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Life-time estrogen exposure and cognitive functioning in later life

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Summary
Context: While recent studies suggest that exogenous estrogen treatment could help reduce age-related cognitive decline and delay the onset of dementia, this has not been found consistently. Few studies have considered the influence of life-time estrogen exposure which may have an independent effect on cognition and/or modulate treatment response.
Objective: The aim of this study was to examine whether factors related to estrogen exposure across the life-time were associated with cognitive function in postmenopausal women.
Design: A battery of cognitive tests were administered at baseline and at 2 and 4 years of follow-up to evaluate cognitive performance among a population-based cohort of 996 French women aged 65 years or older, who were recruited as part of the ESPRIT study. Detailed reproductive histories were also obtained. Logistic regression models, controlling for an extensive range of potential confounding factors, were generated to determine whether hormone-related factors across a woman's lifetime were associated with poor cognitive performance in later life.
Results: Age at first menses was negatively associated with performance on the tasks of visual memory and psychomotor speed, while a longer reproductive period was associated with better verbal fluency. Likewise, women who had their first child at a young age performed significantly worse on each of these tasks, as well as on a measure of global cognitive function. The results also suggest that current hormone therapy may be beneficial for a number of cognitive domains, however, in multivariate analysis, women performed significantly better on the task of visual memory only. In contrast, in analysis adjusted for baseline cognitive performance and a range of other factors, none of the reproductive variables were associated with a decline in cognitive performance or the incidence of dementia during the 4-year follow-up period.

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Conclusions: In addition to hormone therapy, certain hormone-related events across the lifetime are also associated with cognitive functioning in later life. They were not observed in this study to modulate dementia risk; however, this should be verified over a longer follow-up period. Further studies will also be required to determine whether lifetime hormonal exposure may modify women's response to hormone therapy after the menopause.

1. Introduction

Epidemiological studies suggest that elderly women have the highest prevalence of both dementia and more specifically Alzheimer's disease (AD) (Gao et al., 1998; Andersen et al., 1999), and that reduced levels of estradiol that accompany the postmenopausal period, may be partly responsible. Estrogen affects the structure and function of the nervous system and appears to be involved in brain maturation and memory processing (Behl, 2002). Estrogen has been shown to have a positive influence on brain neurotransmitter levels and the identification of estrogen receptors in the brain suggests they mediate some of the hormone's cognitive effects (see for review Ancelin and Ritchie, 2005). The potential for estrogen to reduce age-related cognitive problems and delay the onset of more severe cognitive deficits such as dementia, is therefore of strong interest. However, despite relatively clear evidence for a biological link between estrogen and cognitive function, a protective effect has not been consistently demonstrated in clinical studies (see for review Sherwin and Henry, 2008).

The vast amount of work in this field has come from studies of hormone therapy (HT), which have investigated the potential therapeutic role of estradiol, with or without progesterone, on cognitive function (see for review Ryan et al., 2008a; Sherwin and Henry, 2008). Meta-analyses of observational studies have reported predominantly positive effects of HT on cognitive function, most notably with respect to verbal memory, and a diminished risk of AD has also been reported in users of HT compared to non-users (Yaffe et al., 1998; Leblanc et al., 2001; Maki and Hogervorst, 2003). However, the "gold-standard" randomised controlled-trials (RCTs) have been mixed and the Women's Health Initiative Memory Study (WHIMS), an ancillary study to the much publicised WHI, actually found that women using HT had an increased risk of developing all cause-dementia (Shumaker et al., 2003). In addition, women using treatment were not at an increased risk of mild cognitive impairment (MCI) and the risk of overall cognitive dysfunction was not modified compared with women taking placebo (Rapp et al., 2003; Shumaker et al., 2003). Subsequent criticisms of this study have pointed out that the female participants were aged at least 65 years and therefore this is not truly representative on the usual clinical situation, where women often seek treatment around the time of the menopause. These women were furthermore treated with a particular type of HT, an orally administered conjugated equine estrogen compound that is used widely in the USA but not necessarily elsewhere in the world. Treatment with transdermal estradiol compounds may produce quite different results (Sherwin and Henry, 2008).

The current inconsistencies in the literature may therefore result from differences in study designs; notably types of HT, age of the populations involved and differences in the type and measurement of the cognitive functions examined. While there is evidence to suggest that HT may preferentially benefit short-term verbal memory (Hogervorst et al., 2002b; Sherwin, 2003), positive associations have also been reported with other less extensively studied cognitive domains, including verbal fluency (Grodstein et al., 2000), visual memory (Resnick et al., 1997) and psychomotor speed (MacLennan et al., 2006). It is also possible that rather than focusing solely on HT, it may be important to consider other hormonal factors that could contribute to late-life cognitive function, such as other forms of exogenous treatment (principally oral contraceptives) and factors which influence endogenous estrogen exposure across the lifetime.

Data from epidemiological studies provide some indication of an association between increased life-time endogenous exposure and decreased risk of poor cognitive function (Smith et al., 1999; Lebrun et al., 2005; Rasgon et al., 2005), cognitive decline (McLay et al., 2003) or AD (Paganini-Hill and Henderson, 1994; Ptok et al., 2002; Colucci et al., 2006). However, studies have tended to focus on only a small number of reproductive events, principally age at menopause (Dunkin et al., 2005; Lebrun et al., 2005) or considering in addition the timing of first menses (Paganini-Hill and Henderson, 1994; Geerlings et al., 2001; Low et al., 2005). Of the studies which have looked at a number of reproductive factors (age at menarche and menopause, as well as parity) (Rasgon et al., 2005; Colucci et al., 2006), including one of the scant longitudinal studies to be undertaken in this area (McLay et al., 2003), none of these have examined which specific areas of cognitive functioning are most susceptible to hormone exposure.

The aim of this study was to determine whether factors that influence both endogenous and exogenous hormone exposure across the lifetime, are associated with cognitive function in later life or the decline in cognitive function over a 4-year period. In addition to verbal memory, other less extensively studied cognitive domains were also investigated. In this study, we considered the multiple competing causes of cognitive decline in the elderly and the incidence of dementia was also evaluated, to determine whether hormonal factors can modify dementia risk. We hypothesised that increased endogenous estrogen exposure across the lifetime or current HT would be associated with better cognitive function in later life.

2. Methods

2.1. Participants

Details regarding the design of the ESPRIT study and participant recruitment have been published in detail (Ritchie et al., 2004). Participants were recruited over a 2-year period from 1999 to 2001, by random selection from the electoral