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The Effects of Age on Reward Magnitude Processing in the Monetary Incentive Delay Task

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Abstract

Previous studies have suggested age-related differences in reward-directed behavior and cerebral processes in support of the age effects. However, it remains unclear how age may influence the processing of reward magnitude. Here, with 54 volunteers (22 to 74 years of age) participating in the Monetary Incentive Delay Task (MIDT) with explicit cues ($1, ¢1, or nil) and timed response to win, we characterized brain activations during anticipation and feedback and the effects of age on these regional activations. Behaviorally, age was associated with less reaction time (RT) difference between dollar and cent trials, as a result of slower response to the dollar trials; i.e., age was positively correlated with RT dollar – RT cent, with RT nil as a covariate. Both age and the RT difference ($1 - ¢1) were correlated with diminished activation of the right caudate head, right anterior insula, supplementary motor area (SMA)/pre-SMA, visual cortex, parahippocampal gyrus, right superior/middle frontal gyri, and left primary motor cortex during anticipation of $1 vs. ¢1 reward. Further, these regional activities mediated the age effects on RT differences. In responses to outcomes, age was associated with decreases in regional activations to dollar vs. cent loss but only because of higher age-related responses to cent losses. Together, these findings suggest age-related differences in sensitivity to the magnitude of reward. With lower cerebral responses during anticipation to win large rewards and higher responses to outcomes of small loss, aging incurs a constricted sensitivity to the magnitude of reward.

Keywords

aging; reward; MIDT; fMRI; ventral striatum

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1. Introduction

Reward motivates and shapes behaviors (Balodis, et al., 2015; Knutson and Greer, 2008; Schultz, 2015). Much of our understanding of reward-related neural processes builds on animal studies (Everitt, et al., 2008; Haber and Knutson, 2010; Schultz, 2006; Schultz, 2015; Schultz, et al., 1997) and involves a network of brain regions centered on the ventral striatum (VS). The VS receives dopaminergic inputs from the ventral tegmental area (VTA) and projects to the medial prefrontal cortex (mPFC) via the globus pallidus. The mPFC sends glutamatergic inputs to the VS, forming a circuit to support motivated behaviors (Haber and Knutson, 2010; Knutson, et al., 2000; Lutz and Widmer, 2014; Samanez-Larkin and Knutson, 2015). Dysfunction of the reward circuit is implicated in many neuropsychiatric conditions, including age-related neurodegenerative illnesses (Knutson and Heinz, 2015; Oldham, et al., 2018; Whitton, et al., 2015). For instance, individuals with Parkinson's disease show deficits in reward feedback processing (Di Rosa, et al., 2015) and reward-related learning (Freedberg, et al., 2017). People with mild cognitive impairment and Alzheimer's disease are altered in delayed discounting (Thoma, et al., 2017) and impaired in assigning a reward value to self-related processing (Shany-Ur, et al., 2014). Thus, understanding the psychological and neural bases of age-related changes in reward processing is of translational significance.

Aging is associated with changes in multiple domains of cognitive and affective function. Older people exhibit a positivity bias in emotional experience and memory (Charles, et al., 2003; Joubert, et al., 2018) while showing less novelty seeking behavior (Sakaki, et al., 2018). In a delay discounting task older adults prefer more delayed choices, switch earlier from immediate to delayed reward, and show reduced VS activation to immediate reward (Eppinger, et al., 2012). In humans and non-human primates, aging is associated with deficits in reward-related learning (Eppinger, et al., 2011). On the other hand, older people appear to be more sensitive to negative outcomes and ready to adjust behavior on the basis of negative outcomes (Eppinger and Kray, 2011; Frank and Kong, 2008; Hammerer, et al., 2011; Simon, et al., 2010). Numerous imaging studies have described age-related changes in these reward-related processes, and those combining molecular imaging provide an opportunity to relate functional deficits to molecular changes (Berry, et al., 2018).

1.1 Outcome anticipation in the monetary incentive delay task and the effects of age

Investigators have employed functional magnetic resonance imaging (fMRI) to study the neural bases of reward processing with behavioral tasks that involve "secondary" rewards such as money or social approval (Izuma, et al., 2008; Lutz and Widmer, 2014; Rademacher, et al., 2014). In the monetary incentive delay task (MIDT) (Knutson, et al., 2000), participants are shown a bet (money at stake) and respond within a time window to win and/or avoid a loss. Reward processing can thus be distinguished for anticipation and feedback (Berridge and Robinson, 1998; Knutson, et al., 2001b; Knutson and Heinz, 2015; Rademacher, et al., 2010). Reward anticipation appears to consistently activate the VS (Diekhof, et al., 2012; Knutson and Greer, 2008; Knutson and Wimmer, 2007; Liu, et al., 2011; Lutz and Widmer, 2014; O'Doherty, et al., 2004; Oldham, et al., 2018) with activation increasing with reward magnitude (Knutson, et al., 2001b; Knutson, et al., 2000). A meta-

analysis of the MIDT and other tasks reports activations of bilateral VS, right caudate nucleus and thalamus during reward anticipation (Diekhof, et al., 2012). Another meta-analysis of the MIDT reports anticipation-related activations of the ventral and dorsal striatum, insula, amygdala, thalamus, and supplementary motor area (SMA) independent of valence (win or loss), suggesting a broader role of a cortical subcortical network in supporting anticipation of a salient outcome (Oldham, et al., 2018). In contrast, the ventrolateral prefrontal cortex appears to respond specifically to the anticipation of loss (Dugre, et al., 2018).

Aging is associated with altered striatocortical dopaminergic transmission (Berry, et al., 2018; Dreher, et al., 2008; Rinne, et al., 1990; Volkow, et al., 1998). Older as compared to younger adults show reduced VS activation to reward anticipation in variants of the MIDT (Dreher, et al., 2008; Samanez-Larkin, et al., 2007; Schott, et al., 2007; Vink, et al., 2015). They also show decreased medial caudate and anterior insula activation during loss anticipation (Carstensen, 2006; Samanez-Larkin, et al., 2007). This has been attributed to phase-of-life related reduction in negative affect, in keeping with socioemotional selectivity theory across the lifespan. Socially rewarding stimuli become potentially more salient with age (Carstensen, 1995; Carstensen and Turk-Charles, 1994; Kryla-Lighthall and Mather, 2009). In a modified MIDT offering monetary or social reward, both younger and older adults show VS, thalamic, and anterior cingulate response to anticipation of both incentives (Rademacher, et al., 2010). However, anticipation of social and monetary reward results in greater right VS activation in older and younger adults, respectively (Rademacher, et al., 2014). Together, these studies suggest that aging is associated with diminished regional responses to anticipation of monetary reward.

1.2 Outcome processing in the monetary incentive delay task and the effects of age

The medial orbitofrontal and ventromedial prefrontal cortex (mOFC/vmPFC) respond consistently to feedback, with activity increasing and decreasing in response to gain and loss, respectively (Diekhof, et al., 2012; Dugre, et al., 2018; Knutson, et al., 2003; Liu, et al., 2011; Lutz and Widmer, 2014; Oldham, et al., 2018; Rademacher, et al., 2010). The mOFC/vmPFC may also play a role in outcome-based behavior adjustment (Forbes, et al., 2014). Activation of the dorsal striatum increases with the magnitude of monetary gain and decreases with magnitude of loss (Delgado, et al., 2004; Lutz and Widmer, 2014). A meta-analysis of the MIDT and other tasks with lower predictability of outcome implicates the VS in response to unpredictable outcomes, with responses scaling to the magnitude of reward (Diekhof, et al., 2012). Receipt of reward also engages the parietal and posterior cingulate cortex, bilateral anterior cingulate cortex and paracingulate gyri, subcallosal cortex and thalamus (Bartra, et al., 2013; Clithero and Rangel, 2014; Diekhof, et al., 2012; Dugre, et al., 2018; Knutson, et al., 2003; Knutson and Greer, 2008; Oldham, et al., 2018).

Studies using MIDT variants that require learning of stimulus-reward associations or more complex cognitive operations show increased VS activation to reward feedback in older adults, suggesting age-sensitive responses to positive prediction error (Samanez-Larkin, et al., 2014; Schott, et al., 2007; Vink, et al., 2015). A study of card guessing with unpredictable outcome reports VS activation and valence-discriminating caudate activity at

reward feedback in both young and old adults (Cox, et al., 2008). Similarly, a combined PET and MR imaging study of a learning-dependent "slot machine" task found greater activation of the anterior medial prefrontal cortex (PFC), posterior cingulate cortex and inferior parietal cortex in older adults at the outcome phase. The same study finds that older adults with lower midbrain dopamine levels show greater PFC activity while the converse is true in younger adults, suggesting compensatory prefrontal activity to reduced striatocortical dopaminergic signaling with age (Dreher, et al., 2008). In paradigms with explicit cues ("WIN $5", "LOSE $5", etc.) that require no learning, old and young adults show comparable VS, medial PFC and medial caudate activation to both wins and losses (Haber and Knutson, 2010; Samanez-Larkin, et al., 2007; Samanez-Larkin, et al., 2014). In sum, although age-related changes in response to feedback in the MIDT appear to be less than consistent, cerebral activations to outcomes do not appear to diminish with age, as with anticipation of reward. The magnitude of reward as well as differences in reward contingencies, including whether learning is involved, how cue predicts reward, and whether cues predict solely wins or both wins and losses, may contribute to the complexity to the findings.

1.3 The present study

The current study investigates the effects of age on cerebral activations during anticipation and feedback in the MIDT. Specifically, we examined whether age is associated with diminished response to anticipation to win large vs. small amount of money as well as to the outcomes of wins and losses of large vs. small reward. We hypothesized that if age is associated with a global decrease in motivation for monetary reward, one would expect age-related decreases in brain activations during both anticipation and feedback of a large vs. small reward irrespective of the outcome. Alternatively, older and younger adults demonstrate comparable responses to feedback in the MIDT, as discussed earlier, while older adults show greater responses to salient external stimuli in other cognitive tasks (Hahn, et al., 2006; Hu, et al., 2012; Wiegand and Sander, 2019)). Thus, age may be associated with diminished effort to acquire monetary reward but not necessarily with diminished responses to the outcome of win or loss of a large vs. small reward. To test these hypotheses, we employed a MIDT with unambiguous cues that predicted only reward and involved no learning. Successful performance required effort or a speeded motor response to acquire the reward and the overall success rate was held relatively constant across participants by staircasing the time window for the motor response. In addition to no reward (nil) trials as a control for reaction time (RT), we included large ($1) and small (¢1) reward trials to elicit trial-by-trial variation in motivation and effort. We examined differences in RT between dollar and cent trials, with nil RT as a covariate to quantify age-related differences in motivation, and examined regional activations to large vs. small reward both during anticipation and in response to feedback.

2. Methods

2.1 Subjects and informed consent

Fifty-four adults (30 men; 22–74 or 40 ± 14, mean ± SD, years of age) participated in this study. There was no age difference between men and women ($p = 0.77$, two-sample t test).

All subjects were healthy with no current use of prescription medications. None reported a history of head injury or neurological illness. Other exclusion criteria included current or past Axis I Disorders including dependence on a psychoactive substance, according to DSM-IV. The Human Investigation Committee at Yale University School of Medicine approved the study and all subjects gave written informed consent prior to participation.

2.2 Behavioral task

In the monetary incentive delay task or MIDT (Figure 1A), a bet (a dollar, a cent, or no money) appeared on the screen at the beginning of each trial. After a randomized interval (fore-period) between 1 and 5 s (uniform distribution), a target box appeared on the screen and disappeared after a short period (response window). Subjects were told to press a button as quickly as possible to collect the money in the target box (win) before it disappeared. An accurate trial is defined by a button press on time and before disappearance of the target box. Otherwise, subjects would lose the bet, with the amount deducted from the total win. A premature button press prior to the appearance of the target box terminated the trial, and similarly resulted in loss. Feedback was shown on the screen after each trial to indicate the amount of money won or lost. Approximately 42% of all trials were dollar trials, 42% were cent trials, and “no money” constituted the remaining trials. There was an inter-trial-interval of 1.5 s. The response window started at 300ms, and was staircased for each trial type (dollar/cent/no money trials, separately): for instance, if the subject succeeded at two successive dollar trials, the window decreased by 30ms, making it more difficult to win again; conversely, if a subject failed for two successive trials, the response window increased by 30 ms, making it easier to win. We anticipated that the subjects would win in approximately 67% each for dollar and cent trials. Each subject completed two 10-minute runs of the task.

2.3 Imaging protocol, data preprocessing, and modeling

Brain images were collected using multiband imaging with a 3-Tesla MR scanner (Siemens Trio, Erlangen, Germany). Conventional T1-weighted spin echo sagittal anatomical images were acquired for slice localization. Anatomical 3D MPRAGE image were next obtained with spin echo imaging in the axial plane parallel to the AC–PC line with TR = 1900 ms, TE = 2.52 ms, bandwidth = 170 Hz/pixel, field of view = 250 × 250 mm, matrix = 256 × 256, 176 slices with slice thickness = 1 mm and no gap. Functional, blood oxygen level-dependent (BOLD) signals were then acquired with a single-shot gradient echo echoplanar imaging (EPI) sequence. Fifty-one axial slices parallel to the AC–PC line covering the whole brain were acquired with TR = 1000 ms, TE = 30 ms, bandwidth = 2290 Hz/pixel, flip angle = 62°, field of view = 210 × 210 mm, matrix = 84 × 84, 51 slices with slice thickness = 2.5 mm and no gap, multiband acceleration factor = 3. Images from the first ten TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between RF pulsing and relaxation.

Data were analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). Standard image preprocessing was performed. Images of each individual subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each

subject per run from the realigned image volumes. These mean images were co-registered with the high-resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation (Friston et al., 1995, Ashburner and Friston, 1999). The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Finally, the images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum.

We examined event-related BOLD signals in two different models, each focusing on anticipation or "bet" and feedback or "result." In the "bet" model three trial types were distinguished: dollar, cent, and no money. In the "result" model five trial types of trials were distinguished: dollar win, dollar loss, cent win, cent loss, and no money. A statistical analytical design was constructed for each individual subject, using a general linear model (GLM) with the onsets of "bet" and "result", respectively, of each trial convolved with a canonical hemodynamic response function (HRF) and with the temporal derivatives of the canonical HRF and entered as regressors in the model (Friston, et al., 1995). Realignment parameters in all six dimensions were also entered in the model. Serial autocorrelation caused by aliased cardiovascular and respiratory effects was corrected by a first-degree autoregressive or AR (1) model. The GLM estimated the component of variance explained by each of the regressors.

In group level or random effects analyses, we examined one-sample t test results of individual contrasts (see below). To investigate age-related effects, we conducted whole-brain linear regressions with age as the regressor. All models were evaluated with a threshold combining voxel $p<0.001$, uncorrected and cluster $p<0.05$ family-wise error (FWE) corrected, following current reporting standards. Under this threshold some of the clusters were extensive and we tabulated the clusters using a more stringent threshold – voxel $p<0.05$ FWE corrected – to identify distinct brain regions with peak activities. Voxels with peak activity were indicated with Montreal Neurological Institute (MNI) coordinates.

2.4 Mediation analysis

We examined whether activations of the regions of interest mediated the correlation between age and reaction time. We performed mediation analyses(MacKinnon, et al., 2007), using the toolbox M3, developed by Tor Wager and Martin Lindquist (http://wagerlab.colorado.edu/tools).

In a mediation analysis, the relation between the independent variable X and dependent variable Y, i.e. X➔ Y, is tested to see if it is significantly mediated by a variable M. The mediation test is performed by employing three regression equations (MacKinnon, et al., 2007):

$$Y=i_1+cX+e_1$$

$$Y = i_2 + c'X + bM + e_2$$

$$M = i_3 + aX + e_3$$

Where a represents X➔ M, *b* represents M➔ Y (controlling for X), *c*′ represents X➔ Y (controlling for M), and *c* represents X➔ Y. The constants i_1, i_2, i_3 are the intercepts, and e_1, e_2, e_3 are the residual errors. In the literature, *a*, *b*, *c* and *c*′ were referred as path coefficients or simply paths (MacKinnon, et al., 2007; Wager, et al., 2008), and we followed this notation. Variable M is said to be a mediator of the correlation X➔ Y if ($c - c'$), which is mathematically equivalent to the product of the paths $a \times b$, is significantly different from zero (MacKinnon, et al., 2007). If the product $a \times b$ and the paths *a* and *b* are significant, one concludes that X➔Y is mediated by M. In addition, if path *c*′ is not significant, there is no direct connection from X to Y and that X➔Y is completely mediated by M. Note that path *b* is the relation between Y and M, controlling for X, and should not be confused with the correlation coefficient between Y and M.

3. Results

3.1 Behavioral performance

Figure 1B and 1C show the accuracy rate and reaction time (RT) of dollar, cent and nil trials. Across subjects 6.2 ± 6.3% of loss trials resulted from premature responding, and the rest (93.8 ± 6.3%) resulted from the responses being too slow.

In a one-way analysis of variance (ANOVA) with dollar, cent, and nil trials as within-subject factors, the results showed a significant variation in accuracy rate across trial types (F = 21.27, p = 6.5e-09). In post-hoc comparisons, participants showed higher accuracy rate in dollar as compared to nil (t = 5.11, p = 1.41e-06, two-tailed paired t test) and in cent as compared to nil (t = 4.37, p = 2.91e-05) trials, but only a trend-level difference between dollar and cent trials (t = 1.82, p = 0.072). Participants also showed a significant variation in RT across trial types (F = 29.68, p = 1.12e-11). In post-hoc comparisons participants showed faster RT in dollar as compared to nil (t = −6.10, p = 1.75e-08) and in cent as compared to nil (t = −5.39 p = 4.38e-07) trials, but no difference between dollar and cent trials (t = −1.524 p = 0.13).

We examined the relationship between behavioral performance and age. In linear regressions, age was negatively correlated with the accuracy rate of dollar (r = −0.29, p = 0.03) but not cent (r = −0.14, p = 0.32) trials and at a trend level with the accuracy rate of nil trials (r = −0.24, p = 0.08). Age was positively correlated with RTs of dollar (r = 0.25, p = 0.07) and nil (r=0.24, p=0.08) trials at a trend level, but not significantly with cent trials (r = 0.11, p = 0.45).

We further considered whether age was related to change in the motivation to acquire a large vs. small reward. In a covariance analysis, we performed a regression of difference in RT of dollar vs. cent trials (RT_dollar – RT_cent) against age, with the RT_nil as a covariate. The results showed a significant positive correlation: r = 0.34, p = 0.01 (Pearson regression); r = 0.38, p = 0.006 (Spearman regression). That is, age was associated with diminished differences in RT to acquire a large vs. small reward or RT_dollar – RT_cent (Fig. 1D).

3.2 Regional activations to reward anticipation and the effects of age

In a one-sample t test, we evaluated regional activations to anticipation to dollar vs. nil, cent vs. nil and dollar vs. cent (Supplementary Fig. 1). Anticipation of reward involved activation of the ventral striatum (VS), dorsal striatum, thalamus, midbrain, as well as primary and supplementary motor and visual cortical areas.

In a linear regression, age was correlated with less activation of the VS and other areas of the basal forebrain such as the basal nucleus of Meynert (BNM), dorsal striatum, thalamus, primary motor, supplementary motor and visual cortical areas during reward anticipation, particularly during anticipation of a dollar reward. Figure 2 shows regional activations to anticipation of dollar vs. nil, cent vs. nil, and dollar vs. cent in linear correlation with age. The contrast of dollar vs. nil and dollar vs. cent identified a large cluster of brain regions. We thus applied a more stringent threshold of voxel $p<0.05$ FWE corrected to distinguish the individual brain regions (Table 1).

3.3 Regional activations to reward anticipation in relation to difference in RT

Age was positively correlated with differences in RT between dollar and cent trials, with RT of nil trial as a covariate, suggesting less differentiated motivation in older people to acquire a large vs. small reward. Thus, as with the analysis of behavioral data, we conducted a whole-brain regression of anticipation-related activations to dollar vs. cent trials against the RT difference of dollar and cent trials (RT_dollar – RT_cent) with RT_nil as a covariate. The results showed that the RT difference was negatively correlated with activation of the supplementary motor area, right superior/middle frontal gyrus, left primary motor cortex, bilateral occipital cortex including the parahippocampal gyrus, right anterior insula, caudate nucleus, lentiform nucleus and thalamus (Fig. 2D). Voxels that overlapped with those of age regression were primarily in the supplementary motor area, right superior/middle frontal gyrus, left primary motor cortex, bilateral occipital cortex including the parahippocampal gyrus, right anterior insula, and caudate nucleus (Fig. 2E).

We combined all clusters in Fig. 2E as a single region of interest and computed the β contrast of anticipation of a dollar vs. cent reward to visualize the correlation between the β contrast with age and with “RT_dollar – RT_cent” (Supplementary Fig. 2).

3.4 Mediation analyses

We examined whether activations of the regions of interest (ROI) mediated the correlation between age and RT difference between dollar and cent trials. The voxels that overlapped between the two regressions (Fig. 2E) were combined as a single ROI. Of the 6 possible models of mediation, we excluded the two with age as a dependent variable and tested the remaining four models. The results showed that regional activities significantly mediated the correlation between age and RT difference, and none of the other three models showed significant mediation (Fig. 3).

3.5 Regional activations to outcomes and the effects of age

In a one-sample t-test, we evaluated regional activations to dollar win vs. nil, cent win vs. nil, dollar win vs. cent win, dollar loss vs. nil, cent loss vs. nil, and dollar loss vs. cent loss (Supplementary Fig. 3).

In whole-brain regression with age for each of these contrasts, we observed age-related increases in activation in the left superior frontal gyrus/sulcus and middle frontal gyrus to feedback of dollar win vs. nil (Fig. 4A) as well as in the right ventrolateral prefrontal and superior temporal cortex and left superior frontal gyrus/sulcus to cent loss vs. nil (Fig. 4D). Activation in the thalamus to dollar vs. cent win decreased with age (Fig. 4E). Activations in bilateral insula and orbitofrontal cortex, right superior temporal gyrus, bilateral anterior cingulate cortex, and right pre-supplementary motor area to dollar vs. cent loss decreased with age (Fig. 4F). These clusters are summarized in Table 2.

We combined all clusters in Figure 4F as a single region of interest, and plotted the β value of dollar loss vs. age and of cent loss vs. age, as well as the β contrast of dollar loss – cent loss vs. age to visualize the correlations in Supplementary Figure 4. In Supplementary Figure 5 we show the same for only the largest cluster – the right insula/IFG/OFC.

4. Discussion

We studied age-related alterations in reward processing in 54 healthy adults aged 22–74 years during a MIDT. We used unambiguous pictorial stimuli for bets and participants responded to a target to win the monetary reward. We assessed the behavioral performance and neural processes underlying reward anticipation and feedback and how age influenced these processes. The results showed that age was associated with decreases in activation in a wide swath of cortical and subcortical structures, including the ventral striatum (VS) to reward anticipation, as well as decreases in activation in the cingulate cortex and orbitofrontal cortex (OFC) to gain and loss feedback of higher magnitude (a dollar vs. a cent) respectively. On the other hand, age was associated with increases in activation in the ventrolateral and ventromedial prefrontal cortex (VLPFC and VMPFC) to the feedback of cent vs. dollar loss. Age was also associated with diminished differences in RT but reduced activations to reward anticipation during dollar and cent trials, and these differences in regional activities modulated the influences of age on the differences in RT. These results suggest that age incurs decreased neural responses to anticipation of higher monetary gain and increased responses to smaller monetary loss, together reflecting an age-related constriction in sensitivity to the magnitude of monetary reward (Fig. 5). We highlight the major findings for discussion.

4.1 Age-related differences in response to reward anticipation

Older adults showed reduced VS activation to the anticipation of a dollar vs. cent or no reward, in accord with an earlier study that employed ROI analysis to examine age-related VS responses (Vink, et al., 2015). Dreher and colleagues also reported reduced ventral and dorsal striatal responses to reward anticipation in older as compared to younger participants (Dreher, et al., 2008). Using the MIDT along with a variant that replaced monetary with

social rewards, others have reported age-related reduced VS activation to monetary vs. social rewards (Rademacher, et al., 2014). Thus, age may influence VS response to monetary but not social reward, in keeping with the role of dopaminergic signaling of incentive salience (Berridge and Robinson, 1998; Robinson and Berridge, 2000) and individual differences in reward preference (McClure, et al., 2004; O'Doherty, et al., 2006), with social affective reward more valued by older adults (Carstensen, 2006; Carstensen and Turk-Charles, 1994; Samanez-Larkin and Knutson, 2015). Age-related reduction in activation in the bilateral occipital cortex during reward anticipation in older adults could similarly be explained by the same proposition that monetary reward is less salient and thus receives less visual attention by older adults (Guerreiro, et al., 2010; Stormer, et al., 2014; Vollstadt-Klein, et al., 2012). Age-related reduction in VS activation may reflect fewer dopaminergic receptors or reduced signaling from the VTA (Kumakura, et al., 2010; Reeves, et al., 2002), and, together with reduced anterior insula activation (Oldham, et al., 2018), altered saliency of monetary reward in older adults (Knutson and Greer, 2008).

Age was also associated with a diminished difference in reaction time (RT) between dollar and cent trials, largely driven by an age-related increase in RT to dollar trials despite stair-casing of the response window. Activation of the right anterior insula, caudate nucleus, supplementary motor area, right superior and middle frontal gyri, motor cortex and visual cortex diminished both with age and with RT difference between dollar and cent trials. The primary motor cortex is known to exhibit motor preparatory activity (Hirose, et al., 2018; Wang, et al., 2018; Yoshida, et al., 2013). The age-related decreases in motor cortical activations to anticipation of dollar vs. cent (Figure 2C) may have to do with age-related decrement in RT difference or other cognitive processes in relation to RT difference between dollar and cent trials (Figure 1D). Further, these reductions in activation mediated the relationship between age and diminished RT difference between dollar and cent trials, suggesting that these neural correlates support age-related differences in behavioral performance. Together, these findings confirmed age-related decrease in motivation to obtain a large vs. small reward.

4.2 Age-related differences in response to reward feedback

Age was associated with increases in prefrontal cortical, but not VS, response to dollar win vs. nil, in keeping with studies employing classic MIDT paradigms (Samanez-Larkin, et al., 2007) and in contrast to studies involving uncertainty in reward predictability (Marschner, et al., 2005; Schott, et al., 2007; Vink, et al., 2015). Dreher et. al. demonstrated an inverse association between midbrain dopamine stores and prefrontal cortical activation to reward processing with age (Dreher, et al., 2008). Thus, age-related increases in the recruitment of the prefrontal cortex during dollar wins may reflect a compensatory mechanism to counter the depletion of mesocortical dopaminergic signaling in the aging brain (Volkow, et al., 1996; Wenk, et al., 1989).

Further, age was associated with increases in activation of the insula, OFC, and ACC to dollar over cent losses, largely driven by increased age-related response to cent loss. These findings suggest that, although equally aversive to dollar loss, older as compared to younger people are more aversive to cent loss. The literature on the effects of age on loss sensitivity

is sparse. An earlier study of decision making during aging showed that older as compared to younger adults were significantly more uncertainty-averse in the loss but not in the gain domain (Kurnianingsih, et al., 2015). Another study reported no age-related changes in loss sensitivity but increases in differential sensitivity of the VS to negative valuations of emotional faces (Viswanathan, et al., 2015). Thus, older as compared to younger people may be more sensitive to negative outcomes both in the financial and social domains.

4.3 Age-related constriction in sensitivity to the magnitude of reward

While neural sensitivity to anticipation of higher reward decreased, sensitivity to loss of smaller reward increased with age, as discussed above and depicted in Fig. 5. These findings together represent an age-related constriction in sensitivity to the magnitude of reward. Neural sensitivity to anticipating gains of different magnitude develops during adolescence and attains near-linearity during adulthood; that is, adults demonstrate a more or less linear increase in VS activity to anticipation of reward of increasing objective value (Knutson, et al., 2001a; Vaidya, et al., 2013). The current findings thus extend this picture into the later stages of life (up to 74 years of age), when older people show diminished responses to reward anticipation. The findings are in keeping with previous findings that the neural sensitivity to anticipated gain (higher vs. lower magnitude of reward) is associated with trait impulsivity (Vaidya, et al., 2013) and that older adults demonstrate lower trait impulsivity (Eppinger, et al., 2012). Further, the current findings add to this literature by showing the opposite during feedback. Loss of a smaller scale appears to figure more prominently for older people.

4.4 Implications for clinical research

The current findings may have implications for research of neuropsychiatric illnesses that implicate altered reward processing. For instance, decreased neural response to reward has been reported in individuals who misuse cocaine (Goldstein, et al., 2007; Rose, et al., 2017). A recent meta-analysis of fMRI studies revealed significantly reduced striatal activation in depressed compared with healthy individuals during reward feedback and anticipation, with the latter showing a stronger effect in young adults (Keren, et al., 2018). Consistent with the current findings, striatal reward response may be a less sensitive marker of addiction and depression in the elderly. In particular, as age represents of the primary risk factor of many neurodegenerative conditions that implicate altered reward processing (Perry and Kramer, 2015), the findings may inform research of biomarkers of these age-related illnesses.

4.5 Limitations and conclusions

A few limitations and issues of the study need to be considered. First, subject characteristics including personality traits and socio-economic status may influence inter-subject variation in behavioral and imaging findings. Future work with a larger sample size and detailed assessment of these characteristics would help evaluate whether the current findings can be generalized to the larger populations. Second, age was correlated with less activation of the ventral striatum (VS) and other areas of the basal forebrain such as the basal nucleus of Meynert (Li, et al., 2014) during reward anticipation. Although not typically implicated in reward processing, the BNM along with the projection nuclei of the midbrain may undergo major functional changes during aging (Peterson and Li, 2018). The BNM plays a critical

role in regulating attention (Wan et al., 2019), motivational salience, and decision speed (Raver and Lin, 2015). Studies are warranted to investigate whether VS and BNM functioning is differentially influenced by aging.

We conclude that age is associated with diminished cerebral response to anticipation of large versus small monetary reward and heightened response to the outcome of small versus large monetary loss, reflecting an overall constricted sensitivity to reward magnitude. Further research may examine whether this asymmetric response to reward anticipation and loss feedback influence decision making across the life span.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements and Disclosures

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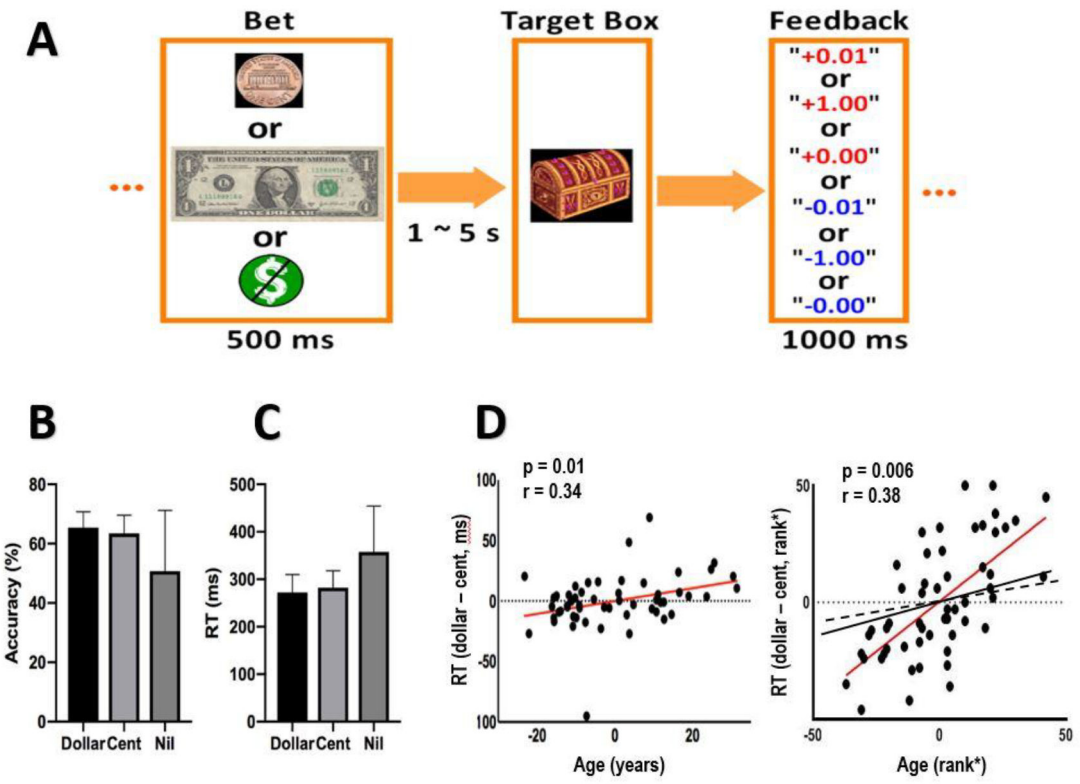

Figure 1.

Behavioral paradigm and performance. **(A)** Monetary incentive delay task: A bet (a dollar, a cent, or no money) appeared at the beginning of each trial. After a randomized interval between 1 and 5 s, a target box appeared on the screen and disappeared after a short period (response window). Subjects were told to press the button as quickly as possible to collect the money in the target box (win) before it disappeared. Otherwise, subjects would lose the bet, with the amount deducted from the total win. A premature button-press prior to the appearance of the target box terminated the trial, and similarly resulted in loss. A feedback window was shown on the screen after each trial to indicate the amount of money won or lost. **(B)** Accuracy rate and **(C)** RT of dollar, cent and no money (nil) trials (mean ± SD). **(D)** Pearson's linear and Spearman's rank partial correlations of RT difference (RT dollar – RT cent) versus age (red lines), controlling for RT no money trials (RT nil). In the right panel, we also plotted Spearman's partial correlation of RT dollar vs. age (black, solid; r=0.177, p=0.204) and of RT cent vs. age (black, dashed; r=0.004, p=0.975) with RT nil as a covariate. Note that residuals, not original data values, were plotted in partial regressions.

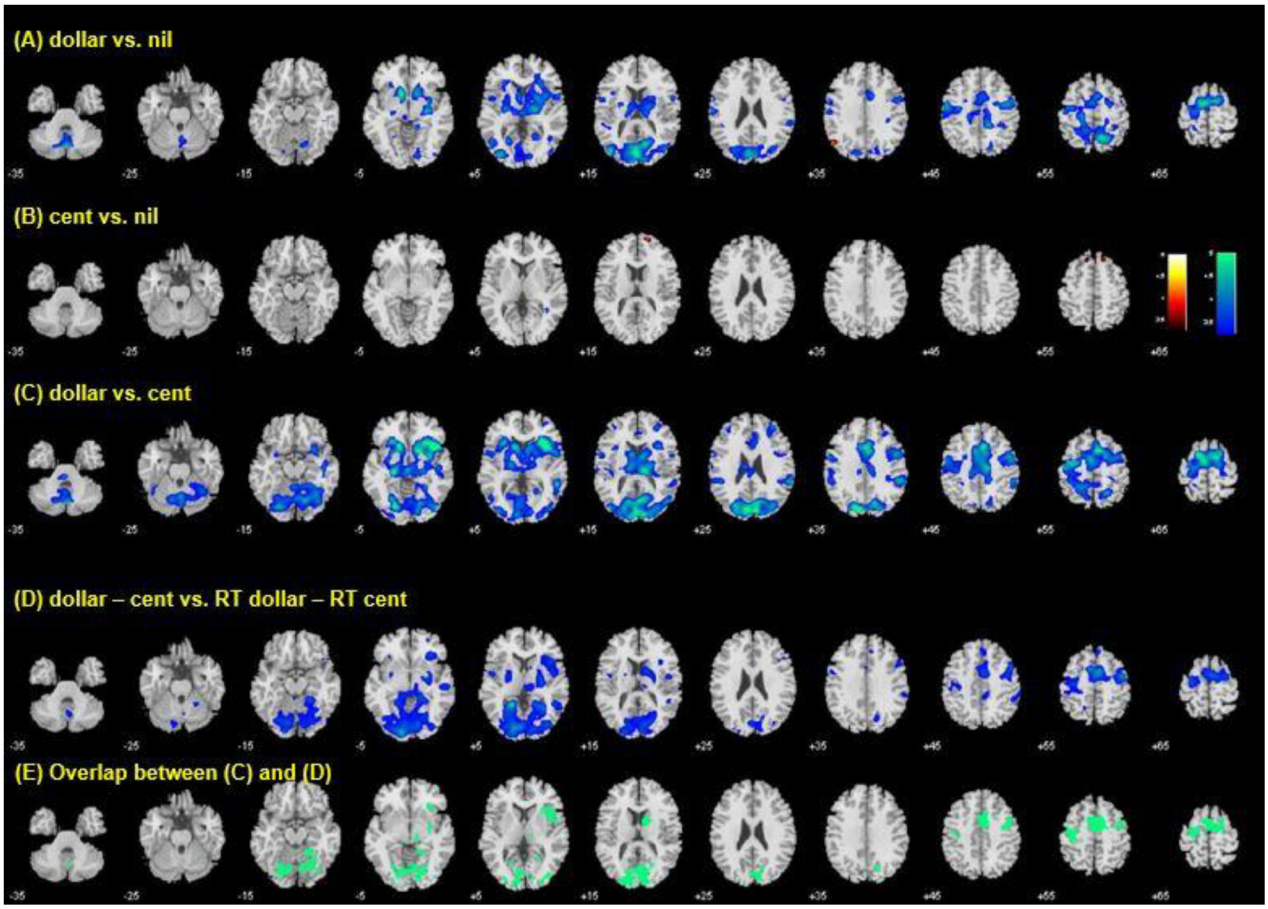

Figure 2.

Regional activations to anticipation of **(A)** dollar vs. nil, **(B)** cent vs. nil, and **(C)** dollar vs. cent in correlation with age. The contrast of dollar vs. nil and dollar vs. cent identified a large cluster of brain regions. We thus applied a more stringent threshold of voxel $p<0.05$ FWE corrected and summarized the individual clusters in Table 1. **(D)** Regional activations to anticipation of dollar vs. cent in correlation with RT difference between dollar and cent trials, with RT of no money (nil) trials as a covariate. **(E)** Voxels that overlap between **(C)** and **(D)**. These voxels together formed the region of interest for mediation analysis.

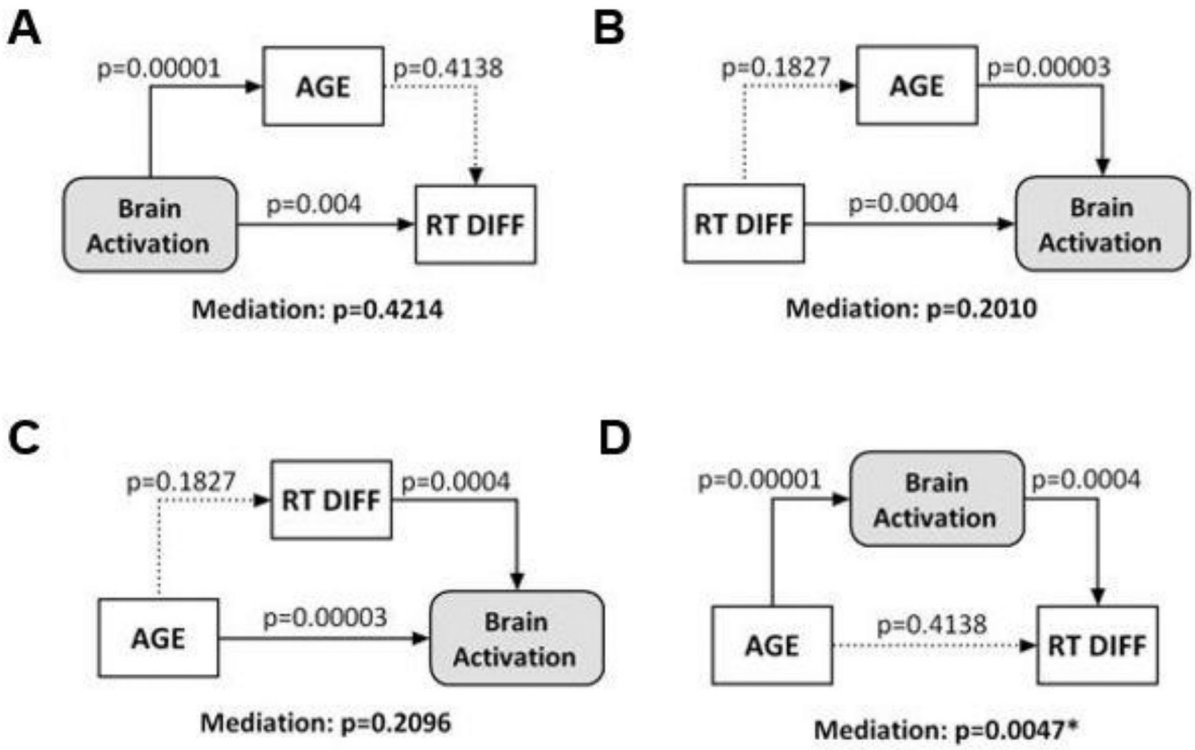

Figure 3.

The results of mediation analyses showed that (D) regional activities (β contrast) mediated the correlation between age and RT difference between dollar and cent trials. None of the other models (A, B, C) showed significant mediation.

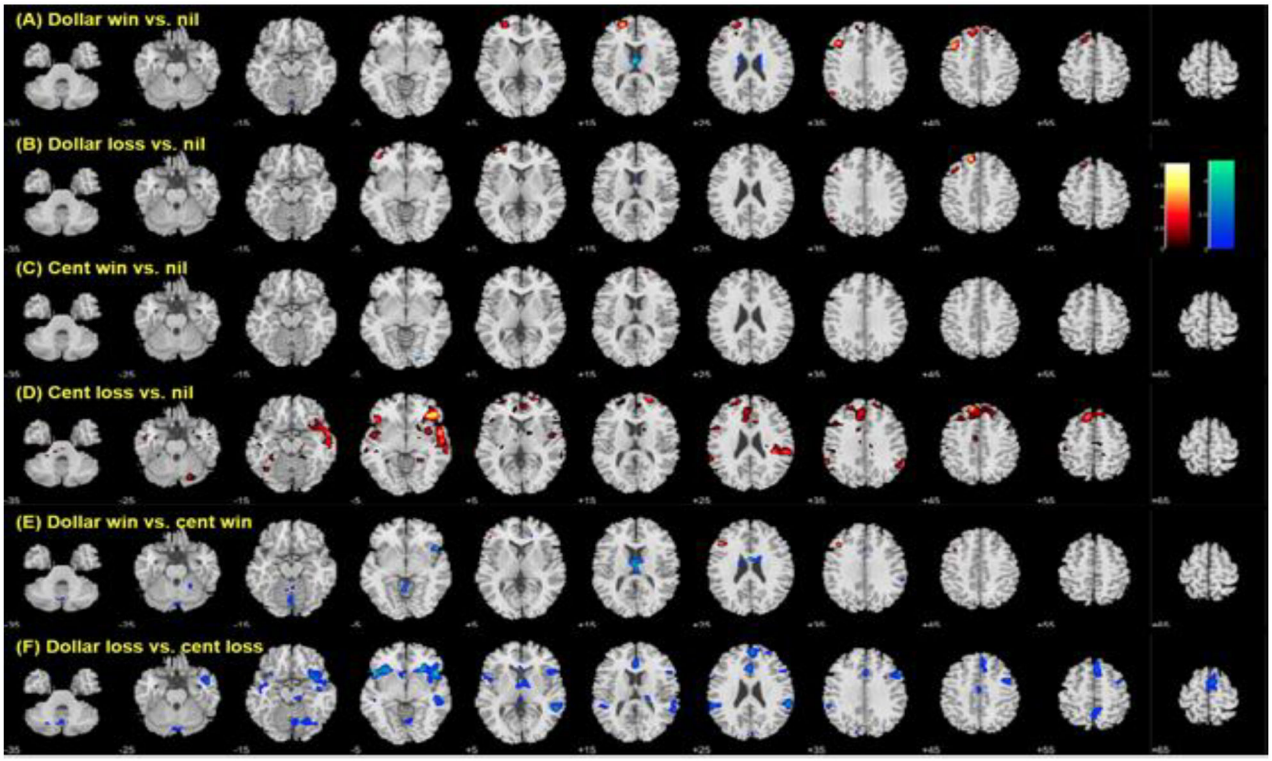

Figure 4.

Age-related differences in response to outcomes. Voxel $p<0.001$, uncorrected. Age was associated with differences in activity to feedback of **(A)** dollar win compared to nil, but not **(B)** dollar loss or **(C)** cent win as compared to nil. Age was also associated with higher regional activations during **(D)** cent loss vs. nil and with lower activations during **(F)** dollar vs. cent loss. Clusters meeting cluster $p<0.05$ FWE corrected are summarized in Table 2.

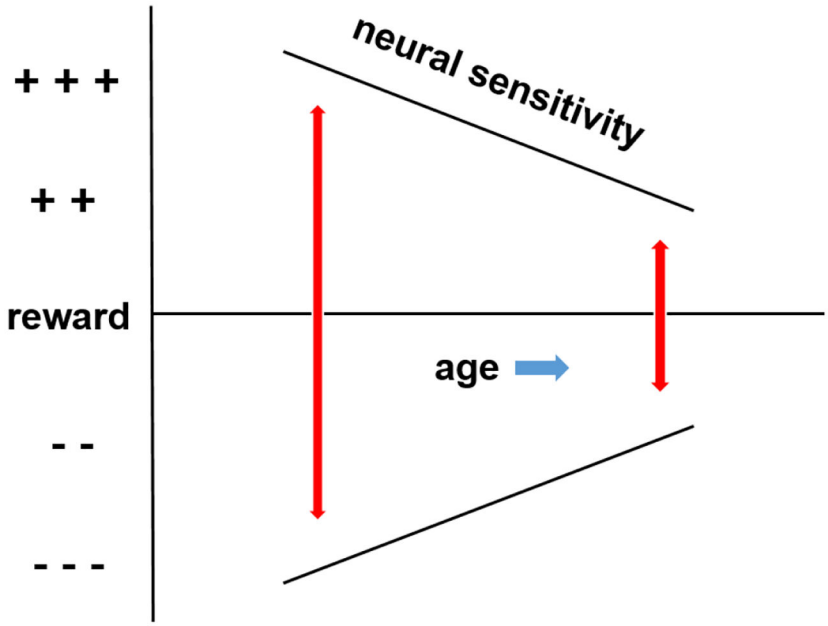

Figure 5:

Diagrammatic representation of age-related constriction in sensitivity to reward magnitude. Age is associated with diminished cerebral response to anticipation of a large vs. small reward. Age is also associated with higher response to the outcome of loss of a small vs. large reward. Blue arrow: direction of aging; red arrows: range of neural sensitivity; black lines: neural sensitivity.

Table 1:

Age-related regional responses to reward anticipation

Volume (mm3)	Peak voxel (Z)	MNI coordinates (mm) x	y	z	Side	Identified brain region
Dollar > Nil						
297	−4.68	−12	11	−5	L	VS/BNM
594	−4.67	−3	−82	16	L/R	OC
Dollar > Cent						
3,240	−4.99	36	20	7	R	Insula
621	−4.93	−9	−82	37	L	OC
810	−4.89	−15	5	64	L	Pre-SMA
351	−4.75	−15	17	−5	L	VS/BNM
405	−4.74	6	8	58	R	Pre-SMA
324	−4.59	15	11	−5	R	VS/BNM

Note: voxel $p<0.05$, FWE; R: right; L: left. The sign of Z value indicates the direction of correlation. VS/BNM: ventral striatum/basal nucleus of Meynert; OC: occipital cortex; Pre-SMA: pre-supplementary motor area.

Table 2:

Age-related regional responses to feedbacks

Volume (K_E)	Peak voxel (Z)	MNI coordinates (mm) x	y	z	Side	Identified brain region
Dollar win > Nil						
151	4.51	−21	56	19	L	SFG/SFS
142	4.47	−39	23	40	L	MFG
Cent loss > Nil						
603	4.66	45	35	−8	R	VLPFC
467	4.22	−12	44	46	L	SFG/SFS
96	3.98	39	−31	25	R	STG
Dollar win > cent win						
141	−4.03	0	−1	22	R/L	Thalamus
Dollar loss > Cent loss						
178	−4.57	−51	14	−2	L	IFG/Insula
454	−4.42	24	23	−8	R	Insula/IFG/OFC
236	−4.33	57	−43	7	R	STG
123	−3.95	0	26	22	L/R	ACC
211	−3.87	6	38	49	R	Pre-SMA

Note: voxel $p<0.001$ uncorrected; cluster $p<0.05$ FWE; R: right; L: left. The sign of Z value indicates the direction of correlation. SFG/SFS: superior frontal gyrus/superior frontal sulcus; MFG: middle frontal gyrus; VLPFC: ventrolateral prefrontal cortex; STG: superior temporal gyrus; IFG: inferior frontal gyrus; OFC: orbitofrontal cortex; ACC: anterior cingulate cortex; Pre-SMA: pre-supplementary motor area.