

## Males and females differ in brain activation during cognitive tasks

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To examine the effect of gender on regional brain activity, we utilized functional magnetic resonance imaging (fMRI) during a motor task and three cognitive tasks; a word generation task, a spatial attention task, and a working memory task in healthy male ( $n = 23$ ) and female ( $n = 10$ ) volunteers. Functional data were examined for group differences both in the number of pixels activated, and the blood–oxygen-level-dependent (BOLD) magnitude during each task. Males had a significantly greater mean activation than females in the working memory task with a greater number of pixels being activated in the right superior parietal gyrus and right inferior occipital gyrus, and a greater BOLD magnitude occurring in the left inferior parietal lobe. However, despite these fMRI changes, there were no significant differences between males and females on cognitive performance of the task. In contrast, in the spatial attention task, men performed better at this task than women, but there were no significant functional differences between the two groups. In the word generation task, there were no external measures of performance, but in the functional measurements, males had a significantly greater mean activation than females, where males had a significantly greater BOLD signal magnitude in the left and right dorsolateral prefrontal cortex, the right inferior parietal lobe, and the cingulate. In neither of the motor tasks (right or left hand) did males and females perform differently. Our fMRI findings during the motor tasks were a greater mean BOLD signal magnitude in males in the right hand motor task, compared to females where males had an increased BOLD signal magnitude in the right inferior parietal gyrus and in the left inferior frontal gyrus. In conclusion, these results demonstrate differential patterns of activation in males and females during a variety of cognitive tasks, even though performance in these tasks may not vary, and also that variability in performance may not be reflected in differences in brain activation. These results suggest that in functional imaging studies in clinical populations it may be sensible to examine each sex independently until this effect is more fully understood.

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### Introduction

It has long been recognized that males and females exhibit differential performance on various cognitive tasks, including tests of visual–spatial and verbal domains (Kimura, 1996; Wegesin, 1998). Moreover, males and females experience different propensities for the development of neuropsychiatric disorders, may report different symptom profiles clinically, and present with altered levels of functioning and comorbidity (Kessing, 2004; Marneros et al., 2004; Winkler et al., 2004; Riecher-Rossler and Hafner, 2000; Weinstock, 1999; Endicott, 1998). These differences may reflect innate functional brain differences between the genders.

Sexual dimorphism of cognitive ability has consistently been shown to occur in two domains; in tests of spatial ability (mental rotation and spatial perception) where men outperform women and in tests of verbal ability (particularly verbal fluency), where women outperform men (Wegesin, 1998). Thus, most studies suggest that females perform better than males in tasks of verbal fluency, manual speed (i.e. finger tapping), and verbal and item memory, while males perform better than females in visuospatial tasks such as mental rotation, spatial rotation, and mathematical tasks (for full review see Kimura, 1996).

Previously, functional asymmetries in cerebral organization between males and females have been observed using positron emission tomography (PET) and single photon emission computed tomography (SPECT) in the study of cerebral metabolic rate and resting state cerebral blood flow, respectively (Li et al., 2004; Kastrop et al., 1999; Gur et al., 1995; Gur and Gur, 1990; Rodriguez et al., 1988). In general, this research seems to suggest that females have a higher regional cerebral blood flow than males (Kastrop et al., 1999). More recently, functional imaging studies, including functional magnetic resonance imaging (fMRI) studies, have been conducted to investigate gender influence upon regional brain activity changes and regional cerebral blood flow changes occurring during stimulus presentation. Tasks of mental rotation, visual stimulation, emotional recognition, verbal processing, and object construction have all shown significant patterns of differential activation between the sexes (Fischer et al., 2004; Lee et al.,

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2002, 2005; Weiss et al., 2003; Georgopoulos et al., 2001; Cowan et al., 2000; Ragland et al., 2000; Speck et al., 2000; Levin et al., 1998; Shaywitz et al., 1995). Gender-specific alterations in brain activation have been observed (across the various paradigms) in insular and thalamic regions (Lee et al., 2002, 2005), occipital and cingulate regions (Fischer et al., 2004; Lee et al., 2002), frontal regions (Lee et al., 2002), parietal regions (Weiss et al., 2003), and temporal regions (Ragland et al., 2000), as well as altered lateralization between the hemispheres (Lee et al., 2002; Georgopoulos et al., 2001; Speck et al., 2000; Levin et al., 1998; Shaywitz et al., 1995). Despite the general consensus that suggests differences between males and females, not all studies have found a significant gender effect (Schlosser et al., 1998). Excluding those fMRI studies which have employed emotional paradigm challenges (for which results are dependent on several factors including the emotion induced, the modality of the paradigm as well as gender specifics of the induced emotion), other studies suggest that females have greater bilateral activation during a phonological language task (Shaywitz et al., 1995), and greater lateralization to the left hemisphere during a working memory task (Speck et al., 2000). Additionally, females have demonstrated more frontal activation, compared to more parietal activation in males, during a mental rotation task (Weiss et al., 2003), and males have demonstrated a greater bias towards right hemisphere activation (and females to left hemisphere activation) during a task requiring a judgement of a whole object from its parts (Georgopoulos et al., 2001). Finally, females have also demonstrated a greater bilateral regional cerebral blood flow in temporal regions during performance of the Wechsler Memory Scale for memory recall (Ragland et al., 2000).

While some of the cognitive paradigms have demonstrated gender biases in terms of performance (females perform more accurately (although slower) on working memory task (Speck et al., 2000) and on memory recall (Ragland et al., 2000), others have not (verbal test of orthographic, semantic, and phonological processing; Shaywitz et al., 1995; visuospatial test of mental rotation; Weiss et al., 2003).

The idea of teasing out gender effects in brain activation is difficult when we know that previous neuropsychological evidence supports gender-specific performance abilities in males and females on a variety of cognitive domains. For this reason, it is important to try and understand the possible relationships between gender, cognitive performance, and brain activation. In fact, findings from a recent study by Unterrainer et al. (2005) have shown both sex-specific and individual task performance-specific influences upon regional brain activity during a planning task.

Using the blood–oxygen-level-dependent (BOLD) response, we have assessed differences in regional brain activation in a group of male and female healthy volunteers over a variety of cognitive domains; verbal fluency, spatial attention, working memory, and motor tasks. Our hypotheses were first, that males and females would differ in brain activation patterns during spatial attention (for which males outperform females) and during verbal fluency (where females outperform males) but not necessarily during a motor task or in working memory performance where neuropsychological data do not support sexual dimorphism. In conjunction to this, we hypothesized that gender differences in cognitive performance on the tasks would be reflected by gender differences in the same direction on measures of brain activation. Thus, females would demonstrate a greater activation during the

verbal task; males during the spatial attention task and both genders would show equivalent brain activity during the motor tasks. We did not make any hypothesis regarding the direction that either findings of performance or brain activation during the working memory task might take, although Speck et al. (2000) have demonstrated increased left hemisphere lateralization in females in this domain.

## Methods

### *Subjects and study design*

The ethics board of the University of Alberta Hospital approved this study.

### *Subjects*

Thirty-three right-handed healthy volunteers (23 males, 10 females) were recruited through poster advertising from the university community. Subjects underwent a medical exam and medical history, and a detailed semi-structured clinical interview (structured clinical interview for DSM-IV) to rule out past or present psychiatric illness. Past and present drug and alcohol use was assessed and subjects were excluded based on current abuse of these substances. Subjects who had used recreational drugs in the past 6 months, or amphetamine in the past year were excluded from participating.

### *Tasks*

The tasks are those we have used and described in previous research studies (Willson et al., 2004; Bell et al., 2005). All tasks were blocked design; the working memory task was composed of seven 24 s blocks of each control (arrow condition) and test condition (5-digit memory condition); the spatial attention task was composed of 10 blocks of each control (attended stimuli) and test (unattended condition) of 24 s duration; the word generation task was composed of five 40-s blocks of each control (pseudo REST condition) and test (word generation) conditions; the motor tasks were composed of four blocks of on and off finger tapping each for 40 s.

*Working memory task.* The working memory task consisted of two conditions. In the first condition, there was a series of 10 arrows pointing to the left or to the right. Subjects responded by pressing the left or right button. In the second condition, a five-digit number was displayed for 4 s with the instruction 'Remember this Number'. Immediately after, a series of 10 random single digits was presented. Subjects were asked to respond by pressing one button for yes and one for no if the single digit was or was not in the memorized number. In all, each condition was presented seven times in 24 s blocks pseudo-randomly arranged.

*Spatial attention task.* For this task, subjects were asked to respond as quickly as possible to a certain criteria. First, a black cross appeared on the screen. Soon after, the black cross would appear with the target (a black square). Whenever the black cross and square appeared together, subjects responded by pressing the button in their dominant hand as fast as possible. The delay between the appearance of the cross and the target was varied randomly from 300 to 1100 ms. Approximately 10% of the trials were actually catch trials designed to ensure that subjects were

engaged in the task. In a catch trial, another black cross appeared instead of the target and subjects were instructed not to respond. Any responses to catch trials were considered errors, and the error rate could therefore be measured. In this experiment, two conditions of the reaction task were alternated to maintain spatial attention (Beauchamp et al., 2001; Cabeza and Kingstone, 2001). In the first condition, the cross and square appeared in the same location (attended location), and in the second condition, the target appeared a distance away from the cross (unattended). There is significant evidence to suggest that spatial attention, such is needed to do this task, is analogous to a “mental spotlight” that requires a certain connectivity to operate properly (Willson et al., 2004). This task was performed in 10 alternating blocks of each condition, 24 s in duration each.

*Word generation paradigm.* The verbal task utilized a word generation paradigm in which there were two conditions. In the first condition, subjects were asked to repeat the word ‘REST’ silently until another instruction was given. In the second condition, a series of 10 single letters randomly chosen from the alphabet were displayed at 4-s intervals. During the display of a single letter, subjects responded by thinking of as many words as possible that begin with that letter and repeating them silently until another letter is presented or the ‘REST’ instruction appears. The experiment consisted of five 40-s blocks of each condition beginning with ‘REST’.

*Motor task.* The motor task involved rapidly tapping the index finger. Subjects were instructed to “tap the index finger of the (given hand) as fast as you can comfortably while maintaining a steady pace”. Instructions for the “Rest” and “Tapping” condition were given by a visual signal. Each condition (Rest or Tapping) was performed in four alternating blocks each lasting 40 s. This experiment was done twice, once with the left hand and then again with the right hand.

The four tasks were administered in a fixed manner starting with the motor tasks followed by the memory task, the spatial attention task, and finally the word generation task.

#### *Behavioral measurements*

Response data were collected for the spatial attention task, the working memory task, and motor tasks. Due to the nature of the verbal fluency task, no behavioral measures were obtained. Reaction time (ms) was assessed for each condition in the working memory (arrow control condition and 5 digit condition) and spatial attention tasks (attended stimuli and unattended stimuli) and the average tapping rate (Hz) was assessed during finger tapping (left and right hand). Student’s independent *t* test was used to assess between group differences in the reaction times at baseline and to assess between group differences on the spatial attention and working memory task errors.

#### *Image acquisition*

The fMRI study was conducted on a 1.5-T Siemens Sonata scanner (Siemens, Erlangen, Germany) with a single shot echo-planar image (EPI) gradient echo sequence (TR = 4010 ms, TE = 50 ms,  $1.7 \times 1.7$  mm, 4 mm thick) to acquire 30 contiguous slices obtained at an oblique angle along the anterior commissure–posterior commissure (AC–PC) line. A high-resolution T1-

weighted magnetization prepared rapid gradient echo sequence was also acquired during the imaging session to overlay the functional analysis (Willson et al., 2004).

#### *fMRI data analysis*

fMRI data analysis was conducted according to previously published methods (Willson et al., 2004, Bell et al., 2005). Preprocessing and analysis were performed using Statistical Parametric Mapping (SPM99), 1999 version (SPM99–Wellcome Department of Cognitive Neurology, University College London). All functional images were realigned during preprocessing to accommodate and correct for any head motion. Realignment was performed using a 6-parameter rigid body transformation and a mean image was created of the entire time series for each data set. Sessions with realignment parameters of greater than 4 mm in the direction of translation (along the *x*, *y*, *z* axis) were excluded from the final statistical analysis, as were sessions with motion greater than 0.05 radians in a rotational plane (pitch, roll, yaw). The mean image was then spatially normalized to the MNI template brain using a 12-parameter affine transformation with 12 non-linear iterations and  $7 \times 8 \times 7$  basis functions. The spatial transformations derived from normalizing the mean image to the template were then applied to the T2\*-weighted EPI functional images. After normalization, all volumes were resampled to  $2 \times 2 \times 2$  mm voxels using trilinear interpolation in space. Finally, all functional images were smoothed with an 8-mm full width at half-maximum isotropic Gaussian kernel to compensate for between subject variability and allow Gaussian random field theory to give corrected statistical inferences (Friston et al., 1994). Initial analysis was performed separately for each subject for each task. The model specified for each task was kept identical for all subjects and sessions to create identical design matrices. As part of this analysis, three more preprocessing steps were performed using SPM99. First, the data were high pass filtered to remove low-frequency drifts in the signal. In addition, the data were low pass filtered using the hemodynamic response function to remove high-frequency noise. Effects due to global intensity fluctuations were removed when the data were proportionally scaled to a global mean of 100. The time series for each data set was analyzed according to the general linear model. Previously, we have performed a group analysis on 18 of these volunteers (5 females, 13 males) (Willson et al., 2004) by constructing a fixed effects model for each task. Regions of interest (ROI) for each task were then compiled based on those anatomical areas which were activated to meet a threshold of *P* (corrected) of less than 0.05 and a cluster size of 10 voxels or more. These *most significantly activated voxels* from the group average generation maps were used to localize activation anatomically and the ROI images were constructed using automated anatomical labeling (AAL) software (Tzourio-Mazoyer et al., 2002), running with MRICro software (Rorden and Brett, 2000). These ROIs have been assessed in the current study. Regions of interest for tasks: *working memory task*, right insula, left inferior parietal gyrus, right inferior parietal gyrus, left superior parietal gyrus, right superior parietal gyrus, left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, left inferior frontal gyrus, right inferior frontal gyrus, left middle frontal gyrus, right middle frontal gyrus, left superior frontal gyrus, right superior frontal gyrus, left inferior occipital gyrus, right inferior occipital gyrus, left precentral gyrus, right precentral gyrus, left insula and cingulate gyrus; *spatial attention task*, cuneus, left middle occipital gyrus, right middle occipital gyrus, left lingual gyrus, right lingual gyrus, right superior

parietal gyrus, precuneus, left superior parietal gyrus, right middle occipital gyrus; *word generation paradigm*, left inferior parietal gyrus, left superior parietal gyrus, right inferior parietal gyrus, right superior parietal gyrus, broca's area, left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, left precentral gyrus, right precentral gyrus, cingulate gyrus, supplementary motor area, left superior temporal gyrus, right superior temporal gyrus, thalamus; *motor task*, left primary motor cortex, right primary motor cortex, supplementary motor area, left superior temporal gyrus, right superior temporal gyrus, left inferior parietal gyrus, right inferior parietal gyrus, left inferior frontal gyrus and right inferior frontal gyrus.

For each subject, the individual activation maps generated during single-subject analysis were used to identify the number of activated pixels and BOLD signal magnitude within each ROI. In each individual activation map, for each task, a small volume correction (SVC) was applied to compute the activation within each ROI. We have used a SVC because we previously have defined areas of activation (ROIs) in the statistical parametric map according to the results the 18 subject, fixed-effects analysis. Applying the SVC allows the choice of appropriate thresholds, given that we are confining our analysis to ROIs of defined shape and size. We have used a corrected  $P$  value threshold of 0.05 in the evaluation of the number of activated pixels in each ROI. The number of activated pixels in each ROI was counted for each subject in each ROI, in each task.

For each subject, the individual activation maps generated during single-subject analysis were used to identify the change in BOLD signal magnitude. The BOLD signal intensity change was calculated based on regions of interest using the MARSBAR toolbox for SPM (Brett et al., 2002) over a seven-voxel sphere centered on the *most* significantly active voxel in each ROI. The fitted response (or BOLD signal intensity change) is expressed in percentage of whole brain mean. Because the global brain mean in the voxel-wise analysis was scaled to 100, this signal change represents the percentage of signal change with respect to the global mean intensity of the scaled images. The number of voxels over which the fitted response was calculated was kept small in order to minimize averaging over non-significant voxels or large veins (Mulderink et al., 2002). Subsequently, statistical calculations for BOLD signal magnitude were based on the average response calculated from the plateau portion of the hemodynamic response (8 s after stimulus origination until stimulus termination) (Willson et al., 2004).

The mean number of pixels activated across all ROIs for all female and male subjects was calculated as well as the mean BOLD signal magnitude across all ROIs for all female and male subjects. Independent Student's  $t$  test was used to determine differences between the two groups. If this was significant, *additional* independent Student's  $t$  test were used to assess each ROI for differences between males and females in the task. For the motor tasks, a two-way ANOVA full factorial design was applied to test for the main effects of gender and hand of task as well as for an interaction effect.

## Results

Thirty-three subjects participated in the study. There were no significant differences between these groups in terms of age (mean age  $\pm$  SEM; males  $26.7 \pm 1.5$ , females  $25.2 \pm 2.0$ ). One male

subject failed to complete the baseline word generation paradigm. This subject was excluded from the analysis for this task.

### Behavioral performance

#### Working memory task

There were no significant differences in reaction time during the control or test condition between males or females in the working memory task. In the control (arrow) condition, males had a reaction time of  $430.28 \pm 27.0$  and females performed at  $541.80 \pm 57.7$  ( $P = 0.081$ ). During the memory condition, males performed with a reaction time of  $841.22 \pm 38.2$  and females with a reaction time of  $944.88 \pm 74.1$  ( $P = 0.235$ ) (see Fig. 1a). There was no significant difference between males and females on errors in the task (males,  $2.56 \pm 2.06$ ; females,  $1.80 \pm 1.64$ ,  $P = 0.41$ ).

#### Spatial attention task

There was a significant difference in performance during both the control (attended) and test (unattended) conditions in males and females. The male subjects had significantly faster reaction times than the females in the attended condition (males  $291.9 \pm 8.2$ , females  $348.5 \pm 19.0$ ;  $P = 0.004$ ) and during the unattended condition (males  $316.8 \pm 10.2$ , females  $372.7 \pm 16.1$ ,  $P = 0.006$ ) (see Fig. 1b). The number of errors made during the catch trials was not significantly different in males and females (males,  $4.17 \pm 2.43$ ; females,  $2.63 \pm 1.69$ ,  $P = 0.118$ ).

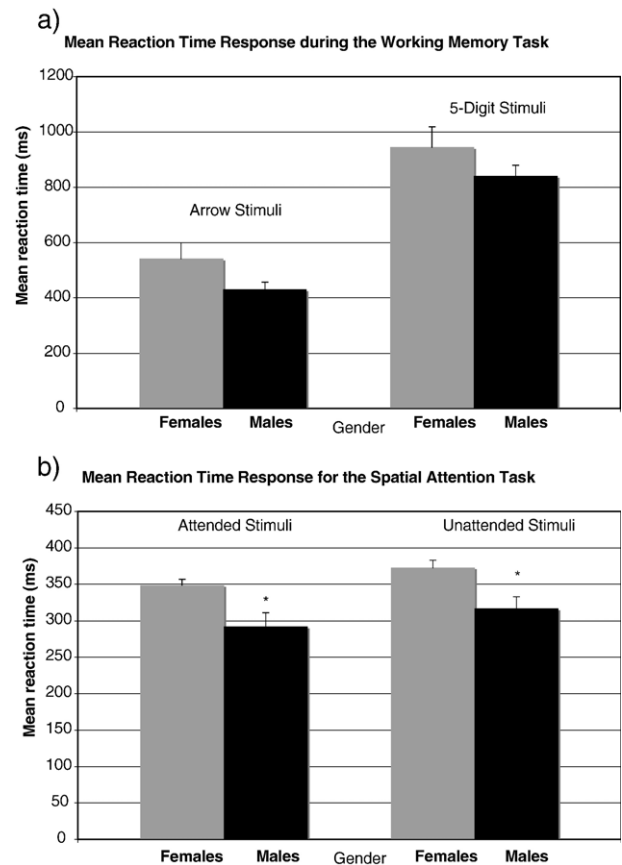


Fig. 1. Mean reaction time (ms) of response for females and males during the two conditions in each (a) working memory task and (b) spatial attention task. Where \* indicates significance at  $P = 0.05$ .

*Motor tasks*

There were no significant differences between males and females in the performance of either the right or left finger tapping task, measured by the mean tapping frequency ( $P = 0.964$  and  $P = 0.313$ , respectively). The mean tapping frequency for males was 2.98 Hz with the right hand and 2.43 Hz with the left hand. The mean tapping frequency for females was 3.00 Hz with the right hand and 2.80 Hz with the left hand.

*fMRI results*

*Working memory task*

Independent  $t$  test demonstrated that males had significantly higher mean number of pixels activated ( $P = 0.003$ ; Fig. 2a) and a greater mean BOLD signal magnitude ( $P = 0.012$ ; Fig. 3a) than females in the working memory task. Additional analysis demonstrated that males had a greater number of pixels activated in the right superior parietal gyrus and the right inferior occipital gyrus, and a greater BOLD signal magnitude in the left inferior parietal gyrus (Table 1).

*Spatial attention task*

There was no significant difference between groups on the mean of the number of activated pixels or the mean BOLD magnitude ( $P = 0.660$ ; Fig. 2b and  $P = 0.924$ ; Fig. 3b) (Table 1).

*Word generation paradigm*

Males had a significantly larger mean number of pixels activated than females ( $P = 0.005$ ; Fig. 2c), and a significantly greater BOLD magnitude than females ( $P = 0.000$ ; Fig. 3c). Additional analysis of the individual ROI in this task showed no significant differences between males and females in the number of pixels activated, but did show greater mean BOLD magnitude in males in the right and left dorsolateral prefrontal cortex, the right inferior parietal gyrus, and the cingulate (Table 1).

*Motor task*

A two-way ANOVA revealed no main effect of gender or hand of task performance for the number of activated pixels (gender effect  $P = 0.762$ , hand effect = 0.811) or the BOLD magnitude (gender effect = 0.133, hand effect = 0.776). There was also no

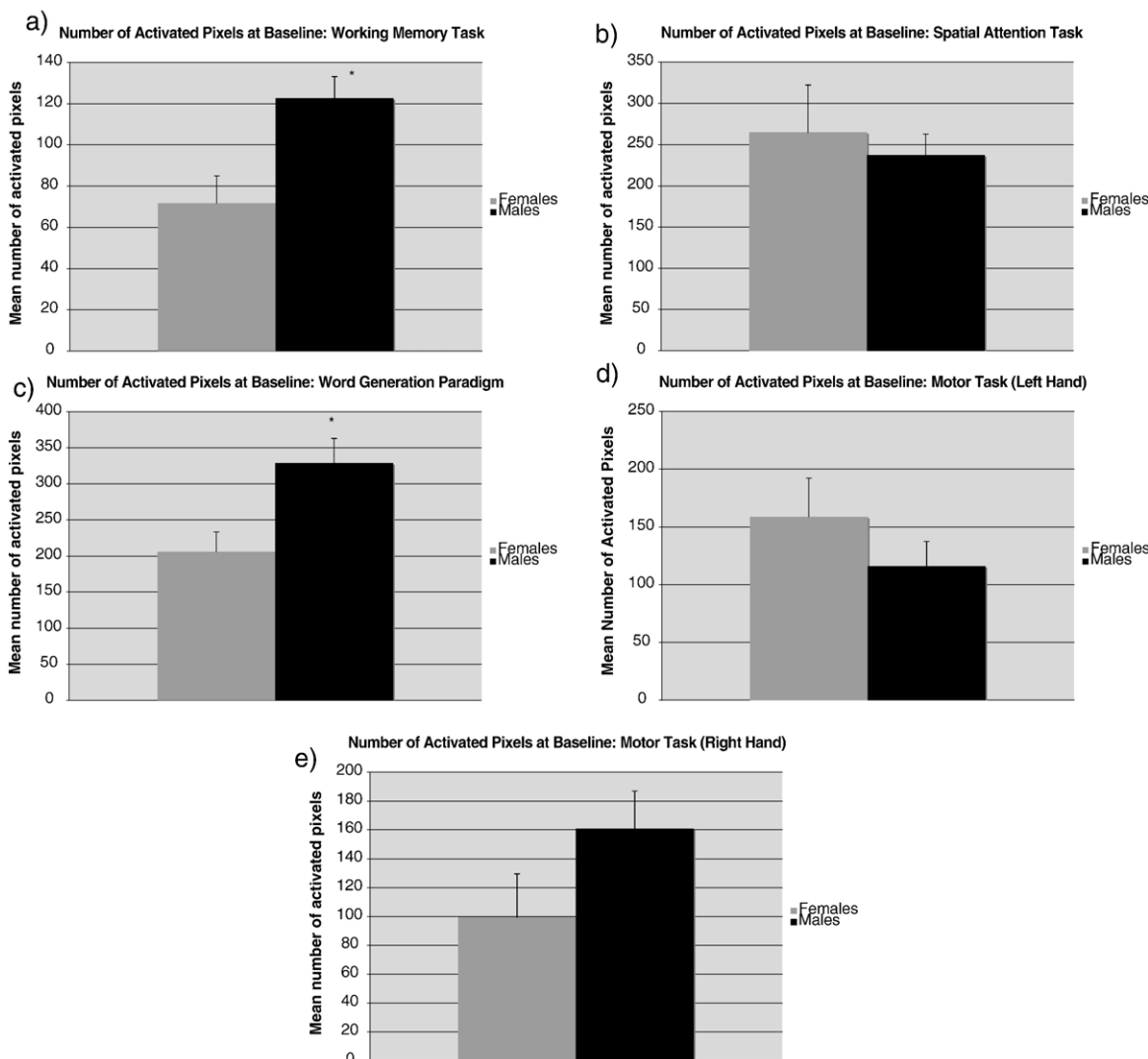


Fig. 2. Mean number of activated pixels across regions of interest for each task: (a) working memory task, (b) spatial attention task, (c) word generation paradigm, (d) motor task (left hand), (e) motor task (right hand), in males and females.

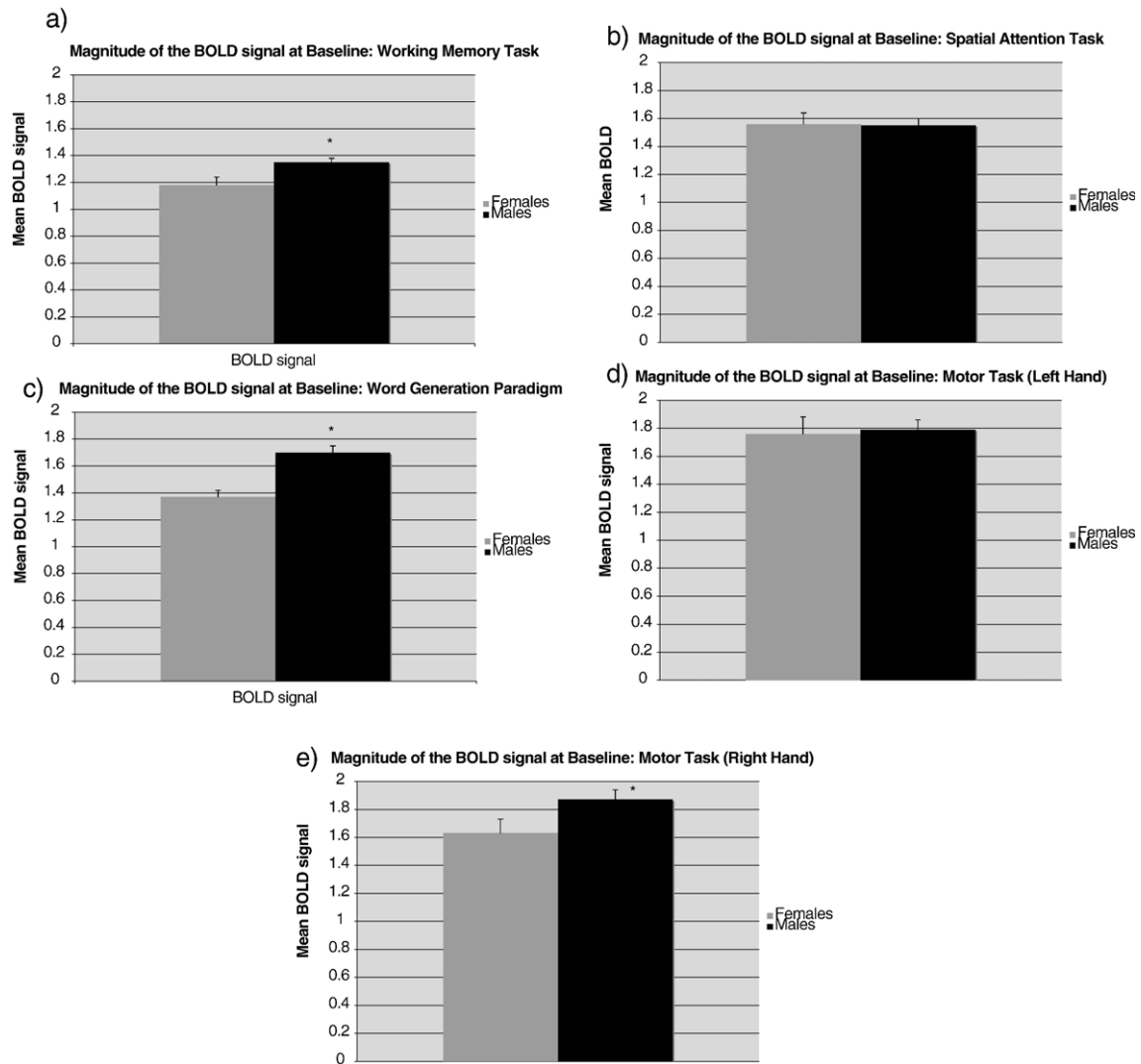


Fig. 3. Mean magnitude of the BOLD signal across the regions of interest of each task: (a) working memory task, (b) spatial attention task, (c) word generation paradigm, (d) motor task (left hand), (e) motor task (right hand), in females and males. Where \* indicates a  $P$  value significance of < 0.05.

significant interaction effect between gender and hand of task performance for either fMRI measure ( $P = 0.089$ ,  $P = 0.242$ , respectively).

#### Left hand

There were no significant differences between males and females on either the number of activated pixels or BOLD signal magnitude specifically noted in any of the regions of interest during performance on the left finger tapping task (Figs. 2d, 3d) (Table 1).

#### Right hand

Males had a significantly greater mean BOLD magnitude than females during performance of the right hand finger tapping task ( $P = 0.053$ ). However, there were no significant differences between the two genders in terms of the number of activated pixels in this task ( $P = 0.178$ ). Additional  $t$  tests demonstrated that males had a significantly larger BOLD signal magnitude in the right inferior parietal gyrus ( $P = 0.029$ ) and left inferior frontal gyrus ( $P = 0.013$ ) as well as a significantly larger amount of pixels activated in the left superior temporal gyrus ( $P = 0.036$ ) (Table 1, Figs. 2e, 3e).

## Discussion

The present study demonstrates specific task-dependent effects of gender on both cognitive performance and on brain activation as measured by both BOLD signal extent and change in the number of pixels. Interestingly, however, our initial hypotheses were not upheld. While we found that males and females did indeed differ in brain activation patterns on several cognitive tasks (but not necessarily on those that we had hypothesized), we found that differences in cognitive performance were not reflected in brain activation, and conversely that changes in brain activation were not reflective of differences in cognitive activation. Recently, Unterhiner et al. (2005) have also found that gender and performance can both influence brain activation independently during a planning task (Tower of London). In their investigation of both gender influence and individual task performance influence upon brain activity, the authors have observed a positive relationship between brain activity in the right dorsolateral prefrontal cortex and individual performance level. Additionally, they have observed sex-specific activation on the task in the right hippo-

Table 1  
Mean value of the number of activated pixels and BOLD signal in each task

	ROI <sup>a</sup>	Males (mean value ± SEM)	Females (mean value ± SEM)	<i>P</i> value
<i>Memory</i>				
Mean number of activated pixels		122.69 ± 10.4	71.71 ± 13.2	0.003 <sup>a</sup>
	RSPG	46.30 ± 15.3	0.00 ± 0.0	0.007 <sup>a</sup>
	RIOG	285.20 ± 47.0	84.20 ± 37.4	0.050 <sup>a</sup>
Mean BOLD magnitude		1.35 ± 0.03	1.18 ± 0.06	0.012 <sup>a</sup>
	LIPG	1.63 ± 0.13	1.22 ± 0.09	0.016 <sup>a</sup>
<i>Spatial attention</i>				
Mean number of activated pixels		237.33 ± 25.3	264.94 ± 57.3	0.660
Mean BOLD magnitude		1.55 ± 0.05	1.56 ± 0.08	0.924
<i>Word generation</i>				
Mean number of activated pixels		328.75 ± 34.2	206.08 ± 27.2	0.005 <sup>a</sup>
Mean BOLD magnitude		1.70 ± 0.05	1.37 ± 0.05	0.000 <sup>a</sup>
	RDLPFC	1.64 ± 0.14	1.18 ± 0.07	0.028 <sup>a</sup>
	LDLPFC	2.05 ± 0.17	1.52 ± 0.19	0.058 <sup>b</sup>
	RIPG	1.46 ± 0.21	1.00 ± 0.06	0.046 <sup>a</sup>
	CING	1.76 ± 0.18	1.36 ± 0.09	0.056 <sup>b</sup>
<i>Motor (left)</i>				
Mean number of activated pixels		116.13 ± 21.3	158.82 ± 33.4	0.290
Mean BOLD magnitude		1.79 ± 0.07	1.76 ± 0.12	0.819
<i>Motor (right)</i>				
Mean number of activated pixels		160.75 ± 26.2	99.58 ± 29.9	0.178
	LSTG	239.00 ± 71.5	68.33 ± 28.1	0.036 <sup>a</sup>
Mean BOLD magnitude		1.87 ± 0.07	1.63 ± 0.10	0.053 <sup>a</sup>
	RIPG	1.32 ± 0.11	0.88 ± 0.13	0.029 <sup>a</sup>
	LIFG	1.44 ± 0.13	0.85 ± 0.10	0.013 <sup>a</sup>

Mean value for the number of activated pixels and/or BOLD signal in post hoc analysis when significant ( $P = 0.05$ ), or trend to significance, in regions of interest (ROI) as identified in Willson et al. (2004). Where right superior parietal gyrus (RSPG), right inferior occipital gyrus (RIOG), left inferior parietal gyrus (LIPG), right dorsolateral prefrontal cortex (RDLPFC), left dorsolateral prefrontal cortex (LDLPFC), right inferior parietal gyrus (RIPG), cingulate (CING), left superior temporal gyrus (LSTG).

<sup>a</sup>  $P < 0.05$ .

<sup>b</sup> Trend.

campus. We believe we have expanded upon this investigation by examining the effects of gender and gender performance, as a whole, on the BOLD signal in four tasks assessing different cognitive domains.

#### Working memory

Men exhibited a larger extent and magnitude of regional brain activation than females during performance of a numerical working memory task. There was a significantly greater regional

brain activity in men in the right superior frontal and inferior occipital gyrus (number of pixels) and in the left inferior parietal gyrus (BOLD signal), when compared to women. The increases we observed in the right hemisphere support observations by Speck et al. (2000) during a verbal working memory task of an increased right hemisphere dominance in men (or symmetric activation), compared to the left hemisphere dominance they observed in women during the task. However, unlike Speck et al. (2000), we did not observe a significant difference in performance between the two genders on our working memory task. This would tend to indicate that in men, regardless of performance, there is an increase in regional brain activity during a working memory task, in which the spatial extent of activation is increased in frontal and occipital regions of the right hemisphere.

#### Spatial attention task

Repeated studies have suggested that males perform better than females on tests of visuospatial functioning (Kimura, 1996). Our results support this, and males in the current study performed with significantly faster reaction times than females. However, the difference in performance between these groups was not accompanied by significant alterations in functional activation. In contrast, although using a radically different and perhaps more challenging visuospatial paradigm, Weiss et al. (2003) observed greater parietal activation in males and greater frontal activation in females challenged with a mental rotation task using fMRI.

#### Word generation paradigm

Previous studies suggest that males perform better than women in cognitive measures of visuospatial ability, while it is believed that in general females perform better than males in tests of verbal function (Kimura, 1996). In an investigation of verbal fluency using fMRI, Schlosser et al. (1998) observed “no gross differences in activation patterns” between male ( $n = 6$ ) and female ( $n = 6$ ) healthy subjects. However, in the current study, we have observed a significantly increased activation, over the regions involved in carrying out a verbal fluency task, in males compared to females. A regional analysis revealed that a greater BOLD signal magnitude was observed in males, compared to females in several brain regions (right and left dorsolateral prefrontal cortex, cingulate and right inferior parietal cortex). While it would be expected that the female subjects performed better on this verbal task, we do not have performance data due to the nature of the task. In the future, behavioral data would be an asset in the interpretation of this regional brain difference. However, the functional data seem to support that men recruit the prefrontal cortex to a greater degree than women in the performance of this task. Moreover, men have activated the cingulate to a greater degree than females. While we have not assessed differential activity across this structure, in anterior and posterior regions, there are suggestions that parts of the anterior cingulate play an important cognitive role in attending to stimuli and in mediating cognitive interference (Bush et al., 1998). Moreover, Vogt et al. (1992) suggest that the posterior aspects of the cingulate are involved in spatial orientation, memory, and evaluation of sensory stimuli.

### Motor tasks

While males and females did not differ in their performance of either the right or left hand finger tapping tasks, there were two regions where males demonstrated a significantly greater BOLD signal magnitude than females during the right hand motor task. This demonstrates an inconsistency between performance measures and functional imaging results, and we are uncertain why these specific regions may be altered during the performance of only one of the motor tasks. However, upon analysis using a two-way ANOVA, we did not actually find that either gender or hand of task had a main effect upon the number of pixels activated or the BOLD magnitude, and this is likely a more significant finding than the separate analyses.

### Other male vs. female differences

Several groups have suggested that there are significant differences between males and females functionally in aspects of brain metabolism and cerebral blood flow. Gur et al. (1995) demonstrated a higher cerebral glucose metabolism in males in the cerebellum, basal ganglia, and brainstem and a lower metabolism in the middle and posterior cingulate gyrus. Most studies, investigating resting state cerebral blood flow, have largely supported a bias of increased global cerebral blood flow in females (Ragland et al., 2000; Gur and Gur, 1990; Rodriguez et al., 1988). Regionally, it has been noted that males have a more strongly lateralized cerebral blood flow in frontal regions, in the right hemisphere (Rodriguez et al., 1988), while females have a higher regional cerebral blood flow than males in mid-temporal regions (Ragland et al., 2000).

The reasons that functional differences may exist between men and women are numerous. Several researchers have reported structural differences in limbic areas such as the amygdala and the caudate in male and female children (Durstun et al., 2001) as well as in regions of the cingulate, hippocampus, parietal, and occipital regions in adult men and women (Raz et al., 2004). Moreover, it has been reported that women possess a greater proportion of brain grey matter, in comparison to men; although researchers explain that brain volume rather than sex is the main variable in the determination of grey matter volume (Luders et al., 2002). Gur et al. (1999) have also reported a disconnect in the percentages of grey and white matter between men and women. While they report a larger percentage of grey matter in women, they also observed a higher percentage of white matter and cerebrospinal fluid in men. Additionally, they noted that in men and women the correlation between intracranial volume and grey and white matter varied (Gur et al., 1999). The authors suggest that alterations in neural tissue volumes between the sexes may contribute to gender differences in cognitive abilities (Gur et al., 1999).

In addition, there is some evidence to support an endocrine effect upon functional brain activity and brain perfusion (Smith and Zubieta, 2001). In women assessed after treatment with estrogen replacement therapy, Okhura et al. (1995) observed an increase in global cerebral and cerebellar blood flow, compared to a control group of women and modulation of cerebral blood flow during performance of the Wisconsin Card Sorting task has also been observed in women with experimentally manipulated estrogen or progesterone levels (Berman et al., 1997). Dietrich et al. (2001) investigated word stem completion in women (at different times in

their menstrual cycle) using fMRI. Their results suggest altered regional brain activation during this task, in women, during the high estrogen phase compared to during menses. Similarly, Shaywitz et al. (1999) observed an altered pattern of functional activation during fMRI of a working memory task in women on estrogen who took part in a double-blind, crossover study treated with 21 days of estrogen crossed over with placebo. Unfortunately, because we have not assessed menstrual cycle in the group of females taking part in the current study, we cannot rule out various effects that hormonal influences may have exerted on our results.

Finally, we must consider that physiological differences involved in the generation of the BOLD signal contrast exist between females and males. Indeed, aforementioned structural brain differences and brain composition differences may influence the BOLD signal, as well as regional cerebral blood flow, blood volume, and cerebral metabolic rate of oxygen (Kastrup et al., 1999). Moreover, recent studies investigating simple visual stimulation in males and females have suggested that a greater number of undetectable BOLD signals are present in males than in females (Marcar et al., 2004; Hedera et al., 1998). However, Marcar et al. (2004) also conclude that while females have a higher cerebral glucose metabolism than males, this fact is not reflected in the peak of the BOLD signal amplitude. In a similar investigation, Levin et al. (1998) found a decreased BOLD signal response in females during binocular visual stimulation, compared to males. They conclude that this is most likely based on a variety of factors influencing blood flow, volume, and oxygenation and also possibly by the fact that lower levels of hemoglobin are observed in females than in males.

The functional imaging literature to date suggests that there are significantly different patterns of activation between men and women on various cognitive tasks and in various paradigms. The current study reinforces the fact that gender matching is essential in functional imaging studies, both clinically and in healthy individuals. Furthermore, it appears that unique patterns of activation between men and women exist during cognitive task performance, which may or may not influence their performance on the task. It is evident that gender-specific changes in functional activation are very much a product of the task performed. However, we must acknowledge that while we believe that this point is well demonstrated by the finding of the current study, we have used a limited sample size for this analysis, and had in particular fewer females take part. The findings, therefore, should be substantiated by further exploration of gender and performance effects on a variety of different tasks using a larger population of female subjects. The fact that we tested fewer females than males in the study may partly explain why regionally there was no accord between gender differences in BOLD signal magnitude changes and the number of activated pixels. Potentially, a larger sample of females would contribute to our ability to distinguish between the genders in a regional analysis.

Taking all of these studies together, along with the findings from the present study, there appears considerable evidence of differences between males and females in brain activation in response to cognitive challenges. They would suggest that in clinical studies of brain activation the sexes should be analyzed separated and that studies should have control populations closely matched for sex distribution. In neuropsychiatric studies, however, interpreting the results can be challenging. While various limbic, subcortical, and cortical dysregulations have been observed in studies of depression, bipolar disorder, and anxiety disorders (for

reviews see Silverstone et al., 2005; Haldane and Frangou, 2004; Kanner, 2004; Anand and Shekhar, 2003), these populations are often biased in terms of gender prevalence (Arnold, 2003; Gavranidou and Rosner, 2003; Cassano and Fava, 2002; Kessler et al., 2001; Piccinelli and Wilkinson, 2000; Brady and Randall, 1999; Pigot, 1999; Weinstock, 1999; Gold, 1998). As well, because women may seek treatment more than men, it may be easier for a researcher to recruit females. Both of these factors may lead to a patient sample predisposed to an uneven gender distribution.

In conclusion, the functional imaging literature to date suggests that there are significantly different patterns of activation between males and females on various cognitive tasks and in various paradigms. The current study reinforces the fact that gender matching is essential in clinical functional imaging studies, and supports the idea of exploring male and female populations as distinct groups.

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