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Gender differences in neural–behavioral response to self-observation during a novel fMRI social stress task

Mary R. Lee [a,*], Kelsey Cacic [b], Catherine H. Demers [c], Maleeha Haroon [d], Stephen Heishman [d], Daniel W Hommer [a], David H. Epstein [e], Thomas J. Ross [c], Elliot A. Stein [c], Markus Heilig [a], Betty Jo Salmeron [c]

[a] Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892, United States
[b] Department of Psychology, University of Maryland, College Park, MD 20742, United States
[c] Neuroimaging Research Branch, Intramural Research Program, National Institute on Drug Abuse, 251 Bayview Boulevard, Baltimore, MD 21224, United States
[d] Nicotine Psychopharmacology Section, Intramural Research Program, National Institute on Drug Abuse, 251 Bayview Boulevard, Baltimore, MD 21224, United States
[e] Treatment Section, Clinical Pharmacology and Therapeutics Research Branch, Intramural Research Program, National Institute on Drug Abuse, 251 Bayview Boulevard, Baltimore, MD 21224, United States

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ABSTRACT

The neural correlates of response to psychosocial stress and gender differences therein are difficult to model experimentally as this type of stressor is difficult to induce in a brain imaging environment. The Trier Social Stress Test (TSST), a behavioral paradigm that reliably induces moderate levels of stress was thus modified for the MRI environment. To determine the neurobehavioral basis of gender differences in response to *observing oneself under* social evaluative stress, 26 subjects (14 females) performed the TSST while being videotaped. During fMRI scanning, subjects were shown alternating video clips of two CONDITIONS: SELF or a same-sex OTHER performing the TSST. Subjects rated their stress level immediately after the video clips. GENDER differences in the [SELF–OTHER] contrast were analyzed. There was a GENDER × CONDITION interaction such that only women reported increased subjective stress during video feedback of their TSST session. A whole brain analysis (SELF vs. OTHER) showed activation in the bilateral insula, inferior, middle and superior frontal gyri. Greater recruitment was seen among males in some of these same areas in the context of significantly lower stress ratings. Activation of areas involved in inhibitory control and sensory awareness might contribute to the significantly lower stress ratings in males. Understanding these gender differences is relevant to disorders of stress and self-concept.

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1. Introduction

Previous studies have found that women subjectively experience more stress than men (Matud, 2004) and demonstrate more vulnerability to stress (Troisi, 2001). Longitudinal studies have demonstrated that stress appraisal and resultant coping responses affect women's health outcomes and health-related quality of life (Taylor & Brown, 1988; Rao, 2009). One factor that has been shown to worsen the psychological distress resulting from diverse psychosocial stressors is the tendency to direct attention inwardly to one's thoughts and feelings rather than toward the external environment (Crandall & Perrewe, 1995) . Female gender is associated with a greater tendency to self-focus and greater negative affect resulting from experimental manipulations designed to engender self-focus, such as viewing the self, compared to another (Ingram, Cruet, Johnson, & Wisnicki, 1988).

In the laboratory, under conditions of psychosocial stress, engendered by observation by others while performing cognitive tasks, as in the Trier Social Stress Test, TSST (Kirschbaum, Pirke, & Hellhammer, 1993), females have higher ratings of fear, irritability and unhappiness compared to men (Kelly, Tyrka, Anderson, Price, & Carpenter, 2008) while men demonstrate a greater physiological response, as measured by cortisol and ACTH, and autonomic reactivity (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004), (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999), unrelated to levels of self-reported stress (Kudielka & Kirschbaum, 2005).

Numerous studies have explored neural activation (regardless of gender) during acute stress induction using aversive stimuli (Hermans et al., 2011), personalized stress script feedback (Sinha,

* Correspondence to: 10 Center Drive, 10-CRC, Room 1-5330, Bethesda, MD 20892-1108, 301-827-0545. Tel.: +1 301 827 0545.
E-mail address: leemary@mail.nih.gov (M.R. Lee).

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Lacadie, Skudlarski, & Wexler, 2004), mental math (Dedovic et al., 2005, 2009), speech preparation (Wager et al., 2009) and social exclusion (Eisenberger, Lieberman, & Williams, 2003). While studies have examined sex differences in neural responses during processing of emotional stimuli (Stevens & Hamann, 2012; Whittle, Yucel, Yap, & Allen, 2011), no neuroimaging studies have explored gender differences in self-observation under social stress conditions.

Given these gender differences in the propensity to self-focus and in the response to psychosocial stress, we sought to explore whether there were gender differences in the subjective response and underlying neural circuitry during self-observation (a process akin to self-focusing) of a psychosocially stressful experience. To this end, we developed a novel fMRI task to probe self-observation under social evaluative threat by combining a social stressor with direct self-observation. Participants completed the TSST outside the scanner, and then, during fMRI scanning, were subsequently shown video clips of their own performance during the TSST during moments when they were making errors or were being given negative feedback and that of a gender-matched compatriot who was performing adequately and did not appear stressed.

2. Methods

2.1. Participants

A total of 26 right-handed participants (Table 1) gave written informed consent to the study, which was approved by the Institutional Review Board of the National Institute on Drug Abuse, Intramural Research Program. Participants were recruited from the Baltimore area using print advertisements and referrals. Exclusionary criteria included pregnancy, claustrophobia, significant neurological or medical diagnoses and current dependence on any drug other than nicotine. Participants were instructed not to consume any alcohol for 24 h and no more than half a cup of caffeinated beverages 12 h prior to each scanning visit. Those who were smokers (males=4, females=8), were allowed to smoke as usual before their study session. Participants were tested for current drug and alcohol use and could not participate if they had a positive alcohol breathalyzer or urine drug screen. They were excluded from participation if there was evidence of current DSM-IV Axis I disorder (other than nicotine dependence) as assessed by The Structured Clinical Interview for DSM IVTR (SCID), computerized version, clinical interview and Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) scores. They were also excluded if their Wechsler Abbreviated Scale of Intelligence (WASI) vocabulary sub score was less than 48, corresponding to a total IQ score of 85.

2.2. Behavioral task

TSST sessions were performed in the morning to minimize cortisol and stress response variation (Van Cauter, 1990). Methods have been described in detail elsewhere (Kirschbaum et al., 1993). Briefly, participants were knowingly videotaped while they performed two TSST components: a 5-min speech where they spoke about why they would be a good candidate for their ideal job and a 5-min math exercise involving serial subtraction (by 13 starting from 1022 and restarting upon any failure), in front of three dispassionate observers who were strangers to them. Participants were not debriefed until following the scanning session. Subjects rated stress levels before and immediately after the TSST on a visual analog scale (VAS).

Table 1
Participant demographics and characteristics: Mean ± SD There were no significant differences between males and females. AA=African American.

	Males	Females	Difference
N	12	14	
Age	37.08 ± 10.72	32.69 ± 6.68	$p=0.177$
Race	8(66.7%)AA	6(42.9%)AA	$p=0.207$
WASI verbal score	60.64 ± 9.29	58.77 ± 12.31	$p=0.684$
BDI	2.67 ± 3.47	2.93 ± 3.20	$p=0.843$
BAI	1.33 ± 2.96	1.64 ± 1.91	$p=0.751$
TAS	34.33 ± 5.85	36.07 ± 7.53	$p=0.523$
Menstrual cycle (Follicular/Luteal/No cycle		5/5/4	
Scan day (same/different)	5/7	7/7	$p=0.671$

2.3. Imaging task

Following the behavioral sessions, the audio-visual recordings were reviewed and edited into five, approximately 30-s epochs. Video clips of SELF were chosen during periods where participants appeared uncomfortable or were making errors. Five similar clips were obtained from a volunteer, OTHER, who performed the TSST and were matched to the subjects with respect to gender, but were chosen during periods where subject's performance was unremarkable so as to avoid the confound of an empathic response to stress during the OTHER condition or feelings of inferiority from viewing a highly competent OTHER.

Imaging sessions were done on the same day, in the afternoon at least 2 h after the TSST (males=5, females=7) or on a different day from the TSST (males=7, females=7). The fMRI task consisted of alternating presentation in fixed order of SELF and OTHER video clips, each of 30 s duration, totaling 5-SELF and 5-OTHER video clips. Subjects rated stress on a visual analogue scale (VAS) immediately after the first, third and fifth video clips of each type (3 SELF and 3 OTHER). Rest blocks (30 s) followed the second and fourth video clips of each type (2 SELF and 2 OTHER). The VAS question, 'How stressed are you' was anchored by 'not at all' on the left and 'extremely' on the right. Behavioral data were collected in E-Prime Software Suite (Psychology Software Tools).

Imaging data were acquired on a 3T Siemens TRIO scanner (Erlangen, Germany) using a standard 12 element head coil. A whole-brain oblique axial T1-weighted structural image was obtained (MPRAGE) for registration purposes. Functional images were obtained using a gradient-echo, echo-planar sequence sensitive to blood oxygen level-dependent (BOLD) contrast (TR=2, TE=27 ms, FOV=220 mm^2, Matrix=64 × 64). Thirty-nine 4-mm oblique axial slices (30° from the AC-PC line) were obtained for each participant.

2.4. Demographic and behavioral data analysis

Behavioral data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL USA). Gender groups were compared with respect to mean age, WASI vocabulary sub score, BDI, BAI and Toronto Alexithymia Scale (TAS) using two tailed *t*-tests. Gender-group difference in race and scan day was analyzed using chi-squared analysis. For the TSST, stress ratings were analyzed with a repeated measure ANOVA: 2 (2 rating time points, pre and post TSST) × 2 (male/female). For the stress ratings during the fMRI task, a repeated measure ANOVA in a 2 (male/female) × 2 (SELF/OTHER) × 3 (rating time points) × 2 (SCAN DAY) design was applied to mean VAS responses for stress ratings. The effect of menstrual cycle stage on stress ratings for the self–other condition during the fMRI task was done with a repeated measures ANOVA with 3 rating time points as the within subject factor and 3 menstrual groups as the between subject factor (Table 1). The effect of smoking was similarly analyzed with gender and smoking status as between subjects' factors.

2.5. Imaging data analysis

Functional imaging data were analyzed using the Analysis of Functional NeuroImaging software package (AFNI); (Cox, 1996). Preprocessing included volume registration to correct for head motion and slice timing correction. Data time series were analyzed using voxel-wise, multiple regression analysis in which regressors were expressed as boxcars convolved with a hemodynamic response function. The regressors of interest were the video types- SELF and OTHER. Rating periods and six motion parameters were included as regressors of no interest. Time points showing excessive head motion (> 0.3 mm change between successive frames along any axis) were excluded from the analysis. One participant showed persistent (> 25% of scan) excessive head motion and was excluded from further analysis. A voxel-wise average amplitude (β) equal to the percentage signal change from baseline was calculated for each participant for each video type. The resultant activation maps were resampled to standard (Talairach) space at a 3 × 3 × 3 mm^3 resolution and spatially blurred to a 6 mm full-width at half-maximum, using AFNI program 3dBlurToFWHM.

A mixed effects meta-analysis (MEMA) in AFNI was performed for the group analysis. The first analysis consisted of a SELF vs. OTHER contrast to produce a group task map. To examine gender differences in the SELF vs. OTHER contrast, a whole-brain MEMA ANOVA compared SELF vs. OTHER (male) to SELF vs. OTHER (female). A voxel-wise threshold ($p < 0.005$) and a cluster threshold (27 voxels, faces touching) calculated using AFNI 3dClustSim (smoothness estimated from the residuals) was used to yield an omnibus $p < 0.05$ corrected for multiple comparison for the gender comparison. As the task was quite robust, we used a more stringent threshold of .0001 and cluster size of 27 voxels for the SELF vs. OTHER contrast.

3. Results

3.1. Demographic and behavioral results

There were no significant gender differences in the results obtained from any of the demographic or cognitive and emotional