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Brain activation during episodic memory retrieval: Sex differences

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Abstract

Behavioral studies have shown a tendency for women to outperform men on episodic memory tasks. Here, data from a series of positron emission tomography (PET) studies were analyzed to examine sex differences in brain activity associated with episodic memory retrieval (yes/no recognition). A total of 17 women and 17 men were included in the analyses. The strongest effect of the design was a retrieval-related increase in activity, involving right prefrontal and anterior cingulate regions, that was common to women and men. In addition, a significant task-by-sex interaction effect was observed which involved a distributed set of brain regions, including several frontal areas. These results suggest that while the neural correlate of episodic memory retrieval is largely the same for men and women, some differences do exist. Possible explanations for the observed differences are discussed, and it is concluded that biological and experiential factors jointly contribute to sex differences in brain activity. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Brain activity; PET; Sex differences; Episodic memory

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1. Introduction

Functional neuroimaging studies have identified several brain regions, including prefrontal, medial parietal, medial temporal, and cerebellar regions, whose activity is associated with components of episodic memory retrieval (Cabeza & Nyberg, 2000). Many of the studies that contributed to establish this association included both female and male subjects, suggesting that the activation pattern for episodic retrieval generalizes across gender groups. However, to the best of our knowledge, formal analyses of gender differences in the functional neuroanatomy of episodic memory have not been presented, likely due to limited statistical power to detect gender differences in individual studies. The purpose of the research to be reported here was to use data from a series of positron emission tomography (PET) experiments to explore gender differences in the neural correlates of episodic memory retrieval. We start by presenting a brief review of cognitive studies of gender differences in episodic memory, followed by an overview of functional neuroimaging studies of gender differences in various cognitive domains.

In addition to the well-known differences between men and women in visuospatial (men > women; Voyer, Voyer, & Bryden, 1995) and verbal abilities (women > men; Hyde & Linn, 1988), a number of studies have reported that women outperform men in episodic memory tasks (see Herlitz, Nilsson, & Bäckman, 1997). Performance differences have been found from age 5 (Kramer et al., 1997) to age 75 (Herlitz et al., 1997), and are typically smaller in recognition tasks (i.e., effect size $d \approx 16$) than in recall tasks (i.e., effect size $d \approx 27$; Herlitz, Airaksinen, & Nordström, 1999). The advantage women have over men in episodic memory is evident when the material to be remembered is words (e.g., Kramer, Delis, & Daniel, 1988), stories (e.g., Hultsch, Masson, & Small, 1991), concrete pictures (e.g., Herlitz et al., 1999), faces (e.g., Wahlin et al., 1993), locations (Eals & Silverman, 1994), and odors (Lehrner, 1993). No sex differences have been found in recognition of abstract pictures (Herlitz et al., 1999; Lewin, Wolgers, & Herlitz, 2000) and of unfamiliar odors (Öberg, Larsson, & Bäckman, 2000). This pattern of findings has been taken to indicate that women will outperform men in episodic memory tasks in which verbal processing is required or can be used, whereas no differences between men and women will be found when verbalization of the material is inhibited (Lewin et al., 2000). Given that women excel in episodic memory tasks in which verbalization is possible, it is possible that this advantage is linked to women's higher verbal ability. However, women do not show higher performance in all verbal tasks, but rather in verbal fluency or verbal production tasks (Hyde & Linn, 1988). The common cognitive operation in episodic memory tasks and verbal production tasks may be that they require rapid access to and use of information in memory (Halpern, 1997).

Guided by sex differences in behavioral performance, several imaging techniques have been used to study sex differences in the brain's structural and functional organization. This includes analyses of differences in brain anatomy (e.g., Gur et al., 1999), analyses of differences in temporal responses (e.g., Reite, Cullum, Stocker, Teale, & Kozora, 1993; Skrandies, Reik, & Kunze, 1999), and analyses of differences in regional cerebral glucose metabolism during rest (e.g., Gur et al., 1995). Of main concern here is analyses of sex differences in hemodynamic responses in cognitive activation studies.

Wendt and Risberg (1994) used xenon technology to study cerebral blood flow (CBF) in males and females during rest and three visuospatial tasks. They observed higher global CBF in females than in males in all three visuospatial tasks. However, as females also showed higher global CBF during rest, these data do not constitute evidence for a task-related sex difference in global CBF. Esposito, Van Horn, Weinberger, and Faith Berman (1996) used PET to measure CBF in males and females while they performed three non-verbal neuropsychological tasks linked to prefrontal cortex (Wisconsin Card Sorting, Delayed Alteration task, Spatial Delayed Response Task) and three sensorimotor control tasks, none in which behavioral sex differences could be expected. In agreement with the Wendt and Risberg study, they found that females had higher global CBF than males across the six tasks. More detailed analyses revealed that the effect of sex on global CBF varied across tasks such that it was significant for the neuropsychological tasks, but not for the control tasks. Hence, these findings indicate that gender differences in CBF vary as a function of cognitive state.

Buckner, Raichle, and Petersen (1995) used PET to measure regional CBF in males and females while they performed verbal production tasks (stem completion or verb generation) and control tasks. Relative to the control tasks, increased activity was observed in left prefrontal cortex during both speech tasks. This was true for both sexes, but the magnitude of left prefrontal activity during verb generation was greater for males than for females. Shaywitz et al., 1995 (see also Pugh et al., 1996) used functional magnetic resonance imaging (fMRI) to explore sex differences in brain activation while subjects performed various language tasks. When phonological processing was required, male subjects activated left inferior frontal gyrus. By contrast, inferior frontal activation was bilateral for females. Small sex differences in brain activation were also observed in an fMRI study of verbal fluency (Schlösser et al., 1998). In the latter study, similarities in patterns of brain activity for males and females were emphasized, which is in agreement with a recent large-scale fMRI analysis of sex differences in brain activity during a language comprehension task (Frost et al., 1999).

A final example comes from a recent fMRI study of brain activation in male and female subjects when they searched the way out of a complex virtual-reality maze (Grön, Wunderlich, Spitzer, Tomczak, & Riepe, 2000). Men and women activated several regions in common, but reliable differences were observed as well. Specifically, men differentially recruited the left hippocampal region whereas women differentially activated right fronto–parietal regions. These differences were seen as differentiating male from female subjects in navigation.

Taken together, functional neuroimaging studies of cognitive functions suggest that, although subtle, task-related sex differences in hemodynamic responses exist. Together with documented behavioral sex differences in various cognitive domains, including episodic memory, this pattern of results prompted us to look for sex differences in the functional neuroanatomy of episodic memory retrieval. To ensure reasonable statistical power to detect differences, data from three previous PET studies of episodic memory were aggregated (Nyberg et al., 1995, 1996a, 2000). Common to all three studies was that they included two conditions which did not put demands on episodic retrieval (baseline/reference conditions), and two conditions that involved yes/no recognition. The type of information (words, sentences, pictures) and the way the information was acquired (incidental/intentional encoding) differed across studies, as did the compatibility between the study and test modality (auditory–visual; visual–visual). What was common across studies was that subjects in all studies were engaged in a *retrieval mode* (Tulving, 1983) during the recognition tasks but not during the reference tasks. Retrieval mode has been defined as "a neurocognitive set, or state, in which one mentally holds in the background of focal attention a segment of one's personal past, treats incoming and on-line information as "retrieval cues" for particular events in the past, refrains from task-irrelevant processing, and becomes consciously aware of the product of successful ecphory, should it occur, as a remembered event" (p. 506, Lepage, Ghaffar, Nyberg, & Tulving, 2000). Previous studies show that a robust response associated with retrieval mode is increased activity in frontal brain regions (Cabeza & Nyberg, 2000; Lepage et al., 2000). Guided by these previous studies, we were especially interested in similarities and differences in brain activity in frontal brain areas for females and males. Moreover, sex differences in imaging studies have been claimed to be particularly prevalent in frontal brain regions (see e.g., Esposito et al., 1996).

2. Methods

Subjects. The aggregated data set involved 17 females (mean age = 28, range = 20–40) and 17 males (mean age = 27, range = 22–37). They were all right-handed and gave written informed consent.

PET methods and procedure. In all studies, PET scans were obtained with a GEMS-Scanditronix PC2048-15B head scanner using bolus injections of $^{15}O–H_2O$. Data were collected using blocked-trial designs (60 s acquisition scans). The experimental procedure varied between studies in several respects, and different reference tasks were used (see Table 1 for study-specific information). Common to all studies was that the subjects were tested for their memory of material that had been presented in the experimental setting by means of a visual yes/no recognition test.

Data processing and analysis. Realigned, normalized, and smoothed (to 10 mm) images were taken from each study (images were preprocessed using SPM-95 and SPM-96). All of the images were translated to conform to the brain atlas of Talairach and Tournoux, 1988. The peaks of activations will be described according to their location (in mm) in the (x) medial/lateral (positive x-values refer to right hemisphere), (y) anterior/posterior, and (z) superior/inferior dimensions.

Statistical analyses were done using *partial least squares* (PLS; McIntosh, Bookstein, Haxby, & Grady, 1996). For each subject, the mean of every voxel across all the scans was set to 0. This eliminates the main effect of gender, but improves cross-study/cross-subject comparisons (see Cabeza et al., 1997). For males and females, the two baseline and two retrieval conditions were averaged to yield one condition of

Table 1
Summary table for the three component studies

Study	Memory task[a]	% Studied test items during scan interval	Baseline task[b]	Material	# Scans/ condition	Modality (study-test)	# Subjects (female/ male)
Nyberg et al. (1995)	Yes/no recognition	100	Silent reading	Single words	2	Auditory–visual	6/5
Nyberg et al. (1996a)	Yes/no recognition	50	Silent reading	Single words	1	Visual–visual	7/5
	Yes/no recognition	50	Intentional encoding	Single words	1	Visual–visual	
Nyberg et al. (2000)	Yes/no recognition	100	Intentional encoding	Sentences	1	Visual–visual	4/7
	Yes/no recognition	100	Intentional encoding	Land-scapes	1	Visual–visual	

[a] Subjects responded by pressing the left mouse button if they recognized an item, and the right if they did not recognize an item.
[b] Subjects pressed any of the two mouse buttons after reading each word.

each. A task PLS-analysis was then conducted with four conditions: male-baseline, male-retrieval, female-baseline, female-retrieval. This analysis can reveal main effects of condition and sex by condition interactions. Such effects are expressed in latent variables (LVs). One component of the LV is a contrast between conditions that represents the effect (e.g., retrieval vs. baseline across sex). The other component is the pattern of brain voxels that shows the effect that is represented by the contrast.

To assess the significance of observed sex differences, a permutation test (500 permutations) was used to determine whether random assignment of subjects would produce results as robust as those observed. That is, it was explored whether LVs would be identified that accounted for as much of the contrast-image covariance if subjects were assigned randomly to "male" and "female" groups as was observed when subjects were correctly assigned (for a similar approach to significance assessment of sex differences, see Frost et al., 1999). Finally, the reliability of activations within voxel patterns was assessed using a bootstrapping procedure (Grady, McIntosh, Rajah, & Craik, 1998). All regions that will be discussed had a salience > 4.0 ($P < 0.0001$) and a size of 50 or more voxels (when plotted at a threshold of 1.96).

3. Results

Analyses of the behavioral data revealed no sex differences. Mean hit rate across the three studies was 0.75 (S.D. = 0.02) for females and 0.74 (S.D. = 0.05) for males. To get an estimate of false alarm rates for males and females, we also analyzed behavioral data from scans during which only non-studied items were presented. On average, females had a false alarm rate of 0.17 and males a false alarm rate of 0.08 ($t = 1.97$, $P > 0.05$).

The first LV from the PLS-analysis distinguished between the retrieval and reference conditions across sex groups ($P < 0.001$). Retrieval-related activations are shown in black in Fig. 1. In keeping with previous studies, increased retrieval-related activity was observed in right prefrontal cortex ($x, y, z = 30, 24, 4; 32, 46, 8$) and in the anterior cingulate gyrus ($x, y, z = -4, 28, 28; 10, 26, 32$). Increased activity was also strong in midline occipital–parietal cortex ($x, y, z = 8, -78, 20$).

The second LV distinguished between the retrieval and reference conditions as a function of gender group ($P < 0.001$). For one set of regions, activity was increased during retrieval compared to baseline for females. By contrast, for males, the change in activity between baseline and retrieval was weaker or in the opposite direction. These regions are marked in white in Fig. 2. The response of the most salient frontal regions is plotted as a function of condition and gender in Fig. 3(a). Two of these regions were located in the anterior cingulate gyrus ($x, y, z = 12, 28, 40; -16, 32, 20$), and one in right inferior frontal cortex ($x, y, z = 18, 32, -16$). Other salient regions were located in right fusiform ($x, y, z = 58, -56, -16$) and parietal ($x, y, z = 32, -24, 32$) cortex and in the cerebellum ($x, y, z = 20, -68, -24; -6, -46, -20$).

For another set of regions, activity increased during retrieval compared to baseline for males whereas the change in activity between baseline and retrieval was weaker or in the opposite direction for females. These regions are marked in black in Fig. 2. The response of the most salient frontal regions is plotted as a function of condition and gender in Fig. 3(b). The frontal regions were located in bilateral inferior frontal cortex ($x, y, z = -56, 22, 8; 48, 14, 12$), in or near Brodmann areas 44 and 45. Other salient regions were located in bilateral inferior temporal ($x, y, z = -56, -26, -16; 58, -26, -24$) and parietal ($x, y, z = 46, -52, 32; -46, -58, 16$) cortex and in the posterior cingulate cortex ($x, y, z = 6, -62, 28$).

4. Discussion

The purpose of the present study was to explore sex differences in the neural correlates of episodic memory retrieval. Our data-analytic approach provided some indication on the relation between differences and similarities in activation patterns across sexes. The strongest effect of the design was a retrieval-related effect that was common to males and females, hence suggesting that similarities were more pronounced than differences. As discussed in the introduction, this seems to be in agreement with the majority of results from previous cognitive brain imaging studies comparing activation patterns for females and males. Our finding that results seem to generalize across men and women is important in that it suggests that it is possible to generalize PET results from episodic retrieval studies even if different sex ratios are used in different studies (for a similar point in the context of language, see Frost et al., 1999).

Notwithstanding the fact that activation patterns largely overlapped for males and females, reliable sex differences were observed as well. The robustness of this sex

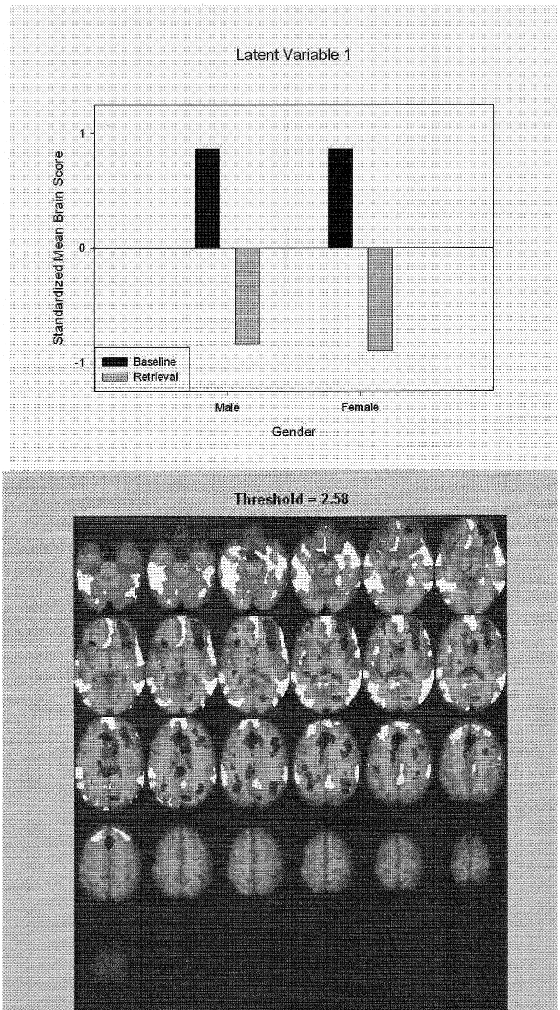

Fig. 1. The graph at the top corresponds to standardized mean brain scores for the first (LV1) pattern of activation identified by the PLS analysis. As shown by the distribution of scores across conditions and groups, the graph describes a difference between retrieval and baseline that was common to both sexes. The amount of cross-block covariance accounted for by this LV was 79%. Below, on a standard MRI template, brain regions are shown in which activity was positively (white) and negatively (black) associated to the pattern of activation in the top graph (i.e., regions which showed increased activity during retrieval relative to baseline are displayed in black). The image was thresholded at 2.58 ($P < 0.01$). The horizontal slices are at intervals of 4 mm from $z = -28$ mm below the anterior/posterior commissure (AC–PC) line (top left slice). Right/left in the image is right/left in the brain.

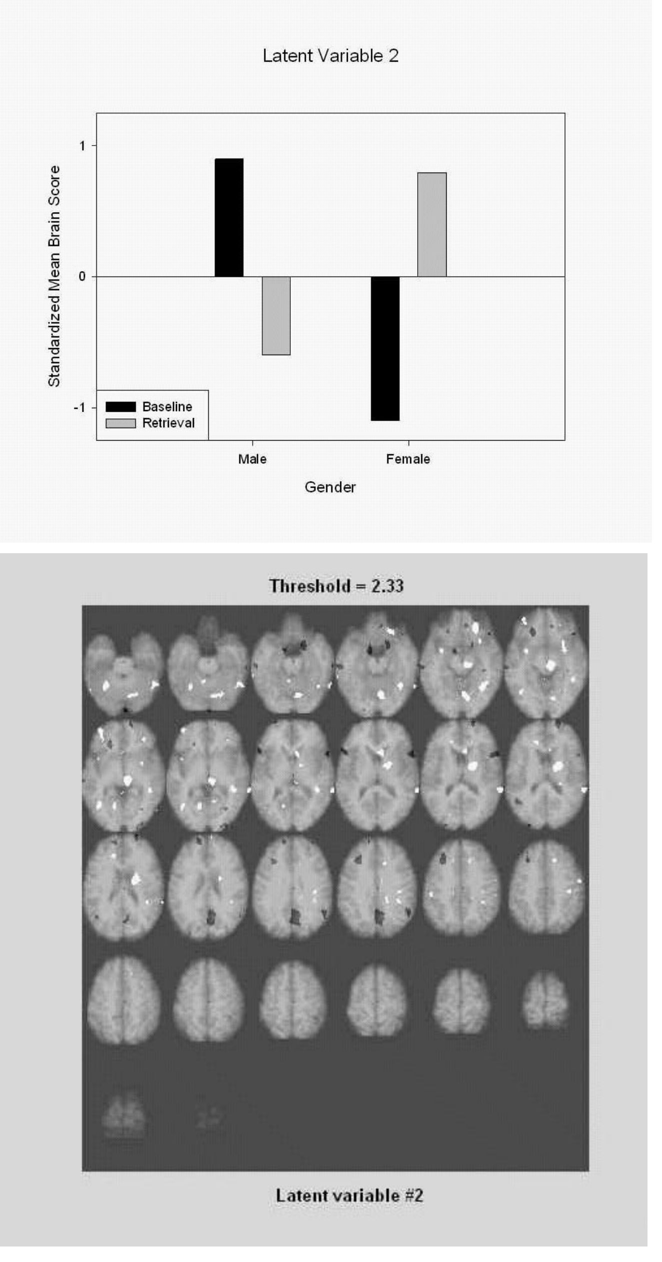

Fig. 2. Scores and brain regions associated with LV2 (task by group interaction). The amount of cross-block covariance accounted for by this LV was 21%. Regions in white are those for which females showed increased activity from baseline to retrieval, whereas regions in black are those for which males showed increased activity from baseline to retrieval. The image was thresholded at 2.33 ($P < 0.025$). For details, see legend to Fig. 1.

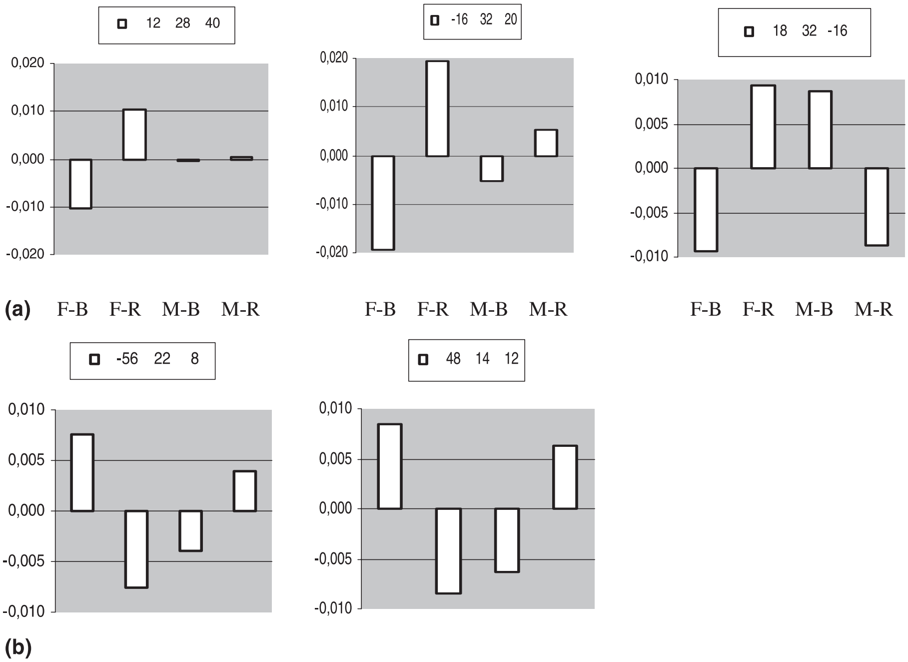

Fig. 3. Changes in frontal regional activity as a function of group and condition. (a) Frontal brain regions showing retrieval-related increases for females and weaker increases or decreases for males; (b) frontal brain regions showing retrieval-related increases for males and decreases for females. In both (a) and (b), the *y*-axis shows adjusted CBF and the *x*-axis, type of condition. Abbreivations: F-B = female-baseline; F-R = female-retrieval; M-B = male-baseline; M-R = male-retrieval.

effect was assessed by a permutation test that effectively compared the strength of the effect associated with the ''real'' group distinction (females vs. males) with the effects associated with 500 random constellations. We also a priori created a random grouping and compared the strength of an interaction effect involving the random groups with the strength of the interaction effect associated with the female–male grouping (data not shown). It was found that the amount of cross-block covariance accounted for by the real grouping (0.208) was about twice that of the random grouping (0.115). All in all this indicates that there are reliable sex differences in brain activation patterns associated with episodic memory retrieval.

Before discussing the differential activation patterns in more detail, it should be noted that there were minimal sex differences in memory performance. Reliable sex differences in brain activity patterns along with lack of differences in behavioral performance have been reported previously (e.g., Jaeger et al., 1998), and there need not be a conflict between these outcomes (for an example of differences in activation patterns related to episodic memory for young and old, despite comparable behavioral performance, see Cabeza et al., 1997). It should nevertheless be of importance to take the behavioral similarities into account when the neural differences are interpreted. One possibility is that identical retrieval processes are carried out with equally good net result (memory performance) using partly differently organized neural systems. [1] Another possibility is that the neural sex differences actually do map on to behavioral differences, but more sensitive measures are necessary to reveal such differences. For example, as noted in the introduction, sex differences are typically much more pronounced in recall than in recognition tasks. Future studies are needed to determine whether the observed sex differences in episodic retrieval brain activity patterns generalize across retrieval tasks and are associated with sex differences in behavioral performance when more demanding tests are used.

For both females and males, episodic retrieval was associated with activation of right prefrontal and anterior cingulate regions. As discussed in the introduction, in previous studies, these regions have been related to *episodic retrieval mode* (cf., Cabeza & Nyberg, 2000; Lepage et al., 2000). In light of the strong association between episodic retrieval and the frontal lobes, it is interesting to note that several of the most salient peaks of the activation patterns that differentiated males and females fell in the frontal lobes. Of particular interest are the selective activity increases in the anterior cingulate gyrus for females. These sites were in close proximity to the anterior cingulate regions associated with the common effect, which may indicate sex differences in the neural correlates of retrieval mode per se. While further attempts at interpreting these regional differences seem premature and are clearly post-hoc, some general comments will be offered.

Females showed a stronger increase in activity from baseline to retrieval than males in two regions of the anterior cingulum. Also, activity in a right inferior frontal region increased during retrieval relative to baseline for females, whereas activity in this region was higher during baseline than during retrieval for males. Regions in the anterior cingulate cortex have been found to show increased activity during many cognitive tasks, including attention (Stroop) tasks, working memory tasks, semantic generation tasks, and episodic memory tasks (Cabeza & Nyberg, 2000). In keeping with anterior cingulate activation across many cognitive domains, this region has been pointed out as a center for *executive attention* (see Posner, 1995). It might be speculated that higher activation of anterior cingulate for females underlie their tendency to perform better than males on attention demanding tasks that require response selection, such as recall and fluency tasks.

Males showed increased activity during retrieval compared to baseline in bilateral inferior frontal cortex, near Brodmann areas 44 and 45. By contrast, for females the opposite pattern was observed. In fact, numerically, the magnitude of the decrease in activity from baseline to retrieval for females exceeded the activity increase that was seen for males. Increased activity in the vicinity of left area 44/45 has been observed in several tasks that require semantic processing including reading, verbal working memory, and semantic generation (Cabeza & Nyberg, 2000). By contrast, inhibition of semantic processing (e.g., spread of activation) could be an important component

[1] We acknowledge that memory performance is not only a function of the effectiveness of retrieval operations, but also encoding processes. An interesting future task is to examine sex differences related to encoding processes.

of episodic retrieval (Nyberg et al., 1996b). On basis of these prior findings, it might be speculated that the observed difference in inferior frontal cortex, at least in the left hemisphere, reflects sex differences in the ability to initiate and inhibit semantic processing.

We have focused on differences in frontal activations, but it should be noted that differences in activation patterns were also observed outside the frontal lobes. Salient peaks of the voxel patterns that were associated with the group-interaction effect included regions in cerebellar, temporal, parietal, and posterior cingulate cortex. This is not surpring. For one thing, sex differences have been demonstrated at the level of primary visual cortex (Levin et al., 1998). Moreover, episodic memory, with all its component processes, seems to be mediated by a distributed set of frontal and non-frontal brain regions (Cabeza & Nyberg, 2000). Indeed, sex differences may best be described at the network level rather than at the regional level, and it is possible that future studies will detect group differences in inter-regional connectivity (for network analyses of group-differences, see Nyberg & McIntosh, 2000).

In conclusion, while the functional neuroanatomy of episodic memory retrieval is similar for females and males, notable differences seem to exist as well. Given that our finding of significant sex differences in brain activity is true, the basis for this effect remains to be explained. One hypothesis, receiving increasing support, is that gonadal hormones during prenatal and neonatal development influence brain organization and later behavior (Collaer & Hines, 1995). Most results within this area have been derived from animal research. For example, sex differences exist in brain regions that have receptors for binding or metabolizing gonadal hormones, such as the hippocampal formation (Desmond & Levy, 1997; Gould, Woolley, & McEwen, 1991) and corpus callosum (Fitch & Denenberg, 1998). In humans, active estrogen later in life appears to influence neuronal communication in production of both hippocampal synapses and cholinergic neurons, possibly resulting in the occasional positive reports of exogenous estrogen on cognition (e.g., Kimura, 1995). A masculinizing effect of androgens on cognition (i.e., visuospatial skills) and behavior (i.e., more male than female typical juvenile play) has repeatedly been seen in women with a prenatal exposure to androgens (e.g., Resnick & Berenaum, 1982). Another possibility is that sex differences in brain organization are the result of experiential factors. Evidence supporting this hypothesis comes from results showing structural modifications in the rat visual cortex and hippocampus following environmental changes (Torasdotter, Metsis, Henriksson, Winblad, & Mohammed, 1998), and from demonstrations of changes in cortical representations after specific experiences (Ungerleider, 1995). This leaves open the possibility that it is not sex per se that explains differences, but environmental factors which, in our society, tend to co-vary with sex (for a recent example of environmental/cultural influences on brain organization, see Paulesu et al., 2000). Of course, biological and experiential factors may jointly contribute to sex differences in brain organization, and more generally, this study may be seen as a step towards a consideration of individual-difference factors when brain activation patterns are interpreted.

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