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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 ^{18}FDG-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; ^{18}FDG-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 and Hazlett, 1997; De Santi et al., 1995; Hazlett et al., 1998a; Kuhl et al., 1982; Loessner et al., 1995; Rajah and D'Esposito, 2005; Reuter-Lorenz et al., 2000). Studies examining sex differences in brain activity, most commonly report women more active than men during the resting state (Andreason et al., 1994; Gur et al., 1995, 2000; Haut and Barch, 2006; Hofer et al., 2007; Rossell et al., 2002; Shaywitz et al., 1995; Willis et al., 2002), as well as, during various tasks (Andreason et al., 1994; Jaeger et al., 1998; Mansour et al., 1996; Nyberg et al., 2000; Ragland et al., 2000). 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 et al., 1997; Tisserand and Jolles, 2003).

Consistent with a frontal aging hypothesis (Tisserand and Jolles, 2003; West, 1996), we have previously shown an age-associated shift from anterior regions to more posterior

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regions of the frontal lobe in healthy individuals performing a verbal learning task (Brickman et al., 2003; Hazlett et al., 1998a). 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 and 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 and Roselli, 1989; Daigneault et al., 1992; MacPherson et al., 2002; Whelihan and Lesher, 1985), which are thought to be mediated by the frontal lobe (Elliott, 2003) and by frontal-subcortical circuitry (Alexander et al., 1986). These cognitive changes may be reflective of selective loss of neural tissue (Bartzokis et al., 2001; Bartzokis, 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., 1998a).

In the present study, a modification of the California Verbal Learning Task (CVLT; Delis et al., 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 et al., 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. (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-min 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., 1998a) 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 (BAs). 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 frontal and especially medial frontal regions 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 20 s through to 80 s (men: mean age = 54.5, S.D. = 20.1; women: mean age = 54.4, S.D. = 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 et al., 1992). Exclusion criteria included neurologic disorders, history of head injury with loss of consciousness greater than 5 min 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