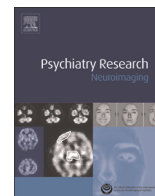




ELSEVIER

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Short communication

Gender moderates the association between dorsal medial prefrontal cortex volume and depressive symptoms in a subclinical sample

Joshua M. Carlson^{a,*}, Emily Depetro^a, Joshua Maxwell^a, Eddie Harmon-Jones^b, Greg Hajcak^c^a Department of Psychology, Northern Michigan University, Marquette, MI 49855, USA^b School of Psychology, The University of New South Wales, Sydney, Australia^c Department of Psychology, Stony Brook University, Stony Brook, NY, USA

ARTICLE INFO

Article history:

Received 31 October 2014

Received in revised form

5 February 2015

Accepted 16 June 2015

Available online 20 June 2015

Keywords:

Brain morphometry

Depression

Negative affect

Gender difference

Prefrontal cortex

ABSTRACT

Major depressive disorder is associated with lower medial prefrontal cortex volumes. The role that gender might play in moderating this relationship and what particular medial prefrontal cortex sub-region(s) might be implicated is unclear. Magnetic resonance imaging was used to assess dorsal, ventral, and anterior cingulate regions of the medial prefrontal cortex in a normative sample of male and female adults. The Depression, Anxiety, and Stress Scale (DASS) was used to measure these three variables. Voxel-based morphometry was used to test for correlations between medial prefrontal gray matter volume and depressive traits. The dorsal medial frontal cortex was correlated with greater levels of depression, but not anxiety and stress. Gender moderates this effect: in males greater levels of depression were associated with lower dorsal medial prefrontal volumes, but in females no relationship was observed. The results indicate that even within a non-clinical sample, male participants with higher levels of depressive traits tend to have lower levels of gray matter volume in the dorsal medial prefrontal cortex. Our finding is consistent with low dorsal medial prefrontal volume contributing to the development of depression in males. Future longitudinal work is needed to substantiate this possibility.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

According to the 2014 US Bureau Center for Disease Control and Prevention, approximately 19 million Americans suffer from depressive disorders and many other individuals experience non-clinical levels of depression. There are well-documented gender differences in the prevalence of depression, with higher rates in females compared with males (Kessler, 2003). Accumulating research and recent meta-analyses suggest that clinical depression is linked to reduced gray matter volume (GMV) in a variety of brain regions including the medial prefrontal cortex (mPFC) (Lorenzetti et al., 2009; Kempton et al., 2011; Bora et al., 2012; Du et al., 2012; Sacher et al., 2012; Grieve et al., 2013). However, there is inconsistency as to the particular sub-region within the mPFC that is associated with depression. The human PFC has a high concentration of sex hormone receptors (Bixo et al., 1995), which are a critical mechanism for the development of the brain and resultant gender differences in GMV (Goldstein et al., 2001; Cahill, 2006). As a group, females tend to have larger GMV within the anterior

cingulate cortex (ACC; Mann et al., 2011) and ventromedial PFC (vmPFC; Gur et al., 2002; Welborn et al., 2009) regions. As noted in a recent review of the literature (Lorenzetti et al., 2009), a major limitation with the current state of research on mPFC volume and depression is the potential role of gender in moderating this relationship. Depression-related reductions in hippocampal (Frodl et al., 2002) and ACC (Hastings et al., 2004) GMV have previously been found in males relative to females (but see Botteron et al., 2002). Yet, little is known about how gender may contribute to the relationship between depression and mPFC GMV. Traditionally, reduced mPFC volumes, as well as reductions in the volumes of other brain regions, in depression were hypothesized to be caused by stress-initiated hypercortisolemic glucocorticoid-mediated cell death (Manji et al., 2001; Frodl et al., 2008). Sex hormones have been shown to play a role in mediating the effects of stress on the PFC (Shansky et al., 2004), and may therefore contribute to gender differences in depression-related mPFC GMV. On the other hand, research of patients with ventromedial or dorsomedial PFC lesions has found that patients with vmPFC lesions were seemingly protected against depression while patients with dmPFC lesions were more susceptible (Koenigs et al., 2008). Thus, the roles that gender and stress play in the relationship between depression and mPFC GMV remain poorly understood. The aim of

* Corresponding author.

E-mail address: joshcarl@nmu.edu (J.M. Carlson).

this study was to examine whether non-clinical levels of stress, anxiety, and depression were related to GMV in dorsal and ventral mPFC regions of interest (ROIs) and to test for a moderating effect of gender.

2. Methods

2.1. Participants

Forty-two (male=25; right-handed=37) consenting adults between the ages of 19 and 25 ($M=21.14$, $SD=1.30$) participated (see Table 1 for participant characteristics). Participants were recruited with advertisements posted on campus and in the surrounding community. Thus, participants were primarily university students. Before scanning, participants were screened for contraindications to magnetic resonance imaging (MRI) and history of head injury. After completing the study, participants were monetarily compensated for their time. The Institutional Review Board of Stony Brook University approved this study.

2.2. Self-report measure of depressive traits

The Depression, Anxiety, and Stress Scale (DASS) is a 42-item questionnaire with three 14-item scales, which measure participants' self-report levels of depression, anxiety, and stress (Lovibond and Lovibond, 1995). The scale was designed to better differentiate between depression, anxiety, and stress. The depression scale measures a number of facets related to depression including hopelessness and lack of interest, while the anxiety scale measures situation-specific anxiety including automatic, somatic, and subjective symptoms whereas the stress scale measures more general non-specific chronic stress. Scores on the depression (range=7–22, $M=10.24$, $SD=3.85$), anxiety (range=7–25, $M=9.93$, $SD=3.41$), and stress (range=7–22, $M=11.62$, $SD=3.62$) scales ranged from normal to severe levels.

2.3. Structural MRI acquisition and analysis

A 3 T Siemens Trio whole body scanner was used to acquire T₁ images with the following parameters: repetition time=1900 ms, echo time=2.53, flip angle=9°, field of view=176 × 250 × 250 mm³, matrix=176 × 256 × 256, and voxel size=1 × 0.98 × 0.98 mm³. We used voxel-based morphology (VBM) as an automated user-independent voxel-wise measurement of the association between regional brain volumes and individual differences in depressive traits. The VBM methodology used in this report is similar to the procedures described previously by others (Ashburner and Friston, 2000) as well as our group (Carlson et al., 2012, 2015). First, we manually adjusted brain volumes to an origin at the anterior commissure. All images were then pre-processed using standard VBM procedures in SPM8 ([http://www.fil.](http://www.fil.ion.ucl.ac.uk/spm)

[ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Images were segmented into gray matter, white matter and cerebrospinal fluid. Images were then normalized to standard templates in SPM8 using a modulation step. Tissue probability maps were obtained by averaging across participant data, using an 8-mm full width at half-maximum Gaussian smoothing kernel. Measures of total gray matter volume (GMV) were obtained from summed global signal of segmented images of gray matter.

The participant's depression score was used as our predictor variable with GMV as the dependent variable using multiple regression within SPM8. We specifically tested whether increased levels of depression would correlate with decreased GMV. Age and whole brain gray matter volume (WBGV) were included as covariates to control for their potentially confounding effects on regional gray matter (Ge et al., 2002). We used the MAsks for Region of Interest Analysis (MARINA) software to create dmPFC (2949 voxels), vmPFC (1571 voxels), and anterior cingulate (1400 voxels) mPFC ROIs (see Fig. 1). We used alpha sim to determine a cluster-level adjusted $p < 0.05$ ($p < 0.01$, $k > 93.5$). Data were extracted from significant clusters (see Section 3) to assess the uniqueness of this association with depression as opposed to anxiety or stress. Extracted mPFC GMV data were entered as the dependent measure into a linear regression model including gender, age, WBGV, depression, anxiety, stress, and the gender × depression interaction term as predictor variables. We used Fisher's Z-tests to test for differences in correlations between mPFC GMV and depression compared with mPFC GMV and anxiety and mPFC GMV and stress as well as differences in the association between the mPFC and depression in males and in females.

3. Results

Depression scores were moderately correlated with anxiety ($r=0.59$, $p < 0.001$) and stress ($r=0.55$, $p < 0.001$) scores. Anxiety and stress were also moderately correlated ($r=0.46$, $p=0.001$).

As can be seen in Fig. 1, within the dmPFC ROI, a cluster of voxels correlated with depressive symptoms such that greater levels of depression were associated with lower GMV, peak voxel 4, 52, 2; $k=99$, $t=3.56$, $r=-0.49$, $p_{corrected} < 0.05$. When participants' levels of anxiety and stress were included as additional control variables in a partial correlation, depression still correlated with dmPFC volume ($r=0.45$, $p_{single-tailed}=0.002$). On the other hand, neither anxiety ($r=0.05$, $p_{single-tailed}=0.39$) nor stress ($r=0.09$, $p_{single-tailed}=0.30$) correlated with dmPFC volume when controlling for depression and stress or anxiety, respectively. Using Fisher's Z-tests, it was determined that the correlation between mPFC volume and depression was significantly stronger than the correlations between dmPFC volume and anxiety ($z=1.92$, $p_{single-tailed}=0.03$) or stress ($z=1.74$, $p_{single-tailed}=0.04$).

Stepwise linear regression indicated that dmPFC GMV was predicted by depression ($\beta=-0.44$, $p < 0.001$), the interaction between depression × gender ($\beta=0.30$, $p=0.02$), and WBGV ($\beta=0.97$, $p < 0.001$), $F_{3,29}=54.08$, $p < 0.001$, adjusted $R^2=0.80$. Age, anxiety, and stress did not contribute significantly to the variance explained. To better understand the interaction between depression and gender, we ran separate partial correlations between dmPFC GMV and depression (controlling for age and WBGV) for males and females. For males there was a high correlation between depression and dmPFC GMV ($r=-0.67$, $p < 0.001$), but for females the association was not significant ($r=-0.08$, $p=0.39$). Using a Fisher's Z-test, it was determined that the correlation between dmPFC volume and depression was significantly stronger for males than for females ($z=2.14$, $p=0.03$), indicating that gender moderates the association between dmPFC volume and depression.

Table 1
Participant demographics and characteristics.

	Handedness	Age	Depression	Anxiety	Stress
Male	Right $n=23$	$M=21.44$	$M=10.48$	$M=10.20$	$M=11.44$
	Left $n=2$	$SD=1.39$	$SD=4.13$	$SD=3.99$	$SD=3.33$
Female		Range 19–25	Range 7–22	Range 7–25	Range 7–18
	Right $n=14$	$M=20.71$	$M=9.88$	$M=9.53$	$M=11.88$
	Left $n=3$	$SD=1.05$	$SD=3.48$	$SD=2.37$	$SD=4.11$
		Range 19–23	Range 7–20	Range 7–14	Range 7–22
Total	Right $n=37$	$M=21.14$	$M=10.24$	$M=9.93$	$M=11.62$
	Left $n=5$	$SD=1.30$	$SD=3.85$	$SD=3.41$	$SD=3.62$
		Range 19–25	Range 7–22	Range 7–25	Range 7–22

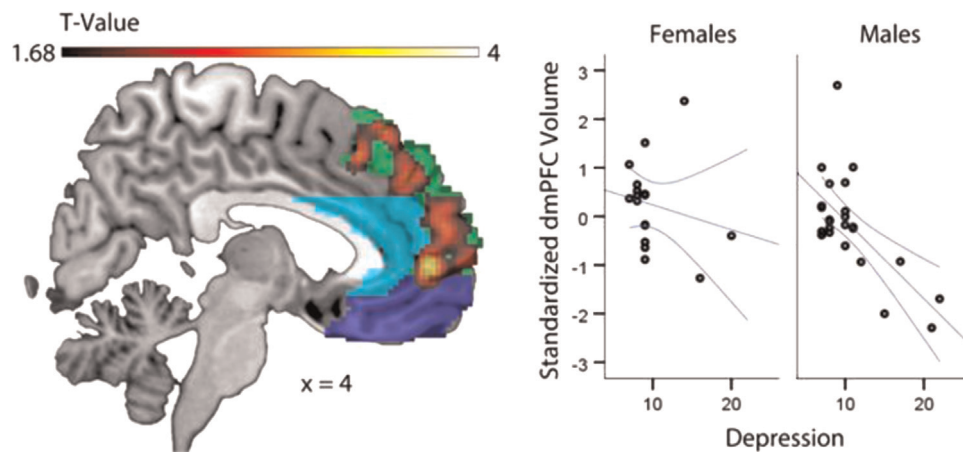


Fig. 1. (left) A cluster of voxels within the dorsomedial prefrontal cortex where greater levels of depressive symptoms are associated with lower gray matter volume. This effect was localized to the dorsal medial superior frontal gyrus (in green) compared with the anterior cingulate (light blue) and ventral medial prefrontal cortex (dark blue). For visualization purposes, the image is thresholded at $0.05_{\text{uncorrected}}$. As can be seen, depression is diffusely associated with gray matter volume within the dorsal medial superior frontal gyrus, but this association did not extend into ventral medial prefrontal cortex or anterior cingulate cortex. (right) This association was moderated by gender: males displayed a strong negative association between depression and dorsal medial prefrontal gray matter volume, but in females this association was not significant. Regression lines with 95% confidence intervals are plotted. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

We found that greater levels of depression were associated with lower dmPFC GMV. This relationship with the dmPFC was not observed for measures of anxiety or stress when controlling for depression. The effect, however, was moderated by gender, where males had a strong negative association between dmPFC GMV and females did not. Linear regression analysis found that depression and the interaction between depression and gender significantly contributed to variability explained in dmPFC GMV, while stress, anxiety, and age did not.

Our finding of lower GMV in the dmPFC is consistent with a recent meta-analysis of structural neuroimaging studies of depression showing lower dmPFC in clinical depression (Bora et al., 2012; Sacher et al., 2012). The mPFC has received a lot of recent attention for its role in depression (Drevets et al., 2008). A number of neuroimaging studies have found abnormally high or low activity in the mPFC and abnormal dmPFC activity has been linked to altered self-reflection and rumination in depression (Lemogne et al., 2012). Women are more likely to attend to and ruminate about their emotions. In women low in depression, attention to emotion is not linked to depressive symptoms; however, for those high in depression, greater rumination is linked with greater depressive symptoms (Thayer et al., 2003). The complex nature of this relationship may partially explain why we did not observe a linear relationship between dmPFC GMV and depressive symptoms in females. The dmPFC has been implicated in emotion-regulation processes and, in particular, the down-regulation of negative affect (Ochsner et al., 2004). There are gender differences in prefrontal emotion-regulation processes. Compared with men, women tend to recruit the vmPFC, anterior cingulate, and lateral prefrontal regions more during emotion regulation (Koch et al., 2007; Mcrae et al., 2008; Mak et al., 2009) and vmPFC volume mediates sex differences in emotion regulation (Welborn et al., 2009). Thus, given that males tend to recruit fewer PFC regions during emotion regulation, volume loss in the dmPFC may be particularly problematic for males, leading to a dysregulation of negative affect and increased depressive symptoms. Recent research on patients with selective dorsal PFC (highest lesion overlap in the dmPFC) and vmPFC lesions found that vmPFC lesions were associated with stronger resistance to depression, whereas lesions on the dmPFC were associated with vulnerability to depression

(Koenigs et al., 2008). Based on the results of our study in conjunction with the evidence from lesion research, it appears that lower dmPFC GMV in subclinical depression may serve as a vulnerability mechanism for the development of depression in male participants. Future studies might test this possibility by examining dmPFC GMV in relation to other known risk factors for depression (e.g., maternal history) and using longitudinal designs.

There were several limitations of the study that should be noted. First, our sample consisted of younger adults (aged 18–25) with normative levels of depression, and it is unclear whether the relationship observed here will generalize to older or younger samples, or to those with more severe depressive symptoms. Although males and females were matched for age and depression, the group sizes in our study were relatively small and we did not measure participants' drug history. Thus, future research should be aimed at replicating these initial results in a larger sample. We assessed the relationship between dmPFC GMV, gender, and depression by looking at depression along a continuum; future research might dichotomize depression into high and low groups. Nevertheless, the results of this experiment suggest that even within a non-clinical sample of younger adults, male individuals who have higher levels of depression tend to have lower levels of dmPFC GMV.

References

- Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry – the methods. *Neuroimage* 11, 805–821.
- Bixo, M., Backstrom, T., Winblad, B., Andersson, A., 1995. Estradiol and testosterone in specific regions of the human female brain in different endocrine states. *J. Steroid Biochem. Mol. Biol.* 55, 297–303.
- Bora, E., Fornito, A., Pantelis, C., Yucel, M., 2012. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. *J. Affect. Disord.* 138, 9–18.
- Botteron, K.N., Raichle, M.E., Drevets, W.C., Heath, A.C., Todd, R.D., 2002. Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biol. Psychiatry* 51, 342–344.
- Cahill, L., 2006. Why sex matters for neuroscience. *Nat. Rev. Neurosci.* 7, 477–484.
- Carlson, J.M., Beacher, F., Reinke, K.S., Habib, R., Harmon-Jones, E., Mujica-Parodi, L.R., Hajcak, G., 2012. Nonconscious attention bias to threat is correlated with anterior cingulate cortex gray matter volume: a voxel-based morphometry result and replication. *Neuroimage* 59, 1713–1718.
- Carlson, J.M., Foti, D., Harmon-Jones, E., Proudfit, G.H., 2015. Midbrain volume predicts fMRI and ERP measures of reward reactivity. *Brain Struct. Funct.* 220 (3), 1861–1866.

- Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct. Funct.* 213, 93–118.
- Du, M.Y., Wu, Q.Z., Yue, Q., Li, J., Liao, Y., Kuang, W.H., Huang, X.Q., Chan, R.C., Mechelli, A., Gong, Q.Y., 2012. Voxelwise meta-analysis of gray matter reduction in major depressive disorder. *Prog. Neuro-psychopharmacol. Biol. Psychiatry* 36, 11–16.
- Frodil, T., Meisenzahl, E.M., Zetzsche, T., Born, C., Groll, C., Jager, M., Leinsinger, G., Bottlender, R., Hahn, K., Moller, H.J., 2002. Hippocampal changes in patients with a first episode of major depression. *Am. J. Psychiatry* 159, 1112–1118.
- Frodil, T.S., Koutsouleris, N., Bottlender, R., Born, C., Jager, M., Scupin, I., Reiser, M., Moller, H.J., Meisenzahl, E.M., 2008. Depression-related variation in brain morphology over 3 years: effects of stress? *Arch. Gen. Psychiatry* 65, 1156–1165.
- Ge, Y., Grossman, R.L., Babb, J.S., Rabin, M.L., Mannon, L.J., Kolson, D.L., 2002. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. *AJNR Am. J. Neuroradiol.* 23, 1327–1333.
- Goldstein, J.M., Seidman, L.J., Horton, N.J., Makris, N., Kennedy, D.N., Caviness Jr., V.S., Faraone, S.V., Tsuang, M.T., 2001. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cereb. Cortex* 11, 490–497.
- Grieve, S.M., Korgaonkar, M.S., Koslow, S.H., Gordon, E., Williams, L.M., 2013. Widespread reductions in gray matter volume in depression. *NeuroImage: Clin.* 3, 332–339.
- Gur, R.C., Gunning-Dixon, F., Bilker, W.B., Gur, R.E., 2002. Sex differences in temporo-limbic and frontal brain volumes of healthy adults. *Cereb. Cortex* 12, 998–1003.
- Hastings, R.S., Parsey, R.V., Oquendo, M.A., Arango, V., Mann, J.J., 2004. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology* 29, 952–959.
- Kempton, M.J., Salvador, Z., Munafo, M.R., Geddes, J.R., Simmons, A., Frangou, S., Williams, S.C., 2011. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch. Gen. Psychiatry* 68, 675–690.
- Kessler, R.C., 2003. Epidemiology of women and depression. *J. Affect. Disord.* 74, 5–13.
- Koch, K., Pauly, K., Kellermann, T., Seiferth, N.Y., Reske, M., Backes, V., Stocker, T., Shah, N.J., Amunts, K., Kircher, T., Schneider, F., Habel, U., 2007. Gender differences in the cognitive control of emotion: an fMRI study. *Neuropsychologia* 45, 2744–2754.
- Koenigs, M., Huey, E.D., Calamia, M., Raymond, V., Tranel, D., Grafman, J., 2008. Distinct regions of prefrontal cortex mediate resistance and vulnerability to depression. *J. Neurosci.* 28, 12341–12348.
- Lemogne, C., Delaveau, P., Freton, M., Guionnet, S., Fossati, P., 2012. Medial prefrontal cortex and the self in major depression. *J. Affect. Disord.* 136, e1–e11.
- Lorenzetti, V., Allen, N.B., Fornito, A., Yucel, M., 2009. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *J. Affect. Disord.* 117, 1–17.
- Lovibond, S.H., Lovibond, P., 1995. *Manual for the Depression Anxiety Stress Scales*. Psychology Foundation, Sydney.
- Mak, A.K., Hu, Z.G., Zhang, J.X., Xiao, Z., Lee, T.M., 2009. Sex-related differences in neural activity during emotion regulation. *Neuropsychologia* 47, 2900–2908.
- Manji, H.K., Drevets, W.C., Charney, D.S., 2001. The cellular neurobiology of depression. *Nat. Med.* 7, 541–547.
- Mann, S.L., Hazlett, E.A., Byne, W., Hof, P.R., Buchsbaum, M.S., Cohen, B.H., Goldstein, K.E., Haznedar, M.M., Mitsis, E.M., Siever, L.J., Chu, K.W., 2011. Anterior and posterior cingulate cortex volume in healthy adults: effects of aging and gender differences. *Brain Res.* 1401, 18–29.
- Mcrae, K., Ochsner, K.N., Mauss, I.B., Gabrieli, J.J.D., Gross, J.J., 2008. Gender differences in emotion regulation: an fMRI study of cognitive reappraisal. *Group Process. Intergr. Relat.* 11, 143–162.
- Ochsner, K.N., Knierim, K., Ludlow, D.H., Hanelin, J., Ramachandran, T., Glover, G., Mackey, S.C., 2004. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. *J. Cogn. Neurosci.* 16, 1746–1772.
- Sacher, J., Neumann, J., Funfstuck, T., Soliman, A., Villringer, A., Schroeter, M.L., 2012. Mapping the depressed brain: a meta-analysis of structural and functional alterations in major depressive disorder. *J. Affect. Disord.* 140, 142–148.
- Shansky, R.M., Glavis-Bloom, C., Lerman, D., McRae, P., Benson, C., Miller, K., Cosand, L., Horvath, T.L., Arnsten, A.F., 2004. Estrogen mediates sex differences in stress-induced prefrontal cortex dysfunction. *Mol. Psychiatry* 9, 531–538.
- Thayer, J.F., Rossy, L.A., Ruiz-Padial, E., Johnsen, B.H., 2003. Gender differences in the relationship between emotional regulation and depressive symptoms. *Cogn. Ther. Res.* 27, 349–364.
- Welborn, B.L., Papademetris, X., Reis, D.L., Rajeevan, N., Bloise, S.M., Gray, J.R., 2009. Variation in orbitofrontal cortex volume: relation to sex, emotion regulation and affect. *Soc. Cogn. Affect. Neurosci.* 4, 328–339.