Journal of Clinical and Experimental Neuropsychology

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ncen20

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Published online: 19 Feb 2015.

Journal of Clinical and Experimental Neuropsychology, 2015
http://dx.doi.org/10.1080/13803395.2014.1000267

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(*Received 15 December 2013; accepted 15 December 2014*)

Introduction. This study was designed to assess sex differences in older adults (55–65 years old) in executive functions and to examine the influence of hormone therapy (HT) in postmenopausal women. *Method*. We have assessed task performance in memory, visuospatial, and executive functions in 29 women using HT, 29 women who never used HT, and 30 men. *Results*. Men outperformed never users in task switching and updating. HT users outperformed never users in updating. HT users outperformed never users and men in visual divided attention. *Discussion*. The present study support previous findings that sex and HT impact cognition and bring new insights on sex and HT-related differences in executive functions.

Keywords: Executive functions; Sex differences; Hormone therapy; Cognitive aging; Postmenopausal women.

The proportion of individuals aged 60 years or over increases worldwide and causes significant challenges due to age-related decline in physical and cognitive capacities. It is now well established that cognitive performance tends to decline with age (Craik & Salthouse, 2008), and, more particularly, aging is associated with less efficient executive functions (West, 1996). Age-related impairment in executive functions has been linked to neurobiological changes in the prefrontal cortex (Raz & Rodrigue, 2006). This age-related deficit on executive functioning could increase the risk of gait disturbances with age (Yogev-Seligmann, Hausdorff, & Giladi, 2008). Nevertheless, evidence suggests that some older adults can maintain intact cognitive functioning even at an advanced age (Daffner, 2010). This heterogeneity in cognitive aging suggests that some factors can protect against age-related cognitive decline. Among those factors, physical exercise, nutrition, and intellectual stimulation have been associated with improved cognitive performance in older adults (Churchill et al., 2002; Hillman, Erickson, & Kramer, 2008). Another important factor that is known to influence cognitive function in aging is sexual hormonal fluctuations, notably changes in estrogen levels in both men and women (Janicki & Schupf, 2010). Finally, one more factor that could be pertinent in cognitive aging studies is gender. Indeed, some studies tend to show sex-related differences in aging cognition (Jansen & Heil, 2010; Stein et al., 2012).

Many studies have reported sex-related differences in cognition in young adults, with women generally outperforming men on tasks of verbal fluency and episodic memory, and men generally outperforming women on tasks of spatial skills and mathematical reasoning (Gale, Baxter, Connor, Herring, & Comer, 2007; Halpern, 2000; Voyer, Voyer, & Bryden, 1995). The same pattern

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This research was supported in part by a fellowship from the Canadian Institutes of Health Research (N.C.), the Canada research Chair program (L.B.) and a discovery grant from the Natural Sciences and Engineering Research Council of Canada (L.B.).

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of sex-related differences in cognitive performances has been reported in older adults as well (Beeri et al., 2006; Gale et al., 2007; Gerstorf, Herlitz, & Smith, 2006; Herrera-Guzman, Pena-Casanova, Lara, Gudayol-Ferre, & Bohm, 2004; Jansen & Heil, 2010; Stein et al., 2012; van Hooren et al., 2007). In studies focusing more on sex-related differences in working memory and executive functions, younger women tend to outperform men in working memory tasks (Duff & Hampson, 2001) and in inhibition tests (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006), whereas men outperformed women in task switching (Tun & Lachman, 2008) and divided-attention tasks (Goddard, Dritschel, & Burton, 1998; McGowan & Duka, 2000). In older adults, few studies of sex-related differences have examined working memory and executive functions, and the results are quite inconsistent. In some studies, the female advantage observed in younger adults in working memory was not replicated (Parsons, Rizzo, van der Zaag, McGee, & Buckwalter, 2005), and one study even found the opposite pattern, with men outperforming women (Maller et al., 2007). As observed in younger adults, older women perform better than older men in inhibition tasks (Seo et al., 2008; Van der Elst et al., 2006), but other studies did not find sex-related differences in inhibition tasks (Daniel, Pelotte, & Lewis, 2000; Li, Huang, Constable, & Sinha, 2006). Although older men outperform older women in task switching in some studies (Beeri et al., 2006; Parsons et al., 2005), findings from another study did not find such sex-related differences (Munro et al., 2012). To our knowledge, only one study of sex-related differences in older adults assessed auditory divided attention, and no sex-related difference was observed (Munro et al., 2012). Giving the acknowledged age-related deficit observed in dual-task performances (see Verhaeghen, 2011) and the growing importance of divided attention in the study of gait and posture in older adults (see Fraser & Bherer, 2013, for a review; Li et al., 2010), future studies are required to better understand how sex might influence divided attention.

While some studies suggest that the same pattern of sex-related differences in cognitive performances has often been observed among different age groups (de Frias, Nilsson, & Herlitz, 2006; Gerstorf et al., 2006; Maylor et al., 2007), other studies have reported a steeper age-related decline in cognition among women than among men (Ho, Woo, Sham, Chan, & Yu, 2001; Meinz & Salthouse, 1998; Proust-Lima et al., 2008; Read et al., 2006). Reduction of estrogen levels in the aging brain of both men and women has been associated with accelerated age-related cognitive decline and with a higher risk of Alzheimer disease (Janicki & Schupf, 2010). In women, menopause is associated with a rapid estrogen depletion. In men, production of testosterone never completely stops, and a small part of the testosterone is converted into estradiol by the enzyme aromatase. Thereby, endogenous estrogen levels are slightly higher in elderly men than in postmenopausal women (Janicki & Schupf, 2010). Estrogen has been associated with many neuroprotective effects (Genazzani, Pluchino, Luisi, & Luisi, 2007). Menopause transition stage is associated with a reduction of estrogen, which could explain that women have higher risk of cognitive decline than men (Irvine, Laws, Gale, & Kondel, 2012). Consequently, hormone therapy (HT) in postmenopausal women is considered as a potential moderator of sex-related differences in cognitive functioning in older adults. However, almost all studies on sex-related differences in older adults did not control for either current or past HT use, which may have led to inconsistent results.

Estrogen induces plasticity in the frontal lobes and the hippocampus (Brinton, 2009; Genazzani et al., 2007), and these brain structures play a critical role in episodic memory, working memory, and executive functions (Stuss, 2011). Menopause transition in women should thus be associated with a decline in cognitive functions related to the integrity of the prefrontal cortex and the hippocampus. However, to date, results supporting an association between menopausal transition and cognitive functioning have been inconsistent (Fuh, Wang, Lee, Lu, & Juang, 2006). Cross-sectional data demonstrated an association between menopausal transition and decline of performances in planning and task switching, verbal memory, and verbal fluency (Berent-Spillson et al., 2012; Elsabagh, Hartley, & File, 2007; Herlitz, Thilers, & Habib, 2007). In longitudinal designs, menopause transition has been associated with a decline in spatial abilities, verbal fluency, and verbal memory, and this effect did not correlate with age (Epperson, Sammel, & Freeman, 2013; Thilers, Macdonald, Nilsson, & Herlitz, 2010).

The most convincing evidence supporting the potential maintaining role of estrogen on cognitive functioning comes from studies of estrogen therapy in postmenopausal women. Indeed, HT may be a potential therapeutic strategy to enhance hippocampal and frontal dependent cognitive functions in postmenopausal women by elevating serum estrogen levels. Numerous studies have attempted to address this question. Typically, in cross-sectional studies, postmenopausal women

using HT are compared to postmenopausal women not using HT on a variety of cognitive tasks. Most of these studies have demonstrated better performances in women using HT in tasks of verbal and visual memory, working memory, and executive functions (Duff & Hampson, 2000; Henderson & Popat, 2011; MacLennan et al., 2006; Maki & Sundermann, 2009; see Sherwin, 2006, for a review; Sherwin & Henry, 2008; Wegesin & Stern, 2007). However, results from randomized controlled trials (RCTs) have been more controversial. Some studies have reported better performances in postmenopausal women taking HT compared to placebo in verbal and visual memory, working memory, and executive functions (Duka, Tasker, & McGowan, 2000; Joffe et al., 2006; Krug, Born, & Rasch, 2006), but other RCTs did not find an association between HT and cognitive performances or even reported an increasing risk of cognitive decline in postmenopausal women using HT (Maki, Gast, Vieweg, Burriss, & Yaffe, 2007; Shumaker et al., 2004; Shumaker et al., 2003). Differences between RCTs concerning the type and the dose of HT, the route of administration of HT, and the age of women at the time of treatment may have led to inconsistent results (Sherwin, 2006).

The critical window of opportunity hypothesis (Lord, Buss, Lupien, & Pruessner, 2008; MacLennan et al., 2006; Resnick & Henderson, 2002; Sherwin, 2005, 2007b) has been an attempt to explain inconsistent results in RCTs. According to this hypothesis, estrogen treatment in postmenopausal women should be initiated at the time of menopause to maintain cognitive functioning, whereas a late onset of treatment would be associated with no effect on cognitive functions or may even increase the risk of cognitive decline and dementia (see Maki, 2013, for a review). Interestingly, it has been reported that the beneficial effect of early postmenopausal HT on cognition may last even after the cessation of the treatment (Bagger, Tanko, Alexandersen, Qin, & Christiansen, 2005; Boccardi et al., 2006). A recent study has shown larger hippocampus volume in postmenopausal women using HT than in age-matched never users when HT was initiated at the time of the menopause (Erickson, Voss, Prakash, Chaddock, & Kramer, 2010). In accordance with the critical window for beneficial effects of HT on cognition, the present study includes only women who had initiated HT at the time of menopause.

In sum, HT in postmenopausal women should be considered as a factor that may influence sex-related differences in cognition in older adults due to the neuroprotective effects of estrogen. To our knowledge, only one study took into account the use of HT in the study of sex-related differences in cognitive aging, and its results showed that HT may influence cognitive sex differences (Miller, Conney, Rasgon, Fairbanks, & Small, 2002). Sex-related differences in older adults have been replicated several times in tasks of verbal memory and spatial abilities, but remain understudied in tasks measuring executive functions. Similarly, HT-related differences in cognition have been well documented in tasks of verbal memory, but few studies included measures of executive functions. It is now well established that executive control does not represent a unitary concept but, rather, consists of a set of relative independent cognitive mechanisms (i.e., inhibition, updating, task switching, divided attention) that play a role in the management of cognitive processes involved in a goal-directed behavior (Miyake et al., 2000; Stuss & Alexander, 2000). Importantly, they are not equally affected by aging. Whereas age-related deficits in inhibition are mainly affected by the age-related general slowing effect, dual-task and switching performances show an significant and specific age-related decline beyond the effects of speed (Verhaeghen, 2011). However, studies of sex or HT-related differences in older adults in executive functions have more often used tests assessing only one specific executive control process such as problem-solving strategy (Wegesin & Stern, 2007), working memory (Duff & Hampson, 2000, 2001; MacLennan et al., 2006), inhibition (Seo et al., 2008), task switching (MacLennan et al., 2006; Munro et al., 2012), and divided attention (Munro et al., 2012). In the present study, a comprehensive executive functions battery was used to assess sex-related differences in executive control tasks, while controlling for HT use.

The present study investigated sex-related cognitive differences in adults aged 55 to 65 years while taking into account the potential moderating effect of HT. Men, women using HT, and women who had never used HT were compared using a comprehensive neuropsychological battery, with a specific interest on executive functions and episodic memory. As previously mentioned, executive control is not a unitary concept. Based on previous studies, we expected differential sex and HT differences depending on the distinct executive mechanisms. Notably, switching, updating, and dual-task ability should be sensitive to sex-related and HT differences. Moreover, in line with previous findings, it was expected that women would outperform men in episodic memory tasks and that men

would outperform women in visuospatial tasks. It was also expected that HT use would moderate these sex differences.

METHOD

Participants

Eighty-eight community-dwelling adults aged 55 to 65 years participated in the present study. They were recruited by ads in local newspapers, flyers, community centers, laboratory web site, participant pool of the research center where the study took place, and word of mouth. A brief explanation of the study was given during a first telephone contact, and upon agreement of the participant, a screening telephone interview was immediately completed to assess health exclusion criteria, health status using a self-reported 5-point scale, and vision and hearing condition. Three groups of participants were recruited: postmenopausal women who had never used HT (never users), postmenopausal women who had started to use HT at the time of their menopause (HT users), and men. Postmenopause is defined as the period after one year following the final menstrual period. This was obtained by self-report. All subjects received a financial compensation (30 CAD) for their time. The study received approval of the ethical review board of the geriatric hospital where the study took place, and all participants provided written informed consent.

Participants had no history of severe neurological conditions (i.e., moderate or severe traumatic brain injury, stroke, brain tumor, epilepsy, dementia), they had not undergone a major surgery in the last 6 months, they were free from antidepressant or anxiolytic medications, and their body mass index (BMI) ranged from 18.5 to 30. Participants were included in the study only if they scored 27 or higher on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and lower than 21 on the Geriatric Depression Scale (GDS; Yesavage et al., 1982). Women were excluded from the study if they had early menopause (e.g., before 45 years old) or bilateral oophorectomy. Moreover, consistent with the critical window of opportunity hypothesis of estrogen effects on cognitive functions (Erickson et al., 2010; MacLennan et al., 2006; Sherwin, 2006, 2007a), only women who initiated HT less than one year after menopause were included in the HT users group.

To participate in the study, women using HT had to have taken hormones for at least one year, and they were asked to bring a copy of their hormonal prescription to check HT specificities. Otherwise, self-reported information was used. Because long-term effects of past HT use on cognition have been associated with a duration of treatment of 2–3 years (Bagger et al., 2005), we included in the never users group women who did not use HT for more than 6 months (6 months use: 1 woman; 3 months use: 1 women; <1 month use: 2 women). A modified version of a self-reported questionnaire by Lord, Duchesne, Pruessner, and Lupien (2009) was used to obtain information about HT and lifetime estrogen exposure in women. Given the possible confounds of the period of use of HT (past vs. current users) in HT users (Matthews, Cauley, Yaffe, & Zmuda, 1999), preliminary analyses were performed to compare past and current users. Of all HT users, 51.7% were still current users. Current users had been taking this treatment for 9.71 ± 4.75 years while past users had been taking the treatment for 6.67 ± 3.27 years, which was significantly lower, $F(1, 27) = 4.09$, $p < .05$, $\eta^2_p = .53$. Current HT users initiated their treatment 1.58 ± 1.50 years after their first menstrual irregularities and 0.7 ± 2.27 years prior to their last menses, while past HT users initiated their treatment 1.00 ± 2.48 years after their first menstrual irregularities and 1.93 ± 2.69 years prior to their last menses. Both groups were statistically comparable on both measures (*p*s > .25). Past users had ceased the treatment for 6.7 ± 3.2 years on average. Statistical analyses revealed that the two subgroups were similar on age, education, depression, age of menopause, and all cognitive measures (all *p*s > .25). Therefore, past and current HT users were pooled together for subsequent analyses. Four women initiated their HT in the year following their final menstrual period, and only two women initiated HT prior to their first menstrual irregularities due to symptoms of menopause hot flushes. Table 1 presents demographic data and cognitive screening measures. The three groups (HT users, never users, and men) were comparable in demographic data and general cognitive functioning (all *p*s > .05).

Procedure and material

All participants were tested in two separate sessions, and the presentation order of tests was the same for all participants. The first session lasted approximately 1 hour 45 min. Participants were tested individually with a comprehensive paper and pencil neuropsychological battery including screening tests of general verbal abilities

TABLE 1
Means and standard deviations of demographic and screening measures and menopausal and hormone therapy data

Measure	*HT users (N = 29)*	*Never users (N = 29)*	*Men (N = 30)*
Age (years)	61.76 (2.23)	61.31 (2.71)	61.57 (2.03)
Education (years)	15.28 (2.51)	15.10 (3.04)	15.50 (2.19)
Health[a]	4.28 (0.61)	4.34 (0.60)	4.39 (0.64)
MMSE (dementia)	29.24 (0.87)	28.93 (0.96)	29.00 (0.87)
GDS (depression)	4.52 (4.01)	3.17 (3.15)	3.00 (2.94)
BMI	24.02 (3.46)	25.33 (2.91)	23.86 (3.15)
Physical activity	22.03 (2.86)	20.55 (2.50)	22.33 (3.79)
PSQI (Sleep)[a]	7.21 (4.19)	5.07 (3.53)	5.19 (4.10)
Cognitive activity[b]	77.83 (14.94)	77.17 (14.86)	75.68 (19.29)
Similarities	22.31 (4.69)	23.03 (4.69)	22.33 (4.28)
Digit Span Forward	9.97 (2.28)	10.03 (2.43)	9.73 (2.46)
Digit Span Backward	7.90 (2.62)	7.10 (2.51)	6.87 (2.64)
Digit Symbol	71.79 (12.21)	71.03 (12.52)	69.30 (11.43)
Age at last menses	51.45 (2.82)	50.76 (3.74)	
Years of HT	8.02 (4.31)		
MRS (symptoms)	10.14 (5.19)	7.55 (6.34)	

Note. HT = hormone therapy; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale; BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index; MRS = Menopause Rating Scale.
[a]Missing data for 4 participants. [b]Missing data for 2 participants.

(*Wechsler Adult Intelligence Scale–Third Edition*, WAIS–III, Similarities; Wechsler, 1997), attention and working memory (WAIS–III, Digit Span), and processing speed (WAIS–III, Digit Symbol). Participants also completed tests of episodic memory, visuospatial abilities, and executive functions (see test description below). At the end of the first session, participants received questionnaires to be completed at home and to brought back at Session 2. These questionnaires assessed cognitively stimulating activities across the life span (Wilson, Barnes, & Bennett, 2003), physical activities (Robert et al., 2004), and sleep habits (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Questionnaires on menopausal symptoms (Menopause Rating Scale, MRS; Greene, 2002) and lifetime estrogen exposure (Lord et al., 2009) were also included for women. Questionnaires were all screened for missing answers during the second session, and participants were asked to complete blank responses when needed.

Within 2 weeks of the first session, participants completed a second session that lasted approximately one hour and took place in small groups (maximum of 8 participants). In a quiet room, each participant performed two computerized dual tasks comfortably seated in front of a computer (PC Pentium 4 with a 19″ flat screen). Each participant used a computer isolated in a cubicle from the other participants to avoid distraction. Visual stimuli appeared in the middle of the screen in white on a black background at a viewing distance of approximately 45 cm. At this distance, visual stimuli subtended a vertical visual angle of 1.15° and a horizontal visual angle of 0.76°. Auditory stimuli were presented via headphones with a volume control so that participants could adjust sound level at their convenience.

Rey Auditory Verbal Learning Test

In the Rey Auditory Verbal Learning Test (RAVLT), a verbal episodic memory task, participants had to memorize a list of 15 unrelated words (Rey, 1964). To measure the learning slope, the words were repeated over five different trials. A second list of 15 new and unrelated words was presented once immediately after the learning trials, after which participants again repeated the first list and then again after a delay of 30 minutes. In a delayed recognition trial, words of the first list had to be recognized among a set of words that included words of the second list and new words. Variables of interest were the number of words recalled over Trials 1 to 5 (*RAVLT total*), immediately after the presentation of the second list (*immediate recall*), and after a long delay (*delayed recall*), and the number of words recognized after a long delay (*recognition trial*).

Mental Rotation Task

The Mental Rotation Task (MRT) requires the comparison of 3D objects such as the Shepard–Metzler 3D rotation task (Vandenberg & Kuse, 1978). The test contains 20 problems. For each problem, a target object should be paired with two correct answers among four choices. Score for each item was obtained by adding the number of correct answers (1 or 2). When one correct and one false answer was given, the item was scored zero to exclude the random effect. The task started with three practice items with explanations and feedback. Then, two sections containing 10 problems each were given within a time limit of five minutes for each section. Participants were asked to answer as many problems as possible within the time limit. The total score for both sections was used as the dependent variable.

Two-back task

Updating was assessed with the 2-back task (Lezak & Lezak, 2012). In this task, a list of 28 letters was read, and participants had to say, for

each letter, whether it was the same or not as two letters back. The next letter was given immediately after the participants' answer. Number of correct responses and completion time were used as dependent variables.

Number–letter task

This paper and pencil switching task included a *letter task* (vowel–consonant) and a *digit task* (odd–even), which were presented under three different conditions: *single letter, single digit,* and *switching* (Rogers & Monsell, 1995). Each condition consisted of a series of 32 squares divided into four parts in which a pair made of one letter and one digit (*letter–digit pair*) was presented in one of the four parts of the square. In the single-letter condition, the letter–digit pair was presented in one of the two parts located on the top row of the square, and participants were asked to answer if the letter was a vowel or a consonant. In the single-digit condition, the letter–digit pair was presented in the bottom row of the square, and participants had to say whether the number was odd or even. Finally, in the switching condition, both tasks were randomly presented. The completion time and the number of errors in each condition were measured. Mean completion time of both the single-letter and the single-digit conditions was used as a performance measure of the *single condition*. A *switching cost* was computed by subtracting mean completion time of the single condition from that of the switching condition.

Stroop test

The Modified Stroop Color Word Test is a measure of inhibition and selective attention (Bohnen, Jolles, & Twijnstra, 1992; Lezak & Lezak, 2012). It includes four conditions and four colors (green, blue, red, and yellow). In the *word reading* condition, participants had to read color-words written in black ink. In the second *color naming* condition, participants had to name the color of strings of rectangles. The third *color–word interference* condition required participants to name the color of color-words printed in a color that differed from their meaning (e.g., yellow printed in red). In the *switching* condition, participants had to either name the color of the word or read the word when it appeared within a square. Completion time and number of errors were the dependent variables of interest.

Paper and pencil dual task

The paper and pencil dual-task paradigm assesses divided attention (Della Sala, Baddeley, Papagno, & Spinnler, 1995). In this task, the baseline digit span was first assessed. Then, two single-task conditions were completed, followed by a dual-task condition. In the first *digit* single-task condition, participants recalled lists of digits at the length of their baseline span for two minutes. Participants were asked to execute the task as accurately as possible. The proportion of correct lists of digits was scored (p_s = number of lists correctly recalled divided by the number of presented lists). The next single-task condition was a *tracking* task in which blank boxes were filled with an "X" for 2 min. Participants were instructed to execute the task as fast as possible without making mistakes. The total number of boxes correctly filled was scored (t_s). Finally, in the *dual-task* condition, both tasks were executed simultaneously. Two scores were obtained from this dual-task condition, one for each task: the proportion of correct lists of digits (p_d) and the total number of boxes correctly filled (t_d). Then, the difference between the proportion of correct lists of digits in the single-task and in the dual-task condition was computed ($p_s - p_d = p_m$). The difference between the total number of boxes correctly filled in the single-task and in the dual-task condition was calculated and transformed into a proportion $[(t_s - t_d)/t_s = p_t]$. Finally, a dual-task *index* was obtained from both proportions by the following formula: index $= [1 - (p_m + p_t)/2] \times 100$. The dual-task index was the dependent variable of interest and represented the decrease of performance in the dual-task condition compared to the single conditions.

Computerized dual tasks

Computerized divided-attention tasks used in this study were similar to those used by Bherer et al. (2005, 2008). Participants completed two different task combinations measuring divided attention and using different modalities. In the *visual dual task*, the two tasks were a letter (A, B, or C) and an arrow direction (left, right, or up) identification task. Responses were provided by pressing down appropriate keys on the computer keyboard. The *auditory dual task* involved a tone identification task (high vs. low) and a tone localization task (indicate whether the tone came from the left or the right ear of the headphone). Response hand assignment was counterbalanced across participants only for the auditory dual task. For the visual task, the letter task was responded to with the left hand, and the arrow task was responded to with the right hand. The visual dual task was completed first and was followed by the auditory dual task. Task instructions

were given by a trained experimenter and were also presented on the screen before the beginning of each block. Participants were asked to respond as quickly and as accurately as possible without prioritizing one task over the other. Procedure was the same for both tasks. In each task, six blocks of trials were presented. First, two single blocks, one for each task, were presented. Each block included 24 single-pure trials. In the third block, 48 single-mixed trials were presented—that is, stimuli of both tasks could appear in the same block, but only one at a time. The two following blocks included 60 dual-mixed trials in which both tasks were presented simultaneously with a randomly varying interstimulus interval of between 850 and 2850 ms. A final block of single-mixed trials was then presented. Participants initiated each block by pressing the spacebar, and the answer to each trial prompted the next trial. Trials answered after 4000 ms were removed from reaction time analyses. Mean reaction time (RT) and accuracy were computed for each type of trial (single-pure, single-mixed, and dual-mixed) and for each task. Two attentional costs were analyzed. The *task-set cost* (i.e., the difference between single-pure and single-mixed trials) represents the additional cost required to prepare and maintain multiple task sets. The *dual-task cost* (i.e., the difference between the single-mixed and the dual-mixed trials) refers to the attentional demand required to coordinate multiple stimulus perceptions and motor responses.

Data analysis

Statistical analyses were performed with SPSS Version 19. Sex and HT-related differences in performances were examined using an analysis of variance (ANOVA) with group as the between-subjects factor (HT users, never users, and men). Bonferroni-corrected post hoc analyses were conducted. In addition, tasks with repeated conditions (number–letter task, modified Stroop task, and computerized dual tasks) were analyzed using repeated measures ANOVAs with condition as the within-subjects factor. Greenhouse–Geisser correction for within-subjects factors was used when the assumption of sphericity was not met—that is, when the Mauchly's test was significant. Significant interactions were analyzed with simple effects, and repeated contrasts were used in the case of a significant interaction with more than two levels of a repeated factor, which provided a comparison of differences between two consecutive levels. Partial eta squares were used to indicate effect sizes of an effect or an interaction. To obtain effect sizes for each comparison of interest (HT users vs. never users, HT users vs. men, and never users vs. men), Cohen's d was also calculated. A Cohen's d effect size may be negligible ($d < 0.15$), small ($0.15 \leq d < 0.40$), medium ($0.40 \leq d < 0.75$), large ($0.75 \leq d < 1.10$), or very large ($1.10 \leq d < 1.45$; Cohen, 1992).

RESULTS

Table 2 presents neuropsychological data for all groups.

Episodic memory

Group differences were observed in RAVLT total, $F(2, 85) = 13.88$, $p < .001$, $\eta^2_p = .25$, immediate recall, $F(2, 85) = 9.60$, $p < .001$, $\eta^2_p = .18$, and delayed recall, $F(2, 85) = 6.92$, $p < .01$, $\eta^2_p = .14$. Post hoc analysis revealed that both groups of women (HT users and never users) recalled more words than men in RAVLT total (all ps $< .01$). RAVLT total was equivalent between HT users and never users ($p = .268$). In immediate recall, HT users outperformed men ($p < .001$) and never users ($p < .02$). In delayed recall, HT users also outperformed men ($p < .01$) and never users ($p < .05$). No sex or HT effect was observed in the recognition trial.

Visuospatial abilities

A significant group effect was observed for the total score of the MRT, $F(2, 85) = 7.26$, $p < .01$, $\eta^2_p = .15$. Men outperformed HT users ($p < .01$) and never users ($p < .01$). Performance was equivalent between HT users and never users ($p = 1.000$).

Executive functions

Task switching

Two women (one HT user and one never user) were excluded from the analysis of the number–letter task because they could not distinguish vowels and consonants. Completion time analysis revealed a main effect of condition, $F(1, 83) = 330.95$, $p < .001$, $\eta^2_p = .80$, which revealed that execution time was longer in the switching condition than in the single condition. With regards to the question of interest, the interaction between condition and group also reached significance, $F(2, 83) = 5.29$, $p < .02$, $\eta^2_p = .11$. Post hoc analyses indicated that never users executed the single condition faster than men ($p < .05$). There

TABLE 2
Means and standard deviations for neuropsychological measures for all groups, *F* and *p* values for group effects, and effects sizes for comparisons of interest

	HT users (N = 29)		*Never users (N = 29)*		*Men (N = 30)*		*Group*				
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	*HT users vs. never users d*	*HT users vs. men d*	*Never users vs. men d*
RAVLT											
Trials 1–5	57.34	7.14	53.93	7.20	47.17	8.27	13.88	**.00**	0.48	1.32	0.87
Immediate Recall	12.59	2.24	10.62	3.00	9.80	2.19	9.60	**.00**	0.75	1.26	0.32
Delayed Recall	12.24	2.36	10.52	2.97	9.80	2.38	6.92	**.00**	0.65	1.03	0.27
Recognition	14.17	1.28	13.55	1.92	13.53	1.48	1.54	.22	0.39	0.46	0.01
MRT											
Total score	9.90	4.58	9.90	4.73	15.07	8.05	7.26	**.00**	0.00	0.82	0.81
Number–letter task											
Single, time in seconds	57.04	13.95	54.68	10.34	63.30	12.03	3.90	**.02**	0.19	0.48	0.77
Single, number of errors	0.30	0.90	0.29	0.69	0.27	0.58	0.02	.98	0.01	0.04	0.03
Switching, time in seconds	83.93	17.94	89.93	20.17	86.40	17.47	0.74	.48	0.31	0.14	0.19
Switching, number of errors	0.54	0.84	1.14	1.48	0.90	1.18	1.82	.17	0.52	0.36	0.18
Switching cost, time in seconds	26.89	12.95	35.25	17.52	23.10	12.56	5.29	**.01**	0.55	0.30	0.81
Switching cost, number of errors	0.23	1.29	0.86	1.25	0.63	1.10	1.91	.15	0.50	0.33	0.20
2-back task											
Number correct	23.48	1.90	23.97	2.51	23.77	1.87	0.38	.68	0.22	0.15	0.09
Time in seconds	76.96	22.30	94.74	27.74	77.36	16.01	4.93	**.01**	0.71	0.02	0.79
Baddeley dual task, Index	92.05	9.09	92.55	8.88	88.82	9.25	1.48	.23	0.06	0.35	0.41
Stroop task, time in seconds											
Word reading	41.95	7.12	43.95	5.59	45.60	7.19	2.21	.12	0.31	0.51	0.26
Color naming	60.98	9.68	64.75	14.54	66.54	12.38	1.55	.22	0.31	0.50	0.13
Color–word interference	106.28	19.10	110.20	30.64	111.90	23.31	0.40	.67	0.16	0.27	0.06
Switching	132.15	25.15	126.04	32.87	130.68	31.13	0.33	.72	0.21	0.05	0.15

Notes. HT = hormone therapy; RAVLT = Rey Auditory Verbal Learning Test; MRT = Mental Rotation Task. Values with $p < .05$ are in bold.

was no group difference in the execution time for the switching condition. When comparing the switching costs between groups, which control for processing speed, post hoc tests showed that never users had a higher switching cost than men ($p < .01$), but not than HT users ($p = .101$). Switching cost was equivalent between HT users and men ($p = .965$).

Analysis of the number of errors revealed a significant effect of condition, $F(1, 83) = 19.25$, $p < .001$, $\eta^2_p = .19$, indicating that participants made more errors in the switching condition than in the single condition. The interaction between condition and group did not reach significance, $F(2, 83) = 1.91$, $p = .154$.

Updating

Analysis of the 2-back task revealed no significant group effect for the total number of correct answers, $F(2, 85) < 1$, $p = .683$. Time to complete the task was also analyzed, but only for 75 participants for which completion time was collected (HT users: 25; never users: 22; and men: 28). Analysis revealed a main effect of group, $F(2, 72) = 4.93$, $p < .02$, $\eta^2_p = .12$. Never users completed the task slower than HT users ($p < .05$) and men ($p < .05$). The completion time was equivalent between HT users and men ($p = 1.00$).

Inhibition

Completion time analysis of the modified Stroop task revealed a main effect of condition, $F(3, 255) = 593.08$, $p < .001$, $\eta^2_p = .88$, with execution time becoming slower from one condition to another, as shown by significant repeated contrasts, which replicate the typical Stroop effect (all $ps < .001$). The interaction between

group and condition did not reach significance, $F(6, 255) < 1$, $p = .544$.

Analysis of errors also revealed a typical Stroop effect with a significant condition effect, $F(3, 255) = 48.79$, $p < .001$, $\eta^2_p = .37$. Repeated contrasts showed that the number of errors increased from one condition to another (all ps $< .01$). There was no significant interaction between group and condition, $F(6, 255) < 1$, $p = .605$.

Divided attention

Paper and pencil dual task. No group difference was observed for the paper and pencil dual task, $F(2, 85) = 1.48$, $p = .234$.

Computerized visual dual task. Table 3 shows reaction time and accuracy data of the visual dual task and the auditory dual task. Data were missing for one participant from the HT users group. A main effect of task was observed, $F(1, 84) = 187.22$, $p < .001$, $\eta^2_p = .69$, indicating that RT was overall longer for the letter task (977 ms) than for the arrow task (828 ms). A main effect of trial type also reached significance, $F(2, 168) = 224.66$, $p < .001$, $\eta^2_p = .73$. Repeated contrasts showed that RT was shorter in the single-pure trials (660 ms) than in the single-mixed trials (807 ms), $F(1, 84) = 239.96$, $p < .001$, $\eta^2_p = .74$ (showing a significant task-set cost), and that single-mixed trials were executed faster than dual-mixed trials (1241 ms), $F(1, 84) = 165.02$, $p < .001$, $\eta^2_p = .66$ (showing a significant dual-task cost). A significant interaction between task and trial type also reached significance, $F(2, 168) = 32.76$, $p < .001$, $\eta^2_p = .28$, and this interaction was qualified by a higher order interaction between group, task, and trial type, $F(4, 168) = 2.89$, $p < .05$, $\eta^2_p = .06$. Repeated contrasts reached significance only for the task-set cost, $F(2, 84) = 3.43$, $p < .05$, $\eta^2_p = .08$, but not for the dual-task cost, $F(2, 84) = 2.30$, $p = .106$. Group differences in task-set cost were observed in both tasks (see Figure 1). In never users and men, task-set cost was smaller for the letter task than for the arrow task (all ps $< .05$). In HT users, task-set cost was equivalent in both

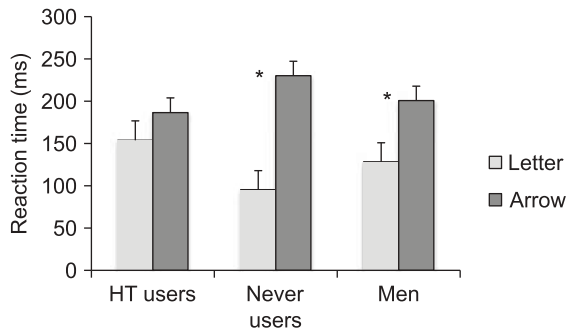

Figure 1. Comparisons between task-set cost (ms) of each task of the visual dual task for the three groups. HT = hormone therapy. Vertical lines represent standard errors. *$p < .05$.

TABLE 3
Mean reaction time and error rate for each task and group in the three trial types for the two dual tasks

		HT users				*Never users*				*Men*			
		Task 1		*Task 2*		*Task 1*		*Task 2*		*Task 1*		*Task 2*	
Task	*Measure*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Visual dual task	Reaction time (ms), $n = 87$												
	Single pure	733	41	582	26	798	40	535	25	781	40	532	25
	Single mixed	862	29	754	26	877	29	756	26	872	28	719	25
	Dual mixed	1288	72	1200	72	1294	71	1174	71	1287	70	1203	70
	Error rate (%), $n = 86$												
	Single pure	1.43	0.62	0.61	0.47	1.93	0.60	0.16	0.45	1.67	0.59	1.35	0.44
	Single mixed	1.42	0.45	0.30	0.14	1.01	0.43	0.08	0.13	2.11	0.43	0.33	0.13
	Dual mixed	3.18	0.53	1.05	0.42	2.64	0.52	1.56	0.40	4.15	0.51	1.36	0.40
Auditory dual task	Reaction time (ms), $n = 84$												
	Single pure	673	27	651	41	685	27	638	41	711	26	745	39
	Single mixed	1019	33	948	38	1068	33	1039	38	1022	31	992	36
	Dual mixed	1298	50	1249	48	1314	50	1229	48	1332	47	1309	45
	Error rate (%), $n = 83$												
	Single pure	2.82	1.09	4.19	1.71	2.53	1.07	4.07	1.68	3.11	1.01	5.46	1.59
	Single mixed	3.46	1.33	4.58	1.61	5.11	1.30	6.16	1.58	6.04	1.24	6.53	1.50
	Dual mixed	12.83	2.63	9.66	1.68	11.65	2.58	8.67	1.65	11.50	2.44	9.14	1.56

Note. HT = hormone therapy. Reaction times in ms; error rates in percentages. Trial types: single pure, single mixed, and dual mixed.

tasks. The mean task-set cost of both tasks together was equivalent between groups, as observed by a nonsignificant Group × Trial Type interaction, $F(4, 168) < 1$, $p = .955$.

Accuracy data from two HT user participants were missing. Analysis of accuracy data showed a main effect of task, $F(1, 83) = 66.31$, $p < .001$, $\eta^2_p = .44$, indicating that accuracy was lower for the letter task (97.8 %) than for the arrow task (99.2 %). A main effect of trial type was also observed, $F(2, 166) = 21.59$, $p < .001$, $\eta^2_p = .21$, and repeated contrasts indicated that accuracy was equivalent between single-pure trials (98.8%) and single-mixed trials (99.1%), $F(1, 83) = 1.59$, $p = .210$ (no significant task-set cost), but that accuracy was higher in the single-mixed trials than in the dual-mixed trials (97.7%), $F(1, 83) = 49.20$, $p < .001$, $\eta^2_p = .37$ (significant dual-task cost). Interaction between task and trial type did not reach significance, $F(2, 166) = 2.66$, $p = .077$. With regards to the question of interest, no main effect of group was observed, $F(2, 83) = 1.47$, $p = .236$. Interaction between trial type and group did not reach significance, $F(4, 166) < 1$, $p = .963$.

Computerized auditory dual task. RT and accuracy data from three participants (2 never users and 1 HT user) were excluded because of unilateral deafness. RT data were missing for one HT user participant, and accuracy data were missing for two HT user participants. Reaction time analysis showed a main effect of task, $F(1, 81) = 7.30$, $p < .01$, $\eta^2_p = .08$, indicating that RT was faster for the task responded to with the right hand (978 ms) than for the task responded to with the left hand (1014 ms). A main effect of trial type also reached significance, $F(2, 162) = 399.59$, $p < .001$, $\eta^2_p = .83$. Repeated contrasts showed that participants were faster in the single-pure trials (684 ms) than in the single-mixed trials (1015 ms), $F(1, 81) = 423.76$, $p < .001$, $\eta^2_p = .84$ (significant task-set cost) and that participants were faster in the single-mixed trials than in the dual-mixed trials (1288 ms), $F(1, 81) = 174.12$, $p < .001$, $\eta^2_p = .68$ (significant dual-task cost). No main effect of group was observed, $F(2, 81) < 1$, $p = .529$, and the interaction between trial type and group did not reach significance, $F(4, 162) = 1.41$, $p = .242$, indicating equivalent task-set and dual-task costs across groups.

Accuracy data were missing for two HT user participants. Accuracy analysis showed a main effect of trial type, $F(2, 160) = 35.82$, $p < .001$, $\eta^2_p = .31$. Repeated contrasts indicated that participants were more accurate in the single-pure trials (96.3%) than in the single-mixed trials (94.7%), $F(1, 80) = 4.66$, $p < .05$, $\eta_p^2 = .06$ (significant task-set cost), and that participants were less accurate in the dual-mixed trials (89.4%) than in the single-mixed trials, $F(1, 80) = 40.28$, $p < .001$, $\eta_p^2 = .34$ (significant dual-task cost). Interaction between task and trial type reached significance, $F(2, 160) = 4.80$, $p < .02$, $\eta^2_p = .06$. This was due to a higher dual-task cost for the task answered by the left hand (7.1%) than for the task answered by the right hand (3.4%), $F(1, 80) = 4.92$, $p < .05$, $\eta^2_p = .06$. No main effect of group was observed, $F(2, 80) < 1$, $p = .836$, and the interaction between trial type and group did not reach significance, $F(4, 160) < 1$, $p = .585$, indicating equivalent task-set and dual-task costs across groups.

DISCUSSION

The goal of the present study was to assess sex-related differences in executive functions in healthy men and postmenopausal women aged 55 to 65 years, while taking into account HT use in women. Verbal memory, mental rotation, inhibition, task switching, divided attention, and updating were measured. To assess the role of HT in maintaining cognitive functioning in aging women, women currently using or who have used HT (HT users) and women who had never used HT (never users) were compared with men. In line with recent scientific evidence for a critical window of opportunity of HT effects on cognition, only women who initiated HT at the time of menopause were included in the HT users group.

Consistent with previous findings in episodic memory (Yonker et al., 2006), results revealed strong sex and HT-related differences in the verbal memory task performances, both groups of women outperforming men in the total number of words recalled over Trials 1 to 5 and with large to very large effect sizes. Moreover, only HT users performed better than men in immediate and delayed recalls, whereas never users and men did not significantly differ. These results suggest that HT use around the menopause preserves the difference between men and women in episodic memory since higher scores were found in HT users, followed by never users, and then by men. In the mental rotation task, men outperformed both groups of women, and no difference was observed between HT users and never users. Effect sizes for comparisons of interest were large. Consistent with these results, Yonker et al. (2006) also found no difference between HT users and never users in a visuospatial task. These results suggest that sex differences in mental rotation are independent of HT use in women and may rather reflect the long-lasting organizational effects of sex hormones.

Results observed in executive function tasks provide significant insights into sex and HT effects in cognition. First, the present study showed a smaller switching cost in men than in never users, with a large effect size, whereas the switching cost was equivalent between men and HT users. Thus, a sex-related difference in favor of men was observed only when HT influence was accounted for, which suggests that HT use decreases the magnitude of the difference between older men and women in task switching. Consistent with our results, Tun and Lachman (2008) also found a male advantage in a stop and go switch task in older adults. However, Munro et al. (2012) found no sex effect in older adults in the Trail Making Test Part B. A possible explanation for diverging results between studies is the fact that previous studies did not take into account the current and past HT use and that different switching tasks were used.

Results of the present study also revealed sex-related differences in updating. Men and HT users completed the 2-back task faster than never users, whereas accuracy was equivalent between groups. The size of this effect was large. Again, sex-related differences seem to be moderated by HT use since only the never users group differed from men. Moreover, the fact that HT users completed the 2-back task faster than never users suggests an HT effect on updating performances. Parsons et al. (2005) found no difference between older men and women on the Digit Span Backward, and it is possible that the absence of control for HT use in women contributed to conceal differences between men and women. In a study using the digit ordering task, a working memory task, HT beneficial effects have been reported in women aged from 45 to 65 years (Duff & Hampson, 2000). Moreover, Dumas, Kutz, Naylor, Johnson, and Newhouse (2010) reported a greater prefrontal activation in HT users than in never users during a n-back task. However, women from the Dumas et al. (2010) study initiated HT after the window of opportunity, on average 11 years after their menopause.

To our knowledge, the present study is the first to assess sex-related differences in divided attention using computerized dual tasks while taking into account HT use. Results of the visual dual task have revealed a better ability to share attention between two concurrent tasks in HT users than in never users and men. This group difference was observed only for the task set cost but not for the dual-task cost, which suggests sex- and HT-related differences in the ability to mentally maintain two tasks that may randomly occur. No group difference was observed in the task set cost of the auditory dual task, and this may reflect that sex- and HT-related differences are specific to visual divided attention. Munro et al. (2012) also reported no sex-related difference in older adults for the Brief Test of Attention, a measure of auditory divided attention, but the lack of control for HT effects may also have influenced their results. Further studies are needed to replicate these differential effects of modality in divided-attention tasks.

No sex or HT-related differences were observed in the Stroop task. This is less consistent with previous studies that reported a female advantage in this task in older adults (Seo et al., 2008). However, Seo et al., reported a sex difference not only in the inhibition part of the test, but also in the two conditions measuring processing speed, which suggests that the effect of sex may be more sensitive to the processing speed component of the task rather than to the inhibition component. However, another study reported that the female advantage remains even after controlling for processing speed (Van der Elst et al., 2006).

It has been hypothesized that prenatal exposure to different sexual hormone levels plays a critical role in prenatal organization of brain structure and function, which is then activated by the action of sexual hormones after puberty (Zaidi, 2010). These developmental organizational and lifelong activation effects of sexual hormones on the brain have been hypothetically associated with sex-related differences in cognition. Activation effects of sex hormones on the brain have been proposed as a consequence of currently circulating sexual hormones. However, recent evidence that HT in women may have long-term effects on cognition even after the cessation of treatment suggests that sex hormone activation effects are more complex and stable in time than initially thought. Results of the present study tend to argue in favor of a long-term activation effect of sex hormones, since no differences have been observed between past and current users of HT on cognitive performances. However, the small sample size limits inferences about long-term effects of HT use.

No association has been found between endogenous estrogen levels and episodic memory in postmenopausal women (Yonker, Eriksson, Nilsson, & Herlitz, 2003). A possible explanation is that maintaining effects of HT on cognition result from the reduction of the drop of estrogen at the time of menopause maintaining higher circulating estrogen levels than the endogenous one at this time of life. Thus, there would be a window of opportunity for HT to have protective effects on the brain, before the organism begins to adapt and the brain to reorganize itself to face low levels of circulating estrogen.

The fact that differences in episodic memory performances seem to remain between men and never users suggests that HT does not represent the only factor that contributes to sex-related differences in cognition. Organizational effects are most probably at play as well as environmental and experimental influences. In accordance with an environmental hypothesis of sex-related differences, a 10-hour training session with an action video game has been associated with a decrease in the sex-related difference in spatial abilities (Spence, Yu, Feng, & Marshman, 2009). Future studies should thus investigate both HT use and cognitive training as moderating factors of sex-related differences in cognition in older adults.

It has been previously suggested that progestin may reduce positive estrogen effects on cognition (Maki & Sundermann, 2009; Sherwin, 2006, 2007a; Sherwin & Henry, 2008). Since HT is either a combination of estrogen and progesterone or estrogen therapy only, when estrogen-only users are compared with estrogen + progesterone users, these two groups seem to differ only in executive measures, but not in episodic memory performances (Wegesin & Stern, 2007). In the present study, all women of the user group have used estrogen + progesterone. Since results of the present study revealed no detrimental effects of HT on cognition, it is possible that the timing of initiation of the treatment is a more significant factor than the type of treatment for HT protecting effects on cognition. Future studies should address specifically the effects of the type of treatment on cognition while controlling for the timing of initiation of HT.

One important limitation of our study is it observational nature. Randomization of the sample would have allowed controlling for health and demographic factors. Age, education, general cognitive functioning, sleep habits, cognitive activity, age at menopause, and menopausal symptoms were equivalent between both groups of women. Similarly, in a large sample of 127 Australian women aged 50 years and over, no difference was found in demographics and quality of life measures between HT users and never users except for menopausal symptoms (Taylor, MacLennan, & Avery, 2006).

Another limitation of our study is the small sample size, which limits the generalization of our results. We also included past and current users in the HT users group. A recent study have shown that HT users had larger right hippocampal volume than past users (Lord et al., 2008). Thus, inclusion of past and current HT users in the same group may have introduced selection bias into the research. Future studies of HT effects on cognition should include current users and past users in separate groups. Another limitation of the present study was that data relative to menopause occurrence were obtained through self-report. It is therefore possible that age of onset and treatment may lack precision. Future randomized controlled trials or longitudinal observations would allow better understanding of the effect of menopause and HT on cognition.

In sum, this study is the first, to our knowledge, to show that both sex and HT in postmenopausal women impact some specific executive functions, notably task switching, updating, and visual divided attention. Despite the limitations of our research, this study has considerable implications for research and clinical settings. Previous research suggested that aged women are more likely to develop dementia of the Alzheimer's type. Furthermore, in normal aging, there is limited evidence that suggests a higher risk of falls in men than in women in dual-task situations (Hollman, Youdas, & Lanzino, 2011). Thus, understanding the key factors that may influence cognitive aging in men and women may bring new insights to better prevent age-related cognitive decline. Despite the hormonal influences, our results and those of previous studies strongly suggest that other factors may interact with HT effects, such as fitness or cognitive training (Erickson et al., 2007). The probable complex interaction between hormonal influences and environmental factors associated with sex-related differences in executive functions should be investigated in future studies.

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