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Effects of sex and normal aging on regional brain activation during verbal memory performance

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Abstract

This study examined the main and interactive effects of age and sex on relative glucose metabolic rate (rGMR) within gray matter of 39 cortical Brodmann areas (BAs) and the cingulate gyrus using ¹⁸FDG-PET during a verbal memory task in 70 healthy normal adults, aged 20–87 years. Women showed significantly greater age-related rGMR decline in left cingulate gyrus than men (BAs 25, 24, 23, 31, 29). Both groups showed a decline in the anterior cingulate—a neuroanatomical structure that mediates effective cognitive-emotional interactions (BAs 32, 24, 25), while the other frontal regions did not show substantial decline. No sex differences in rGMR were identified within temporal, parietal and occipital lobes. Sex differences were observed for rGMR within subcomponents of the cingulate gyrus with men higher in BA25 and BA29, but lower in BA24 and BA 23 compared to women. For men, better memory performance was associated with greater rGMR in BA24, whereas in women better performance was associated with orbitofrontal-BA12. These results suggest that both age-related metabolic decline and sex differences within frontal regions are more marked in medial frontal and cingulate areas, consistent with some age-related patterns of affective and cognitive change.

Keywords

Aging; healthy adults; sex differences; ¹⁸FDG PET; cingulate; prefrontal cortex

1. Introduction

Functional neuroimaging studies involving memory tasks have fairly consistently reported age-related decline in prefrontal cortex and cingulate (Buchsbaum & Hazlett, 1997; De Santi et al., 1995; Hazlett et al., 1998; Kuhl, Metter, Riege, & Phelps, 1982; Loessner et al., 1995; Rajah & D'Esposito, 2005; Reuter-Lorenz et al., 2000). Sex differences in patterns of brain activation,

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Conflicts of Interest

None.

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most commonly women more active than men during the resting state (Andreasson, Zametkin, Guo, Baldwin, & Cohen, 1994; Gur et al., 1995; 2000; Haut & Barch, 2006; Hofer et al., 2007; Rossell, Bullmore, Williams, & David, 2002; Shaywitz et al., 1995; Willis et al., 2002), as well as, during various tasks (Andreasson, Zametkin, Guo, Baldwin, & Cohen, 1994; Jaeger et al., 1998; Mansour, Haier, & Buchsbaum, 1996; Nyberg, Habib, & Herlitz, 2000; Ragland, Coleman, Gur, Glahn, & Gur, 2000) have also been reported. In one study the women>men finding was most prominent in the cingulate (Gur et al., 1995). Sex-related differences in rate of activity decrease with age were not significant in a large study using an auditory vigilance task (Willis et al., 2002) and not found in any cortical area but restricted to thalamus and hippocampus in a study using a resting condition (Murphy et al., 1996). Neuropsychological testing found some evidence for different trajectories for age-related cognitive decline for men and women (Elias, Elias, D'Agostino, Silbershatz, & Wolf, 1997; Tisserand & Jolles, 2003).

Consistent with a frontal aging hypothesis (Tisserand & Jolles, 2003; West, 1996), we have previously shown an age-associated shift from anterior regions to more posterior regions of the frontal lobe in normal individuals performing a verbal learning task (Brickman et al., 2003; Hazlett et al., 1998). Moreover, in a review of functional neuroimaging studies of normal aging, Cabeza (2001) described consistent findings of either lower activation or absent activation in older normal adults compared to younger adults during tasks of episodic encoding or semantic retrieval. Areas of the frontal lobe were particularly involved, including anterior cingulate/medial frontal lobe (Brodmann area (BA) 24 and 32), dorsolateral prefrontal cortex (BA 44, 45, and 46), orbital frontal lobe (BA 47), and lateral frontal lobe (BA 6, 8, and 10). A more recent review also concluded that there are region-specific changes in prefrontal cortex function with age (Rajah & D'Esposito, 2005).

Evidence from neuropsychological studies of normal aging suggest selective decreases in executive functioning, the cognitive processes involved in complex goal-directed behavior, planning, and cognitive flexibility (Ardila & Roselli, 1989; Daigneault, Braun, & Whitaker, 1992; MacPherson, Phillips, & Della Sala, 2002; Whelihan & Leshner, 1985), which are thought to be mediated by the frontal lobe (Elliott, 2003) and by frontal-subcortical circuitry (Alexander, DeLong, & Strick, 1986). These cognitive changes may be reflective of selective loss of neural tissue (Bartokis, 2001; 2003; Resnick et al., 2000) and/or a shift in brain networks or metabolism from more anterior networks to more posterior ones (Brickman et al., 2003; Hazlett et al., 1998).

In the present study, a modification of the California Verbal Learning Task (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) was used to examine simultaneous memory performance and regional brain metabolism in men and women across the lifespan. On a similar verbal learning task, younger adult participants performed better than older adults, and sex differences in verbal memory performance increased with age with women performing better than men (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1998). Other sex differences in verbal task performance have been reported and indicate better scores in women (Ragland et al., 2000). Using the CVLT, Kramer et al. (Kramer, Delis, & Daniel, 1998) found that women consistently performed better than men on immediate and delayed free recall and used a semantic-clustering strategy more than men. The modified version used here is ideal for studying regional metabolic correlates of normal aging and sex differences because it can be adapted for the 32-minute radiotracer uptake period. Furthermore, because the task comprises stimuli from four semantic exemplars, there is a higher-order executive demand for successful performance and analyses of both recall and performance strategy can be carried out.

The purpose of the current study was to advance over earlier largely negative studies of sex difference in aging by employing a task of known sensitivity to both aging and sex effects

(verbal memory performance) across the lifespan with FDG-PET. It is an novel extension of our previous work with this cohort of healthy volunteers (Brickman et al., 2003; Hazlett et al., 1998) where we showed frontal lobe metabolic and verbal memory performance declines with normal aging, a correlation between good cognitive performance and greater metabolism in posterior regions in older individuals, and a relative age-related shift marked by less caudate metabolism and greater putamen metabolism. In the present study, we make a comprehensive analysis of relative glucose metabolic rate (rGMR) within the gray matter of cortical regions approximating 39 cortical Brodmann areas. Although we examined regional metabolism differences, we focused in particular on prefrontal and cingulate regions, as these areas seem to be particularly vulnerable to the effects of age. We hypothesized (a) marked age-related decline in frontal lobe metabolism, particularly in dorsolateral and medial/cingulate areas, in the context of relative “sparing” of other lobes; (b) men and women would exhibit different patterns of rGMR in prefrontal cortex and cingulate regions given that they may employ different strategies for task performance (e.g., semantic clustering vs. serial ordering) and that frontal and especially medial frontal may differ in hormone responsiveness; and (c) men and women would exhibit different regional patterns of age-related decline in rGMR.

2. Methods

2.1. Study participants

Seventy right-handed, healthy normal adults (age range = 20–87) participated in this study. They were recruited through advertisements in the community. There were five men and five women within each of seven consecutive decades from 20s through to 80s (men: mean age = 54.5, SD = 20.1; women: mean age = 54.4, SD = 20.4; mean age for men and women within each of the seven decades also did not significantly differ). Inclusion criteria included a minimum of a high school education and English as the primary language. The study protocol was explained and all participants signed an informed consent approved by the Institutional Review Board of Mount Sinai School of Medicine describing the purpose of the study, the tests performed, and the risks involved. Participants were reimbursed for their time, completed a medical and psychiatric examination and were evaluated with a structured psychiatric interview (Comprehensive Assessment of Symptoms and History; Andreasen, Flaum, & Arndt, 1992). Exclusion criteria included neurologic disorders, history of head injury with loss of consciousness greater than five minutes or with neurocognitive sequelae, mental retardation, or medical illness associated with significant neurocognitive impairment, history of treatment with psychoactive medication, any history of substance abuse or dependence, psychiatric illness, family history (first-degree relatives) of psychiatric illness or substance abuse/dependence, and positive urine test for drugs of abuse on the day of the PET scan. Participants were within normal limits for intelligence based on the Wechsler Adult Intelligence Scale Revised (Wechsler, 1981) and a detailed neuropsychological battery. We have previously published age-related studies which included these same participants (Hazlett et al., 1998; Brickman et al, 2003). However, the current study employed novel methods involving analysis of gray matter rGMR in cortical BAs and analyses examining sex differences and age-by-sex interactions.

2.2. PET/MRI Imaging

Participants were scanned with Positron Emission Tomography (PET) using ^{18}F -deoxyglucose (^{18}FDG) to determine regional relative glucose metabolic rate (rGMR). PET scans were obtained on a head-dedicated scanner (GE PC2048B, in-plane resolution 4.5 mm FWHM, 6.5 mm FWHM axially) with ^{18}FDG (5 mCi). We obtained 20 slices with calculated attenuation correction. An individually-molded thermoplastic face mask held the participant stationary during both PET and MRI image acquisition. Each participant also received a magnetic resonance imaging (MRI) scan with the GE Signa 5X system (repetition time = 24 ms, echo

time = 5 ms, flip angle = 40°, slice thickness = 1.2 mm, pixel matrix = 256 × 256, field of view = 23 cm, total slices = 128). PET scans were coregistered to MRI oriented in standard Talairach position as described earlier (Hazlett et al., 1998).

2.3. Image Analysis

A detailed analysis of glucose metabolism was conducted for the frontal, parietal, temporal and occipital lobes subdivided into regions that approximate 39 Brodmann areas. Because the variations in cellular composition and lamination that form the basis of Brodmann's cortical parcellation do not correspond exactly to gyral patterns, parcellation of the cortex into Brodmann areas requires careful microscopic analysis of histological sections. Although this method of parcellation is not feasible *in vivo*, we have developed a method for approximating Brodmann areas in MRI scans. Our earlier use of this brain atlas (Buchsbaum et al., 2002; Hazlett et al., 1998; Mitelman, Shihabuddin, Brickman, & Buchsbaum, 2005) describes the method in greater detail. The Perry coronal atlas of the brain (R.H. Perry, personal communication, 1993) is composed of 33 equally spaced coronal maps of Brodmann's areas, based on microscopic examination of one entire hemisphere of a postmortem brain (see Mitelman et al 2005 for full illustration of the 33 coronal maps and Figure 1). Each cerebral slice is drawn with the margins of each Brodmann area marked. For each MRI, coronal slices perpendicular to the anterior commissure-posterior commissure line were reconstructed in a 256×256 pixel matrix. To match the Perry atlas, we first identified 33 evenly spaced slices such that the first slice began 1/34th of the distance from front to back. On these slices the frontal, parietal and occipital lobes were traced. For each temporal lobe, we identified the temporal pole and the most posterior extent of the Sylvian fissure and divided the space into 14 equally spaced slices. The brain edge was obtained on the approximately circular 33 non-temporal slices and 28 (14 in each hemisphere) temporal lobe slices by depositing points visually on the tips of the gyri and then fitting a spline curve to the points. Each slice was then divided into 20 radial sectors on each hemisphere surface and 10 midline sectors. Brodmann's areas were then assessed for the PET pixels coregistered to the gray matter pixels within all sectors identified with each Brodmann area. Some of the smallest Brodmann's areas are combined (e.g. 3-1-2-5) for conservative simplicity. The dependent measure for all PET analyses was relative glucose metabolic rate (rGMR). This is expressed as the mean activity value (in nanocuries) for all gray matter pixels in each of the cortical regions of interest divided by the mean value for the whole brain. Data from 39 Brodmann's areas identified by Perry (1-2-3-5, 4, 6, 8, 9, 10, 11, 12, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 7a and 7b) were obtained. We examined between-group differences in a subset of these variables developed on a theoretical and anatomical basis which we entered into a series of statistical analyses (described in section 2.5).

2.4. Verbal memory task

During the 32-minute uptake period for the ¹⁸FDG, participants performed a serial verbal learning task (SVLT) in a darkened, acoustically attenuated isolation room. Immediately after the uptake period, participants were scanned in an adjacent room. ¹⁸FDG serves as a tracer and marks the metabolic rate, remaining in place after the uptake period. The SVLT, based on the principles of the CVLT (Delis et al., 1987), consisted of five different word lists containing 16 words each. In each list there were 4 words from 4 different semantic categories (e.g. colors, animals, desserts, drinks). Each of the five lists was presented five times on a computer monitor at a rate of one word every 1.5 s. The order of the words in each list was determined randomly with the criteria that words from the same semantic category were not displayed consecutively. Ordering of the words within each list, as well as, the presentation order of each list was the same for all participants. The participants read each word aloud as it appeared on the computer monitor to ensure attention to the task. After the last word of each 16-word list was displayed, the participant was asked to recall as many words as they could remember. Next, the same list

was presented again a second time and they were asked to recall the words. This list was repeated for a total of five times and then the second list of 16 new words was presented in the same manner. This process continued through all five presentations of each of the five lists or until the 32-minute uptake period has ended.

This task engages the participant in cognitive processing throughout the entire 32-minute uptake period and is advantageous over functional MRI because it allows for the examination of brain activation during simultaneous cognitive performance in a quiet environment while the participant is seated comfortably which is analogous to collecting data in a typical neuropsychological-task environment. For each participant, task performance was scored for number of correctly recalled words, perseverations (repetition of any word on the same trial), intrusions (words not in list), semantic clustering and serial ordering. Each of these scores was averaged across trials. Semantic clustering is defined as the number of contiguously recalled correct words from the same category divided by the number of correctly recalled words. Serial ordering is defined as the number of contiguously recalled correct words in the same order as the original list (divided by the number of correctly recalled words). The scores for correctly recalled words, intrusions, semantic clustering, and serial ordering do not include words that were perseveration errors.

Analysis of the rate of learning, internal consistency of the task, and consistency of performance from one word list to the next has been examined previously and is reliable (Hazlett et al., 1998).

Although ^{15}O methods (and fMRI) methods are better suited to the dissection of components of memory processes, our goal was more general: to relate one summative measure of verbal memory known to be sensitive to age effects to concomitantly assessed age-related changes across the lifespan in regional brain activity in men and women. Moreover, the resolution of PET with ^{18}F FDG as tracer is not limited by the reduced counting time and the three-to fourfold longer 8-mm path of the positron emitted by ^{15}O , which would substantially diminish our scanner's 4.5mm resolution.

2.5. Statistical analyses

We tested our specific interregional hypotheses by using groupings based on the 39 Brodmann areas. The Brodmann areas were sub-grouped on a theoretical basis and entered as repeated measures into a series of mixed-design multivariate analysis of variance (MANOVA) analyses. The series of MANOVAs included sex (men vs. women) and decade (20s vs. 30s vs. 40s vs. 50s vs. 60s vs. 70s vs. 80s) as the between-group factors. The repeated measures included region (e.g., frontal, temporal, parietal, and occipital lobe), selected sets of Brodmann areas within each region (e.g., dorsolateral prefrontal: BA44, BA45, BA46, occipital: BA17, BA18, BA19) and hemisphere (left, right). This allowed specific testing of hypotheses concerning differential age effects in different Brodmann areas and differential age effects in different Brodmann areas in men and women. The multivariate F (Wilks lambda) from Statistica (StatSoft, 2003) is reported to adjust probabilities for repeated-measure effects with more than two levels. Fisher's Least Significant Difference (LSD) tests were used to follow-up significant between-group interaction effects. This approach helps minimize Type I statistical error involved with t-tests for each brain area, group contrast, and hemisphere. In a further effort, we only examine significant main effects for the between-group factors (i.e. age and sex) and age-by-sex interactions with brain region or hemisphere. However, we recognized that this method might lack power to detect age trends and therefore, we also used a more powerful linear regression method homogeneity-of-slopes model (StatSoft, 2003) where appropriate to test whether relative metabolic rate decreased with age, decreased at a different rate in the cingulate and medial frontal areas than other areas or at a different rate in men and women in different Brodmann areas. On an exploratory basis, we also systematically examined the age

regression slopes in all 39 Brodmann areas for the left and right hemispheres and average across hemispheres and present the age regression slopes for areas that showed statistically significant age effects. This approach is used as an analogue of significance probability mapping which is often used in group contrast.

The current study examined the association between age and performance on the verbal memory task separately for men and women and we used the homogeneity-of-slopes test to determine whether there were significant sex differences in age-related change. We also conducted between-group t-tests to examine whether there were overall sex differences (averaged across the seven decades) in the number of correctly recalled words, perseverations, intrusions, semantic clustering and/or serial ordering.

3. Results

3.1. Verbal Memory Performance: Effects of Age and Sex

The age-related decline from age 20 to 87 among men was more marked with the average number of correctly recalled words falling from 13.4 (out of 16) to 10.2 (−0.51 words/decade, $r=-0.47$, $p=0.004$). Among women, the age-related decline was not significant with the average number of correctly recalled words falling from 14.8 to 12.9 (−0.18 words/decade, $r=-0.20$, $p=0.25$). However, the rate of change with age (age-regression slope) was not significantly different between men and women (homogeneity-of-slopes test, $F[1,66]=2.10$, $p=0.15$).

Perseveration errors did not increase with age in men ($r=0.29$, $p=0.09$) or women ($r=0.15$, $p=0.39$). The rate of change with age (age-regression slope) also did not significantly differ between the groups (homogeneity-of-slopes test: $F[1,66]=0.05$, $p=0.83$). Among the men, there was a trend for serial ordering of the words to decline with age ($r=-0.32$, $p=0.06$), but not for women ($r=-0.11$, $p=0.55$) yet, the age-regression slopes did not significantly differ between groups ($F[1,66]=1.00$, $p=0.32$). Intrusion errors increased with age in women ($r=0.31$, $p=0.07$; trend level) but not men ($r=0.15$, $p=0.40$) and the age-regression slope, once again, did not significantly differ between groups ($F[1,66]=0.08$, $p=0.78$). For both men and women, use of the semantic-clustering strategy did not show an age-related decline ($r=-0.25$, $p=0.15$ and $r=-0.08$, $p=0.66$ respectively; and for the age-regression slope: $F[1,66]=0.54$, $p=0.47$).

Overall, averaged across the lifespan, men and women did not significantly differ in any of the memory task performance variables examined (correctly recalled words: men=12.3, $sd=2.2$, women=13.1, $sd=1.8$, $t(68)=1.5$, $p=0.14$; perseveration errors: men=0.6, $sd=0.7$, women=0.6, $sd=1.0$, $t(68)=0.07$, $p=0.95$; intrusion errors: men=0.2, $sd=0.2$, women=0.1, $sd=0.1$, $t(68)=-1.23$, $p=0.22$; semantic clustering: men=7.2, $sd=2.7$, women=8.0, $sd=2.6$, $t(68)=1.16$, $p=0.25$; serial ordering: men=0.6, $sd=0.5$, women=0.5, $sd=0.5$, $t(68)=-0.48$, $p=0.63$).

3.2. Regional brain glucose metabolism during verbal memory performance: Effects of age, sex, and age $\times$ sex interactions

3.2.1. Cingulate gyrus analysis—We conducted an anterior to posterior gradient analysis of the cingulate gyrus, using a 2 (Sex) $\times$ 7 (Decade: 20s vs. 30s vs. 40s vs. 50s vs. 60s vs. 70s vs. 80s) $\times$ 5 (Cingulate BA: 25, 24, 31, 23, 29) $\times$ 2 (Hemisphere) mixed-design MANOVA. Sex and age were used as between-group factors. Cingulate BA and hemisphere were within-subjects or repeated-measures. Men had higher rGMR in BA25 and BA 29 of the cingulate gyrus compared with women but lower rGMR in BA 24 and BA 23 as indicated by a significant Sex $\times$ Cingulate BA interaction ($F[4,53]=3.83$, $p=0.008$, Wilks; Figure 2).

Using age as a continuous variable in a slope analysis resulted in a significant Sex $\times$ Age $\times$ Hemisphere interaction ($F[1,66]=5.02$, $p=0.028$, Wilks) indicating age-related decline in left cingulate rGMR was greater in women compared with men. Correlational analyses indicating

age-related decline in left cingulate rGMR was greater in women compared with men confirmed that left cingulate decline with age was observed in women ($r=-0.49$, $p=0.003$) but not men ($r=-0.25$, $p=0.141$; Figure 3). There was also a significant overall aging effect which indicated that BA 23, 24, and 25 declined to a significantly greater extent with age than BA 29 and 31 (Age $\times$ Cingulate BA interaction, $F[4,63]=8.53$, $p<0.0001$, Wilks). This was also confirmed with the dichotomous grouping for Decade (Decade $\times$ Cingulate BA interaction, $F[24,186]=2.51$, $p=0.0003$). Slope analysis revealed that BA 24 decreased to the greatest extent with age while area 31 and 29 did not decrease (Figure 4). When used as a continuous variable in the slope analysis, age was highly significant ($F=14.82$; $df=1,66$; $p<0.001$) indicating that rGMR within the anterior cingulate (BA 25 and BA 24) declined across the lifespan.

Figure 4 (bottom) shows the correlations between age and rGMR within each cingulate BA averaged across hemisphere. Anterior cingulate regions showed a significant age-related decline in rGMR (BA 25: $r=-0.37$, $p=0.002$; BA 24: $r=-0.58$, $p=0.000$) as did BA 23 ($r=-0.28$, $p=0.02$). In contrast, rGMR in more posterior cingulate regions, i.e. BA 31 and BA 29 did not show an association with age ($r=-0.04$, $p=0.76$ and $r=-0.06$, $p=0.61$, respectively).

The main effect of Decade was also significant ($F[6,56]=3.68$, $p=0.004$) indicating that rGMR averaged across the five BAs within the cingulate declined with normal aging across the lifespan. This was also observed by calculating the correlation coefficient between age and mean rGMR in the cingulate gyrus averaged across all five cingulate BAs ($r=-0.43$, $p=0.0001$).

3.2.2. Frontal lobe—We performed a 2 (Sex) $\times$ 7 (Decade) $\times$ 4 (Frontal lobe region) $\times$ 3 (Brodmann area) $\times$ 2 (Hemisphere) mixed-design MANOVA. Sex and age were used as between-group factors. Frontal lobe region (lateral, medial, orbital, dorsolateral), Brodmann area (Lateral: 8, 9, 10; Medial: 32, 25, 24; Orbital: 47, 11, 12; and Dorsolateral: 44, 45, 46) and Hemisphere (left, right) were repeated-measures. A significant Decade $\times$ Frontal lobe region interaction ($F[18,153]=2.93$, $p=0.0002$, Figure 5) indicated that medial regions of the frontal lobe (rGMR averaged across Brodmann areas 32, 24, 25) showed significant age-related decline in rGMR (confirmed with slope analysis, $F(1,66)=29.90$, $p<0.0001$) and this was less prominent in lateral (slope analysis: $F[1,66]=0.93$, $p=0.34$), dorsolateral ($F[1,66]=0.22$, $p=0.64$), and orbital regions ($F[1,66]=0.02$, $p=0.88$). This finding was also highly significant when age was used as a continuous variable (slope analysis), Age $\times$ Cortical region; Wilks: $F[3,64]=16.79$, $p<0.0001$).

The Decade $\times$ Frontal lobe region $\times$ Brodmann area interaction ($F[36,227]=2.22$, $p=0.0002$) was highly significant. This interaction also was observed when age was used as a continuous variable ($F[6,61]=4.45$, $p<0.001$). In order to interpret this higher-order interaction, we conducted a simple-effects MANOVA for each of the four frontal lobe regions, as well as, correlational analyses. The MANOVAs indicated that the largest aging effect was in the medial frontal region which showed a main effect for Decade ($F[6,63]=5.48$, $p=0.0001$) and a Decade $\times$ BA interaction ($F[12,124]=2.11$, $p=0.02$; all other interactions with Decade were ns). For the lateral region, there was only a Decade $\times$ BA interaction ($F[12,124]=1.99$, $p=0.03$; main effect of Decade and all other interactions with Decade were ns). There was no significant main effect of Decade or any interaction with Decade for dorsolateral and orbital frontal regions.

We also conducted individual correlational analyses for every Brodmann region. All three of the medial frontal regions (BA 32, 24, and 25) showed a significant and negative correlation with age ($r=-0.41$, $r=-0.57$, $r=-0.37$, respectively, all $p<0.002$). Of the three lateral regions (BA 8, 9, 10), only Brodmann area 8 showed a negative correlation with age ($r=-0.32$, $p=0.01$). None of the regions within the dorsolateral (BA 44, 45, 46) or orbital frontal (BA 47, 11, 12)

cortex were significantly correlated with age. Figure 4 depicts medial and lateral views of the brain showing linear slopes for relative metabolic rate vs. age.

The Decade $\times$ Frontal lobe region $\times$ Hemisphere interaction was also significant ($F[18,153] = 1.95$, $p=0.02$). The main effects for Sex and Decade were not significant, none of the interactions with Sex were significant, and none of the remaining interactions with Decade were significant.

3.2.3. Analysis of the four lobes of the brain—Regional rGMR was examined using a 2 (Sex) $\times$ 7 (Decade) $\times$ 4 (Lobe) $\times$ 3 (Brodmann area) $\times$ 2 (Hemisphere) mixed-design MANOVA. Sex and Decade were between-group factors and Lobe (frontal, parietal, temporal, occipital), Brodmann area (Frontal Brodmann areas: BA 32, 24, 25; Parietal: BA 39, 40, 7a; Temporal: BA 22, 21, 20; Occipital: BA 17, 18, 19) and Hemisphere (left, right) were repeated measures. As can be seen in Figure 6, a significant Decade $\times$ Lobe interaction ($F[18, 153] = 2.52$, $p=0.001$) indicated an age-related decline in rGMR in the frontal lobe regions (confirmed with one-way MANOVA: $F[6,63]=5.48$, $p=0.0001$; homogeneity-of-slopes test: $F[1,66]=29.90$, $p=0.000001$) and a reciprocal increase in rGMR in the occipital lobe (one-way ANOVA: $F[6,63]=4.32$, $p=0.001$; homogeneity-of-slopes test: $F[1,66]=7.97$, $p=0.006$) with normal aging. In contrast, average rGMR in the parietal (one-way ANOVA: $F[6,63]=1.45$, $p=ns$) and temporal (one-way ANOVA: $F[6,63]=1.39$, $p=ns$) lobes did not show significant age-related change. These findings were essentially the same when age was used as a continuous variable, resulting in a highly significant interaction ($F[3.64]=11.10$, $p<0.00001$, Wilks) for frontal and occipital regions, but not for temporal and parietal.

Lastly, a multivariate analysis with the full set of Brodmann areas found a significant age effect when medial frontal, temporal, parietal and occipital areas were included ($F[23,43]=4.08$, $p=0.000030$; interactions with sex ns) and when dorsolateral frontal areas (BA 44, 45, and 46) were included ($F[24,43]=2.06$, $p=0.018$).

The Decade $\times$ Lobe $\times$ Brodmann area $\times$ Hemisphere interaction was also significant ($F(36, 227)=1.57$, $p=0.03$). As can be seen in Figure 4, there was age-related decline in rGMR in frontal and temporal lobe, parietal regions were spared, and occipital lobe regions showed increased rGMR. We present post-hoc examination of the age-regression for the frontal, parietal, temporal, and occipital lobe in Figure 4.

The main effects for Sex and Decade were not significant, none of the interactions with Sex were significant, and none of the remaining interactions with Decade were significant.

3.2.4. Correlations between verbal memory performance and rGMR in men and women—In order to examine the relationship between memory performance and regional rGMR, we conducted Pearson correlations between serial verbal learning task variables (mean number correct and semantic categorization) and rGMR. To minimize the number of correlations, we only included Brodmann areas within the frontal and temporal lobe—the regions of greatest age-related metabolic decline. Men and women were analyzed separately for comparison purposes. As can be seen in Figure 7, among the women, better memory performance (mean number correct) was associated with increased rGMR in BA 12 ($r=0.34$, $p<0.05$) and semantic clustering was associated with increased rGMR in BA 45 ($r=0.35$, $p<0.05$) and these correlation coefficients significantly differed between women and men (Fisher's Z, $p<0.05$). There were no significant correlations in the right hemisphere or in the temporal lobe.

In contrast, for men better memory performance (mean number correct) was associated with greater rGMR in left BA 24 ($r=0.37$, $p=0.029$) and less rGMR in left BA 47 ($r=-0.47$, $p=0.004$).

Semantic clustering was associated with less rGMR in left BA 47, 11, and 12 ($r=-0.46$; $r=-0.36$; $r=-0.39$; all p values <0.05). Correlations were significantly different between groups (Fisher's Z , $p<0.05$; Figure 7). There were no significant correlations in the right hemisphere or in the temporal lobe for either women or men.

4. Discussion

This first use of a verbal memory task during tracer uptake appeared to enhance sex and sex/age interactions in functional brain activity. The main findings of this study are as follows: (1) Women had greater age-related decline in the left cingulate gyrus than men while no other brain regions examined showed sex differences in age-related change; (2) Medial frontal regions including anterior cingulate showed significant age-related decline in rGMR while age-related changes in rGMR were not significant in lateral, dorsolateral, and orbital frontal regions; (3) In the cingulate gyrus, women had greater rGMR in anterior cingulate (BA 24) and men were higher in posterior cingulate (BA 29); (4) Sex differences in temporal, parietal, and occipital lobes were not significant; and (5) Men and women used different brain regions in order to achieve good memory performance.

Gur and colleagues (Gur et al., 1995) found that women had lower metabolic rates in temporal/limbic areas and greater glucose metabolism in the cingulate gyrus compared to men. Medial frontal and cingulate areas were found hypometabolic in women taking the estrogen-inhibitor tamoxifen (Eberling et al., 2004). Normal men had even higher medial frontal areas than women (Kawachi et al., 2002), suggesting that medial frontal areas might be among the most different between the sexes. Other studies have found global differences in activation with women having higher absolute and normalized regional metabolic rate than men and higher regional rates in the orbital frontal lobe during a continuous performance task (Andreasson et al., 1994). Laterality differences between men and women have been demonstrated in several studies, but are not entirely consistent. For example, greater left hemisphere activation in men than in women was evident during a grammatical task (Jaeger et al., 1998), whereas women had higher left hemisphere metabolic rate than men in the orbital frontal cortex, posterior cingulate, and posterior corpus callosum during a resting state (Gur et al., 1995). Others have reported no gross sex differences during a resting state (Azari et al., 1992), or during a task (Schlosser et al., 1998; Willis et al., 2002). For a complete review on sex differences see (Cosgrove, Mazure, & Staley, 2007).

Frontal lobe decline with normal aging has been rather consistently reported in PET studies (Cabeza, 2001; Esposito, Kirkby, Van Horn, Ellmore, & Berman, 1999; Loessner et al., 1995; Martin, Friston, Colebatch, & Frackowiak, 1991) and our findings extend this line of work by showing that this age-related decline is most prominent in medial frontal and anterior cingulate regions and proceeds more rapidly in women than men. Our findings are consistent with a recent structural MRI study which showed that sex differences in aging are localized to medial prefrontal regions (Cowell et al., 2007). However, Cowell et al reported that men experience earlier changes in medial orbital regions than do women. Future studies examining both structural and functional change on a within-subjects basis will be needed to further clarify age by sex interactions in the frontal lobe.

Consistent with some previous work (Murphy et al., 1996), we did not detect sex-differences in rGMR within temporal, parietal, or occipital lobes. However, men and women differed in rGMR within distinct subregions of the cingulate gyrus, but not other medial, lateral, dorsolateral, or orbital frontal areas. Men had higher rGMR in BA 25, but lower rGMR in BA 24 of the anterior cingulate compared with women. Both lesion and functional imaging studies indicate separate roles for rostral-ventral versus more dorsal areas of anterior cingulate cortex in affective and cognitive processing, respectively (Bush, Luu, & Posner, 2000). The more

rostral-ventral subdivision of the cingulate (BA 25) has its strongest connections to limbic and paralimbic brain regions such as the amygdala and orbitofrontal cortex (Devinsky, Morrell, & Vogt, 1995) and is primarily involved in assessing the salience of emotional stimuli and in regulating affective responses (Bush et al., 2000). In addition to similar limbic connections (Vogt, Finch, & Olson, 1992), the more dorsal subdivision of the anterior cingulate (BA 24) is part of a distributed cortical network including lateral prefrontal, parietal, premotor, and supplementary motor areas (Devinsky et al., 1995). This network is involved in attentional modulation (Bush et al., 2000; Vogt et al., 1992). In our study which involved a verbal memory task, men had lower rGMR than women in the more dorsal “cognitive” subdivision of the anterior cingulate and higher rGMR than women in the more ventral “affective” subdivision. However, correlational analysis showed that among the group of men, better task performance was associated with greater rGMR in the dorsal-cognitive region.

Animal studies show that the cingulate cortex is rich in estrogen receptors (Butler, Kallo, Sjöberg, & Coen, 1999; Gerlach, McEwen, Toran-Allerand, & Friedman, 1983), lacking in the aromatase enzyme that synthesizes estrogen from testosterone (Abdelgadir, Roselli, Choate, & Resko, 1997), and relatively poor in androgen receptors (Abdelgadir, Roselli, Choate, & Resko, 1999; Pomerantz & Sholl, 1987). To our knowledge, a fine grained analysis of the localization of these gonadal hormone receptors and converting enzymes is lacking for the brain of any species and little work has been done in humans (Miller et al., 2004). In contrast to functional imaging studies suggesting that sex hormones selectively activate particular brain regions (Azad, Pitale, Barnes, & Friedman, 2003; Joffe et al., 2006; Rasgon et al., 2005), there is little variation across cortical regions in the mRNA expression of these genes for the relevant hormonal receptors and converting enzymes (available online from the Genomics Institute of the Novartis Research Foundation <http://www.gnf.org>). Findings that show subregions of the cingulate are activated by estrogen and/or testosterone (Azad et al., 2003; Rasgon et al., 2005), combined together with our observation of sex differences in the subregions of the cingulate emphasizes the need for detailed localization studies in humans. These studies need to be carried out at the anatomical level of particular Brodmann areas and at the molecular level of protein expression in addition to mRNA expression. If differences in cingulate activation reflect differences in ambient estrogen levels (and the cingulate lacks aromatase enzyme), one might expect to see a decade by sex interaction with activity differing between younger women and men of all age groups. While such an interaction was not seen in the present study, Gur et al. (1995) reported that men showed lower rGMR in middle and posterior cingulate gyrus compared with women. However, age (mean age 27 in Gur et al.'s study vs. 54 in the present study) and uptake task (resting condition vs. SVLT) differences could explain this disparity. In a smaller and older sample (Rasgon et al., 2001), no sex differences were reported in rGMR in posterior cingulate during resting. However, this same group subsequently reported a menopausal decrease in rGMR in the posterior cingulate that was prevented by estrogen administration (Rasgon et al., 2005). Several plausible scenarios could account for the absence of such an interaction in the present study: (1) aromatase enzymes might be expressed in the human cingulate but not in the animal models studied; (2) primate studies show that the cingulate receives heavy projections from other brain regions that are rich in aromatase, thus providing an indirect pathway for excitation by estrogen derived from androgen within the brain (Roselli, Klosterman, & Resko, 2001); and (3) testosterone might be able to activate the human cingulate without conversion to estrogen by directly interacting with androgen receptors. BA 24 has been shown to be activated by testosterone (Azad et al., 2003) but whether or not that activation was mediated by androgen receptors or via aromatization and estrogen receptors is unknown.

Our correlational analysis showed that better memory performance among the men was associated with greater rGMR in anterior cingulate (BA 24) and less rGMR in orbital frontal regions (BA 12). In contrast, better memory performance in women was associated with greater

rGMR in BA 12 and there was no correlation with anterior cingulate. Our study shows that rGMR in the cingulate gyrus declines across the adult lifespan, although better performance among men on this task was associated with greater rGMR in BA 24—a key subregion of the anterior cingulate important in attentional and affective processing. In contrast, better performance among women was associated with greater rGMR in the orbital frontal cortex—a brain area that showed relatively little age-related differences in rGMR.

Surprisingly, we did not find a sex difference in any of the verbal memory performance measures (number of correctly recalled words, intrusions, perseverations, or semantic clustering). Previous work has shown that as a group women have better verbal memory performance on the CVLT (e.g., Ragland et al 2000) which our FDG-uptake SVLT task is based upon. However, this difference may be due to differences in task administration. For example, sex differences in the Ragland study were most striking for immediate stages of learning and recall and the data in the current study are averaged across all trials, possibly diminishing sex differences.

Some limitations of our study include: (1) The use of a single PET scan session rather than a two-session approach to assess activation from baseline; (2) The stereotaxic Perry atlas has limitations both analogous and complementary to the limitations of significance probability mapping. Both methods combine subjects and are limited by the quality of brain normalization. Our study is limited by the accuracy of the Perry's atlas, lack of statistical information on its variability across subjects and imperfections in the application of atlas with segmentation to individual subjects as discussed elsewhere (Mitelman, Shihabuddin, Brickman, Hazlett, & Buchsbaum, 2003); (3) Additionally, segmentation of gray and white matter may vary and threshold error could generally increase or decrease gray estimates affecting relative glucose metabolic rate. If the cortex became thinner with age, fewer voxels might be identified as gray. It might be argued that slightly wider sulcal markings with age might be more likely to contain voxels identified as CSF in older individuals and not included in the gray matter mask used to assess metabolic rate. It is interesting to note that we addressed this issue in our earlier metabolic rate/year slope maps by parceling out the MRI intensity value (Buchsbaum & Hazlett, 1997); this approach diminished the age-associated decline in the dorsolateral frontal cortex but not in the medial region and produced maps more similar to those obtained with the current analysis. Diminished glucose metabolic rate in the frontal regions with age was found to be non-significant following partial volume correction based on MRI (Ibanez et al., 2004). In our cohort, frontal glucose change with age was maximal in BA 24, an area which showed no volumetric change (Brickman et al., submitted), making it unlikely that our changes are due entirely to partial volume effects. Our findings were also based on participants performing a memory task with demonstrated age-related decline, rather than resting as in the partial volume correction study (Ibanez et al., 2004). Our larger sample (n=70), containing the full adult lifespan might have also increased statistical power over the partial volume study (n=24); and (4) our use of a cross-sectional design is not as ideal for inferring decline as a longitudinal design (as indicated in Kraemer et al. 2000). However, given that our study examined differences in rGMR across much of the lifetime (seventy years), there would also be confounds with a longitudinal design. There would be significant participant attrition in a study with a sample size as large as ours (n=70) over time and there would be reduced statistical power in inferring age change even with an interval as long as 5 years between scans. Further, practice effects over repeated neurocognitive testing contaminate the results. Sustaining identical scanner mechanics over long time intervals also poses important logistical problems. Lastly, educational level is an important factor and might be the most probable source of strong cohort effects in our cross-sectional design, but was controlled in our study whose population showed no cohort effect (college education in nearly all participants).

In our study, the frontal lobe compared with the other lobes showed a greater rate of metabolic decline with age which is consistent with several previous studies (De Leon et al., 1987; De Santi et al., 1995; Loessner et al., 1995). This finding supports the “frontal aging hypothesis” and indicates that the prefrontal cortex is particularly vulnerable to the effects of aging. However, our data also support others (Tisserand & Jolles, 2003) who argue that this hypothesis needs refinement in so that it acknowledges distinct subregions within the prefrontal cortex, a subset of which show age-related decline. Consistent with this refined frontal aging hypothesis, our data indicate that distinct subregions of the prefrontal cortex (predominantly medial and anterior cingulate: BA 32, 24, 25) are more susceptible to normal age-related decline in rGMR than other prefrontal regions.

We did not have information on the hormonal status of our study participants (e.g., phase of menstrual cycle or hormonal replacement status of postmenopausal women). The variability due to cyclic menstrual changes could decrease the likelihood of detecting sex differences in brain activation, whereas, changes due to hormonal changes at menopause could be masked by hormonal replacement therapy. These are important considerations that must be taken into account by the design of future studies that assess sex differences and sex by age interactions in regional brain metabolism.

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Figure 1.

Delineation of cortical Brodmann areas. Upper left: Perry brain atlas for slice #5 showing frontal pole Brodmann areas (e.g., 9, 46, 45...) in raw drawing and with sectors added. Upper right: Coronal brain edges are traced on individual MRI slices and set of sectors applied by computer algorithm, 20 sectors on the lateral and orbital surface (white numbers) and 10 in the medial portion (green numbers) for a total of 30. Bottom Left: Perry atlas in three-dimensional perspective within MRI surface. Gray and white matter volume within each Brodmann area is calculated. Bottom right: Diagram of frontal Brodmann areas as colored stick diagram: area 10 is magenta, area 9 is blue, area 46 yellow, as example.

Sex Differences in Cingulate Gyrus rGMR (Men minus Women)

Figure 2.

Sex differences in rGMR in the cingulate gyrus arch. A significant Sex $\times$ BA interaction is shown ($F[4,53]=3.83$, $p=0.008$, Wilks. Men had higher rGMR in BA 25 and BA 29, but lower rGMR in BA 24 and BA 23 compared with women.

Figure 3.

Age and sex interaction in the left cingulate gyrus. Using age as a continuous variable in a slope analysis resulted in a significant Sex $\times$ Age $\times$ Hemisphere interaction ($F[1,66]=5.02$, $p=0.028$, Wilks) indicating age-related decline in left cingulate rGMR was greater in women compared with men. Correlational analyses indicating age-related decline in left cingulate rGMR was greater in women compared with men confirmed that left cingulate decline with age was observed in women ($r=-0.49$, $p = 0.003$; left graph) but not men ($r= -0.25$, $p=0.141$; right graph).

Figure 4.

Age vs. relative metabolic rate linear slopes. Lateral and medial views of the brain showing slopes for age vs. rGMR in right hemisphere (top row), left hemisphere (middle row), and the mean of left and right hemisphere (bottom row). Color bar indicates change in relative glucose metabolic rate per year $\times 1000$. Thus, -2.25 indicate a relative change of about .10 in 50 years (effect size about 1.0) or 0.002/year. Colored areas showed significant age versus rGMR correlations ($p < 0.05$) while white areas did not show significant age-related change in rGMR.

Figure 5. Relative metabolic rate change with age in frontal lobe regions. As shown here, greater age-related decline in rGMR was observed in medial areas while lateral, dorsolateral, and orbital frontal regions showed less age-related decline (Decade $\times$ Frontal lobe type interaction, $F [18,168]=2.93$; $p<0.0002$).

Figure 6.

Relative metabolic rate change with age. A significant Decade $\times$ Lobe interaction ($F[18, 153] = 2.23, p = 0.004$, Wilks; $F[18, 168] = 1.95, p = 0.02$, H-F) indicated that rGMR decreased in the medial frontal lobe and increased in the occipital lobe with normal aging. In contrast, rGMR in parietal and temporal lobes did not show a dramatic age-related change.

Figure 7.

Memory performance and rGMR correlations in frontal BAs in men and women. Significant group differences (Fisher's Z test, $p < 0.05$) in correlation coefficients for rGMR versus CVLT performance are shown for men and women. White areas were not significant. For men, better memory performance (mean number correct) was associated with increased rGMR in left BA 24 and less rGMR in BA 47. Semantic clustering was associated with less rGMR in left BA 47, 11, and 12. For women, better memory performance (mean number correct) was associated with increased rGMR in BA 12 and semantic clustering was associated with increased rGMR in BA 45.