adults showed greater activation in rostral striatum for reward compared to neutral cues (Fig. 3A and B respectively) ($p < .05_{corrected}$). Younger Adults showed greater activation in rostral striatum in response to

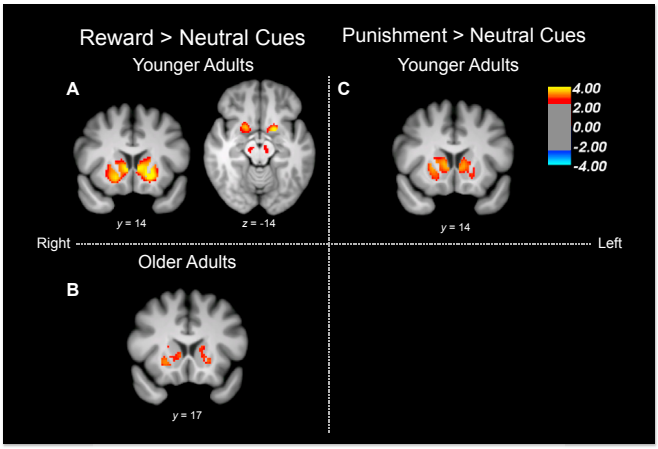

Fig. 3. Activations during the monetary incentive delay task. Activation of substantia nigra/ventral tegmental area and rostral striatum in Younger Adults (A) and rostral striatum in Older Adults (B) during reward greater than neutral cue intervals. Younger Adults showed activation in rostral striatum during punishment greater than neutral cues (C) whereas Older Adults did not. There were no significant between group differences. Voxelwise analyses were masked with anatomical ROIs. Activations are overlaid on mean structural image of all participants and corrected for multiple comparisons.

punishment compared to neutral cues (Fig. 3C) ($p < .05_{corrected}$). Neither contrast showed significant group differences, congruent with the lack of group interaction in MID behavioral performance. Overall, Older Adults had weaker responses, but still exhibited a significant response to at least reward. Direct comparison of reward versus punishment conditions revealed greater activation in rostral striatum in Younger Adults in the reward cue compared to the punishment cue condition ($p < .05_{corrected}$), and there were no group differences.

Incentivized encoding during the target interval

To test BOLD effects within memory and reward/punishment-related anatomical ROIs for the parametric ESM during the target interval, analyses were initially performed in Younger Adults and Older Adults separately. In Younger Adults, parametric ESM in reward greater than neutral trials (tested contrast: parametric ESM in reward trials > neutral trials at target, $p < .05_{corrected}$) and punishment greater than neutral trials (tested contrast: parametric ESM in punishment trials > neutral trials at target, $p < .05_{corrected}$) were associated with activation of hippocampus and SN/VTA region, effects which survived small volume correction for multiple comparisons. An identical analysis in Older Adults did not show activation in the *a priori* ROIs for the contrasts of interest (parametric ESM in punishment trials > neutral trials at target; parametric ESM in reward trials > neutral trials at target, $p < .05_{corrected}$).

Analyses examining group differences (Younger Adults > Older Adults) in the two contrasts of interest showed significantly greater recruitment of the SN/VTA region and hippocampus in Younger Adults compared to Older Adults for the reward greater than neutral and punishment greater than neutral parametric ESM for the target word interval ($p < .05_{corrected}$) (Fig. 4A and B). Younger Adults showed enhanced activation in the nucleus accumbens compared to Older Adults for reward greater than neutral and punishment greater than neutral trials at target, however, the nucleus accumbens activation did not survive correction for multiple comparisons. The reverse analysis (Older Adults > Younger Adults) did not reveal brain differences in the *a priori* ROIs. To characterize activation outside of the *a priori* ROIs and allow comparison to prior fMRI studies, we performed exploratory whole-brain analyses of parametric encoding success modulation at target (Supplementary Tables 1 and 2). A caveat of these analyses is that true whole-brain coverage was not achieved due to incomplete coverage of the superior parietal lobes.

Given the larger age variability of the Older Adults group, we performed a within-group linear regression analysis in *a priori* ROIs within the motivational network (SN/VTA and nucleus accumbens) to identify whether brain activation in these regions was inversely related to age with the parametric ESM of motivational versus neutral trials for the target interval. We hypothesized that the effect of age on motivational network activation would be smaller within the Older Adults group than between Older Adults and Younger Adults. In order to increase our ability to detect an effect within the Older Adults group if one existed, we confined this analysis to a pre-threshold mask that consisted only of the SN/VTA and nucleus accumbens (and did not include the hippocampus). Parametric ESM of reward greater than neutral trials revealed an inverse relationship with age in SN/VTA ($p < .05_{corrected}$). Parametric ESM of punishment greater than neutral trials did not show significant activation clusters after small volume correction ($p < .05_{corrected}$). Similar to the main parametric ESM analysis, this and the following analysis also weighted trials differently based on the relative encoding accuracy of 'remember' and 'familiar' responses.

Incentivized encoding during the cue interval

For the cue period, within-group activation was identified in the SN/VTA region and hippocampus in Older Adults and Younger Adults (tested contrast: parametric ESM in punishment trials > neutral trials at cue, $p < .05_{corrected}$; Fig. 5). There were no significant within-group activations during reward greater than neutral trials or between-group differences for either reward greater than neutral or punishment greater than neutral trials. Exploratory whole-brain analyses of parametric ESM for the cue interval showed significant within-group activation in visual association cortex in Older Adults and between-group enhanced activation in visual association cortex in Older Adults greater than Younger Adults for the punishment greater than the neutral condition ($p < .05_{corrected}$.) (Supplementary Table 3). There were no significant whole-brain within- or between-group differences in reward greater than neutral trials at cue.

Main effect of motivation during cue and target periods

In order to compare our results to those of Cohen et al. (2016), we also investigated the main effect of motivation in the MIE task by confining

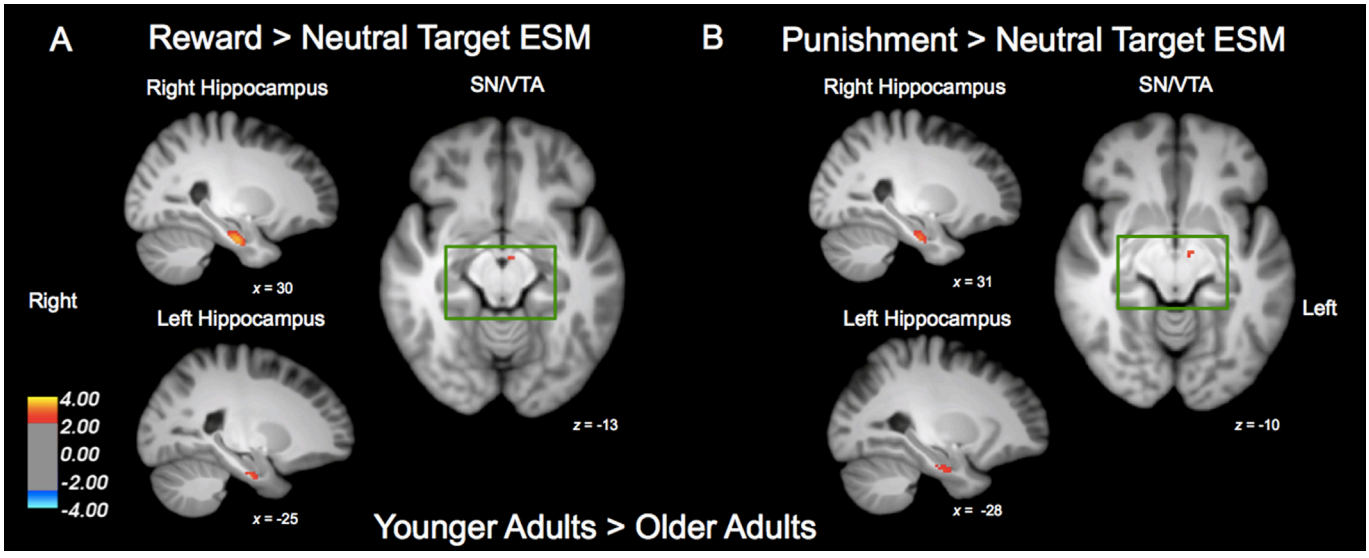

Fig. 4. Group activation differences in the vicinity of substantia nigra/ventral tegmental area (SN/VTA) and hippocampus for parametric encoding success modulation (ESM) during reward greater than neutral trials (A) and punishment greater than neutral trials (B) during target word encoding. Younger Adults showed greater motivational (SN/VTA) and memory-related (hippocampus) activations compared to Older Adults during successful incentivized learning. Voxelwise analyses were masked with anatomical ROIs. Activations are overlaid on the mean structural image of all participants and corrected for multiple comparisons.

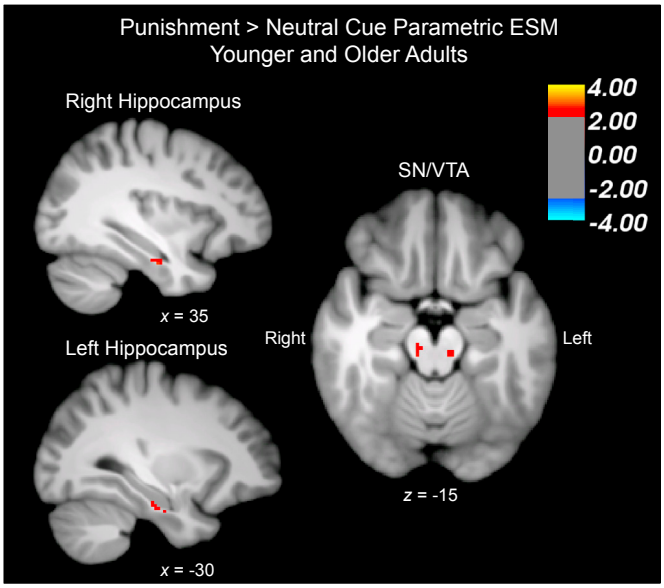

Fig. 5. Activations in the vicinity of substantia nigra/ventral tegmental area (SN/VTA) and hippocampus during anticipatory cue presentation for the parametric ESM analysis in punishment greater than neutral trials in Younger Adults and Older Adults. There were no group differences identified during presentation of the cue. Voxelwise analyses were masked with anatomical ROIs. Activations are overlaid on the mean structural image of all participants and corrected for multiple comparisons.

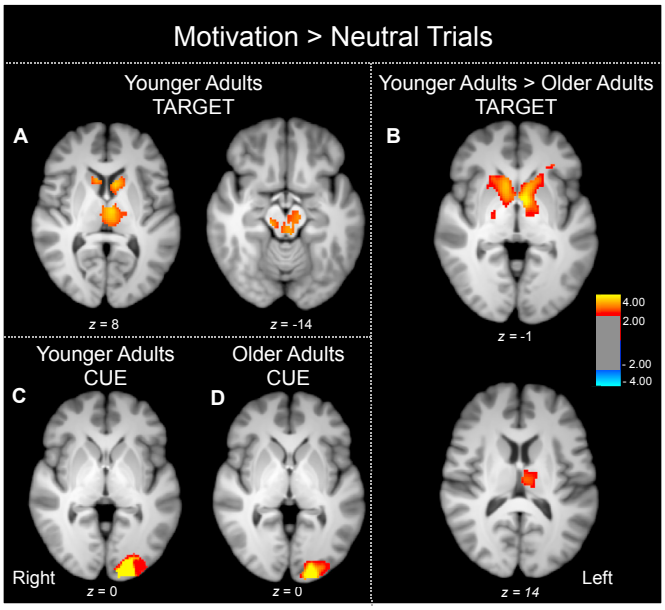

Fig. 6. Main effect of motivation within and between groups during target and cue periods. During the target period of the monetary incentive encoding task, Younger Adults showed activation in thalamus, midbrain and bilateral caudate (A) and also showed greater activation in thalamus and bilateral caudate compared to Older Adults (B). Older Adults did not show significant activation during target periods. During cue intervals, both Younger (C) and Older Adults (D) showed activation of left visual association area and there were no between group differences. Voxelwise analyses were masked with functional ROIs. Clusters were corrected for multiple comparisons and superimposed on mean anatomical image for all participants.

our analyses to voxels within the reward network defined by an *a priori* functional ROI. Cohen et al. (2016) used a large functional ROI of the reward network that was defined by a meta-analysis of published literature using Neurosynth.org that included midbrain, ventral striatal and PFC regions. We also used a functional ROI of the reward network defined by activation across the whole brain during reward greater than neutral anticipatory cue intervals in all participants (Younger Adults and Older Adults) on the MID task, gathered within the same participants who performed the MIE task (Supplementary Fig. 1). The MID functional ROI included occipital cortex in addition to midbrain, ventral striatal, thalamic and PFC regions. As in other fMRI MID studies, this contrast produced activation in a large contiguous ROI that included the reward network and visual association cortex (Adcock et al., 2006; Spaniol et al., 2015) consistent with previous research showing visual cortex activation in motivated attention (Bradley et al., 2003; Buschschulte et al., 2014; Murty et al., 2017; Schupp et al., 2003). We examined MIE activation clusters within the functional ROI during motivational (reward and punishment combined) cue and target periods compared to neutral trials within and between groups irrespective of memory outcome (as in Cohen et al., 2016).

During the MIE target word period in Younger Adults there was significant activation in left thalamus, midbrain, and bilateral caudate in the functional ROI (tested contrast: motivation trials > neutral trials, $p < .05_{corrected}$) (Fig. 6A) and Younger Adults had greater activation than Older Adults (peak difference in right caudate, $p < .05_{corrected}$) (Fig. 6B). During the target period, Older Adults did not show significant activation in the reward network. During the cue period, there were significant within-group activations in the functional ROI in Younger Adults (Fig. 6C) and Older Adults (Fig. 6D) with an activation peak in left visual association area, Brodmann area (BA) 18 ($p < .05_{corrected}$). There were no significant between group differences during the cue period.

Next, we examined individual differences in motivation-related brain activation and behavioral gain in memory performance for items endorsed as 'remember' with motivation during the cue and target intervals. We focused on 'remember' responses as this response type showed an influence of motivation on memory. During the cue interval, the activation cluster across all participants (Younger Adults and Older Adults) from the main effect of value analysis was used to select the voxels in which activity was averaged to determine parameter estimates. Because Older Adults did not show a main effect of value in the functional ROI during target intervals, the Younger Adults activation cluster was used to define voxels across from which parameter estimates were generated for Younger and Older Adults. A linear regression analysis was performed between parameter estimates at cue or target intervals and behavioral motivated memory gains ('remember' hit rate minus false alarm rate for reward and punishment compared to neutral trials). Younger Adults showed a significant correlation between motivated memory gains and parameter estimates for the effect of motivation greater than neutral trials in the functional ROI activation cluster during target ($r = 0.65$, $p = .001$; Fig. 7) and cue periods ($r = 0.69$, $p = .0006$). The target period results remained significant after removal of a single Younger Adult outlier ($r = 0.54$, $p = .01$) but the cue period results did not remain significant after the outlier removal ($r = 0.31$, $p = .18$). Older Adults showed a trend correlation between motivated memory gain and parameter estimates during the target period ($r = 0.44$, $p = .06$; Fig. 7) that was largely driven by a single outlier (after outlier removal: $r = 0.17$, $p = .51$) and did not show a correlation between motivated memory and parameter estimates during the cue period ($r = 0.05$, $p = .83$).

Discussion

This study compared between younger and older adults the influences of motivation (reward and punishment) on long-term intentional memory formation for words. In younger adults, both the motivation to obtain reward and to avoid punishment enhanced learning, specifically for recollected memories. Older adults exhibited diminished overall memory and no influence of reward or punishment on learning. Brain activation differences during the target period mirrored the mnemonic differences between groups. Younger adults exhibited modulation of motivation-

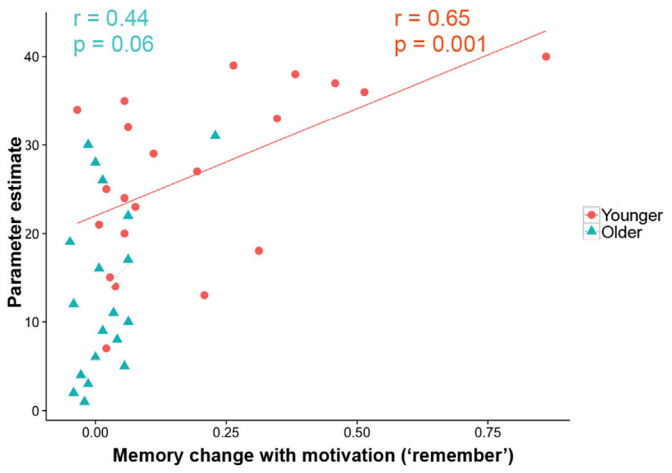

Fig. 7. In Younger Adults (red circles), there was a correlation between brain activation during target intervals for motivational greater than neutral trials in the MID functional ROI and motivated memory ('remember' hit rate minus false alarm rate for reward and punishment compared to neutral trials). In Older Adults (blue triangles), there was a trend in correlation between brain activation and change in memory performance with motivation.

related activations associated with encoding in motivational (SN/VTA region) and memory (hippocampus) circuitry to a greater extent than older adults. Indeed, older adults did not exhibit any significant difference between motivational and neutral conditions in either memory performance or brain activation in response to target words. In contrast, while viewing the anticipatory motivational cue in the MIE task, older and younger adults showed activation of motivational and memory-related brain regions. Relatedly, behavioral performance and brain activation on an MID task showed relatively preserved motivational sensitivity in older adults compared to younger adults. Overall, our results suggest a putative dissociation in healthy aging between tasks requiring intentional motivated learning with delayed feedback compared to tasks requiring incidental processing of motivational cues with low effort and immediate feedback or payoff.

Dissociable effects of motivation on behavioral measures of recognition

Although the current study was not designed to distinguish between dual and single-process models of recognition memory, in younger adults we found that monetary reward and punishment enhanced recognition memory via improved recollection (with no influence of motivation on familiarity). This finding is congruent with the results of behavioral studies that have shown dissociations in how reward (points and money) affects measures of recognition memory (Cohen et al., 2017; Hennessee et al., 2017; Wittmann et al., 2011). One behavioral study found that point-based reward enhanced word recollection, but not familiarity, after a short (five-minute) delay (Hennessee et al., 2017). The authors proposed that value might increase memory strength in a non-linear way by disproportionately enhancing recognition at high levels of memory strength (see also Mickes et al., 2007). Another behavioral study examined the effect of study context and strategy in how value (reward and punishment) affects measures of recognition memory for words (Cohen et al., 2017). They found that value strengthened recollection and familiarity when retrieval tests were interspersed with learning, and enhanced recollection, but not familiarity, when memory was tested at the end, as in the present study. Similarly, an fMRI study has shown that recollection, but not familiarity, was enhanced when items were encoded in high reward contexts and this behavioral effect was associated with post-learning changes in midbrain-hippocampal functional connectivity (Gruber et al., 2016). A behavioral study has shown that younger adults, but not older adults, had enhanced recognition confidence with reward when there was a large, but not small, effect of reward on recognition (Spaniol et al., 2014). Overall, therefore, our finding that reward enhanced recollection but not familiarity in younger adults is largely consistent with prior studies.

Overlapping brain networks for punishment and reward-related learning in young adults

Anticipation of monetary reward and punishment enhanced memory formation in younger adults and was associated with activation in midbrain and hippocampal regions. Our findings replicate human behavioral and fMRI studies that have shown monetary reward and punishment anticipation enhance episodic memory formation via a midbrain-hippocampal network (Adcock et al., 2006; Callan and Schweighofer, 2008; Kahn and Shohamy, 2013; Shigemune et al., 2014; Shohamy and Adcock, 2010; Wittmann et al., 2005, 2013; Wolosin et al., 2012). The overlapping activations that we identified for reward and punishment motivation may reflect the fact that punishment was avoidable if a word was remembered rather than forgotten. Motivational opponent process theory (Solomon and Corbit, 1978) posits that the termination of a positively or negatively valenced process triggers the onset of an affective response of the opposite valence. Relatedly, functional neuroimaging studies have shown that receipt of reward and successful avoidance of punishment recruit overlapping brain regions (Kim et al., 2006). Thus, in the present study, the opportunity to avoid monetary loss by remembering a word may have been interpreted as equivalent to a reward.

The observed overlap in brain networks associated with reward and punishment incentivized encoding in younger adults could alternatively reflect reward- and punishment-related regional specificity in the vicinity of SN/VTA. There are spatially proximal, yet separate, populations of neurons in SN/VTA that code rewarding or punishing alerting events (Brischoux et al., 2009; Bromberg-Martin et al., 2010). The functional diversity of dopamine neurons within SN/VTA supports the theory that neighboring neuronal populations code 'motivational value' (excited by reward and inhibited by aversive stimuli) or 'motivational salience' (excited by both reward and punishment processing) (Bromberg-Martin et al., 2010; Matsumoto and Hikosaka, 2009). FMRI studies have also shown that SN/VTA is recruited during anticipation of reward and punishment, further supporting a role of this region in bivalent motivational salience (Carter et al., 2009; Jensen et al., 2003). Hence, the overlapping activation in midbrain we observed during reward- and punishment-based encoding in younger adults may reflect excitation of proximal, yet dissociable, neuronal populations. However, an analysis of SN/VTA neuronal subpopulations is beyond the spatial resolution typical in fMRI.

Age differences in memory encoding

Consistent with the literature on aging and episodic memory (Luo and Craik, 2008; Mather, 2010), older adults exhibited worse declarative memory performance than younger adults, irrespective of motivational condition. Memory was above chance across motivational conditions for both younger and older adults and false alarm rates were not significantly higher in older adults compared to younger adults. To minimize post-encoding word rehearsal, our study design included an arrow distractor task. Analysis of the arrow distractor task RT data showed no evidence of mnemonic strategy depending on memory outcome, trial type, or age group. We found that recollection-based recognition accuracy was diminished in older compared to younger adults. In contrast, familiarity-based recognition accuracy and false alarm rates did not differ between groups. These findings are consistent with behavioral and fMRI studies that have shown reduced recollection and relative preservation of familiarity in healthy aging (Anderson et al., 2008; Daselaar et al., 2006; Koen and Yonelinas, 2014; Yonelinas, 2002).

Task context in age-related positive and negative reinforcement learning

The variability of results in reward and punishment learning in healthy aging emphasize the importance of task context. There are opposing findings from aging studies examining positive and negative feedback learning in probabilistic versus deterministic or active versus observational paradigms (Bellebaum et al., 2012; Frank and Kong, 2008; Simon et al., 2010a; van de Vijver et al., 2015). For example, older adults showed a bias towards learning from positive versus negative material in observational contexts (Bellebaum et al., 2012) and with deterministic versus probabilistic stimulus-reward associations (Samanez-Larkin et al., 2007; van de Vijver et al., 2015). In contrast, older adults have benefited more from negative than positive feedback during active learning (Eppinger et al., 2013; Frank and Kong, 2008) and with probabilistic reward contingencies (Hammerer et al., 2011). Differences in task context contributes to the mixed evidence from aging research supporting diminished responsiveness to reward in some studies or punishment in others (reviewed by Samanez-Larkin and Knutson, 2015).

Two behavioral studies have examined the influence of reward on declarative memory formation in older adults. One study investigated incidental memory of object pictures with reward and punishment anticipation and outcome in a MID task (Mather and Schoeke, 2011). Older and younger adults had similar overall incidental memory for the pictures, and similarly better memory for pictures associated with reward anticipation or outcome (relative to neutral and punishment conditions) (Mather and Schoeke, 2011). Perhaps reward has a different influence on declarative memory in older adults depending on whether encoding is intentional (as in the present study) or incidental (as in Mather and Schoeke, 2011). Another study, however, reported that older and younger adults had similar levels of reward influence on intentionally encoded long-term memory for pictures of scenes at 24 h, although neither older nor younger adults had an influence of reward on immediate recognition (Spaniol et al., 2014). Although the present and prior intentional encoding studies appear to be inconsistent with one another, the actual findings are somewhat similar. At the longer delay, the prior study (Spaniol et al., 2014) found that younger adults had greater overall memory (signal detection indices) and over twice the absolute memory gains of older adults on reward versus neutral trials, with a trend towards an age group by reward interaction (reported $p = .09$). In their study, the absolute difference in older adults' memory gain for reward versus neutral trials was similar to the absolute difference we found (3% versus 2% respectively). However, we observed greater absolute memory gains among younger adults during reward greater than neutral trials compared to the gains of younger adults in the Spaniol et al. (2014) study (20% versus 7% respectively). Thus, both studies point towards greater influences of reward on intentional memory formation in younger than older adults, with one study reporting more than a doubling of reward influence in younger adults (Spaniol et al., 2014) and our study reporting a ten-fold increase in younger adults. In addition, Spaniol et al. (2014) (Experiment 1) observed that younger adults were more confident in recognition of high-reward compared to low-reward targets whereas older adults did not show a difference in confidence as a function of reward. Although the effect of motivation on difference retrieval processes was not the focus of the current study and we did not control for memory strength, we observed that anticipation of monetary reward and punishment enhanced recollection, and not familiarity, in younger adults. Thus, our behavioral findings largely parallel those from Spaniol et al. (2014).

The stronger influence of reward on memory formation in younger adults in the present study may reflect the type of mnemonic stimuli. Studies examining MIE in younger adults have shown modest motivational benefits for pictures (e.g., 10% memory gain for reward versus neutral trials in Adcock et al., 2006 vs. 20% gain for words in the present study). Independent of motivation manipulations, there are different influences of aging on memory for complex scenes and words. Older adults often exhibit memory equivalent to younger adults for pictures despite consistent reduction in memory for words (Ally et al., 2008; Grady et al., 1999; Park et al., 1986; Smith et al., 1990). Only studies with larger groups that involve both pictures and words can resolve what stimulus factors interact with motivation and aging.

Comparing value-directed remembering to monetary incentive encoding

An encoding paradigm that is related to the MIE task has shown an impact of value on memory selectivity in older adults that was comparable to that of younger participants (Castel et al., 2002, 2007; Cohen et al., 2016). In the 'value-directed remembering' (VDR) paradigm, participants undergo multiple study-test cycles of short lists of words. Words are paired with point values, rather than monetary incentives, and participants receive feedback on their score after each test cycle. Younger and older adults preferentially encoded high-value compared to low-value words across multiple versions of this task. When longer word lists were used or retrieval was delayed (e.g., Experiment 4 Castel et al., 2002), older adults showed a relative reduction in memory selectivity for high-value compared to low-value words. Recognition-based retrieval (e.g., Experiment 1 Castel et al., 2007) or encoding that was interleaved with a vowel-consonant task (e.g., Cohen et al., 2016) produced a value by age interaction such that the influence of value on memory was weaker in older adults compared to younger adults.

An fMRI study examined the neural mechanisms underlying VDR in younger and older adults (Cohen et al., 2016). Both age groups showed an association between the degree that value affected immediate free recall performance and value-related changes in activation of regions associated with semantic processing during word encoding. In younger adults, parameter estimates extracted from a Neurosynth-derived reward network ROI were significantly higher during cue and target encoding intervals of high-value relative to low-value words. During target, but not cue, intervals there was also a correlation between value-related activity in the reward network and memory selectivity for high-value compared to low-value words in younger adults. In contrast, older adults did not modulate the reward network in response to value despite a behavioral impact of value in this group. Thus, although the VDR and MIE paradigms relate reward and memory in quite different ways, older adults appear to show reduced motivational influences on reward-related brain regions across the two paradigms.

In the present study, we examined the effect of motivation in an analysis based on Cohen et al. (2016) and found that motivational cues increased activation in the reward network during the target period for younger, but not older, adults. In younger adults, we found a correlation between brain activation in a functional ROI of the reward network during target intervals and memory improvement with motivation. This association was not present in older adults. Relatedly, Cohen et al. (2016) found that older adults did not show effects of value in reward-sensitive brain regions, while also demonstrating that older adults were better able to compensate for reduced sensitivity of the reward system with contexts that encourage selective strategy use. Congruent with the results of Cohen et al. (2016), we found activation of the left inferior prefrontal cortex, a semantic-processing region, in younger and older adults during punishment greater than neutral trials at target for the whole-brain parametric ESM analysis.

VDR and MIE paradigms differ in important ways that may account for different aging effects on behavior between tasks. One difference is the timing of retrieval: VDR involves immediate free recall whereas the present MIE task involved 24-hour delayed recognition. Behavioral MIE studies have shown time-dependent influence of monetary rewards on memory where the impact of value on memory performance occurs at longer, but not shorter, delays (Murayama and Kuhbandner, 2011; Spaniol et al., 2014; Steiger and Bunzeck, 2017). This is consistent with the putatively dopamine-driven hippocampal consolidation model of reward learning (Lisman and Grace, 2005). VDR and MIE paradigms also differ in their delivery of feedback. In VDR, there is immediate feedback after each study-test block that allows participants to optimize their

encoding strategy. This is reflected by a gradual increase in memory selectivity across blocks consistent with strategic and selective control of encoding and retrieval operations. MIE, conversely, provides no feedback. Jenkins' tetrahedral model of memory experiments (Jenkins, 1979) captures the potential impact of these differences by emphasizing the sensitivity of memory to context, participant goals, cognitive strategy and the way performance is assessed (see Castel, 2008).

Temporal characteristics of motivation-related modulation of memory

Animal and human studies have shown that dopamine-dependent modulation of hippocampal memory formation occurs over a broad range of timescales before, during and after an event (Lisman et al., 2011; Shohamy and Adcock, 2010). FMRI reward learning experiments have shown recruitment of motivation-sensitive brain regions during anticipatory cue and target encoding intervals. In younger adults, we found that activation in motivation-sensitive and memory-related regions during target word periods and activation of these regions to a greater degree compared to older adults was correlated with motivation-related memory gains. Some fMRI studies have shown reward system activation during the period before a mnemonic event: Adcock et al. (2006) identified anticipatory activation of reward and memory networks during presentation of high-value cues, and activation of memory networks during mnemonic stimulus presentation. In contrast, other fMRI reward- and punishment-related learning studies have shown activation of nucleus accumbens and SN/VTA at the time of target word encoding (Cohen et al., 2016; Shigemune et al., 2014). A behavioral study reported episodic memory improvement in humans when the reward cue was presented after the mnemonic stimulus (Murayama and Kitagami, 2014). The variability in timing of reward-system engagement across these and animal studies suggests that there is a broad time window when hippocampal memory formation is influenced by dopamine (Shohamy and Adcock, 2010) beginning before an event is experienced (Adcock et al., 2006), during the experience itself (Cohen et al., 2016; Shigemune et al., 2014; Wittmann et al., 2005) and extending to the consolidation phase hours to days later (Lisman et al., 2011; Rossato et al., 2009; Singer and Frank, 2009).

FMRI studies of aging have shown differences between younger and older adults in both pre-stimulus and target processing. Memory studies have shown a temporal shift in brain activation from proactive engagement at cue in younger adults to reactive target-related activity in older adults (Bollinger et al., 2011; Cohen et al., 2016; Dew et al., 2012). This shift has been described as the "expectation deficit hypothesis of cognitive aging" (Bollinger et al., 2011) and an "early to late shift in aging" (Dew et al., 2012). In the VDR paradigm, Cohen et al. (2016) observed value-related increased activation during the cue interval in semantic and reward-sensitive regions in younger adults but not in older adults. In contrast, in our study older adults exhibited preserved activation in visual association cortex during the cue period for motivational compared to neutral trials but diminished activation in reward regions during the target period compared to younger adults. Motivation-related activation of visual cortex in younger and older adults may reflect heighted visual attention in both groups in response to reward or punishment cues. This finding is consistent with human neurophysiological and fMRI studies that have shown that motivationally relevant stimuli engaged attentional processes and facilitated perceptual encoding in extrastriate cortices (Bradley et al., 2003; Buschschulte et al., 2014; Murty et al., 2017; Schupp et al., 2003) and that top-down enhancement of attentional processes in visual association cortex was relatively preserved in human aging (Gazzaley et al., 2005). An fMRI study has shown experience-dependent enhancement of visual cortex, hippocampus and VTA connectivity for reward-motivated declarative memory, indicating that there may be interactions between brain systems that support mesolimbic dopamine activation, episodic memory and perception (Murty et al., 2017). Importantly for the present study, the activation in visual association cortex for older and younger adults suggests that both groups were more interested in the motivational cues than the neutral cues.

Age-related impacts on incidental versus intentional processing

We found relatively intact age-related behavioral performance and neural response in the MID task. Younger adults exhibited anticipatory activation for both reward and punishment trials in reward-related brain regions. The findings from older adults were somewhat equivocal. On the one hand, they exhibited reward-related anticipatory activation in reward regions, did not differ significantly from younger adults in either reward or punishment anticipatory activation, and exhibited parallel behavioral effects of motivation to the younger adults. On the other hand, anticipatory activations appeared weaker than those in younger adults, and were not above threshold in the punishment condition. During the MIE task, older adults showed activation in visual association cortex, motivation- and memory-related brain regions during the cue period. Thus, the behavioral differences in motivated learning on the MIE task cannot be ascribed to a disinterest in reward/punishment or a global dysfunction of the reward system. Instead other factors must account for the age-related differences in the MIE task. While the MIE task requires high effort, delayed payoff, and interaction between motivation and memory brain networks, the MID task entails incidental processing of motivation cues, immediate reward feedback, and does not require learning.

In the MID task, there was no significant age difference in neural response to motivational compared to neutral cues, congruent with previous fMRI MID studies in aging (Rademacher et al., 2014; Samanez-Larkin et al., 2014; Spaniol et al., 2015). Age differences are often minimized in learning-free motivational tasks (Samanez-Larkin et al., 2014; Spaniol et al., 2015) and are typically found when there is a need for acquisition of stimulus-reward associations (Chowdhury et al., 2013; Samaenz-Larkin et al., 2014). Similar to our findings, an fMRI study found intact age-related reward sensitivity in an MID task and reduced probabilistic reward learning and ventral striatal activation in the same group (Samanez-Larkin et al., 2014). Overall, our results point to an age-related dissociation between declining motivational influence on effortful, intentional learning and relative preservation of incidental motivational cue processing.

The potential importance of self-initiated versus instructed or environmentally supported influences on aging and verbal memory is suggested by contrasting the present findings with the study of the influence of depth-of-processing on memory. In the present study, we manipulated reward motivation, but participants were left to their own, self-initiated devices as to how to translate the motivation into enhanced memory formation. In the depth-of-processing manipulation, participants are instructed to process words on the basis of meaning (deep processing which leads to superior incidental memory) or a perceptual attribute (shallow processing which leads to inferior incidental memory) (Craik and Lockhart, 1972). Although older adults have overall reduced verbal memory, they have exhibited the same or even greater mnemonic benefits of deep encoding as have younger adults (Grady et al., 1999). Deep processing in older and younger adults was accompanied by equivalent activation in PFC and medial temporal regions, suggesting that older and younger adults engaged the same neural systems to enhance memory (Grady et al., 1999). Consistent with that finding, older adults have shown an influence of value on memory in the VDR paradigm where study context encourages selective strategy use. Taken together, these findings highlight the importance of both intentional versus incidental and self-initiated versus instructed encoding in widening or narrowing the influence of age on memory.

Limitations and future directions

Several limitations of the present study, such as the potential

influence of stimulus materials, have been noted above, but another limitation could be age differences in the motivational value of the monetary incentives. In addition, we did not gather data on the socio-economic status of participants, limiting our inferences about how younger and older groups may have differentially valued potential rewards. Consistent with the socioemotional selectivity theory positing that older adults place greater value on emotional wellbeing, one fMRI study found age differences in motivation by reward type: compared to younger adults, older adults showed relatively increased nucleus accumbens activation for social rewards and relatively diminished activation for monetary rewards (Rademacher et al., 2014).

Alternatively, older adults may have already been maximally engaged during the neutral condition of our task due to a high degree of interest, and did not benefit from additional external incentives. However, the increased activation of perceptual, reward and memory-related regions during motivational compared to neutral trials during the cue period argues against this interpretation. FMRI and behavioral studies support an undermining effect of extrinsic rewards on motivation if the level of interest and intrinsic motivation are already high (Deci et al., 1999; Murayama and Kuhbandner, 2011; Murayama et al., 2010). Future aging research could investigate whether individual characteristics such as personality traits (Cohen et al., 2005; Jimura et al., 2010; Simon et al., 2010b), motivational orientation (i.e., to internal desires versus external compensation) (Linke et al., 2010), and dopamine functioning (Cohen et al., 2005) might optimize reward sensitivity and valuation.

Although dopamine has been especially linked to reward, multiple neurotransmitter systems demonstrate age-related loss (Goldman-Rakic and Brown, 1981; Li and Rieckmann, 2014; Wenk et al., 1989; Wong et al., 1984). It will be important to seek direct evidence linking diminished motivational learning to changes in the dopaminergic system using neurochemical imaging or pharmacological manipulation. It is an open question whether dopamine administration would boost motivated learning in older adults as it does in probabilistic reward learning (Chowdhury et al., 2013) and episodic memory (Chowdhury et al., 2012; Morcom et al., 2010).

Conclusions

This study provides novel evidence for an age-related decrement in reward and punishment-motivated long-term declarative memory formation that was evident both in memory performance and in activation of the midbrain-hippocampal circuit that is thought to mediate the influence of reward on declarative memory. We found relatively preserved processing of motivational cues in a learning-free MID task and during the cue period for the MIE task. The association between aging and a reduced influence of motivation upon intentional memory formation was not only apparent between younger and older adults, but was apparent across the ages of the older adults. These findings highlight altered interaction between motivation and memory networks and the potential dissociation between incidental and intentional motivation processing in healthy aging. In addition, our results may be relevant to disorders that target midbrain dopaminergic systems including alpha synucleinopathies such as Parkinson's disease and dementia with Lewy bodies.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2017.12.053.

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