Sex Differences in Brain Activation During Virtual Navigation: A Functional MRI Study

Nicole T. Nowak (at3125@wayne.edu)
Department of Psychology
5057 Woodward Ave. 7th Floor
Detroit, MI 48202

Susan M. Resnick (resnicks@grc.nia.nih.gov)
Laboratory of Behavioral Neuroscience
Biomedical Research Center, room 04B317
251 Bayview Boulevard, Suite 100
Baltimore, MD 21224-6825

Wendy Elkins (wendy.elkins@nih.gov)
Laboratory of Behavioral Neuroscience
Biomedical Research Center, room 04C106
251 Bayview Boulevard
Baltimore, MD 21224-6825

Scott D. Moffat (moffat@wayne.edu)
Institute of Gerontology and
Department of Psychology
87 E. Ferry St.
Detroit, MI 48202

Abstract

A male advantage is often reported for measures of visuospatial performance, including measures of spatial navigation; however, few papers have addressed sex differences in brain activity during performance of these navigation tasks. We used functional MRI to compare the brain activation between young adult men and women during performance in a virtual environment (VE). Men and women did not differ in performance, but sex differences were apparent in the functional neuroanatomical correlates of navigation. In particular there was increased activation of the posterior cingulate retrosplenial cortex in men, and, in women with perfect recall performance, increased activation of the parahippocampal gyrus. These two areas are keys to successful navigation. Our results demonstrate that even when men and woman are well-matched on navigation performance, they appear to use different brain mechanisms to achieve the same behavioral end point.

Keywords: virtual navigation; sex differences; functional MRI

Spatial navigation is one domain of human cognition where a male advantage has been reported. In a review of sex differences in navigational performance Coluccia and Louse (2004) reported that a male advantage was found in over half of the studies; a female advantage was found in approximately 18 percent of the studies which involved map learning and memory, but women as a group never outperformed men in real or simulated environments. The effect size (Cohen's *d*) of the sex difference varies from small to large. For example, a moderate effect size favoring males was reported for a map-based route learning task (Galea & Kimura, 1993), while a large effect size was found for an orienteering drill (Malinowski & Gillespie, 2001). Effect sizes favoring men during performance of computerized maze navigation are moderate to large (e.g., Grön, Wunderlich, Spitzer, Tomczak, & Riepe, 2000; Moffat, Hampson, & Hatzipantelis, 1998). A sex difference favoring men in virtual Morris Water Task (vMWT) performance has also been reported (Astur, Ortiz, & Sutherland, 1998; Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005; Nowak & Moffat, 2010; Sandstrom, Kaufman, & Huettel, 1998) with several effect sizes as large as or larger than one standard deviation (e.g., Astur et al., 1998; Nowak & Moffat, 2010).

Sex differences at the behavioral level imply that sex differences at the neural level may be one source of explanation for this group difference; therefore, it is logical to hypothesize that men and women may be recruiting different brain regions to solve navigation tasks. To our knowledge, only two papers have addressed sex differences in blood oxygen level dependent response (BOLD; i.e., brain activation) during the performance of VE tasks in samples of healthy young participants.

In the first fMRI study of this nature, men and women were tested while they navigated as quickly as possible through a number of unfamiliar computerized mazes (Grön et al. 2000). Behaviorally, men found their way to the goal location of the mazes significantly faster than women, and the effect size of this sex difference was large. During maze navigation, activation in the right prefrontal cortex and right inferior and superior parietal lobes was greater for women than men. Activation during navigation was greater for men than women in the regions of the left hippocampus, right parahippocampal gyrus, and left posterior cingulate/retrosplenial cortex. The authors interpreted the sex difference in brain activation as a product of the differential use of egocentric and allocentric strategies. However, due to the large, statistically uncontrolled sex difference in navigation *performance*, this study cannot rule out the possibility that men and women matched in navigation accuracy and speed may show a more similar pattern of brain activation during maze performance.

Ohnishi et al. (2006) categorized participants by sex and navigation ability, which provided the opportunity to test the main effects and interactions of each of these variables on brain activation during passive maze navigation.

Participants passively viewed movement through nine mazes from a first-person perspective, and then were presented with two mazes from a bird's-eye perspective and were directed to determine which maze represented the environment they had passively viewed. Navigation ability (good or poor) was based on participants' Sense of Direction Questionnaire scores (SDQ-S; Takeuchi, 1992), an inventory composed of two scales relating to awareness of orientation and memory for spatial behavior. There was no main effect of sex, or interaction between sex and ability, on brain activation during maze navigation; however, the main effect of ability was significant. Participants with good navigation ability as determined by SDQ-S scores had greater activation in the parahippocampal gyri and precuneus, whereas poor navigators had greater activation in the right inferior parietal lobe. There was a positive correlation between accuracy in choosing the correct bird's-eye view maze during the passive navigation task and activation in the left hippocampus and parahippocampal gyrus; whereas a negative correlation was found between accuracy and right superior parietal lobe activation. Interpretation of this group difference was similar to that made by Grön in that better navigation ability was attributed to the use of an allocentric strategy whereas poor ability was related to an egocentric strategy.

Although the methods used to study the neural substrates of navigation differed between Grön et al. (2000) and Ohnishi et al. (2006), it is worth comparing the two. The brain areas involved in the maze performance of men (Grön et al.) coincide well with areas of activation found in the good navigators (Ohnishi et al.); likewise, results from the women correspond well with those of the bad navigators. The left hippocampus and parahippocampal gyri were associated with the best navigation performance, whereas activity in the right inferior and superior parietal lobes was correlated with relatively poor performance.

Clearly there is a gap in our knowledge between sex differences at the behavioral level and those at the functional neuroanatomical level. Conclusions from the behavioral literature are consistent; there is often a moderate to large male advantage on real world and virtual navigation tasks. The primary aim of this neuroimaging study was to investigate sex differences in brain activation during a virtual navigation task, and to correlate brain activity with performance. Collectively, the results from Grön et al. (2000) and Ohnishi et al. (2006) led us to hypothesize that the hippocampus and parahippocampal gyri would be associated with relatively good navigation performance, whereas the right parietal cortex would underlie poorer performance. Given the volume of research demonstrating sex differences in navigation-related behavior, we also hypothesized that men would complete our maze task with greater accuracy than women, and that group differences in brain activation would be apparent.

Method

Participants

Thirty healthy men and women (n = 15 men), age 21-39 years, who fit the MRI safety criteria, were recruited from newspaper advertisements. Men and women did not differ in age, $t(28) = .87$. It is unknown whether the groups differed in level of education or occupation.

Procedures

Prior to completing the VE tasks in the scanner, participants received extensive training outside of the scanner to familiarize them with the specific procedures and goals of the VE.

Navigation Tasks We used functional MRI to compare the brain activation between young men and women during performance in a VE. The virtual maze used in this task was a combination of interconnected hallways and small rooms, where there were six common objects placed throughout. This assessment had two parts: encoding and recall. The encoding phase of the navigation task required participants to actively explore the virtual maze and learn the location of six objects, as well as the spatial layout of the environment. Participants were instructed to learn the location of all of the objects, the interconnections of the hallways, and the general layout of the maze such that they could create an accurate overhead map of the environment. The recall phase required participants to remember the locations of the six objects encountered during the encoding phase and to move from object to object quickly and accurately using the shortest possible route. Presumably, the task as a whole required both object and object location memory along with a broader viewer-independent cognitive map of the environment which enabled participants to make decisions about the shortest routes possible between six objects. For each of the encoding and recall condition a control task was used that required participants to follow a winding hallway without having to learn the location of objects, locate objects, or make any navigation decisions; however, the control task required focused attention, the same joystick movements, visual stimulation, optic flow and other motion sensations as the navigation task.

A block design was employed and consisted of two phases: encode versus control, and recall versus control. The first phase involved a total of 10 blocks, which alternated between encode and control every 60 sec. The second phase was also composed of 10 blocks, alternating between the recall and control tasks every 60 sec.; therefore, the total duration of the functional task was 20 minutes.

fMRI Data Acquisition & Analysis Images were acquired on a 1.5 Tesla Phillips Gyroscan NT Intera parallel to the plane containing the anterior and posterior commissures. Following high resolution anatomical images, functional images were obtained using echo-planar imaging (TR = 3000 ms; TE = 30 ms; field of view= 64×64; voxel size= 3.75mm×3.75mm×5.5 mm). The first eight preliminary volumes of a session were discarded to achieve equilibrium. Statistical analysis was performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 5. All images were motion corrected by realigning to the first image of each subject. All images were spatially normalized to the standard template provided in SPM2 which is based on the reference brain provided by the Montreal Neurological Institute. Volumes were smoothed using an 8mm full width half maximum height Gaussian filter.

For primary analysis, each imaging run was analyzed using a box car function convolved with the hemodynamic response function. Contrast images producing t-statistics for each voxel were calculated for each subject based on the primary analysis. Voxels were thresholded at $p < 0.01$. These contrast images were then incorporated into second level group comparisons using a random effects model. Men and women were examined separately using one-sample *t*-tests comparing the navigation and control conditions. For comparisons between men and women during maze encoding, two-sample *t*-tests were used; and for group comparisons during maze recall, analysis of covariance was performed with sex as a grouping variable and speed during maze recall used as a covariate in the model. For all random effects analyses, height threshold was set at $p < 0.01$. Figures 1-3 represent group composite images created for the groups of men and women separately.

Results

Navigation Performance

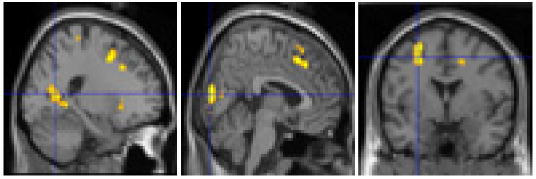
To investigate sex differences on behavioral outcome variables, we performed independent sample *t*-tests. Men traveled at a faster speed than women during the recall trials, $t(28) = 1.99$, $p = .057$, and this group difference was due to men moving at a faster speed during the first, $t(28) = 2.70$, $p = .01$, and final, $t(28) = 2.25$, $p = .03$, recall trials. Due to men travelling at a significantly faster speed on two of the five recall trials, speed was used as a covariate in the analyses of the recall task fMRI data. Also, the uncontrolled sex difference in speed was one of the drawbacks in the study by Grön et al. (2000), and we aimed to avoid this problem. Men and women did not differ in percent accuracy during recall, $t(28) = .36$, $p = .73$, and were well-matched on the other navigational variables.

BOLD Response in Men and Women During Navigation Encoding

One sample *t* –tests were used to determine areas of brain activation specific to maze learning by subtracting activation during the control trials from activation during the exploration trials. For the sample as a whole, activation was found in the following regions during maze exploration: bilateral precuneus, middle frontal gyri, and claustrum; left medial frontal gyrus, and left superior frontal gyrus.

Two sample *t* –tests were used to analyze sex differences in brain activation during maze learning. Activation during the encoding trials was greater in men than women in the following regions: bilateral middle frontal and cingulate gyri; right cuneus, putamen, superior parietal lobe, angular and medial frontal gyri; left posterior cingulate, insula, and lingual gyrus. Women, compared to men, had greater activation in the right amygdala and inferior parietal lobe, and left paracentral lobule. The top panel in Figure 1 highlights some of the regions that were more active in the group of men than group of women during encoding (i.e., Men > Women), and the bottom panel of Figure 1 displays some of the regions that were more active in women than men (i.e., Women > Men).

Results: Men > Women: left posterior cingulate, right cuneus, left middle frontal gyrus



Results: Women > Men: right inferior parietal lobe and amygdala

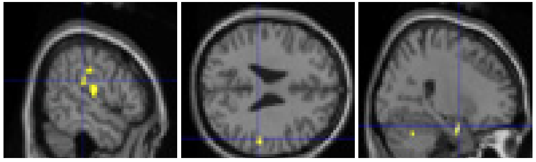


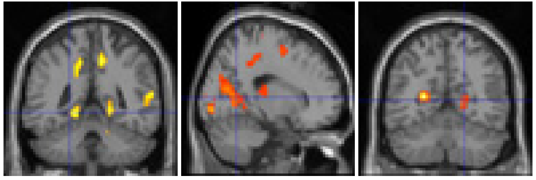
Figure 1: Sex Differences During Encoding

BOLD Response in Men and Women During Navigation Recall

A one sample *t* –test was used to determine areas of brain activation specific to maze recall by subtracting activation during the control trials from activation during the recall trials. For the sample as a whole, activation was found in the following regions during the maze recall task: bilateral precuneus and thalamus; right posterior cingulate, claustrum, cerebellum, and superior frontal gyrus; left insula, and precentral, inferior occipital, medial, and middle frontal gyri.

Analysis of covariance controlling for speed of movement during the recall task was used to analyze sex differences in brain activation during maze recall. By using speed as a covariate, we were able to control for any group differences in brain activation that may have been attributable to men moving faster than women, especially on the first and final trials of the recall task. Activation during the recall trials was greater in men than women in the following regions: bilateral parahippocampal gyri; right cingulate, cuneus, thalamus, and lingual, middle frontal, and superior temporal gyri; and left precuneus .Women, compared to men, had greater activation in the left superior and medial frontal gyri. Figure 2 highlights some of the sex differences in brain activation during the recall task.

Results: Men > Women: Bilateral parahippocampal gyrus; Right posterior cingulate



Results: Women > Men: Left frontal cortex

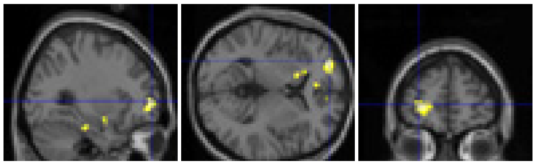


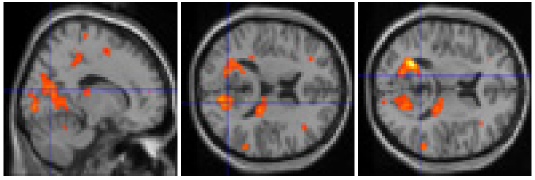
Figure 2: Sex Differences During Recall

BOLD Response in Men and Women with Perfect Accuracy Scores During Maze Recall

Because of controversy associated with interpreting group differences in brain activation data when groups may differ in behavioral performance, we employed strict matching criteria to investigate sex differences in brain activation completely independent of performance differences. We selected only those men and women who performed *perfectly* on the recall portion of the study (i.e. they made no mistakes when directed to move to any specific object). There were 18 subjects (9 women) who met this criterion.

Activation was greater in men than women in the following regions: bilateral precuneus, cuneus, and precentral gyrus; right thalamus, red nucleus, lingual and superior temporal gyri; left posterior cingulate and middle frontal gyrus (Figure 3, top panel). Women, compared to men, had greater activation in the right anterior cingulate, precuneus, and inferior frontal gyrus; left inferior parietal lobe, middle frontal and parahippocampal gyri (Figure 3, bottom panel).

Results: Men > Women: Bilateral cuneus; Left posterior cingulate



Results: Women > Men: Left parahippocampal gyrus

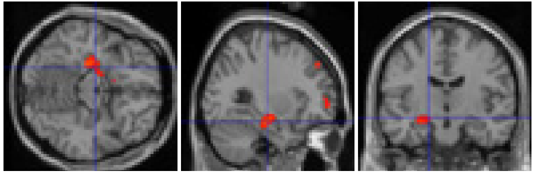


Figure 3: Sex Differences During Recall in Men and Women Matched on Recall Accuracy

Relationships Between Navigation Performance and BOLD Response During Encoding

Regression analysis was used to assess the relationship between brain activation during the exploration phase and accuracy scores during the recall phase for men, women, and the sample as a whole. The region most strongly correlated with good recall performance in the whole sample was the right middle frontal gyrus. For men, a positive association was found between performance and activation in the left posterior cingulate, precuneus, and superior frontal gyrus. The right middle frontal gyrus, cingulate and insula cortex, and left superior frontal gyrus were positively correlated with recall performance in women.

Relationships between Navigation Performance and BOLD Response During Recall

Regression analysis was used to assess the relationship between brain activation during the recall phase and accuracy on the recall task. Greater accuracy in the whole sample was most strongly correlated with left paracentral lobule activation. For men, the most robust positive association was found between performance and activation of the left posterior cingulate cortex. The right middle frontal and cingulate gyri were positively correlated with recall performance in women.

Conclusion

The primary contributions of this paper are the demonstration of sex differences in brain activation during navigation encoding and recall. Most importantly, we demonstrated that men and women showed different patterns of brain activation even when the groups each performed at 100 percent accuracy.

The fact that women and men both performed well on this task is an exception to the male advantage reported in many studies of navigation-related tasks, and this is likely due to the difficulty level of the task. Participants performed the recall task with an average of 80% accuracy.

Several group differences in brain activation emerged from our analyses, but it is beyond to scope of this paper to discuss the possible functional significance of each area. Two regions of interest which have been discussed consistently in the literature regarding navigation are the posterior cingulate/retrosplenial cortex and the parahippocampal gyrus. The posterior cingulate/retrosplenial cortex has been recognized for its role in visuospatial orientation (e.g., Vogt, Finch, & Olson, 1992), and neuropsychological studies suggest it is a necessary component of successful navigation because it allows us to orient ourselves in space and integrate egocentric and allocentric frames of reference (for review, see Epstein, 2008; Maguire, 2001). The posterior cingulate/retrosplenial cortex has been associated with mental navigation from one landmark to another (Ghaem et al., 1997), expertise in the encoding of a virtual town (Wolbers & Büchel, 2005), reporting the location of a familiar place (Epstein, Parker,&Feiler, 2007), and in several other neuroimaging studies of navigation-related tasks (e.g., for review, see Maguire, 2001; for meta-analysis, see Spreng, Mar, & Kim, 2008) including one very similar in design to the current study (Aguirre et al., 1996).

The parahippocampal area is another key component of successful navigation as it allows us to identify and remember landmarks, scenes (e.g., Epstein, 2008), and spatial layouts, even those scenes without objects/landmarks (Epstein, 2008; Epstein &Kanwisher, 1998). Involvement of the parahippocampal gyrus has been associated with viewing of landmarks within a virtual town (Ekstrom et al., 2003);and learning and recall phases of a VE task similar to ours (Aguirre et al., 1996).

Of particular interest is the pattern of posterior cingulate/retrosplenial cortex and parahippocampal activation. In a recent review, Epstein (2008) discussed these two regions as having “distinct but complementary roles” in spatial navigation. The parahippocampal region subserves our ability to identify and remember landmarks and scenes, whereas the posterior cingulate/retrosplenial cortex subserves spatial orientation. In men, increased BOLD response was seen in the posterior cingulate/retrosplenial cortex for all statistical analyses conducted, and parahippocampal gyrus activation was found during recall. Although we did not measure or manipulate strategy in this study, the ubiquitous activation of the posterior cingulate region supports previous observations and interpretations that men conceptualize the environment through an allocentric, or viewer-independent framework. Additionally, bilateral activation of the parahippocampal gyrus suggests that men were utilizing combined “scene” and “spatial” representations of the environment to solve the recall task. The pattern of results was less consistent for women. The frontal lobe activation in women during recall performance suggests that the task may have been approached in terms of object location and working memory. Greater BOLD response in the left parahippocampal gyrus than men during recall in the subsample of participants with perfect accuracy scores is consistent with data and interpretations that suggest women rely more heavily on memory for landmarks and scenes when navigating through the environment. We can infer from our data that more than one effective means of conceptualizing the spatial environment exists, and that these different strategies may lead to similar behavioral performance.

Behavioral studies suggest that men prefer allocentric strategies and are more adept at using them than women, and that women prefer egocentric strategies (e.g., Coluccia & Louse, 2004; Galea & Kimura, 1993; Malinowski & Gillespie, 2001), but to our knowledge an fMRI study in which men and women were matched on strategy and accuracy has not been done; therefore, we can speculate that strategy partially accounts for the difference in brain activation. Future neuroimaging studies that experimentally manipulate strategy *and* match men and women on behavioral outcomes within each strategy will provide a more definitive discussion about the effects of sex and strategy on the functional neuroanatomical correlates of navigation. While studies of this nature will be valuable, it is also important to think of these frameworks of spatial orientation as complementary (Eptstein, 2008) in that it behooves us in our large-scale environments to fluidly translate between first-person/egocentric and world-centered/allocentric perspectives.

Acknowledgments

Funded in part by NIH Intramural Research Program and by grant R01 AG028466 awarded to Scott Moffat.

References

Aguirre, G. K., Detre, J. A., Alsop, D. C., D'Esposito, M. (1996). The parahippocampus subserves topographical learning in man. *Cerebral Cortex,6,* 823-829.

Astur, R.S., Ortiz, M.L., & Sutherland, R.J. (1998). A characterization of performance by men and women in a virtual Morris Water task: A large and reliable sex difference. *Behavioral Brain Research, 93,* 185-190.

Coluccia, E. & Louse, G. (2004). Gender differences in spatial orientation: A review. *Journal of environmental psychology, 24,* 329-340.

Driscoll, I., Hamilton, D.A., Yeo, R.A., Brooks, W.M., & Sutherland, R.J. (2005). Virtual navigation in humans: the impact of age, sex, and hormones on place learning. *Hormones and Behavior, 47,* 326-335.

Ekstrom, A.D., Kahana, M.J., Caplan, J.B., Fields, T.A., Isham, E.A., Newman, E.L., & Fried, I. (2003).Cellular networks underlying human spatial navigation. *Nature, 425,* 184-187.

Epstein, R. A. (2008). Parahippocampal and retrosplenial contributions to human spatial navigation. *Trends in Cognitive Sciences, 12(10),* 388-396.

Epstein, R. & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature, 392(6676),* 598-601.

Epstein, R. A., Parker, W. E., &Feiler, A. M. (2007). Where am I now? Distinct roles for parahippocampal and retrosplenial cortices in place recognition. *The Journal of Neuroscience, 27(23),* 6141-6149.

Galea, L.A.M. & Kimura, D. (1993). Sex differences in route learning. *Personality and Individual Differences, 14(1),* 53-65.

Ghaem, O., Mellet, E., Crivello, F., Tzourio, N., Mazoyer, B., Berthoz, A., & Denis, M. (1997). Mental navigation along memorized routes activates the hippocampus, precuneus, and insula. *Cognitive Neuroscience and Neuropsychology, 8,* 739-744.

Grön, G., Wunderlich, A.P., Spitzer, M., Tomczak, R., & Riepe, M.W. (2000). Brain activation during human navigation: gender-different neural networks as substrate of performance. *Nature Neuroscience, 3(4),* 404-408.

Maguire, E. A. (2001). The retrosplenial contribution to human navigation: A review of lesion and neuroimaging findings. *Scandinavian Journal of Psychology, 42,* 225-238.

Malinowski, J.C. & Gillespie. W.T. (2001). Individual differences in performance on a large-scale, real-world wayfinding task. *Journal of Environmental Psychology, 21,* 73-82.

Moffat, S.D., Hampson, E., & Hatzipantelis, M. (1998). Navigation in a "virtual" maze: Sex differences and correlation with psychometric measures of spatial ability in humans. *Evolution and Human Behavior, 19,* 73-87.

Nowak, N. T., & Moffat, S. D. (2010). The relationship between second to fourth digit ratio, spatial cognition, and virtual navigation. *Archives of Sexual Behavior,* DOI 10.1007/s10508-010-9668-2.

Ohnishi, T., Matsuda, H., Hirakata, M., & Rahman, Q., & Koerting, J. (2008). Sexual orientation-related differences in allocentric spatial memory tasks. *Hippocampus, 18,* 55-63.

Sandstrom, N.J., Kaufman, J., & Huettel, S. (1998). Males and females use different distal cues in a virtual environment navigation task. *Cognitive Brain Research, 6,* 351-360.

Spreng, R. N., Mar, R. A., & Kim, A. S. N. (2008). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: A quantitative meta-analysis. *Journal of Cognitive Neuroscience, 21(3),* 489-510.

Takeuchi, Y. (1992). Sense of direction and its relationship with geographical orientation, personality traits and mental ability. *Japanese Journal of Educational Psychology, 40,* 47-53.

Wolbers, T., &Büchel, C. (2005). Dissociable retrosplenial and hippocampal contributions to successful formation of survey representations. *The Journal of Neuroscience, 25(13),* 3333-3340.