Gender differences in aging: cognition, emotions, and neuroimaging studies

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Gender and aging moderate brain–behavior relationships. Advances in neuroscience enable integration of neurobehavioral, neuroanatomic, and neurophysiologic measures. Here we present neurobehavioral studies that examine cognitive and emotion processing in healthy men and women and highlight the effects of sex differences and aging. Neuroanatomic studies with magnetic resonance imaging (MRI) indicate that the progressive decrease in brain volume affects frontotemporal brain regions in men more than in women. Functional imaging methods suggest sex differences in rate of blood flow, pattern of glucose metabolism, and receptor activity. The role of ovarian hormones is important in elucidating the observed relationships. A life span perspective on gender differences through the integration of available methodologies will advance understanding healthy people and the effects of brain disorders.

Age and gender effects on cognition and emotion processing

Age effects on cognition have been studied extensively. Measures of intellectual abilities and vocabulary, the “crystallized” abilities, are more resistant to age effects than “fluid” abilities, such as attention and executive functions. There is age-related decline in processing speed. Memory functions seem most affected, particularly those related to source memory (“episodic” or “explicit”). Sex differences in cognition have been well documented. Women perform better on verbal and memory tasks, whereas men excel in spatial tasks. However, sex differences in aging effects have not been established across the life span. Some evidence suggests that women show less age-associated cognitive decline than men. Our data on young adults (age 18–45 years) indicate that men show significant decline in several neurocognitive domains while women evince no decline. However, in small samples of older adults the decline rate seems similar.

We have initially studied sex difference in neurocognitive measures with a standardized battery that examines changes in men than in women. Sex differences are salient in the aging process, and there is increasing evidence for the role of ovarian hormones in mediating behavior and brain function. Therefore, an integrative approach to examining the aging process in men and women, through the application of neuroimaging, can be helpful in elucidating the neurobehavioral differences.

Here is extensive literature documenting the moderating effects of healthy aging and gender on cognition. Convergent multidisciplinary efforts, mostly in young adults, have helped identify neural systems associated with behavioral domains. Age effects on behavior and brain parameters are already observed in young adulthood. These indicate more pronounced age-related

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8 neurobehavioral domains. In a sample of 241 healthy young adults, aged 18 to 45 (124 men, 117 premenopausal women), we have observed sex differences in 3 of the 8 behavioral domains. Women had better verbal memory, and men performed better on spatial and motor tasks. However, we did not observe better performance in women for the language domain (Figure 1). In examining components of domains that show sex differences, we find that the verbal memory advantage for women is accounted for primarily by performance on the California Verbal Learning Test (CVLT, Figure 2), whereas the advantage for men in spatial abilities is accounted for by performance on Benton’s Line Orientation Test.

Some sex differences are manifested not in the profile of abilities, but in the effects of aging within the range of young adulthood. In our sample, no significant correlations were observed between age and any of the behavioral measures in women (correlations ranged from -0.15 to 0.09). For men, however, increased age was associated with decrease in performance on attention (r=-0.43, P=0.0001), verbal memory (r=-0.20, P=0.029), spatial memory (r=-0.34, P=0.0001), and spatial abilities (r=-0.33, P=0.0002) (all df=122, all P values are 2-tailed) (Figures 3 and 4). It would be interesting to examine the associations of these measures with testosterone levels.

We noted several limitations to the traditional battery approach. The battery is lengthy, and each test provides measures that are difficult to link with current knowledge on brain systems regulating behavior. Furthermore, tests comprising such batteries are not readily applied in functional imaging studies, and few alternative forms are available for repeated testing. To address these limi-
Figure 2. Sex differences in verbal learning as measured with the California Verbal Learning Test (CVLT). M1 to M5, Monday lists 1 through 5; Tue, Tuesday (interference) list; SD, short delay; SD-C, short delay–cued recall; LD, long delay; LD-C, long delay–cued recall; REC, recognition.

Figure 3. Correlations of neurocognitive domains with age in healthy controls (aged 18–45 years) for men and women. ABF, abstraction/flexibility; ATT, attention; VMEM, verbal memory; SMEM, spatial memory; LAN, language; SPA, spatial; SEN, sensory; MOT, motor.
iterations, we have developed a set of computerized neuro-behavioral measures aiming specifically at integration with structural and functional neuroimaging studies. Our general approach to task development and validation process was detailed in Gur et al.\textsuperscript{22} Advantages of the computerized battery include: (i) each measure is designed to probe a narrow and well-defined neurobehavioral domain; (ii) more uniform presentation of test stimuli; (iii) errorless data entry and scoring; (iv) availability of reaction time data; (v) shorter time for administration; and (vi) alternative forms can be readily generated using set algorithms. The main disadvantages of computerized testing are: (i) it is more “impersonal”; (ii) some participants, particularly the elderly, dislike computers or require training; and (iii) tests are not yet available for some well-validated indices of language functioning, particularly those involving verbal output (eg, vocabulary, verbal fluency). However, our experience with computerized testing indicates that the first two disadvantages can be overcome, and the third can be addressed with available technology. Most older adults respond well to computerized testing, if approached properly, and we have developed a short module that trains participants in the use of the mouse to the level required for testing. The advantages of computerized testing have been clearly manifested.\textsuperscript{23} The normative data have shown very favorable psychometric characteristics such as high inter-item consistency (Cronbach’s alpha), test–retest reliability, and comparable levels of difficulty (at 70% to 80% correct for the normative sample) and true-score variance. Our efforts to generate the kind of sensitivity that will permit differentiation within healthy people have also been successful. As can be seen in Figure 5, the summary scores show sex differences in young adults. The pattern of sex differences duplicates that obtained with traditional batteries, but adds the finding that women do better in facial memory, not available in the traditional battery. Measures of reaction and testing time provide an efficiency (accuracy/time) index, used to calculate comparable z scores across tests. Algorithms can generate multiple forms for repeated administration, and error analysis is performed for items and parameters to examine strategy and persistence.\textsuperscript{24,25}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scatterplot.png}
\caption{Scatterplot showing the correlation between age and performance in healthy subjects on the attention domain for men and women.}
\end{figure}
Less is known about age effects on emotion processing. Perceiving, experiencing, and expressing emotions seem essential capacities, and more recently the study of emotion has benefited from converging methodologies in animals and humans.26,27 The face has been the main target of study in humans, and methods were applied to quantify expression of emotion with cross-cultural consistency.28-31 Standardized tools have been developed for measuring emotion discrimination,32 mood induction,33,34 affective valence, and arousal.35 Emotional displays that can be reliably coded in the face are happiness, sadness, anger, fear, and disgust (surprise is more controversial). There is also increased agreement that emotion processing is not restricted to the “limbic system” and involves cortical regions, where it seems to be organized, perhaps parallel to the “cognitive” system, along laterality and anterior–posterior dimensions.36-38 There is controversy about whether emotional expression is lateralized, although a meta-analysis by Borod et al39 seems to confirm that negative emotions are expressed more intensely on the left side of the face, whereas the opposite holds for positive emotions.40 There is more agreement, though fewer data, that receptive, experiential, and expressive aspects of emotion processing can be mapped to frontal, temporal, and parieto-occipital involvement, respectively. This interaction between the emotion and cognitive systems,41-43 particularly as it applies to memory, is an issue of current interest.44-52 Large-scale studies with standardized measures53 have indicated that elderly people are in better mood than their young counterparts.54,55 Nonetheless, studies measuring emotion processing suggest some deficits.56 Gross et al57 examined cross-cultural samples for age differences and concluded that older adults reported fewer negative emotional experiences and greater emotional control. However, findings regarding emotional expressivity were less consistent, with older participants reporting less expressivity. There is also evidence that the elderly are more vulnerable than the young to adverse effects of negative emotional states on memory58 and other cognitive abilities. Indeed, it has been suggested that depressed mood is the strongest predictor of health decline in the elderly.59 Sex differences were observed in affect and emotion processing.60-62 Women perform better in speeded emotion recognition tasks63 and in tasks requiring facial expression.

**Figure 5.** Sex differences by function in the computerized battery. ABF, abstraction/flexibility; ATT, attention; VMEM, verbal memory; FMEM, facial memory; SMEM, spatial memory; LAN, language; SPA, spatial; SEN, sensory; MOT, motor.
of emotions. In a study of facial recognition, we reported sex differences in sensitivity to happy and sad expressions depending on the poser’s sex. Women were more sensitive to opposite than to same-sex expressions, whereas men were differentially poor at detecting sadness in female faces. Regarding emotional experience, women are more prone to clinical depression, mood fluctuations associated with phases of the menstrual cycle have been documented, and such phase-associated hormonal changes may relate to cognitive performance. Sex differences in aging may interact with these effects, but systematic data are not available.

**Age effects on brain anatomy related to memory and emotion processing**

Magnetic resonance imaging (MRI) studies of the brain have documented that aging is associated with progressive parenchymal volume decrease and cerebrospinal fluid (CSF) volume increase. The effect is consistent with neuronal atrophy, but the cellular changes accounting for the volumetric findings are still unclear. Brain volume shows small but consistent correlations with cognitive performance. Some studies suggest that the volume decrease with age is in gray matter (GM) tissue, while others report a decrease also in the white matter (WM) compartment. There is more consistency in the regional distribution of effects, with mesolimbic, temporal, and frontal regions showing greater vulnerability. Sex differences have been observed in the compartmental composition of intracranial volumes, in the volume and density of language-associated cortex, and in the rate of age-associated changes. While the data indicate less parenchymal loss in women than in men, particularly for frontal and temporal regions, samples were limited in the elderly cohorts. Our data in the elderly suggest similar rates of tissue loss in men and women, perhaps reflecting an acceleration following menopause. These neuroanatomic findings seem congruent with age-related changes in memory and emotion. Henkel et al concluded that age-related decline in source memory affects “processes involved in binding features into complex memories and [...] contextual features of memories.” Neural substrates for the source memory system implicate the mesial temporal and frontal regions. While the volume of limbic structures was unrelated to cognitive functions across the age range, in older participants reduction predicted declines in explicit memory.

Neural substrates for age-related changes in affect are less clearly defined, although recent work affords some hypotheses that should be tested. Studies on networks for emotion have implicated the amygdala, hypothalamus, mesocorticolimbic dopaminergic systems, and projections to orbital and dorsolateral frontal, temporal, and parietal cortex. Studies in patients with brain lesions support the role of these regions in emotion regulation. The link between age-related changes in neuroanatomy and performance on such tasks has not been established.

To evaluate how these effects extend across age-groups, we have examined whole-brain volumes for young and older adults. The correlation between age and total intracranial volume was nil (r=0.02), indicating no secular drift in head size. For the young (<50 years) sample considered separately, there was a small yet significant correlation between age and GM volume (r=-0.17, df=130, P<0.05). This correlation was higher in men (r=-0.27, df=74, P<0.01) than in women (r=-0.01, df=54, ns). Age did not correlate significantly with WM or CSF volumes in this age-group. For the entire age range, GM continues to decline in volume with aging, r(184)=-0.49, r(92)=-0.52, and r(90)=-0.40 for the whole sample, males and females, respectively, all P<0.0001, whereas the volume of CSF continues to increase with age (the corresponding correlations were 0.31, 0.45, and 0.29, all P<0.0001). WM changes are less clear. Although the correlation with age is not significant for the entire sample, r=0.09, within each sex the correlations were small but positive, r=0.28, P=0.01 and r=0.24, P=0.02. This likely reflects the large sex difference in the volume of WM. We conclude that GM volume is reduced with aging, CSF volume increases concomitantly, while WM volume does not change appreciably and is perhaps increased slightly. While the effects of GM and CSF agree with a recent study by Guttmann et al, their conclusion regarding WM was that its percentage of the intracranial compartments is reduced with aging. In comparing our results on WM, it appears that they examined only percentages and not raw volumes. In the case of Guttmann et al’s study, reduced %WM could reflect age effects on another compartment, for example,
increased CSF. Perhaps the paucity of subjects in our elderly group is matched by the paucity of theirs in the young group (10 participants <40 years). This underscores the need for large samples across the life span. Our sample also enabled examination of whether these volume changes are related to cognitive performance. While the young and elderly participants received age-appropriate neuropsychological batteries, both groups received several identical tests. Most relevant is the CVLT, which measures rate of verbal learning. The total number of items recalled during the memorization trials was correlated with the volumes of brain parenchyma (GM and WM combined), partialling out age. As can be seen in Figure 6, parenchymal volume goes down with age, number of words recalled also declines, and the parenchymal volume is associated with memory (even with age effects partialled out).

Age effects on brain physiologic activity related to memory and emotion processing

The feasibility of studying neural substrates of behavior is enhanced by functional imaging methods for measuring regional brain activity. Activation patterns are linked to performance on cognitive tasks requiring verbal, spatial, attention, memory, and facial processing. The study of age effects on regional brain physiology has been quite extensive, with considerable agreement that cerebral blood flow (CBF) shows age-related decline even in people screened for cerebrovascular disorders.\textsuperscript{94-97} Similarly, measures of neurotransmitter function have shown reduced availability of both dopaminergic and serotonergic transmitter activity.\textsuperscript{98-101} The decline has been linked to performance on behavioral tasks related to the dopaminergic system.\textsuperscript{100,101} The effects of aging on glucose metabolism are less clear, although it too shows
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decline, particularly in frontal and temporal regions. Of most relevance to the study of the memory and emotion systems, Cherrier et al. have examined correlations between mood state self-ratings and cerebral metabolism during PET 18F-FDG in 27 persons with age-associated memory impairment (aged 44–81 years). Specifically, regions involved in both mood and memory had similar abnormalities. There have been reports of boredom related to mesial temporal and parietal asymmetry as well as decreased parietal metabolism. Mood ratings of fatigue correlated with basal ganglia asymmetry and left mesial temporal metabolism. These findings suggest that mood changes may influence metabolism in brain regions implicated in emotion and memory function. There are fewer data on the effects of aging on regional brain activation in response to task demands. Using the 133Xe method, we found substantial age-related decline in overall CBF values, but the pattern of lateralized changes in response to verbal and spatial tasks was identical in young and elderly people. However, we tested tasks that are quite resistant to age effects, and the results may differ for tasks showing greater age-related decline. Indeed, Cabeza et al. found less frontal activation, measured with H215O PET CBF, in elderly people for a memory task. Madden et al. in a CBF study using SPECT reported that several CBF activations were greater for young than for older adults. However, they observed that, although performance demonstrated a greater age-related slowing for visual encoding than for semantic retrieval, these changes were not associated with corresponding changes in rCBF activation. The association between CBF activation and performance, and the effects of aging on this association, merit further elucidation.

Several studies examined emotion processing with functional neuroimaging methods in healthy people. With the 133Xe method for measuring cortical CBF during processing emotional facial expressions, we noted increased right temporoparietal activity. With a mood induction procedure, increased CBF was observed during sad induction and correlated with mood change. In a PET study with H215O, we reported a CBF increase in the left amygdala and a CBF decrease in the right amygdala during sad mood. We found a reciprocal relationship between subcortical and cortical activation. These changes correlated again with a shift in affect. Subsequent studies with PET and functional MRI (fMRI) have confirmed the lesion data, implicating amygdala and anterior brain regions in mood, while posterior regions seem activated in visual emotion discrimination. Unlike neuroanatomic studies that have consistently examined sex differences and age effects, there is a paucity of neurophysiologic studies that have examined these factors. Using the 133Xe CBF method, we reported that women have higher rates of cortical CBF, and this finding was replicated and extended to other methods that measure CBF for the entire cranium. We found about equal rates of age-associated reduction in CBF in men and women, and this has also been reported in other studies, although samples were usually small in the elderly range. No studies have linked changes in CBF activation to sex differences in age-related neuroanatomic changes and to performance of memory and emotion tasks.

More recently, fMRI has been increasingly used for measuring regional brain activation. The method has several potential advantages: higher spatial and temporal resolution, noninvasiveness and lack of ionizing radiation, direct correlation with anatomical imaging, greater repeatability, and economy. The disadvantages of fMRI techniques include: loud background noise generated by the gradients; difficulties in presenting stimuli and performing tasks in the magnet bore; claustrophobia; low signal-to-noise for most methods; and lack of quantification in physiologic units for most methods. Among the various fMRI methods, blood oxygenation level–dependent (BOLD) imaging has been most widely applied. This technique relies on magnetic susceptibility effects of deoxyhemoglobin, which cause regional decreases in signal in imaging sequences sensitive to susceptibility (e.g., echoplanar). With regional brain activation studies, a net increase in signal intensity is observed in regions known to be activated by the task. The increase in image intensity corresponds to a local decrease in deoxyhemoglobin. This is attributed to an increase in regional blood flow compared to regional oxygen consumption. A typical response is a 1% to 25% increase in regional image intensity, which develops over 3 to 8 seconds following task initiation. Susceptibility effects are field dependent so, using the 4-T magnet available to us, an initial decrease in signal intensity is detectable in the first 1 to 2 seconds following stimulation, corresponding to a focal increase in deoxyhemoglobin. When combined with ultrafast echoplanar imaging (~100 ms per slice), the time course of signal change in response to individual stimuli can thus be observed.
To evaluate task-induced regional activation, we have applied a verbal and a spatial task previously demonstrating regional activation with other methods. This study examined activation for a spatial task (judgment of line orientation) compared with a verbal reasoning task (analogies) in a sample of 29 healthy participants (15 men and 14 women). Task difficulty was manipulated. An image-based multi-subject analysis was performed by registering the brains of the different subjects. A well-characterized brain registration algorithm was used to register the T1 images from the different subjects to that of one particular subject. The registration transformation was also performed on the statistical images. Once registered, the statistics were summed across subjects and divided by the square root of the number of subjects, as is appropriate for independent, normally distributed variables. The statistical images were smoothed by convolution with a Gaussian kernel with full width at half maximum of 12 mm and thresholded at a $P$ value of 0.05 corrected for multiple comparisons using the theory of Gaussian random fields.

The activation map in Figure 7 indicates that the hypothesized left-lateralized changes were seen for the verbal task in posterior temporal and inferior parietal regions, while right-lateralized increase was seen for the spatial task in these regions. This image-based analysis revealed a distributed network of cortical regions, which expanded for the hard verbal task and became more circumscribed for the hard spatial task. This effect was more pronounced in men than in women. The task by hemisphere interactions for the hypothesized inferior parietal, superior temporal, and planum temporale regions were significant at an order of magnitude comparable to what we have obtained with other methods (all $P<0.001$). Thus, it appears that spatial processing requires, for harder tasks, greater reliance on visual association cortex with minimal activation of other areas. Poorer performance in women may relate to continued reliance on supplementary strategies, perhaps verbal, which are ineffective for the success on the harder spatial items. Such studies may help elucidate neural substrates of cognitive strategies for problem solving. Effects of aging on regional activation in relation to cognitive strategies have not yet been examined with fMRI.

The study of ovarian aging

As is generally the case for age-related changes, the hormonal environment can have pervasive effects that require scrutiny, not only during early development, but also during the perimenopausal phase. Menopause is a single event in a progressive process of ovarian aging beginning with increased frequency of menstrual disturbances and anovulation as follicular units are depleted. The process is accelerated after age 37, ultimately culminating in the virtual absence of follicles and capacity to generate significant quantities of estradiol. The median chronological age at menopause in the USA is 51.4 years (range 48 to 55 years). Estrogen decrease is associated with substantial central nervous system (CNS) alterations including vasomotor instability, insomnia, depression, and cognitive decline. Recent studies suggest that estrogen has a protective effect with respect to onset of Alzheimer’s disease and cognitive decline. There is evidence that neurobiologic processes triggered by the hormonal changes exert influence by affecting neurotransmitter availability, cerebral perfusion, and perhaps by eliminating neuroprotective effects of estrogen. In a recent study by Matteis et al., using transcranial Doppler ultrasonography, they found, as we did, higher flow estimates in women than men overall. However, a subgroup of 15 postmenopausal women aged 48 to 53 years had lower flow values than 15 premenopausal women of the same age, or any other group.

Conclusions

There is increasing evidence across behavioral, neuroanatomic, and neurophysiologic domains that sex differences play a prominent role in modulating the effects of aging on brain function. The overall finding is that age-related decline begins earlier in men than in women. The decline is most pronounced in frontotemporal regions associated with attention, inhibition, and memory. More specific tasks using a computerized approach can help better delineate associations between age-related decline and aspects of cognitive and emotion processing. The sex differences in brain aging may be further investigated on the molecular level and data on other physiologic parameters, such as glucose and oxygen metabolism and receptor function, could help further elucidate mechanisms for explaining these differences. Such studies could ultimately help explain a range of effects associated with ovarian aging.
of phenomena related to sex differences including cognition and emotion processing. Although we have focused on findings in healthy people, the effects have implications for brain disorders where gender differences have been observed across the life span. For example, neurodevelopmental disorders such as attention deficit and learning disabilities are more common in boys, schizophrenia is more severe in young men, and depression is more common in women.

Understanding the neural basis of these disorders can be advanced by considering sex differences in brain function. The clinical implications of these findings need to be examined in relation to disease presentation and course. In view of the greater vulnerability of males in prefrontal regions, one would expect brain disorders affecting these regions to be more severe and perhaps requiring multimodal therapeutic interventions. For females, with improved understanding of regional brain function.

Figure 7. Blood oxygenation level–dependent (BOLD) activation for men and women during performance of easy and hard verbal and spatial tasks. Reproduced from reference 121: Gur RC, Alsop D, Glahn D, et al. An fMRI study of sex differences in regional activation to a verbal and a spatial task. Brain Lang. 2000;74:157-170. Copyright © 2000, Elsevier Science.
activity during emotion processing, we may be in a position to explain the neurobiology of increased vulnerability to depression. Finally, the measures employed in this work seem sensitive to variability in healthy people and may therefore serve as endophenotypic markers of vulnerability to neuropsychiatric disorders in which sex differences are evident and may contribute to developing genetic models.

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El sexo y el envejecimiento moderan las relaciones entre el cerebro y la conducta. Los avances en las neurociencias favorecen una integración de las mediciones neuroconductuales, neuroanatómicas y neurofisiológicas. En este artículo se presentan estudios neuroconductuales que examinan el procesamiento cognitivo y de las emociones en hombres y mujeres sanos, destacándose las diferencias de los efectos del sexo y del envejecimiento. Los estudios neuroanatómicos con imágenes de resonancia nuclear magnética (IRM) indican que la reducción progresiva del volumen cerebral afecta regiones fronto-temporales más en hombres que en mujeres. Los procedimientos con imágenes funcionales sugieren que existen diferencias por sexo en el flujo cerebral, en el patrón del metabolismo de la glucosa y en la actividad de los receptores. Es importante el papel de las hormonas ováricas para aclarar estas relaciones observadas. Desde una perspectiva global que incluya la esperanza de vida y mediante la integración de las metodologías disponibles, se avanzará en la comprensión de las diferencias por sexo en los sujetos sanos y en los efectos provocados por los trastornos cerebrales.

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