Men Show Higher Neural Sensitivity to Wins – Large or Small – than Women in the Monetary Incentive Delay Task

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Research

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Abstract

Background Men and women show differences in sensitivity to reward and punishment, which may impact behavior in health and disease. However, the neural bases of these sex differences remain under-investigated. Here, by combining functional magnetic resonance imaging (fMRI) and a Monetary Incentive Delay Task (MIDT), we examined sex differences in the neural responses to monetary wins and losses and how these regional activities vary with individual reward and punishment sensitivity.

Methods Sixty-three healthy adults (27 women) participated in the fMRI study with a 3-Tesla scanner. Sensitivity to punishment (SP) and sensitivity to reward (SR) were assessed with the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ). In the MIDT, participants pressed a button to collect either $1, 1¢, or nil, with the reaction time window titrated across trials to achieve ~67% success. Imaging data were processed with published routines and evaluated with a corrected threshold.

Results The results showed higher SP score in women vs. men and higher SR score in men vs. women. Compared to women, men also showed higher response to the receipt of dollar or cent reward in the medial prefrontal cortex, in the area of the supplementary motor cortex. Regional responses to loss did not show sex differences. Further, in a whole-brain regression, activation of the caudate head during 1¢ loss was correlated positively with SR score in men but not in women, and the sex difference was confirmed by a slope test.

Conclusions Together, men showed higher SR and neural sensitivity to the receipt of reward, big or small, than women. Individual differences in SR could be reflected by caudate response to a small loss in men. These findings highlight how men and women may differ in reward-related brain activations in the MIDT and add to the imaging literature of sex differences in cognitive and affective functions.

Background

Reward processing in health and illness

Reward-directed behavior is fundamental to survival and well-being (1). We strive to obtain primary (food, water, sex) and secondary (money, social approval) rewards (2, 3). Reward-seeking behavior engages neural circuits central to motivation and learning (4, 5). Numerous studies have identified the ventral tegmental area, ventral striatum (VS), orbitofrontal cortex (OFC), and anterior cingulate cortex as key regions for reward processing (6-10). These structures integrate motivational and cognitive processes to support reward-seeking behavior (4, 8, 11). Further, individuals vary in how they respond to reward-related contingencies (12), and men appear to be more sensitive to reward whereas women are more sensitive to punishment (13, 14).

Many neuropsychiatric conditions implicate motivation deficits and reward processing dysfunction. For instance, anhedonia and compulsive drug seeking represent core symptoms of major depression and substance use disorders (SUDs), respectively, and implicate dysfunction of the reward circuitry (15, 16).

Studies have consistently found reduced striatal response to reward anticipation and feedback (17) and impaired learning of reward contingencies (18) in patients with depression. The neural deficits correlate positively with anhedonia and negatively with treatment outcome (4, 19, 20). Chronic pain is frequently comorbid with depression and associated with deficits in reward responses (21). Substance misuse alters the salience of natural reinforcers and compromises self-control of immediate gratification, perpetuating compulsive drug seeking (4, 22-24). Adolescents exposed prenatally to maternal cigarette smoking are observed to have a weaker bilateral VS response to reward anticipation (25). Importantly, many of these neuropsychiatric conditions demonstrate sex differences in their clinical profiles and etiological processes, with, for instance, women more vulnerable to depression and men to SUDs. Thus, it is important to better understand how men and women process reward differently.

Sex differences in reward and punishment processing

Biological, including hormonal, and socio-cultural factors may all account for sex differences in reward sensitivity and reward-directed behavior (26, 27). Indeed, the literature has suggested a rather complex picture of sex differences in reward-related behavior and the neural processes underlying such differences. For instance, some studies showed that women were better at delaying gratification than men (28, 29), but others showed no sex differences (30). A study of multiple rodent behavioral paradigms reported no sex difference in reward-guided associative learning. However, females showed faster punishment-avoidance learning and, after learning, were more sensitive than males to probabilistic punishment but less sensitive when punishment could be avoided with certainty (27). Women compared to men tended to pick decks with lower frequency of punishment on a gambling task (31). In a study combining electroencephalography (EEG) and a guessing task with reward (or punishment) feedback, boys showed lower feedback-related negativity (FRN) and less changes in post-punishment behavior (32). Further, only girls demonstrated FRN to monetary punishment in relation to a reward sensitivity trait. In another EEG study of an incentive delay task, boys as compared to girls showed reduced stimulus-preceding negativity when anticipating punishment and greater feedback P3 to monetary than social reward (33). These findings are consistent with a literature of higher female sensitivity to loss, punishment or other negative feedback (27, 34, 35).

In contrast, visual sexual stimuli activated the reward system in both sexes whereas the VS was involved in men but not women in supporting the distractor effects of the stimuli on line orientation judgment (36). Adolescent boys relative to girls showed greater VS activation during reward processing in a risky decision making task, made a higher percentage of risky selections, and self-reported greater motivation to earn money than girls (37). Studying the perceived value of monetary vs. social rewards using a monetary/social incentive delay task, another group reported activation of a wider mesolimbic network in response to anticipation of monetary reward in men and in anticipation of both monetary and social reward in women, in accord with their reaction time performance (38). In a recent work of a reward go/no-go task, men exhibited greater physiological arousal to go responses (predominating monetary wins),

which was also more predictive of go success rate, relative to women (39). On the other hand, females were more accurate than males in learning from positive (but not negative) feedback in a probabilistic selection task (31). In another study examining a large data set of the Human Connectome Project, women relative to men showed greater suppression of the default mode network and higher activation of the dorsal attention network during exposure to reward and punishment, suggesting enhanced saliency of both reward and punishment in women (40). Thus, sex differences in reward-related processing appear to depend on the nature of rewarding stimuli and behavioral contingency.

The effects of reward and punishment sensitivity on reward-related processing

In addition to sex, individuals may also vary in reward-related behavioral and neural processes because of distinct reward and punishment sensitivity. Sensitivity to reward scores correlated positively with reactivity to erotic pictures in the left OFC, left insula, and right VS (41). In a study of reinforcement learning, individual differences in reward sensitivity were positively associated with bilateral VS activation during receipt of reward, while differences in punishment sensitivity were negatively associated with left dorsal striatal activity during loss anticipation and with right lateral OFC activation during loss feedback (42). Another study examined three groups of people, each with low, medium, and high reward sensitivity, in a working memory task with sub- and supra-liminal stimuli. Individuals with medium reward sensitivity improved performance with high reward in both subliminal and supraliminal conditions, whereas the effect of reward was stronger in the supraliminal than subliminal condition for those with high reward sensitivity scores (43). The latter findings highlighted complex effects of individual reward sensitivity on cognitive performance incentivized by monetary reward. Investigators have also associated sensitivity to punishment with higher insula activity during feedback of social loss in a social incentive delay task in people with subthreshold depression (44). On the other hand, despite its wide use in the imaging literature, no studies of the MIDT have examined how neural responses to monetary wins or losses may vary with individual sensitivity to reward or to punishment.

Methods

Aim, design and setting of the study

The present study aims to characterize sex differences in cerebral responses to reward anticipation and feedback and whether women and men differ in the influences of individual reward and punishment sensitivity on these neural processes. We contrasted men and women in regional responses to reward anticipation and feedback in neurotypical populations. We performed linear regression to identify how these regional responses may vary according to individual SR and SP and examined the sex differences in these

correlations with slope tests. Understanding sex differences in reward processing would provide information for translational studies to examine sex-specific neural markers of clinical conditions that implicate reward processing dysfunction.

Subjects and assessments

Sixty-three healthy adults (27 women; 22-55 or 37 ± 11, mean ± SD, years of age) participated in this study. 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. All participants were evaluated with the Sensitivity to Reward and Sensitivity to Punishment Questionnaire (SPSRQ) (45). The SPSRQ contains 48 yes-no items, half concerning the scale for behavioral impulsivity/responsiveness to reward and half concerning the scale for behavioral avoidance in response to potentially adverse consequences. Scores were obtained by totaling the number of yes-answers in each scale, with a higher sub-score each indicating higher sensitivity to reward (SR) and sensitivity to punishment (SP). **Table 1** summarizes subject characteristics.

The Human Investigation Committee at Yale University School of Medicine approved the study and all subjects gave written informed consent prior to participation.

Table 1. Subject characteristics

	Men (n=36)	Women (n=27)	p value
Age (years)	38.3 ± 10.4	34.3 ± 10.2	0.15
Education (years)	15.5 ± 3.7	15.1 ± 2.7	0.62
SR	9.9 ± 5.1	9.0 ± 3.6	0.04*
SP	7.3 ± 4.7	10.0 ± 5.6	0.04*

*$p<0.05$, two-sample t test. SR: sensitivity to reward; SP: sensitivity to punishment

Monetary Incentive Delay Task (MIDT)

In the 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 fore-period between 1 and 5 s (uniform distribution), a target box was shown for a short period (response window, see below). Subjects were told to press a button as quickly as possible to collect the money (win) before the target box disappeared. An accurate trial was defined by a button press 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. The inter-trial-interval was 1.5 s. The response window started at 300 ms, and was stair-cased for each trial type (dollar/cent/no money) separately; for instance, if the subject succeeded at two successive dollar trials, the window decreased by 30 ms, 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.

[Figure 1 about here]

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.

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 segmented for normalization with affine registration followed by nonlinear transformation (46, 47). 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 (48). 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 employed one-sample t tests on individual contrasts (see below) and two-sample t tests to examine sex differences in these contrasts. To investigate the neural correlates of SR and SP, we conducted whole-brain linear regressions of these contrasts on SR and SP, with age as a covariate for men and women combined as well as separately. For sex-specific findings, we defined the functional clusters as regions of interest, extracted the β estimates for all subjects, and performed slope tests to examine sex differences in the correlations. 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. Voxels with peak activity were indicated with Montreal Neurological Institute (MNI) coordinates.

[Figure 2 about here]

Results

Behavioral performance

Figure 1B and **1C** show the accuracy rate and reaction time (RT) of dollar, cent, and nil trials. For both men and women, the accuracy rates were close to 67%, suggesting the success of the staircase procedure. There were no significant sex differences in the accuracy rate of dollar (t_{56}=-0.76; p=0.45), cent (t_{61}=-0.37; p=0.70), or nil (t_{61}=-0.73; p=0.47) trials or in the RT of dollar (t_{56}=0.05; p=0.96), cent (t_{61}=-0.04; p=0.97), or nil (t_{58}=0.04; p=0.97) trials.

Men showed higher sensitivity to reward (SR) score than women, and, in contrast, women showed higher sensitivity to punishment (SP) score than men (**Table 1**). We examined the relationship between behavioral performance and SR and SP for men and women together and separately. In linear regressions, SR score was positively correlated with the accuracy rate of dollar trials in men + women (r_{61}=0.28, p=0.02) and in women (r_{25}=0.52, p=0.006). SR score was also positively correlated with the accuracy rate of cent

trials in men + women (r_{61}=0.33, p=0.008) and in women (r_{25}=0.51, p=0.007). SR score was negatively correlated with the RT of cent trials in women (r_{25}=-0.44, p=0.02), SP score was positively correlated with the RT of dollar trials in women (r_{25}=0.50, p=0.007), and SP was positively correlated with the RT of cent trials in men + women (r_{61}=0.28, p=0.03) (**Figure 2**). The r and p values of all correlations are shown in **Table 2**. However, although women appeared to show more significant correlations between SR/SP scores and performance measures, relative to men, the slope tests did not reveal significant sex differences in any of these correlations (all p's ≥ 0.47).

Table 2. Linear regressions between performance measures and SR/SP.

	AR Dollar (%)		AR Cent (%)		RT Dollar (ms)		RT Cent (ms)	
	r	p	r	p	r	p	r	p
SR (M + F)	0.28	0.02*	0.33	0.008*	-0.19	0.12	-0.22	0.08
SR (M)	0.24	0.17	0.27	0.12	-0.17	0.33	-0.14	0.42
SR (F)	0.52	0.006*	0.51	0.007*	-0.31	0.11	-0.44	0.02*
SP (M+F)	0.04	0.74	0.01	0.92	0.21	0.09	0.28	0.03*
SP (M)	0.08	0.65	-8.47e-4	0.99	0.10	0.53	0.24	0.15
SP (F)	-0.10	0.62	0.001	0.99	0.50	0.007*	0.37	0.06

Accuracy rate (AR, %) and reaction time (RT, ms) and sensitivity to reward (SR) and sensitivity to punishment (SP) scores for men and women combined (M+F), men (M), and women (F). *p<0.05. Degrees of freedom for M + F: 61; M: 34; F: 25.

Sex differences in regional responses to reward anticipation ("bet")

In a one-sample t test, we evaluated regional activations to anticipation to win dollar vs. nil, cent vs. nil and dollar vs. cent in men and women combined (**Figure 3**). 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 covariance analysis with age as a covariate, men and women did not show significant differences in activation to reward anticipation during dollar vs. nil, cent vs. nil, or dollar vs. cent trials.

[Figure 3 about here]

Sex differences in regional activations to feedback (win or loss)

In a one-sample t-test, we evaluated regional activations to dollar win vs. nil, cent win vs. nil, dollar vs. cent win, dollar loss vs. nil, cent loss vs. nil, and dollar vs. cent loss in men and women combined. These results are shown in **Figure 4**.

[Figure 4 and Figure 5 about here]

In covariance analyses to compare men and women with age as a covariate for each of these contrasts, we observed sex differences in activation (men > women) in the right orbitofrontal cortex, left cerebellum, right occipital cortex and supplementary motor area (SMA), for dollar win > nil (**Figure 5A**), and in the left temporal cortex and SMA for cent win > nil (**Figure 5B**). Clusters meeting cluster $p < 0.05$ FWE are summarized in **Table 3**. None of the other contrasts, including dollar win vs. dollar loss and cent win vs. cent loss (not shown in the figure), showed significant sex differences.

Table 3. Sex differences (men > women) in regional activations to reward feedback.

Cluster size (k)	Voxel (peak Z)	MNI coordinates (mm) x	y	z	Side	Brain region
Dollar Win > Nil						
136	4.31	27	44	-8	R	Orbitofrontal cortex
347	3.99	-18	-40	-23	L	Cerebellum
267	3.97	12	-1	58	R/L	SMA
269	3.79	6	-85	28	R	Occipital cortex
Cent Win > Nil						
353	5.40	-48	-4	10	L	Premotor area
336	4.30	-6	-1	58	L	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. SMA: supplementary motor area.

Whole brain regression with SP and SR scores

For each of the six contrasts, we performed a linear regression with both SR and SP scores as regressors and years of age as a covariate for men and women combined as well as separately. A cluster in the right caudate head (x = 9, y = 14, z = 4, voxel Z = 3.81, volume = 3978 mm^3) met the threshold of voxel $p<0.001$, uncorrected and cluster $p<0.05$ FWE-corrected, and showed activity during cent loss vs. nil in positive correlation with the SR score in men and women combined. We extracted the β contrast (cent loss – nil) for all subjects and compared men and women in the correlation with a slope test (49). The results showed that the β contrast was positively correlated with SR score for men ($r_{34} = 0.59$, $p = 0.00016$) but not for women ($r_{25} = 0.14$, $p = 0.48$), suggesting that the correlation was driven primarily by men. Further, a slope test confirmed the sex difference ($z = 2.004$, $p = 0.046$) (**Figure 6**).

[Figure 6 about here]

Discussion

We studied sex differences in reward processing in a sample of 63 healthy adults (27 women) using a monetary incentive delay task (MIDT). The volunteers made a timed response to win “the bet” of $1, ¢1, or nil. We examined how sex influenced behavioral performance and neural activation to monetary reward anticipation and feedback. Our results show that while there are no sex differences during reward anticipation, male sex is associated with increased cerebral activity to feedback of winning $1 (vs. nil) in the right orbitofrontal cortex, left cerebellum, bilateral SMA, and right occipital cortex, as well as increased cerebral activity to winning ¢1 (vs. nil) in the left premotor area and left SMA. These results suggest that males have heightened neural sensitivity to receiving monetary reward of higher or lower magnitude than females. As quantified by the SPSRQ, men showed higher sensitivity to reward (SR) and women showed higher sensitivity to punishment, in keeping with the literature (13, 14, 50). Although these sex differences did not appear to be reflected in behavioral performance in the MIDT, men but not women showed higher caudate response to cent loss in correlation with SR. We highlight the main findings in the discussion below.

Lack of sex differences in response to reward anticipation

Our results showed that there were no significant sex differences in neural activation to reward anticipation. Reward anticipation is central to associative learning, and this finding is broadly consistent with animal behavioral studies reporting no sex differences in reward guided associative learning in male and female rodents (27). In human imaging literature, both men and women have been found to activate a wide neural network to anticipation of monetary reward (38). Similarly enhanced activation in the VS, ventral tegmental area, and ventromedial prefrontal cortex was observed in both sexes in anticipation of smiling faces of the opposite sex (51). No sex differences were found in activation of the reward circuits during anticipation of sexually explicit materials (52-54). However, one study showed increased activation in men vs. women of the ventral putamen during reward anticipation in a gambling task. This same study found that women’s reward circuit was more reactive to anticipation of uncertain reward during the mid-follicular, when estrogen levels are high, than luteal menstrual phase (55). Thus, our findings need to be interpreted with caution because of a limited sample size and lack of control of menstrual phase in female participants. It is also likely that sex differences or the lack thereof in regional responses to reward anticipation may depend on the behavioral contingencies; i.e., whether the motor decision involves learning or simply guessing or a speedy response to acquire the reward.

Sex differences in response to feedback and reward sensitivity

Behaviorally, while men and women each showed higher SR and SP score, in accord with earlier reports using the SPSRQ (14, 56), SP and SR score appeared to influence task performance in both sexes.

However, men and women differed in regional responses to reward. Relative to women, men engaged the right orbitofrontal cortex (OFC), left cerebellum, bilateral supplementary motor area (SMA), and right occipital cortex to a greater extent in response to dollar win vs. nil and the left temporal cortex and SMA to cent win vs. nil. The OFC is involved in learning and optimal decision-making (57), encoding motivational salience of stimuli to support approach behavior (57, 58), and integrating stimulus attributes and emotional value (59-62). Part of the supplementary motor complex, the SMA is crucial to voluntary motor and cognitive control (63-65). Thus, these findings suggest greater male sensitivity to monetary reward, in accord with the literature. For instance, an ERP study in adolescents reported higher feedback P3 amplitude in boys, as compared to girls, in response to monetary rewards (33). Another study reported a preferential response of the OFC to attractive vs. unattractive faces in men but not in women (66).

In addition to these findings from a direct comparison of men and women, men but not women showed higher caudate response to cent loss vs. nil in correlation with SR score, and this sex difference was confirmed by a slope test. The caudate nucleus receives heavy dopaminergic innervations from the midbrain and is highly connected with prefrontal cortical structures central to cognitive control (67, 68). In our previous study of the MIDT task, activation of the right caudate head, along with the SMA and right anterior insula during reward anticipation, was correlated with diminished differences in RT collecting a large vs. small reward, suggesting its role in reward-based cognitive motor control (69). However, here, the response of the caudate is aligned with cent loss, indicating a heightened sensitivity of this subcortical structure to feedback in men with greater sensitivity to reward. This finding highlighted sex differences in the neural correlates of reward sensitivity and suggested a versatile role of the caudate in reward-related behavioral contingencies.

Limitations And Conclusions Of The Study

A number of limitations need to be considered for the study. First, we did not record the menstrual phase of women, which may have introduced variance to influence the current findings. Second, we did not study sex-based variation in general incentive salience. Men relative to women are more motivated by monetary reward; however, the current findings cannot be generalized to other (e.g., social) rewards or behavioral contingencies. Finally, the sample size is relatively small with respect to addressing sex differences. Thus, these findings should be considered preliminary.

To conclude, we replicated higher male sensitivity to reward and female sensitivity to punishment as evaluated by the SPSRQ. Although these individual differences did not translate to influence behavioral performance in the MIDT, likely due to a small sample size, men and women exhibited differences in neural responses to reward. Overall, men relative to women showed higher regional responses to the receipt of reward and higher caudate activation to a small loss in correlation with individual differences in reward sensitivity. These findings demonstrate how men and women may differ in reward-related brain activations in the MIDT and add to the imaging literature of sex differences in cognitive and affective functions.

Perspectives and Significance

Men and women differ in trait and neural sensitivity to reward and punishment. The literature nearly consistently finds men to be more sensitive than women to monetary reward. These heightened neural responses to monetary feedback involve the cognitive motor circuits, including the SMA and caudate nucleus, and would likely influence a wide range of reward-related behavior. The sex differences in reward and punishment sensitivity may have a greater impact on neural activation to reward processing and reward-related decision making than we were able to demonstrate with the data collected of the MIDT. It remains to be seen whether or how these behavioral and neural sensitivity manifest in other laboratory paradigms and real-life decision making. Further, it is unclear how genetic and sociocultural factors may contribute to the sex differences. Sex differences in the incidence and phenomenology of neuropsychiatric and behavioral disturbances such as anxiety, depression, and substance abuse are known to be directly related to reward saliency processing and reward-based learning. It would be of significant interest to public health whether a gender-free or gender-less upbringing, now an emerging trend in child rearing, may alter the picture of sex differences in reward processing and in the susceptibility to neuropsychiatric illness that we find in our society today.

Declarations

Ethics approval and consent to participate

The Human Investigation Committee at Yale University School of Medicine approved the study and all subjects gave written informed consent prior to participation.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study have not been deposited in a public venue but are available on request for non-profit academic research.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

CRL and ShZ contributed to the conceptualization and design of the study. ID and SiZ contributed to participant recruitment and execution of the MR scans. ID, ShZ, TL and WW contributed to data analyses. All authors contributed to the writing and revision of the manuscript.

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Figures

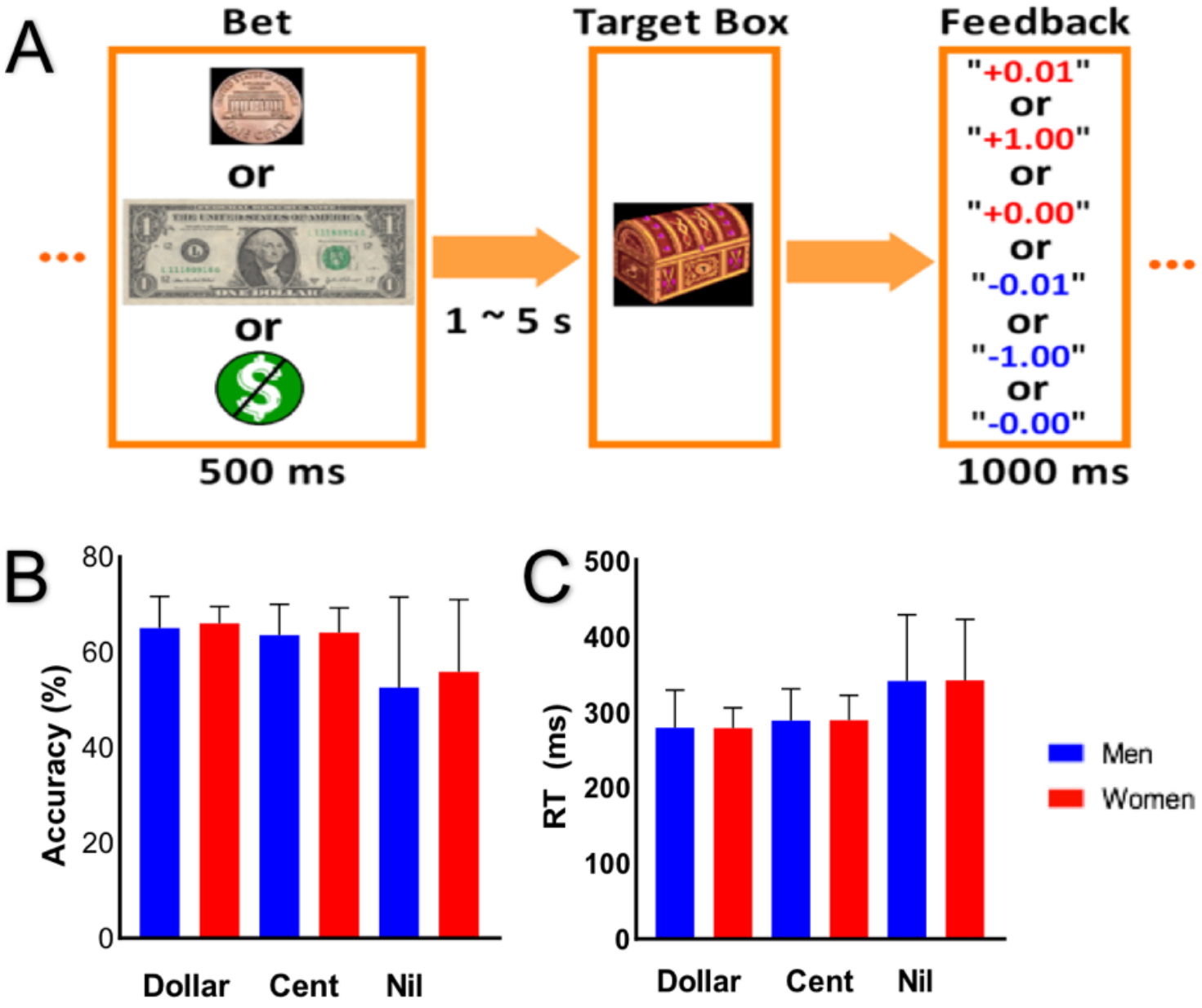

Figure 1

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, then 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. Otherwise, subjects lost the bet, with the amount deducted from their total winnings. 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) for men and women.

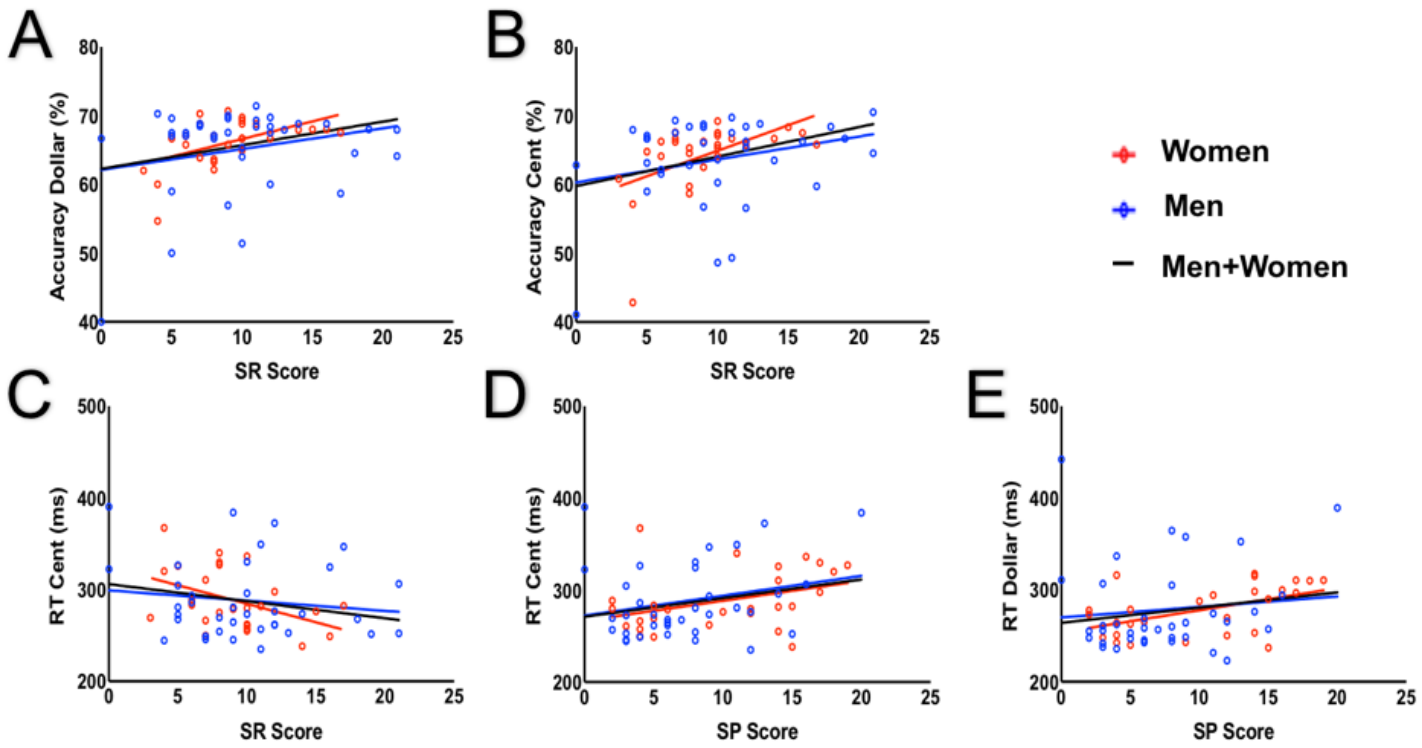

Figure 2

Linear regressions between SPSRQ scores for men, women, and men+women, for Accuracy and RT of dollar and cent trials.

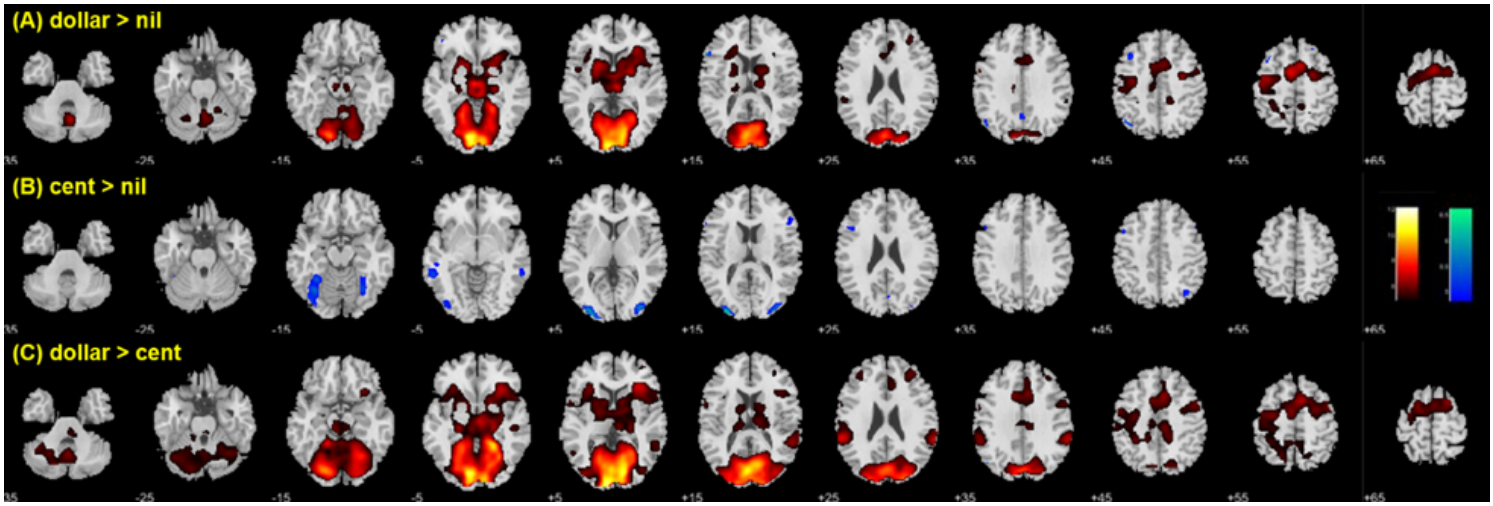

Figure 3

Regional activations during anticipation to win (A) dollar vs. nil; (B) cent vs. nil; and (C) dollar vs. cent. Clusters showing greater response to dollar > nil and nil > dollar, etc., are shown in warm and cool colors, respectively. Color bars indicate voxel T value. Voxel p<0.05 FWE corrected. Neurological orientation: right is right.

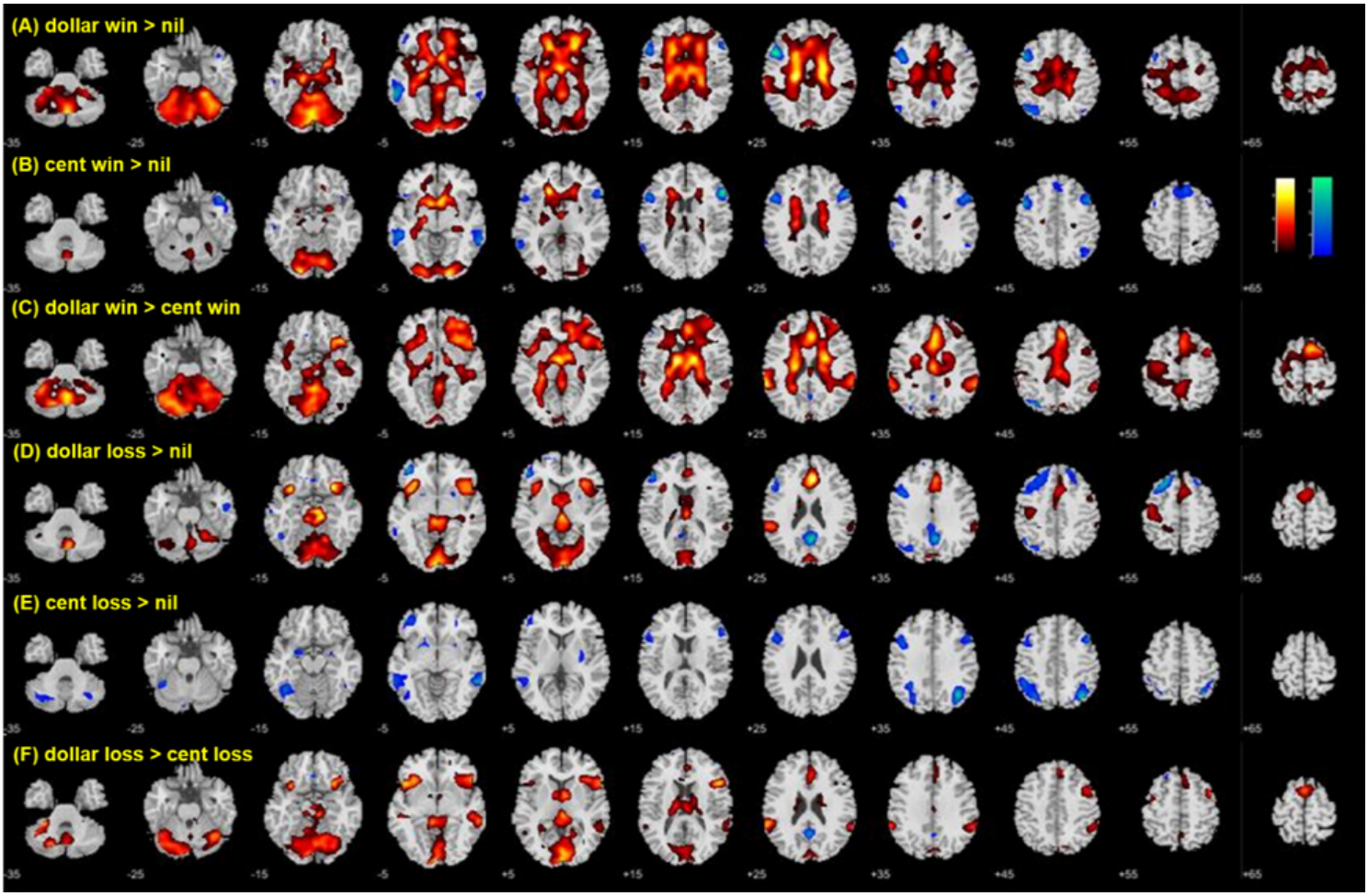

Figure 4

Regional activations to outcomes: (A) dollar win vs. nil; (B) cent win vs. nil; (C) dollar vs. cent win; (D) dollar loss vs. nil; (E) cent loss vs. nil; and (F) dollar vs. cent loss. Clusters showing greater response to dollar > nil and nil > dollar, etc., are shown in warm and cool colors, respectively. Color bars indicate voxel T value. Voxel $p<0.05$ FWE corrected. Neurological orientation: right is right.

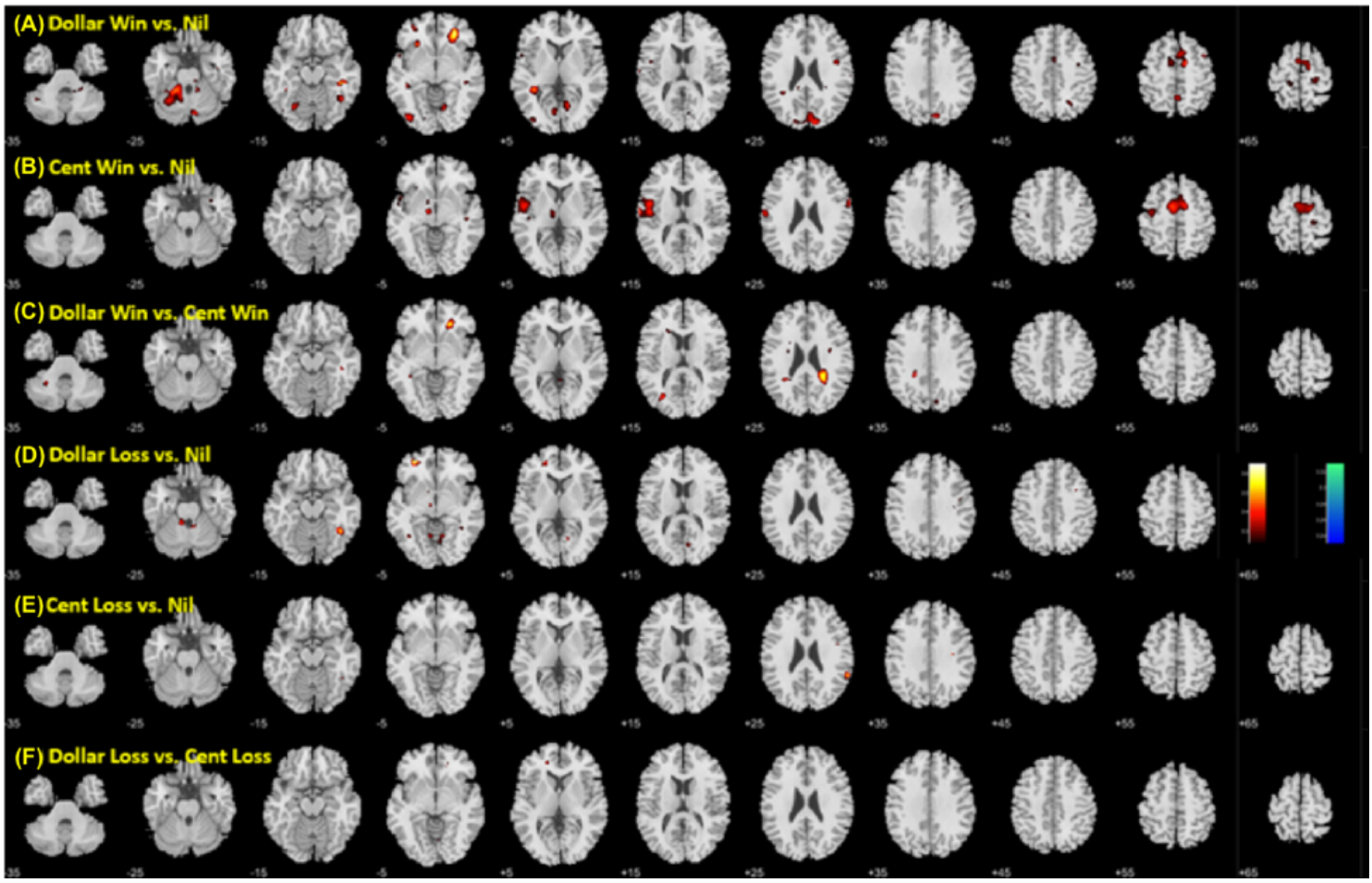

Figure 5

Covariance analyses of men vs. women, with age as a covariate, of (A) dollar win vs. nil (B) cent win vs. nil (C) dollar win vs. cent win (D) dollar loss vs. nil (E) cent loss vs. nil (F) dollar loss vs. cent loss. Clusters showing greater responses in men vs. women and women vs. men are shown in warm and cool colors, respectively. Color bars indicate voxel T value. Neurological orientation: right is right. Voxel $p<0.001$, uncorrected. Clusters that met cluster $p<0.05$ FEW corrected are summarized in Table 3.

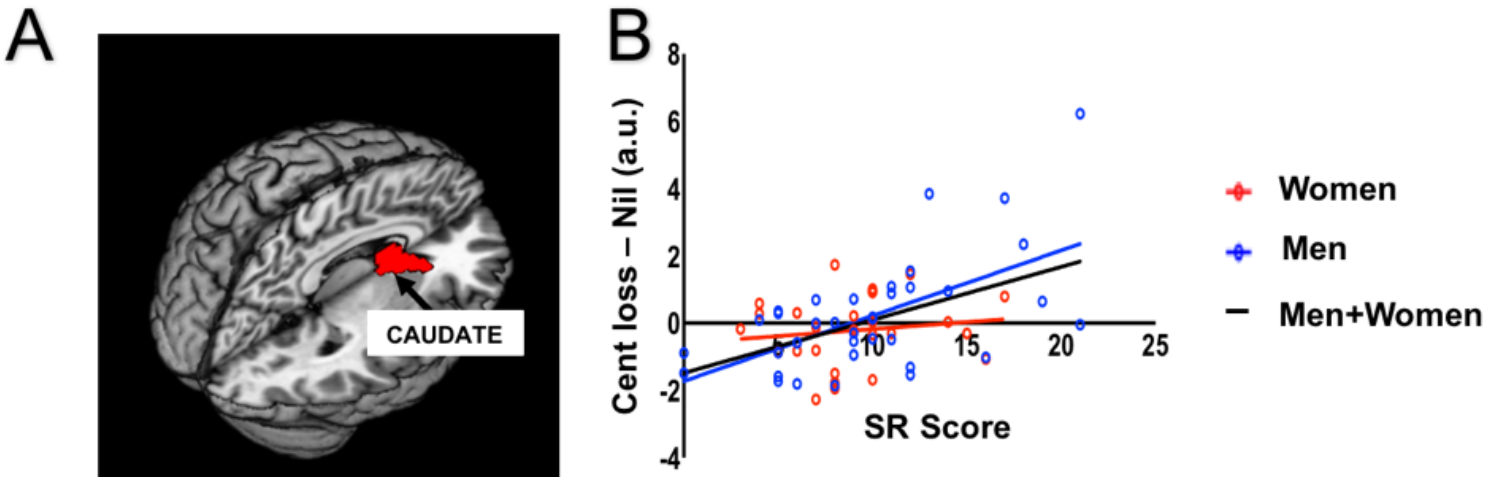

Figure 6

Slope test to confirm sex differences in caudate response to cell loss vs. nil. (A) The caudate head showed higher response to cent loss vs. nil in correlation with SR score in men. (B) Men but not women showed correlation of caudate response with SR score, and the sex difference was confirmed by a slope test (p=0.046).