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Research report

The effects of age on cerebral responses to self-initiated actions during social interactions: An exploratory study

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ABSTRACT

Self-initiated action is critical to social interaction and individuals with social anxiety find it particularly difficult to initiate social interactions. We showed earlier that social exclusion encumbered self-initiated actions in the Cyberball task in young adults. Here, we examined whether the behavioral performance and regional responses during self-initiated actions vary with age in 53 participants (21–74 years; 27 men). Behaviorally, participants were slower in tossing the ball during exclusion (EX) than during fair game (FG) sessions in both men and women. In women but not in men the reaction time (RT) burden (RT_EX – RT_FG; RT prolonged during social exclusion) of ball toss was positively correlated with age despite no observed sex difference in Social Interaction Anxiety Scale scores. The pregenual anterior cingulate cortex, thalamus, left occipital cortex (OC) and left insula/orbitofrontal cortex responded to ball toss in EX vs. FG in negative correlation with age in women but not in men. Further, the activation of left OC fully mediated the relationship between age and RT burden in women. Thus, older women are more encumbered in self-initiated action during social exclusion, although this behavioral burden is not reflected in subjective reports of social anxiety. Age-related diminution in OC activities may reflect the neural processes underlying the difficulty in initiating social interactions in women. Together, the findings identified age-sensitive behavioral and neural processes of self-initiated action in the Cyberball task and suggest the importance of considering age and sex differences in studies of social interaction.

1. Introduction

Human emotion is heavily embedded in a social context and social interaction is essential for psychological well-being. Social interactions can be challenging for the elderly, because of physical limitations, lack of family support, or relatively isolated living conditions. However, while not rare, social anxiety disorder does not appear to affect old people (12-month prevalence rate ~ 2%; [1]) as frequently as the general population (~7%; NIMH, 2016, [2]). One possibility is that, as suggested by decades of affective neuroscience research [3], old and young people employ different emotion regulation mechanisms and the elderly are less vulnerable to negative emotional experiences [4]. However, it remains unclear whether or how the behavioral and neural processes of social interaction may differ between young and older people. Understanding these processes in a controlled, laboratory setting may shed light on the effects of age on social interaction and inform age-sensitive etiologies of social anxiety.

Many studies employed a Cyberball task [5,6] to investigate the neural correlates of social exclusion in health [7] and illness [8]. In the Cyberball tasks, by observing players tossing a ball to fellow players or with themselves engaged in the game, participants are involved in the dynamics of social interactions. A behavioral study showed that social exclusion elicited negative cognitive and affective responses even if the participants were told that they were interacting with a computerized game [9]. Imaging studies showed that social exclusion as compared to inclusion engaged the insula, dorsal anterior cingulate cortex and other prefrontal cortical regions ([6,10–15]; see [16] for a review), cortical circuits that have been implicated in processing negative emotions and

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salient events. In recent work using the Cyberball task, we showed that social exclusion, as compared to a “fair game” scenario, encumbered self-initiated actions and engaged distinct neural processes during self-initiated actions [17,18].

The literature is relatively scanty about the effects of age on brain responses to social exclusion. Behavioral studies show robust emotional effects of social exclusion in younger adults [19], but emotional responses to social exclusion may be less pronounced during middle and late adulthood. In general, aging is associated with a lower frequency of negative social interactions and less intense affective responses during social conflicts [20]. Older as compared to young adults are less likely to report negative responses to social rejection [21]. Socio-emotional selectivity theory suggests that older adults may be less impacted by ostracism because of an age-related positivity bias [22,23]. On the other hand, older people may face more barriers and experience more fear in social interactions [24], and find it more difficult to initiate new friendships [25]. A recent meta-analysis reported higher activity in the lateral and medial prefrontal and posterior cingulate cortex during the Cyberball task during adolescence and emerging adulthood as compared to young adulthood [26]. Whether these cortical activities continue to diminish through late adulthood remains unclear. Together, more research is needed to understand how aging influences social interactions and the neural processes underlying these influences.

Numerous studies have reported sex differences in cerebral responses during exposure to emotional stimuli and emotion regulation. In the Trier Social Stress Test female as compared to male participants showed higher ratings of fear, irritability and unhappiness [27]. Compared to women, men showed higher visual cortical activity during exposure to pleasant pictures [28] and less prefrontal cortical, ventral striatal, and amygdala activity during reappraisal to down-regulate negative emotions [29]. Other studies reported sex differences in a wide range of social cognitive processes [30,31], with women showing greater interest in social information and stronger empathic attitudes than men [32–34]. Men and women each responded more with other- and self- focused attention following negative social feedback [35]. A recent review highlighted that women are more likely to have social anxiety disorder (SAD) and report greater clinical severity, whereas men with SAD seek treatment more frequently [36]. No imaging studies have specifically examined sex differences in the neural processing of social interactions. However, a meta-analysis of the neural effects of acute oxytocin, a hormonal peptide known to regulate social emotion and behavior, suggested sex differences in brain responses to social emotions [37]. Together, these studies indicated the importance of considering sex in research on the behavioral and neural processes of social interactions.

A critical component of social interaction involves self-initiated actions, which engage awareness of one's own intention to influence other people [38]. This intention or self-agency enables understanding of others’ emotions during social interactions [39]. Importantly, initiation of social interaction can be challenging, particularly for those with complex communication needs and social anxiety [40,41]. Here, we explored the effects of age on self-initiated actions and the neural processes underlying these effects. Fifty-three adults participated in fMRI under three different conditions of a Cyberball task: observation (OB) where participants observed two fictive fellows playing; fair game (FG), where participants were equally involved in 3-way interaction; and exclusion (EX), where participants were largely excluded from the game. We focused on ball toss trials between EX and FG to investigate the effects of age and sex on the behavioral and neural processes of self-initiated actions. In considering sex differences, we analyzed the data in men and women combined and separately.

Table 1
Demographic, clinical and performance data.

	men (n = 27)	women (n = 26)	t value	p value
Age (years)	40.3 ± 13.0	46.2 ± 14.1	−1.574	0.1217
SIAS score	36.6 ± 21.8	34.2 ± 21.2	0.409	0.6843
BDI-II score	12.0 ± 11.1	10.4 ± 12.5	0.487	0.6285
RT (s): EX_T-FG_T	0.61 ± 0.72	0.56 ± 0.87	0.238	0.8129

Note: SIAS: Social Interaction Anxiety Scale; BDI: Beck Depression Inventory; RT (s): EX_T-FG_T: reaction time difference in ball toss between exclusion (EX) and fair game (FG) sessions.

2. Materials and methods

2.1. Subjects and assessments

Fifty-three volunteers (21–74 years old; 26 females) (Table 1) participated in the study. Participants underwent clinical evaluation at intake assessment and received urine toxicology tests prior to imaging, as part of our study routine. All were required to be physically healthy with no major medical including neurological illnesses, current use of prescription medications, history of head injury, or history of a psychotic disorder. All participants were right-handed and used the right hand to respond in the behavioral task. Prior to the study, all participants signed an informed consent according to a protocol approved by the Human Investigation Committee at Yale University.

We used the Social Interaction Anxiety Scale (SIAS) to quantify social anxiety [42]. The SIAS evaluates fears of general social interaction, shows excellent internal consistency and test-retest reliability, and captures treatment-related changes in anxiety [42]. Each of the 20 items is scored from 0 to 4, with three items to be reversed scored. Factor analysis revealed one distinct factor – fear of social interaction – with all items showing high loading on the factor. All 20 items of the SIAS significantly distinguished social phobia from agoraphobia, simple phobia and healthy community samples. Individuals with social anxiety disorder showed a score of 33.4 ± 16.4 (mean ± SD) in women and 36.0 ± 16.5 in men, compared to 19.4 ± 11.9 for women and 18.2 ± 11.7 for men in the community sample [42]. The current cohort showed an SIAS score of 34.2 ± 21.2 for women and 36.6 ± 21.8 for men (Table 1). Participants were also evaluated with the Beck Depression Inventory or BDI-II [43]. Each of the 21 answers is scored on a scale from 0 to 3, with a total score of 0–13 suggesting minimal depression; 14-19: mild depression; 20-28: moderate depression; and 29-63: severe depression. The total score of men and women were 12.0 ± 11.1 and 10.4 ± 12.6, respectively. Thus, the current sample comprised some individuals with clinical anxiety but all without prominent depression symptoms.

2.2. Experimental procedures and data analyses

2.2.1. Cyberball task

Participants were engaged in a variant of the Cyberball task [5] during fMRI. Participants were instructed to play a ball game via the Internet with two other individuals as named on the screen, who were fictive figures controlled by a computer program. Ball toss, catch, and drop were each accompanied by a distinct audio. Participants were instructed to do their best to catch the ball by estimating its arrival time and pressing a button; too early or late a response would result in a “drop” (see below). In turn, participants pressed one of two buttons to decide which of the two fictive figures to toss the ball to.

There were three different scenarios: (1) observation (OB), in which participants were instructed to simply watch; (2) fair game (FG), in which participants received/tossed the ball approximately 1/3 of the time; and social exclusion (EX), in which participants were tossed the ball approximately 1/12 of the time. Individual sessions lasted 8 m each, separated by a break in between, with two sessions per scenario and following a fixed order: OB-break (~1 m)-FG-break-EX-break-OB-break-FG-break-EX. Within each session, a trial started with a ball toss initiated by a fictive player. The fictive player was animated to appear to think and look alternatingly at the participant and the other fictive player before tossing (2.0–16.0 s, uniform distribution). The ball traveled at different speeds for 3.4–6.6 s and in FG and EX the participants were allowed a time window of 2 s to catch the ball if tossed to. The fictive player smiled or frowned for 2.4 s (the latter together with a "drop" sound delivered), depending on whether the participant caught the ball, to end the trial. The results showed that in FG participants successfully received the ball most of the time, with an average drop rate of 10.7 ± 10.9 (mean ± SD) %. In EX, the participants failed to catch the ball all the time, an outcome controlled by the program without participants' knowledge. The two fictive players caught the ball successfully in all scenarios.

On average, a trial took 15.8 ± 4.8 s in OB, 14.0 ± 6.7 s in FG, and 15.2 ± 5.4 s in EX. With 16 (8 × 2) m per scenario, there were approximately 61 trials of observation in OB; 23 trials each of observation, ball tossed to, and from the participant in FG; and 51 trials of observation, and 6 trials each with ball tossed to and from the participant in EX. The small number of catch and loss trials were meant to elicit robust perception of exclusion in the EX. The program dictated that participants failed to catch in order to substantiate a rationale for exclusion by the fictive players in EX. We compared the reaction time (RT) of ball toss from participants in EX (EX_T) with that in FG (FG_T), i.e. the RT of EX_T - FG_T, as a behavioral index of the burden of self-initiated actions.

2.2.2. FMRI procedures and data analyses

Imaging was conducted with a 3-Tesla scanner (Siemens Trio, Erlangen, Germany), with scout scans, high-resolution MPRAGE, and blood-oxygenation-level dependent BOLD scans acquired with multi-band-multiplexed T2*-sensitive gradient-recalled, single-shot echo-planar imaging pulse sequence (iPat = 2, multiband = 4, TR = 1 s, TE = 31 ms, FoV = 192 mm, flip angle = 62°, matrix size = 96 × 96). Each volume consisted of 64 slices parallel to the bi-commissural plane (slice thickness 2 mm, no gap), and each BOLD run comprised 8 m or 480 volumes. Each scan comprised six 8-minute BOLD runs of the Cyberball task.

All images were thoroughly inspected before pre-processing. Imaging data were analyzed with SPM12 (Wellcome Department of Imaging Neuroscience, University College London, U.K.). In the pre-processing of BOLD data, images of each participant were realigned (motion-corrected) and corrected for slice timing. A mean functional image volume was constructed for each participant for each run from the realigned image volumes. These mean images were co-registered with the high resolution structural image and then segmented for normalization to an MNI (Montreal Neurological Institute) EPI template with affine registration followed by nonlinear transformation [44,45]. Finally, images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum. Images from the first five TRs at the beginning of each trial were discarded to ensure that the BOLD signals with steady-state equilibrium between radio-frequency pulsing and relaxation were included in the analyses.

A general linear model (GLM) was constructed for each individual subject, with the onsets of ball toss (from the fictive players and the participant) in each trial convolved with a canonical hemodynamic response function (HRF) and with the temporal derivative of the canonical HRF and entered along with realignment parameters as regressors in the model [45]. Head motions in 6 dimensions were entered in the GLM. Serial autocorrelation was corrected by a first-degree autoregressive model and the data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts.

In the first-level analysis, we construct for each individual subject the contrast "EX_T – FG_T" (difference in β) for group-level, random effects analysis (RFX). In the RFX, we examined the neural correlates of self-initiated actions by comparing trials when participants tossed the ball in EX vs. FG with a one sample *t-test* for men and women combined as well as separately. We also conducted simple regressions, each with age and with the SIAS score as a regressor, for men and women combined as well as separately. All group analyses were evaluated at voxel $p < 0.001$, uncorrected, in combination with cluster $p < 0.05$ FWE, on the basis of the Gaussia random field theory.

All data are available on the NIMH Data Archive (NDA) https://ndar.nih.gov/index.html.

2.2.3. Mediation analysis

To examine potential inter-relationships of age, neural activity, and task performance, we conducted mediation analyses using a single-mediator model (MacKinnon et al., 2007), as detailed in our previous work [46–49]. Briefly, in a mediation analysis, the relation between the independent variable X and dependent variable Y; that is, X → Y is tested to determine whether it is significantly mediated by a variable M. The mediation test is performed using the following three regression equations:

$$Y = i1 + cX + e1$$

$$Y = i2 + c'X + bM + e2$$

$$M = i3 + aX + e3$$

Where, a represents X → M, b represents M → Y (controlling for X), c' represents X → Y (controlling for M), and c represents X → Y. In the literature, a, b, c, and c' were referred to as "path coefficients" or simply "paths," and we followed this notation. Variable M is said to be a mediator of connection X → Y, if (c – c'), which is mathematically equivalent to the product of the paths a × b, is significantly different from zero (MacKinnon et al., 2007). If (c – c') is different from zero and the paths a and b are significant, then one concludes that X → Y is mediated by M. In addition, if path c' is not significant, it indicates that there is no direct connection from X to Y and that X → Y is completely mediated by M. Note that path b represents M → Y, controlling for X, and should not be confused with the correlation coefficient between Y and M. Significant correlations between X and Y and between X and M are required for one to perform the mediation test. The analysis was performed with package Lavaan (Rosseel, 2012) in R (https://www.r-project.org). To test the significance of the mediation effect, we used the bootstrapping method (Preacher & Hayes, 2004) as it is generally considered advantageous to the Sobel test (MacKinnon et al., 2007).

Specifically, we evaluated the inter-relationships between age, RT of EX_T – FG_T, and regional activity based on the β contrast (EX_T – FG_T) of left occipital cortex (OC) (see 3.2 Imaging results). Four models with age as the dependent or mediating variable were conceptually implausible; thus, a total of two models were considered. In Model 1, with age as the independent variable (X), RT of EX_T – FG_T as the dependent variable (Y), and neural activation as the mediator (M), age contributed to neural activation and, in turn, RT burden (RT of EX_T - FG_T): age → neural activation → RT burden. In Model 2, age, neural activation, and RT burden served as X, Y, and M, respectively.

3. Results

3.1. Clinical and behavioral findings

Men and women did not differ in age ($t = -1.574$, $p = 0.1217$), SIAS score ($t = 0.409$, $p = 0.6843$), or BDI score ($t = 0.487$, $p = 0.6285$), as shown in Table 1.

Linear regressions showed that age and SIAS score were not correlated in men ($r = -0.31$, $p = 0.1135$), women ($r = -0.18$, $p = 0.3712$), or men and women combined ($r = -0.25$, $p = 0.0678$). Likewise, age was not correlated with BDI score in men ($r = -0.38$, $p = 0.0526$), women ($r = -0.02$, $p = 0.9386$), or men and women combined ($r = -0.19$,

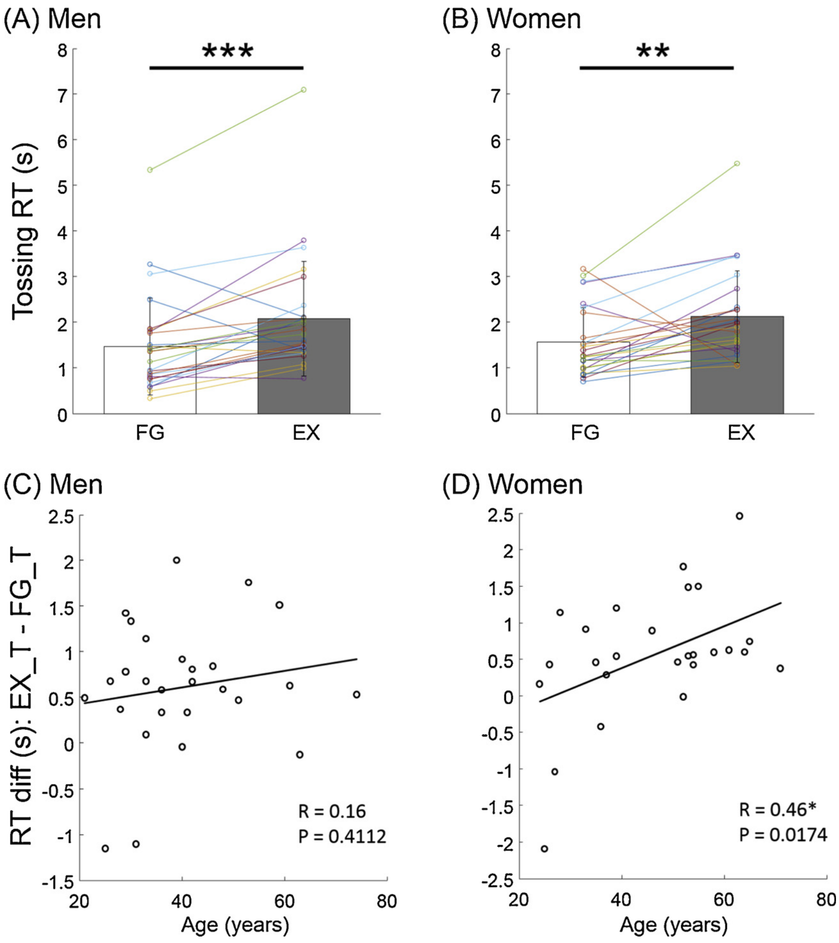

Fig. 1. Behavioral data in the Cyberball task. (A, B) Reaction time (RT) of ball tossing in FG and EX sessions in (A) men and (B) women. Group mean ± S.E. as well as individual data points are shown each for FG and EX. Both men and women were slower in tossing the ball during EX than during FG. ** $P < 0.01$, *** $P < 0.001$, two-tailed paired *t-test*. (C, D) Linear regression showed that the RT "burden" – difference in toss RT between EX and FG sessions (EX_T – FG_T) – was positively correlated with age in women but not in men.

$p = 0.1686$). However, SIAS and BDI scores were positively correlated in linear regressions with (men: $r = 0.64$, $p = 0.001$; women: $r = 0.54$, $p = 0.004$; men and women: $r = 0.57$, $p = 0.0001$) or without (men: $r = 0.68$, $p = 0.0003$; women: $r = 0.58$, $p = 0.0014$; men and women: $r = 0.61$, $p = 0.000$) age as a covariate.

The RT of ball toss was quantified by subtracting the time when the participant got hold of the ball from the time when the participant threw the ball. The RT was computed separately for the FG and EX session. Participants showed a slower RT in throwing the ball during the EX as compared to the FG session: 2.08 ± 1.23 vs. 1.47 ± 1.07 s, $t_{(26)} = 4.43$, $p = 0.0002$, two-tailed paired-sample *t-test* (men); 2.12 ± 1.00 vs. 1.57 ± 0.76 s, $t_{(25)} = 3.26$, $p = 0.0032$ (women) (Fig. 1A and B); 2,10 ± 1.13 vs. 1.52 ± 0.92 s, $t_{(52)} = -5.39$, $p = 0.00002$ (men and women combined). This RT "burden" did not differ between men and women ($p = 0.8129$) (Table 1). Further, RT (EX_T – FG_T) was positively correlated with age in men and women combined ($r = 0.32$, $p = 0.0214$), in women ($r = 0.46$, $p = 0.0174$) but not in men ($r = 0.16$, $p = 0.4112$) (Fig. 1C and D). However, a slope test did not show sex difference in the regressions ($z = 1.15$, $p = 0.2501$, two-tailed).

Reaction time burden (RT: EX_T – FG_T) did not correlate with SIAS (all p's > 0.3664) or BDI (all p's > 0.3529) scores in men, women, or men and women combined with age or without age as a covariate in linear regressions.

3.2. Imaging findings

3.2.1. Neural correlates of self-initiated actions

In imaging data analysis, we identified differences in neural activations to self-initiated actions during social exclusion vs. fair game (EX vs. FG) in men, women, and all. The results showed higher activations in bilateral frontoparietal cortex, medial prefrontal cortex, including the anterior cingulate and pre-supplementary motor area, thalamus, anterior insula, visual and inferior temporal cortex, including parahippocampal gyri, inferior parietal cortex, temporo-parietal junction, and mid-cingulate cortex (Fig. 2). Clusters that met cluster $p < 0.05$ FWE corrected are summarized in Table 2. Women alone showed a largely similar pattern of activations whereas men alone showed activations restricted to bilateral visual and inferior temporal cortices, medial prefrontal cortex, and inferior parietal cortex. However, a two-sample *t-test* did not show any significant sex differences with or without age as a covariate, at $p < 0.001$, uncorrected.

3.2.2. The effects of age on neural responses to self-initiated actions

To examine the effects of age we conducted whole brain regression of the contrast images EX_T – FG_T vs. age for men and women combined as well as men and women separately. The results showed that age was negatively correlated with activity in pregenual anterior cingulate cortex (pgACC) during EX_T vs. FG_T in men and women combined. Men alone showed no significant clusters. In women alone, the thalamus, left occipital cortex (OC) in the area of calcarine sulcus and cuneus, medial prefrontal cortex (mPFC) including the pgACC, and a cluster involving the left insula and orbitofrontal gyrus (OFG) showed activities in negative correlation with age (Fig. 3; Table 3). Age-related reduction in pgACC activity may reflect less emotional engagement in social interactions in older as compared to younger individuals.

To confirm the sex differences in these age-relate regional activities, we extracted the beta weight of EX_T – FG_T of brain regions showing age correlations in women for all subjects. For the thalamus the beta weight was significantly correlated with age in women ($r = -0.79$,

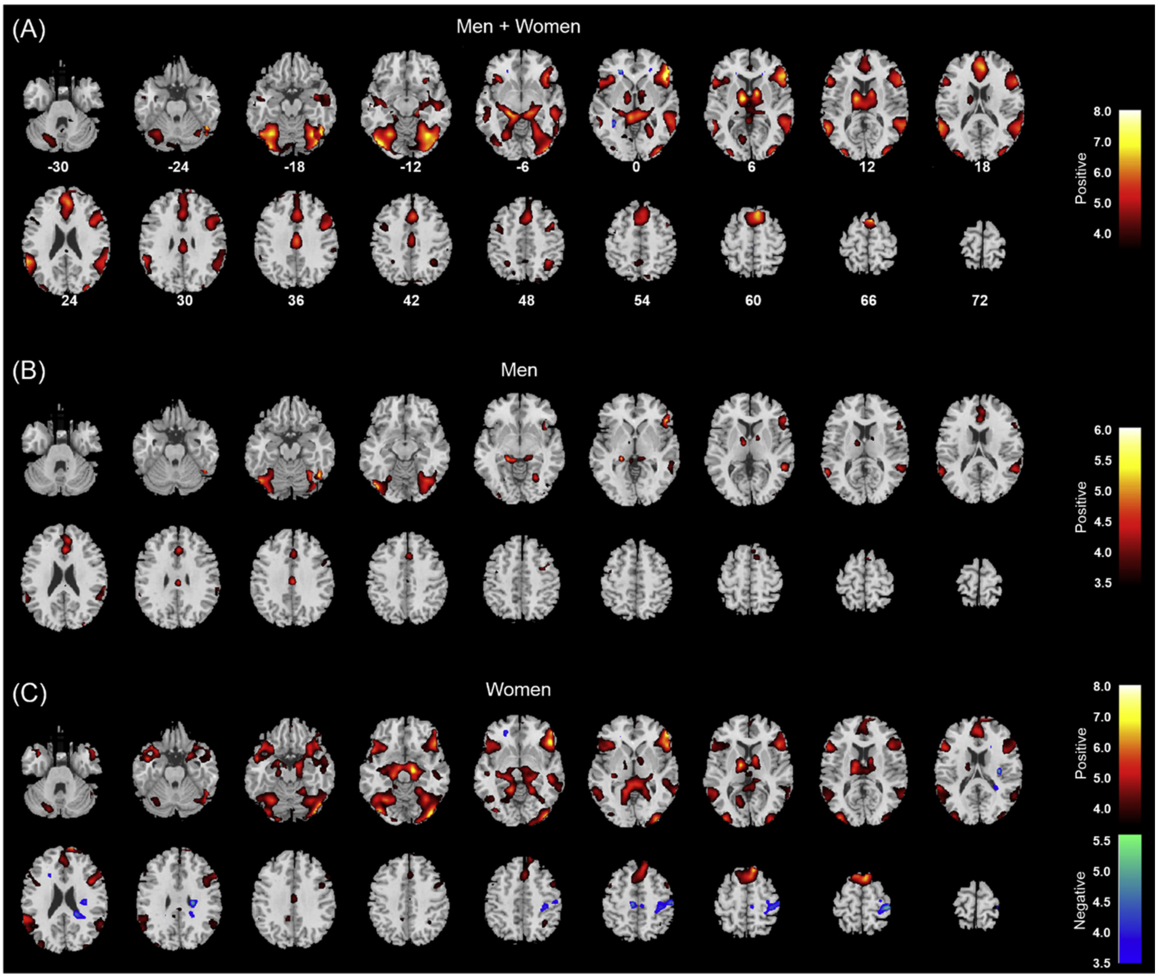

Fig. 2. The neural responses to self-initiated action (ball tossing) during social exclusion (EX) vs. fair game (FG): one-sample *t-test* of EX_T vs. FG_T (warm color: EX_T > FG_T; cool color: FG_T > EX_T) for (A) men + women, (B) men, and (C) women. Clusters are overlaid on a structural template in axial sections, from $z = -30$ to $+72$, with 6 mm between sections. Voxel $P < 0.001$. Color bars show voxel p values. Clusters meeting cluster $p < 0.05$, FWE are listed in Table 2.

$p < 0.001$), as expected, but not in men ($r = -0.10$, $p = 0.6310$); a slope test confirmed sex differences in the slopes of age regression ($z = -3.35$, $p = 0.0008$). For the L OC the beta weight was significantly correlated with age in women ($r = -0.69$, $p < 0.001$) but not in men ($r = -0.10$, $p = 0.6230$); a slope test showed significant sex difference ($z = -2.54$, $p = 0.0111$). For the L Insula/OFC the beta weight was correlated significantly with age in women ($r = -0.74$, $p < 0.001$) but not in men ($r = 0.04$, $p = 0.8372$); a slope test showed significant sex difference in the slope of the regressions ($z = -3.41$, $p < 0.001$). However, for the pgACC the beta weight was significantly correlated with age both in women ($r = -0.70$, $p < 0.001$) and, though with a smaller effect size, in men ($r = -0.41$, $p = 0.0343$); a slope test showed no sex difference ($z = -1.47$, $p = 0.1416$). These results are illustrated in Fig. 4.

We also performed a linear regression of the beta contrast (EX_T – FG_T) of these ROIs against RT (EX_T – FG_T) in women. The results showed that the beta contrast of the left OC ($r = -0.60$; $p = 0.001$) but not the other ROIs (all p's > 0.131) and the RT burden were significantly correlated. These findings suggested an inter-relationship between age, RT burden, and beta contrast of left OC in women. We thus performed a mediation analysis to examine the inter-relationship between age, left OC activity, and RT burden (Section 3.3).

3.2.3. *The effects of social anxiety on neural responses to self-initiated actions*

To examine the effects of SIAS score, we conducted whole brain regression of the contrast images EX_T – FG_T vs. SIAS score for men and women combined as well as men and women separately with age as a covariate. None of the regressions showed significant findings when evaluated at the same threshold (voxel $p < 0.001$, uncorrected).

3.3. *Mediation analysis*

As the results of linear regressions showed pairwise correlations between neural activity in the left occipital cortex (OC, highlighted in light blue in Fig. 3) during self-initiated actions between EX and FG sessions (EX_T - FG_T), age, and RT of EX_T – FG_T in female participants, we examined their inter-relationships in a mediation analysis. The neural activity was represented by the beta contrast extracted and averaged for the voxels within the left OC. As age was unlikely a mediator or dependent variable, we considered only two models with age as the independent variable (X). In Model 1: age → neural activation → RT burden, left OC activity significantly mediated the effect of age on RT of EX_T – FG_T (mediation effect or c - c' = 0.028, $p = 0.035$, 95% confidence interval = [0.006 0.060]). Specifically, the path coefficient c (i.e., X → Y before accounting for the mediating effect) was 0.030 ($p = 0.036$) and the path coefficient c' (i.e., X → Y after accounting for the mediating effect) was 0.002 ($p = 0.875$). Thus, the effect of age on RT burden became non-significant after accounting for the mediator, indicating that the neural activity fully mediated the relationship between age and RT burden. Model 2 (age → RT burden → neural activation) was not significant ($p = 0.080$). The results of

Table 2
One-sample *t-test* of EX_T vs. FG_T across Men + women, Men, and Women.

Group	Region	Cluster Size (voxels)	Voxel Z Value	MNI Coordinates (mm)		
				X	Y	Z
Men + Women	R IFG*	380	6.50	51	29	1
	L IOG*	341	6.50	−42	−79	−14
	Thalamus*	175	6.37	−9	−7	7
	R IOG*	538	6.23	42	−73	−17
	preSMA*	211	6.13	6	20	64
	Thalamus*	217	5.83	−6	−34	−2
	mPFC*	153	5.78	3	44	19
	L SMG*	185	5.67	−60	−46	22
	L MOG*	31	5.49	−33	−91	13
	R PrG*	17	5.35	45	5	49
	L MCgG*	51	5.30	0	−19	37
	R MTG*	287	5.19	60	−49	13
	L FO/lOFC*	86	5.13	−42	20	−5
	R SPL	193	4.64	36	−52	49
Men	R ITG/FuG	408	4.67	45	−61	−17
	L IOG	303	4.59	−45	−76	−11
	R IFG	199	4.44	51	29	1
	L STG	131	4.25	−60	−52	13
	R MTG	248	4.07	54	−43	4
	ACgG	289	3.98	3	29	28
Women	R IOG*	77	5.65	39	−88	−14
	R IFG*	108	5.53	51	44	−2
	midbrain*	29	5.47	15	−16	−11
	L Thalamus*	17	5.33	−12	−7	7
	R SFG*	40	5.12	9	29	61
	L IOG*	13	5.03	−39	−79	−11
	R SFG	404	4.75	15	65	25
	R PIns	149	−4.55	33	−16	19
	R PoG	235	−4.35	42	−28	67

Note: L: left; R: right. IFG: inferior frontal gyrus; IOG: inferior occipital gyrus; preSMA: pre-supplementary motor area; mPFC: medial prefrontal cortex; SMG: supramarginal gyrus; MOG: middle occipital gyrus; PrG: precentral gyrus; MCgG: middle cingulate gyrus; MTG: middle temporal gyrus; FO/lOFC: frontal operculum/ lateral orbitofrontal cortex; SPL: superior parietal lobule; ITG/FuG: inferior temporal gyrus/fusiform gyrus; STG: superior temporal gyrus; ACgG: anterior cingulate gyrus; SFG: superior frontal gyrus; PIns: posterior insula; PoG: postcentral gyrus. peak voxel $P < 0.001$, uncorrected. *Clusters with peak voxel $P < 0.05$, FWE-corrected; the number of voxels shown for these clusters reflected this voxel threshold.

mediation analyses are summarized in Fig. 5.

4. Discussion

Participants showed slower reaction time (RT) in ball toss during social exclusion (EX) as compare to fair game (FG) – a RT burden – in both men and women. The RT burden did not differ between men and women. In men and women combined and in women but not men alone, the RT difference (EX – FG) was positively correlated with age. The latter findings suggested that older as compared to young women but not men were more encumbered in initiating social interactions when they were socially isolated, although a slope test failed to reveal a difference in the regression slope. In imaging findings, we demonstrated the differences between EX and FG in the neural processes of self-initiated actions. Replicating earlier work with a smaller sample size [17], ball toss during EX as compared to FG engaged higher activity in bilateral temporal and occipital cortex, including the fusiform gyrus, anterior pre-SMA, right inferior frontal cortex, bilateral thalamus, bilateral inferior parietal cortex, including the temporal parietal junction, pgACC, dorsal ACC and midcingualte cortex. Age was associated with less activation of the pgACC in men and women combined. In addition, women showed age-related decreases in activity in bilateral thalamus, left anterior insula/orbitofrontal cortex and left occipital cortex (OC). Among these regions, activity of the left OC mediated the relationship between age and RT burden. We highlight the main findings in the following sections.

4.1. Age and self-initiated actions

All participants were slower in tossing the ball in EX than in FG and the RT burden (RT difference between EX_T and FG_T) was positively correlated with age, suggesting that self-initiated action is more burdensome during social exclusion in the elderly. Other behavioral studies have also provided evidence for aging-related difficulty in social interaction. For instance, in social mentalizing, old as compared to younger adults responded less accurately to stories about others' false beliefs, made less use of actors' intentions to judge the moral permissibility of behavior, and showed decreases in dorsomedial prefrontal cortical activity [50].

In men and women combined and in women but not men alone, the medial prefrontal cortex (mPFC), including the pregenual anterior cingulate cortex (pgACC), showed a negative correlation with age during self-initiated actions in EX vs. FG (i.e., EX_T – FG_T). The pgACC has been implicated in theory of mind and social emotional processing [51,52] and the age-related reduction in pgACC activity may reflect less emotional engagement in social interactions in older as compared to younger individuals. This finding is consistent with the role of the ventral ACC in processing social distress [53] and a diminished tendency toward negative emotions in the elderly, as described earlier. These findings also extend the work of Vijayakumar and colleagues, who reported age-related reduction in mPFC activities during the Cyberball task throughout young adulthood [26], although the study did not specify the psychological processes at play in this age-sensitive process. In a study with participants exposed to own-age vs. other-age facial emotions, the authors showed that empathic responses in younger, but not older, participants were positively correlated with engagement of the mPFC during processing of angry own-age faces [54]. Thus, reduction in mPFC activities may broadly underlie changes in social emotion processing during aging. On the other hand, it is important to note that, in our sample, neither social anxiety nor

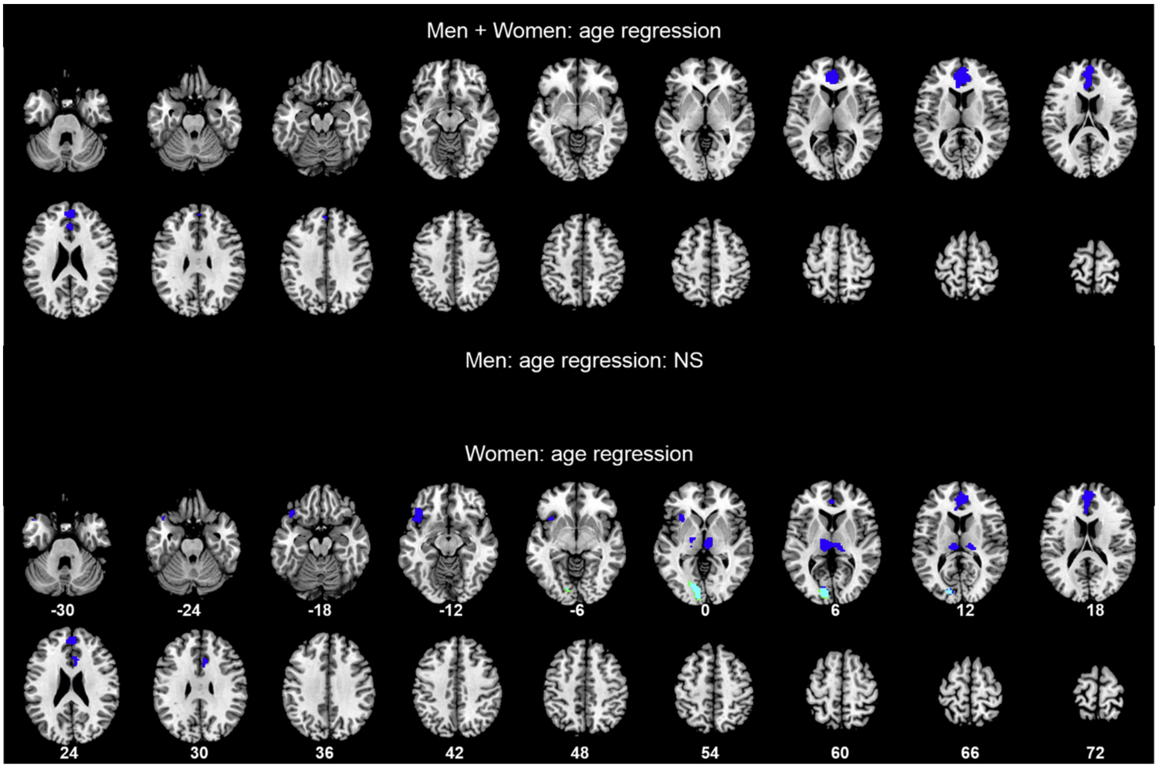

Fig. 3. The effects of age on neural responses to self-initiated activation during social exclusion (EX) vs. fair game (FG). EX tossing – FG tossing (EX_T – FG_T) involved activity of pregenual anterior cingulate cortex (pgACC) in negative correlation with age for men and women combined, and the thalamus, left occipital cortex (OC), medial prefrontal cortex (mPFC), including the pgACC, and left insula/orbitofrontal gyrus (OFG) in women. Voxel $P < 0.001$, and cluster $P < 0.05$ FWE corrected. The OC (light blue) served as a region of interest in mediation analysis (Section 3.3).

depression, evaluated with the Social Anxiety Interaction Scale and Beck Depression Inventory, respectively, appeared to be related to age. One would speculate that the neural markers are more sensitive measures than subjective reports in capturing age-related difficulty in initiating social interactions. Nevertheless, the functional implications of age-related changes in pgACC activation as observed here remain to be investigated.

4.2. Sex differences

Except perhaps for the pgACC, the age-related imaging findings appeared to be driven primarily by women, with the thalamus, left anterior insula/orbitofrontal cortex and occipital cortex showing age-related reduction in activation to self-initiated actions during social exclusion. These brain regions have all been implicated in social affective or conflict-related executive control [51,55–59]. In a structural imaging study of coping style and stress resilience in young adults, positive coping styles were associated with increased pgACC gray matter volume. Further, pgACC volume and positive coping predicted anxiety and depression in a sex-dependent manner with increased positive coping and pgACC volume being related to lower levels of psychopathology in females, but not in males [60]. Another study induced experimental pain by transcutaneous electrical stimulation of the sural nerve while measuring brain activity with evoked potentials and source localization. The results showed that subjective pain was strongly associated with increased pgACC activity in women but with decreased ventromedial prefrontal cortex activity in men [61]. Thus, age-related reduction in pgACC activity during social exclusion may have to do with greater pgACC response to social exclusion in younger as compared to older women. This finding is consistent with an earlier study suggesting that women may use positive emotions in the service of reappraising negative emotions to a greater degree than men [29]. This regulatory process may become more efficient, with less requirement of pgACC activity, as women become older.

The occipital cortex (OC) contains many areas that process visual information [62]. However, many imaging studies have implicated visual cortices in a variety of cognitive and affective processes. For instance, functional connectivity increased between left OC and

Table 3
Age-related regional activations to EX_T – FG_T in men and women, men, and women.

Group	Region	Cluster Size (voxels)	Voxel Z Value	MNI Coordinates (mm) X	Y	Z
Men + Women	pgACC	321	−4.65	−3	41	10
Men		NS				
Women	Thalamus	203	−4.67	−6	−22	7
	L OC	114	−4.03	−15	−88	10
	pgACC	224	−3.96	3	50	16
	L Insula/OFC	117	−3.90	−42	29	−14

Note: L: left; R: right. pgACC: pregenual anterior cingulate cortex; OC: occipital cortex; OFC: orbital frontal cortex. NS: no clusters significant; Voxel $P < 0.001$, and cluster $P < 0.05$ FWE corrected. As reflected in the Z value, all clusters showed negative correlation with age.

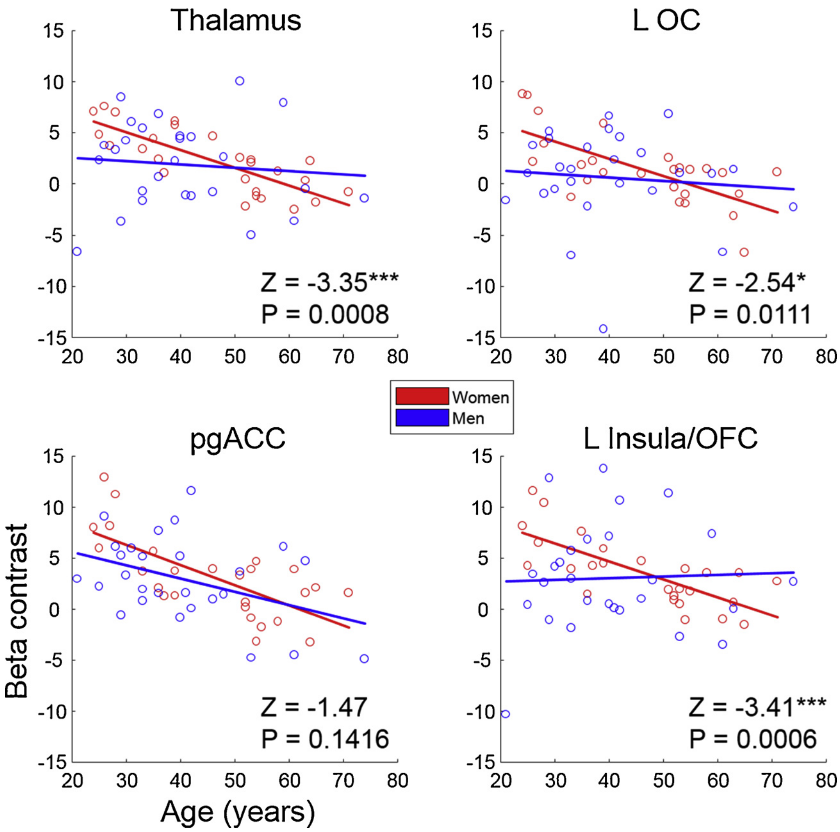

Fig. 4. Sex differences in age regressions of regional activities during self-initiated actions. Except for the pgACC, all regions of interest showed a significant sex difference in the slope of the regressions. L OC: left occipital cortex; pgACC: pregenual anterior cingulate cortex; OFC: orbitofrontal cortex.

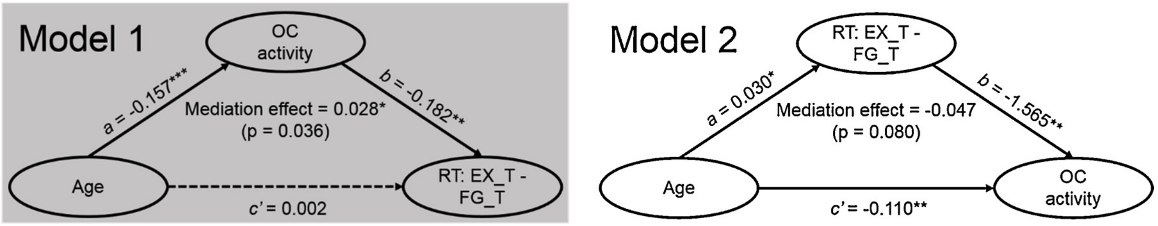

Fig. 5. Mediation models to account for the relationship of age, neural activation (beta contrast of left OC), and RT difference: EX_T - FG_T, in women. Model 1 showed a complete mediation (i.e., significant mediation effect a*b and not significant *c*'). Model 1 suggested that the age effect is associated with encumbered self-initiated actions through the decrease of left OC activity. Solid and dotted arrows each represent significant and non-significant correlations. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

hippocampus, insula, and frontal, parietal, and temporal cortices when individuals were exposed to emotional as compared with control stimuli [63]. Recent work reported greater response in the left OC to empathy during social exclusion as compared to the inclusion condition [64]. Other studies implicated the OC in altered functional connectivity as evaluated by graph theoretic metrics in individuals with social anxiety disorder (SAD) [65]. Further, in an earlier study, patients with SAD as compared to controls showed reduced attentional enhancement of visual regions during exposure to negative facial emotions, which may reflect avoidance of angry faces [66]. Here, we showed in mediation analysis that the left OC mediated the correlation between age and age-related burden in initiating social interactions during social exclusion in women. The finding adds to the literature by highlighting age-related visual cortical activities in self-initiated actions during social interactions. On the other hand, it remains to be clarified whether the reduction in OC activities reflect an active strategy to down-regulate negative emotions or age-related diminution in passive responding to negative social emotions.

4.3. Limitations, conclusions and potential clinical implications

A few limitations should be considered. First, the sample size is small and the findings on sex differences will need to be replicated in a larger sample. In particular, estrogen is known to modulate stress-related responses, and it remains to be seen whether the age-related findings in women reflect individual differences in estrogen level. Second, many participants in this sample have SIAS scores indicative of clinical anxiety. Thus, more research is needed to investigate whether the age-sensitive findings may generalize to non-clinical populations.

The current findings are the first to distinguish the age-associated neural correlates of self-initiated actions by characterizing regional activations during ball tossing in EX vs. FG sessions in the Cyberball task. Although we did not identify the behavioral or neural correlates of social anxiety, the findings may have implications for future research on the complex processes of social interaction across the life span. The age-associated findings characterizing gender-specific cerebral responses to self-initiated actions during social exclusions may help unraveling the neural markers of social anxiety.

Declaration of Competing Interest

We have not conflicts of interest in the current work.

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