Am J Cancer Res 2024;14(7):3652-3664
www.ajcr.us /ISSN:2156-6976/ajcr0157004

Original Article

Androgen deprivation increases frontopolar cortical thickness in prostate cancer patients: an effect of early neurodegeneration?

Shefali Chaudhary[1], Alicia Roy[2], Christine Summers[2], Tim Ahles[3], Chiang-Shan R Li[1,4,5,6], Herta H Chao[2,7]

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; [2]VA Connecticut Healthcare System, West Haven, CT, USA; [3]Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Department of Neuroscience, Yale University School of Medicine, New Haven, CT, USA; [5]Interdepartmental Neuroscience Program, Yale University School of Medicine, New Haven, CT, USA; [6]Wu Tsai Institute, Yale University, New Haven, CT, USA; [7]Department of Medicine and Yale Comprehensive Cancer Center, Yale University School of Medicine, New Haven, CT, USA

Received April 3, 2024; Accepted July 15, 2024; Epub July 15, 2024; Published July 30, 2024

Abstract: Androgen deprivation therapy (ADT) has been associated with adverse effects on the brain. ADT leads to altered testosterone levels that may affect brain morphology as well as cognition. Considering the reliability of cortical thickness (CT) as a marker of cognitive and brain changes, e.g., in Alzheimer's disease, we assessed the impacts of ADT on CT and working memory. Thirty men with non-metastatic prostate cancer receiving ADT and 32 patients not receiving ADT (controls or CON), matched in age and years of education, participated in N-back task and quality-of-life (QoL) assessments as well as brain imaging at baseline and prospectively at 6 months. Imaging data were processed with published routines to estimate CT and the results of a group by time flexible factorial analysis were evaluated at a corrected threshold. ADT and CON did not differ in N-back performance or QoL across time points. Relative to CON, patients receiving ADT showed significantly higher frontopolar cortex (FPC) CT at 6-month follow-up vs. baseline. Follow-up vs. baseline FPC CT change correlated negatively with changes in 2-back correct response rate and in testosterone levels across all participants. In mediation analysis, FPC CT change mediated the association between testosterone level change and 2-back accuracy rate change. Increases in FPC CT following 6 months of ADT may reflect early neurodegenerative changes in response to androgen deprivation. While no significant impact on working memory or QoL was observed over 6 months, further research of longer duration of treatment is warranted to unravel the full spectrum of cognitive and neural consequences of ADT in prostate cancer patients.

Keywords: Prostate cancer, androgen deprivation therapy, MRI, cortical thickness, working memory, testosterone

Introduction

Prostate cancer is the second most frequently diagnosed cancer and the fifth leading cause globally (and second in the U.S.) of cancer-related mortality in men [1]. The incidence rate for prostate cancer has risen by 3% per year from 2014 through 2019 [2] and both localized and metastasized prostate cancer has grown steadily in prevalence over the years [3].

Androgen deprivation therapy (ADT) is widely employed in the treatment of both localized and advanced prostate cancer, with approximately 45% of diagnosed U.S. men receiving ADT during their illness [4, 5]. Despite its efficacy, ADT is accompanied by multiple side effects, including cardiovascular, metabolic, and sexual dysfunction, along with cognitive impairment, all of which have significant impact on patients' quality of life [5-7]. Although a significant concern to clinical outcome, the presence or extent of ADT's impact on cognitive function in patients with prostate cancer remains unclear [8], with reports suggesting impairment [9, 10], no effects [11-13], or even improvement [14]. Meta-analyses on the association between ADT and dementia, including Alzheimer's disease (AD), noted increased risk of dementia/AD due to ADT in prostate cancer

https://doi.org/10.62347/WOLA8904

patients [7, 15, 16]. However, a recent large-sample study did not find a significant association between ADT and the development of AD in men with prostate cancer [17].

Testosterone has been implicated in various aspects of cognition, including memory, attention, spatial ability, and executive functions [18]. Testosterone's effects on cognition can be illustrated in hypogonadism during aging [19]. A study of aged male rats showed that testosterone administration improves spatial working memory possibly through its effects on the hippocampus [20]. Castrated vs. intact male rats demonstrated impaired spatial working memory, which was reversed by physiological levels of testosterone replacement [21]. In the radial arm maze, castrated rats committed significantly more working memory errors than did sham castrated rats [22]. In humans, testosterone supplementation improved working memory, as tested with the Subject Ordered Pointing Test, in older men [23]. In men with newly diagnosed AD and hypogonadism, one year of testosterone substitution vs. placebo treatment resulted in improved visuospatial ability [24]. Further, six weeks of testosterone substitution vs. placebo treatment resulted in better spatial and verbal memory performance in men with mild cognitive impairment (MCI) or AD [25]. Another study noted improved attention, executive function, and psychomotor speed after two-year of testosterone replacement therapy in middle-aged hypogonadal men [26]. However, another study reported contrasting findings in older adults with MCI and hypogonadism, where physiological levels of testosterone substitution vs. placebo treatment did not appear to improve visuospatial or overall cognitive abilities [27]. A review of studies published from 2000 to 2020 on the effects of testosterone replacement therapy on cognition in elderly men found no significant effects of testosterone replacement on cognitive tests across memory, attention, executive function, visuospatial ability, working memory as well as the global cognition-MMSE score in 13 out of 21 studies [28]. Thus, while the findings associating lower testosterone with cognitive dysfunction appears to be more robust, whether hormonal replacement remediates the deficits is less clear.

Lower testosterone may represent a risk of dementia. The Baltimore Longitudinal Study of Aging showed that low testosterone levels at baseline could predict the development of AD during a 10-year period, such that every 10-unit reduction in free testosterone increased the risk of AD by 26% [29]. Another study examined the association between free testosterone level and episodic memory and the interaction between free testosterone and the APOE-ε4 allele - a genetic risk factor for late-onset AD [30] - in determining memory performance in a community-based sample of middle-aged men [31]. The study noted that in APOE-ε4 carriers, free testosterone levels were positively associated with verbal episodic memory performance, suggesting that APOE-ε4 status may elevate the susceptibility of individuals with low testosterone to cognitive decline [31]. Another study noted a negative association between total testosterone and Aβ42, a fibrillogenic 42-amino acid β-amyloid peptide that can trigger neurotoxic events, including tau accumulation, neuroinflammation, neurodegeneration, and cognitive impairment [32], as an early marker of AD in patients with MCI [33]. Together, these findings suggest a potential role of testosterone in influencing cognition and potentially predicting the onset of dementia during aging, although the effects of diminishing levels of testosterone may vary with age and likely other individual factors.

Magnetic Resonance Imaging (MRI) offers a non-invasive approach for assessing brain structure and function. It is becoming an increasingly important tool in the early detection and monitoring of MCI or AD [34]. In addition to gray matter volume (GMV), studies have employed cortical thickness (CT) as a more reliable structural measure of atrophy due to the low variability in the cytoarchitectural structure of the gray matters, lesser susceptibility to potential confounds, such as total intracranial volume, and higher test-retest reliability [35]. Further, relative to GMV, CT appears superior in distinguishing people with MCI/AD from controls and demonstrating a substantial correlation with AD pathology [36, 37]. Elderly patients with MCI vs. healthy individuals showed widespread cortical thinning (except for the occipital cortex) that features most prominently in the medial temporal lobe and inferior orbitofrontal cortex [35]. Another study noted significant cortical thinning in the temporal lobe but not in the frontal, parietal, or occipital lobe in MCI vs. con-

trols [38]. Early MCI patients exhibited medial temporal lobe and insula cortical thinning, whereas late MCI patients exhibited additional thinning in the dorsolateral prefrontal cortex, anterior and medial temporal cortex, temporoparietal association cortices, and precuneus, as compared to healthy controls [39]. In another study, people with verbal but not the visual amnestic MCI presented with anterior and medial temporal cortical thinning as compared with healthy controls [40].

Notably, evidence also suggests a potential inverted-U pattern in changes of CT, wherein CT increases in the very early stages but subsequently decreases with the onset and progression of the diseases [41]. Higher CT observed early in AD and related disorders may represent a response to disease pathology, including neuroinflammation, and its compensatory neural hypertrophy, or a combination of these and other processes that are not fully understood [42, 43]. A recent study of preclinical AD, people in stage 1 (Aβ+/tau-) had lower rates of medial frontal cortical thinning compared to those in stage 0 (Aβ-/tau-), whereas those in stage 2/3 (Aβ+/tau+) showed higher rates of medial temporal cortical thinning as compared to both stage 0 and 1, in agreement with the inverted-U shaped trajectory of cerebral morphological changes in preclinical AD [44]. Another study of cognitively intact individuals showed that higher baseline CT along with greater mean white matter diffusivity predicted AD-related cortical atrophy and decline in episodic memory 12 years later [45]. Thus, elevated CT, even in the absence of behavioral or cognitive changes, may antedate subsequent alterations in brain morphology and the onset of cognitive decline. Together, these findings on MCI/AD may help in unraveling the effects of ADT on cognition and brain in prostate cancer patients.

Indeed, following many studies of the impact of chemotherapy and hormonal therapy on brain structure and function in breast cancer patients [46-49], investigators have employed brain imaging to examine the effects of ADT on brain and cognition in prostate cancer patients. Previous studies of structural and functional MRI showed that, compared to participants who did not receive ADT, prostate cancer patients undergoing ADT did not differ in cognitive performance, but they showed decreases in frontopolar, dorsolateral prefrontal, and primary motor cortical GMVs [11] and diminished prefrontal cortical activity and connectivity during cognitive control [5]. Whereas a cross-sectional study did not find significant differences between ADT and control patients on GMV, white matter lesions or cognition [50], we noted with diffusion tensor imaging reduced fractional anisotropy in the corpus callosum, thalamic radiation and corona radiata following 6-months of ADT [13]. Further, these white matter changes correlated with decline in psychomotor speed in ADT patients [13]. During six months of ADT, structural connectivity did not differ between prostate cancer patients and healthy controls; however, patients performed worse than healthy controls on verbal memory, visuospatial learning, and visuospatial memory [51]. These findings underscore the utility of brain imaging in identifying the impact of hormonal therapy on brain structure and function prior to cognitive or behavioral manifestations. However, experimental design, e.g., cross-sectional vs. longitudinal, clinical heterogeneity, and comparison group may have led to less than consistent findings.

In the present study, we used longitudinal structural MRI to evaluate changes in cortical thickness (CT) among prostate cancer patients who received ADT, as compared with patients who did not receive the treatment. The participants were evaluated both at baseline and at six months of follow-up. We focused on working memory and quality of life in clinical assessment and performed whole-brain analyses to characterize changes in CT in ADT vs. control group with repeated measures analyses of variance.

Methods

Participants and clinical profiles

This is a longitudinal study, and participants were evaluated at baseline and prospectively at 6-month follow-up. We followed our earlier studies in patient recruitment and screening [5, 12]. Patients aged 50 to 75 with biopsy-proven prostate adenocarcinoma and no distant metastases were enlisted from the Medical Oncology and Urology Clinics at the West Haven VA Connecticut Healthcare System. Consistent with the National Comprehensive

Cancer Network and American Urological Society guidelines, treatment decisions were independent of the patient's participation in the study. ADT involved a six-month course of medical castration with an LH-RH agonist (Goserelin or Leuprolide) administered subcutaneously, following a lead-in period with Bicalutamide 50 mg daily. Controls (CON) consisted of non-metastatic prostate cancer patients who had not received ADT. ADT and CONs were matched based on age and level of education. Exclusion criteria for both ADT and CON included Eastern Cooperative Oncology Group Performance Status >1, active second malignancy, significant cardiovascular, liver, renal, or neurological disease, use of investigational drugs or contraindications for MRI, current substance (except nicotine) use disorders as verified by a urine test for illicit substances, history of other Axis I psychiatric illness, and history of traumatic brain injury or concussions causing loss of consciousness. A questionnaire interview was conducted for all participants to ensure MRI eligibility. Participants with prostatectomy were at least 3 months post-surgery before study entry. Those receiving radiation underwent baseline assessment and MR scan before treatment initiation and needed to be fully recovered from acute radiation side effects during follow-up assessments.

Among 90 candidates with non-metastatic prostate cancer, 75 who had never been treated with ADT were enrolled in the study. Thirty-five patients were scheduled for ADT and 40 patients served as CON. Thirty-two ADT and 35 CON completed both baseline and follow-up assessments. However, 2 ADT and 3 CON were excluded due to poor image quality. Thus, the data from 30 ADT and 32 CON were included in the analyses (Supplementary Figure 1).

The study was approved by the Human Investigation Committee of the West Haven VA and Yale University School of Medicine (Ref. No.: HIC#2000020501) and was conducted in accordance with Declaration of Helsinki. All participants provided a written informed consent prior to the study.

Study procedures and assessment of cognition and quality of life

All participants underwent evaluation for quality of life (QoL), working memory assessment with N-back task (outside the scanner), and MRI at baseline and at 6-month follow-up. At baseline, participants were also assessed for global cognition using Montreal Cognitive Assessment (MoCA).

Working memory is a form of short-term memory that provides temporary storage and manipulation of information necessary for complex cognitive tasks [52]. All participants underwent evaluation with the N-back task, a widely used paradigm to assess working memory [53] (Supplementary Figure 2).

As a general measure of QoL, participants completed the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire at baseline and at 6-month follow-up [54, 55]. The cumulative score of FACT-P subscale scores of physical, social, emotional, functional well-being, and prostate cancer subscale score formed the total QoL score.

Imaging protocol and data processing

Participants were scanned on a Siemens 3-Tesla scanner (Trio; Siemens AG, Erlangen, Germany). Data for each participant consisted of a single high-resolution T1-weighted gradient-echo scan: 176 slices; 1 mm^3 isotropic voxels; field of view = 256 × 256 mm; data acquisition matrix = 256 × 256; TR = 2530 ms; TE = 3.66 ms; bandwidth = 181 Hz/pixel; flip angle = 7°.

The raw 3D T1 images first underwent a manual quality check and then were reoriented to set the origin close to anterior commissure. Computational Anatomy Toolbox (CAT version 12) package in Statistical Parametric Mapping or SPM12 [56] was employed to estimate the CT. CT depicts the width of the gray matter ribbon as the distance between its inner and outer boundary. Utilizing a projection-based thickness method [57], the surface pipeline in CAT estimates initial CT and central surface in a combined step, accommodating partial volume information, sulcal blurring, and sulcal asymmetries, without the need for explicit sulcus reconstruction. Following this initial process, spherical harmonics [58] are employed to rectify topological defects, addressing anatomically incorrect connections between gyri or sulci. Subsequently, surface refinement yields the final central, pial, and white surface mesh-

Table 1. Demographic and clinical characteristics of the patients

	ADT (n = 30)		CON (n = 32)		$t_{60}/F_{1,60\ g\times t}/\chi^2$, p
Age (yr)	67.13 ± 6.57		66.59 ± 6.84		0.32, 0.753
Education (yr)	13.53 ± 3.29		14.65 ± 2.91		1.43, 0.160
MoCA score	25.03 ± 2.02		26.78 ± 2.16		3.28, 0.002
Cancer Staging	Stage I: 2 Stage II: 14 Stage III: 11 Stage IV: 3		Stage I: 8 Stage II: 13 Stage III: 11 Stage IV: 0		6.58, 0.087
Local therapy	Radiation: 96.67% Cryoablation: 3.33%		Active Surveillance: 40.62% Radiation: 15.62% Surgery: 37.50% Surgery + Radiation: 6.25%		-
	Baseline	FU	Baseline	FU	
T level (ng/ml)	3.72 ± 1.51	0.16 ± 0.07	3.94 ± 1.52	3.48 ± 1.58	76.62, <0.001

Note: MoCA: Montreal Cognitive Assessment, T: testosterone, FU: follow-up. For T levels, the statistics reflect treatment × time interaction, while for the other variables the statistics reflect two-sample t-tests of ADT vs. CON at the baseline. Staging follows the current guidelines of the American Joint Committee on Cancer (AJCC) that include Gleason score in the staging.

es. Next, the resulting individual surfaces were registered to standard 32k mesh for each hemisphere using a spherical mapping with minimal distortions [59], and smoothed using a 15 mm Gaussian kernel.

Statistical analyses of clinical, behavioral, and imaging data

All statistical analyses of clinical and behavioral data were conducted with Stata (Stata Corp LLC, Texas, USA). We used repeated measures ANOVA with group (ADT/CON) as a between-subject factor and time point (baseline/6-month follow-up) as a within-subject factor to assess the changes during follow-up from baseline in longitudinal variables. The ANOVA model was adjusted for baseline age, education, and MoCA score. The results that met two-tailed P<0.05 were considered statistically significant.

We used CAT's flexible factorial modelling with group (ADT and CON) and time (baseline and 6-month follow-up) as factors, and baseline age, education and MoCA score as covariates of no interest, to identify longitudinal changes in CT between ADT and CON in repeated-measures analysis of variance (ANOVA). We examined clusters showing significant treatment (ADT/CON) × time (baseline/follow-up) interactions at voxel P<0.001, uncorrected and cluster P<0.05 FWE, corrected, according to current reporting standards [60], and extracted the cortical thickness (CT β) across all participants for further statistical analyses.

Results

Baseline clinical profile of the participants

At baseline, ADT and CON patients were comparable in age, years of education, and testosterone levels (T-level) (t_{60} = 0.59, P = 0.559) (**Table 1**). MoCA score was significantly higher in CON than in the ADT group at the baseline. In addition, we observed a significant treatment × time interaction in T-level, as expected of the effects of ADT (**Table 1**; **Figure 1A**).

Follow-up vs. baseline changes in N-back task performance and quality of life did not differ across groups

N-back task performance and QoL scores are presented in Supplementary Table 1. In repeated measures ANOVA adjusted for baseline age, education, and MoCA scores, treatment × time interaction was not significant for N-back performance or QoL score (Supplementary Table 2). **Figure 1B** shows bar plots of mean ± SD of 2-back hit rates.

Increased cortical thickness in ADT during follow-up

Flexible factorial analysis showed significant treatment × time interaction in the left frontopolar cortex (FPC) (**Figure 2A**). We extracted the

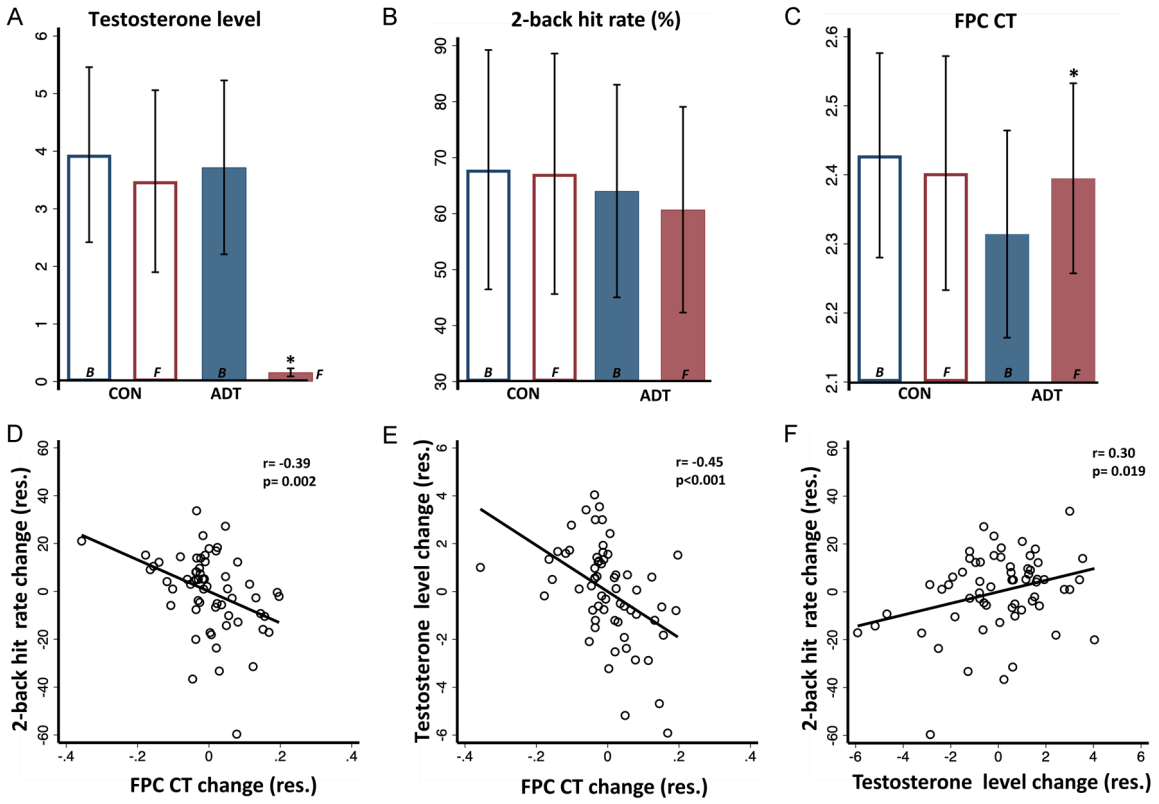


Figure 1. Baseline and 6-month follow-up (A) testosterone levels (ng/ml), (B) 2-back hit rate, and (C) frontopolar cortical (FPC) thickness in CON (open bars) and ADT (solid bars). * Indicates significant follow-up vs. baseline changes. Correlation between (D) 2-back hit rate change vs. FPC thickness change, (E) testosterone level change vs. FPC thickness change, and (F) 2-back hit rate change vs. testosterone level change in all (ADT+CON) participants. Data points in the scatter plots are shown as residuals, with baseline age, education, MoCA score as covariates; F: follow-up, B: baseline, CT: cortical thickness.

FPC CT β and in post-hoc test showed significant follow-up vs. baseline change (i.e., increased CT) in ADT (t_{29} = 5.88, P<0.001) but not in CON (t_{31} = 1.59, P = 0.122). **Figure 1C** shows bar plots of mean ± SD of FPC CT β's. In another pos-hoc analysis, we used baseline FPC CT as an additional covariate (other covariates: age, education, MoCA score), and showed significant treatment × time interaction ($F_{1,60}$ = 26.01, P<0.001).

Changes in frontopolar cortex thickness correlated with changes in working memory and testosterone levels

We evaluated whether the follow-up vs. baseline change in FPC CT β correlated with the changes in N-back performance metrices or the change in QoL score in ADT, CON, and all (ADT+CON) participants. Follow-up vs. baseline change in FPC CT β significantly and negatively correlated with 2-back hit rate change in CON and in all participants, and with change in T-level in all participants (**Table 2**). None of the other correlations were significant (**Table 2**).

Frontopolar cortex thickness change mediated the association between working memory and testosterone level changes

We are specifically interested in assessing impact of T-level changes on cognition and the neural correlates of the impact. We observed significant correlations amongst FPC CT β change, 2-back hit rate change, and T-level change at follow-up vs. baseline across all participants (**Figure 1D-F**). We thus performed mediation analyses to examine the inter-relationship of the three variables. We tested all 6 possible models and noted complete mediation for the models: 2-back hit rate difference → CT difference → T-level difference and T-level difference → CT difference → 2-back hit rate difference; and partial mediation for the

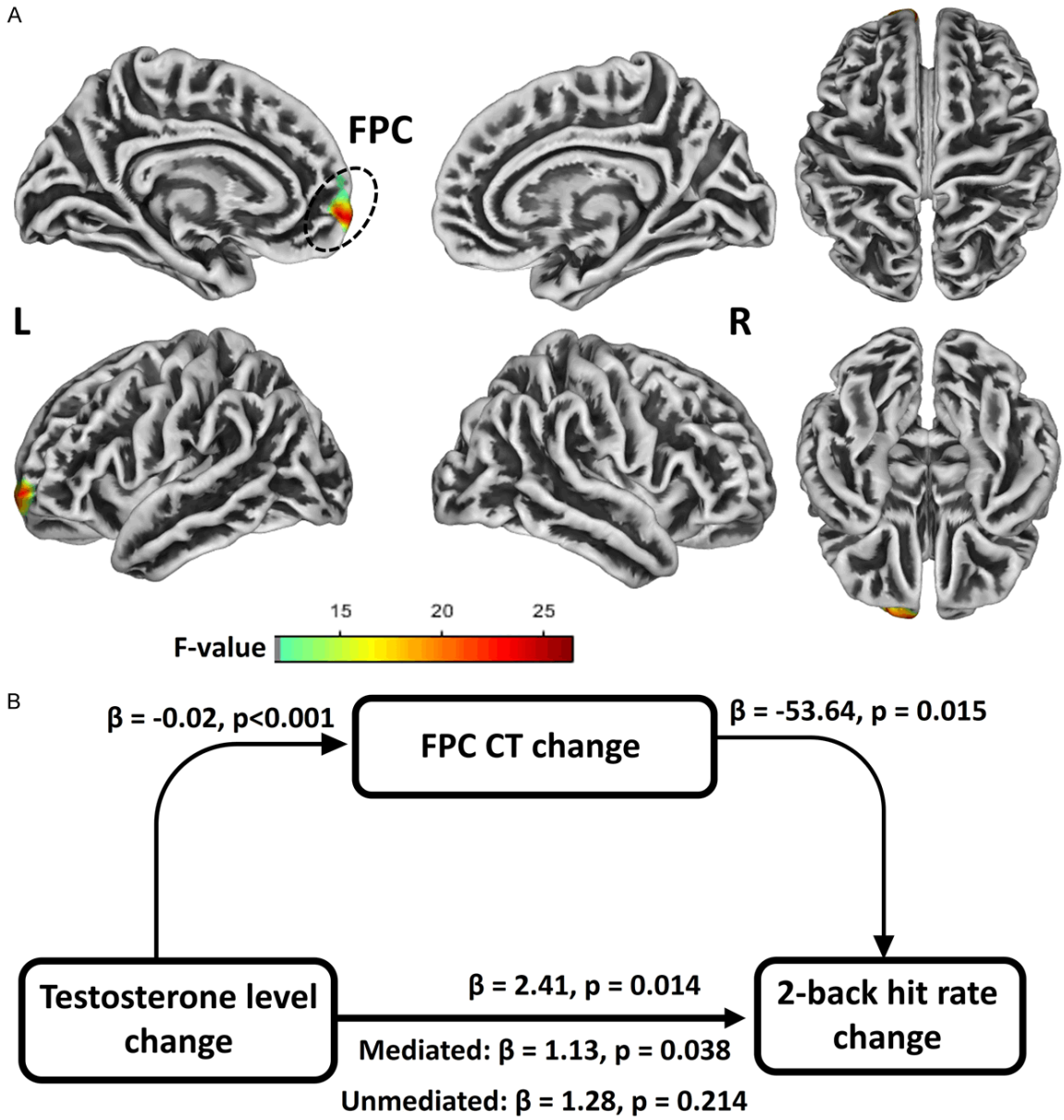


Figure 2. A. The left frontopolar cortex (FPC) thickness showed significant treatment × time interaction at voxel P<0.001 uncorrected and cluster P<0.05 FWE in repeated measures ANOVA with baseline age, education and MoCA as covariates. B. FPC thickness change mediated the association between testosterone level change and 2-back hit rate change across all (ADT+CON) participants. Cortical regions were identified using Desikan-Killiany (DK40) cortical atlas [71]. The statistics reported in the mediation model include beta coefficients (β), *p*-values.

model: 2-back hit rate difference → T-level difference → CT difference (Supplementary Table 3). As the two models with 2-back hit rate difference (i.e., performance outcome) as the independent variable was conceptually untenable, only the model T-level difference → CT difference → 2-back hit rate difference with complete mediation is considered valid (**Figure 2B**).

Analysis in matched sample replicated the findings in original sample

We repeated the analyses in demographically matched ADT (n = 30) and CONs (n = 28) (Supplementary Table 4). Following the original findings, testosterone (Supplementary Figure 3A), but not the 2-back hit rate (Supplementary Figure 3B) showed significant treatment × time

Table 2. Association between the frontopolar cortical thickness change (follow-up minus baseline) and changes in N-back performance metrics and testosterone levels (follow-up minus baseline)

	ADT		CON		All (ADT+CON)	
	r	p	r	p	r	p
0-back hit rate	-0.16	0.414	0.009	0.962	0.06	0.649
1-back hit rate	-0.004	0.983	-0.24	0.214	-0.13	0.334
2-back hit rate	-0.22	0.268	-0.53	0.003*	-0.39	0.002*
0-back RT	-0.08	0.675	-0.05	0.795	-0.02	0.856
1-back RT	-0.05	0.778	-0.13	0.502	-0.09	0.458
2-back RT	0.058	0.771	-0.19	0.312	-0.07	0.584
QoL	0.14	0.489	-0.09	0.656	0.06	0.624
Testosterone level	-0.15	0.464	-0.16	0.394	-0.45	<0.001*

Note: *P<0.05 Pearson regression with baseline age, years of education, and MoCA score as covariates.

interaction. We also noted significant treatment × time interaction for FPC CT ($F_{1,56}$ = 19.19, P<0.001) (Supplementary Figures 3C, 4A). Further, we observed significant correlations amongst FPC CT change, 2-back hit rate change, and T-level change at follow-up vs. baseline across all participants (Supplementary Figure 3D-F), and a trend-level significance in mediation effects for the model: 2-back hit rate difference → CT difference → T-level difference (Supplementary Figure 4B).

Discussion

ADT has been associated with physiological, metabolic, and cognitive side effects, which can potentially impact the quality of life (QoL) of prostate cancer patients [61]. Here, we showed that N-back working memory and QoL did not appear to be significantly influenced by ADT for a duration of 6 months. With structural brain imaging, we observed higher cortical thickness (CT) of the frontopolar cortex (FPC) in patients undergoing 6 months of ADT, but no changes in patients who did not receive ADT. Further, the changes in FPC CT at follow-up vs. baseline were significantly and negatively correlated with changes in 2-back correct response rate and testosterone level across all participants. In mediation analysis, FPC CT change mediated the association between testosterone level and 2-back accuracy rate changes. These findings support the impact of ADT on the brain, potentially reflecting neurodegenerative changes early during the course of treatment. It remains to be seen whether ADT for a longer duration may lead to impairment in QoL, working memory, and other cognitive functions.

The FPC is considered an important region for working memory, amongst other cognitive processes, including planning and management of multiple behavioral goals [62-65]. We did not observe significant follow-up vs. baseline changes in working memory accuracy or reaction time in patients undergoing ADT. However, the changes in FPC CT correlated negatively with 2-back accuracy rate change across all participants (ADT+CON). That is, an increase in thickness corresponds to decrease in working memory accuracy. This association seems to be driven more by the CON than by ADT group, possibly suggesting that, first, changes in CT transpires during this time period of cancer diagnosis and/or aging in prostate cancer patients, including those who did not receive ADT, and second, the pathophysiological processes elicited by androgen deprivation (chemical castration) may have obscured inter-subject variability such that the correlation was less detectable in the ADT group. A question concerns why increases in FPC thickness were associated with impairment in working memory. We speculated that this may have to do with the unique roles of the FPC in managing multiple behavioral goals. In an earlier study of non-human primates, unlike other prefrontal cortical lesions, circumscribed FPC lesions did not impair primates' ability to learn task-switching during an analog of the Wisconsin Card Sorting Task [65]. Rather, FPC-lesioned monkeys were more successful than control animals at remembering the relevant rule across experimentally imposed distractions involving either an intervening secondary task or a surprising delivery of free reward. The FPC may be specialized for disengaging executive control from the current task and redirecting resources to explore new opportunities or goals [65]. Thus, monkeys with FPC lesions were able to perform the task better without "having to be" distracted by the intervening stimuli. The current findings of elevated FPC thickness in six months and of negative correlation between FPC thickness and memory per-

formance appear to reflect this unique role of the FPC. With FPC engaged to a great extent, participants are perhaps more vulnerable to the intervening non-target stimuli in the N-back task.

Here, higher FPC cortical thickness in prostate cancer patients following 6-month of ADT may indicate hypertrophy in a cognitive brain region, in response to neuroinflammation or other, less understood pathological changes that also occur in cognitively normal elderly [42-44]. Notably, this morphometric change mirrors the findings in people with early stages of MCI and AD [41]. For instance, in cognitively normal elderly at different stages of preclinical AD, those in stage 0 (Aβ-/tau-) had higher rates of medial frontal cortical thinning compared to those in stage 1 (Aβ+/tau-), whereas those in stage 2/3 (Aβ+/tau+) showed higher rates of medial temporal cortical thinning as compared to both stage 0 and 1 [44]. Another study showed that early preclinical stage of AD, estimated at 20 to 15 years before symptom onset, was characterized by an increase in occipitoparietal cortical thickness, which was followed by cortical thinning in later, symptomatic stages. Further, this pattern of cortical thickness changes aligned with the cerebrospinal fluid (CSF) p-Tau AD marker [66]. A more recent study observed that greater baseline cortical thickness was associated with higher odds (odds ratio = 1.65) of progressing to MCI over a 12-year period [45]. Thus, the increase in cortical thickness as observed here may indicate early morphometric brain changes due to ADT, which might reverse its course with longer duration of ADT.

We also noted significantly reduced testosterone levels in ADT vs. CON for 6 months follow-up. This was expected as ADT works by reducing the levels of testosterone [67]. Across all participants, the follow-up vs. baseline changes in testosterone level correlated with both FPC thickness and 2-back accuracy rate changes. These findings are consistent with testosterone's role in cognitive functioning [19, 68] and supporting brain structure and function [11, 69]. Adding to our earlier report of prefrontal cortical volumetric changes as a result of ADT [11], the current findings highlighted the impact of altered testosterone levels induced by ADT on FPC thickness. Additionally, we observed with mediation analyses that testosterone levels can influence working memory through changes in FPC thickness. Thus, altered testosterone levels can impact cognitive functioning by altering brain morphology. Long-term consequences of such alterations remain to be studied.

A number of limitations need to be considered. First, the study involved a small sample, and the results would need to be replicated. On the other hand, we wish to emphasize that the imaging results were obtained at a corrected threshold and would likely be robust. Second, working memory represents one aspect of cognitive functions. Studies are needed to employ a more comprehensive battery of neuropsychological tests and other neural metrics to fully investigate potential cognitive dysfunction in prostate cancer patients receiving ADT [70]. Third, although we assessed cortical thickness changes in the current study, future research should consider other valuable MRI metrics, including the resting-state metrices, e.g., amplitude of low frequency fluctuations (ALFF) and functional connectivity (FC). Finally, as patients may undergo ADT for a longer duration, the current findings should be considered as specific to patients with only 6 months of exposure to ADT. A longer follow-up would allow us to determine the longitudinal validity of elevated frontopolar CT and its potential association with cognitive dysfunction.

In summary, our study reveals that 6 months of ADT leads to increases in FPC thickness, potentially indicating early neurodegenerative changes in response to hormonal treatment, in prostate cancer patients. Testosterone level changes were associated with alterations in FPC thickness and working memory across all participants, highlighting the role of testosterone in cognitive functions and brain structure. While no significant impact on working memory or quality of life was observed over six months, research over longer duration of treatment is warranted to unravel the full spectrum of cognitive and neural consequences of ADT in prostate cancer patients.

Acknowledgements

We are grateful for all patients' participation in the study and for the help of the Urology clinic at the CT West Haven VA in assistance with the

recruitment. We are indebted to our colleague and friend Dr. Ruth McCorkle for her assistance in study design in the early phase of this work. The current study is supported by NIH grant CA218501 and VA Merit Award CX001301.

All participants provided a written informed consent prior to the study.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shefali Chaudhary, Department of Psychiatry, Yale University School of Medicine, CMHC S110, No. 34 Park Street, New Haven, CT 06519, USA. Tel: 1-203-974-7891; E-mail: shefali.chaudhary@yale.edu; Dr. Herta H Chao, Cancer Center, VA Connecticut Healthcare System, No. 950 Campbell Avenue, West Haven, CT 06516, USA. Tel: 1-203-937-3421; E-mail: herta.chao@yale.edu

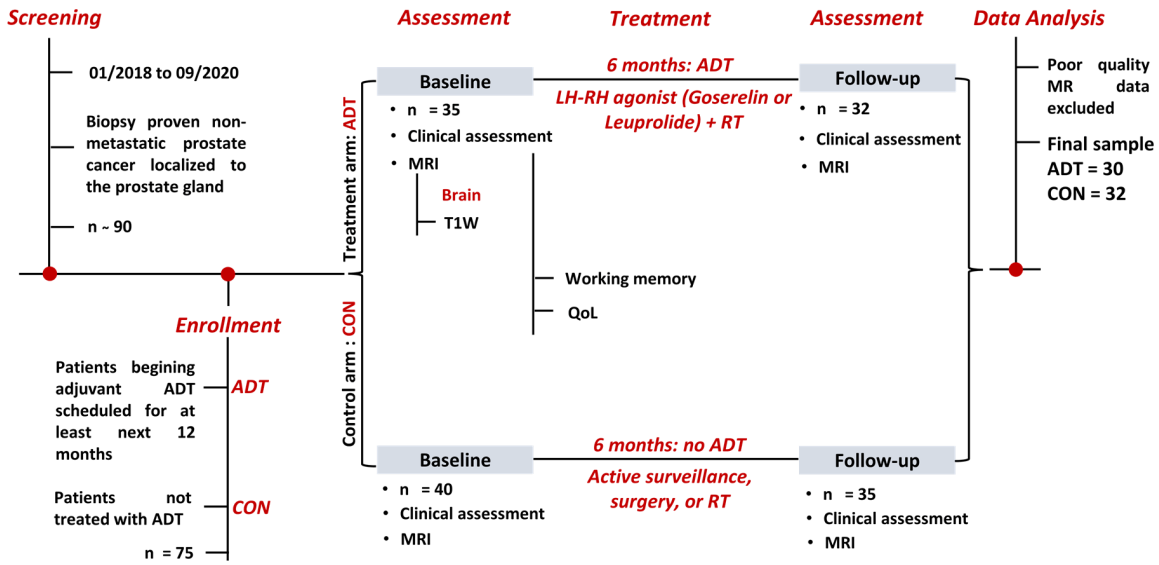
References

[1] Rawla P. Epidemiology of prostate cancer. World J Oncol 2019; 10: 63-89.
[2] Siegel RL, Miller KD, Wagle NS and Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023; 73: 17-48.
[3] Abudoubari S, Bu K, Mei Y, Maimaitiyiming A, An H and Tao N. Prostate cancer epidemiology and prognostic factors in the United States. Front Oncol 2023; 13: 1142976.
[4] Hu JC, Williams SB, O'Malley AJ, Smith MR, Nguyen PL and Keating NL. Androgen-deprivation therapy for nonmetastatic prostate cancer is associated with an increased risk of peripheral arterial disease and venous thromboembolism. Eur Urol 2012; 61: 1119-28.
[5] Chao HH, Uchio E, Zhang S, Hu S, Bednarski SR, Luo X, Rose M, Concato J and Li CS. Effects of androgen deprivation on brain function in prostate cancer patients - a prospective observational cohort analysis. BMC Cancer 2012; 12: 371.
[6] Freedland SJ and Abrahamsson PA. Androgen deprivation therapy and side effects: are GnRH antagonists safer? Asian J Androl 2021; 23: 3-10.
[7] Nead KT, Sinha S and Nguyen PL. Androgen deprivation therapy for prostate cancer and dementia risk: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2017; 20: 259-64.
[8] Sun M, Cole AP, Hanna N, Mucci LA, Berry DL, Basaria S, Ahern DK, Kibel AS, Choueiri TK and Trinh QD. Cognitive impairment in men with prostate cancer treated with androgen deprivation therapy: a systematic review and meta-analysis. J Urol 2018; 199: 1417-25.
[9] Almeida OP, Waterreus A, Spry N, Flicker L and Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. Psychoneuroendocrinology 2004; 29: 1071-81.
[10] Green HJ, Pakenham KI, Headley BC, Yaxley J, Nicol DL, Mactaggart PN, Swanson C, Watson RB and Gardiner RA. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial. BJU Int 2002; 90: 427-32.
[11] Chao HH, Hu S, Ide JS, Uchio E, Zhang S, Rose M, Concato J and Li CS. Effects of androgen deprivation on cerebral morphometry in prostate cancer patients--an exploratory study. PLoS One 2013; 8: e72032.
[12] Chaudhary S, Zhornitsky S, Roy A, Summers C, Ahles T, Li CR and Chao HH. The effects of androgen deprivation on working memory and quality of life in prostate cancer patients: the roles of hypothalamic connectivity. Cancer Med 2022; 11: 3425-3436.
[13] Chaudhary S, Roy A, Summers C, Ahles T, Li CR and Chao HH. Effects of androgen deprivation on white matter integrity and processing speed in prostate cancer patients. Am J Cancer Res 2022; 12: 4802-14.
[14] Salminen E, Portin R, Korpela J, Backman H, Parvinen LM, Helenius H and Nurmi M. Androgen deprivation and cognition in prostate cancer. Br J Cancer 2003; 89: 971-6.
[15] Sari Motlagh R, Quhal F, Mori K, Miura N, Aydh A, Laukhtina E, Pradere B, Karakiewicz PI, Enikeev DV, Deuker M and Shariat SF. The risk of new onset dementia and/or Alzheimer disease among patients with prostate cancer treated with androgen deprivation therapy: a systematic review and meta-analysis. J Urol 2021; 205: 60-7.
[16] Cui H, Wang Y, Li F, He G, Jiang Z, Gang X and Wang G. Quantifying observational evidence for risk of dementia following androgen deprivation therapy for prostate cancer: an updated systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2021; 24: 15-23.
[17] Lehrer S and Rheinstein PH. Androgen deprivation therapy unrelated to Alzheimer's disease in the UK biobank cohort. Anticancer Res 2023; 43: 437-40.
[18] Cai Z and Li H. An updated review: androgens and cognitive impairment in older men. Front Endocrinol (Lausanne) 2020; 11: 586909.
[19] Janowsky JS. Thinking with your gonads: testosterone and cognition. Trends Cogn Sci 2006; 10: 77-82.

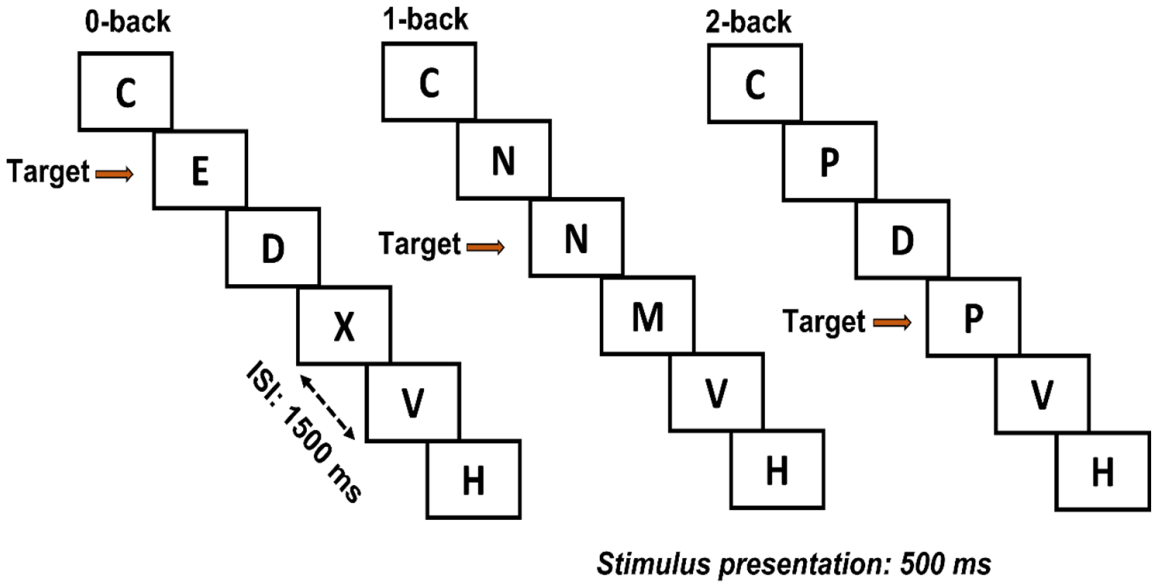
[20] Bimonte-Nelson HA, Singleton RS, Nelson ME, Eckman CB, Barber J, Scott TY and Granholm AC. Testosterone, but not nonaromatizable dihydrotestosterone, improves working memory and alters nerve growth factor levels in aged male rats. Exp Neurol 2003; 181: 301-12.
[21] Sandstrom NJ, Kim JH and Wasserman MA. Testosterone modulates performance on a spatial working memory task in male rats. Horm Behav 2006; 50: 18-26.
[22] Spritzer MD, Gill M, Weinberg A and Galea LA. Castration differentially affects spatial working and reference memory in male rats. Arch Sex Behav 2008; 37: 19-29.
[23] Janowsky JS, Chavez B and Orwoll E. Sex steroids modify working memory. J Cogn Neurosci 2000; 12: 407-14.
[24] Tan RS and Pu SJ. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. Aging Male 2003; 6: 13-7.
[25] Cherrier MM, Matsumoto AM, Amory JK, Asthana S, Bremner W, Peskind ER, Raskind MA and Craft S. Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. Neurology 2005; 64: 2063-8.
[26] Lašaitė L, Čeponis J, Preikša RT and Žilaitienė B. Effects of two-year testosterone replacement therapy on cognition, emotions and quality of life in young and middle-aged hypogonadal men. Andrologia 2017; 49.
[27] Kenny AM, Fabregas G, Song C, Biskup B and Bellantonio S. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. J Gerontol A Biol Sci Med Sci 2004; 59: 75-8.
[28] Lisco G, Giagulli VA, De Tullio A, De Pergola G, Guastamacchia E and Triggiani V. Age-related male hypogonadism and cognitive impairment in the elderly: focus on the effects of testosterone replacement therapy on cognition. Geriatrics (Basel) 2020; 5: 76.
[29] Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM and Resnick SM. Free testosterone and risk for Alzheimer disease in older men. Neurology 2004; 62: 188-93.
[30] Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR and Alberts MJ. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993; 43: 1467-72.
[31] Panizzon MS, Hauger R, Xian H, Vuoksimaa E, Spoon KM, Mendoza SP, Jacobson KC, Vasilopoulos T, Rana BK, McKenzie R, McCaffery JM, Lyons MJ, Kremen WS and Franz CE. Interaction of APOE genotype and testosterone on episodic memory in middle-aged men. Neurobiol Aging 2014; 35: 1778, e1-8.
[32] Findeis MA. The role of amyloid beta peptide 42 in Alzheimer's disease. Pharmacol Ther 2007; 116: 266-86.
[33] Verdile G, Laws SM, Henley D, Ames D, Bush AI, Ellis KA, Faux NG, Gupta VB, Li QX, Masters CL, Pike KE, Rowe CC, Szoeke C, Taddei K, Villemagne VL and Martins RN; AIBL Research Group. Associations between gonadotropins, testosterone and β amyloid in men at risk of Alzheimer's disease. Mol Psychiatry 2014; 19: 69-75.
[34] Yin C, Li S, Zhao W and Feng J. Brain imaging of mild cognitive impairment and Alzheimer's disease. Neural Regen Res 2013; 8: 435-44.
[35] Singh V, Chertkow H, Lerch JP, Evans AC, Dorr AE and Kabani NJ. Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. Brain 2006; 129: 2885-93.
[36] Schwarz CG, Gunter JL, Wiste HJ, Przybelski SA, Weigand SD, Ward CP, Senjem ML, Vemuri P, Murray ME, Dickson DW, Parisi JE, Kantarci K, Weiner MW, Petersen RC and Jack CR Jr; Alzheimer's Disease Neuroimaging Initiative. A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity. Neuroimage Clin 2016; 11: 802-12.
[37] Mak E, Zhang L, Tan CH, Reilhac A, Shim HY, Wen MOQ, Wong ZX, Chong EJY, Xu X, Stephenson M, Venketasubramanian N, Zhou JH, O'Brien JT and Chen CL. Longitudinal associations between β-amyloid and cortical thickness in mild cognitive impairment. Brain Commun 2023; 5: fcad192.
[38] Im K, Lee JM, Seo SW, Hyung Kim S, Kim SI and Na DL. Sulcal morphology changes and their relationship with cortical thickness and gyral white matter volume in mild cognitive impairment and Alzheimer's disease. Neuroimage 2008; 43: 103-13.
[39] Ye BS, Seo SW, Yang JJ, Kim HJ, Kim YJ, Yoon CW, Cho H, Noh Y, Kim GH, Chin J, Kim JH, Jeon S, Lee JM and Na DL. Comparison of cortical thickness in patients with early-stage versus late-stage amnestic mild cognitive impairment. Eur J Neurol 2014; 21: 86-92.
[40] Kim MJ, Im K, Lee JM, Park A, Chin J, Kim GH, Kim JH, Roh JH, Seo SW and Na DL. Cortical thinning in verbal, visual, and both memory-predominant mild cognitive impairment. Alzheimer Dis Assoc Disord 2011; 25: 242-9.
[41] Williams ME, Elman JA, Bell TR, Dale AM, Eyler LT, Fennema-Notestine C, Franz CE, Gillespie NA, Hagler DJ Jr, Lyons MJ, McEvoy LK, Neale MC, Panizzon MS, Reynolds CA, Sanderson-

Cimino M and Kremen WS. Higher cortical thickness/volume in Alzheimer's-related regions: protective factor or risk factor? Neurobiol Aging 2023; 129: 185-94.
[42] Iacono D, O'Brien R, Resnick SM, Zonderman AB, Pletnikova O, Rudow G, An Y, West MJ, Crain B and Troncoso JC. Neuronal hypertrophy in asymptomatic Alzheimer disease. J Neuropathol Exp Neurol 2008; 67: 578-89.
[43] Torso M, Ridgway GR, Hardingham I, Schwarz AJ and Chance SA. In vivo detection of changes related to cortical columnar organization and neuroinflammation across the AD continuum. J Prev Alzheimers Dis 2022; 9: 769-79.
[44] Montal V, Vilaplana E, Alcolea D, Pegueroles J, Pasternak O, González-Ortiz S, Clarimón J, Carmona-Iragui M, Illán-Gala I, Morenas-Rodríguez E, Ribosa-Nogué R, Sala I, Sánchez-Saudinós MB, García-Sebastian M, Villanúa J, Izagirre A, Estanga A, Ecay-Torres M, Iriondo A, Clerigue M, Tainta M, Pozueta A, González A, Martínez-Heras E, Llufriu S, Blesa R, Sanchez-Juan P, Martínez-Lage P, Lleó A and Fortea J. Cortical microstructural changes along the Alzheimer's disease continuum. Alzheimers Dement 2018; 14: 340-51.
[45] Williams ME, Elman JA, McEvoy LK, Andreassen OA, Dale AM, Eglit GML, Eyler LT, Fennema-Notestine C, Franz CE, Gillespie NA, Hagler DJ Jr, Hatton SN, Hauger RL, Jak AJ, Logue MW, Lyons MJ, McKenzie RE, Neale MC, Panizzon MS, Puckett OK, Reynolds CA, Sanderson-Cimino M, Toomey R, Tu XM, Whitsel N, Xian H and Kremen WS. 12-year prediction of mild cognitive impairment aided by Alzheimer's brain signatures at mean age 56. Brain Commun 2021; 3: fcab167.
[46] Castellon SA, Silverman DH and Ganz PA. Breast cancer treatment and cognitive functioning: current status and future challenges in assessment. Breast Cancer Res Treat 2005; 92: 199-206.
[47] Eberling JL, Wu C, Tong-Turnbeaugh R and Jagust WJ. Estrogen- and tamoxifen-associated effects on brain structure and function. Neuroimage 2004; 21: 364-71.
[48] Ferguson RJ, McDonald BC, Saykin AJ and Ahles TA. Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. J Clin Oncol 2007; 25: 3866-70.
[49] Silverman DH, Dy CJ, Castellon SA, Lai J, Pio BS, Abraham L, Waddell K, Petersen L, Phelps ME and Ganz PA. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5-10 years after chemotherapy. Breast Cancer Res Treat 2007; 103: 303-11.
[50] Plata-Bello J, Plata-Bello A, Pérez-Martín Y, Fajardo V and Concepción-Massip T. Androgen deprivation therapy increases brain ageing. Aging (Albany NY) 2019; 11: 5613-27.
[51] Buskbjerg CR, Amidi A, Buus S, Gravholt CH, Hadi Hosseini SM and Zachariae R. Androgen deprivation therapy and cognitive decline-associations with brain connectomes, endocrine status, and risk genotypes. Prostate Cancer Prostatic Dis 2022; 25: 208-18.
[52] Baddeley A. Working memory. Science 1992; 255: 556-9.
[53] Chaudhary S, Roy A, Summers C, Zhornitsky S, Ahles T, Li CR and Chao HH. Hypothalamic connectivities predict individual differences in ADT-elicited changes in working memory and quality of life in prostate cancer patients. Sci Rep 2022; 12: 9567.
[54] Esper P, Mo F, Chodak G, Sinner M, Cella D and Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology 1997; 50: 920-8.
[55] Esper P, Hampton JN, Smith DC and Pienta KJ. Quality-of-life evaluation in patients receiving treatment for advanced prostate cancer. Oncol Nurs Forum 1999; 26: 107-12.
[56] Farokhian F, Beheshti I, Sone D and Matsuda H. Comparing CAT12 and VBM8 for detecting brain morphological abnormalities in temporal lobe epilepsy. Front Neurol 2017; 8: 428.
[57] Dahnke R, Yotter RA and Gaser C. Cortical thickness and central surface estimation. Neuroimage 2013; 65: 336-48.
[58] Yotter RA, Thompson PM and Gaser C. Algorithms to improve the reparameterization of spherical mappings of brain surface meshes. J Neuroimaging 2011; 21: e134-47.
[59] Yotter RA, Nenadic I, Ziegler G, Thompson PM and Gaser C. Local cortical surface complexity maps from spherical harmonic reconstructions. Neuroimage 2011; 56: 961-73.
[60] Wang W, Zhornitsky S, Le TM, Dhingra I, Zhang S, Krystal JH and Li CR. Cue-elicited craving, thalamic activity, and physiological arousal in adult non-dependent drinkers. J Psychiatr Res 2019; 116: 74-82.
[61] Sountoulides P and Rountos T. Adverse effects of androgen deprivation therapy for prostate cancer: prevention and management. ISRN Urol 2013; 2013: 240108.
[62] Bludau S, Eickhoff SB, Mohlberg H, Caspers S, Laird AR, Fox PT, Schleicher A, Zilles K and Amunts K. Cytoarchitecture, probability maps and functions of the human frontal pole. Neuroimage 2014; 93 Pt 2: 260-75.
[63] Tsujimoto S, Genovesio A and Wise SP. Frontal pole cortex: encoding ends at the end of the endbrain. Trends Cogn Sci 2011; 15: 169-76.

[64] Law CK, Kolling N, Chan CCH and Chau BKH. Frontopolar cortex represents complex features and decision value during choice between environments. Cell Rep 2023; 42: 112555.
[65] Mansouri FA, Buckley MJ, Mahboubi M and Tanaka K. Behavioral consequences of selective damage to frontal pole and posterior cingulate cortices. Proc Natl Acad Sci U S A 2015; 112: E3940-9.
[66] Montal V, Vilaplana E, Pegueroles J, Bejanin A, Alcolea D, Carmona-Iragui M, Clarimón J, Levin J, Cruchaga C, Graff-Radford NR, Noble JM, Lee JH, Allegri R, Karch CM, Laske C, Schofield PR, Salloway S, Ances B, Benzinger T, McDale E, Bateman R, Blesa R, Sánchez-Valle R, Lleó A and Fortea J; Dominantly Inherited Alzheimer Network (DIAN). Biphasic cortical macro- and microstructural changes in autosomal dominant Alzheimer's disease. Alzheimers Dement 2021; 17: 618-28.
[67] Sharifi N, Gulley JL and Dahut WL. Androgen deprivation therapy for prostate cancer. JAMA 2005; 294: 238-44.
[68] Resnick SM, Matsumoto AM, Stephens-Shields AJ, Ellenberg SS, Gill TM, Shumaker SA, Pleasants DD, Barrett-Connor E, Bhasin S, Cauley JA, Cella D, Crandall JP, Cunningham GR, Ensrud KE, Farrar JT, Lewis CE, Molitch ME, Pahor M, Swerdloff RS, Cifelli D, Anton S, Basaria S, Diem SJ, Wang C, Hou X and Snyder PJ. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA 2017; 317: 717-27.
[69] Shim M, Bang WJ, Oh CY, Lee YS and Cho JS. Androgen deprivation therapy and risk of cognitive dysfunction in men with prostate cancer: is there a possible link? Prostate Int 2022; 10: 68-74.
[70] R Buskbjerg C, Zachariae R, Buus S, H Gravholt C, Haldbo-Classen L, Hosseini SMH and Amidi A. Cognitive impairment and associations with structural brain networks, endocrine status, and risk genotypes in patients with newly diagnosed prostate cancer referred to androgen-deprivation therapy. Cancer 2021; 127: 1495-506.
[71] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS and Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006; 31: 968-80.



Supplementary Figure 1. Study timeline. Note: Treatment for the patients followed current guidelines and were independent of the current study. Three patients of the ADT group had previously undergone surgery. ADT: androgen deprivation therapy, CON: control, MRI: magnetic resonance imaging, QoL: quality of life, LH-RH: luteinizing hormone releasing hormone, RT: radiation therapy. Treatment decisions for all participants followed current National Comprehensive Cancer Network and American Urological Society practice guidelines and were independent of participation in this research protocol. Thus, the enrollment was not random. Briefly, therapeutic interventions for prostate cancer depend on a number of factors, most importantly the extent of tumor staging (with stage I-III indicating disease affecting part or whole of the prostate and stage IV indicating disease spreading outside the prostate) and the Gleason score (with higher score indicating more poorly differentiated and prognostically more aggressive disease). Only patients with localized prostate cancer without distant metastatic spread were invited to participate. Aside from symptoms related to prostatic enlargement, this patient group is usually asymptomatic from their cancer. Gleason scoring is a histologic grading system for prostate adenocarcinomas used for risk stratification and is not a reflection of a patient's general health and performance status. Patients in the control group (CON) had never received any hormonal therapy and were either on active surveillance or treated with surgery or radiation alone. Patients with localized prostate cancer who were scheduled to undergo radiation therapy followed by at least 6 months of adjuvant ADT and patients starting ADT for biochemical recurrence without evidence for any metastatic disease were recruited to the ADT arm (ADT).



Supplementary Figure 2. N-back working memory task. A stream of fifteen phonologically distinct letters appears in sequency each for a duration of 500 ms and with an inter-stimulus-interval of 1500 ms. There are three different conditions: 0-, 1-, and 2-back, differing in working memory load. In the 0-back trials, participants identified a pre-specified target (e.g., letter "E"); in the 1- and 2-back trials, there is no fixed target; in contrast, a letter that is the same as the one 1- and 2-time steps back represents the target, respectively. Participants were instructed to response as accurately and as fast as possible. N-back task was administered at baseline and 6-month follow-up outside the scanner. Each subject completed 3 sessions of the task, with each session containing two each of 0-, 1-, and 2-back blocks, the order of which was counter-balanced across sessions. Each block began with an information screen showing the "working memory load" for that block (5 s) and contained 24 trials, with one-third showing a target. Correct response rate and reaction time, averaged across blocks and sessions, each for 0-, 1- and 2-back trials, serves as an outcome measure of N-back performance.

Supplementary Table 1. N-back performance and QoL score (mean ± SD) in ADT and CON at baseline and six-month follow-up

Variables	ADT		CON	
	Baseline	Follow-up	Baseline	Follow-up
0-back hit rate	96.03 ± 10.06	96.25 ± 6.89	99.77 ± 0.70	96.35 ± 9.71
1-back hit rate	86.03 ± 11.86	79.76 ± 21.81	89.65 ± 13.78	89.36 ± 18.28
2-back hit rate	63.01 ± 18.47	59.77 ± 17.87	67.85 ± 21.37	67.11 ± 21.47
0-back RT	525.71 ± 101.60	542.87 ± 69.46	506.22 ± 97.50	513.78 ± 88.48
1-back RT	640.24 ± 121.48	658.37 ± 109.21	613.69 ± 162.59	632.07 ± 150.08
2-back RT	782.38 ± 190.81	758.70 ± 194.69	712.41 ± 177.96	714.75 ± 161.75
QoL	111.33 ± 18.34	111.26 ± 18.52	124.06 ± 17.43	122.87 ± 20.12

Supplementary Table 2. Treatment (ADT vs. CON) and time (follow-up vs. baseline) main and interaction effects of N-back performance and QoL scores: repeated measures ANOVA

Variables	Group		Time		Treatment × time	
	F-value	*p*-value	F-value	*p*-value	F-value	*p*-value
0-back hit rate	0.43	0.515	1.35	0.250	1.76	0.189
1-back hit rate	0.65	0.425	1.56	0.216	1.29	0.259
2-back hit rate	0.01	0.934	0.85	0.359	0.33	0.565
0-back RT	0.62	0.432	0.94	0.337	0.14	0.709
1-back RT	0.04	0.254	1.33	0.254	0.00	0.994
2-back RT	0.96	0.331	0.17	0.677	0.26	0.612
QoL	6.16	0.016*	0.10	0.747	0.08	0.773

Note: *P<0.05 adjusted for baseline age, years of education, and MoCA score.

Supplementary Table 3. Mediation model β and *p* values (X/M/Y: independent/mediating/dependent variable with baseline age, education, MoCA as covariate)

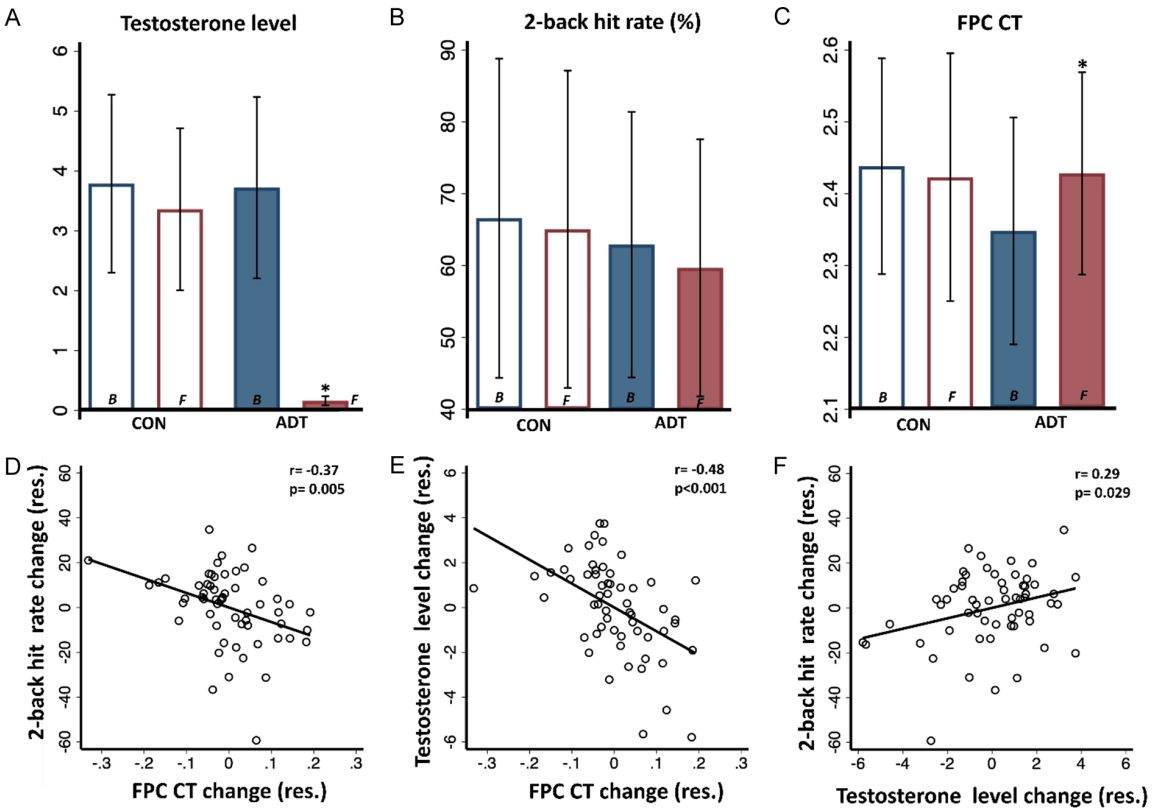
X	M	Y	β, p				
			X → M	M → Y	X → Y	Direct X → Y	Indirect X → Y
CT diff	2-back diff	T-diff	-66.03, 0.001	0.02, 0.214	-9.66, <0.001	-8.41, 0.001	-1.25, 0.245
CT diff	T-diff	2-back diff	-9.66, <0.001	1.28, 0.214	-66.03, 0.001	-53.64, 0.015	-12.38, 0.236
2-back diff	CT diff	T-diff	-0.002, N0.001	-8.42, 0.001	0.04, 0.012	0.02, 0.214	0.02, 0.021**
2-back diff	T-diff	CT diff	0.04, 0.012	-0.02, 0.001	-0.002, 0.001	-0.002, 0.015	-0.0006, 0.048*
T-diff	CT diff	2-back diff	-0.02, <0.001	-53.64, 0.015	2.41, 0.012	1.28, 0.214	1.13, 0.038**
T-diff	2-back diff	CT diff	2.41, 0.012	-0.002, 0.015	-0.02, <0.001	-0.02, 0.001	-0.004, 0.081

Note: **complete and *partial mediation.

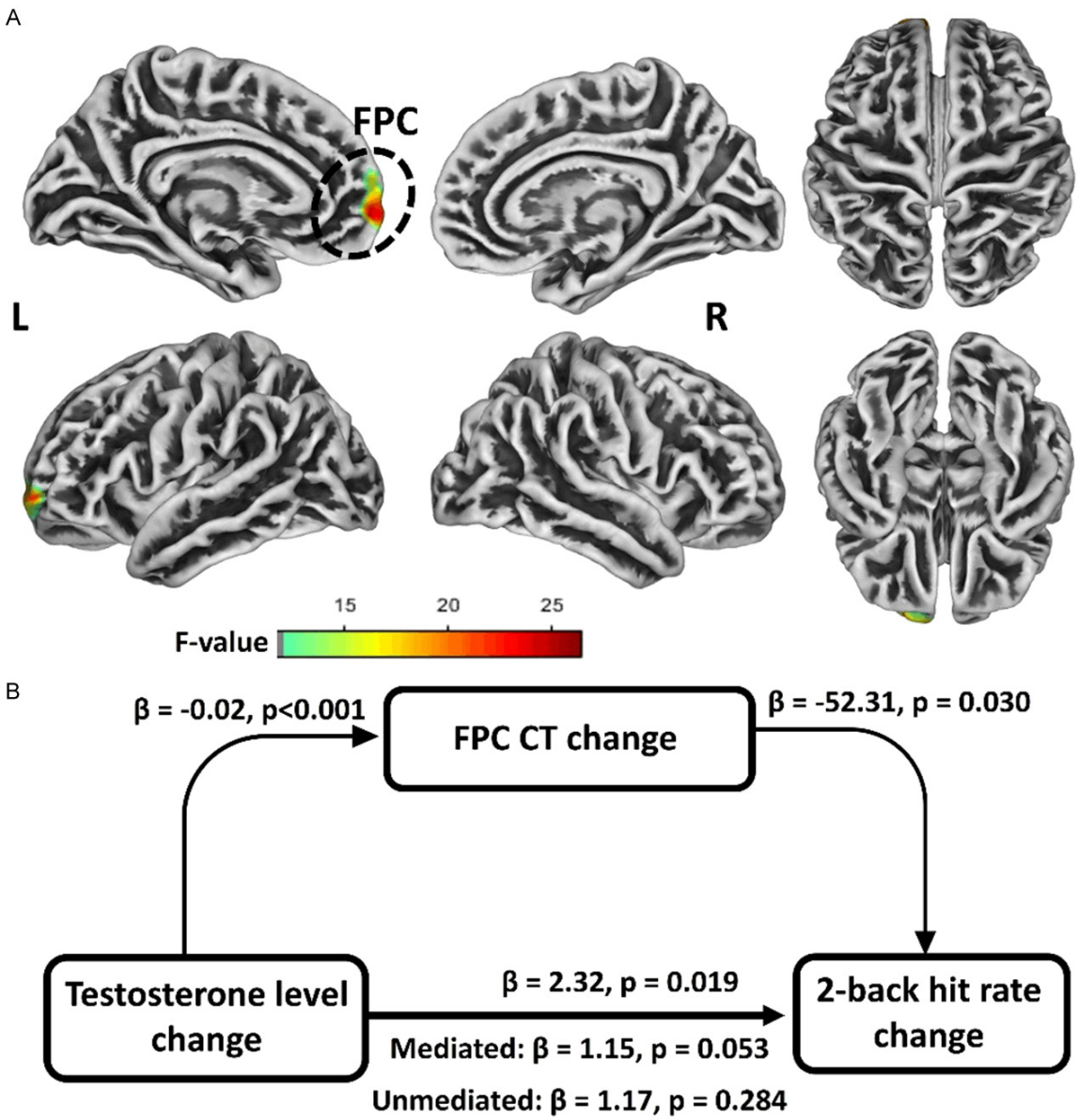
Supplementary Table 4. Demographic and clinical characteristics of the patients matched in demographics

	ADT (n = 30)		CON (n = 28)		$T_{56}/F_{1,56\ g\times t}/\chi^2$, p
Age (yr)	67.13 ± 6.57		66.32 ± 7.00		0.46, 0.651
Education (yr)	13.53 ± 3.28		14.92 ± 3.00		1.43, 0.160
MoCA score	25.03 ± 2.02		25.96 ± 1.71		1.88, 0.064
Cancer Staging	Stage I: 2 Stage II: 14 Stage III: 11 Stage IV: 3		Stage I: 6 Stage II: 12 Stage III: 10 Stage IV: 0		5.14, 0.162
Local therapy	Radiation: 96.67% Cryoablation: 3.33%		Active Surveillance: 46.63% Radiation: 14.28% Surgery: 35.71% Surgery + Radiation: 3.57%		-
	Baseline	FU	Baseline	FU	
T level (ng/ml)	3.72 ± 1.51	0.16 ± 0.07	3.94 ± 1.52	3.48 ± 1.58	98.37.62, <0.001

Note: MoCA: Montreal Cognitive Assessment, T: testosterone, FU: follow-up. For T levels, the statistics reflect treatment × time interaction, while for the other variables the statistics reflect two-sample t-tests of ADT vs. CON at the baseline. Staging follows the current guidelines of the American Joint Committee on Cancer (AJCC) that include Gleason score in the staging.



Supplementary Figure 3. Baseline and 6-month follow-up (A) testosterone levels (ng/ml), (B) 2-back hit rate, and (C) frontopolar cortical (FPC) thickness in CON (open bars) and ADT (solid bars). * Indicates significant follow-up vs. baseline changes. Correlation between (D) 2-back hit rate change vs. FPC thickness change, (E) testosterone level change vs. FPC thickness change, and (F) 2-back hit rate change vs. testosterone level change in all (ADT+CON) participants. Data points in the scatter plots are shown as residuals, with baseline age, education, MoCA score as covariates; F: follow-up, B: baseline, CT: cortical thickness.



Supplementary Figure 4. A. The left frontopolar cortex (FPC) thickness showed significant treatment × time interaction at voxel P<0.001 uncorrected and cluster P<0.05 FWE in repeated measures ANOVA with baseline age, education and MoCA as covariates. B. FPC thickness change mediated (at trend significance) the association between testosterone level change and 2-back hit rate change across all (ADT+CON) participants. Cortical regions were identified using Desikan-Killiany (DK40) cortical atlas [71]. The statistics reported in the mediation model include beta coefficients (β), *p*-values.