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Gender differences in unilateral spatial neglect within 24 hours of ischemic stroke

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ABSTRACT

Hemispatial neglect is a common and disabling consequence of stroke. Previous reports examining the relationship between gender and the incidence of unilateral spatial neglect (USN) have included either a large numbers of patients with few neglect tests or small numbers of patients with multiple tests. To determine if USN was more common and/or severe in men or women, we examined a large group of patients (312 right-handed) within 24 hours of acute right hemisphere ischemic stroke. Multiple spatial neglect tasks were used to increase the sensitivity of neglect detection. No differences based upon gender were observed for the prevalence, severity, or a combined task measure of USN.

1. Introduction

Small but robust gender differences in cognitive task performance have led to enormous interest in this topic (Vandenberg & Kuse, 1978). These differences are most significant for a subset of language production tasks, with women outperforming men, and on visuospatial tasks, with men outperforming women (for review see Halpern, 2000; Levy & Heller, 1992; Linn & Petersen, 1985; Masters, 1998; McGlone, 1980; Voyer, Voyer, & Bryden, 1995). These differences in spatial performance are reported in approximately 80% of studies (Sanders, Sjodin, & De Chastelaine, 2002), although this estimation may slightly over represent true gender or sex differences because of biases for publishing only statistically significant differences (Dickersin & Min, 1993; Rosenthal, 1979).

Gender differences have also been observed in fMRI studies during: (1) mental rotation in both gross anatomical activation volume and location (Butler et al., 2006; Fink et al., 2003; Jordan, Wustenberg, Heinze, Peters, & Jancke, 2002); (2) line orientation determination (Gur et al., 2000); and (3) distributed intra-hemispheric activation on mental rotation tasks (Butler et al., 2006; Seurinck, Vingerhoets, De Lange, & Achten, 2004; Weiss et al., 2003). For the allocation of spatial attention, however, no differences were observed using fMRI (Bell, Willson, Wilman, Dave, & Silverstone, 2006).

Women on average have larger corpus callosums especially in the region of the splenium (Aboitiz, 1992; Davatzikos & Resnick, 1998). This increased connectivity has been hypothesized to underlie and facilitate more bilateral processing through efficient intra-hemispheric communication (Davatzikos & Resnick, 1998). It is possible that spatial neglect would be more severe post-stroke in men when compared to women due to women possessing a greater ability to compensate for right hemisphere unilateral damage through more efficient recruitment of left hemisphere areas on visuospatial tasks. Unilateral spatial neglect (USN) following brain damage is often defined as the inability to attend to or respond to space contralateral to the damage, not attributable to a primary sensory or motor deficit (Heilman, Watson, & Valenstein, 1994). This definition does not capture the heterogeneity of neglect, but can be considered 'descriptive shorthand' signifying a breakdown in visuospatial processing at one or multiple separate levels in a multifaceted set of cognitive processes (Halligan & Marshall, 1992). Varieties of USN can be distinguished on the basis of sensory modality, regions of space affected, reference frame, or mode of output (for review see Hillis, 2006; Vallar, Borrini, & Paulesu, 2003). The possible dissociations in visuospatial task performance (Chatterjee, 1994; Halligan & Marshall, 1992; Hillis et al., 2005) between multiple neglect tasks and types of neglect (egocentric or allocentric) make it difficult to determine if USN is "present" unless multiple tasks for different types of neglect are administered (Azouvi et al., 2002).

Lesion studies of USN have suggested that there may be no difference between genders in frequency or severity of neglect (McGlone, Losier, & Black, 1997; Ringman, Saver, Woolson, Clarke, &

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Adams, 2004); however, the studies have been inconclusive due to any of the following factors: limited task number, the time frame (post-stroke) of testing, small sample size, mean age within each gender group, variability of lesion volume, or any combination of these factors. Azouvi et al. (2002) studied a large number of patients (386 with right hemisphere damage on CT) but used only two tasks, description of the "cookie theft" and tactile extinction. They showed no differences in USN based upon gender. McGlone and colleagues described 71 right-handed right hemisphere stroke patients (46 men, 26 women). These patients were tested (but with no set time-point) within two months of stroke on a series of USN tasks (McGlone et al., 1997). Lack of observed differences could be due to the fact that men or women may have recovered faster. Our present study examines a large sample of right-handed men and women for symptoms of USN on multiple bedside paper and pencil tests within 24 hours of stroke, to determine if there are gender differences in severity, frequency, or type of neglect in the acute stage post-stroke.

2. Methods

2.1. Patients

From 1999 to 2006 a consecutive series of 312 (157 men, 155 women) right-handed patients were studied within 24 hours of right hemisphere ischemic stroke confirmed by imaging (MRI in nearly all cases; patients with contraindication for MRI had CT scans). All patients provided informed consent for the study, using methods and consent forms approved by the Johns Hopkins Institutional Review Board. Exclusion criteria included the following: altered level of consciousness, left-handedness, educational level less than 10th grade (for reading tasks), ongoing sedation, or hemorrhage.

2.2. Neglect testing

Tests of USN included the following: copying a scene of two trees, a house, and a fence (Ogden, 1985); modification of the line cancellation test (Albert, 1973); line bisection (270 mm), in which the page was presented 45° to the left and 45° to the right of the midsagittal plane and at the midsagittal plane of the viewer (25–30 cm from the trunk); clock copy; reading words; reading sentences; and oral spelling. Visual and tactile extinction were defined as the ratio of left-sided stimuli perceived with unilateral stimulation to the left-sided stimuli perceived with bilateral stimulation. Presence of extinction is defined as a ration of >2:1 for unilateral versus bilateral stimulation. Patients may not have completed all tasks due to patient preference or interruption for clinical care.

2.3. Statistics

Performance was scored using error rates both as continuous measures (percent error) and as categorical measures. For categorical analyses, presence of neglect was defined in a dichotomous way as >10% error versus $\leqslant$10% error on each test. Tasks were scored as 100% error when the patient attempted to perform the task but could not perform it at all because of the severity of their neglect (e.g. a patient unable to "see" the page when presented in the left hemi-field due to neglect). Patients were only scored as 100% error when inability to perform the task was most likely attributable to USN as determined by the trained research assistant that administered and scored the tasks. Comparison between men and women was made using Student's *t*-tests (for continuous results) and chi-squared tests (for dichotomized results), using Stata version 8.0 for Macintosh. A composite rating of any neglect ($*$ in Table 1) was defined as at least 10% error on any of the following: line bisection, line cancellation, copy scene, or line bisection 45° left of midline.

3. Results

The patient population, consisting of 157 men and 155 women, ranged in age from 24 to 95. See Table 1 for demographics and results. Men were on average 3 years younger than the women in this sample ($p = .04$). When mean percent error was compared for men versus women for each of the previously described neglect tests, no differences were found. For example, on the line cancellation task, a commonly used test of neglect, men and women had

Table 1
Demographic information and task performance are shown above

Task	Men	Women	Statistic	Sample size
Population (312)	50.3%	49.7%		157M/155W
Mean age ± *SD*	60.8 ± 14.0	64.25 ± 15.6	$p = .04$	157M/155W
Age range	26–89	23–95		
Mean error rate ± SD (as a percentage)				
Oral reading	17.4 ± 26.5	20.6 ± 30.1	$p = .38$	113M/117W
Vertical reading	16.0 ± 26.3	10.0 ± 16.3	$p = .27$	33M/33W
Copy scene	24.1 ± 32.8	24.7 ± 30.8	$p = .88$	141M/133W
Clock copy	16.5 ± 29.4	18.6 ± 29.0	$p = .57$	133M/122W
Line cancellation	15.1 ± 28.8	13.5 ± 26.1	$p = .64$	138M/126W
Line cancellation 45° left of midline	14.7 ± 30.9	12.9 ± 28.0	$p = .65$	129M/113W
Line cancellation left side of page	16.4 ± 32.5	15.3 ± 31.0	$p = .79$	135M/124W
Line Bisection	11.4 ± 16.0	13.6 ± 20.1	$p = .30$	142M/126W
Line bisection 45° left of midline	12.1 ± 22.5	16.4 ± 36.8	$p = .25$	138M/123W
Mean ratio				
Tactile extinction, mean ± *SD*	2.0 ± 3.2	2.4 ± 9.4	$p = .66$	131M/114W
Visual extinction, mean ± *SD*	2.0 ± 3.3	2.9 ± 9.7	$p = .37$	131M/112W
Prevalence of neglect				
Copy scene >10% error	43% (61)	49% (65)	$\chi^2 = 0.87$, $p = .35$	141M/133W
Line cancellation >10% error	25% (34)	21% (27)	$\chi^2 = 0.38$, $p = .54$	138M/126W
Line cancel left midline >10% error	23% (30)	20% (20)	$\chi^2 = 0.30$, $p = .59$	129M/113W
Line bisection >10% error	29% (41)	35% (44)	$\chi^2 = 1.13$, $p = .29$	142M/126W
Neglect on any task ($*$)	45.3%	46.4%	$p = .86$	128M/112W

Mean error rate ± *SD* is listed as a percentage. ($*$) The incidence of USN when assessed as a single measure based upon >10% error on any of the following: line bisection, line cancellation, copy scene, and line bisection 45° left of midline.

Table 2
The incidence of USN, reported as a (%) and patients with neglect/total sample size, in each age group when assessed as a single measure based upon >10% error on any of the following: line bisection, line cancellation, copy scene, and line bisection 45° left of midline

Age	Men (%) neglect/total sample	Women (%) neglect/total sample
<40	(30) 3/10	(20) 1/5
40–49	(40) 10/25	(18.8) 3/16
50–59	(30.3) 10/33	(28.6) 6/21
60–69	(50) 13/26	(38.1) 8/21
70–79	(59.1) 13/22	(66.7) 16/24
80 and older	(75) 9/12	(72) 18/25
Total	(45.3) 58/128	(46.4) 52/112

Results were non-significant for all age ranges, but in comparison to the other age ranges (40–49) approached significance ($\chi^2 = 2.03$, $p = .19$).

percent error scores of 15% and 13.5%, respectively ($p = .64$ for difference), and similar non-significant result held across all of the other tasks (see Table 1). In addition, on some tasks men outperformed women (e.g. line bisection), whereas on others women outperformed men (e.g. line cancellation).

For categorical analysis, when performance was defined as at least 10% error on a task, similar patterns were seen without any difference between men and women. In addition, when neglect was defined more broadly as >10% error on either line bisection, line cancellation, copy scene, or line bisection 45° left of midline, no difference in the occurrence of USN was found between genders. Multiple cutoffs for severity were tested to determine if mean error rate "masked" observable differences in severity, but no matter how the groups were determined (worst 10%, 25%, 50%, etc.), there were no differences between the men and women. When patients were categorized in groups based upon age and incidence of USN symptoms (see Table 2), no differences were found between genders. For example, the incidence of USN for 50–59 year old men and women was 30.3% and 28.6%, respectively ($p = .89$). Non-significant results held across all age ranges, although some age ranges (40–49) approached significance ($\chi^2 = 2.03$, $p = .19$) in comparison to the nearly equal results for all other age ranges.

4. Discussion

In comparison to previous studies, ours had the advantage of a large sample size giving us a greater statistical power to detect gender differences. Despite this, we detected no differences between men and women in performance on tests of neglect. We also administered a large number of tests within 24 hours of acute stroke minimizing the likelihood of differences in: (1) compensatory strategies, (2) practice effects (from differences in type of rehabilitation or access to rehabilitation), and (3) rate of recovery or reorganization that may confound possible observable differences in the more chronic stage of stroke. As discussed earlier, the fact that USN is multifaceted forces the analysis to focus on each individual test separately, because there is no one area of the brain that allocates attention and influences performance for all tests of USN. Therefore, we also looked for gender differences in neglect frequency or severity on each test, in case men and women have different types of USN. Multiple cutoffs for severity (categorical analyses) were used to determine if men and women differed in severity. These additional analyses were performed to determine if mean error rate had masked subtle severity differences. These multiple analyses showed no difference between genders on any neglect task. Furthermore, when we categorized patients based upon age, no significant differences were found in the incidence of neglect between genders. The trend for increased prevalence of neglect in young men (40–49 year old), may not be a manifestation of true spatial processing differences, but differences in stroke volumes. Unfortunately, this hypothesis cannot be accurately assessed in the current study, and would require further research.

Our results may differ with respect to previously reported gender distinctions regarding visuospatial processing due to differences in the subject population. In most previously reported studies assessing visuospatial processing (in normals), the subjects are generally young undergraduate or graduate students with relatively high circulating androgen levels (in the males). These differences are exemplified by the data from a recent meta-analysis (Voyer et al., 1995). A large number of spatial processing studies (286) were assessed; only three of these studies investigated a population of subjects with an age range similar to our study (Blum, Fosshage, & Jarvik, 1972; Robert & Tanguay, 1990; Schwartz & Karp, 1967), and all found no difference in visuospatial abilities based on gender. Therefore, even for normal subjects few data exist for this age group regarding spatial processing differences (while there are data for younger age groups). Our study population was older, suggesting most women would be postmenopausal and men would have lower levels of androgen. The effect of androgens on cognitive performance cannot be discussed here in detail, although they provide a fascinating possible explanation for observed performance differences in young (normal) individuals in other studies of cognitive performance (see Aleman, Bronk, Kessel, Koppenschaar, & Van Honk, 2004; Hampson, 1990; Imperato-McGinley, Pichardo, Gautier, Voyer, & Bryden, 1991; Janowsky, Oviatt, & Orwoll, 1994; Kimura, 2002; Voyer et al., 1995; Van Goozen, Cohen-Kettenis, Gooren, Frijda, & Van De Poll, 1994).

In summary, the effects of unilateral right hemisphere stroke on attentional skills seem similar between genders. At the hemispheric level, these data suggest that both neglect incidence and severity are similar between genders on the tasks we administered. The effect of precise location and volume of lesion on cognitive function could not be assessed with this sample because not all patients had digital images available for volumetric analysis. The fact that qualitatively men performed better on some tasks, while women performed better on others, suggests that although our sample size is large, there is still variability in test performance creating trends. The limitations in our study included the use of paper tasks, which do not allow for accurate measures of reaction time and time to task completion for each patient. In the future, reaction time and task completion time may be used to assess visuospatial processing (in addition to percent error). Computerized tasks may allow for a measure of visuoprocessing speed, which is an important factor in everyday function. For example, if a person can process visuospatial information with minor errors on paper and pencil tasks, but takes extraordinary amounts of time to do so, they functionally are performing poorly. Without timing or filming these tasks, this data is lost, and significant information regarding visuospatial processing is also not recognized. Therefore, although gender differences in USN are not observed in our sample, this does not preclude the possibility that differences in accuracy and response time may be present on computerized tests of visuospatial performance when speed is measured. In addition, gender differences in recovery rates may lead to gender differences within the chronic stage of stroke (Farne et al., 2004). If this result were found, it would be imperative to determine if there is selection bias for testing and follow up based upon gender. These results, along with those reported by McGlone et al. (1997) and Azouvi et al. (2002), strongly suggest that there are no differences in severity and incidence of neglect between genders for: visual spatial perception reflected in description of a complex picture, tactile extinction, line bisection, line cancellation, copy scene, clock copy, oral reading words, oral reading of sentences, or gap detection on the right or left. These data do not prove that there is no difference in performance between men and women on visuospatial tests

(like mental rotation) for our age group, but to our knowledge there are no reported differences. The lack of statistically distinct performance characteristics between genders in the current data is important due to the potential publication bias for positive studies.

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