Sex differences in the behavioral inhibition system and ventromedial prefrontal cortex connectivity

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Abstract

The reinforcement sensitivity theory proposes brain–behavioral systems that underlie individual differences in sensitivity to punishment and reward. Such trait sensitivity is assessed using the behavioral inhibition/activation system (BIS/BAS) scales. Recent studies have reported sex-linked neuroanatomical correlates of the BIS/BAS, especially in the regions belonging to the valuation and salience networks that are associated with the representation of subjective value (SV), whereas less effort has been focused on investigating the neurofunctional aspects associated with sex differences in the BIS/BAS. We tested whether functional connectivity (FC) of the regions associated with the representation of SV mediates the relationship between sex and BIS sensitivity in healthy young adults by using resting-state functional magnetic resonance imaging data and self-reported BIS/BAS measures. Compared with males, females had heightened BIS sensitivity and increased FC between the ventromedial prefrontal cortex (vmPFC) seed and posterior parietal areas; this FC mediated the impact of sex on BIS sensitivity. Given that the observed vmPFC FC maps are considered part of the default-mode network, which is involved in ruminative processes, and that the BIS is associated with rumination and negative affect, our results may have implications for psychiatric disorders such as depression and anxiety, both of which have high incidence in females.

Key words: BIS/BAS; functional connectivity; medial prefrontal cortex; resting-state fMRI

Introduction

Reinforcement sensitivity theory (RST), which is the biopsychological theory of personality, proposes the concept of brain and behavioral systems underlying individual differences in sensitivity to reinforcement, including punishment (behavioral inhibition system, BIS) and reward (behavioral activation system, BAS) (Gray, 1972; Carver and White, 1994). Levels of this sensitivity can be objectively assessed by the BIS/BAS scale (Carver and White, 1994). Although there have been a number of alternative and revised models of the theory (Gray and McNaughton, 2000), it has generally been suggested that the BIS responds to punishment, regulates avoidance behaviors, leads to behavioral inhibition and heightened arousal and is associated with negative emotions (e.g. anxiety, frustration and sadness), whereas the BAS is sensitive to reward, regulates approach behaviors, promotes goal-directed behaviors and is associated with positive emotions. Therefore, aberrant sensitivity of the BIS and BAS can result in various behavioral and psychopathological problems, such as addictive and impulsive behavior, depression and anxiety (Johnson *et al.*, 2003).

Based on observations that negative emotion and avoidance, which are related to BIS sensitivity, occur more in females than in males (Stoyanova and Hope, 2012; Meyers-Levy and Loken, 2015), BIS/BAS scores may reflect a sex difference in BIS. Indeed, previous investigations have repeatedly reported that adult females have higher BIS scores but not higher BAS scores than males (Carver and White, 1994; Leone *et al.*, 2001; Pagliaccio *et al.*, 2016; Ma-Kellams and Wu, 2020), although not all studies are in agreement (Li *et al.*, 2014). Based on these previous findings, we focused the present study on confirming whether there is a sex difference in BIS scores and investigating its sex-linked neural correlates.

Given that the BIS/BAS scale measures trait sensitivity to incentives (i.e. punishment and reward) and that the subjective value (SV; also referred to as utility) of incentives is a major construct in decision making and motivation, it is suggested that brain regions associated with the BIS and BAS may overlap with regions involved in representing SV. Indeed, regions associated with the BIS and BAS correspond to parts of two brain systems associated with representing the SV of available alternatives

(Bartra *et al.*, 2013): (i) the valuation system, consisting of the vmPFC and ventral striatum, which are reliable positive correlates of SV, and (ii) the salience system, consisting of the anterior cingulate cortex (ACC) and anterior insula, which are related to the salience of incentives or their ability to generate psychological arousal (Knutson and Cooper, 2005; Knutson and Greer, 2008; Bartra *et al.*, 2013). For instance, functional neuroimaging studies using a variety of different incentive (reward or punishment) tasks have observed that the BAS is correlated with brain areas belonging to the mesolimbic and mesocortical dopamine systems [including the striatum, orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC)], which are associated with reward sensitivity (Kennis *et al.*, 2013; Fuentes-Claramonte *et al.*, 2015; Costumero *et al.*, 2016), whereas the BIS involves brain areas associated with avoidance and negative emotion, including the amygdala, septohippocampal system, insula, ACC and prefrontal cortex (Reuter *et al.*, 2004), as well as in brain areas (OFC and vmPFC) associated with reward sensitivity (Fuentes *et al.*, 2012; Shinagawa *et al.*, 2015).

Previous studies have reported sex differences in decision making (e.g. the Iowa gambling task) and its neurological correlates, especially suggesting the involvement of the medial and lateral OFC (Bolla, 2004; van den Bos *et al.*, 2013). Another study showed sex differences in delay discounting rates (the decline in the SV of a reward if it is delayed), showing that females discount future rewards less than males (Silverman, 2003). These previous studies provide evidence for sex differences in the SV, and such differences may be related to sex-related functional differences in regions belonging to the valuation and salience systems, which are associated with SV. Furthermore, these sex-linked functional differences may be related to sex differences in the BIS.

Recently, several studies have demonstrated the relationship between individual variations in BIS and in task-independent brain measures (e.g. gray matter volume, GMV), showing that BIS scores are associated with the GMV in various brain areas, such as the medial and lateral OFC, anterior insula and hippocampus (Cherbuin *et al.*, 2008; Fuentes *et al.*, 2012; Shinagawa *et al.*, 2015). Another aspect of evidence has demonstrated sex differences in scores from the BIS/BAS scale including a neuroanatomical sex-based difference. A study demonstrated a negative relationship between the BIS score and parahippocampal GMV, particularly in females, although there were no statistically significant sex differences in BIS scores in that study (Li *et al.*, 2014). However, few studies to date have investigated the neurofunctional basis of sex differences in the BIS. Therefore, in the current study, we examined the neurofunctional correlates of sex differences in the BIS using resting-state functional magnetic resonance imaging (RS-fMRI) data.

Functional connectivity (FC) is a measure of the functional integration among disparate regions, which is estimated by the temporal correlations of neural activity in remote brain regions (Friston, 1994). Estimating FC during the resting state (referred to as resting-state FC) provides insight into how certain brain areas work in tandem, suggesting intrinsic functional brain networks and promoting our understanding of the brain as a complex network (Cohen *et al.*, 2009; Jung *et al.*, 2018). Recent studies have shown that variations of resting-state FC within a network characterize the specific functioning of processes associated with the network (Hampson *et al.*, 2006; van Marle *et al.*, 2010). For example, variation in resting-state FC of dorsolateral prefrontal cortex within the central executive network (also referred to as the frontoparietal network) correlates with visuospatial working memory performance (Faraza *et al.*, 2021). Moreover, individual variation

in resting-state FC is associated not only with stable individual traits, such as personality (Nostro *et al.*, 2018), moral reasoning level (Fang *et al.*, 2017), individual discounting rate (Li *et al.*, 2013) and risk attitude (Jung *et al.*, 2018), but also with psychiatric patients' clinical symptoms (Jang *et al.*, 2010; Jung *et al.*, 2012; Lee *et al.*, 2021). Another set of evidence has demonstrated that resting-state FC estimated from brain regions recruited during a task (the task of calculating the SV of a given option/incentive) is associated with one's performance during the task (Li *et al.*, 2013; Jung *et al.*, 2018). It is suggested that examining the resting-state FC of a priori defined regions of a network related to specific functions (e.g. motivation and SV) may provide clues for understanding the state of the brain during those specific functions. In this regard, it may be important to understand the results of task-based studies when interpreting resting-state FC results and vice versa. To date, however, there have been no studies exploring the relationship between BIS sensitivity, which is expected to be related to the valuation and salience systems and show a significant sex difference, and the resting-state FC of the core regions associated particularly with SV and motivation behaviors.

Considering all of the above, investigating the resting-state FC of key regions related to the BIS may provide insight into the neural mechanisms involved in sex differences in the BIS. Under the assumption that a biological parameter (sex as the variable *X*; see *Whole-brain voxel-wise mediation analysis* below) is associated with differences in behavior (BIS scores as the variable Y) and that this is enabled by a neurobiological factor (FC as the mediator M), we aimed to investigate whether there are sex differences in BIS sensitivity and whether such sex differences are mediated by the strength of resting-state FC involving key regions associated with the representation of SV, including the valuation system (the vmPFC, left ventral striatum and right ventral striatum) and the salience system (the ACC, left anterior insula and right anterior insula). To do so, we employed seed-based FC and whole-brain voxel-level mediation analyses to directly explore whether the FC strength of the six core areas of the valuation and salience systems mediates the impact of sex on the BIS in healthy young adults. Our results would inform the very baseline on which task-based research is performed regarding SV and motivation.

Materials and methods
Participants

All imaging data ($n = 120$) were collected from October 2010 to October 2018 in imaging studies containing large cohorts of individuals with psychiatric disorders, including obsessive-compulsive disorder and schizophrenia, and healthy controls (Jung *et al.*, 2017; Lee *et al.*, 2021). All subjects in the present study were young healthy controls and were screened using the Structured Clinical Interview for DSM-IV Axis I Disorders Non-Patient edition to exclude individuals with Axis I psychiatric disorders. None of the subjects had a history of brain injury, neurological disease or significant medical illness or an IQ < 70. From this dataset, 10 individuals were excluded due to excessive head motion, defined as (i) > 2 mm translation or 2° of rotation and (ii) a mean framewise displacement (FD) > 0.3 mm (>2 SD from the group mean; Power *et al.*, 2012), to reduce the effect of head motion on FC maps. Then, 22 were excluded because they had no BIS/BAS scores. Therefore, a total of 88 participants (57 males and 31 females) were included in the final analyses.

The study was approved by the Institutional Review Board of Seoul National University Hospital, and all participants signed an

Table 1. Demographic characteristics and BIS/BAS scores

Variables	Males (*n* = 57)	Females (*n* = 31)	*t*-Value	*P*-value
Age (year)	23.89 (4.89)	24.94 (7.39)	−0.704	0.485
IQ[a]	114.46 (11.80)	112.35 (13.57)	0.757	0.451
Education (year)	14.16 (1.81)	14.52 (1.86)	−0.878	0.382
Total BAS	33.70 (6.11)	32.45 (6.51)	0.896	0.373
RR	13.26 (2.46)	12.58 (2.63)	1.213	0.228
Drive	10.32 (2.38)	9.48 (1.82)	1.691	0.094
FS	10.12 (2.49)	10.39 (2.86)	−0.451	0.653
BIS	16.58 (3.28)	18.03 (2.93)	−2.058	0.043[*]

Data are presented as the mean (SD).
[a]IQ was estimated by the Korean-Wechsler Adult Intelligence Scale. IQ, intelligent quotient; BAS, behavioral activation system; RR, Reward Responsiveness subtest; FS, Fun Seeking subtest; BIS, behavioral inhibition system.
*$P < 0.05$.

informed consent form prior to their participation. The demographic and clinical information for both groups is provided in Table 1.

Measurement of the behavioral inhibition system/behavioral activation system

All participants completed the validated Korean version of the BIS/BAS scale (Carver and White, 1994; Kim and Kim, 2001). The BIS/BAS scale is a self-report questionnaire designed to measure dispositional sensitivity to the BIS and BAS as two motivational systems; the BIS corresponds to motivation to avoid adverse outcomes, whereas the BAS corresponds to motivation to approach goal-oriented outcomes. The BIS/BAS scale is composed of 20 items using four-point Likert scales and two total scores, one for the BIS and one for the BAS. The BAS also includes three subscales: Reward Responsiveness (to measure a propensity for reward anticipation or occurrence); Drive (to measure a propensity for the pursuit of desired goals); and Fun Seeking (to measure a propensity for a desire to obtain new rewards and an impulsive approach to potential rewards).

Image data acquisition and preprocessing

All image data were acquired on the same 3T MRI scanner (Siemens Magnetom Trio, Erlangen, Germany) and at the same facility (Seoul National University Hospital). RS-fMRI data were collected using a T2*-weighted gradient echo-planar imaging (EPI) sequence [echo time (TE)/repetition time (TR) = 30 ms/3500 ms, flip angle (FA) = 90°, voxel size = 1.9 × 1.9 × 3.5 mm³ and interleaved axial slices = 35]. During RS-fMRI scanning, participants were asked to relax with their eyes closed while a 6 min and 53 s RS-fMRI scan was collected. To ensure that subjects did not fall asleep, they were reminded to stay awake through microphones immediately before RS-fMRI scanning. After scanning, a simple questionnaire was given to confirm that they had not fallen asleep. High-resolution T1-weighted magnetization-prepared rapid-gradient echo anatomical images were obtained (TE/TR = 1.89 ms/1670 ms, FA = 9°, voxel size = 1.0 × 0.98 × 0.98 mm³ and sagittal slices = 208).

Image preprocessing was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and the DPABI V5.0 toolbox (http://rfmri.org/dpabi; Yan *et al.*, 2016). After discarding the first four volumes, data were corrected for slice timing acquisition, head motion and nuisance signal correction and then spatially normalized to the Montreal Neurological Institute template brain. For nuisance signal correction, the following nuisance parameters were included as regressors within the general linear model: six motion parameters and their first derivatives, head

motion scrubbing regressors (FD > 0.5, one volume before and two volumes after the bad time point), five principal components extracted from a combined white matter and cerebrospinal fluid mask using a component-based noise correction method (Behzadi *et al.*, 2007) and two polynomial trending terms. Then, spatial smoothing [full width at half-maximum kernel: 6 mm] and temporal bandpass filtering (0.01–0.1 Hz) were performed.

Seed-based functional connectivity analysis

We specifically focused on six a priori defined regions of interest (ROIs), selected as seed regions based on a previous meta-analysis study by Bartra *et al.* (2013), which provided mask images for key regions sensitive to reward valuation and SV across prior studies (https://www.sas.upenn.edu/psych/kable_lab/Joes_Homepage/Resources.html). These six seed regions generally cover the core regions of the valuation system [the vmPFC, left ventral striatum and right ventral striatum (Figure 1A)] and of the salience system [the ACC, left anterior insula and right anterior insula (Figure 1B)]. To generate seed-based FC maps for each of the six seeds, we first defined the seed regions based on Bartra *et al.* (2013), and then, the Pearson correlation coefficients were calculated between the mean time series for each seed and the time series for all other voxels throughout the rest of the brain. These correlation coefficients were converted into z-values using Fisher *r*-to-z value transformation. The z-transformed FC maps were used for subsequent whole-brain voxel-level mediation analyses to test the effect of FC on the relationship between sex and the BIS scores.

Whole-brain voxelwise mediation analysis

To examine the effect of FC on the relationship between sex and BIS scores, we used the M3 Mediation Toolbox (https://github.com/canlab/MediationToolbox) to test whether the direct effect of sex (*X*) on BIS scores (*Y*) could be explained in terms of the indirect influence of each FC map (*M*) as a mediator (Figure 1C). Participants' age was used as a covariate of no interest. For statistical inferences, voxelwise significance was determined using bootstrapping with 10 000 iterations, and then, the AlphaSim (Monte Carlo simulation) program as implemented in the software DPABI was applied to correct for multiple comparisons, with the statistical thresholds being $P < 0.001$ (uncorrected) for voxel height and $P < 0.0083$ (i.e. $P < 0.05/6$ based on six seed-based FC maps used) for cluster extent, to determine the cluster size threshold (cluster size of 1944 mm³). The bug reported by Eklund *et al.* (2016) has been resolved in the software version used in this study (DPABI V5.0). Although there is debate regarding the vulnerabilities of cluster-based inference procedures (Eklund *et al.*, 2016), we used AlphaSim correction to detect
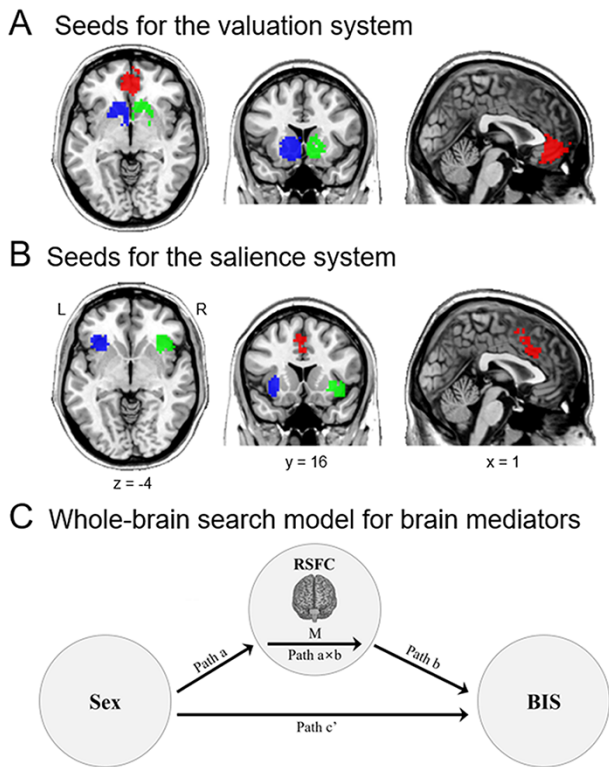
Fig. 1. Seed regions and the model used for seed-based FC and subsequent mediation analyses. (A) The regions belonging to the valuation system, including the vmPFC (red), left ventral striatum (blue) and right ventral striatum (green), were used for seeds. (B) The regions belonging to the salience system, including the ACC (red), left anterior insula (blue) and right anterior insula (green), were also used for seeds. (C) Whole-brain search model used to investigate brain mediators of the association between sex and BIS sensitivity, consisting of seed-based FC maps to each of the six seeds. RSFC, resting-state functional connectivity; BIS, behavioral inhibition system score.

significant clusters in the maps for the mediation effects estimated by the M3 Medication Toolbox for our hypothesized model (Figure 1C) and it is worth emphasizing that the cluster-defining threshold used ensures appropriate control of cluster-level familywise error (FWE) rates in SPM (Flandin and Friston, 2019).

Supplementary analyses

First, to clarify whether the regions (in this case, the posterior parietal areas; see the Results section) showing significant mediation effects through functional coupling with the seed (in this case, the vmPFC seed; see the Results section below) have, on average, positive or negative connections with the seed, we performed the following supplementary analyses. Individual z-transformed vmPFC seed-based FC maps were analyzed with a random-effects one-sample t-test to identify voxels showing a significant positive or negative correlation with the seed time series for males and females, respectively. Significant clusters were set at a cluster-level threshold of $P < 0.05$, FWE-corrected for multiple comparisons, with a primary threshold (i.e. cluster-defining threshold) of $P < 0.001$, uncorrected. We used the atlas created by Yeo *et al.* (2011) as a reference for the spatial definition of group vmPFC seed-based FC maps. We then extracted z-transformed vmPFC FC strengths with the regions showing significant mediation effects as ROIs to compare the FC strengths between males and females. Second, to show the specificity of the effects of

target seeds, we performed additional exploratory analysis with the auditory area as a control site. The control auditory area seed was defined as a 5 mm radius sphere centered on the coordinates used by previous studies (x, y, $z = 44$, −36, 13) (Konova *et al.*, 2013). For FC maps of the control seed, we repeated the abovementioned whole-brain voxelwise mediation analysis for comparison with the target seed results.

Results

BIS/BAS scores

Table 1 provides statistical information about demographic characteristics and BIS/BAS scores. There were no significant differences in demographic variables, including age, IQ and duration of education, between males and females (all Ps > 0.05). As we expected, females had higher BIS scores than males ($t = −2.058$, $P = 0.043$), whereas the total BAS score did not significantly differ between males and females ($t = 0.896$; $P = 0.373$). The two groups also did not show significant differences in scores for each of the BAS subscales, including the Reward Responsiveness, Drive and Fun Seeking subscales (all Ps > 0.05).

Mediation effects of FC

The FC map to the vmPFC seed showed a significant mediation effect on the relationship between sex and the BIS (at an uncorrected $P < 0.001$ for height and a corrected $P < 0.0083$ for extent) (Figure 2); in particular, two significant clusters on the map were located in the posterior parietal cortex, including the left inferior parietal gyrus (IPG; x, y, $z = −36$, −69, 48; $P < 0.001$) and right angular gyrus (AG; x, y, $z = 42$, −63, 48; $P < 0.001$). In other words, females had higher FC strengths between the vmPFC seed and the left IPG and between the vmPFC seed and the right AG than males (positive Path a; Figure 2A). These FC strengths were positively correlated with BIS scores (positive Path b; Figure 2B). Finally, positive mediation effects were observed in these two regions (positive Path a × b; Figure 2C and D).

In contrast to the vmPFC FC map, the other five seed-based FC maps and the control auditory seed-based FC map exhibited no mediation effects on the relationship between sex and the BIS.

Sex differences in the FC between the vmPFC seed and posterior parietal areas

Figure 3A shows within-group seed-based FC maps derived from the vmPFC seed for males and females. The spatial pattern of these maps corresponded to the default mode network (DMN; Power *et al.*, 2011; Yeo *et al.*, 2011). Females, compared to males, had higher FC between the vmPFC seed and the left IPG and between the vmPFC seed and the right AG. In particular, the vmPFC seed in females showed strong positive FC strengths with the left IPG and the right AG, whereas that in males showed reverse FC (i.e. negative FC) to the right AG or very low positive FC strength to the left IPG (Figure 3B).

Discussion

To uncover neural mechanisms underlying sex differences in the BIS sensitivity of the BIS/BAS scale, we tested whether the FC strength of the regions associated with representation of the SV at rest mediated the impact of sex on the BIS in young, healthy adults. We found that females, compared to males, had greater BIS sensitivity, consistent with previous studies (Leone *et al.*, 2001; Pagliaccio *et al.*, 2016; Ma-Kellams and Wu, 2020), and greater FC
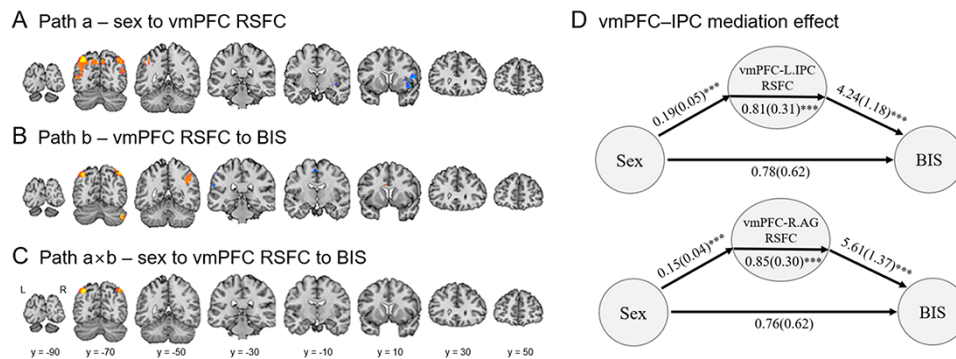
Fig. 2. Mediation analysis results with the vmPFC seed-based FC map. The left three panels show individually significant voxels for (A) Path a, (B) Path b and (C) Path a × b from the mediation analysis (at a height threshold of $P < 0.001$, uncorrected, and an extent threshold of $P < 0.0083$, corrected). (D) The association between sex and BIS sensitivity was mediated by FC strength between the vmPFC and the posterior parietal areas, including the left inferior parietal cortex and right angular gyrus (see two clusters in Figure 2C). In other words, greater connectivity between these areas mediated higher BIS sensitivity in females. For illustration purposes, all values (path coefficients and their standard errors in parenthesis) for all Paths (refer to Figure 1C) in (D) were calculated by performing mediation analyses with FC strengths (as M values) extracted by clusters identified from the whole-brain voxel-level mediation analysis. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. vmPFC, ventromedial prefrontal cortex; RSFC, resting-state functional connectivity; BIS, behavioral inhibition system score; L, left; R, right; IPC, inferior parietal cortex; AG, angular gyrus.
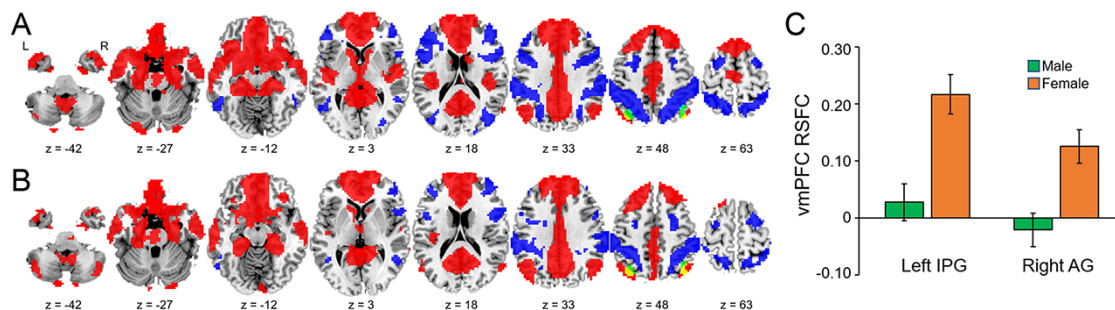

Fig. 3. The overlap (yellow) between the posterior parietal clusters (light green and yellow), identified by mediation analysis with vmPFC seed-based FC maps, and within-group FC maps (red) of the vmPFC seed in (A) males and (B) females. Red and blue, respectively, represent positive and negative FC with the vmPFC seed. Yellow represents the overlap of the posterior parietal clusters with the within-group vmPFC seed-based FC map in each group. (C) The bar graph (green and orange) displays the average FC between the vmPFC seed and the posterior parietal clusters across subjects in each group. The error bars represent the standard error of the mean. Females showed strong positive connectivity between the vmPFC seed and the posterior parietal areas, whereas males exhibited attenuated positive connectivity or reverse connectivity between these areas.

between the vmPFC seed and posterior parietal areas, including the left IPG and the right AG, which mediated the impact of sex differences on BIS sensitivity. In particular, the vmPFC seed in females at rest exhibited strong positive FC to the left IPG and the right AG, whereas males had attenuated positive FC to the left IPG and negative FC to the right AG. Therefore, when interpreting vmPFC-posterior parietal area FC in task-based investigations with regard to motivation and emotion, it would be important to consider the current findings showing that FC strengths differ between males and females at rest because resting-state FC as a portion of the variability between task conditions could affect the sensitivity in detecting task-based changes.

The vmPFC has long been implicated in decision making, emotion regulation and memory processes. In functional neuroimaging studies across a wide variety of decision-making tasks, vmPFC activity encodes the SV that could be used to guide choices between alternatives (Kable and Glimcher, 2007; Bartra et al., 2013; Clithero and Rangel, 2014). In this context, people with damage to the region could have difficulties making a choice between options with uncertain outcomes, referred to as a 'risk' (Fellows and Farah, 2007; Jung et al., 2018), and with a moral dilemma (Bechara et al., 2000). Notably, the region plays a vital role in assigning SV and in regulating emotion, which triggers our actions, and all the items for assessing BIS features in the

BIS/BAS scale are questions related to particularly negative emotion regulation (e.g. 'I worry about making mistakes'). Therefore, it is conceivable that our results showing the involvement of the vmPFC in BIS sensitivity may reflect sex differences in SV and emotion regulation to even the same stimuli, events or environment. Indeed, previous studies have demonstrated sex differences. For example, females are more capable than males of delaying gratification, representing a lower delay discount rate in females (Bjorklund and Kipp, 1996; Silverman, 2003). Females, compared with males, also report more negative affect, which could be explained by emotion regulation (Thomsen et al., 2005; Fernández et al., 2012). Future research is needed to clarify sex differences in the association between the BIS/BAS and SV or emotion regulation and in related neural correlates.

The posterior parietal cortex plays a role in motor planning, and its different portions are involved in multiple cognitive processes, such as spatial attention, working memory and decision making (Grubb et al., 2016; Whitlock, 2017). Kahnt et al. (2014) investigated the areas representing value and salience in the human brain and found that multivoxel activity patterns in the posterior parietal cortex, particularly in superior (z-axis coordinate > 43) and inferior compartments, predicted value and salience, respectively. In the study, the positions of clusters associated with value representation correspond to those of the

posterior parietal areas functionally connected to the vmPFC observed in the current study. In this regard, a functional interaction between the vmPFC and posterior parietal areas may be related to value representation.

Many studies have consistently demonstrated the involvement of the medial part of the brain, including the vmPFC, posterior cingulate cortex (PCC) and ventral striatum, in the processing of value (Bartra *et al.*, 2013). In addition to the posterior parietal areas, the vmPFC and PCC are components of the DMN. Consistent with these previous findings, our data also showed positive connectivity within the regions (the vmPFC, PCC and parietal areas) belonging to the DMN across groups. However, interestingly, the posterior parietal areas had a strong positive FC to the vmPFC seed but only in females. The DMN is thought to be activated when one is engaged in internally focused tasks, such as self-referential processing, autobiographical memory retrieval and imaging the future, yet is deactivated during cognitive task performance (Andrews-Hanna, 2012). The DMN shares a subset of regions in common with the valuation system associated with SV (Kable and Glimcher, 2007; Levy *et al.*, 2010; Bartra *et al.*, 2013), although there is only a partial degree of overlap with the DMN regions (Acikalin *et al.*, 2017; Toro-Serey *et al.*, 2020). Several fMRI studies have reported sex differences in the DMN, suggesting that females have stronger DMN responses than males. For instance, a large sample RS-fMRI study (2750 females *vs* 2466 males) showed that females had higher resting-state FC within the DMN than males (Ritchie *et al.*, 2018). Furthermore, a recent task-based fMRI study examined DMN suppression and showed that females, compared with males, had increased deactivation in the DMN during exposure to reward and punishment; this finding may provide neurobiological evidence supporting the observation that females are more prone to psychiatric illnesses (e.g. depressive or anxiety disorders) characterized by altered processing of such valenced stimuli (Dumais *et al.*, 2018).

Sex differences in the BIS we observed (i.e. higher BIS scores in females) may be due to females' higher expression of a negative affect that could be partly explained by rumination (Thomsen *et al.*, 2005). Indeed, females tend to ruminate when distressed, which partially accounts for their greater rates of depression than males because repetitive ruminative responses to one's own distress exacerbate and prolong a person's depressed mood (Nolen-Hoeksema *et al.*, 2008; Johnson and Whisman, 2013). Khosravani *et al.* (2019) recently reported that high BIS scores had an indirect effect on depression via increased rumination in 300 individuals who had attempted suicide. Several studies have argued that the DMN, especially the vmPFC, is thought to underlie ruminative responses through the integration of negative emotion into self-referential thinking subserved by the DMN (Zhou *et al.*, 2020). Luo *et al.* (2016) investigated the association between the level of rumination and the DMN created by independent component analysis of RS-fMRI data and found that an increased inclination to ruminate was associated with greater FC of the MPFC, PCC and inferior parietal lobule within the DMN subcomponents. Therefore, our findings may have implications for research on psychiatric illnesses such as depression and anxiety symptoms following repetitive rumination in females.

This study has some limitations that require consideration. First, although the sample size used in the present study ($n = 88$) was even higher than most of the other previous studies of the BIS/BAS scale (see Kennis *et al.*, 2013 for review), replicating the present results in a larger sample (e.g. open data with $n > 10\,000$)

is necessary to improve their generalizability. Second, a recent study reported that sex differences in the BIS were observed in adolescents and adults but not in childhood (Pagliaccio *et al.*, 2016). Considering such changes in sex differences in the BIS according to human development, future developmental studies would be valuable to clarify the association between age-related changes in the BIS and brain function. Third, there is still debate regarding the interpretation of negative FC (illustrated in our case by Figure 3) identified by seed-based analysis (Murphy *et al.*, 2009; Chen *et al.*, 2011; Zhan *et al.*, 2017). Several studies demonstrated that this negative FC could be an artifact generated by a global signal regression (Murphy *et al.*, 2009; Saad *et al.*, 2012), and it correlates with spatial distance (i.e. the shortest path; Chen *et al.*, 2011). Global signal regression was not used in this study because it may enhance the extent of negative correlations (Murphy *et al.*, 2009; Saad *et al.*, 2012). Fourth, the present findings were based on RS-fMRI rather than on task-based fMRI. Recent studies have demonstrated that FC is modulated by certain cognitive states (Arbabshirani *et al.*, 2013; Jung *et al.*, 2013) and that task-state FC may represent the functional dynamics underlying task states more acutely than resting-state FC does (Cole *et al.*, 2021). Given that the DMN, as the primary task-negative network, is likely to be reconfigured more extensively than other networks during task states, FC in the DMN may change according to cognitive states. Moreover, given that there is remarkable overlap in constructs between cognitive control and the traits measured by the BIS/BAS scales (goal pursuit, conflict monitoring, etc.), the networks associated with cognitive control may also be associated with the BIS/BAS. Therefore, future studies of FC in several networks identified from task-based fMRI (such as reinforcement learning or incentive processing) are needed to confirm and extend the current findings and related interpretations. Finally, although we used the BIS/BAS scale by Carver and White (1994) based on the initial conceptualization of the RST, there is a new questionnaire (Reuter *et al.*, 2015) to measure individual differences in the revised BIS and BAS and in the newly proposed fight, flight, freezing system (FFFS); this new instrument is based on the revised RST by Gray and McNaughton (2000). Our findings may be of interest when comparing the results of the newly revised BIS/BAS/FFFS scale.

In summary, this study shows the neural mechanisms underlying sex differences in the BIS sensitivity of the BIS/BAS scale in healthy young adults. In particular, our results show that females, compared to males, have greater BIS sensitivity and greater FC between the vmPFC seed and posterior parietal areas at rest, mediating the impact of sex differences on BIS sensitivity. Our findings could be used as an appurtenance to interpret response variability during task performance in relation to motivation and emotion. Our findings may also have implications for psychiatric disorders, such as depression and anxiety, that occur more often in females than males.

Conflict of interest

The authors declare that there are no conflicts of interest.

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