

Sex Differences in Prefrontal Cortical Brain Activity During fMRI of Auditory Verbal Working Memory

Jill M. Goldstein

Harvard Medical School, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Massachusetts Mental Health Center, and Massachusetts General Hospital

Russell Poldrack

University of California, Los Angeles

Hans C. Breiter, Nikos Makris, and
Julie M. Goodman

Massachusetts General Hospital and Harvard Medical School

Matthew Jerram

Harvard Medical School, Massachusetts Mental Health Center, and Massachusetts General Hospital

Robert Anagnoson

Harvard Medical School, Massachusetts Mental Health Center, and Massachusetts General Hospital

Ming T. Tsuang

Harvard Medical School, Massachusetts Mental Health Center, Massachusetts General Hospital, Harvard School of Public Health, and University of California, San Diego

Larry J. Seidman

Harvard Medical School, Massachusetts Mental Health Center, and Massachusetts General Hospital

Functional imaging studies of sex effects in working memory (WMEM) are few, despite significant normal sex differences in brain regions implicated in WMEM. This functional MRI (fMRI) study tested for sex effects in an auditory verbal WMEM task in prefrontal, parietal, cingulate, and insula regions. Fourteen healthy, right-handed community subjects were comparable between the sexes, including on WMEM performance. Per statistical parametric mapping, women exhibited greater signal intensity changes in middle, inferior, and orbital prefrontal cortices than men (corrected for multiple comparisons). A test of mixed-sex groups, comparable on performance, showed no significant differences in the hypothesized regions, providing evidence for discriminant validity for significant sex differences. The findings suggest that combining men and women in fMRI studies of cognition may obscure or bias results.

Keywords: sex differences, working memory, attention, fMRI

Working memory (WMEM) is a mental function typically defined as the temporary maintenance and manipulation of information during which one maintains an internal representation of a stimulus in order to perform cognitive processes (Baddeley, 1986; Goldman-Rakic, 1987). WMEM also reflects the capability to maintain representations in the presence of interference, otherwise known as the *executive-attentional component* (Kane & Engle,

2002). The neuroanatomy of WMEM includes a network of regions—particularly dorsolateral and inferior prefrontal cortices, cingulate gyrus, parietal cortex, insula, and thalamus (Fuster, 1989; Goldman-Rakic, 1987)—most recently studied using functional imaging (Barch et al., 1997; Cohen et al., 1994; D'Esposito et al., 1995; McCarthy et al., 1994; Paulesu, Frith, & Frackowiak, 1993; Petrides, Alivisatos, Meyer, & Evans, 1993; Schumacher et

Jill M. Goldstein, Departments of Psychiatry and Medicine, Harvard Medical School, Division of Women's Health, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital, Boston, Massachusetts; Department of Psychiatry, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Division of Public Psychiatry, Harvard Medical School, Massachusetts Mental Health Center, Jamaica Plain, Massachusetts, and Massachusetts General Hospital, Boston, Massachusetts; Athinoula Martinos Center for Biomedical Imaging, Massachusetts General Hospital. Matthew Jerram, Robert Anagnoson, and Larry J. Seidman, Department of Psychiatry, Harvard Medical School, Massachusetts Mental Health Center and Massachusetts General Hospital; and Athinoula Martinos Center for Biomedical Imaging, Massachusetts General Hospital. Russell Poldrack, Department of Psychology, University of California, Los Angeles. Hans C. Breiter and Julie M. Goodman, Athinoula Martinos Center for Biomedical Imaging, Massachusetts General Hospital; and Department of Radiology, Harvard Medical School, Massachusetts General Hospital. Nikos Makris, Athinoula Marti-

nos Center for Biomedical Imaging, Massachusetts General Hospital; Departments of Neurology and Radiology, Harvard Medical School, Center for Morphometric Analysis, Massachusetts General Hospital. Ming T. Tsuang, Department of Psychiatry, Harvard Medical School, Massachusetts Mental Health Center and Massachusetts General Hospital; Department of Epidemiology, Harvard School of Public Health; and Department of Psychiatry, University of California, San Diego.

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Correspondence concerning this article should be addressed to Jill M. Goldstein, Brigham and Women's Hospital, Division of Women's Health, One Brigham Circle, 1620 Tremont Street, 3rd Floor, Boston, MA 02120. E-mail: jill_goldstein@hms.harvard.edu

al., 1996; Seidman et al., 1998; Smith & Jonides, 1999; Wagner, 1999).

Human imaging and postmortem studies of sexual dimorphisms have reported that men have larger cerebrums than women (Filipek, Richelme, Kennedy, & Caviness, 1994; Rabinowicz, Dean, Petetot, & de Courten-Myers, 1999; Witelson, Glezer, & Kigar, 1995). Nevertheless, there are significant sex differences, relative to cerebrum size, in volumes and neuronal densities of a number of specific regions, including those implicated in WMEM (Fredrikse, Lu, Aylward, Barta, & Pearlson, 1999; Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Goldstein et al., 2001; Harasty, Double, Halliday, Kril, & McRitchie, 1997; Paus et al., 1996; Schlaepfer et al., 1995; Yücel et al., 2001). Further, sex differences in cognition have been reported in a number of domains, such as verbal fluency, visual-spatial skills, and motor function (Collaer & Hines, 1995). WMEM, however, is a functional domain in which population studies have, in general, not reported significant sex differences in function (Collaer & Hines, 1995). Thus, a fundamental question is how can significant neuroanatomical sex differences in regions implicated in WMEM be reconciled with similarities in levels of cognitive performance in this domain in men and women?

In a review of 22 neuroimaging studies in the WMEM literature, 12 studies (or 54.5%) were constituted of equal samples of men and women (including 2 that directly investigated sex differences), 8 studies (or approximately 36.4%) sampled primarily or exclusively men, and 2 studies (or only 9.1%) sampled primarily or exclusively women (Barch et al., 1997; Cohen et al., 1994; D'Esposito et al., 1995; McCarthy et al., 1994; Paulesu et al., 1993; Petrides et al., 1993; Schumacher et al., 1996; Seidman et al., 1998; Smith & Jonides, 1999; Wagner, 1999). Men and women activated dorsolateral prefrontal cortex (DLPFC), inferior parietal lobule (IPL), cingulate gyrus, and caudate in studies that directly compared men and women during WMEM (Lauber et al., 1994; Speck et al., 2000) and in mixed-sex samples in which men and women were not directly compared. In addition to the areas mentioned above, studies of mixed-sex samples found activation in inferior prefrontal cortex (IPFC), insula, occipital cortex, and thalamus (Carlson et al., 1998; Crottaz-Herbette, Anagnoson, & Menon, 2004; Haxby et al., 1996; Kondo et al., 2004; McCarthy et al., 1994; Owen, Evans, & Petrides, 1996; Ragland et al., 1997; Schumacher et al., 1996).

The only two published functional imaging studies of sex effects in WMEM demonstrated significant sex differences in the anterior cingulate gyrus and somatosensory cortex, dependent on task nature and difficulty, using positron emission tomography (PET; (Esposito, Van Horn, Weinberger, & Berman, 1996; Speck et al., 2000), and laterality of activations in prefrontal (particularly DLPFC) and parietal cortices using functional MRI (fMRI), although the results from this study uncontrolled for performance (Speck et al., 2000). Men exhibited right hemispheric or bilateral activation in DLPFC, and women showed left hemispheric activation. These results were supported by studies that used primarily single-sex samples. Studies using primarily or exclusively male samples generally found bilateral activation in one or more of the following areas: DLPFC, IPFC, IPL, cingulate gyrus, occipital cortex, caudate, and thalamus (Barch et al., 1997; Callicott et al., 1999; Cohen et al., 1994; D'Esposito et al., 1995; Gruber & von Cramon, 2003; Haxby et al., 1996; Klingberg, O'Sullivan, &

Roland, 1997; Paulesu et al., 1993). In studies using primarily or exclusively female samples, results generally included left hemispheric activation in the same regions and right hemispheric activation in IPL (particularly Brodmann's area [BA] 7; Awh et al., 1996; Fiez et al., 1996).

Laterality differences between the sexes were also found in spatial WMEM (Lauber et al., 1994) and other cognitive domains, such as phonological processing (R. C. Gur et al., 2000) and other verbal and spatial tasks (Shaywitz et al., 1995). Thus, a number of anatomic and functional studies have suggested the presence of significant sex effects, although most of these studies were not designed to assess sex effects.

This study, which used fMRI with an auditory WMEM task, is a first step toward testing of hypotheses about sex differences in brain activity given similar performance. On the basis of previous functional imaging studies and the literature on normal sexual dimorphisms of the prefrontal cortex, we hypothesized that controlled for performance, during verbal WMEM, women compared with men would show greater positive signal-intensity changes in the middle, inferior, and ventral prefrontal cortices and anterior cingulate gyrus.

Method

Subject Ascertainment and Characteristics

Subjects were a consecutive series of healthy controls participating in a large neuropsychological study who volunteered to participate in an fMRI study of WMEM as a vulnerability indicator for schizophrenia (Thermenos et al., 2004). Subjects had to be less than 60 years of age at the initial evaluation, have at least an eighth-grade education, speak English as their first language, have no current psychiatric disorders, and have been free of psychosis during their lifetime. The exclusion criteria also required absence of (a) substance abuse within the last 6 months, (b) history of head injury with any documented cognitive sequelae or loss of consciousness longer than 5 min, (c) neurologic disease, (d) mental retardation, and (e) medical illness that might significantly impair neurocognitive function. Subjects were screened for psychopathology using a short form of the Minnesota Multiphasic Personality Inventory (MMPI; Vincent et al., 1984) and excluded if they or their first-degree biological relatives had a history of psychosis or psychiatric hospitalization. Potential subjects were also excluded if any MMPI clinical or validity scale, except for Masculinity-Femininity, was above 70.

Subjects received the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale—Revised (WAIS-R; Brooker & Cyr, 1986; Wechsler, 1981), which were used as estimates of current general intellectual function (Brooker & Cyr, 1986; Wechsler, 1981); the Reading subtest of the Wide Range Achievement Test—Revised (Jastak, Wilkinson, & Jastak, 1985), used as an estimate of verbal ability; and a measure of hand preference (Annett, 1970). The interviews were carried out by BA- and MA-level research assistants who had received extensive training in diagnostic and neuropsychological testing.

Fourteen healthy, right-handed Caucasian subjects from the community participated in this study, equally divided and comparable within sex on age, ethnicity, socioeconomic status, and task performance (see Table 1). They were, on average, approximately 33 years of age, with an average of 15 years of education and an estimated IQ in the high average range (approximate average of 111), based on the Vocabulary and Block Design subtests of the WAIS-R (see Table 2 for details of sample description by sex and their scaled scores on cognitive tasks). All subjects were unmedicated and free of medical, neurologic, and psychiatric illness and sensory impairments. All subjects gave written informed consent according to

Table 1
Sample Characteristics by Subjects' Sex

Variable	Men (<i>n</i> = 7)		Women (<i>n</i> = 7)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age (years)	32.1	6.6	34.1	12.2
Education (years)	14.9	1.9	14.6	2.0
Single oral word reading on WRAT-R	104.9	6.6	110.0	9.1
IQ estimate ^a	113.1	9.9	109.4	14.4

Note. Per *t* tests, there were no significant sex differences on any subject characteristic. WRAT-R = Wide Range Achievement Test—Revised (Jastak, Wilkinson, & Jastak, 1985).

^a Derived from age-scaled scores on the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981; see Brooker & Cyr, 1986).

Massachusetts General Hospital (MGH) and Harvard Medical School Institutional Review Boards' standards and were given an honorarium for participation.

Behavioral Paradigm

Subjects were scanned while performing an effortful auditory WMEM task compared with a simple attentional task. Two versions of an auditory continuous performance test (CPT) were used: QA (simple vigilance CPT) and Q3A-INT (CPT with a delay and multiple embedded distractors; Seidman et al., 1998; Thermenos et al., 2004). Q3A-INT is an effortful, attentionally demanding task requiring WMEM and interference-filtering resources, similar to an AX-CPT task (Seidman et al., 1998). WMEM is crucial for the performance of Q3A-INT because the task requires subjects to hold multiple stimuli in mind and screen out distractors while continuously updating the identity of sequential stimuli. The experimental run was constructed in a block design (ABAB format), using QA as the baseline condition, for which order was counterbalanced across subjects. Letters of the alphabet were presented binaurally via headphones at the rate of 1/s for 90 s (i.e., four sets of stimuli per run, or 6 min of stimuli). The baseline (QA) condition required subjects to respond to each "A" if and only if it was preceded by a "Q" (e.g., "Q"-"A"). Target probability was approximately 20%. Subjects also had to inhibit their responses to "A" or "Q" alone; these "foil" trials each occurred approximately 5% of the time.

In Q3A-INT, subjects responded to "A" when it was preceded by a "Q" separated by three letters (e.g., "Q"-"R"-"C"-"T"-"A"). Target Q3A sequences were interspersed with randomly selected letters of the alphabet, which also included freestanding "Q"s and "A"s alone (11%). To make this task more difficult, combinations of "Q," "A," or "Q"-"A" were embedded between "Q" and "A" (24%; e.g., "Q"-"Q"-"C"-"Q"-"A"-"A"). Trials interspersed with "Q"s and interleaved series were designed to produce distraction, divide attention, and prevent counting. Given that subjects were episodically required to maintain two separate attentional tracks simultaneously (in the situation in which a second "Q" appeared before the conclusion of the Q3A sequence), this task stressed the capacity to perform dual tracking.

Prior to each condition, subjects were instructed regarding which particular target stimuli they should respond to. Subjects responded to targets by buttonpress, using the index finger of the left hand, and did not respond to nontargets. QA and Q3A-INT were matched on important parameters—for example, auditory sensory modality, stimuli (letters), target-response signal ("A"), warning-cue signal ("Q"), rate of presentation, interstimulus interval, signal probability, sensory clarity, and frequency of expected motor response. Differences between the tasks were the degree of WMEM and interference control.

Experimental Procedures

A Macintosh computer (Apple Computer, Cupertino, CA) running the MacStim experimental presentation program (WhiteAnt Occasional Publishing, West Melbourne, Victoria, Australia) was used to produce the auditory stimuli and to record subject responses. Auditory stimuli were amplified by a stereo amplifier and delivered to a pneumatic transducer next to the scanner, which forced sound waves through plastic tubing into headphones worn by the subjects. Prior to scanning, subjects were screened with a standard instrument used at the MGH Athinoula Martinos Center for Biomedical Imaging for conditions or presence of foreign bodies that are potentially dangerous within strong magnetic fields. They also received out-of-scanner presentations of the task for practice. Subjects were reminded of task instructions and fitted with earplugs to attenuate scanner noise. Subjects lay prone on the scanner gurney, and foam padding was placed across the forehead above the eyebrows to assist in the prevention of head motion. Prior to image acquisition, subjects listened to a 1-min version of the QA task to optimize the sound level for each person.

Imaging

Scanning was performed with a quadrature full head coil and a 1.5-T Signa MR scanner (General Electric, Milwaukee, WI), modified for echo-planar imaging (Advanced NMR Systems, Wilmington, MA). First, a single-slice 2-D spoiled gradient recall (SPGR) axial localizer scan was acquired, followed by a 60-slice sagittal localizer scan (conventional T1-weighted SPGR sequence: FOV = 23 × 17.25 cm; matrix = 256 × 192; in-plane resolution = 0.90 mm; slice thickness = 2.8 mm) to orient. For subsequent scans, 15 contiguous axial slices along the AC-PC line covering the whole brain were obtained. This was followed by an automated shim procedure to improve B₀ field homogeneity (Reese, Davis, & Weiskoff, 1995) and an SPGR T1-weighted flow-compensated scan (FOV = 40 × 20 cm; matrix = 512 × 256; in-plane resolution = 0.78 mm; slice thickness = 7 mm; 15 slices coplanar with the functional slices). The fifth scan was a 15-slice T1-weighted echo-planar inversion recovery sequence (TR = 20 s; TE = 40 ms; TI = 1,100 ms; FOV = 40 × 20 cm; matrix = 256 × 128; in-plane resolution = 1.57 mm; slice thickness = 7 mm) coplanar to the functional images for the anatomic localization of preliminary statistical maps. Finally, a series of functional scans were acquired, using an asymmetric spin-echo, T2*-weighted sequence (TR = 3,000 ms; TE = 70 ms; refocusing pulse offset by -25 ms; 1 excitation; FOV = 40 × 20 cm; matrix = 128 × 64; in-plane resolution = 3.125 mm; slice thickness = 7 mm; 15 contiguous slices along the AC-PC line). This pulse sequence had excellent sensitivity to parenchymal signal changes concur-

Table 2
Continuous Performance Test Task Performance (Hit Rates and Reaction Times) in Men and Women

Test	Men (<i>n</i> = 7)		Women (<i>n</i> = 7)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
	Out of scanner			
QA	97.7%	2.3	98.8%	1.7
Q3A-INT	74.3%	15.2	68.0%	12.0
	In scanner			
Q3A-INT	72.1%	16.8	72.9%	9.2
Reaction time (ms)	930	90	960	60

Note. There were no significant sex differences in performance in or out of the scanner. QA = simple vigilance continuous performance test (CPT); Q3A-INT = CPT with a delay and multiple embedded distractors.

rent with experimental perturbation and reduced macrovascular sensitivity. Functional scans were acquired for 120 time points for the experimental ABAB block.

Data Analyses

Preprocessing and statistical analyses of the fMRI data were performed using statistical parametric mapping (SPM99 software; Wellcome Department of Cognitive Neurology, University College London, London, United Kingdom; Friston et al., 1995) implemented in MATLAB (The MathWorks, Sherborn, MA). Preprocessing included motion correction, spatial normalization to the Montreal Neurological Institute–referenced (MNI) stereotactic space, and spatial smoothing with an 8-mm full width at half maximum Gaussian kernel. Following a previous strategy (Seidman et al., 1998), we excluded only 1 male subject who had ≥ 1.5 mm of motion. First-level (fixed-effect) statistical analysis was performed using the general linear model in SPM99. The design was modeled using a boxcar function convolved with a canonical hemodynamic response function. Comparisons of interest were implemented as linear contrasts.

Analysis was performed individually for each subject, and statistical contrast images were developed for each individual. These contrast images were used in second-level analyses treating subjects as random effects in a general linear model. Second-level analyses included within-group comparisons of activation changes from QA to Q3A-INT performance. Statistical contrast images developed in these comparisons were used in a between-groups comparison of activation during Q3A-INT performance. Statistical maps were set at a threshold of at least $p < .005$ (uncorrected for multiple comparisons), with an extent threshold of 5 voxels. The results were further thresholded with a cluster-corrected significance level of $p < .05$, according to the theory of Gaussian random fields (Kiebel, Poline, Friston, Holmes, & Worsley, 1999). Given that the corrected values are very conservative, we also present significantly activated brain regions at uncorrected significance levels for the purposes of replication by other investigators. We checked by visual inspection to ensure that all significant activations reported in this study had time courses that corresponded to the task paradigm, were not in areas of magnetic susceptibility, and were structurally registered to parenchyma. Areas of statistically significant differences reported by SPM99 within each sex group and in the between-groups comparison were also localized with a standardized Talairach brain atlas (as well as MNI coordinates) and confirmed by our neuroanatomist (Nikos Makris). To further ensure that our results were due to subjects' sex, mixed-sex groups were randomly formed—matched on age, education, IQ, and out-of-scanner CPT performance—to test for discriminant validity. This allowed for a test of whether the significant sex effects found in the grouped data were not demonstrated in mixed-sex groups.

Results

Behavioral Measures

There were no significant mean sex differences in performance on the behavioral testing of QA and Q3A-INT (WMEM with interference) regarding hit rates (percentages correct) and reaction times (see Table 2). Although statistical power was low for detecting sex differences in behavioral ratings, the actual performances shown in Table 2 were very similar.

Functional Activations

There were significant differences in activation patterns among men and women (see Table 3). In women, comparing the

Q3A-INT with the QA task, positive activations in right BA 44, bilateral BA 46, and right BA 7 were significant after correction for multiple comparisons at $p < .05$. At $p < .005$ (uncorrected for multiple comparisons), the Q3A-INT task positively activated Broca's area bilaterally (approximate BA 44), bilateral BA 46, right BA 47, bilateral superior parietal lobule (BA 7), left BA 40, right visual association area (BA 19), and left cerebellum (see Table 3). No negative activations in the women were significant after correction for multiple comparisons. However, negative activations were found in the frontal pole (BA 10), left superior temporal gyrus (BA 22), bilateral middle temporal gyrus (BA 21), left inferior temporal gyrus (BA 20), and right primary motor cortex (BA 4) at $p < .005$ (uncorrected for multiple comparisons).

In men, no positive activations were significant after correction for multiple comparisons. However, at $p < .005$ (uncorrected for multiple comparisons), the Q3A-INT task in men positively activated left BA 45, right superior parietal lobule (BA 7), right BA 40, parahippocampal regions bilaterally (BA 20), left planum temporale (BA 41), and right visual association area (BA 19). For negative activations in the men, medial visual association area, angular gyrus, and Broca's area activations were significant after correction for multiple comparisons (at $p < .05$). At the $p < .005$ uncorrected level, negative activations in the men were also observed in left and medial visual association area (BA 19), left angular gyrus (BA 39), and right Broca's area (BA 45).

Women and men were then compared directly on Q3A-INT versus QA, and significant differences were found (see Table 4 and Figure 1). Corrected for multiple comparisons at $p < .05$, women more than men significantly activated right orbitofrontal cortex (BA 47), right Broca's area (BA 45), and left DLPFC (BA 46). Women, at $p < .005$ (uncorrected for multiple comparisons), also activated more than men other regions in right Broca's area (BA 44), IPL bilaterally (BAs 39 and 40), right superior parietal lobule (BA 7), right motor association area (BA 6), right visual association area (BA 19), right middle temporal gyrus (BA 21), medial posterior cingulate gyrus (BA 31), and left cerebellum. None of the hypothesized regions were activated significantly more in men than in women at significance levels corrected or uncorrected for multiple comparisons at $p < .005$. Only one hypothesized area, posterior parietal cortex (BA 7), was activated more in men than in women at uncorrected $p < .06$. In general, posterior parietal cortex was activated similarly in men and women. In addition, left middle temporal gyrus (BA 21), right posterior superior temporal gyrus (BA 31), bilateral parahippocampal regions (BA 20), and right cerebellum were significantly activated at uncorrected significance levels, which did not remain significant after correction for multiple comparisons (see Table 4).

It is important to note that the validity of our results was underscored by the fact that the mixed-sex groups showed no significant differences on the regions of interest (at $p < .005$, uncorrected for multiple comparisons). A single activation in right BA 46 was found in the mixed-sex groups. However, at corrected p levels, there were no significant group differences in our hypothesized regions.

Table 3

Regions of Significant Activation Within Men and Women Comparing Working Memory With Interference and a Simple Attentional Condition

Region	Hemisphere	MNI-space coordinate				Voxels	<i>p</i>	
		<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>		Uncorrected	Corrected
Women: Hypothesized regions								
BA 44	Left	-39	12	18	3.39	7	.043	>.05
BA 44	Right	36	9	27	3.91	10	<.001	.034
BA 46	Left	-48	36	18	3.92	11	<.001	.021
BA 46	Right	30	42	21	3.65	11	<.001	.021
BA 46	Right	48	36	24	4.33	6	.004	>.05
BA 47	Left	-45	42	-3	2.84	5	.081	>.05
BA 47	Right	33	21	-9	3.22	21	.001	>.05
BA 47	Right	48	24	-6	3.10	8	.032	>.05
BA 7	Left	-33	-45	51	3.89	19	.002	>.05
BA 7	Left	-6	-66	57	3.49	11	.014	>.05
BA 7	Right	39	-42	36	4.35	14	<.001	.005
BA 7	Right	36	-63	39	3.51	25	.001	>.05
BA 7	Right	12	-75	45	3.17	6	.001	>.05
BA 40	Left	-33	-57	33	3.03	10	.019	>.05
Women: Other regions								
Cerebellum	Left	-3	-54	-39	4.22	7	.002	>.05
BA 19	Right	33	-78	24	3.44	7	.002	>.05
Men: Hypothesized regions								
BA 45	Left	-36	27	-9	3.63	15	.020	>.05
BA 46	Right	51	27	21	2.83	9	.306	>.05
BA 7	Right	3	-42	63	3.29	6	.040	>.05
BA 7	Right	3	-42	48	2.53	17	.164	>.05
BA 40	Right	45	-27	48	2.77	37	.048	>.05
Men: Other regions								
BA 19	Right	15	-57	-3	3.20	5	.058	>.05
BA 20	Left	-24	-6	-36	3.37	16	.002	>.05
BA 20	Right	51	-6	-24	3.23	6	.040	>.05
BA 41	Left	-36	-33	12	3.05	6	.040	>.05

Note. Regions are given in approximate Brodmann areas (BAs). Tests of significance are based on general linear random effects models in SPM99. Significance levels are for cluster-corrected comparisons; functional activations are identified by voxel-level comparisons. Tests of significance were corrected using whole-brain correction. MNI = Montreal Neurological Institute.

Discussion

This fMRI study demonstrated significant sex effects in the pattern and magnitude of signal-intensity changes during WMEM, despite comparable levels of performance among men and women. In general, women were more likely than men to show significantly greater activations in the hypothesized prefrontal regions, despite the same performance as the men. These regions included middle, inferior, and orbital prefrontal regions, which have been implicated in encoding and retrieval of visuospatial, semantic, and phonological information and inhibitory functions associated with orbitofrontal cortex (Barch et al., 1997; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Carter et al., 1998; Mayberg, 1997; Poldrack et al., 1999; Smith & Jonides, 1999; Wagner, 1999). Further, the findings are consistent with the WMEM literature (reviewed above) for activations that were significant after corrections for multiple comparisons—that is, greater activation in women in right IPL (BA 7) and left DLPFC (BA 46). The validity of our findings was underscored by

our test of discriminant validity based on mixed-sex groups. Imaging studies have associated right BA 46 with retrieval (Wagner, 1999) and left BA 40 with phonological storage (Paulesu et al., 1993). In this study, we demonstrated that women showed significant activation of bilateral BA 46, with greater magnitude of signal change in left BA 46 than men. Thus, activation was similar in right BA 46 and greater in women on the left.

Sex effects in lateralized activations were also evident in Broca's area (BA 44 and BA 45). BA 44 was significantly activated in women in both hemispheres, although only the left BA 44 remained significant at the corrected level. Men significantly activated left BA 45 at the uncorrected level, and there was significantly greater activation of right BA 45 in women. The findings are consistent with two fMRI studies of phonological processing demonstrating bilateral activation of Broca's area in women and left-sided activation in men (Pugh et al., 1997; Shaywitz et al., 1995). Bilateral activation in women and left-sided prefrontal activity in men have also been

Table 4
Regions of Significant Activation Comparing Men and Women on Working Memory With Interference and a Simple Attentional Condition

Region	Hemisphere	MNI-space coordinate				Voxels	<i>p</i>	
		<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>		Uncorrected	Corrected
Women > men: Hypothesized regions								
BA 44	Right	42	18	24	3.31	6	.032	>.05
BA 45	Right	42	27	3	4.41	20	<.001	.016
BA 46	Left	-45	36	21	4.16	23	<.001	.008
BA 47	Right	36	21	-15	4.48	23	<.001	.008
BA 7	Right	12	-75	45	3.64	11	.006	>.05
BA 39/40	Left	-48	-57	30	3.89	13	.003	>.05
BA 40	Right	48	-48	30	3.99	12	.004	>.05
BA 40	Right	60	-33	33	3.34	5	.047	>.05
Women > men: Other regions								
BA 6	Right	54	3	30	4.03	15	.002	.06
Cerebellum	Left	-9	-60	-42	3.75	9	.011	>.05
Cerebellum	Middle	0	-72	-36	4.09	14	.002	.079
BA 1/7	Left	-27	-72	30	3.76	9	.011	>.05
BA 10	Right	30	57	9	3.46	8	.015	>.05
BA 10	Right	27	54	24	3.68	6	.032	>.05
BA 10	Right	27	57	-3	3.57	6	.032	>.05
BA 19	Right	36	-78	30	3.89	11	.006	>.05
BA 19	Right	24	-78	36	3.83	10	.008	>.05
BA 21	Right	60	-39	0	3.26	7	.022	>.05
BA 31	Left	-9	-67	27	3.35	5	.047	>.05
BA 31	Middle	0	-33	36	3.68	7	.022	>.05
Men > women: Hypothesized region								
BA 7	Right	18	-48	63	2.95	9	.061	>.05
Men > women: Other regions								
CC	Right	6	-21	24	3.39	6	.119	>.05
Cerebellum	Right	15	-57	-6	3.14	10	.05	>.05
BA 20	Left	-24	-3	-33	3.67	23	.005	>.05
BA 20	Right	51	-6	-24	2.84	3	.119	>.05
BA 21	Left	-57	-6	-6	3.86	9	.061	>.05
BA 31	Right	39	-33	9	3.71	6	.119	>.05

Note. Regions are given in approximate Brodmann areas (BAs). Tests of significance are based on general linear random effects models in SPM99. Significance levels are for cluster-corrected comparisons; functional activations are identified by voxel-level comparisons. Tests of significance were corrected using whole-brain correction. MNI = Montreal Neurological Institute; CC = corpus callosum.

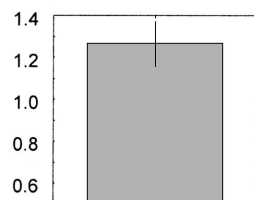
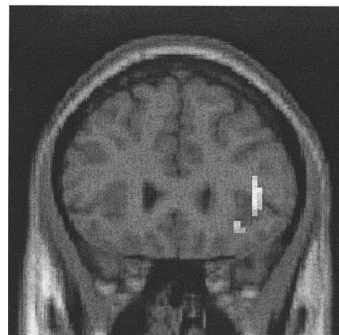
reported in PET and fMRI studies of other aspects of language processing (Baxter et al., 2003; Buckner, Raichle, & Petersen, 1995).

Our findings are also consistent with PET and fMRI studies of WMEM and a verbal analogies task that showed that the greatest sex effects were in the frontal lobes (Esposito et al., 1996; R. C. Gur et al., 1988, 2000; Mathew, Wilson, & Tant, 1986) and were found with increasingly difficult tasks (Esposito et al., 1996; Speck et al., 2000). Finally, there is some consistency of our findings with sex differences in frontal regions during rest, verbal and spatial memory (R. C. Gur et al., 1988, 2000; Mathew et al., 1986), and tactile discrimination (Sadato, Ibañez, Deiber, & Hallett, 2000).

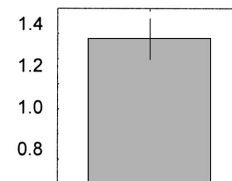
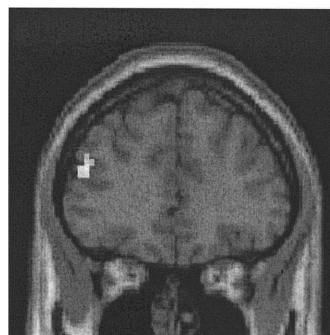
Potential Study Limitations

There are a few limitations to the present study. The sample was relatively small, and thus, statistical power was low for

estimating sex effects, although the sample was similar in size to those in the few other studies of sex effects in WMEM (Esposito et al., 1996; Lauber et al., 1994; Speck et al., 2000). Low statistical power, however, would not result in significant differential effects by sex, although it could attenuate the significance of the sex effects found in prefrontal and parietal regions. That is, although men activated similar prefrontal regions as did the women, results showed that the pattern was more diffuse within the region in men than in women. It is interesting to note that in a recent fMRI study using a semantic decision task with a sample size similar to ours, men also had a more diffuse pattern of activation in, among other regions, inferior prefrontal gyrus, and they had fewer significant activations on the right than did women (Baxter et al., 2003). A more diffuse pattern among the men may have resulted in a lower likelihood of reaching significance at the corrected *p*-level threshold in specific areas

Women > Men (all activations significant at corrected $p < .05$)

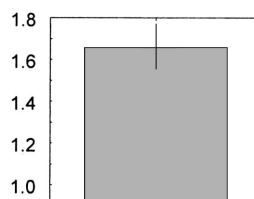
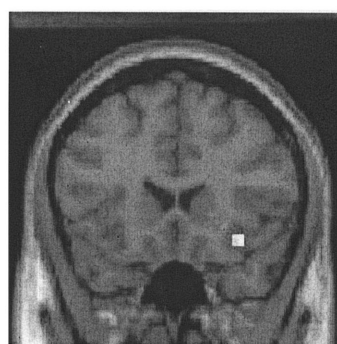
Signal change
effect size
in right BA 45



Signal change
effect size
in left BA 46

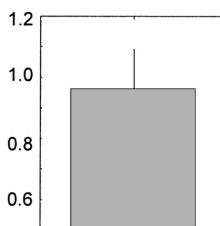
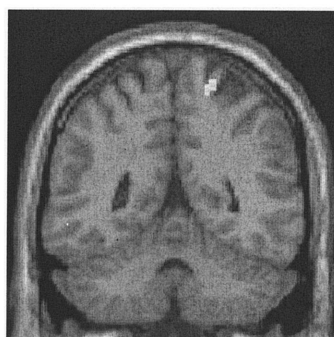
Activation at 42, 27, 3
(Right Broca's Area: BA 45)

Activation at -46, 36, 21
(Left DLPFC: BA 46)



Signal change
effect size
in right BA 47

Activation at 36, 21, -15
(Right Orbitofrontal Cortex: BA 47)

Men > Women (activation significant at uncorrected $p < .005$)

Signal change
effect size
in right BA 7

Activation at 18, -48, 63
(Right Superior Parietal Lobule: BA 7)

Figure 1. Significant positive activations and effect sizes in direct comparisons of women and men regarding signal intensity changes comparing working memory with interference (Q3A-INT) and simple attention (QA). Regions are shown in approximate Brodmann areas (BAs); coordinates are given in Montreal Neurological Institute space. DLPFC = dorsolateral prefrontal cortex.

within a region than in the women, for whom the pattern was more focal within a region. However, the findings still show significant differences in activations in the women compared with the men. The validity of our findings is further underscored by the results from our discriminant validity test based on mixed-sex groups.

There were few repetitions in the task presented here, which lowered the power to activate some of the subcortical regions found previously in WMEM studies (e.g., thalamic activations; Seidman et al., 1998). However, our task activated brain regions consistent with numerous functional imaging studies of WMEM that used current analytic strategies, thus underscoring the validity of the results presented here.

How Can Significant Sex Differences in Activations Be Understood in the Face of Similar Performance Levels?

There are significant normal sexual dimorphisms in regions implicated in WMEM (see the introduction). Thus, one potential explanation of sex differences in brain function could be differential regional volumetric sizes. Women have relatively larger bilateral volumes of dorsolateral (BA 46), orbital (BA 47), and inferior prefrontal cortices (adjusted for cerebral size; Goldstein et al., 2001; Harasty et al., 1997; Schlaepfer et al., 1995). The findings presented here, however, show that there were lateralized sex effects such that women showed greater activation than men only on left BA 46, right orbitofrontal, and right inferior frontal cortex. Thus, if larger structural volume was driving the sex differences in activation, both hemispheres should have shown sex differences rather than just one hemisphere. The absence of this finding suggests that size does not wholly account for sex effects.

Previous studies demonstrated that significant sex differences in cerebral blood flow were not attributable to differences in overall brain size, peripheral physiology (e.g., arterial oxygen-carrying capacity, blood viscosity, or arterial carbon dioxide), or technical features of the scanning procedure (Esposito et al., 1996; Mathew et al., 1986). Functional MRI and PET studies, however, have implicated gonadal hormonal differences as one potential explanatory mechanism (Baxter et al., 1987; Berman et al., 1997; McEwen, Alves, Bulloch, & Weiland, 1997; Shaywitz et al., 1999). Animal studies have shown a high density of gonadal hormone receptors in limbic and paralimbic brain regions during development (Clark, MacLusky, & Goldman-Rakic, 1988; Kolb & Stewart, 1991; MacLusky, Clark, Naftolin, & Goldman-Rakic, 1987; Pfaff & Keiner, 1973; Shughrue, Stumpf, MacLusky, Zielinski, & Hochberg, 1990; Sibug, Stumpf, Shughrue, Hochberg, & Drews, 1991; Simerly, Chang, Muramatsu, & Swanson, 1990; Tobet, Chickering, Fox, & Baum, 1993) and a relatively high level in dorsolateral and orbital prefrontal cortices (Clark et al., 1988; MacLusky et al., 1987; Simerly et al., 1990). We found normal sexual dimorphisms in adult humans in brain regions homologous to regions in these animal studies (Goldstein et al., 2001). Further, animal studies have shown that there is a differential distribution of gonadal hormones in different hemispheres (Sholl & Kim, 1990), perhaps contributing to sex differences in laterality in activation patterns.

Circulating gonadal hormones also impact regional cerebral blood flow and signal-intensity changes not wholly dependent on

region size (Daniel, Mathew, & Wilson, 1989; R. E. Gur et al., 1995, 2000; Mathew et al., 1986). Experimental manipulations of gonadal hormones in animals have demonstrated significant effects on WMEM and other prefrontal tasks (Clark & Goldman-Rakic, 1989; O'Neal, Means, Poole, & Hamm, 1996). Estradiol has enhanced WMEM and increased emotional arousal (O'Neal et al., 1996), suggesting differential effects of estradiol on cognition and emotion. PET and fMRI studies in healthy women have shown that during WMEM, estrogens are significantly associated with increased signal-intensity changes in dorsolateral, superior and inferior prefrontal, parietal, and temporal regions (Berman et al., 1997; Shaywitz et al., 1999) and decreased signal-intensity changes in the insula (Shaywitz et al., 1999). Furthermore, an fMRI study of WMEM in postmenopausal women receiving hormone replacement suggested that estradiol's strongest effect on verbal WMEM was on phonologic processing (Shaywitz et al., 1999), for which Broca's area and the insula have been implicated. We demonstrated significantly higher signal-intensity changes in Broca's area in women than in men.

Finally, human studies have shown that cognitive performance can vary with menstrual-cycle status (Hampson & Kimura, 1988; Phillips & Sherwin, 1992; Shaywitz et al., 1999; Sherwin, 1998) and abnormal exposure to prenatal gonadal hormones (Collaer & Hines, 1995). Taken together, these studies suggest that gonadal hormones play a role in cognitive performance and brain activity, thus potentially contributing to understanding of sex differences in WMEM processing. That is, given similar performance, men and women may activate brain regions responsible for WMEM somewhat differently, in part due to differences in how gonadal hormones modulate brain activity. Further work accounting for menstrual-cycle timing in relation to WMEM processing would contribute to understanding of this process.

Other possible explanations for sex differences in brain activity in WMEM may involve the idea that men and women solve problems differently in order to achieve the same performance. Thus, future work should also assess strategies for performance that may contribute to understanding variability in brain activations in men and women. In addition, our QA and Q3A-INT tasks included distractors and necessitated dual tracking and inhibitory controls. It has been suggested by Kane and Engle (2002) that maintaining representations in the face of interference is the key executive-attentional component of WMEM, which contributes to individual variability on WMEM and is dependent on DLPFC. Our findings show that both men and women used the DLPFC for this task; however, the women showed a higher level of activation in this region to achieve the same level of performance. This may mean that women were working harder to achieve control of distractors (i.e., increased activation may have been associated with increased neuronal activity) or that men were using a broader network of brain areas to achieve control of distractors (i.e., the increased activation may have been a result of the women using a relatively small region at a high level to complete the task, whereas men may have been using many regions at a lower level to complete the task). Thus, one way to characterize individual variability in WMEM—that is, control of interference effects dependent on DLPFC (Kane & Engle, 2002)—may be with regard to individual subjects' sex.

Finally, investigators have demonstrated that increased task difficulty increases affective arousal (R. C. Gur et al., 1988) and is

associated with greater number of activations, particularly in frontal regions (Esposito et al., 1996; R. C. Gur et al., 1988; Speck et al., 2000), and greater sex differences in cerebral blood flow (Esposito et al., 1996). Thus, a difficult task like Q3A-INT may increase arousal more in women than in men, thus necessitating greater activation of right BA 47 in women, which has been found to be involved with inhibitory mechanisms related to affective processing.

In summary, this study demonstrated significant sex differences in brain activity during WMEM in the face of comparable performance, particularly in prefrontal cortices. This suggests that the same brain regions can function differently in men and in women to produce the same behavioral responses. Although the sex effects reported here may not extend to all types of WMEM paradigms, either according to sensory function (e.g., visual-auditory-tactile) or associated cognitive processes (e.g., phonological-retrieval), these findings underscore the importance of designing studies that can account for sex differences in brain function, because current thinking on the neuroanatomy of WMEM, in part, relies on fMRI studies. This has been argued more extensively in structural MRI and postmortem studies of healthy populations (Goldstein et al., 2001; R. C. Gur et al., 1999; Witelson et al., 1995), but it has not yet been addressed adequately in functional imaging studies, with the exception of a few (e.g., Berman et al., 1997; Cahill et al., 2001; R. C. Gur et al., 2000; Shaywitz et al., 1999). Future imaging studies of sex differences in WMEM should incorporate tests of sex effects on specific components of WMEM; this will better contribute to understanding of the mechanisms behind these effects. The present findings may help to explain results from population studies of cognition showing a small advantage in verbal fluency and perceptual speed in women (Collaer & Hines, 1995). Further, gonadal hormones may play an important role in sex differences in brain activations, a hypothesis that warrants further study. Finally, our findings have important implications for studies of pathological groups using fMRI or other functional paradigms, given the presence of sex differences in neuroanatomical abnormalities and functional deficits in these regions in a number of neuropsychiatric disorders (Goldstein et al., 1998; R. E. Gur et al., 2000; Shaywitz et al., 1995). Thus, inattention to the sex of subjects in functional imaging studies of cognition may obscure or bias study results.

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