



ACADEMIC
PRESS

Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

Brain and Language 84 (2003) 264–272

Brain
and
Language

www.elsevier.com/locate/b&l

Sex differences in semantic language processing: A functional MRI study

L.C. Baxter,^{a,b} A.J. Saykin,^{a,c,d,*} L.A. Flashman,^{a,d}
S.C. Johnson,^b S.J. Guerin,^a D.R. Babcock,^a and H.A. Wishart^a

^a *Brain Imaging Laboratory, Department of Psychiatry/DHMC, Dartmouth Medical School, Lebanon, NH 03756, USA*

^b *Barrow Neurological Institute, Phoenix, AZ 85013, USA*

^c *Department of Radiology, Dartmouth Medical School, Lebanon, NH 03756, USA*

^d *New Hampshire Hospital, Concord, NH 03301, USA*

Accepted 14 May 2002

Abstract

Predictions based on two models of sex differences in cerebral organization of language were compared by examining fMRI patterns of 10 females and 9 males during a semantic processing task. Both groups displayed activation of left inferior frontal gyrus (IFG), left superior temporal gyrus (STG), and cingulate. Females, but not males, showed bilateral IFG and STG activation. Further analyses revealed females had less diffuse left activation and greater right posterior temporal and insula region activation than males. Results support both an interhemispheric and an intrahemispheric model of sex differences in language, suggesting that the models may not be mutually exclusive.

© 2002 Elsevier Science (USA). All rights reserved.

Keywords: Sex differences; Language; Lateralization; Functional MRI; Semantic memory

1. Introduction

While there is some debate as to whether sex differences in language exist, a small but significant behavioral sex difference favoring females has been observed for some types of language-based abilities (see Hampson & Kimura, 1992 for review). Two models of differences in neural representation of language, both based on language deficits in males and females following stroke, have been proposed to explain the differences observed on behavioral tasks. McGlone (1977) suggested that females have greater bihemispheric representation of language than males because aphasia was more common in males with left hemisphere damage (48% in males vs. 13% in females). Furthermore, she found that for females only, language deficits were observed after both right and left hemisphere damage. Alternately, Kimura (1983)

* Corresponding author. Fax: 1-603-650-5842.

E-mail addresses: lbaxter@chw.edu (L.C. Baxter), saykin@dartmouth.edu (A.J. Saykin).

proposed that males have diffuse left hemisphere representation of language while females have more focal anterior left hemisphere language representation, an explanation suggesting intrahemispheric, rather than interhemispheric, sex differences in language representation. In a group of over 200 stroke patients, there were no sex differences in aphasia rates after right hemisphere damage (2% males, 1% females); however, the majority of the females with aphasia (80%) had anterior left hemisphere lesions compared to males who showed no relationship between left hemisphere lesion location and aphasia. The current study was designed to determine whether functional magnetic resonance (fMRI) activation patterns of males and females during a language task are different, and if so, whether the observed patterns support either of these models.

Functional magnetic resonance imaging provides a noninvasive opportunity to examine potential differences between males and females in brain activation patterns during language tasks. To date, the few published studies in this area have yielded conflicting results. Several studies have found greater bihemispheric activation during language tasks in females compared to males, supporting the “interhemispheric” model proposed by McGlone. For example, Shaywitz et al. (1995) reported significant sex differences in activation patterns associated with phonological processing. Participants determined if visually-presented words matched on a phonological basis. Females showed bilateral inferior frontal activation, but males showed only left inferior frontal activation. Similar findings of lateralized sex differences in anterior regions have been reported by Pugh et al. (1996). Schlosser et al. (1998) reported primarily left frontal activation for both males and females during a silent verbal fluency task; however, a small but significant region of activation in the right orbitofrontal region was observed only in the group of females. Evidence for sex differences in posterior language areas was found by Kansaku, Yamaura, and Kitazawa (2000). Their task was designed to evaluate higher order language processing by having participants listen to short stories vs. hearing narratives in reverse. Females showed bilateral middle temporal gyrus activation, while activation was primarily in the left superior and middle temporal region for males. Jaeger et al. (1998) found greater bilateral PET cerebral blood flow in the temporal and inferior frontal regions for females when generating past tense forms of verbs. To our knowledge, the only published fMRI study to date that has reported findings consistent with the Kimura model is that of Pugh et al. (1996). They reported that males and females showed different patterns of activation during semantic and phonological tasks. Females showed greater overlap of activation within the left hemisphere during semantic and phonological language tasks compared to males. This was interpreted to be consistent with Kimura’s model because the overlap reflected more circumscribed language-relevant regions in females. Not all neuroimaging studies have found significant sex differences. For example, Frost et al. (1999) found no sex differences during a language comprehension task in a large group of subjects and in the study by Schlosser et al., the authors note that only 2 of the 6 females showed right frontal activation.

We examined sex differences in neural organization among males and females using a “category-exemplar” task emphasizing understanding of semantically meaningful words that we predicted would produce different activation patterns among males and females. In this task, described by Saykin et al. (1999), participants decide if word pairs match on a semantic level. Saykin et al. reported that healthy participants showed left frontal and left superior temporal activity consistent with prior reports on semantic memory tasks. In the current study, we tested specific hypotheses based on the two models of sex differences in cerebral organization discussed above. Greater bilateral activation in females than males would lend

support to McGlone's *interhemispheric* model, whereas more diffuse left hemisphere activation in males compared to females would favor Kimura's *intrahemispheric* model.

2. Methods

Participants were recruited as healthy controls for studies of semantic language processing and included 19 (10 females) right-handed, neurologically healthy adults for whom English was the first language. Demographic information is provided in Table 1. No significant differences in age, education, or vocabulary ability (WAIS-R) were observed between males and females.

2.1. fMRI activation task

The activation task, a semantic decision task involving categorical knowledge, is reported in detail in Saykin et al. (1999). Briefly, binaural stimuli were presented to participants delivered through 2–3 mm polyethylene tubing earplugs. During the task, participants were presented with word pairs consisting of a superordinate category (e.g., beverage) and a subordinate category exemplar (e.g., milk). During each block of 4 trials, one of the word pairs consisted of a correct pairing of category and exemplar (e.g., beverage–milk), and three word pairs consisted of incorrect pairings (e.g., vehicle–carrot). The task was presented in a cyclical blocked design consisting of eight cycles of 10.5 s of rest alternated with 28 s of decision-making. At the beginning of each decision-making cycle, participants were provided with a 3.5 s reminder to “Squeeze the bulb if the category and example match,” followed by presentation of four word pairs, with an inter-pair interval of 7.0 s. To indicate an affirmative decision, participants were requested to squeeze a pneumatic bulb with both hands. Responses were registered at the operator console. Across the eight blocks of trials, word pairs were arranged so that correct pairings were represented twice at each of the four ordinal positions within a trial block. The number of correct targets and false positives was recorded for each participant. Accuracy was measured as correct decisions adjusted for response bias [(true positives – .33 × false alarms) × 100].

2.2. Imaging procedures

A full description of imaging methods used is presented in Saykin et al. (1999). Briefly, all structural and functional MRI scans were obtained using a General Electric Sigma scanner (1.5 T magnet) during the same session. A three-dimensional coronal series was acquired using a spoiled gradient echo (SPGR) sequence (TR = 24, TE = 8, flip = 40, NEX = 1, slice thickness = 1.5 mm, no skip, in-plane resolution = .9375 mm², FOV = 24 cm). T2-weighted axial survey images were also acquired to screen for abnormalities such as focal lesions. All functional scans were acquired using a multi-axial

Table 1
Summary of demographic data and behavioral performance data (mean ± SD)

	Males (<i>n</i> = 9)	Females (<i>n</i> = 10)	<i>P</i>
Age (years)	47.4 ± 23.0	53.9 ± 20.4	.54
Education (years)	14.0 ± 2.2	14.6 ± 2.1	.57
Vocabulary (WAIS-R)	12.9 ± 2.3	13.4 ± 3.7	.74
Task accuracy (% correct)	93.23 ± 6.28	95.43 ± 7.45	.52

local gradient head coil system (Medical Advances, Milwaukee, WI). A single shot, gradient echo, echo planar functional scan sequence was implemented to measure the whole brain (TR = 3500 ms, TE = 40 ms, interleaved, slice thickness = 6 mm, NEX = 1, flip angle = 90, FOV = 24 cm), yielding 23 contiguous sagittal slices in a 64×64 matrix with an in-plane resolution of 3.75 mm^2 at 96 time points.

2.3. Functional image analysis

Preprocessing steps. Spatial realignment using the SPM96 six parameter model was performed on all raw scan data prior to further analysis to remove any minor (subvoxel) motion-related signal change. Prior to multi-subject analyses, mean condition images were calculated as described below and spatially normalized to approximate the atlas space of Talairach and Tournoux (1988) using a 12 parameter affine approach and a T2*-weighted template image. The optional use of nonlinear warping by spatial basis functions was limited to $2 \times 2 \times 2$ and 8 iterations. During normalization, the mean condition scans were resampled to 2 mm^3 isotropic voxels. Spatial smoothing using a Gaussian filter (15 mm^3 FWHM) was then applied.

Statistical analysis. Functional MRI analyses included statistical parametric mapping, on a voxel-by-voxel basis, using a general linear model approach (Friston et al., 1995; Worsley & Friston, 1995; Worsley et al., 1996) as implemented in SPM96 (Wellcome Department of Cognitive Neurology, University College, London). Global signal was controlled using analysis of covariance. The main analyses reported here used the Random Effects procedure proposed by Holmes and Friston (1998). For multi-subject/between group analyses, the random effects procedure assumes input of one scan per subject for each condition and then performs a mixed model analysis to account for both Random Effects (participant) and fixed effects (condition; rest/activation). The mean input images for each subject were obtained by calculating the mean image for the rest and activation conditions of each task after taking into account the hemodynamic response function.

Analyses of simple effects (separate analyses of activation for each group) were conducted to allow visual comparison of sex differences in hemispheric activation patterns. Further analyses were conducted to directly compare sex differences in activation by examining the main effect of sex (Males, Females) and the interactions (M > F; F > M) designed to detect voxels showing directional group differences. A threshold value of $\alpha = .01$ was used in analyses of the main effects and interactions. The threshold method, as implemented in SPM96, simultaneously accounts for peak amplitude and spatial extent of clusters to reduce Type I error. We chose the .01 probability value threshold because prior reports of sex differences in language have generally observed a reliable effect of small to moderate size.

3. Results

3.1. Behavioral performance

No sex differences in performance were observed for task accuracy; mean accuracy scores were above 90% for both groups (Table 1).

3.2. Activation patterns for task and sex effects

Maximum intensity projection maps showing activation patterns for males and females analyzed separately are shown in Fig. 1. Males showed primarily left

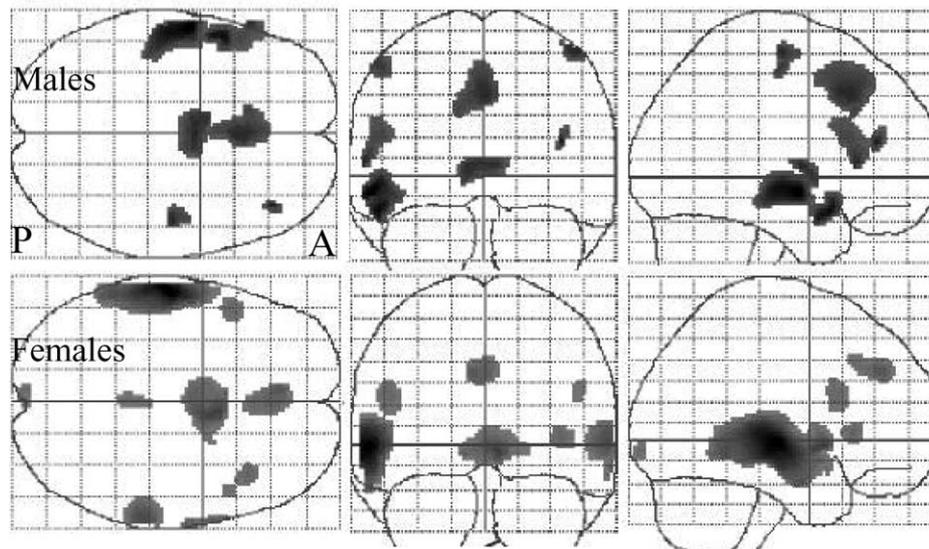


Fig. 1. Activation patterns for males and females on a semantic language task. Maximum intensity projections (MIP) of activation during the language task analyzed separately for males and females. The top series of three panels shows the regions of activation for males. Activation is almost exclusively in the left hemisphere. Activation for the group of females is depicted on the bottom series of panels. This group of females showed several regions of activity in the right hemisphere, primarily in the STG region. Voxels shown exceeded $p < .01$ threshold.

hemisphere activation, with large sites of focal activation seen in the left IFG, left STG and cingulate regions, whereas right hemisphere activity was generally absent in males. In contrast, females showed both right and left hemisphere activation. Significant areas of activation were observed in both the left and right STG. Strong left IFG activation was also observed.

Regions differentially activated as a function of sex were assessed by examination of the Group (Males vs. Females) \times Activation State (Active vs. Rest) interaction (Fig. 2). Greater diffuse activation in the left hemisphere in males vs. females was observed ($M > F$ interaction), but there was no significant differential right hemisphere activation in this analysis. Greater activation in females ($F > M$) was seen in the right hemisphere in the region of the posterior temporal lobe and insula.

4. Discussion

As expected, this group of normal participants showed significant left hemisphere activation specific to the STG and IFG regions when performing a task involving semantic language processing, as reported previously (Saykin et al., 1999). However, when grouped by sex, differences in the activation patterns emerged. This suggests that subtle neural differences in language processing exist between males and females. Females showed greater right hemisphere activation than males, particularly in the right STG. Very little right hemisphere activation was observed for the group of males. On further evaluation, females showed small but significant regions of activation in the right insula and right posterior temporal region. No right hemisphere activation specific for males was observed. Instead, males showed a more diffuse pattern of left hemisphere activity compared to females.

The findings of this study provide some support for both of the proposed models. Our study suggests that females have greater bilateral language representation;

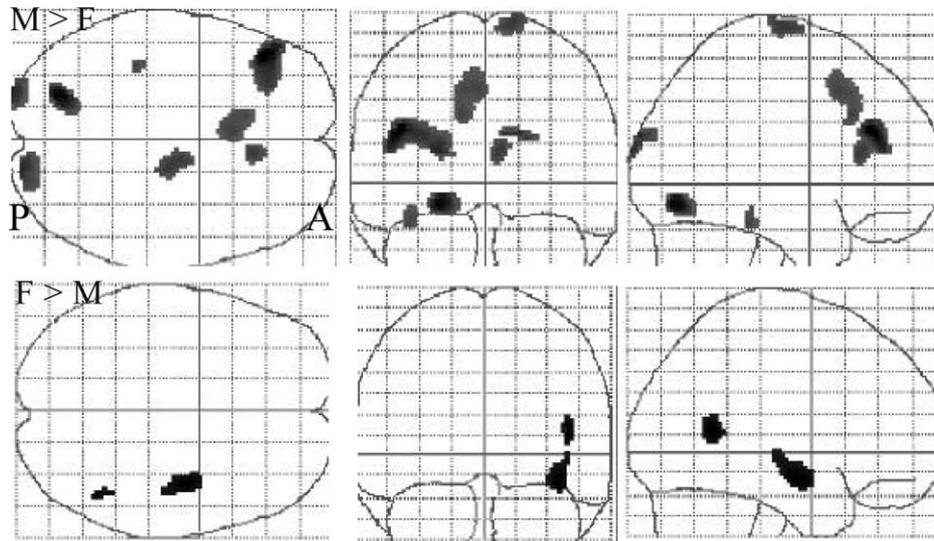


Fig. 2. Regions of significant differential activity in males vs. females. This figure shows maximum intensity projections (MIP) for the Sex by Condition (active vs. rest) interaction. The top panel shows activation that is significantly greater in males than females. A diffuse pattern of greater left hemisphere activity was seen in males compared to females. The bottom panel shows regions where females have greater activity compared to males including regions in the insula and posterior temporal regions. Voxels shown exceeded $p < .01$ threshold.

females showed greater right hemisphere activity when performing a language task, a result consistent with McGlone's interhemispheric model. However, we found differences in left hemisphere activation as well, with males displaying a more diffuse pattern of left hemisphere activity. This finding provides some support for Kimura's model (1983) that males have more diffuse left hemisphere language representation than females. Kimura contended that this reflects intrahemispheric sex differences rather than differences in the degree of language lateralization as proposed by McGlone. Support found for both of these models using fMRI suggests that these two models of language differences may not be mutually exclusive.

Though significant sex differences in language were revealed with a relatively small number of participants in the current study, not all neuroimaging studies have concurred. Methodological differences may account to some extent for the inconsistency in detection of sex differences across studies. One critical methodological issue is the language task used to elicit activation. Behavioral studies suggest that tasks emphasizing associational aspects of verbal ability, including verbal fluency tasks (Hines, 1991), as well as organizational aspects of verbal learning (Cox & Waters, 1986; Kramer, Delis, & Daniel, 1988) consistently show sex differences. Indeed, verbal memory tests that require effortful organization or semantic manipulation of verbal information, such as rote word list learning, produce a sex effect of over 1 standard deviation favoring females (Kramer et al., 1988), while language and memory tests providing information that is inherently organized (e.g., stories) have not shown consistent sex differences (Baxter & Seidenberg, 1997).

We used a language task that required participants to make a hierarchical semantic decision involving retrieval processes similar to those required by verbal fluency tasks, where sex differences have been reported. Other studies that have shown sex differences in language also used tasks that appear to require some aspect of higher order language processing. For example, Kansaku et al. (2000) found significant sex differences in posterior language regions when listening to stories vs. the control task in

which subjects heard narratives in reverse. Bilateral activation of the middle temporal gyrus was observed in the group of females, but males activated the superior and middle temporal activation in the left hemisphere only. Others have also reported less lateralization in frontal lobe activity among females during phonological decoding of word pairs (Pugh et al., 1996; Shaywitz et al., 1995). In other studies that do not find sex differences, language processing may represent a smaller component of the overall task demand. For example, Frost et al. (1999) used a semantic decision making task (hearing a noun designating animals and deciding if they were used by humans in the US and were domestic). The emphasis on other processes such as decision-making and imagery, which may not be language-based, may be masking the subtle language sex effect. Schlosser et al. (1998) found only slight sex differences in lateralization during verbal fluency, a task that has shown robust and consistent sex differences in behavioral studies (Hampson & Kimura, 1992).

Results from the Pugh et al. (1996) study supported both models, but differed from the current study in several ways. Briefly, they evaluated activation during several tasks, including semantic and phonologic tasks. Support for the interhemispheric model was based on comparison of activation patterns in both hemispheres during the phonologic task. Females showed a similar degree of activation in both hemispheres and males showed greater activation in the left hemisphere. Unlike the present study where we found greater activation for females in the right hemisphere, in the Pugh et al. study, males and females showed a similar level of right hemisphere activity. Support for the intrahemispheric model was based on differences in comparison of activation patterns during the semantic and phonologic tasks. Males showed increased activation in the semantic condition relative to the phonologic condition but no task difference was observed for females in this comparison. These findings were interpreted to reflect greater overlap in phonologic and semantic networks in females and are consistent with the notion of more focal representation of language in females compared to males. In some of the previous studies in which the bihemispheric model has been tested (Kansaku et al., 2000; Shaywitz et al., 1995) the focus was primarily on specific regions of interest relative to the language task used (e.g., anterior or posterior regions) and intrahemispheric sex differences in activation were not explicitly assessed.

Conclusions from the present study may be limited because the sample size was relatively small. Furthermore, while semantic processing was necessary to accurately perform the task, the semantic processing demands of this task were not particularly difficult and most participants made few errors. It is also possible that these lateralization differences in brain activation as well as those reported in other studies would be more likely to be observed on tasks emphasizing higher order language processing demands. Further investigation is needed to understand the mechanism underlying the sex difference observed on fMRI studies. Presumably future studies will determine if these results represent a sexual dimorphism of structures associated with language (Gur et al., 1999; Harasty, Double, Halliday, Kril, & McRitchie, 1997; Jancke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Schlaepfer et al., 1995; Witelson, Glezer, & Kigar, 1995), possible factors associated with circulating estrogen (Brinton, Proffitt, Tran, & Luu, 1997; Gibbs & Aggarwal, 1998; McEwen & Alves, 1999; Woolley, 1998), or other, as yet unknown, mechanisms.

Acknowledgments

This work was made possible as a result of support from the Alzheimer's Association, NARSAD, The Ira DeCamp Foundation, and New Hampshire Hospital,

Concord, NH. The authors wish to thank Chad Moritz, Robert Ferranti, Alexander C. Mamourian, Thomas W. McAllister, Molly B. Sparling, John B. Weaver, James C. Ford, and Fillia Makedon for their help with various aspects of the study.

References

- Baxter, L. C., & Seidenberg, M. (1997). Sex differences in verbal memory: Findings from a literature review. *Journal of the International Neuropsychological Society*, 3, 43.
- Brinton, R. D., Proffitt, P., Tran, J., & Luu, R. (1997). Equilin, a principal component of the estrogen replacement therapy Premarin, increases the growth of cortical neurons via an NMDA receptor-dependent mechanism. *Experimental Neurology*, 147(2), 211–220, doi:10.1006/exnr.1997.6619.
- Cox, D., & Waters, H. S. (1986). Sex differences in the use of organization strategies: A developmental analysis. *Journal of Experimental Child Psychology*, 41, 18–37.
- Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. P., Frith, C. D., & Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, 2, 189–210.
- Frost, J. A., Binder, J. R., Springer, J. A., Hammeke, T. A., Bellgowan, P. S. R., Rao, S. M., & Cox, R. W. (1999). Language processing is strongly left lateralized in both sexes: Evidence from functional MRI. *Brain*, 122, 199–208.
- Gibbs, R. B., & Aggarwal, P. (1998). Estrogen and basal forebrain cholinergic neurons: Implication for brain aging and Alzheimer's disease-related cognitive decline. *Hormones and Behavior*, 34(2), 98–111, doi:10.1006/hbeh.1998.1451.
- Gur, R. C., Turetsky, B. I., Matsui, M., Yan, M., Bilker, W., & Hughett, P., et al. (1999). Sex differences in brain gray and white matter in healthy young adults: Correlations with cognitive performance. *Journal of Neuroscience*, 19(10), 4065–4072.
- Hampson, E., & Kimura, D. (1992). Sex differences and hormonal influences on cognitive function in humans. In J. B. Becker, M. Breedlove, & D. Crews (Eds.), *Behavioral endocrinology*. Cambridge, MA: MIT Press.
- Harasty, J. M., Double, K. L., Halliday, G. M., Kril, J. J., & McRitchie, D. A. (1997). Language-associated cortical regions are proportionally larger in the female brain. *Archives of Neurology*, 54, 171–176.
- Hines, M. (1991). Gonadal hormones and human cognitive development. In J. Balthazart (Ed.), *Hormones, brain, and behavior in vertebrates*. Basel: Karger.
- Holmes, A. P., & Friston, K. J. (1998). Generalisability, random effects, and population inference. *Neuroimage*, 7(4), S754.
- Jaeger, J. J., Lockwood, A. H., Van Valin, R. D., Kemmerer, D. L., Murphy, B. W., & Wack, D. S. (1998). Sex differences in brain regions activated by grammatical and reading tasks. *NeuroReport*, 9, 2803–2807.
- Jancke, L., Staiger, J., Schlaug, G., Huang, Y., & Steinmetz, H. (1997). The relationship between the corpus callosum size and forebrain volume. *Cerebral Cortex*, 7, 48–56.
- Kansaku, K., Yamaura, A., & Kitazawa, S. (2000). Sex differences in lateralization revealed in posterior language areas. *Cerebral Cortex*, 10, 866–872.
- Kimura, D. (1983). Sex differences in cerebral organization for speech and praxic functions. *Canadian Psychology*, 38, 19–35.
- Kramer, J. H., Delis, D. C., & Daniel, M. (1988). Sex differences in verbal learning. *Journal of Clinical Psychology*, 44, 907–915.
- McGlone, J. (1977). Sex differences in the cerebral organization of verbal function in patients with unilateral brain lesions. *Brain*, 100, 775–793.
- McEwen, B. S., & Alves, S. E. (1999). Estrogen actions in the central nervous system. *Endocrine Reviews*, 20(3), 279–307.
- Pugh, K. R., Shaywitz, B. A., Shaywitz, S. E., Constable, R. T., Skudlarski, P., & Fulbright, R. K., et al. (1996). Cerebral organization of component processing in reading. *Brain*, 119(4), 1221–1238.
- Saykin, A. J., Flashman, L. A., Frutiger, S., Johnson, S. C., Mamourian, A., & Moritz, C. H., et al. (1999). Neuroanatomic substrates of semantic memory impairment in Alzheimer's Disease: Patterns of functional MRI activation. *Journal of the International Neuropsychological Society*, 5, 377–392.
- Schlaepfer, T. E., Harris, G. J., Tien, A. Y., Peng, L., Lee, S., & Pearlson, G. D. (1995). Structural differences in the cerebral cortex of healthy female and male subjects: A magnetic resonance imaging study. *Psychiatry Research*, 61, 129–135.

- Schlosser, R., Hutchinson, M., Joseffer, S., Rusinek, H., Saarimaki, A., & Stevenson, J., et al. (1998). Functional magnetic resonance imaging of human brain activity in a verbal fluency task. *Journal of Neurology, Neurosurgery and Psychiatry*, *64*(4), 492–498.
- Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Constable, R. T., Skudlarski, P., & Fulbright, R. K., et al. (1995). Sex differences in the functional organization of the brain for language. *Nature*, *373*, 607–609.
- Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system; An approach to cerebral imaging*. New York: Thieme.
- Witelson, S. F., Glezer, L. L., & Kigar, D. L. (1995). Women have greater density of neurons in posterior temporal cortex. *Journal of Neuroscience*, *15*(5 Pt 1), 3418–3428.
- Woolley, C. S. (1998). Estrogen-mediated structural and functional synaptic plasticity in the female rat hippocampus. *Hormones and Behavior*, *34*, 140–148, doi:10.1006/hbeh.1998.1466.
- Worsley, K. J., & Friston, K. J. (1995). Analysis of fMRI time-series revisited-again. *Neuroimage*, *2*(3), 173–181, doi:10.1006/nimg.1995.1023.
- Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Riston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping*, *4*(1), 58–73.