Journal of Psychiatric Research 47 (2013) 733–739

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Sex differences of gray matter morphology in cortico-limbic-striatal neural system in major depressive disorder

Lingtao Kong [a], Kaiyuan Chen [a], Fay Womer [b], Wenyan Jiang [a], Xingguang Luo [c], Naomi Driesen [c], Jie Liu [c], Hilary Blumberg [c], Yanqing Tang [a], Ke Xu [d,*], Fei Wang [c,d,**]

[a] Department of Psychiatry, The First Affiliated Hospital, China Medical University, 155 Nanjing North Street, Shenyang 110001, Liaoning, PR China
[b] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA
[c] Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06511, USA
[d] Department of Radiology, The First Affiliated Hospital of China Medical University, 155 Nanjing North Street, Shenyang 110001, Liaoning, PR China

ARTICLE INFO

Article history:
Received 8 August 2012
Received in revised form
31 January 2013
Accepted 7 February 2013

Keywords:
Major depressive disorder
Magnetic resonance imaging
Voxel-based morphometry
Caudate
Amygdala
Hippocampus

ABSTRACT

Sex differences are observed in both epidemiological and clinical aspects of major depressive disorder (MDD). The cortico-limbic-striatal neural system, including the prefrontal cortex, amygdala, hippocampus, and striatum, have shown sexually dimorphic morphological features and have been implicated in the dysfunctional regulation of mood and emotion in MDD. In this study, we utilized a whole-brain, voxel-based approach to examine sex differences in the regional distribution of gray matter (GM) morphological abnormalities in medication-naïve participants with MDD. Participants included 29 medication-naïve individuals with MDD (16 females and 13 males) and 33 healthy controls (HC) (17 females and 16 males). Gray matter morphology of the cortico-limbic-striatal neural system was examined using voxel-based morphometry analyzes of high-resolution structural magnetic resonance imaging scans. The main effect of diagnosis and interaction effect of diagnosis by sex on GM morphology were statistically significant ($p < 0.05$, corrected) in the left ventral prefrontal cortex, right amygdala, right hippocampus and bilateral caudate when comparing the MDD and HC groups. Posthoc analyzes showed that females with MDD had significant GM decreases in limbic regions ($p < 0.05$, corrected), compared to female HC; while males with MDD demonstrated significant GM reduction in striatal regions, ($p < 0.05$, corrected), compared to HC males. The observed sex-related patterns of abnormalities within the cortico-limbic-strial neural system, such as predominant prefrontal-limbic abnormalities in MDD females vs. predominant prefrontal-striatal abnormalities in MDD males, suggest differences in neural circuitry that may mediate sex differences in the clinical presentation of MDD and potential targets for sex-differentiated treatment of the disorder.

1. Introduction

Sex differences are observed in both epidemiological and clinical aspects of major depressive disorder (MDD). Studies have consistently shown that MDD is more prevalent in females than males (Kessler et al., 2005, 1994; Kuehner, 2003). Females with MDD are more likely to show increased anxiety including higher rates of comorbid anxiety disorders (Kornstein et al., 2000; Marcus et al., 2005), while males with MDD are more likely to show more psychomotor agitation and to have comorbid substance abuse disorders (Kessler et al., 1997; Marcus et al., 2005; Roeloffs et al., 2001). Although females with MDD are more likely to attempt suicide than males (Marcus et al., 2005), males with MDD are more likely to be successful when they attempt suicide, and thus are at higher risk for completed suicide (Blair-West et al., 1999; Oquendo et al., 2001). While sex differences in the clinical presentation of MDD are apparent, the neural mechanisms that underlie these differences remain unclear.

The cortico-limbic-striatal neural system including the prefrontal cortex (PFC), amygdala, hippocampus and striatum, is implicated in the dysfunctional regulation of emotion in MDD (Drevets, 1998; Marchand, 2010). The sexually dimorphic development of cortico-limbic-striatal neural system has been implicated to

* Corresponding author. Tel.: +8624 8328 2999; fax: +86 24 8328 2997.
** Corresponding author. Department of Psychiatry, Yale University School of Medicine, 300 George Street, Suite 901, New Haven, CT 06511, USA. Tel.: +1 203 737 2507; fax: +1 203 737 2513.
E-mail addresses: kexu@vip.sina.com (K. Xu), fei.wang@yale.edu (F. Wang).

0022-3956/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2013.02.003

contribute to sex differences in psychiatric disorders (Giedd et al., 1997, 1996; Lenroot et al., 2007; Neufang et al., 2009; Teicher et al., 2004). For example, regions (PFC, amygdala and hippocampus) subserving emotions might be related with increased depression or anxiety risk in females (Davis et al., 2012; Kessler et al., 1993; Lieberwirth et al., 2012), and regions (PFC and striatum) subserving impulse control might be associated with increased risk for substance abuse (Nagoshi et al., 1991; Nolen-Hoeksema & Hilt, 2006). Additionally, preclinical studies indicate particular vulnerability to stress in the PFC-amygdala/hippocampus system in females, with estrogen-dependent effects observed, while this system appears relatively resilient in males. However, males may be more vulnerable to stress effects on the PFC-striatum system than females; for example, estrogen has been shown to be protective in caudate (Arnsten & Shansky, 2004; Dluzen & McDermott, 2000; McEwen, 2010; Shansky et al., 2010). The sexually dimorphic features in cortico-limbic-striatal neural system may reflect the sex differences in clinical observations of MDD, such as MDD females with more comorbid anxiety disorders, and MDD males with more comorbid substance abuse and higher risk for completed suicide.

Sex differences in cortico-limbic-striatal morphology have been reported in human brain studies (Biswal et al., 2010; Cosgrove et al., 2007; Goldstein et al., 2001). Recently, our group found sexually dimorphic effects of child maltreatment (CM) on cortico-limbic-striatal morphology in adolescents. In adolescent females, CM was associated with more robust effects in brain regions that subserve emotional regulation, including the PFC, amygdala and hippocampus, whereas in adolescent males, effects were more prominent in brain regions that subserve impulse control, including PFC and striatum (Edmiston et al., 2011). Several morphological studies using region of interest (ROI) tracing technique examined sex differences in the cortico-limbic-striatal neural system in MDD; however there are some inconsistencies in findings (Frodl et al., 2002; Hastings et al., 2004; Vakili et al., 2000). In this study, we utilized a whole-brain, voxel-based approach to examine sex differences in gray matter (GM) density and volume within the cortico-limbi-striatal neural system in medication-naïve participants with MDD. Given the sex differences in clinical features of MDD, we anticipated that GM morphological alterations in cortico-limbic-striatal brain regions subserving emotional regulation might be more prominent in MDD females, while GM morphological changes in MDD males might be more apparent in region subserving impulse control.

2. Methods

The MDD group was comprised of 29 participants [mean age 29.5 ± SD 6.84 years, 16 females (55%), 13 males (45%)] who met DSM-IV criteria for MDD, were currently depressed as determined by the consensus of two psychiatrists using the Structured Clinical Interview for DSM-IV (First et al., 1995), had a score of at least 24 on the 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1960), and had never taken any psychotropic medications. No MDD participants had current comorbid Axis I diagnosis. The healthy control (HC) group included 33 participants with neither personal Axis I disorder or first-degree relatives with psychiatric disorder [mean age 29.9 ± SD 8.27 years, 17 females (51%), 16 males (49%)]. No participant had a history of neurological illness, head trauma with loss of consciousness of 5 min or more, or major medical disorder. After a complete description of the study, written informed consent was obtained from all participants in accordance with the human investigation committees of China Medical University.

High-resolution structural magnetic resonance imaging (MRI) scans were obtained on a 3T MR scanner (General Electric, Milwaukee, USA) using a three-dimensional Fast Spoiled Gradient-Echo (FSPGR) T1-weighted sequence (TR = 7.1 ms, TE = 3.2 ms, FOV = 240 × 240 mm^2, matrix = 240 × 240, slice thickness = 1.0 mm without gap). Images were processed according our previous protocol (Blumberg et al., 2008; Kalmar et al., 2009; Tang et al., 2007; Wang et al., 2011). In brief, segmentation function in the Statistical and Parametric Mapping 5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm) was used for bias correction, segmentation and spatial normalization. Segmented unmodulated GM images (representing gray matter density, GMD) and modulated GM images (representing gray matter volume, GMV) were normalized to Montreal Neurological Institute (MNI) space using the SPM5 GM tissue probability map (voxel size 2 × 2 × 2 mm^3) as a template and spatially smoothed using an 8-mm full width at half maximum Gaussian kernel.

Two-way analysis of variance (ANOVA) with diagnosis (MDD/HC) and sex (M/F) as between subject factors was used to compare demographic data (age and education) and HDRS with SPSS 13.0 software (SPSS Inc, Chicago, Illinois). Two-sample *t*-test was used to compare illness duration between males and females with MDD. Full factorial ANOVA (two-way ANOVA) was performed in SPM5 with group (MDD/HC) and sex (male/female) as between-subject factors to investigate the morphological differences between HC and MDD groups. Significant diagnostic group by sex interactions were interpreted using graphical displays and by performing post-hoc two-sample *t*-tests separately for males and females or HC and MDD groups. To test region-based hypotheses regarding group differences, we performed region of interest (ROI) analyzes. ROIs included the bilateral amygdala, hippocampus, striatum, and PFC, including Brodmann areas (BA) 9–12, 24, 25, 32, and 44–47, defined by WFU PickAtlas Utility (http://www.fmri.wfubmc.edu/cms/software#WFU_PickAtlas). Consistent with our previous study (Blumberg et al., 2008; Tang et al., 2007; Wang et al., 2009), findings were considered significant at $p < 0.005$ (uncorrected) for the hypothesized regions. To minimize false discovery, cluster-level correction was applied to the hypothesized regions using AlphaSim (http://afni.nimh.nih.gov/) correction. The program determined a minimum cluster size in each ROI with Monte Carlo simulation to achieve a corrected significance of $p < 0.05$ with a voxelwise threshold of $p < 0.0005$ (see program AlphaSim by B.D. Ward in AFNI software). Additionally, potential associations between the morphological measurements (GMD or GMV) and HDRS, as well as duration of illness were performed separately in MDD females and MDD males and were corrected in AlphaSim.

3. Results

There was no significant effect of diagnosis, sex or interaction of diagnosis and sex in age and education. The effect of diagnosis in HDRS was significant, with significant higher HDRS scores in the MDD group, compared to the HC group. There was no significant effect of sex in HDRS. Two-sample *t*-tests showed no difference in the illness duration between MDD female and MDD male subgroups (Table 1).

The effect of diagnosis on GMD was significant in the left ventral prefrontal cortex (VPFC; BA 11/10, cluster size = 107 voxels, maximal point MNI coordinate: $x = -20$ mm, $y = 66$ mm, $z = -12$ mm, $T = 3.75$, $p < 0.05$, corrected) (Fig. 1), with significantly reduced GMD in the VPFC in the MDD group, compared to the HC group. The effect of sex on GMD was significant in the left caudate (cluster size = 131 voxels, maximal point MNI coordinate: $x = -8$ mm, $y = 8$ mm, $z = 8$ mm, $T = 4.94$, $p < 0.05$, corrected), with significantly reduced GMD in the caudate in the male participants, compared to the female participants (Fig. 2). Diagnosis by sex effects on GMD was significant in the right amygdala, right hippocampus, and left caudate (Table 2, Fig. 3). Post-hoc two-sample