

REVIEW ARTICLE

Cognitive Impacts of Estrogen Treatment in Androgen-Deprived Males: What Needs to be Resolved

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Abstract: Background: Many prostate cancer (PCa) patients are on androgen deprivation therapy (ADT) as part of their cancer treatments but ADT may lead to cognitive impairments. ADT depletes men of both androgen and estrogen. Whether estradiol supplementation can improve cognitive impairments in patients on ADT is understudied.

Objective: To summarize data on the effects of estradiol treatment on cognitive function of androgen-deprived genetic male populations (PCa patients and male-to-female transsexuals) and castrated male animals.

Method: Publications were identified by a literature search on PubMed and Google Scholar.

Results: While some studies showed that estradiol improves cognitive function (most notably, spatial ability) for castrated rats, what remains uninvestigated are: 1) whether estradiol can improve cognition after long-term androgen deprivation, 2) how estradiol affects memory retention, and 3) how early vs. delayed estradiol treatment after castration influences cognition. For androgen-deprived genetic males, estradiol treatment may improve some cognitive functions (e.g., verbal and visual memory), but the findings are not consistent due to large variability in the study design between studies.

Conclusion: Future studies are required to determine the best estradiol treatment protocol to maximize cognitive benefits for androgen-deprived genetic males. Tests that assess comparable cognitive domains in human and rodents are needed. What particularly under-investigated is how the effects of estradiol on cognitive ability intersect with other parameters; sleep, depression and physical fatigue. Such studies have clinical implications to improve the quality of life for both PCa patients on ADT as well as for male-to-female transsexuals.

Keywords: Estradiol, cognition, prostate cancer, androgen deprivation therapy, male-to-female transsexuals, verbal memory, visual memory, spatial memory.

1. INTRODUCTION

Androgen deprivation therapy (ADT) is the primary treatment for systemic prostate cancer (PCa), with more than a half million men on ADT in North America [1]. ADT has many deleterious side effects, including potential deficits in cognitive function (reviewed in [2-4]). Furthermore, ADT can also result in suboptimal sleep, fatigue, and depression [5-12], all of which may contribute to cognitive decline.

The cognitive impairment after androgen loss is also observed in animal models. Castration in rodents influences

both spatial [13-19] and non-spatial [15, 20-22] abilities. For example, castrated rats are slower to acquire spatial working memory [13, 14, 23, 24]. However, findings on how castrated rats learn spatial reference memory have been inconsistent [16, 17, 25, 26].

The cognitive impact of ADT may be associated with the loss of both testosterone and estradiol (E2), which in males is mainly derived from the aromatization of testosterone [27]. Decline in gonadal hormones decreases ligand bioavailability to bind to sex steroid receptors which are present in various brain areas, including those involved in cognition, such as the hippocampus and prefrontal cortex [28-31]. The activation of brain sex steroid receptors plays a role in normal cognitive functions. For example, without functional androgen receptors, male rodents have deficits in spatial reference memory [32, 33]. Furthermore, individuals

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with androgen insensitivity syndrome [34] and idiopathic hypogonadotropic hypogonadism [35] have reduced cognitive ability (in the spatial domain).

Replacing testosterone is not considered a safe option for PCa patients with androgen-sensitive PCa because testosterone can activate androgen receptor and stimulate PCa growth [36]. Estrogen replacement therapy is currently being studied, though, in clinical trials for patients who are on ADT [37, 38]. However, data on how E2 influences cognitive function on androgen-deprived males are sparse, as compared to data for hormone-deprived females (see the special 2015 issue on “Estradiol and Cognition” in *Hormones and Behavior* vol. 74, and recent reviews [39, 40]). This sex/gender disparity reflects the fact that E2 is the dominant sex steroid in females and is present more than ten times the concentrations in females than in males (for example, see [41] vs. [42] for rodents data; and [43] vs. [44] for human data).

Even in eugonadal males, there is no consensus on how endogenous E2 modulates cognition. A few studies have shown that men with higher E2 levels have better visual [45], visuospatial [46] and verbal [47, 48] memory performances. However, most studies found that higher plasma E2 concentrations in older men have either no or negative association with cognitive functions [49]. The varying data on the influence of endogenous E2 in eugonadal men could partially be because serum E2 assessment may not reflect the actual impact of E2 in the brain. This is because neurons in many brain areas—including those for cognitive functions—can directly aromatize testosterone into E2 [50, 51]. Determining the effects of endogenous E2 in eugonadal men is also confounded by the presence of endogenous androgens and sex hormone binding globulin, which may affect the bioavailability of gonadal steroids. Suffice to say, a few studies show that reduced E2 bioavailability in male rodents due to aromatase-knock out [52] or administration of aromatase inhibitor [53] impairs spatial task performances, though conflicting data have been reported [54, 55].

This paper reviews studies that have investigated the effects of E2 on cognitive function of androgen-deprived genetic males of our species—*i.e.*, PCa patients on ADT and male-to-female transsexuals (MtFs) on hormone therapy (HT)—as well as castrated male rodents. These studies help isolate the effects of E2 on male cognition without the impacts of endogenous testosterone. Many MtFs are androgen-deprived due to surgical castration as part of sex reassignment surgery or HT with a dose high enough to suppress testosterone. Data from MtFs brings additional insight on how HT affects cognition of genetic male population. Data on castrated male rats are also reviewed because they served as a preclinical model for men who are on ADT. Admittedly there are limitations on animal research but they can provide insights on how E2 modulates cognitive function in androgen-deprived males. This paper points out areas that are understudied, but would be important to consider in the future when researchers investigate cognitive impact of ADT on PCa patients with or without E2 treatment. Studies in this area are clinically relevant to other genetic male populations who receive E2 treatment, such as MtFs [56, 57] and castrated men [58, 59].

2. METHODS

PubMed and Google Scholar were searched for terms including “estradiol”, “estrogen”, “cognition”, “male”, “prostate cancer”, “androgen deprivation therapy”, “male-to-female transsexuals”, and “cross-sex hormones”. From this search I identified publications that investigated the impact of E2 treatment on castrated male rats, PCa patients on ADT, and MtFs on HT. Additional publications were located in the references cited for papers found in the original search. Findings on how E2 affects specific cognitive domains are summarized on Tables 1 to 3. Experimental details, including E2 dose and duration, are summarized in Supplementary Tables 1 and 2.

3. STUDIES ON CASTRATED MALE RATS

3.1. Experimental Details

Ten studies have investigated how E2 influences the cognitive performances of castrated male rats (Supplementary Table 1). In seven studies, the rats received E2 treatment immediately after castration whereas, in the other three studies [23, 26, 60], the rats started E2 treatment at 1-2 weeks after castration. Most studies administered E2 *via* a Silastic capsule or slow-release E2 pellets. The only exceptions were Hodosy *et al.* [26] and Lagunas *et al.* [23] who injected E2 intramuscularly and intraperitoneally respectively.

Plasma E2 levels were only measured in two studies [26, 61]. E2 levels were similar to female diestrus levels in both studies, but Hodosy *et al.* [26] also treated one more group of rats with a dose resulting in a plasma E2 levels almost four times higher than female proestrus levels [see Butcher *et al.* [41] for normal female E2 levels in estrus cycle]. Five studies used the same E2 dose as the one in the Kritzer’s study [62], which increased the plasma E2 levels to ~26.5 pg/mL (*i.e.*, similar to diestrus levels in females). The remaining three studies used E2 doses that have been used by other researchers for raising plasma E2 levels of female rats to either diestrus [23] or proestrus [60, 63] levels. However, whether such doses in fact increased plasma E2 levels to those levels are not known. In my previous study [64], male rats required higher E2 dose than female rats to achieve similar E2 levels [see Deurveilher *et al.* [65] for comparison]. Therefore, there is a possibility that the plasma E2 levels in those studies [23, 60, 63] may be lower than expected. To date, a dose of E2 that only brings plasma E2 levels into the range of intact males (*i.e.*, ~2 pg/mL [42, 61, 66]) has not been tested in cognitive studies on castrated rats. As such, it remains unknown as to how an E2 dose that raises the plasma E2 levels to the levels of intact male rats would influence cognitive function for the castrated male rats.

One factor, which is rarely investigated in animal studies, is how the interval between castration and the initiation of E2 treatment (Supplementary Table 1) influences the effects of E2 treatment on cognitive function. Except in three studies [23, 26, 60], the rodents started receiving E2 treatment immediately after castration. In female rats, the effectiveness of E2 in improving cognitive performance is known to be sensitive to the time when the treatment begins after ovariectomy [67]. Similar findings have also been observed in

women, who receive E2 treatment after menopause [68]. It remains unknown, though, how long-term hormone deprivation affects male cognitive function, and when the best time might be to start E2 treatment after castration to maximize any cognitive benefit.

One possible factor that likely contributes to the time-sensitive nature of E2's effectiveness in restoring cognition is the autoregulation of estrogen receptor α (ER α) in brain areas for cognition. In female rats, early but not delayed E2 administration after ovariectomy increased ER α in the hippocampus, and the opposite results were found in the prefrontal cortex [69]. Changes in ER α autoregulation in both brain areas after prolonged hormone-deprivation have also been observed in male rodents. In male rats, hippocampal ER α decreases with early, but not delayed, E2 treatment after castration [30]. The opposite was found in the prefrontal cortex; *i.e.*, ER α in the prefrontal cortex decreases with delayed E2 treatment [30]. How those results translate into cognitive performances for male rats has not been assessed (but see the discussion below on visual attention of androgen-deprived PCa patients with and without E2), and there may be other factors that may explain why the effect of E2 on cognition after hormone deprivation is time-sensitive. Interestingly, the patterns of brain ER α autoregulation in response to E2 treatment between sexes differ; *i.e.*, down-regulated in male [30] and upregulated in female [69] rats. Additionally, a recent study [70] showed that how E2 induces synaptic potentiation in the hippocampus is not the same in males and females. Specifically, E2 can increase pre-synaptic glutamate release probability in the hippocampus *via* ER α in males, but *via* ER β in females. That same study also found that E2 can increase post-synaptic sensitivity to glutamate *via* ER β in males, but *via* the G-protein coupled ER-1. These data suggest that there may be true sex differences in how E2 modulates cognition in males versus females.

3.2. Behavioural Findings

Among the reviewed studies, the cognitive domain that is most commonly assessed is spatial ability (Table 1; Supplementary Table 1). These include spatial learning, spatial working memory, and spatial reference memory. Learning tasks involving spatial memory in castrated rats are improved by E2 treatment in some studies [23, 25, 61, 71] but not in others [13, 15, 60]. Obviously, the type of testing apparatus/mazes differs between studies, leading to variation in the difficulty of the tasks in the different tests. As such, this variation may contribute to discrepancy in findings on spatial learning.

Spatial working memory of castrated rats is improved by E2 treatment in some studies [23, 25, 63, 71], but not in other studies [60, 61] (Table 1). Again, the variance in results could be because of the different testing apparatus. Unlike the apparatus in other studies, the T-maze in the Gibbs' study [61] was walled (5-inches high) so the rats may have less extra-maze cues. In addition, the radial maze in the Luine and Rodriguez study [60] has 8 arms so performance on this maze may have higher working memory demand. Negative impact of E2 on spatial working memory of castrated rats was also reported in one study [26], but that study used

the Morris water maze, so their data could be confounded by stress due to water immersion [72].

Several studies have examined how E2 treatment affects spatial reference memory (Table 1)-a type of long-term memory that is constant from trial to trial [73, 74]. When there are minimal delays between testing, the acquisition of spatial reference memory is not significantly different between castrated rats with and without E2 [25, 26, 60, 71]. However, when a time delay is introduced between testing [25, 60], E2-treated castrated rats performed better on spatial reference memory task than do castrated rats with no hormone replacement. This suggests that a substantial delay between tests may be necessary to assess the beneficial effect of E2 on spatial reference memory. Future studies with such delay would more closely reflect real life situations for men, where the concern is on both previously learned and newly acquired spatial tasks.

The effect of castration with and without E2 replacement on non-spatial tasks has also been studied, but to a lesser extent (Table 1). For example, Aubele *et al.* [21] assessed object recognition memory, which requires visual memory, and found that E2 does not improve object recognition memory after castration. Kritzer *et al.* [15] also examined several other non-spatial tasks, but the only two tasks in which they found improvement with E2 treatment in castrated rats were the learning of withholding response (holding back from getting a reward) and motivational (motivation to get a reward) tasks. Therefore, though only reported in one study [15], E2 treatment in androgen-deprived males may also have some benefits on non-spatial cognitive functions.

4. STUDIES ON ANDROGEN-DEPRIVED GENETIC MALE HUMAN

4.1. Androgen-Deprived Men with Prostate Cancer

Three studies (total sample size = 41 patients; mean ages = ~70 years old) have investigated how E2 treatments affect cognitive functions for PCa patients on ADT (Supplementary Table 2). Serum testosterone levels of the patients were in the castrate range in all studies. Patients received 0.6-1 mg E2 daily for 4 to 12 weeks. Serum E2 levels reached supra-physiological levels in one study [75], but not in the other two [76, 77].

Compared to the performance of androgen-deprived PCa patients without E2, scores on verbal memory tests of E2-treated patients were better in the Beer *et al.* study [75], but worse in the Matousek and Sherwin study [76] (Table 2). Verbal memory was also assessed by Taxel *et al.* [77], but by using a different test than the one used in the other two studies. However, Taxel *et al.* did not find a significant difference in verbal memory performance between the E2- and placebo-treated PCa patients. Considering that patients in the Beer *et al.* study [75] had supra-physiological E2 levels, but not in the other two studies, an E2 dose that yields supra-physiological E2 levels may be required to benefit verbal memory for androgen-deprived PCa patients.

Visual attention was tested with Trail tests in two of these studies [75, 77]. E2 treatment improved visual

Table 1. Summaries on the effects of E2 treatment on cognitive performance of castrated male rats. Data were compared to the Control group, which consists of castrated rats without E2 treatment.

Cognitive Domain Tested (Testing Apparatus)	Studies	Effects of E2 Treatment	Parameters Measured
Spatial learning			
Barnes maze	[71]	↑	Changes in path length, latency to find a goal box, and number of errors on Day 1 testing.
Barnes maze	[25]	↑	Changes in path length, latency to find a goal box, and number of errors on Day 1 testing.
Cross-maze	[23]	↑	Percentage of correct choices between the first and fourth day of testing.
Operant conditioning chamber	[15]	0	Number of sessions to reach 25 correct choices in a single session; <i>i.e.</i> , to alternately press 2 levers for water reward.
T-maze	[61]	↑	Percentage of trials with a correct response; <i>i.e.</i> , to visit an arm in which the rats previously received a food reward.
T-maze	[13]	0	Number of sessions to reach 7 correct choices in 9 tests; <i>i.e.</i> , to visit alternating baited (with water reward) arm consecutively.
Radial arm maze	[60]	0	Number of trials to obtain 7 correct choices in the first 8 visits—to get food reward in 8 arms—in 5 consecutive trials.
Spatial working memory			
Barnes maze	[71]	↑ on Day 1 0 on Day 2	Spatial working memory error was measured from the number of re-investigation of incorrect holes.
Barnes maze	[25]	↑ on Day 1 0 on Day 2	Spatial working memory error was measured from the number of re-investigation of incorrect holes.
Open field with 2 identical objects	[63]	↑	Time spent exploring moved and unmoved objects.
Morris water maze	[26]	↓ with EB 0 with ED	Changes in escape latency between the final and first day of testing.
T-maze	[61]	0	Percentage of trials with a correct response (to visit an arm in which the rats previously received a food reward) after the maze was rotated and inter-trial delay was increased.
Radial arm maze	[60]	Data not shown	The number of re-entries into previously visited arm was collected (indicative of working memory errors) but data were not shown.
Spatial reference memory			
Barnes maze	[71]	0	Path length and latency to find a goal box on Day 2 (1 day delay) testing. Spatial reference memory error was measured from the number of first-time investigation of incorrect holes.
Barnes maze	[25]	0 on Day 2 ↑ on Day 7	Path length and latency to find a goal box on Day 2 (1 day delay) and Day 7 (1 week delay) testing. Spatial reference memory error was measured from the number of first-time investigation of incorrect holes.
Morris water maze	[26]	0	Escape latency (<i>i.e.</i> , time to find a submerged platform).
Cross-maze	[23]	↑	Averaged percentage of correct choices in 4 days of testing.
T-maze	[61]	0	Percentage of trials with a correct response; <i>i.e.</i> , to visit an arm in which the rats previously received a food reward.
Radial arm maze	[60]	0 with no delay ↑ with delay	Number of correct choices (visits to baited arms) in the first 8 visits. Trials were done with and without 1-hour delay between the 4 th and 5 th arm visits.

(Table 1) contd....

Cognitive Domain Tested (Testing Apparatus)	Studies	Effects of E2 Treatment	Parameters Measured
Object recognition memory			
Open field with 2 objects	[21]	0	Time spent exploring novel and old objects.
Learning of extradimensional shift			
Operant conditioning chamber	[15]	0	Number of sessions to reach 90% accuracy of a task; <i>i.e.</i> , to press a lever with a cue light in order to receive a water reward; another lever with unlit lamp was present simultaneously.
Withholding response			
Operant conditioning chamber	[15]	↑	Percentage of impulsive lever press over total lever press.
Motivation for reward			
Operant conditioning chamber	[15]	↑	Number of water reward obtained.
Behavioural flexibility (learning of match or non-match-to-position)			
Operant conditioning chamber	[15]	0	Number of sessions to reach 90% accuracy of a task; <i>i.e.</i> , in a pair of testing phases, rats needed to either press the same (match) or a different (non-match) lever in the second test as that in the first test in order to get a water reward.
Learning of configural association negative patterning			
Operant conditioning chamber	[61]	0	Changes in the number of responses (<i>i.e.</i> , to enter a food cup for reward) and time to respond following a tone, light or both stimuli.

↑↓ = Significantly better or worse performance than castrated rats with no hormone treatment. 0 = No significant effect. E2 = Estradiol. EB = Estradiol benzoate. ED = Estradiol dipropionate.

attention in the Taxel *et al.* study, but not in the Beer *et al.* study. One possible reason for this inconsistency could be because of the difference in the length of time between the initiation of ADT and the onset of E2 treatment. Patients in the Beer *et al.* study had been androgen-deprived for an average of 5.32 years when they began E2 treatment. In contrast, patients in the Taxel *et al.* study had been androgen-deprived for a shorter time; some had been on continuous ADT for an average of 2.6 years, whereas others were only on ADT for 3 weeks. Thus, E2 may not be able to improve visual attention in men, who have been androgen-deprived for a prolonged period of time. If this is true, such finding will be consistent with the data in females (discussed in the “Studies in Castrated Male Rats” section above), showing that the effect of E2 treatment is sensitive to when the treatment is started after hormone deprivation.

Visuospatial ability was tested in the Matousek and Sherwin study [76], but E2 treatment did not improve performance in visuospatial tests. This could be because the men in that study were only androgen-deprived for 12 weeks. Similar lack of impact of E2 on visuospatial ability was also found in healthy men [78] or PCa patients [79], who were on ADT for less than 6 months. Currently, data on visuospatial ability of PCa patients, who have been on ADT for 9-12 months, have been inconsistent (see [80-83] vs. [83-85]). How long-term ADT (*i.e.*, >1 year) affects cognitive functions has not been studied, but warrants investigation

because PCa patients with progressing systemic disease typically are on sustained ADT that can last for many years.

4.2. Male-to-Female Transsexuals

Seven studies have investigated the cognitive performances of MtFs, who are on HT (total sample size = 179 MtFs; mean ages vary between 22 and 40.3 years old). Admittedly, the participants of these studies are younger than PCa population (Supplementary Table 2). HT regimens are heterogeneous among studies (Supplementary Table 2); MtFs received estrogen as oral ethinyl E2, transdermal E2 or Premarin, and in some cases combined with progesteric compounds, such as cyproterone acetate. Most studies did not measure plasma E2 levels, so the participants’ E2 concentrations are not known. The only exceptions are the studies by Schoning *et al.* [86] and Sommer *et al.* [87], but in both cases the plasma E2 levels did not reach supraphysiological levels. Whether higher E2 doses (*i.e.*, as high as female E2 levels at the peak of their menstrual cycle) have different cognitive effects than lower dose treatments remains to be determined.

Generally, there are many inconsistencies on how HT affects cognitive performances for MtFs, which could be partially attributed to the varying tests, doses and hormone combinations used in the studies. For example, visual memory is improved after long-term HT [88], but that same study also found that performance on a different visual memory

test is better after HT is stopped for ≥8 weeks. Unfortunately, no other studies on MtFs assessed visual memory so the findings from the Miles *et al.* study [88] cannot be compared.

Visuospatial ability of MtFs appears to be minimally affected by HT. Van Goozen *et al.* [89] found worsening performance on visuospatial ability after 3 months of HT. However, such visuospatial ability deficit is not found when assessed with a different test (*i.e.*, mental rotation test) in other studies. In contrast, better mental rotation ability was observed after 14 weeks of HT [90], though the authors suggested that this could be a learning effect, because non-MtFs groups in the study also have similar improvements. In other studies, HT does not significantly affect mental rotation ability of MtFs [86-88, 90-92].

Data on verbal ability of MtFs on HT were not consistent across studies. In term of language skills, verbal reasoning was not affected by HT [89-91], whereas verbal fluency was better after HT in the Van Goozen *et al.* [89] study, but not in other studies [88, 91]. Verbal memory appears to improve for MtFs with HT [92] but, depending on the tests used, conflicting findings have also been reported [88, 89, 91, 92]. Potentially, the large heterogeneity between studies (*e.g.*, type, dose, duration of HT, age) is the reason for the high variability on the effects of E2 on MtFs' verbal ability.

5. SEXUAL COGNITION

One domain that has not been well explored is how E2 influences sexual cognition. Eugonadal males may first look at faces when viewing images of other humans, but their visual attention quickly shifts to the torso and pelvic area, when viewing sexually explicit images [93, 94]. Prolonged fixation of one's gaze on sexual images may lead to sexual arousal [95-97], and men with sexual dysfunction may show reduced visual attention to sexual images [95]. A recent pilot study found that ADT may impair visual attention to sexual (swimsuit models) images [98]. The Skead *et al.* study provides an objective way to measure how ADT diminishes men's attention to sexual stimuli. However, whether the decrease in attention to sexual images is due solely to androgen deprivation or also due in part to estrogen deprivation was not explored.

Whether E2 can improve visual attention to sexual stimuli in androgen-deprived men is not known, but warrants further investigation. Other studies have shown that E2 helps restore sexual interest in most castrated mammalian species [99]. High dose E2 treatment in eugonadal men reduces sexual desire but sexual interest appears to be higher in androgen-deprived men with E2 treatment than those without E2 treatment [99, 100]. Finkelstein *et al.* [101] recently found that testosterone improves sexual desire in androgen-deprived men, but the effect is dampened when testosterone is administered in combination with an aromatase inhibitor. That affirms a role for E2 in raising libido in androgen-deprived men. In addition, Handy *et al.* [58] provided independent evidence of estrogen's preservative effect on libido for castrated men. That study showed that castrated men with no hormonal treatment are more likely to be sexually inactive than those on some form of estrogen treatment.

Table 2. Summaries on the effects of E2 treatment on cognitive performance of PCa patients who are on ADT. Categories were from McGinty *et al.* [4]. The three studies were longitudinal studies. Two studies [76, 77] were double blind RCTs, but one study [75] was not a blinded and treatment assignment was not randomized. More details can be found in Supplementary Table 2.

Cognitive Domain Tested (Test used)	Studies	Effects of E2 Treatment
Attention and working memory		
Trail making test A	[77] [75]	↑ 0
Digit span	[77]	0
Digit symbol test (WAIS-III)	[76]	0
Letter-number sequencing task	[76]	0
Subject-ordered pointing	[75]	0
Executive function		
Stroop test	[77]	↑
Trail making test B	[77] [75]	0 0
Language		
Controlled oral word association test	[77]	0
Verbal fluency test	[76]	0
Verbal memory		
Logical memory task (WMS-R)	[76] [75]	< ADT group ↑
Verbal paired associates (WMS-R)	[76]	0
Rey auditory verbal learning test	[77]	0
Visual memory		
Benton visual retention test	[77]	0
Visuomotor skill		
Digit symbol test	[76]	0
Block design	[76]	0
Paper folding	[76]	0
Visuospatial ability		
Mental rotation test	[76]	0

↑↓ = Significantly improved or worse performance at follow-up visit. ADT group = patients on ADT but do not receive E2. RCT = Randomized controlled trial. WAIS-III = Wechsler Adult Intelligence Scale-Third Edition. WMS-R = Wechsler Memory Scale - Revised.

6. CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

A clinical trial [38, 100] is currently underway, exploring the use of high dose parenteral E2 as an alternative to the

Table 3. Summaries on the effects of E2 treatment on cognitive performance of MtFs who are on HT. Some categories were from McGinty *et al.* [4]. Two studies [86, 92] were cross-sectional studies, and the rest were longitudinal studies. All cases were non-blinded studies. More details can be found in Supplementary Table 2.

Cognitive Domain Tested (Test used)	Studies	Effects of E2 Treatment
Attention and working memory		
Digit span	[92] [88]	0 ↑ after HT
Language		
Controlled association test	[92] [88]	0 0
Paced verb generation test	[87]	0
Paced categorical decision test	[87]	0
Verbal fluency test (word production)	[89] [91]	↓ 0
Verbal fluency test (sentence production)	[89] [91] [88]	↑ 0 0
Verbal reasoning test	[89] [91] [90]	0 0 0
Vocabulary	[92] [88]	0 0
Verbal memory		
Logical memory task (WMS-R)	[92] [88]	0 ↑ after long-term HT
Verbal paired associates (WMS-R)	[92] [88]	> MtFs group ↑ after off HT
Visual memory		
Visual reproduction test	[88]	0
Visual paired associate learning	[88]	0 ↑ after off HT for ≥8 weeks
Figural memory test	[88]	↑ after long-term HT
Visual memory span	[88]	0
Object memory test	[88]	0
Location memory test	[88]	0
Visuomotor skill		
Fine motor movement test	[91]	0
Targeted throwing	[90]	0
Visuospatial ability		
Line orientation test	[90]	0
Judgment of line angle and position	[88]	0
Mental rotation (2-dimensional)	[91] [90]	↓ at 3 months; but 0 post-SRS and 5 weeks off HT ↑ but other groups ↑ too*
Mental rotation (3-dimensional)	[86] [87] [92] [91] [90] [88]	= MtFs group 0 0 0 ↑ but non-MtF groups ↑ too* 0
Mental rotation (3D, same-different)	[90]	↑ but non-MtF groups ↑ too*
Hidden figure test	[91]	↑ at 3 months; but 0 post-SRS and 5 weeks off HT
Perceptual speed test	[91]	0
Card rotation test	[89]	↓

↑↓ Significantly improved or worse performance at follow-up visit. 0 no significant difference at follow-up. HT = hormone therapy. MtFs group = MtFs who do not receive HT. RCT = Randomized controlled trial. SRS = sex-reassignment surgery. WMS-R = Wechsler Memory Scale – Revised. * = the study included males and females without gender dysphoria.

lutinizing hormone-releasing hormone (LHRH) agonists and antagonists for androgen suppression in PCa patients. If E2 treatment is shown to improve cognitive functions in these PCa patients, it may help justify the use of high dose E2 therapy for ADT or supplemental E2 therapy for patients who are on ADT achieved with other drugs, such as the LHRH drugs. However, one needs to also be aware of non-cognitive effects associated with E2 treatment such as breast and cardiovascular events as well as concerns on potential breast and prostate cancer risks [38, 102, 103]. Certainly, in the case of MtFs, breasts enlargement due to E2 treatment is a desired effect, but may be bothersome to PCa patients [104].

Future researchers investigating the effects of E2 on cognitive functions of PCa patients on ADT or MtFs on HT needs to consider several factors in study design, such as the type of cognitive tests used, E2 dose, treatment duration and follow-up time. Although short-term androgen deprivation impairs various cognitive ability of male rodents, it remains unclear why the cognitive deficits androgen-deprived PCa patients and MtFs are more subtle. One possibility is that, other than visual memory, most tests used in human studies may not measure comparable cognitive domains as those in the animal studies. As an example, spatial ability in rodents are measured using spatial navigation tests; *i.e.*, locating object, rewards, or a goal hole (Table 1). However, visuospatial tests that have been used in human participants only assessed mental visualization ability (Tables 2 and 3). Other human studies have utilized different techniques to assess spatial memory, for example, by using virtual reality software [105-107] or a real-life wayfinding task [108]. These tests may more realistically reflect the spatial ability tests used in animal studies. However, such methods have not been used to examine how E2 treatment influences cognitive function for androgen-deprived PCa patients or MtFs who are on HT.

Two factors that need more investigations are E2 dosing and the timing of follow-up assessment. Animal studies have shown that an E2 dose higher than intact levels can have positive cognitive effects, but whether a lower dose, that raises E2 only to normal physiological levels, can still improve cognition has not been explored. However, based on the findings by Beer *et al.* [75], E2 may need to reach supra-physiological levels in order to bring cognitive benefits in androgen-deprived men. Furthermore, long-term studies of E2 treatment for androgen-deprived men are necessary to reflect the clinical reality that many PCa patients are on ADT for years at a time. This is particularly relevant since, for post-menopausal women (and in ovariectomized rodents [67]), supplemental estrogens may have different risks and benefits depending on how long they have been hormone-deprived before starting estrogen therapy [68]. It is thus possible that cognitive responses to supplemental E2 treatment will differ between androgen-deprived males with and without E2 treatment, if the men are on ADT for a longer time or the delay between E2 treatment and the onset of ADT is short. If early E2 treatment preserves cognition better, it may support the use of add-back E2 around the onset of ADT.

In addition, what needs to be explored in future studies is other factors known to be linked to cognition, such as sleep function. Based on self-reports from PCa patients, ADT results in sleep disturbance [5-8]. Using actigraphy, Hanisch *et al.* [109] found that, on average, PCa patients on ADT required more than 30 minutes to fall asleep, slept for only about 6 hours, and woke up 2.7 times per night. Not surprisingly, ADT patients often reported daytime sleepiness and took frequent naps [109]. However, whether the sleep problems correlate with cognitive impairment has not been explored.

Castration may also alter sleep-wake patterns in male rodents. Increased period of rapid eye movement (REM) sleep during the animals' active period [110] and dampened REM sleep recovery after acute sleep deprivation [64] are found in castrated rats. However, other studies did not report such findings [64, 111, 112]. Among these studies, how partial sleep deprivation (*i.e.*, not getting sufficient sleep on consecutive nights) impacts sleep/wake behaviour have not been studied in castrated animals, but will be important to investigate for several reasons. First, such study reflects what PCa patients on ADT experience in real life; *i.e.*, having sleep loss for days in a row. Second, increased allostatic load (including metabolic, immune and neural changes) may occur with repeated sleep deprivation [113, 114], and may directly influence sleep-wake behaviour. Third, whether chronic sleep deprivation can exacerbate other side effects of androgen deprivation—such as cognitive impairment, depression and metabolic syndrome—have not been explored.

Lastly, future clinical research that investigates how E2 influence cognition of PCa patients on ADT should also take into account any effects of E2 on fatigue, depression and anxiety. ADT has been shown to cause fatigue, depression and anxiety [10, 11, 115, 116]. Preclinical research showed that E2 has beneficial effects on these parameters [64, 117, 118], but those findings have not been explored in PCa patients on ADT. There are, though, some evidence that HT may help reduce psychological symptoms (*e.g.*, depression and anxiety) symptoms in MtFs [56]. Changes in these behaviours may interlink between each other as well as with cognitive function. Therefore, if E2 can alleviate one of these symptoms, other symptom(s) may also be potentially improved.

CONCLUSION

While some studies have suggested that E2 may have some protective role in cognitive function of androgen-deprived male rats and humans, there are still major knowledge gaps on the roles of E2 in male cognition. This is partly due to the fact that studies on genetic males treated with E2 are scarce, and there are large variations between studies (*e.g.*, type of cognitive tests, E2 treatment regimen). Future studies need to explore which E2 treatment protocol can most effectively improve cognitive functions in androgen-deprived males. Such studies have important implications to improving the quality of life of not just androgen-deprived PCa patients, but also for MtFs.

LIST OF ABBREVIATIONS

ADT = Androgen deprivation therapy
 CA = Cyproterone acetate
 DS = Digit span
 E2 = Estradiol
 EB = Estradiol benzoate
 ED = Estradiol dipropionate
 ER = Estrogen receptor
 fMRI = Functional magnetic resonance imaging
 FtMs = Female-to-male transsexuals
 HT = Hormone therapy
 LHRH = Luteinizing hormone-releasing hormone
 MtFs = Male-to-female transsexuals
 NMDA = N-methyl-d-aspartate
 PAL = Paired associate learning
 PCa = Prostate cancer
 REM = Rapid eye movement
 SRS = Sex-reassignment surgery
 WMS-R = Wechsler Memory Scale-Revised

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher’s web site along with the published article.

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