Brain and Cognition 80 (2012) 89–95

Contents lists available at SciVerse ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Cumulative estrogen exposure and prospective memory in older women

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ARTICLE INFO

Article history:
Accepted 2 May 2012
Available online 28 May 2012

Keywords:
Estrogen
Prospective memory
Aging

ABSTRACT

This study looked at cumulative lifetime estrogen exposure, as estimated with a mathematical index (Index of Cumulative Estrogen Exposure (ICEE)) that included variables (length of time on estrogen therapy, age at menarche and menopause, postmenopausal body mass index, time since menopause, nulliparity and duration of breastfeeding) known to influence estrogen levels across the life span, and performance on prospective and retrospective memory measures in a group of 50 postmenopausal women (mean age = 69.3 years) who, if they were current or former users of estrogen therapy, had started therapy within 5 years of menopause. The ICEE was found to be a significant predictor of performance on the Prospective Memory task ($F(1) = 4.21$, $p = .046$, $\eta_p^2 = .084$). No significant relationship was noted between the ICEE and performance on measures of retrospective memory. The results suggest that the level of cumulative lifetime exposure to estrogen a woman has influences her prospective memory performance later in life and that the influence of reproductive and biological markers of endogenous estrogen exposure are relevant factors to consider when studying the effect of estrogen therapy on cognitive functioning in postmenopausal women. In addition, the finding that performance on a measure of prospective memory, but not performance on measures of retrospective memory, was associated with the ICEE adds further support to the theory that the frontal cortex may be especially sensitive to estrogen.

1. Introduction

While considerable evidence from basic science research supports a role for estrogen in cognitive function, the research findings from the clinical literature on estrogen therapy (ET) have been less conclusive. It has been suggested that some of the inconsistent findings could be attributed to differences in the age at which women in the studies began taking ET and that there is a "critical window" of time around the menopause when ET may produce a protective effect on cognitive function in postmenopausal women (Brinton, 2004; Maki, 2006; Sherwin, 2006; Sturdee & MacLennan, 2006). The concept of a "critical window" is supported by the findings of a number of studies in rodents (Daniel, Hulst, & Berbling, 2006; Silva, Mello, Freymuller, Haidar, & Baracat, 2003) as well as observational (Henderson, Guthrie, Dudley, Burger, & Dennerstein, 2003; Kang, Weuve, & Grodstein, 2004; Matthews, Cauley, Yaffe, & Zmuda, 1999) and randomized controlled studies (Bagger, Tanko, Alexandersen, Qin, & Christiansen, 2005; Dunkin et al., 2005; Maki, 2005) with postmenopausal women.

The failure of previous studies that have looked at the effect of ET on cognition to include variables known to influence endogenous estrogen across the lifespan could also account for some of the inconsistencies in the findings. Age at menarche (Paganini-Hill & Henderson, 1994), age at menopause (McLay, Maki, & Lyketos, 2003), pregnancy (Chubak et al., 2004; Dorgan et al., 1995; Sobow & Kloszewska, 2004), breastfeeding (Bernstein, 2002) and postmenopausal body mass index (BMI; Grodstein, Clarkson, & Manson, 2003) all affect a woman's lifetime exposure to endogenous estrogen and there is evidence to suggest that the clinical response to ET may depend on its interaction with these variables (Dunkin et al., 2005; Rasgon et al., 2005). Smith et al. (1999) developed an Index of Estrogen Exposure (IEE) that included variables that are well recognized to effect estrogen levels (time on ET, age at menarche and menopause, parity, postmenopausal weight and time since menopause) and examined the relationship between scores on the IEE and four factors that consisted of statistically related neuropsychological measures. After controlling for age and education, scores on the IEE were significantly related to a factor that reflected global cognitive functioning. Examining the results of a series of post hoc analyses, Smith et al. (1999) reported that no individual marker of estrogen exposure, including duration of ET, showed as consistent a pattern of relationships with

Abbreviations: Estrogen therapy, ET; Body Mass Index, BMI; Index of Cumulative Estrogen Exposure, ICEE; prefrontal cortex, PFC; Spot-the-Word-Test, STW; Speed and Capacity of Language Processing Test, SCOLP; Geriatric Depression Scale, GDS; Wechsler Memory Scale – Third Edition, WMS-III; Index of Estrogen Exposure, IEE.

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http://dx.doi.org/10.1016/j.bandc.2012.05.001

cognitive performance as the IEE. Smith et al. (1999) concluded that combining the effects of markers of endogenous and exogenous estrogen might be the most beneficial approach when trying to understand the effects of estrogen on the brain and cognitive functioning.

Duff and Hampson (2000) suggest that some of the inconsistency in the ET literature with regard to the effects of estrogen on cognition could be explained by the degree to which the tasks used in the various studies depend upon frontal lobe functions.

It has been suggested that, rather than the hippocampus, the prefrontal cortex (PFC) and its circuitry are the prime mediators of estrogen's role in cognition (Keenan, Ezzat, Ginsburg, & Moore, 2001; Krug, Born, & Rasch, 2006), and there is some evidence from clinical studies to support this (Duff & Hampson, 2000; Joffe et al., 2006; Keenan et al., 2001; Krug et al., 2006).

Prospective memory is one aspect of cognition for which the PFC has been identified as the primary neuroanatomical substrate (Burgess, Quayle, & Frith, 2001; Okuda et al., 1998). Einstein and McDaniel (1996) define prospective memory as "memory for actions to be performed in the future". Similar to retrospective memory (Rendell & Thomson, 1999), declines in prospective memory are observed with ageing (Huppert, Johnson, & Nickson, 2000; Maylor, Smith, Della Sala, & Logie, 2002; Mäntylä & Nilsson, 1997; Rendell & Thomson, 1999).

Prospective memory is of considerable relevance for the older woman, in that deficits in prospective memory greatly influence an individual's ability to live independently (Einstein & McDaniel, 1996: Flannery et al., 1997) and may be an early indicator of dementia (Duchek, Balota, & Cortese, 2006; Huppert et al., 2000; Jones, Livner, & Backman, 2006).

There are reasons to expect that greater cumulative estrogen exposure may improve an older woman's prospective memory. Estrogen receptors have been detected in the human PFC (Perlman, Matsumoto et al., 2005; Perlman, Tomaskovic-Cook et al., 2005), and the results of neuroimaging studies indicate that estrogen is capable of modulating regional cerebral blood flow (rCBF) and brain activation patterns in the PFC of premenopausal (Berman et al., 1997) and postmenopausal women (Joffe et al., 2006; Resnick, Maki, Golski, Kraut, & Zonderman, 1998; Shaywitz et al., 1999; Smith et al., 2006; Stevens, Clark, & Prestwood, 2005). In addition, women who take ET have been found to perform better than untreated women on frontal-mediated tasks in a number of studies (Duff & Hampson, 2000; Erickson et al., 2007; Grodstein et al., 2000; Keenan et al., 2001; Kimura, 1995; Wolf & Kirschbaum, 2002.).

To date, there have been several hormone therapy studies that have included a measure of prospective memory, although it was not the focus of the studies. Of these studies, one found no difference in prospective memory scores between postmenopausal women receiving ET (Resnick et al., 1998) while two found that ET users performed significantly better than nonusers on a measure of prospective memory (Maki & Resnick, 2000; Stephens, Hamilton, & Pachana, 2003). No study to date has determined whether cumulative lifetime estrogen exposure has any bearing on prospective memory in later life. Therefore, the purpose of the present study was to look at whether there is a relationship between a woman's level of cumulative estrogen exposure and her performance in later life on a task designed to assess prospective memory. In keeping with Rasgon et al.'s (2005) description of cumulative lifetime exposure to estrogen as the "sum of endogenous exposure throughout the reproductive period and exogenous exposure via use of hormone therapy in menopause" (p.559), cumulative estrogen exposure was determined with an index of variables known to influence estrogen levels throughout a woman's life. In keeping with the findings from the basic science literature and the clinical studies of endogenous estrogen and ET, it was hypothesized that higher levels of cumulative estrogen exposure would be associated with better prospective memory performance.

2. Materials and methods

2.1. Participants

Participants in this study were 50 women who voluntarily responded to advertisements placed in local publications and community centers seeking volunteers for a study on memory in older women. Women were screened over the telephone for study eligibility when they called in response to the advertisement and were considered for inclusion if they considered themselves to be in good physical and mental health and were able to provide information with regard to the timing and nature of menopause as well as use of hormone replacement. In keeping with the idea of a "critical window" of time around the menopause, women who would be considered "late initiators" of hormone therapy were not included. For the purposes of the present study, "late initiators" were defined as women who had commenced ET 5 or more years after menopause. The cutoff of 5 years was chosen based on MacLennan et al.'s (2006) criteria and Clarkson and Appt's (2005) review of estrogen and atherosclerosis in which they concluded that the beneficial effects of ET against the development of coronary artery atherosclerosis are completely lost when treatment is delayed for 6 or more years after menopause. Additional exclusionary criteria included self-reported history of hysterectomy without bilateral oophorectomy (as age at hysterectomy in these women would, according to Younan et al. (2002), underestimate their age at menopause), central nervous system disease (e.g., Parkinson's, Multiple Sclerosis, clinical history of stroke, epilepsy and other neurological disorders), psychiatric diagnosis, severe cardiac disease (including history of myocardial infarction, coronary bypass surgery or angioplasty), or metastatic cancer. In the current sample, three women had undergone a "surgical menopause" as a result of hysterectomy with bilateral oophorectomy while the remaining 47 women reported experiencing a natural menopause. 10 women in the study were nulliparous. Descriptive statistics for the participants are presented in Table 1 of the results section.

2.2. Assessment measures

2.2.1. Intellectual functioning

The Spot-the-Word-Test (STW) from the Speed and Capacity of Language Processing Test (SCOLP; Baddeley, Emslie, & Nimmo-Smith, 1992) was administered as a measure of current intellectual functioning. Possible raw scores on this measure range from 0 to 60. Raw scores were converted to IQ estimates as per Crowell, Vanderploeg, Small, Graves, and Mortimer (2002).

Table 1
Means and standard deviations of scores of the demographic and reproductive variables.

	Mean	Standard deviation
Age (years)	69.3	3.3
Education (years)	15.1	3.7
Age at menarche (years)	13.1	1.9
Age at menopause (years)	49.9	4.6
Number of pregnancies	2.3	1.7
Average duration of breast feeding (months)	5.1	11.2
Average duration of estrogen therapy (months)	62.7	93.5
Average body mass index since menopause	27.0	6.1
Average time since menopause (months)	19.6	6.8