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Estrogen, Testosterone, and Sequential Movement in Men

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Abstract

Behavioral and physiological data suggest that the striatal dopaminergic system is important in the production and execution of sequential movements. Striatal function is also modulated by sex hormones, and previous studies show that estradiol is related to sequential movement in women. We examined whether sex hormones are involved in the production of sequential movement in healthy older and younger men. Testosterone was modified for a 6 week period such that levels in older men matched those of younger men, the conversion of testosterone to estradiol was blocked, the production of testosterone was blocked, or the men received no treatment (placebo). Sequential movement was measured before and after hormone treatment. Older men were slower and more accurate than younger men on the sequential movement task pre- and post-treatment. Hormone manipulation had no effect on movement speed. Hormone levels were not correlated with sequential movement performance in either older or younger men, suggesting that sex hormones do not modulate sequential movement in men, and hormone replacement may not restore a loss of sequential movement ability in elderly men or men with Parkinson's disease.

Keywords

Estrogen; testosterone; sequential movement; striatum; Parkinson's disease

The planning and production of sequential movements are dependent on the striatum (Taniwaki et al., 2003; Mallol et al., 2007) and the striatal dopaminergic system (Goerendt et al., 2003). Striatal dopaminergic function is compromised in healthy aging: dopamine transmission (Zelnik et al., 1986), dopamine levels (Kish et al., 1992), and the number of nigrostriatal axons and dopamine uptake sites (McGeer et al., 1977; de Keyser et al., 1990; van Dyck et al., 1995) decline with age in humans. This decline in striatal dopamine function is thought to result in slowing of fine motor control in the elderly (Volkow et al., 1998; Smith et al., 1999).

Deterioration of the striatal dopaminergic system is also a significant feature of Parkinson's disease, in which bradykinesia, muscle rigidity, and tremors are common symptoms (Graybiel et al., 1990; Graybiel, 1990; Okun et al., 2006; Hunter et al., 2007). Striatal damage has selective effects on sequential movement. In patients with Parkinson's disease (PD), the coordination between the programming of sequential movements and their execution is temporally disorganized. Patients will begin movement execution before the entire movement program is available, and thus they are slowed on subsequent steps in the sequence because additional motor programming must occur during sequence execution (Jennings, 1995). This

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results in difficulty switching between randomly organized movement sequences where the motor program must be newly reinitiated with each execution. However, there is little difficulty repeating the same or simple sequences. The neural basis of these components of motor sequencing has been partially delineated with stimulation, lesion and neuroimaging studies [for reviews see (Harrington et al., 2000; Lehericy et al., 2006)]. There are at least two different striatal processes that are part of cortical-striatal movement networks (Harrington et al., 2000). The caudate and anterior putamen activate for changes in movement sequences that require complex programming and that often include working memory or attention. In contrast, brain activity is similar in posterior putamen and globus pallidus for complex versus simple movements, suggesting these regions do not play a role in the programming of complex movement sequences (Lehericy et al., 2006). Activation of the striatum during well-learned sequential movements is reduced in unmedicated individuals with PD, but a compensatory increase in activity in ipsilateral premotor and thalamus regions occurs (Mallol et al., 2007).

Loss of endogenous sex hormones is also a feature of aging. Total and free (bioavailable) testosterone levels in men decline with age (Davidson et al., 1983; Vermeulen, 1991; Mohr et al., 2005) due to impairments in testicular testosterone production and increases in gonadotropins. In addition, increases in sex hormone binding globulin (SHBG) with aging further decreases the amount of testosterone that has biologic activity (free/bioavailable testosterone) (Swerdlow et al., 1992; Chahal and Drake, 2007). Testosterone can be converted to estradiol in the brain by the enzyme aromatase (Lephart, 1996). Free estradiol declines with age in men due to loss of circulating testosterone, and increased SHBG (Ferrini and Barrett-Connor, 1998; Leder et al., 2004). However, these factors are not the only determinant, as systemic free testosterone and free estradiol are only moderately correlated (Orwoll et al., 2006). Peripheral higher aromatase activity with aging likely plays a role in the variability of estradiol levels in older men (Ferrini and Barrett-Connor, 1998; Leder et al., 2004). Moreover, aromatase activity in the brain does not appear to change significantly with age (Roselli et al., 1986).

Estrogen (β subtype) and androgen receptors are located in striatal dopaminergic neurons (Creutz and Kritzer, 2004), as is a G protein-coupled estrogen-specific membrane receptor (Mermelstein et al., 1996; Xiao et al., 2003). These receptors permit sex hormones to modulate striatal function. For instance, estrogen restores ovariectomy-induced loss in dopamine and locomotor activity in female rats (Ohtani et al., 2001) and prevents ovariectomy-induced loss of substantia nigra dopaminergic neurons in nonhuman primates (Leranth et al., 2000). A number of studies suggest that estrogen is a neuroprotectant of the nigrostriatal dopamine system, especially in females (for a review see Dluzen and Horstink, 2003). However, the interpretation of the interaction between estrogen and the striatal dopaminergic system is complicated by the finding that neither hormonal status nor estrogen supplementation modifies age-related deficits in nonhuman primates on a fine-motor coordination hand retrieval task (Lacourse and Herndon, 2003). Studies of PD have also yielded conflicting results, with some suggesting that premenopausal estrogen use in women results in less severe PD motor symptoms (Saunders-Pullman et al., 1999) and others indicating no effect of estrogen treatment in postmenopausal women with PD (Strijks et al., 1999). Testosterone also modulates striatal dopaminergic function, as shown by the finding that testosterone partially restores cocaine-induced decreases in striatal dopamine reuptake (Chen et al., 2003). However, testosterone treatment does not alter striatal dopamine loss resulting from MPTP-induced neurotoxicity in mice (Dluzen, 1996). Nor in a pilot study did it improve motor symptoms in hypogonadal men with PD (Okun et al., 2006). The current study sought to investigate the roles of estrogen and testosterone in striatal-mediated movement in men, focusing on the potential of hormones to modulate motor function in aging.

Striatal-mediated movement can be measured using a choice reaction time task with sequential responses (CRT-SR; Jennings, 1995; Jennings et al., 1998). The CRT-SR measures two important aspects of motor performance: movement programming and movement execution. Movement programming encompasses the organization of a series of muscle commands into sequential order. Movement execution is the performance of the movement sequence in its entirety and can be quantified by the time required to complete the sequence. The CRT-SR can therefore be used to measure an individuals' ability to plan, coordinate, and program a movement sequence as well as execute the sequence. On this task, patients with PD have normal response times to execute the first key press in a sequence, but are slowed to complete the sequence, suggesting that the striatum is critical for coordinating motor programming with execution. Higher estradiol, but not testosterone, levels were associated with faster movement execution but not movement programming on the CRT-SR in younger women (Jennings et al., 1998). Similar results were shown by others with faster performance on sequential or repetitive movements when estradiol levels were higher in women. This relationship is not found for simple reaction time (Pierson and Lockhart, 1963). Neither estrogen nor testosterone levels were associated with sequential movement in younger men (Jennings et al., 1998). However, in the prior study, hormone levels were not modified in the participants and the range in the younger men was limited. Thus, we examined whether changes in sex hormones would affect sequential movement and whether effects differed in older versus young men.

Method

Participants

Men were recruited from the community by mail and newspaper advertisements and were participants in a larger study of hormone effects on cognition and emotion. Inclusion criteria required that the older men had no sign of dementia (Mini-Mental State Exam (MMSE) > 26; (Folstein et al., 1975) or depression (Geriatric Depression Scale (GDS) < 10; Yesavage et al., 1983). The Wechsler Adult Intelligence Scale-Revised (WAIS-R) Vocabulary subtest was administered to both age groups to include men with normal functional intelligence (age-scaled score > 8; Wechsler, 1981). The Vocabulary subtest was used as a measure of education since years of education may not reliably reflect intelligence in the elderly due to changing education requirements in the last century. The age ranges were chosen to include men in the same older age range used in other studies of aging so that data can be compared among studies, but to limit the older age range so that we would not have men screen out or drop out due to the age-related medical problems common over the age of 80. We compare the elderly to a group of younger subjects who are younger than the age when one typically finds age-related cognitive changes, but beyond college age in order to better equate old and young on lifestyle and experience. The participants were matched between the age groups for years of education and WAIS-R scores (Table 1). Men taking medications that would interfere with sex hormones or cognition (i.e. testosterone gel, antidepressants, anti-anxiety medications, etc.) were excluded from participation. Older men were required to have a prostate-specific antigen level of < 4 ng/mL and a normal manual prostate exam. The participants were in good health with total testosterone or free testosterone levels within two standard deviations of the mean for men of their age (example ranges for men: total testosterone 241–827 ng/dl; free testosterone 52–280 pg/mL; Bagatell et al., 1994; Schatzl et al., 2003; Mohr et al., 2005). All participants gave written consent approved by the Institutional Review Board and were paid \$325 for their participation in the full study of hormone effects in aging.

Older (60–80 years) and younger (25–35 years) men were assigned in a randomized double blind manner to 1 of 4 treatment groups that resulted in: eugonadal testosterone (i.e. testosterone levels equal to endogenous levels in young men; group 1), eugonadal testosterone but low estradiol (group 2), hypogonadism (group 3), or no change (placebo; group 4). Table

2 shows the treatment group descriptions and the number of men in each group. The treatment groups permitted us to assess the effects of testosterone versus its conversion to estradiol on sequential movement performance, to assess whether movement improved when older men were brought to the testosterone level of younger men, or declined when testosterone was depleted.

A GnRH agonist (Depot-Lupron; 7.5mg; TAP Pharmaceuticals, Chicago, IL) was used to suppress gonadal function and stop natural production of testosterone in groups 1, 2, and 3. It was administered intramuscularly in two injections 4 weeks apart to maintain cessation of endogenous testosterone production. We halted endogenous production in order to control testosterone levels. Otherwise, exogenous testosterone supplementation can result in down regulation of endogenous production, and this can result in little increase (in the older men) or variable testosterone levels. We then replaced testosterone with a daily dose of transdermal testosterone (T-gel; 75mg for older men and 100mg for younger men. Auxilium Pharmaceutical, Inc., Malvern, PA) in groups 1 and 2. Target total and free testosterone, and estradiol levels for these two groups were within the normal range of young men, and thus higher, on average, than pretreatment levels in the older men for the duration of the study (See Table 2). The treatment doses were designed to obtain target total testosterone levels in all men in the normal range of 400–600ng/dl. The different T-gel doses in younger and older men were due to the fact that older men clear testosterone more slowly. If the same dose was used in both groups, older men would have higher levels than younger men and we would not know if group differences in motor performance were due to age or due to hormone level. As our question was whether normal testosterone levels in aging play a role in sequential movement, we did not consider raising levels to higher-than-normal. In addition, higher than normal levels could put older men at increased risk of prostate enlargement and difficulty urinating, and a risk of coagulation (Calof et al., 2005). We could not justify extending our study to the effects of high levels of testosterone without a reasonable argument for a significant benefit that would outweigh the risks in these healthy men. The dose regimen used permitted a comparison of young and old when testosterone levels were the same, and also a comparison between older men with levels normal for their age versus at the same levels as younger men. Group 2 received a daily dose of aromatase inhibitor anastrozole (Arimidex; 1mg; AstraZenca Pharmaceuticals, Wilmington, DE), with the intent to reduce estradiol while maintaining normal testosterone levels. Group 3 received placebo T-gel and thus were hypogonadal throughout the study. To maintain blinding, groups 1 and 3 also received placebo anastrozole pills. Finally, group 4 received all placebo medications and served as a control group with unaltered hormone levels. The Research Pharmacy dispensed the medications, which were administered by the Oregon Clinical and Translational Research Institute staff at Oregon Health & Science University. The researcher administering the cognitive test was blind to participants' treatment group. The dispensing physician (MHS) was unblinded to the treatment group, and monitored serum testosterone levels obtained for each subject on a weekly basis, adjusting doses as needed to obtain the target testosterone levels for each group. To maintain blinding, each time a subject's active testosterone gel dose was changed, another subject's placebo gel dose was changed within the same age group (groups 3 or 4). Dose adjustment was rare. In total, two older men and two younger men had dose adjustments (one from each age from groups 1 and 2). The sequential movement task was administered before and after approximately 6 weeks of treatment. Prior to treatment, there were no hormone differences among treatment groups suggesting that treatment group assignment by randomization was successful. Treatment groups were matched for mean years of education and WAIS-R Vocabulary subtest scores.

Hormone Assays

Blood samples were stored at -70°C until assayed so that pre-, post and interim samples for each subject were in the same assay batch. Serum estradiol (Diagnostic Systems Laboratory;

sensitivity threshold 2.2 pg/mL; mean interassay coefficient of variation (CV) of 10.9 %) and total testosterone (Siemens Medical Solutions Diagnostics; sensitivity threshold 4.0 ng/dL; mean interassay CV of 7.4%) levels were quantified using radioimmunoassay procedures according to the standard procedures for the assay kits. Free testosterone levels were calculated using total testosterone levels and the SHBG levels (Vermeulen et al., 1999). SHBG levels were quantified using a chemiluminescent enzyme assay (Siemens Medical Solutions Diagnostics; sensitivity threshold 0.2 nmol/L; mean interassay CV of 5.5%).

Sequential Movement Task

The same sequential movement task as used in a prior study of younger men and women was used here (Jennings et al., 1998). The task was administered before any hormone treatment and again after approximately 6 weeks of hormone treatment, using an iMac computer with a standard keypad. Participants placed their index, middle, and ring finger of the dominant hand over the numbers 1, 2, and 3 on the keypad. The participants then memorized two keypad sequences associated with a specific character shown on the screen: the letter “T” was associated with the sequence 1-3-2 and the letter “H” with the sequence 3-1-2. A trial consisted of the presentation of a 1000 msec fixation spot (+) at the center of the screen followed by the character presentation. Once a keypad sequence was performed, the screen cleared and the next trial began with the presentation of the fixation spot. All participants completed 18 practice trials followed by 10 blocks of 18 experimental trials each and were instructed to perform the sequences as quickly as possible.

Four measures of performance were assessed: 1. movement programming was the amount of time between the character presentation and the first keypad press (reaction time; RT). 2. Movement execution was the amount of time to complete the entire movement sequence (movement time; MT). 3. Total movement time (TMT) was the sum of RT and MT. 4. The percent of correct responses was the measure of accuracy. Not included in the description of the participants or data analysis were 2 older men who were removed from the analysis based on pharmacy dispensing errors, 6 older men and 1 younger man who were removed due to outlier performance on the sequential movement task (greater than 3 standard deviations from the mean), and 2 older men and 1 younger man who were removed from the analysis due to incomplete sequential movement data.

Data Analysis

Median RT, MT, and TMT scores were calculated from the correct responses in the remaining 55 older and 24 younger men. Medians were used to prevent occasional trials where participants were inattentive or anticipated a response from overly influencing the data. Separate repeated measures (pre/post-treatment) ANOVAs were used to determine treatment and age effects on RT, MT, TMT, and percent accuracy. *Post hoc* Tukey’s HSD analyses were conducted for significant main effects.

The relationships between hormone levels and RT, MT, TMT, and percent accuracy were assessed using separate correlation analyses. Multiple regression analyses with age included as a predictor variable assessed the mediating effect of age. All statistical tests were conducted with a two-tailed significance alpha level of .05.

Results

Hormone Treatment and Sequential Movement

Hormone treatment successfully altered hormone levels as planned (pretreatment level compared to the level on the day of cognitive testing after approximately 6 weeks of treatment;

Table 2). Hormone treatment did not have a significant effect on any of the measures (F_s (3, 71) < 1.35, p_s > .10 for RT, MT, TMT and percent accuracy).

Older men were slower than the younger men across all measures of movement time (F_s (1, 71) > 35.00, p_s < .01 for RT, MT, and TMT; Figure 1). Response times decreased during the study (F_s (1, 71) > 25.00, p_s < .01 for RT, MT, and TMT), revealing a practice effect that was similar in across treatment and both age groups, as there was no interaction with treatment or age group (p_s > .10). Older men were more accurate than younger men (F (1, 71) = 18.08, p < .01) and there was no significant change in performance during the study (p > .05). However, there was a marginally significant interaction for percent accuracy between treatment group and pre/post-treatment test session (F (3, 71) = 2.76, p = .05). The simple main effects between groups were not significant in *post hoc* analyses, although there was a trend for the testosterone replacement plus anastrozole men (group 2) to become more accurate over time (p = .10). There were a significant number of men who made no errors, so this analysis is hampered by a ceiling effect.

One possibility is that performance in the younger men was obscuring treatment effects in older men. Thus, we examined treatment group effects amongst the older men in an exploratory analysis to better understand this interaction. Within the older men, there was no effect of treatment group (F (3, 51) = 1.13, p = .35) or pre/post-treatment test session (F (3, 51) = 0.60, p = .44). However, a significant visit by treatment group interaction arose (F (3, 51) = 4.60, p < .01) because the men with testosterone but not estrogen (group 2) were less accurate than the other groups pre-treatment (p = .06) and more accurate than the other groups post-treatment (p = .03). Men with testosterone deprivation (group 3) were marginally less accurate than the other groups post-treatment (p = .07). In summary, these results show that both the older and younger men became faster with practice and that the older men were slower and more accurate than younger men. In older men, estrogen deprivation in the context of testosterone at the level of healthy younger men moderately improved accuracy. Hormone manipulation had no effect on sequential movement speed in older or younger men.

Hormone Levels and Sequential Movement

The relationships between hormone levels and performance were assessed with correlation analyses. Estradiol was related to MT and TMT (r_s = -.22, p_s = .05) pre-treatment and with RT, MT and TMT (r_s > -.22, p_s < .05) post-treatment. Free testosterone was related to RT, MT and TMT (r_s > -.34, p_s < .01) pre-treatment. There were no correlations between performance and free testosterone post-treatment or between performance and total testosterone either pre- or post-treatment. Another possibility is that the change in hormone levels from pre- to post-treatment would be related to performance. Thus, we also examined the change in hormone levels (estradiol, free and total testosterone) to RT, MT and TMT but found there were no significant relationships (r_s < .17, p_s > .10).

The significant correlations may be an artifact of the co-occurrence of both low testosterone and motor slowing with aging. In order to control for the possibility that the correlations were due to the effects of age, hormone levels that were correlated with performance were analyzed in a multiple regression with age included as a predictor variable. When age was included in the model, hormone levels were no longer significantly correlated with performance, indicating that age accounted for the observed relationship between hormone levels and performance on the sequential movement task.

Discussion

This study showed that modification of estradiol and testosterone did not affect movement programming or execution on a striatal-mediated sequential movement task in men. This result

occurred regardless of age, as both older and younger hypogonadal men performed similarly to men with unaltered or enhanced hormone levels. Furthermore, sequential movement performance was not related to either estradiol or testosterone levels in either age group. However, older men performed slower and more accurately than younger men irrespective of treatment group. The source of the differences in speed and accuracy is not clear but could include central or peripheral physiological slowing (Salthouse, 1996), higher response bias to be accurate by the elderly, and/or changes in executive processes (Chen and Li, 2007) that together appear as a speed-accuracy trade off by the elderly. A marginal effect in an exploratory analysis suggested that in older men, low estrogen in the context of higher testosterone levels (at the level of young men) may increase accuracy while an absence of sex hormones may decrease accuracy on the sequential movement task. Similar effects were not observed for speed of performance. In addition, accuracy was high (84% to 100%) post-treatment suggesting that complete hypogonadism did not severely influence performance. As a number of the men performed at ceiling, the accuracy data is tenuous as an indicator of hormone effects.

Jennings et al. (1998) found that native estradiol levels were positively correlated with faster MT on the CRT-SR in younger women. In younger men, however, no correlations between estradiol or testosterone and MT or RT were found. The results of the current study further support this finding; hormone levels were not related to performance in either younger or older men, even when levels were significantly modified by exogenous hormone treatment. One could imagine that our lack of effects were due to the short term nature of the increase or decrease in hormones. However, previous studies in younger women found effects of estradiol on movement across the few weeks of the menstrual cycle (Hampson and Kimura, 1988; Hampson, 1990) and studies examining the effects of hormone manipulation on other aspects of cognition have found effects before or by 6 weeks of treatment (Janowsky et al., 2000; Cherrier et al., 2001; Cherrier MM et al., 2007). In addition, studies find effects on neurobiological markers of function such as synapse density within one month of gonadectomy in nonhuman primates (Leranth et al., 2004; Hajszan et al., 2008). We cannot know from this study whether longer periods of treatment would result in effects on motor performance. However, one might expect that very long term treatment would have effects on neuroprotective mechanisms as opposed to neuromodulation. Further studies are required to determine if hormone effects would be found following a longer duration of hormone treatment in older or younger men. It is also possible that practice effects obscured very small treatment effects. What we do know is that practice effects did not differ among treatment groups and that there was also no correlation between performance and testosterone level.

There is an established role for estradiol in striatal dopaminergic function (for a review, see Kipp et al., 2006). For example, estrogen prevents ovariectomy-induced loss in substantia nigra dopaminergic neurons in female non-human primates (Leranth et al., 2000) and restores ovariectomy-induced loss in dopamine and locomotor activity in female rodents (Ohtani et al., 2001). There is far less literature on testosterone's role in striatal dopaminergic function in males. Dihydrotestosterone, a metabolite of testosterone, increases the risk for ischemic injury in rodent models of stroke (Cheng et al., 2007), and testosterone increases dopamine depletion induced by methamphetamine (Dluzen and McDermott, 2006). Studies suggest that testosterone plays a role in dopamine transporter function and vesicular storage in such a way that it would promote or decrease the restoration of function depending on whether neurotoxins were sequestered versus concentrated and released (Shemisa et al., 2006). In any case, there are significant sex differences in dopaminergic function both due to the effects of estradiol in females and different effects of testosterone in males. The results from the current study further suggest that the sex hormones estradiol and testosterone in older and younger men do not modulate striatal-mediated movement and thus sex hormone effects are sexually dimorphic for sequential movement.

Aging in humans is associated with striatal-mediated movement impairments (Ranganathan et al., 2001). Low testosterone is associated with loss of function in other cognitive domains such as memory (for a review see Beauchet, 2006; Janowsky, 2006) and moderate increases in testosterone, but not large increases (Cherrier et al., 2007) improve cognition on verbal memory, spatial cognition (Janowsky et al., 1994; Cherrier et al., 2001) and working memory in healthy older men (Janowsky et al., 2000). In contrast, the current study suggests that even large changes in testosterone and estradiol, both increases and decreases, do not affect sequential movement in men. Thus, hormone replacement may not restore age-related deterioration in movement ability.

Striatal dopaminergic deterioration in Parkinson's disease (PD) results in severe movement impairment and difficulty in movement initiation (Graybiel et al., 1990; Graybiel, 1990). Individuals with PD show impaired ability on movement sequencing tasks similar to the CRT-SR (Fama and Sullivan, 2002), specifically the execution of a sequence of movements (Jennings, 1995; Harrington et al., 2000). To date, the effects of sex hormones on motor performance in the context of PD are unclear. Testosterone levels are lower in men with PD (Okun et al., 2004), suggesting that supplementation may be beneficial for individuals with PD where both dopamine and hormone levels are reduced. However, a preliminary study did not find that testosterone treatment alleviated movement deficits (Okun et al., 2006). In agreement, our findings suggest that estrogen and testosterone have no effect on striatal sequential movement in older or younger men. Whether long duration, premorbid, neuroprotective treatment would delay the onset or modify the course of Parkinson's disease is not addressed by this study.

In summary, our data suggest that neither estradiol nor testosterone modulates motor sequencing in adulthood. Although both sex hormones modulate striatal dopaminergic function in studies of animal models, we did not find their influence on striatal-generated movement in men. These findings further suggest that hormone replacement therapy may not be a viable option for movement restoration in the context of healthy or diseased aging in men.

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A.

B.

Figure 1.

The average total movement time (TMT) scores pre/post-treatment for older men (A) and younger men (B). Men became faster at the task from pre-treatment to post-treatment. There was no effect of treatment group on TMT.

Table 1

Participant Characteristics

Group	n	Age		Education		WAIS-R ^a		MMSE		GDS	
		M	SD	M	SD	M	SD	M	SD	M	SD
Older	55	67.9	5.5	15.6	2.9	51.6	9.5	28.4	1.1	2.2	2.6
Younger	24	28.7	3.2	16.8	2.3	53.8	7.4				

Note. WAIS-R = Wechsler Adult Intelligence Scale-Revised vocabulary subtest (Wechsler, 1981), MMSE = Mini Mental State Exam (Folstein et al., 1975), GDS = Geriatric Depression Scale (Yesavage et al., 1983).

^aExpressed as WAIS-R vocabulary subtest raw scores.

Table 2
Treatment Descriptions and Mean ($\pm$ SD) Hormone Levels Pre/Post-Treatment

Group	Tx Group Description	N	Tx	Estradiol ^a M ($\pm$ SD)	Testosterone ^b M ($\pm$ SD)	Free Testosterone ^c M ($\pm$ SD)
Older	1- GnRH Agonist, T-gel	12	Pre Post	16.3 (5.2) 19.0 (7.1)	399.6 (125.5) 533.5 (190.7)	230.5 (55.1) 350.4 (140.2)
	2- GnRH Agonist, T-gel, Arimidex	16	Pre Post	20.4 (4.4) 8.7 (3.8)*	403.7 (96.4) 491.7 (128.1) [†]	279.1 (73.0) 380 (145.7) [†]
	3- GnRH Agonist, Placebo	13	Pre Post	18.1 (5.0) 10.0 (2.9)*	424.7 (168.3) 13.4 (8.6)*	236.3 (56.4) 5.8 (7.1)*
	4- Placebo	14	Pre Post	16.8 (4.6) 16.9 (3.5)	388.9 (82.8) 375.6 (88.7)	236.5 (73.9) 225.4 (56.5)
Younger	1- GnRH Agonist, T-gel	8	Pre Post	24.0 (6.2) 24.8 (7.8)	529.5 (175.0) 656.4 (456.3)	411.0 (125.8) 541.9 (310.2)
	2- GnRH Agonist, T-gel, Arimidex	4	Pre Post	19.8 (4.2) 11.5 (2.1)	530.8 (171.6) 520.2 (161.6)	343.4 (111.1) 336.5 (91.9)
	3- GnRH Agonist, Placebo	7	Pre Post	27.6 (8.7) 16.4 (5.6)	473.8 (81.6) 9.7 (7.7)*	365.1 (83.9) 5.3 (5.1)*
	4- Placebo	5	Pre Post	19.5 (4.6) 22.3 (4.7)	548.5 (164.1) 746.2 (332.8)	361.7 (97.4) 561.3 (329.1)

Note. Hormone levels are from the day of cognitive testing before treatment, and again on the day of cognitive testing after approximately 6 weeks of treatment. Tx = treatment group. T-gel = Transdermal Testosterone Gel;

^aEstradiol measured in pg/mL.

^bTestosterone measured in ng/dL.

^cFree Testosterone measured in pmoles/L.

* Hormone levels significantly differ from those of treatment group 4 in the older or younger men.

[†]Hormone levels are significantly greater post-treatment compared to pre-treatment.