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Sex-related functional asymmetry of the ventromedial prefrontal cortex in regard to decision-making under risk and ambiguity

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Abstract

Previous work has provided preliminary indication of sex-related functional asymmetry of the ventromedial prefrontal cortex (vmPFC) in social and emotional functions and complex decision-making. Findings have been inconsistent, and based on small numbers of patients. Given the rarity of these neurological cases, replicable results across studies are important to build evidence for sex-related functional asymmetry of the vmPFC. Here we used a sample of sixteen neurological patients with unilateral damage to the left or right vmPFC and examined differences between men and women on a task that probed decision-making under risk or decision-making under ambiguity. We found that men with right-hemisphere vmPFC damage and women with left-hemisphere vmPFC damage demonstrated significantly reduced aversion to risk and ambiguity. Men with damage to the left vmPFC and women with damage to the right vmPFC showed aversion to risk and ambiguity comparable to participants with left or right-sided brain damage outside the vmPFC, and to comparison participants without brain damage. Our results add to previous findings of sex-related functional asymmetry of the vmPFC in decision-making. Our study also replicates findings of no observable behavioral differences between men and women without neurological damage on tests of decision-making. This pattern of neurobiological divergence but behavioral convergence between men and women may reflect a complex interplay of neuroendocrine, developmental, and psychosocial factors.

Keywords

sex differences; prefrontal cortex; decision-making

1. Introduction

Studies of neurological and cognitive differences between men and women are often sources of both fascination and controversy. It is commonly accepted that there are sex-related differences in structural and functional brain organization in both animals and humans

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(Cahill, 2006). However, the extent of the differences and the degree to which these neural differences impact behavior vary between the brain areas and behaviors studied. Classically observed differences between men and women on verbal and spatial behaviors have been discussed at length (see Kimura, 1996). However, other cognitive functions such as naming and emotional memory show no sex-related differences at the behavioral level despite clear distinctions between men and women at the neural level (Grabowski, Damasio, Eichhorn, & Tranel, 2003; Piefke, Weiss, Markowitsch, & Fink, 2005).

In the domain of decision-making, evidence is less clear for sex-related differences in neural organization resulting in observed behavioral differences. While decision-making can encompass a wide array of distinct behavior, of particular interest are decisions under risk (where the probability of all outcomes are known), and ambiguity (where the probability of outcomes are unknown). Research from behavioral economics has indicated that women show a greater aversion than men to decision-making under risk as well as ambiguity (Borghans, Golsteyn, Heckman, & Meijers, 2009; Charness & Gneezy, 2012; Powell & Ansic, 1997), while other studies from clinical psychology and neuroscience have found no differences between men and women on other tasks of risky and ambiguous decision-making (Deakin, Aitken, Robbins, & Sahakian, 1999; Gardner & Steinberg, 2005; Lee, Chan, Leung, Fox, & Gao, 2009; Lighthall, Mather, & Gorlick, 2009; Starcke, Wolf, Markowitsch, & Brand, 2008; van den Bos, Homberg, & de Visser, 2013).

The ventromedial prefrontal cortex (vmPFC), along with other areas, has been identified as a critical neural area for decision-making (Damasio, 1994; Sanfey, 2007). Previous studies have found evidence of a ‘reversed asymmetry’ between men and women with damage to the vmPFC, such that men with right-sided vmPFC damage, and women with left-sided vmPFC damage, demonstrate deficits in social-emotional processing and performance on the Iowa gambling task (IGT), a measure of naturalistic decision-making (Bechara, Damasio, Damasio, & Anderson, 1994; Tranel, Bechara, & Denburg, 2002; Tranel, Damasio, Denburg, & Bechara, 2005). This lesion evidence has been complemented by neuroimaging research, which has shown greater right prefrontal activation in men, and greater left prefrontal activation in women during the IGT (Bolla, Eldreth, Matochik, & Cadet, 2004). However, the IGT is a complex measure of decision-making with elements of both decision-making under risk and ambiguity, preventing easy decomposition into discrete cognitive constructs (Schonberg, Fox, & Poldrack, 2011). Closer study of the components of decision-making affected by sex-related, functional asymmetry of the vmPFC is necessary to better understand which cognitive elements are different between men and women. The goal of the current study is to add to previous findings of sex-related, functional asymmetry of the prefrontal cortex, using a task that allows us to examine the decision-making subcomponents of risk and ambiguity in a more conclusive manner. Based on previous work, we predict that men with right-sided, and women with left-sided vmPFC lesions will show deficits in decision-making under risk and ambiguity, while men with left-sided and women with right-sided vmPFC lesions, as well as men and women damage outside vmPFC, will not show deficits in decision-making.

2. Methods

2.1 Participants

Participants with focal, unilateral damage to the vmPFC (n = 16, 9 men/7 women, 10 right-sided/6 left-sided) were recruited from the Patient Registry of the Division of Cognitive Neuroscience at the University of Iowa (Iowa City, IA). The demographic and neuropsychological characteristics of these 16 participants are presented in Table 1. Brain damage was acquired in adulthood for all vmPFC participants with the exception of 2046, 2097, and 2517, whose damage occurred during development (prior to age 18). Our motivation for including these participants in the present study was due to the rarity of unilateral vmPFC cases. Previous reports of patients with developmental onset vmPFC damage (Anderson et al., 1999; Eslinger, Flaherty-Craig & Benton, 2004; Anderson et al., 2006) indicate disruptions in decision-making behavior similar in kind, if occasionally worse in magnitude, to patients with adult-onset vmPFC damage. In addition to our target cases, we also studied adult-onset, focal, unilateral brain damaged comparison (BDC) participants with damage outside of the vmPFC (n = 112, 42 men/66 women, 45 right-sided/63 left-sided). All brain-damaged participants have been extensively characterized neuropsychologically and neuroanatomically (see section 2.2) in the chronic epoch of recovery (at least three months post lesion onset, when the effects of the lesion have mostly stabilized) as part of their inclusion in the Registry. An additional sample of adult, normal comparison (NC) participants (n = 62, 31 men/31 women) with no brain damage was also recruited from the Iowa City area. All participants gave written informed consent. Demographic and neuropsychological characteristics of the groups are described in Table 2. Participants self-reported dichotomous gender identity, either male or female, which we will refer to as sex.

2.2 Lesion Analysis

Neuroanatomical analyses of lesion location and size were based on CT or MR images collected in the chronic epoch of recovery (as above). Brainvox was used to create a 3D reconstruction of each brain lesion (Frank, Damasio, & Grabowski, 1997), which was then manually warped to a custom normal template brain using the MAP-3 technique, consistent with previous studies from our laboratory (Damasio, Tranel, Grabowski, Adolphs & Damasio, 2004). Once transferred to template space, the template brain was diffeomorphically warped to the MNI152 standard 1mm T1-weighted atlas (Mazziotta et al., 2001; Collins, Neelin, Peters, & Evans, 1994; Evans, Dai, Collins, Neelin, & Marrett, 1991), using a Symmetric Normalization algorithm (Avants and Gee, 2004). This transform from lesion template to MNI152 space was applied to each lesion map to register it to a standard space used by a large portion of the literature. Lesion maps in standard space were processed with FSL software package utilities (FSL 5.0.2.2, FMRIB's Software Library) to generate lesion overlap maps of our vmPFC and BDC participants.

Naturally occurring lesions do not respect clean anatomical or functional boundaries, and there are pitfalls to classifying lesions in an all-or-none fashion. While anatomical parcellation approaches provide more nuances for analysis, they can still distort the degree to which a lesion in a non-target but adjacent anatomical region may spill over into the

periphery of the target region of interest, even if it does not affect the core of the target area to a significant extent. We attempted to address these classification issues with two approaches. First, we recruited only participants with known damage to our target region of interest, the vmPFC, for the target group. Secondly, we limited our analyses to participants with unilateral damage to the vmPFC, and excluded participants with damage concentrated at the periphery of our target region of interest. Consistent with previous studies (Koscik & Tranel, 2012; Koscik & Tranel, 2013), we set a lower limit on the proportion of damaged voxels for inclusion at 5% of the volume of the vmPFC in each hemisphere. Figure 1 shows the lesion overlap map for men and women participants in the vmPFC (Figure 1A & B) and BDC groups (Figure 1C & D), respectively.

2.3 Task

Participants completed a series of tasks measuring decision-making under uncertainty that have been reported in detail elsewhere, which for the sake of convenience we will refer to as the Ellsberg task (Ellsberg, 1961; Hsu, Bhatt, Adolphs, Tranel & Camerer, 2005). Briefly, participants completed two conditions that both probed decision-making under risk and ambiguity. In the Card Deck condition, participants were asked to choose between a gamble that a particular color (red or blue) would be chosen from deck of cards or a guaranteed amount. On risk trials (24 trials), the exact numbers of red and blue cards in the deck were known (i.e., the probability of choosing a red or blue cards was explicit), while on ambiguity trials (24 trials), the total number of cards are known, but not the proportion of red and blue cards (i.e., the probability of choosing a red or blue cards is unknown and effectively 50%). In the Knowledge condition, participants were asked to choose between a gamble on a Yes or No knowledge question or a guaranteed amount. Risk and ambiguity trials (24 each) in the Knowledge Deck condition were manipulated by varying the familiarity of the information. In this condition, risk trials reflect knowing more about the question (e.g. “The high temperature in New York City, NY on November 7, 2003 is above 50 Fahrenheit”) relative to having less knowledge about uncertain events in the ambiguity trials (e.g. “The high temperature in Dushanbe, Tajikistan on Novmeber 7, 2003 is above 50 Fahrenheit”). Since the exact familiarity of each trial in the Knowledge condition differs for each subject, the probability of each Yes/No gamble was assumed to be 50% for analytic purposes. Because the Card Deck condition did not depend on the participant’s individual knowledge and quantitatively manipulates risk, it always preceded the Knowledge Condition. Mostly overlapping, but slightly different groups of participants completed each of the two conditions. The demographics reported in Table are for those participants that completed the Card Deck condition. An additional 7 BDC participants and 3 NC participants completed the Knowledge Condition that did not complete the Card Deck, while 2 NC and 4 BDC participants completed the Card Deck condition without completing the Knowledge Condition. There were no significant differences between men and women BDC and NC participants who completed the Card versus Knowledge Conditions in age (BDC, p=0.86; NC, p=0.71), education (BDC, p=0.66; NC, p=0.85), or full-scale IQ (BDC, p=0.89; NC, n/a).

2.4 Analyses

The smaller range of value magnitude in our version of the Ellsberg task prevented us from employing previously used parameter estimation procedures (Hsu et al., 2005). Instead, aversion to risk and ambiguity were measured as the percentage of those trials where the guaranteed option was chosen. We also measured expected value preference, defined as the percentage of trials where the higher expected value was chosen (calculated as the value of the gamble outcome multiplied by gamble probability or the value of the guaranteed option). Multiple univariate analyses of variance (ANOVA) were conducted to look at the effects of sex, lesion group, and lesion laterality on risk aversion, ambiguity aversion, and total utility preference behavior. NC participants were coded as having a “none” for lesion laterality in the group analyses. Because three ANOVA tests were conducted for each task condition, Bonferroni correction was applied to reduce the risk of inflating Type I error, such that an effect was only significant if $p < 0.0167$. In addition, to investigate the unilateral men and women vmPFC cases, we conducted nonparametric Kruskal-Wallis tests on the key vmPFC groups of interest for the Card and Knowledge conditions, followed up by nonparametric Mann-Whitney tests, which were corrected for multiple comparisons using Bonferroni correction. All statistical analyses were conducted in SPSS 21 (IBM, Inc.).

3. Results

We examined vmPFC, BDC, and NC behavior in the Card Deck condition, using univariate ANOVAs to test the interaction of sex, lesion side, and group on risk and ambiguity aversion, as well as expected value preference. The ANOVA tests revealed significant three-way interactions between sex, laterality and lesion location for risk aversion [$F(1,176)=7.31$, $p=0.01$], and ambiguity aversion [$F(1,176)=8.36$, $p=0.004$]. The three-way interaction for expected value preference was nonsignificant [$F(1,176)=3.44$ $p=0.07$]. The two-way interaction between sex and lesion laterality for risk aversion was nonsignificant [$F(1,176)=4.91$, $p=0.03$], but significant for ambiguity aversion [$F(1,176)=9.44$, $p=0.002$]. The interaction between sex and lesion laterality for expected value preference was nonsignificant [$F(1,176)=3.69$, $p=0.06$].

Looking at the pattern of the three-way interactions, we found that men with right-sided vmPFC damage and women with left-sided vmPFC damage had reduced risk and ambiguity aversion. Specifically, risk aversion was lower for male participants with right-sided vmPFC lesions [mean (M)=0.09, 95% confidence interval (CI)= −0.14—0.33] and women with left-sided vmPFC damage [M=0.06, 95% CI= −0.31—0.44] compared to men with left-sided vmPFC lesions [M=0.41, 95% CI=0.14—0.67], women with right-sided vmPFC lesions [M=0.50, 95% CI=0.27—0.74], and both male [left-sided, M=0.34, 95% CI=0.24—0.45; right-sided M=0.31, 95% CI=0.18—0.45] and female [left-sided, M=0.34, 95% CI=0.25—0.43; right-sided M=0.31, 95% CI=0.18—0.45] BDC participants. Men and women NC participants showed similar levels of risk aversion [men, M=0.25, 95% CI=0.16—0.35; women M=0.27, 95% CI=0.17—0.36] (Figure 2A).

Ambiguity aversion was also lower for male participants with right-sided vmPFC lesions [M=0.38, 95% CI=0.08—0.69] and women participants with left-sided vmPFC lesions [M=0.00, 95% CI= −0.48—0.48] compared to men with left-sided vmPFC damage

[M=0.64, 95% CI=0.30—0.98], women with right-sided vmPFC damage [M=0.93, 95% CI=0.62—1.23], and both men [left-sided, M=0.50, 95% CI=0.37—0.63; right-sided M=0.53, 95% CI=0.36—0.71] and women [left-sided, M=0.41, 95% CI=0.30—0.52; right-sided, M=0.48, 95% CI=0.35—0.60] BDC participants. Men and women without brain damage showed similar risk aversion to BDC participants [men, M=0.63, 95% CI=0.51—0.76; women, M=0.61, 95% CI=0.49—0.74] (Figure 2B).

For the Knowledge Condition, univariate ANOVAs indicate a significant interaction between sex and lesion side for risk aversion [F(1,180)=6.30, p=0.01], but not ambiguity aversion [F(1,180)=2.26, p=0.14], or expected value preference [F(1,180)=2.15, p=0.15]. The three-way interaction between group, sex, and lesion side [F(1,180)=4.56, p=0.03] for risk aversion was nonsignificant after correcting for multiple comparisons. There were no significant interactions for ambiguity aversion [F(1,180)=2.64, p=0.11], or expected value preference [F(1,180)=1.37, p=0.24].

In regard to the interaction, men with right-sided vmPFC damage [M=0.16, 95% CI= −0.07—0.39] and women with left-sided vmPFC damage [M=0.10, 95% CI= −0.26—0.47] have lower risk aversion than men with left-sided vmPFC damage [M=0.45, 95% CI=0.19—0.70], women with right-sided vmPFC damage [M=0.51, 95% CI=0.28—0.74], and men [left-sided, M=0.33, 95% CI=0.24—0.43; right-sided M=0.29, 95% CI=0.16—0.43] and women [left-sided, M=0.34, 95% CI=0.26—0.43; right-sided, M=0.36, 95% CI=0.27—0.45] in the brain-damaged comparison group. Men and women without brain damage showed risk aversion similar to BDC participants [men, M=0.35, 95% CI=0.26—0.44; women, M=0.41, 95% CI=0.32—0.50] (Figure 3).

We conducted nonparametric Kruskal-Wallis tests to further examine the differences between men and women with left and right-sided vmPFC damage. For the Card Deck condition, we found significant differences between these groups for risk aversion [H(3)=9.044, p=0.03], and ambiguity aversion [H(3)=9.246, p=0.03]. Follow-up Mann-Whitney tests were Bonferroni corrected for multiple comparisons (p=0.0125), and show support for significant differences between men and women with right-sided vmPFC damage for risk aversion [U=0.50, p=0.008], but not ambiguity aversion [U=1.50, p=0.016]. The comparison between men with left and right vmPFC damage is not significant [risk aversion, U=3.00, p=0.11; ambiguity aversion U=6.00, p=0.41]. Non-parametric tests also do not show a significant difference between left and right-sided women [risk aversion U=0.00, p=0.095; ambiguity aversion U=0.00, p=0.095], or between women and men with left-sided vmPFC damage [risk aversion U=0.500, p=0.13; ambiguity aversion U=0.00, p=0.13].

In the Knowledge Condition, the nonparametric Kruskal-Wallis test showed a significant group difference between the vmPFC groups for risk aversion [H(3)=9.089, p=0.03]. Follow-up Mann-Whitney tests between men with left and right-sided damage [U=2.50, p=0.063], women with left and right-sided damage [U=0.00, p=0.095], men and women with right-sided damage [U=1.50, p=0.016], and men and women with left-sided damage [U=0.00, p=0.133] were nonsignificant after Bonferroni correction for multiple comparisons were applied.

Given the relatively large number of BDC participants with damage to the anterior temporal lobe, we identified a subgroup of participants (n= 51, 18 men/33 women, 18 right-sided/33 left-sided) with damage to the anterior temporal lobe that included damage to the amygdala. We compared this subgroup to participants with damage outside the anterior temporal lobe and ventromedial prefrontal cortex (n= 57, 24 men/33 women, 27 right/ 30 left), as well as our 61 normal comparison subjects. In ANOVAs for the Card Deck Condition, there was no significant three-way interaction for sex, lesion side, and group for risk aversion [$F(1,160)=0.43$, $p=0.51$], for ambiguity aversion [$F(1,160)=1.57$, $p=0.21$], or for expected value preference [$F(1,160)=0.40$, $p=0.53$]. Additional tests for two-way interactions between sex and group, and sex and lesion side for these conditions were also not significant. Looking at these subgroups on the Knowledge Deck Condition, there was no significant three-way interaction for sex, lesion side, and group for risk aversion [$F(1,164)=0.61$,$p=0.44$], ambiguity aversion [$F(1,164)=0.03$, $p=0.88$], or for expected value preference [$F(1,164)=0.07$, $p=0.79$]. Tests for two-way interactions between sex and group, and sex and lesion side were also not significant.

Finally, given previous findings of patients with bilateral vmPFC damage demonstrating deficits on the Ellsberg task (Hsu, et al. 2005), we conducted a follow-up study of 12 patients with bilateral vmPFC damage (7 men/5 women; Mean Age (SD): 55.91 (13.49); Years Education (SD): 13.92 (2.2); Chronicity (SD): 13.04 (11.48); Full-Scale IQ (SD): 102.36 (10.65)). In the Card Deck condition, risk aversion for men with bilateral vmPFC lesions [M=0.26, 95% CI=0.06—0.46] was between risk aversion for left and right-sided men with vmPFC damage, while women with bilateral vmPFC damage [M=0.17, 95% CI= −0.07—0.41] had risk aversion closer to that seen in left-sided women. Ambiguity aversion for men with bilateral vmPFC lesions damage [M=0.57, 95% CI=0.32—0.83] was closer to that seen in men with left vmPFC damage than men with right vmPFC, while women with bilateral vmPFC damage [M=0.18, 95% CI= −0.13—0.48] had ambiguity aversion closer to women with left-sided vmPFC damage than right-sided vmPFC damage.

In the Knowledge Condition, men with bilateral vmPFC damage demonstrated risk aversion [M=0.24, 95% CI=0.06—0.42] closer to that observed in men with right-sided damage, while women with bilateral vmPFC damage demonstrated risk aversion [M=0.24, 95% CI=0.00—0.48] closer to that observed in women with left-sided prefrontal damage.

In summary, men and women with bilateral vmPFC damage tended to show decision-making behavior similar to men with right-sided and women with left-sided unilateral vmPFC damage, respectively.

4. Discussion

On a task of decision-making under risk and ambiguity, we observed significant deficits in risk and ambiguity aversion between men with right-sided and women with left-sided damage to the ventromedial prefrontal cortex (respectively). Men with vmPFC damage to the left hemisphere and women with vmPFC damage to the right hemisphere show normal risk and ambiguity aversion, as do brain-damaged comparison participants of both sexes with damage outside the vmPFC. This evidence is in line with previous findings from our

laboratory (Gaznick, Bechara, & Tranel, 2014; Tranel et al., 2002; Tranel et al., 2005), as well as previous evidence of sex-related lateralization of hemispheric activity during decision-making (Bolla et al., 2004). Previous studies of sex-related prefrontal asymmetry have focused on decision-making during the Iowa Gambling Task (Tranel et al, 2005), which provides a good measure of real-world decision-making, but is not decomposable into distinct risk and ambiguity components (Schonberg et al., 2011). In contrast, the Ellsberg task is decomposable into distinct trials of decision-making under risk and ambiguity, allowing the demonstration that sex-related prefrontal asymmetry applies equally to risk and ambiguity-based decisions. To our knowledge, this was a previously under-explored area in the literature, and provides evidence that the deficits in decision-making observed with unilateral right-sided vmPFC damage in men and left-sided vmPFC damage in women may be related to cognitive and affective processes aside from the ability to distinguish between degrees of uncertainty.

One potential explanation for the current results could be related to sex-differences in lateralization of not only the prefrontal cortex, but also downstream limbic structures. Multiple studies have identified greater functional recruitment of the left amygdala in women, and right amygdala in men during affective ratings (Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004; Stevens & Hamann, 2012; Whittle, Yücel, Yap, & Allen, 2011), as well as differences in right and left amygdala connectivity between men and women, respectively (Kilpatrick, Zald, Pardo, & Cahill, 2006). Studies of nicotine-dependent individuals show differences in gray matter volume (Franklin et al., 2014) and functional recruitment (McClernon, Kozink, & Rose, 2008; Wetherill et al., 2013), of limbic areas (amygdala, hippocampus, medial orbitofrontal cortex) between men and women. Patients with unilateral amygdala damage also demonstrate impaired decision-making and social behavior in the same pattern (men right, women left) as in the prefrontal cortex (Gupta, Koscik, Bechara, & Tranel, 2011; Tranel & Bechara, 2009). Taken together, the observed sex-related asymmetry in structures important for decision-making may stem from a general sex-related, functional asymmetry in structures important for emotion and emotion-regulation (van den Bos et al., 2013). Damage to the left prefrontal cortex in women may impair the ability to integrate and utilize affective signals from the dominant left amygdala in the context of decision-making, while damage to the left amygdala in women may impair the primary affective signals necessary for successful decision-making. In men, a similar but right-sided pattern would be present. In the present study, participants with damage to the anterior temporal lobe, including the amygdala, constituted a large proportion of our brain damaged comparison group. As a follow-up to our main questions of interest, we isolated and tested for sex and laterality interactions in participants with damage to the anterior temporal lobe, including the amygdala, compared to participants with damage outside the anterior temporal lobe and ventromedial prefrontal cortex, but did not observe any significant main effects or interactions between sex and laterality. While preliminary, these data would suggest that previous observations of sex-related functional asymmetry in the amygdala may reflect the influence of top-down signaling from the ventromedial prefrontal cortex rather than sex-related functional asymmetry of the amygdala itself.

Our study does not speak directly to what may underlie sex-related asymmetry of vmPFC function, although we can situate our findings against various biological and psychosocial

mechanisms that have been offered in the literature. Among biological theories, animal studies have suggested that levels of gonadal hormones may play a critical role in tuning of the prefrontal cortex early in life, especially as it applies to performance on tasks such as reversal learning, although sex-differences on this task disappear in older participants (Clark & Goldman-Rakic, 1989). Similarly, sex hormone fluctuations have been linked to changes in cognitive patterns in both men and women (Kimura, 1996). Under the category of psychosocial theories, there is the obvious, but important, distinction is that women bear children while men do not, which may drive differences in individual and societal goals between men and women. The net effect of these divergent goals may ultimately result in differences in brain areas important for socio-emotional processing, leading to the observed sex-related functional asymmetries (Koscik, Bechara, & Tranel, 2010). Additionally, it has been suggested that differences in cognitive style, rather than sex-differences, may account for vmPFC asymmetry, however a full account for how differences in cognitive style may arise independently of sex-related, neurobiological differences has yet to be put forward (Tranel et al., 2005). While a mixture of biological and psychosocial influences are likely, we believe the present findings agree with the influence of sex-related hormonal differences resulting in neurobiological differences in prefrontal lateralization. However, we fully acknowledge that more empirical work is needed and, in human patient studies, additional cases should be collected to help fully tease apart these mechanisms. As a final note, we do not find evidence in the present study of women showing less hemispheric lateralization than men, which has been reported previously (McGlone, 1980; Bryden, 1982). A meta-analysis however, indicates that the this pattern may be more pronounced for cognitive tasks measuring ‘lateralized’ functions (Boles, 2005), allowing for the possibility that social-emotional functions may have different sex-related lateralization than other domains.

It is important to note that we do not observe differences between men and women without brain damage, or with damage outside the vmPFC, in decision-making under risk and ambiguity. This is in line with other studies of decision-making under risk using different tasks such as the Cambridge Gambling Task (Deakin et al., 1999), Balloon Analogue Risk Task (Lighthall et al., 2009), Game of Dice Task (Starcke et al., 2008), Risk Gain Task (Lee et al., 2009), or others (Gardner & Steinberg, 2005; Van den Bos et al., 2012). However, other studies have found differences in decision-making performance between men and women (Reavis & Overman, 2001; van den Bos et al., 2013). One possible explanation for this is that sex differences in decision-making have most reliably been observed with the Iowa Gambling Task (van den Bos et al., 2013), which as mentioned above, tests decision-making under a combination of risk and ambiguity. Additionally, the Iowa Gambling Task combines reward and punishment, while the Ellsberg task only examines decision-making under reward conditions. These differences in decision-making paradigms could explain why we did not observe previously reported sex differences in decision-making performance in comparison subjects.

Limitations for the current study should be noted. First and foremost, we are dealing with a small sample size, particularly regarding left-sided women with vmPFC damage, where we had two cases in the current study. This small sample prevents strong conclusions, although it is notable that the results here are consistent with other findings of sex-related functional asymmetry of the vmPFC from our laboratory (Gaznick et al., 2014; Tranel et al., 2005), and

other studies consisting primarily of men with right unilateral vmPFC damage (Rolls, Hornack, & McGrath, 1994; Gomez-Beldarrai et al., 2004). Our present findings of normal risk and ambiguity aversion in men with left-sided and women with right-sided vmPFC damage are also consistent with a prior report of unimpaired decision-making in five cases with unilateral orbitofrontal cortex damage (Manes et al., 2002). Although the authors do not report individual case performance, two of the cases were men with left-sided damage, while one of the three women had right-sided damage. However, nonparametric tests of group differences between our vmPFC participants only showed significant differences between men with right-sided and women with right-sided vmPFC damage in risk aversion after correcting for multiple comparisons. While we feel the current data add to the literature demonstrating sex-related functional asymmetry of the vmPFC, we acknowledge that larger samples of patients with unilateral vmPFC damage need to be studied to support these findings.

Another limitation of the current work is that there are differences in the extent of damage to dorsomedial and polar regions of the frontal lobe between our left and right-sided men and women vmPFC participants. Cases of unilateral damage to the vmPFC are rare, and rarer still are cases of isolated unilateral damage to other prefrontal structures such as the dorsomedial prefrontal cortex or frontal pole. Data presented here and previously (Hsu et al., 2005) show impairment on the Ellsberg task in patients with bilateral vmPFC damage, which leads us to believe that damage to the vmPFC is driving the observed sex by laterality results. However, we cannot rule out the possibility of differences in lesion distribution between our vmPFC groupings might influence the observed results.

Finally, the Ellsberg task is just one of many decision-making tasks that probe risk and ambiguity. While we have previously found evidence that sex-related asymmetry of the prefrontal cortex is also present in decision-making in the Iowa Gambling Task (Tranel et al., 2005), it will be important to study if the current findings also apply to other well-studied decision-making tasks such as the “cups task” (Levin & Hart, 2003), Balloon Analogue Risk Task (Lejuez et al., 2002), or others (see Schonberg et al., 2011 for a review). Additionally, in the present study we only examined behavioral measures of risky and ambiguous decision-making. Given the importance of autonomic affective signals in guiding advantageous decision-making (Bechara, Damasio, Tranel, & Damasio, 1997; Bechara, Tranel, & Damasio, 2000; A. R. Dmasio, 1994), future work could evaluate whether sex-related laterality effects such as those observed here are also related to physiological measures of risky decision-making.

4.1. Conclusions

The current study replicated and extended previous reports of sex-related asymmetry of the ventromedial prefrontal cortex (Gaznick et al., 2014; Tranel et al., 2005), such that men with right-sided and women with left sided damage show similar deficits in decision-making under risk and ambiguity. While this dissociation provides additional evidence of differences in functional organization of brain regions important for decision-making, this study also supports findings of similarities in decision-making between women and men without the distinct pattern of vmPFC damage observed in our sample. There may be sex-

related asymmetry in the brain structures supporting decision-making under risk and ambiguity, however the ultimate behavioral performance is indistinguishable. These findings are in line with previous reports of sex-related neural asymmetry but behavioral unity in other domains such as language or emotional memory (Grabowski et al., 2003; Piefke et al., 2005). One intriguing description that would explain this phenomena has been termed "neural sexual mosaicism," where the neural organization of men and women may be very similar in some aspects, but drastically different in others (Cahill, 2006; Witelson, 1991). In such an organization, a number of factors including early neuroendocrine events, structural brain differences, psychosocial influences, as well as functional asymmetries may impact how information is processed in a given brain area or network, which in turn may result in identical or divergent behavior in women and men. In the context of the current study, our results support the idea that women and men might utilize partially different neural systems in the course of making decisions, but the decisions they ultimately make are indistinguishable. Further study is warranted to better understand how observed behavioral and neural sex differences might emerge.

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Highlights

- There are sex differences in vmPFC laterality in decision making
- Men with right-sided, women with left-sided vmPFC damage show lower aversion to risk
- Men with right-sided, women with left-sided vmPFC damage show less ambiguity aversion
- Neural substrates supporting similar behavioral performance can differ between sexes

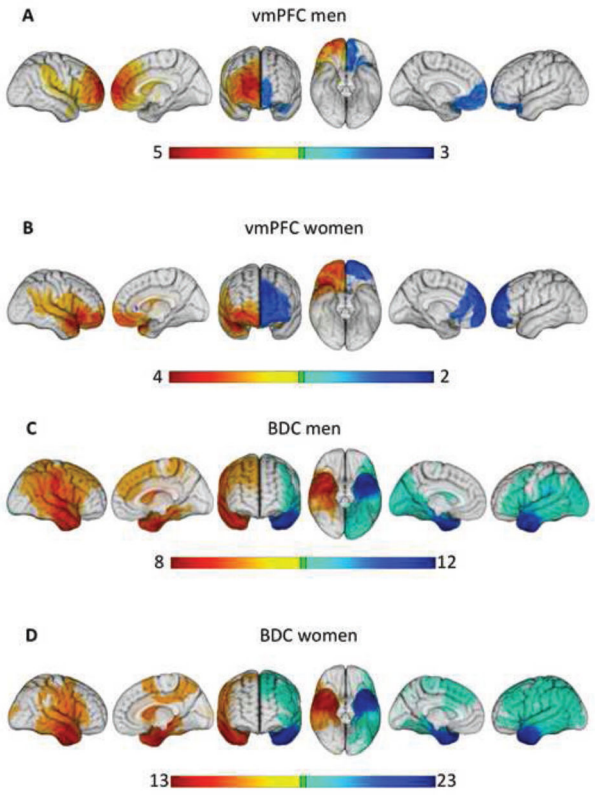

Figure 1. Lesion overlap maps (2 column figure)

Lesion overlap maps for (**A**) men and (**B**) women participants with vmPFC damage and (C) men and (D) women brain damaged comparison (BDC) participants. Right-sided lesion overlap is displayed in red, left-sided lesion overlap in blue. Green reflects interhemispheric overlap. Maximum lesion overlap for left- and right-sided cases in each group is displayed on scale bar.

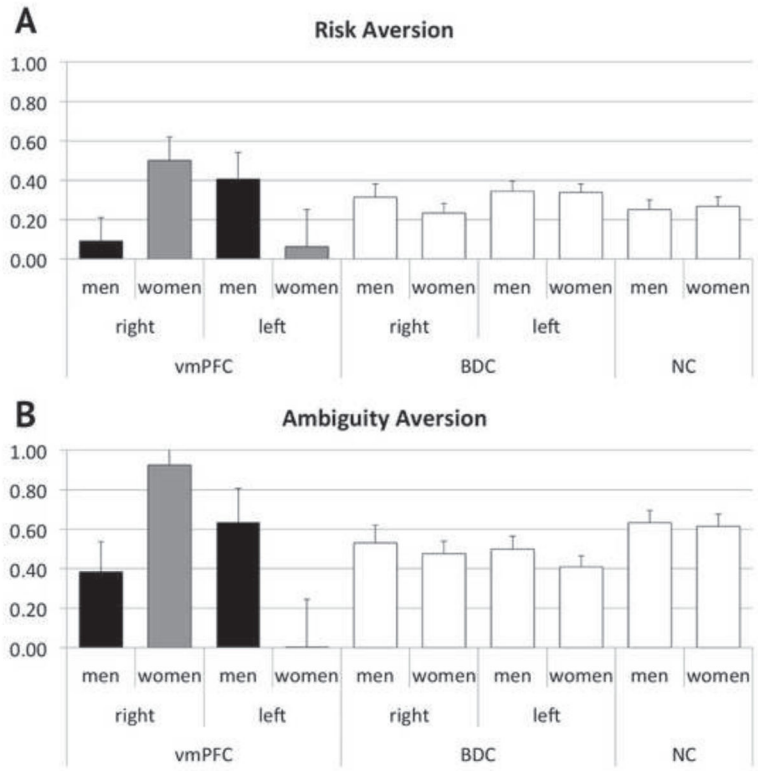

Figure 2. Card Deck performance (1 column figure)

(**A**) Risk aversion, and (**B**) ambiguity aversion for each group in the Card Deck condition. Risk and ambiguity aversion reflect the proportion of trials where the sure option was chosen over the gamble. Error bars indicate standard error of the mean.

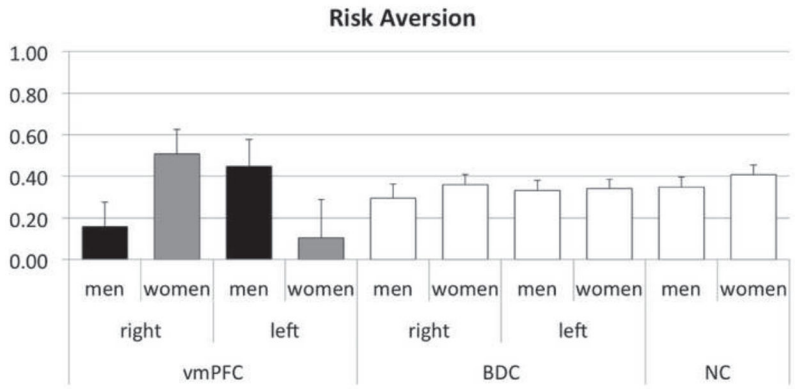

Figure 3. Knowledge Deck performance (1 column figure)

Risk aversion for each group in the Knowledge Deck condition. Risk aversion reflects the proportion of trials where the sure option was chosen over the gamble. Error bars indicate standard error for the mean of each group. There were no significant differences between groups in the Knowledge Condition for ambiguity aversion or expected value preference.

Table 1

vmPFC Patient Demographics

ID	Sex	Hemisphere	Handedness	Years Edu.	Lesion size (%)	Age	Lesion Chronicity	Etiology	FSIQ	PIQ	VIQ	AVLT Recog.	WCST Cat.	WCST PE	COWA	STROOP	Trails B-A
2517	Female	Left	RH	15	2.07	25	8.38	Benign Devel. Tumor	107	98	114	15	6	4	50	73	21
3477	Female	Left	RH	14	3.74	73	1.23	Benign Tumor	119	122	114	15	6	11	31	n/a	37
	2		2 RH	15	2.90	49	5	2 Tumor	113	110	114	15	6	8	41	73	29
1711	Female	Right	RH	13	11.30	45	16.87	Stroke	76	76	80	15	4	32	25	33	68
2025	Female	Right	RH	16	3.52	55	12.32	Stroke	115	116	113	15	6	4	50	58	20
2416	Female	Right	RH	18	5.63	58	9.66	Tumor	114	122	107	15	6	7	36	n/a	37
2615	Female	Right	RH	20	2.79	39	13.14	Benign Tumor	141	122	147	15	6	6	38	n/a	32
3535	Female	Right	RH	16	2.10	64	1.53	Benign Tumor	120	107	118	13	6	3	33	44	29
	5		5 RH	17	5.07	52	11	2 Stroke/3 Tumor	113	109	113	15	6	10	36	45	37
297	Male	Left	RH	16	1.76	59	27.36	Stroke	104	95	109	15	6	14	39	41	43
1652	Male	Left	RH	11	0.23	52	16.85	Stroke	95	94	96	15	6	5	27	49	45
2112	Male	Left	RH	18	1.59	56	12.16	AVM Resection	149	138	148	15	6	9	79	n/a	30
2795	Male	Left	LH	15	0.69	58	9.37	Benign Tumor	99	99	98	13	6	5	44	44	73
	4		3 RH/1 LH	15	1.07	57	16	2 Stroke/1 Resection/1 Tumor	112	107	113	15	6	8	47	45	48
1768	Male	Right	RH	12	5.98	70	15.50	Stroke	94	92	95	13	5	22	34	50	50
2046	Male	Right	LH	12	4.91	35	34.55	Benign Devel. Tumor	98	104	94	14	6	5	29	51	9
2097	Male	Right	RH	16	4.53	35	27.78	Benign Devel. Tumor	125	106	138	15	6	10	34	55	11
3001	Male	Right	RH	14	1.84	65	6.42	Benign Tumor	109*	115*	100*	13	3	26	37	n/a	29
3359	Male	Right	RH	17	10.77	49	1.28	Stroke	84	79	103	15	4	3	35	50	30
	5		4 RH/ 1 LH	14	5.61	51	17	2 Stroke/3 Tumor	100	95	108	14	5	13	34	52	26

Lesion Size —percent of total brain voxels damaged; Lesion Chronicity —time since lesion onset, in years.; FSIQ—full-scale IQ, PIQ—Performance IQ, VIQ—Verbal IQ from the WAIS-III (*scores from the WAIS-IV); AVLT Recog.—Auditory Verbal Learning Test Delayed Recognition Hits; WCST Cat—Wisconsin Card Sorting Test Categories completed; WCST PE- Wisconsin Card Sorting Test Perseverative Errors; COWA—verbal fluency from the Controlled Oral Word Association test; STROOP—Stroop Color-Word Interference (t-score); Trails B-A—Difference in latency (in seconds) between Trail Making Test B and Trail Making Test A

Table 2

Full Sample Demographics

Group	Sex	N	Handedness (R:M:L)	Lesion Side (R:L)	Age (SD)	Years Education (SD)	Lesion Chronicity[a] (SD)	FSIQ[b] (SD)
vmPFC	Male	9	6:1:2	5:4	53.31 (12.28)	14.88 (2.42)	16.81 (11.03)	106.29 (22.63)
	Female	7	7:0:0	5:2	51.38 (16.30)	16.00 (2.38)	9.02 (5.88)	113.14 (19.49)
BDC	Male	42	37:2:3	15:27	50.56 (15.81)	14.03 (2.48)	9.35 (9.20)	104.16 (11.74)
	Female	66	57:3:6	30:36	52.01 (14.15)	14.03 (2.48)	9.11 (10.54)	99.98 (12.45)
NC	Male	31	28:1:2	n/a	54.77 (22.98)	15.94 (2.43)	n/a	n/a
	Female	31	30:0:1	n/a	44.01 (19.51)	13.97 (1.91)	n/a	n/a

[a] Lesion Chronicity—time since lesion onset that data were collected, in years.

[b] FSIQ—full-scale IQ from the WAIS-III.