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Endogenous estradiol is associated with verbal memory in nondemented older men

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ABSTRACT

This study examined the relationship between endogenous hormones and cognitive function in nondemented, ethnically-diverse community-dwelling older men enrolled in the Einstein Aging Study (EAS). All eligible participants (185 men, mean age = 81 years) received neuropsychological assessment (Free and Cued Selective Reminding Test (FCSRT), Logical Memory (LM), Trail Making Test B (TMTB), block design (BD)) and provided blood samples for hormonal assays (total estradiol, total testosterone, calculated free testosterone index). Linear regression analysis adjusted for age, education, body mass index, and cardiovascular comorbidities indicated that men with high levels of total estradiol demonstrated better FCSRT verbal memory performance ($\beta = 0.17$, $p < 0.02$) compared to men with lower levels of total estradiol. The results remained unchanged when the model was further adjusted for ethnicity. We did not detect an association between testosterone and cognitive performance. These findings indicate that high levels of total estradiol in older men are associated with better performance on a cue-based, controlled learning test of verbal memory that is a sensitive predictor of dementia.

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1. Introduction

The aging process is associated with heterogeneous declines in cognition both within and across individuals with normal cognitive abilities, mild cognitive impairment, and dementia (Christensen, 2001; Jak et al., 2009; Zimmerman et al., 2006). Cognitive impairment in elderly adults is a critical public health concern that has been associated with functional decline, increased length of hospital stays, late life depression, and decreased quality of life (Alexopoulos et al., 2002; Gallo & Lebowitz, 1999; Hoogerduijn, Schuurmans, Duijnstee, de Rooij, & Grypdonck, 2007). Identifying predictors of cognitive change is a vital step toward improving the lives of the growing population of elderly individuals. Although the underlying biological causes of individual differences in cognitive function and decline are likely multifactorial, endogenous hormones may be an important determinant of cognitive performance in older adults (e.g., see Yaffe et al., 2007). A wide range of hormones exhibit age-associated alterations (Lamberts, van den Beld, & van der Lely, 1997). Among elderly men, levels of the sex hormones testosterone and estradiol have been shown to decrease with age, while sex hormone-binding globulin (SHBG) levels increase with age (Moffat et al., 2002; Wolf & Kirschbaum, 2002; Yaffe, Lui, Zmuda, & Cauley, 2002).

Studies that examine relationships between cognitive function and endogenous testosterone levels among healthy nondemented older men have generally reported that higher levels of testosterone confer a cognitive advantage. An early study by Barrett-Connor and associates (Barrett-Connor, Goodman-Gruen, & Patay, 1999) found that higher bioavailable testosterone was associated with better performance on tests of general mental status and episodic memory. Five-year intervals separated the time between acquisition of the blood samples and testing of cognitive function. Subsequent cross-sectional reports indicated that higher levels of testosterone in older men were related to better performance on tests of general mental status, executive function, and psychomotor speed (Yaffe et al., 2002), memory (Muller, Aleman, Grobbee, de Haan, & van der Schouw, 2005; Thilers, Macdonald, & Herlitz, 2006), processing speed (Martin, Wittert, Burns, Haren, & Sugarman, 2007; Muller et al., 2005), and visuospatial abilities (Thilers et al., 2006). A recent study of 54 healthy older men reported a curvilinear relationship between free and bioavailable testosterone and performance on tests of working memory (Matousek & Sherwin, 2010). In a longitudinal study, Moffat and colleagues (Moffat et al., 2002) reported that men with higher free

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testosterone levels exhibited better performance on tests of memory and visuospatial skills, and a reduced rate of decline on tests of visual memory over an average follow-up period of 10 years. In addition to these observational studies, Cherrier and colleagues conducted a series of exogenous testosterone supplementation randomized controlled trials in elderly men in which performance on neuropsychological tests was a primary outcome of interest. In hypogonadal men (Cherrier, Craft, & Matsumoto, 2003), testosterone supplementation resulted in an increase in total testosterone and estradiol as well as verbal memory performance. In healthy older men (Cherrier et al., 2005), improvements in verbal memory performance were demonstrated in men who received testosterone supplementation, but not testosterone supplementation plus an aromatase inhibitor, suggesting that verbal memory performance in men may depend, in part, on the conversion of testosterone to estradiol. In contrast to these findings, Fonda and colleagues (Fonda, Bertrand, O'Donnell, Longcope, & McKinlay, 2005) found no association between testosterone levels and cognition in a large sample of men across the age range following adjustment for multiple comorbidities.

Findings from studies that have examined estradiol and cognitive function in nondemented older men have been somewhat mixed. Higher total and bioavailable estradiol have been shown to be associated with poorer performance on a test of general mental status (Barrett-Connor et al., 1999). Similarly, Geerlings and colleagues (Geerlings et al., 2006) found that higher bioavailable estradiol was associated with increased risk for cognitive decline and Alzheimer's disease in older men in the Honolulu-Asia Aging Study using a general assessment of cognitive function administered three times over an average of 6 years. Others have also found a relationship between higher total and bioavailable estradiol and cognitive decline in older men that persisted after controlling for multiple covariates such as age and vascular risk factors (Muller, van den Beld, Grobbee, de Jong, & Lamberts, 2009). In a sample of community-dwelling older men (Yaffe et al., 2002), higher total estradiol was associated with poorer performance on tests of visuomotor speed and executive function, but bioavailable estradiol was not associated with a test of general mental status. In contrast, a more recent longitudinal study by Yaffe and colleagues (Yaffe et al., 2007) identified a trend whereby older men with higher levels of bioavailable estradiol were less likely to experience cognitive decline on tests of general mental status and verbal memory. Still others have reported no relationship between cognitive performance and estradiol in older men (Fonda, Bertrand, O'Donnell, Longcope, & McKinlay, 2005; Martin et al., 2007; Matousek & Sherwin, 2010; Muller et al., 2005; Wolf & Kirschbaum, 2002; Yaffe et al., 2002).

Such diversity of results among studies is likely due to several factors, including inclusion of individuals with varied age ranges as well as differences in hormonal assays, tests used for cognitive assessment, and sources of the study population (e.g., clinic- or community-based). The objective of the current study was to augment our understanding of these complex relationships through an examination of endogenous hormones and cognitive function in nondemented older men. Our study represents a unique contribution to the literature in that our sample is relatively advanced in age (mean age = 81 years, age range 70–94 years) and comprises volunteers from a systematically sampled, ethnically-diverse community who were carefully screened for dementia with comprehensive neuropsychological testing and neurological examination. We focused solely on men because relationships between hormones and cognition may differ as a function of sex. It was hypothesized that older men with high levels of total testosterone would demonstrate better cognitive performance on tests of executive function, visuospatial ability, and memory.

2. Materials and methods

2.1. Participants

One-hundred eighty-five participants in the current study were drawn from the Einstein Aging Study (EAS), a longitudinal community-based volunteer sample of individuals over the age of 70 residing in the Bronx, New York. The Albert Einstein College of Medicine institutional review board approved the use of human subjects included in this study. EAS study design and methods are described in more detail elsewhere (Lipton et al., 2003). Participants were recruited beginning in 1993 using systematic sampling methods that utilized voter registration lists for Bronx County. All participants completed a comprehensive neuropsychological evaluation of attention, executive functions, memory, language, and visuospatial construction abilities at annual visits. Depressive symptomatology was measured using the 15-item Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986). All participants provided information regarding their past and current medical history that included self-report of myocardial infarction (MI), stroke, coronary artery bypass graft (CABG) surgery, diabetes, hypertension, and smoking. Beginning in 2004, hormone assays were completed using blood samples collected at in-person clinic visits. Individuals who reported medical conditions that would interfere with completion of neuropsychological assessment, were non-English speakers, or who were institutionalized were excluded.

Global cognitive function was assessed with the Blessed Information-Memory-Concentration test (BIMC; Blessed, Tomlinson, & Roth, 1968). Cognitive status was determined by a study neurologist and neuropsychologist at a diagnostic case conference. Because the primary objective of this investigation was to examine the cross-sectional relationship between hormone levels and cognitive function in nondemented elderly men, we excluded persons with current dementia based on the criteria provided by the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) (American, 1994) Therefore, 185 nondemented elderly men with available memory and hormone data were included in the current study.

Mild cognitive impairment (MCI) is a clinical term that is commonly used to characterize a transition state between normal cognitive aging and dementia. Based on Petersen criteria (Petersen et al., 1999), three of the participants in this sample met diagnostic criteria for amnestic mild cognitive impairment (MCI) as evidenced by (1) objective memory impairment (free recall FCSRT score $\leqslant$24; described in detail below) and (2) a subjective memory complaint. FCSRT free recall memory impairment cut-scores were derived from prior analyses (Grober & Kawas, 1997; Grober, Lipton, Hall, & Crystal, 2000).

2.2. Neuropsychological evaluation

2.2.1. Verbal memory

Consistent with the hypotheses of the current study, free recall from the FCSRT was selected from the EAS neuropsychological battery as a verbal memory variable of interest (Buschke, 1984; Grober & Buschke, 1987). The FCSRT is a test that controls attention and strategy use in an encoding phase to maximize learning. In the first part of the task, participants name 16 objects that are pictorially displayed. They are then presented with the same 16 objects (four at a time in a 2×2 grid) and asked to identify each object following a cue that is a categorical prompt. In the *free recall* condition, a measure of self-organized retrieval, the participant is immediately asked to recall the 16 objects. If the participant fails to correctly recall an object, they are provided with a category cue to test *cued recall*. There are a total of three free and cued recall trials; scores range from 0 to 48.

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