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Original Article

Effects of androgen deprivation on white matter integrity and processing speed in prostate cancer patients

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 & Yale Comprehensive Cancer Center, Yale University School of Medicine, New Haven, CT, USA

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Abstract: Studies have associated chemotherapy-elicited changes in cognitive function with impaired white matter integrity in cancer patients. Androgen deprivation therapy (ADT) may lead to cognitive deficits in prostate cancer patients; however, whether ADT influences white matter integrity has never been investigated. In a prospective study, 15 men with non-metastatic prostate cancer receiving ADT and 15 not receiving ADT (controls or CON), comparable in age and years of education, participated in N-back task, flankers' task, and quality-of-life (QoL) assessments. All participants underwent diffusion tensor imaging of the brain at baseline and at 6 months. Imaging data were processed with published routines. The results of a paired t-test of 6-month follow-up vs. baseline were evaluated at a corrected threshold for the whole brain each in ADT and CON. ADT patients showed significantly worse 1-back accuracy during follow-up, but the two groups did not differ in 2-back accuracy, 1- or 2-back reaction time (RT), flankers' task RT or QoL across time points. In ADT, significantly reduced fractional anisotropy (FA) was noted in the corpus callosum, forceps minor/anterior thalamic radiation, superior and posterior corona radiata. The differences in FA correlated significantly with changes in 2-back and flankers' task RT. No significant FA changes were noted during follow-up in CON. Six-month ADT affects white matter integrity, and the deficits were associated with slower processing speed. These findings add to the literature supporting the deleterious effects of androgen deprivation on the brain and cognition in prostate cancer patients.

Keywords: Prostate cancer, androgen deprivation therapy, MRI, DTI, cognition, quality of life

Introduction

Cancer-associated cognitive decline is increasingly recognized in patients with non-central nervous system cancers [1]. While effective, many treatments, including chemotherapy, have significant impacts on patients' cognitive status and quality of life. Androgen deprivation therapy (ADT) is widely used for treatment of prostate cancer. While ADT has shown efficacy in the treatment of prostate cancer with metastasis, its indications and duration of use in individuals with non-metastatic cancer and those showing rising levels of prostate specific antigen remain unclear. There has been a growing concern in the wide use of ADT in these conditions without studies confirming its efficacy. ADT incurs a range of constitutional, cardiovascular, endocrine, and musculoskeletal side effects, which need to be taken into consideration when discussing the risk and benefit of ADT [2, 3]. Further, ADT may impact cognitive function and mental health, a major determinant of quality of life (QoL) [4, 5]. This issue is particularly salient in younger men who are expected to be cured from prostate cancer. Thus, a systematic study of the impact of ADT on brain and behavior would facilitate clinical decision making in the treatment of prostate cancer patients.

Previous studies have combined cognitive assessment and brain imaging to understand the neural substrates of cognitive deficits elic-

ited by ADT in prostate cancer patients. For instance, studies have noted reduced parieto-occipital activation during spatial reasoning and memory [6], reduced medial prefrontal cortical activation during visual working memory [7], reduced posterior cingulate, inferior parietal, and middle temporal cortical metabolism and higher inferior parietal cortical metabolism in association with impaired spatial reasoning and verbal memory, respectively [8]. Other studies reported decreased frontal gray matter in link with slower reaction time during working memory processing [9], increased resting state functional connectivity of hypothalamus with the precentral gyrus in cognitive motor processing [10], as well as an overall increase in frontoparietal and temporal cortical connectivity following ADT [11].

However, no studies to our knowledge have investigated the effects of ADT on white matter integrity. Testosterone is known to influence brain development, with higher white matter density in male relative to female adolescents [12]. The sex differences are likely mediated by the direct effects of testosterone or its metabolites on androgen receptors and/or the effects of gonadotropins, such as luteinizing hormone, on the brain [13]. Higher androgen levels through the course of treatment appeared to enhance white matter integrity, as noted by reduced mean diffusivity, in female-to-male transgenders receiving testosterone replacement [14, 15]. Along with lower testosterone levels, altered fronto-temporal cortical white matter integrity and graph-theoretic metrics of structural connectivity were noted in newly diagnosed patients with prostate cancer [16]. In rats, removal of endogenous testosterone by castration led to lower axon diameter and lower g ratio (an index of optimal axonal myelin) in the splenium - the part of the corpus callosum interconnecting right and left posterior cortices - in comparison with sham-operated males [17]. Studies have reported higher activity of 5-alpha-reductase - the enzyme that acts on testosterone to generate 5-alpha reduced metabolites - in the corpus callosum and subcortical white matter [18, 19], suggesting potential effects of testosterone on white-matter structure and function. Further, during early development [20] and possibly throughout lifetime [19], 5-alpha reduced metabolites seem to be involved in myelinogenesis. Thus, there is substantial evidence supporting the effects of testosterone on the structural and functional integrity of white matters. However, it is not clear whether or how androgen deprivation may influence white matter structures in prostate cancer patients.

Numerous studies of neurological disorders including multiple sclerosis (MS), Huntington's disease (HD), Alzheimer's disease (AD), as well as those of healthy aging suggest that white matter integrity is central to cognitive functioning [21]. For instance, in MS, a demyelinating neurodegenerative disease, diminished integrity of anterior thalamic radiation predicted cognitive decline over a period of 10 years [22]. In another study, cognitively impaired patients with MS showed widespread reduced integrity of white matter tracts, including the corpus callosum, superior/inferior longitudinal fasciculi, corticospinal tracts, forceps major, cingulum, and fornices [23]. In HD, the radial diffusivity of fronto-parietal tract negatively [24] and the fractional anisotropy (FA) of genu and body of corpus callosum positively [25] correlated with cognitive function. Similarly, the FA of white matter tracts including the splenium of corpus callosum, parahippocampal white matter, cingulum, and inferior fronto-occipital fasciculus was positively associated with memory function in AD [26]. Mean white-matter diffusivity correlated negatively and FA correlated positively with global cognition in non-demented elderly [27]. With increasing age, a posterior-to-anterior gradient of decline in white-matter integrity is noted that affects overall cognitive functioning [28].

Thus, it is highly likely that ADT would have a significant impact on white matter integrity and lead to cognitive deficits in prostate cancer patients. In the present study, we assessed the effects of ADT on white matter integrity in patients with prostate cancer using diffusion tensor imaging (DTI), a magnetic resonance imaging protocol widely used to investigate white matter integrity in psychiatric and neurological disorders. For instance, individuals with multiple sclerosis are known to have white matter pathology and DTI represents a useful tool in monitoring the progression and treatment outcome of the illness [29]. Many studies have also shown microstructural white matter changes, reflected by a reduction of FA, as a result of chemotherapy [30-32] in patients with different cancers. Further, the severity of white mat-

ter changes correlated significantly with the extent of cognitive impairment [30, 33]. Here, we evaluated the effects of ADT on white matter integrity in prostate cancer patients who received ADT, as compared to those who did not receive ADT in a longitudinal setting. We hypothesized that ADT would lead to changes in white matter integrity, as indexed by FA, information processing speed, working memory, executive control, as well as deterioration in quality of life.

Methods

Participants and clinical profiles

Patient recruitment and methodology follow our earlier studies [7, 9, 10]. Patients 55 to 75 years of age and with biopsy-proven prostate adenocarcinoma without distant metastases were recruited from the Medical Oncology and Urology Clinics at the West Haven VA Connecticut Healthcare System. Following current National Comprehensive Cancer Network and American Urological Society practice guidelines, treatments were not affected by patient's decision of participation in the study. Please see the legend of Supplementary Figure 1 for more details of treatment and recruitment of the participants. All patients prescribed ADT as adjuvant treatment or due to biochemical recurrence were contacted for participation. ADT consisted of medical castration with an LH-RH agonist (Goserelin or Leuprolide) subcutaneously for 6 months, after a lead-in period with Bicalutamide 50 mg daily. Patients with non-metastatic prostate cancer who had never been treated with ADT participated as controls (CON). For both ADT and CON, exclusion criteria were: Eastern Cooperative Oncology Group Performance Status >1; active second malignancy; significant cardiovascular, liver, renal, or neurological disease; use of any investigational drugs or contraindications, including claustrophobia, for magnetic resonance imaging (MRI); current substance (except nicotine) use disorders (use of illicit substances were verified by a urine test); history of Axis I psychiatric illness; history of traumatic brain injury or concussions causing loss of consciousness. All participants underwent a health questionnaire interview to ensure eligibility for MRI. Participants who had a prostatectomy were at least 3 months from their surgery before study entry. Participants who were to receive radiation to the prostate underwent baseline assessment and MR scan before starting any treatment and had to be fully recovered from any acute side effects of radiation at the time of their follow-up assessments. In addition to evaluation of serum testosterone and prostate-specific antigen levels as part of their routine bloodwork at every assessment, all participants underwent determination of other hormonal (e.g., cortisol) levels that could potentially affect cognitive function.

Among 60 candidates with non-metastatic prostate cancer, 46 who had never been treated with ADT were enrolled in the study. Twenty patients were scheduled for ADT and 26 patients served as CON. Sixteen ADT and 17 CON completed both baseline and follow-up assessments. However, 1 ADT and 2 CON were excluded due to excessive head movements during MR scans. Thus, the data from 15 ADT and 15 CON were included in the analyses (Supplementary Figure 1).

The study was approved by the Human Investigation Committee at both 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), cognitive assessment with N-back and flankers' tasks (outside the scanner), and MR imaging at baseline and at 6-month follow-up. At baseline, participants were also assessed for global cognition using Montreal Cognitive Assessment (MoCA).

N-back task is a widely used paradigm to assess working memory, a form of short-term memory that provides temporary storage and manipulation of information necessary for complex cognitive tasks (Supplementary Figure 2) [34]. Briefly, 0-, 1-, and 2-back trials were included in the N-back task, each imposing increasingly higher demand on working memory. As 0-back trials required no working memory, we used the correct response rate (accuracy) and reaction time (RT) of 1- and 2- vs. 0-back scores (i.e., 1-back minus 0-back accuracy, etc.) as outcome measures [35].

Participants typically respond faster and more accurately during 0-back as compared to 1- and 2-back trials. Thus, in evaluating changes at follow-up from baseline, a larger decrease in accuracy and increase in RT indicated more significant impact/deficit.

We used flankers task to assess executive control [35]. Each trial began with the presentation of a fixation point which, after 500 ms, was replaced by a stimulus array consisting of 5 stimuli, spanning 12° in visual angle (Supplementary Figure 3). The array included a target arrow located at the center and two distractors (i.e., flankers) located on each side. Participants were instructed to make a button press in the direction indicated by the target arrow. The stimulus array used to disappear at the button press, and a fixation point appeared for the next trial after an inter-trial-interval of 900 ms. Approximately 2/3 of all trials were congruent trials, with flankers pointing in the same direction as the target arrow at the center. The remaining 1/3 were incongruent trials with flankers pointing in the opposite direction. Congruent and incongruent trials appeared randomly within two blocks each of 120 trials. The primary outcome measure was represented by RT difference between the two types of trials: incongruent minus congruent RT [35]. Participants respond faster during congruent than the incongruent trials, and less RT difference between congruent and incongruent trials - a smaller value of "incongruent minus congruent RT" - indicated better performance or a higher capacity in interference control.

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 [36, 37]. 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

DTI data was obtained at baseline and at 6-months follow-up on a 3-Tesla Siemens Prisma system using echo-planar imaging with b = 1000 s/mm^2 diffusion weighting in 64 directions and one b = 0 image. Whole brain coverage was achieved with 64 consecutive, 2 mm thick axial slices. In-plane resolution was 2 × 2 × 2 mm^3, and acquisition matrix = 110 × 110; TE = 84 ms; TR = 2200 ms; field of view = 220 mm × 220 mm; bandwidth = 1818 Hz/Px, and 90° flip angle. The scan was repeated twice to increase the signal to noise ratio.

First, the images were visually inspected for movement artifacts. Next, images were processed with FMRIB Software Library (FSL 6.0, https://fsl.fmrib.ox.ac.uk/fsl/) following a standard pipeline. Briefly, diffusion-weighted images were corrected for motion and eddy currents using FSL's eddy by registering the diffusion weighted images to the reference b = 0 s/mm^2 (the first non-diffusion weighted volume) [38]. The process also reduced image distortions [38]. Next, non-brain tissue from the b0 image was removed and a brain-mask was generated using FSL's brain extraction toolbox, BET [39]. Corresponding brain mask was applied to the rest of the diffusion-weighted images, and diffusion tensor model was fitted at each voxel using FSL's DTIFIT to construct diffusion tensors and dependent maps, including the fractional anisotropy (FA) maps. Next, we applied tract-based spatial statistics (TBSS) to localize voxel-wise changes in FA [40, 41]. TBSS utilizes a non-linear registration tool FNIRT [42, 43] which uses a b-spline representation of the registration warp field to align all FA images to a 1 × 1 × 1 mm standard FMRIB58_FA template space [44]. Next, the standard space FA images were averaged to create a white matter mean FA skeleton using a threshold of 0.2 to exclude non-white matter voxels, avoid peripheral tracts, and mitigate partial volume effects of gray matter. Each participant's FA map in standard space was projected onto this skeleton, and the resulting central trajectory of white matter pathways across all participants were applied to voxel-wise statistics using the routine *randomize* [45].

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 linear mixed model via restricted maximum likelihood (REML) with random intercept across subjects, and group (ADT vs. CON), time-point (follow-up vs. baseline), and their inteaction as fixed effects to assess the changes during follow-up from baseline in longitudinal variables. We account-

Table 1. Demographic and clinical characteristics of the patients

	ADT (n = 15)		CON (n = 15)		($t_{28}/\chi^2(1)_{group \times time}$, p)
Age (yr)	66.8 ± 7.0		67.0 ± 5.9		0.06, 0.956
Education (yr)	13.6 ± 2.7		14.5 ± 2.9		0.90, 0.375
MoCA score	24.5 ± 2.9		26.9 ± 2.2		2.48, 0.019*
AUDIT score	3.4 ± 3.5		2.0 ± 1.7		1.39, 0.176
Smoker status	0 (n = 4), 1 (n = 7), 2 (n = 4)		0 (n = 3), 1 (n = 10), 2 (n = 2)		1.34, 0.512
	B	F	B	F	
T level (ng/ml)	3.8 ± 1.7	0.2 ± 0.1	4.0 ± 1.7	4.0 ± 2.0	49.25, <0.001*
C level (μg/dl)	7.7 ± 3.4	10.7 ± 5.5	8.4 ± 3.4	10.1 ± 4.3	0.44, 0.508

Note: Data are presented in mean ± SD except for Smoker status where data is frequency; MoCA: Montreal Cognitive Assessment, AUDIT: Alcohol Use Disorder Identification Test, Smoker status (0: never, 1: former, 2: current), T: testosterone, C: cortisol; B: baseline; F: follow-up. For T and C levels, the statistics correspond to treatment × time interaction, while for the other variables the statistics correspond to two-sample t-tests or χ^2-test comparing ADT and CON at the baseline; *P<0.05.

ed for small sample using Kenward-Roger method in the model [46]. Wherever appropriate, model was adjusted for baseline age, education, and MoCA score. The results that met two-tailed P<0.05 were considered statistically significant.

We employed FSL's tool *randomize* [45] for voxel-wise statistical inference of FA maps across the two groups. *Randomize* is a permutation method used for inference (thresholding) on statistical maps when null distribution is not known and is effective in controlling for false-positive results. Using 5000 permutations to allow robust statistical inference, we compared changes at follow-up from baseline in ADT and CON, separately, using non-parametric thresholding in paired T-tests. A family-wise error (FWE) corrected threshold of P<0.05 was selected using threshold free cluster enhancement (TFCE) option in *randomize* to evaluate FA changes across time points. The white matter tracts were identified using JHU DTI-based white-matter atlas as included in FSL [47].

We extracted the mean FA of clusters identified from voxel-wise analyses and assessed clinical correlates of FA changes in ADT (see Results) using Spearman's rank correlation analysis, adjusted for baseline age, education, and MoCA score.

Results

Baseline clinical profile of the participants

At baseline, ADT and CON patients were comparable in age, years of education, testosterone (t_{28} = 0.27, P = 0.786), and cortisol (t_{28} = 0.55, P = 0.589) levels (**Table 1**; Supplementary Figure 4). MoCA score was significantly higher in CON than in the ADT group. In addition, we observed a significant treatment × time interaction in testosterone level, as expected of the effects of ADT, but not in the cortisol level (**Table 1**).

N-back and flankers task performance and quality of life

N-back and flankers task performance metrics and QoL scores are presented in Supplementary Figure 5 and Supplementary Table 1. In mixed model analyses (adjusted for baseline age, education, and MoCA scores), treatment group (ADT/CON) × time (baseline/follow-up) interaction was significant only for the 1-back (vs. 0-back) accuracy, but not for other N-back or the flankers task metrics (**Table 2**). In addition, we did not observe significant group × time interaction in QoL score.

Changes in fractional anisotropy in ADT and in CON, and their clinical correlates

At P<0.05 FWE, the ADT group showed significant decreases in FA at follow-up versus baseline in clusters with peak MNI coordinates at the genu of corpus callosum (x = 4, y = 24, z = 12), forceps minor/anterior thalamic radiation (x = 19, y = 43, z = 20), superior corona radiata (two peaks: x = -18, y = -13, z = 36; x = -25, y = -20, z = 24), body of corpus callosum (x = -6, y = -24, z = 24), posterior corona radiata (x = -19, y = -35, z = 37), splenium of corpus callosum (x = 15, y = -34, z = 24) (**Figure 1**). No significant

Table 2. Treatment (ADT vs. CON) and time (follow-up vs. baseline) main and interaction effects of N-back, flankers task performance and QoL scores: mixed model analysis

	Treatment ($\chi^2(1)$, *p*-value)	Time ($\chi^2(1)$, *p*-value)	Treatment × time ($\chi^2(1)$, *p*-value)
N-back correct response %			
1-back - 0-back	0.79, 0.373	2.53, 0.112	5.04, 0.025*
2-back - 0-back	1.82, 0.178	3.84, 0.050	1.14, 0.286
N-back correct trial RT (ms)			
1-back - 0-back	5.57, 0.018*	1.87, 0.171	0.54, 0.464
2-back - 0-back	1.03, 0.309	0.00, 0.988	0.22, 0.636
Flankers task RT (ms)			
Incongruent - congruent	0.29, 0.593	0.06, 0.799	2.86, 0.091
Quality of life	1.95, 0.162	0.08, 0.779	2.73, 0.098

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

changes were observed for CON at the same threshold. Using the clusters identified from the ADT as masks, we extracted the mean FA for all participants. As expected, the mean FA showed significant differences cross time points for ADT; in contrast, the CON group did not show significant differences in mean FA at follow-up vs. baseline for any of these clusters (**Figure 2**).

The extracted mean FA of these clusters showed significant treatment × time interaction, adjusted for baseline age, education, and MoCA, except for the left posterior corona radiata (**Table 3**).

Further, we assessed for correlation between changes in FA and in N-back/flankers task performance metrics and Qol score at follow-up from baseline in ADT (**Table 4**). In Spearman's rank correlation, adjusted for baseline age, education, and MoCA score, we observed significant correlations between the change in 2-back (vs. 0-back) RT with FA changes in the PCR; and flankers incongruent (vs. congruent) RT changes with FA changes in the CC, genu/body, FM/ATR, and SCR in ADT.

Discussion

Despite a small sample size, the current findings showed statistically significant changes in white matter integrity, as indexed by a diminished FA, in prostate cancer patients receiving ADT. The changes in FA were observed in multiple locales of white matter connecting functionally homologous regions across the hemispheres as well as cortical and subcortical regions. These changes may potentially impact information processing as evidenced in the correlation between the changes in FA and the RT during 2-backs and during interference control in the flanker's task. Together, these results add to the literature in support of deleterious effects of androgen deprivation on cognition in prostate cancer patients.

These findings are broadly consistent with a recent report of impaired white matter integrity in patients with testicular cancer with orchidectomy [48]. Here, we noted FA changes in the corpus callosum in prostate cancer patients receiving ADT. The corpus callosum comprises heavily myelinated nerve fibers that connect left and right cerebral hemispheres with the function of integrating and transferring information across hemispheres [49]. We observed significantly reduced corpus callosum FA during follow-up vs. baseline and greater FA reduction in association with impaired cognitive-motor control in ADT. The findings suggest that compromised corpus callosum integrity due to ADT may lead to worse cognitive control in prostate cancer patients. We also observed reduced FA in superior/posterior corona radiata, forceps minor and anterior thalamic radiation. Corona radiata contains fibers ascending from the thalamus to the cortex and descending from the frontal (superior corona radiata) and parietal lobes (posterior corona radiata) to the basal ganglia, brainstem and spinal cord, in support of cognitive and motor functions [50-54]. For instance, patients with posterior corona radiata infarct, as compared to controls, demonstrated impaired cognitive-motor speed in the

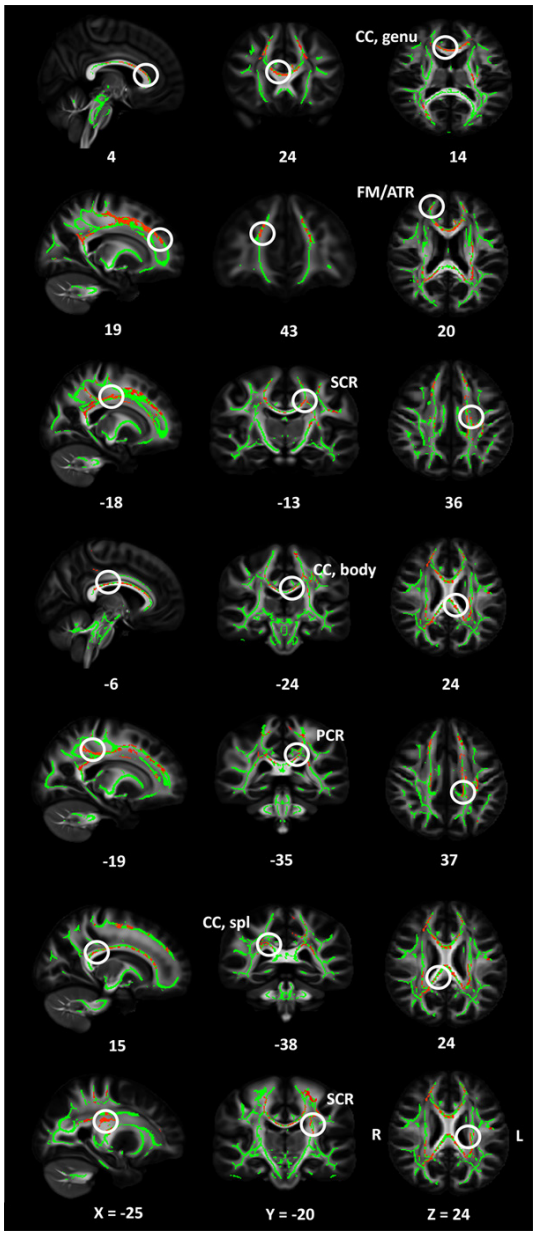

Figure 1. Clusters with significantly decreased FA (P<0.05 FWE corrected) during follow-up as compared to baseline in ADT. Note: mean FA skeleton is shown in Green, and clusters of decreased FA in Red; CC: corpus callosum, FM: forceps minor, ATR: anterior thalamic radiation, SCR: superior corona radiata (two clusters), PCR: posterior corona radiata, spl: splenium. No clusters showed significant differences in CON at the same threshold.

Trail Making Test and worse accuracy in a digit symbol test, both reflecting executive dysfunction [54]. Further, in healthy adults 18 to 83 years of age, lower FA in superior corona radiata correlated with lower cognitive-motor speed in the Trail Making Test [55].

In ADT, along with reduced FA at follow-up from baseline, we observed the FA changes in negative association with processing speed during working memory and cognitive control. Thus, ADT impacts the integrity of superior and posterior corona radiata, and the patients showing less changes in FA demonstrated less impaired cognitive-motor processing. Additionally, the capacity of interference control in the flankers' task, as demonstrated in the RT difference between incongruent and congruent trials, was associated with the FA of forceps minor/anterior thalamic radiation. Forceps minor - the anterior part of corpus callosum - connects homologous anterior frontal cortical regions [56-58]. Anterior thalamic radiation projects from the thalamus to the anterior limb of the internal capsule and carries reciprocal connections from the hypothalamus and limbic structures to the frontal cortex [59]. Earlier studies implicated these fibers in executive functions and processing speed [60, 61]. For instance, white matter hyperintensities in the anterior thalamic radiation predicted slower processing speed in the Trail Making Test in genetically defined small vessel disease [61]. In addition, higher FA in forceps minor and anterior thalamic radiation predicted shorter RT during Stroop-color naming task in healthy adults [60]. Consistent with the literature, our current findings showed that ADT disrupted white matter integrity and cognitive functions and that the changes in cognitive functions can potentially be accounted for by the specific locales of white-matter microstructural changes.

Notably, with the impairment in white-matter integrity and the association between changes in white matter integrity and cognitive performance following 6 months of androgen deprivation, ADT patients overall demonstrated little or no changes in performance metrics or QoL. The only metric showing significant treatment × time interaction was 1-back (vs. 0-back) accuracy, which was significantly decreased in ADT but not in CON at 6 months. These findings are broadly in line with our previous studies [10, 62] and others that showed little significant cognitive decline in prostate cancer patients who received ADT, as compared to those who did not receive ADT [63, 64]. The findings of RT changes in significant association with FA changes but not manifesting in the impact of ADT suggest individual variability in the impact

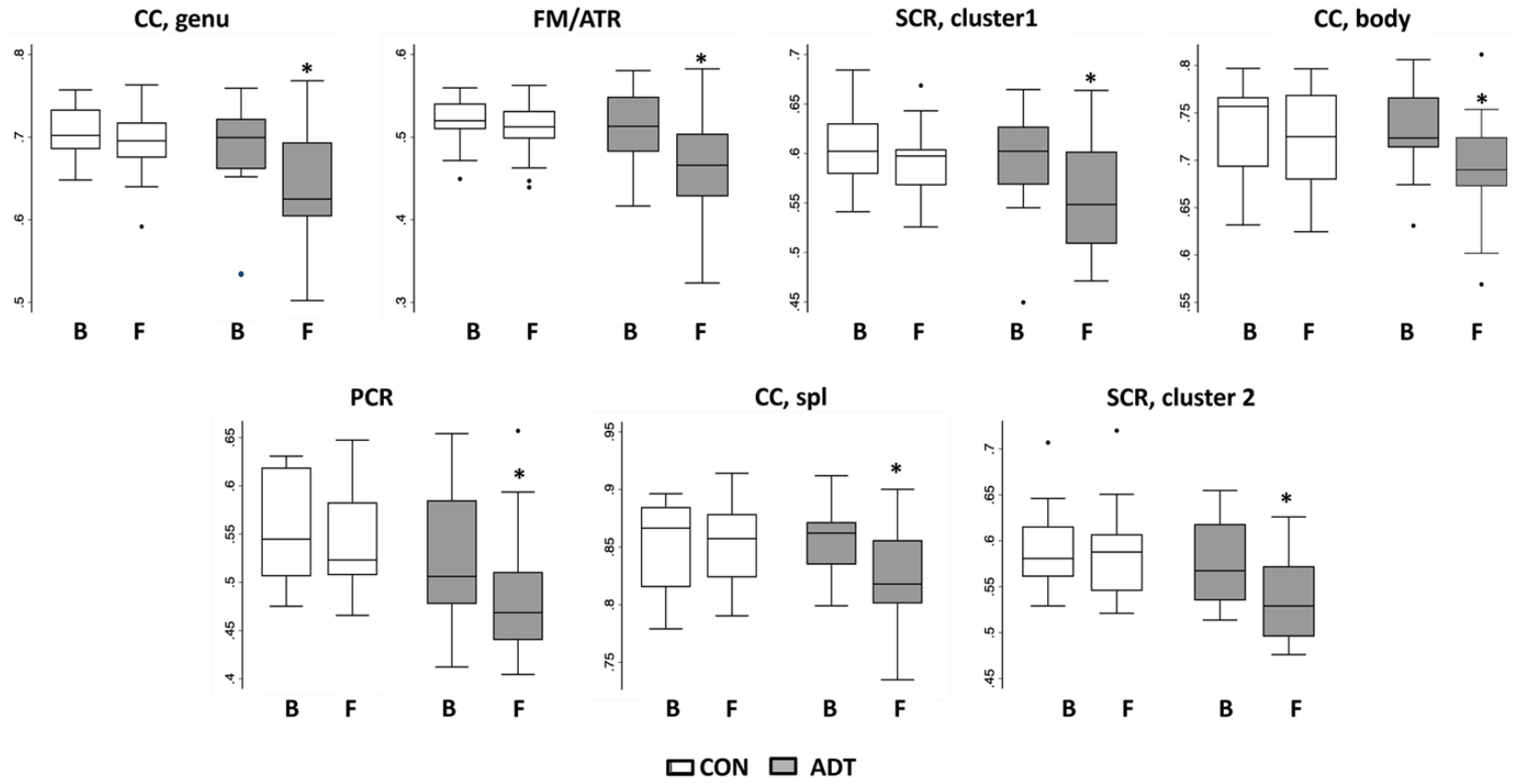

Figure 2. FA (mean ± SD) of the clusters showing significant changes at follow-up from baseline in ADT. The FAs are shown separately for ADT (gray bars) and CON (white bars) and for baseline (B) and follow-up (F). Note: *P<0.05, paired t-test of F vs. B; CC: corpus callosum, FM: forceps minor, ATR: anterior thalamic radiation, SCR (two clusters): superior corona radiata, PCR: posterior corona radiata, spl: splenium.

Table 3. Treatment (ADT vs. CON) and time (follow-up vs. baseline) main and interaction effects of mean FA: mixed model analysis

	Treatment ($\chi^2(1)$, *p*-value)	Time ($\chi^2(1)$, *p*-value)	Treatment × time ($\chi^2(1)$, *p*-value)
CC, genu	4.72, 0.029	15.10, <0.001	5.66, 0.017*
FM/ATR	4.78, 0.029	13.93, <0.001	5.86, 0.016*
SCR, cluster 1	4.35, 0.037	16.70, <0.001	5.23, 0.022*
CC, body	1.67, 0.196	17.82, <0.001	4.71, 0.030*
PCR	3.79, 0.052	10.22, 0.001	1.09, 0.297
CC, splenium	1.45, 0.228	7.36, 0.007	9.75, 0.002*
SCR, cluster 2	6.67, 0.009	8.85, 0.003	4.77, 0.029*

Note: Model was adjusted for baseline age, education, and MoCA score; *P<0.05 treatment × time interaction; CC: corpus callosum, FM: forceps minor, ATR: anterior thalamic radiation, SCR: superior corona radiata, PCR: posterior corona radiata.

Table 4. Clinical correlates of changes in FA at follow-up vs. baseline in ADT

	N-back correct %, relative to 0-back		N-back correct trial RT (ms), relative to 0-back		Flankers task RT (ms)#	QoL
	1-back	2-back	1-back	2-back	Incon vs. cong	
CC, genu	-0.06, 0.846	0.07, 0.817	-0.46, 0.127	-0.40, 0.191	-0.61, 0.04*	-0.46, 0.129
FM/ATR	0.08, 0.787	0.07, 0.819	-0.25, 0.434	-0.36, 0.255	-0.61, 0.033*	-0.49, 0.107
SCR, clsuter 1	0.007, 0.983	0.33, 0.294	-0.41, 0.184	-0.55, 0.065	-0.69, 0.013*	-0.28, 0.381
CC, bd	-0.22, 0.481	0.16, 0.624	-0.45, 0.145	-0.36, 0.252	-0.52, 0.085	-0.35, 0.264
PCR	-0.18, 0.567	0.49, 0.102	-0.39, 0.205	-0.62, 0.032*	-0.49, 0.107	-0.30, 0.336
CC, spl	-0.19, 0.543	0.38, 0.227	-0.57, 0.053	-0.27, 0.398	-0.49, 0.101	0.02, 0.953
SCR, cluster 2	0.04, 0.903	0.28, 0.376	-0.22, 0.485	-0.46, 0.130	-0.66, 0.019*	-0.24, 0.452

Note: Values are ρ and p of Spearman's correlation, adjusted for baseline age, education, and MoCA score. #Incongruent minus congruent. *P<0.05. CC: corpus callosum (bd: body; spl: splenium), FM: forceps minor, ATR: anterior thalamic radiation, SCR: superior corona radiata (two clusters), PCR: posterior corona radiata.

of ADT; although ADT did not influence performance on average, some individuals were able to compensate for the impact of ADT and some were not, as we and others also noted in earlier studies of functional measures [7, 65, 66]. High variability in performance measures and potential practice effects may also make it difficult to see group differences with a relatively small sample size. In our previous functional MRI studies, we too noted middle frontal cortical hypoactivation [7] and altered hypothalamus-middle frontal cortical functional connectivity [10] in association with N-back performance in prostate cancer patients on ADT relative those not on ADT, with few significant differences in performance metrics. Together, these findings suggest the utility of imaging in capturing the effects of ADT on the brain. Along with the findings that brain changes may precede cognitive deficits [62], brain changes reflect a more sensitive measure than neurocognitive testing alone. It remains to be seen whether a longer duration of androgen deprivation may elicit more pervasive changes in cognition and QoL when participants can no longer compensate for the brain changes, as has been observed in long-term survivors of breast cancer [66].

Limitations of the study and conclusions

A number of limitations need to be considered. First, the study included a small sample size, and the results would need to be replicated. On the other hand, we wish to emphasize that the imaging results on white matter FA changes were obtained at a corrected threshold and would likely be robust. Second, we did not observe significant group differences across time points in most of the cognitive measures and, as discussed earlier, individual variation in the capacity of functional compensation may account for the findings. On the other hand, potential practice effects on task performance and small sample size can also mask the results. Third, we assessed only working memory and interference control. Studies are need-

ed 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 [16]. 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.

To conclude, androgen deprivation for 6 months led to worse 1-back accuracy but not significant changes in other measures of the N-back or flankers' task or in quality of life. However, ADT resulted in reduced white matter fractional anisotropy in association with impairment in 2-back and flankers reaction time. These findings support white matter as a critical target for investigation of the influences of ADT on cognition in prostate cancer patients. In particular, it remains to be seen whether or how microstructural white matter changes would continue beyond six months of ADT.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Herta H Chao, Cancer Center, VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516, USA. Tel: 203-937-3421; E-mail: herta.chao@yale.edu; Dr. Shefali Chaudhary, Department of Psychiatry, Yale University School of Medicine, CMHC S110, 34 Park Street, New Haven, CT 06519, USA. Tel: 203-974-7891; E-mail: shefali.chaudhary@yale.edu

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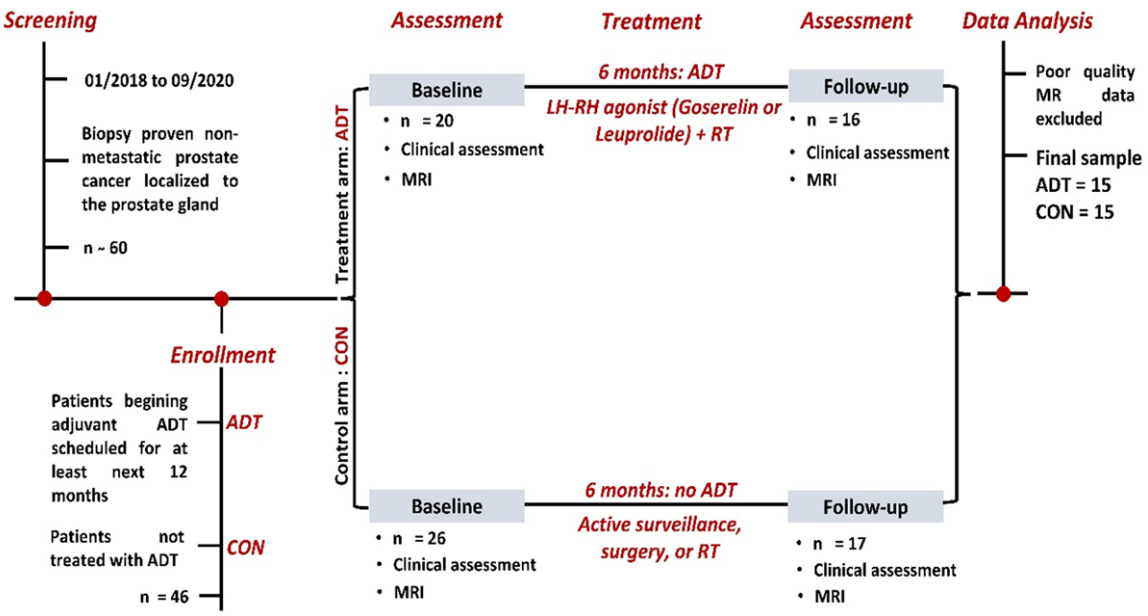
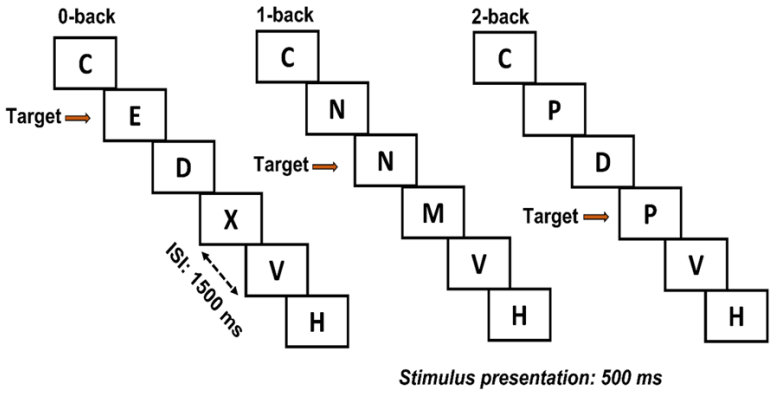
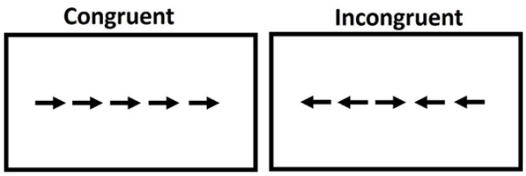


Supplementary Figure 1. Study timeline, subject recruitment and treatment. Note: Treatment for the patients followed current guidelines and were independent of the current study. Three patients of the ADT group had previously undergone surgery. ADT: androgen deprivation therapy, CON: control, MRI: magnetic 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).

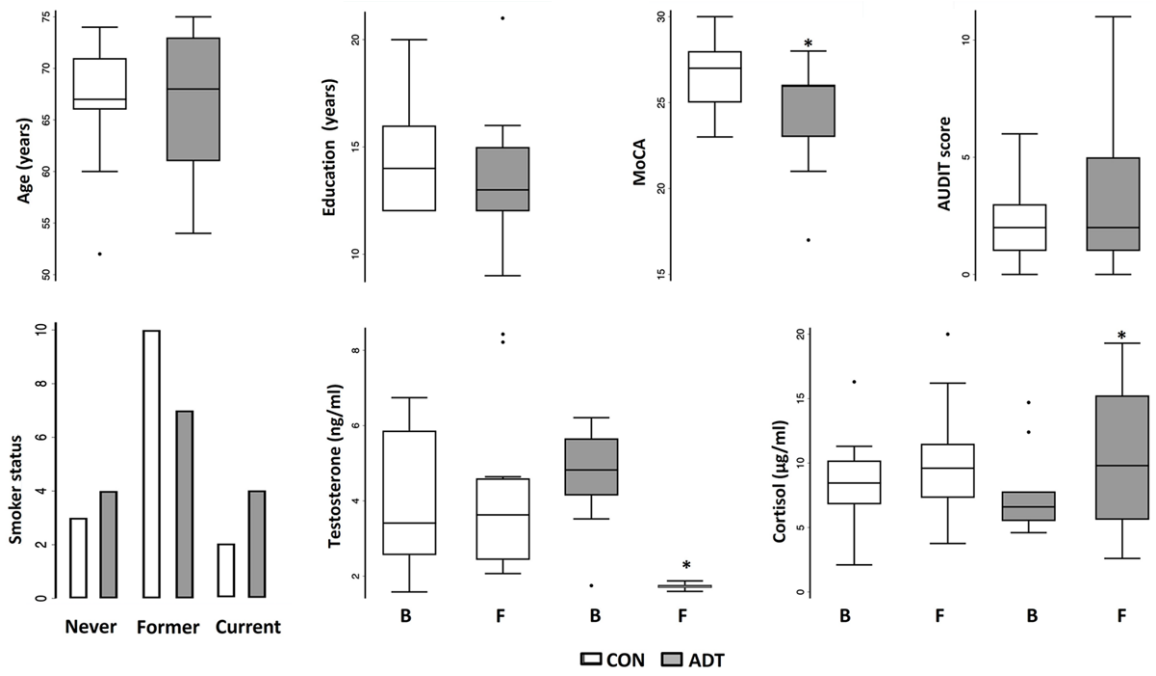


Supplementary Figure 2. N-back working memory task. A stream of fifteen phonologically distinct letters appears in sequency each for a duration of 500 ms and with an inter-stimulus-interval of 1500 ms. There are three different conditions: 0-, 1-, and 2-back, differing in working memory load. In the 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

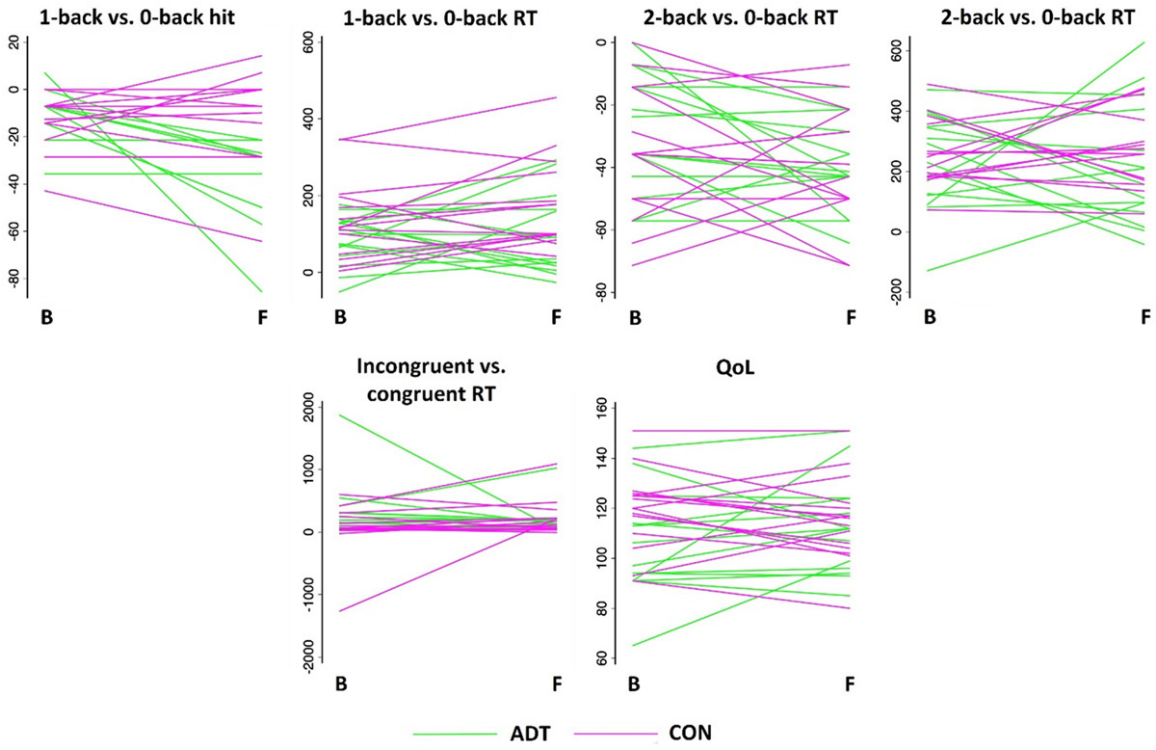
outside the scanner. Each subject completed 3 sessions of the task, with each session containing two each of 0-, 1-, and 2-back blocks, the order of which was counter-balanced across sessions. Each block began with an information screen showing the "working memory load" for that block (5 s) and contained 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 Figure 3. Flankers' task. Subjects typically respond slowly during incongruent than in congruent trials. The difference in RT between incongruent and congruent trials (incongruent minus congruent) reflects the interference from the flankers, with a lower RT difference reflecting better inference control.



Supplementary Figure 4. Distribution of demographic and clinical variables during baseline (B) and 6-months follow-up (F) in CON (white bars) and ADT (gray bars). Note: baseline values of age, education, MoCA, AUDIT and smoker status, while both baseline and follow-up values of Testosterone and Cortisol are presented; *P<0.05 in two sample t-test (MoCA) and paired t-test (testosterone, cortisol).



Supplementary Figure 5. N-back/Flankers' task performance metrics and QoL scores at baseline (B) and 6-months follow-up (F) in ADT and CON.

Supplementary Table 1. Participants' N-back/Flankers' task performance and QoL scores at baseline and 6-month follow-up

	ADT_B	ADT_F	CON_B	CON_F
Correct response rate (%)				
1-back vs. 0-back	-10.9 ± 9.7	-27.0 ± 25.6	-12.6 ± 11.5	-9.8 ± 19.0
2-back vs. 0-back	-30.1 ± 19.1	-41.3 ± 16.2	-35.7 ± 20.7	-39.0 ± 19.0
Reaction time of correct trials (ms)				
1-back vs. 0-back	85.4 ± 65.3	96.9 ± 102.5	138.5 ± 103.9	176.9 ± 114.1
2-back vs. 0-back	229.1 ± 158.1	212.5 ± 201.8	257.4 ± 108.6	275.0 ± 126.5
Flankers' Incongruent vs. congruent	314.5 ± 458.2	190.7 ± 238.9	57.8 ± 405.4	225.4 ± 273.2
Quality of life	106.2 ± 20.4	111.8 ± 18.6	119.4 ± 15.7	115.4 ± 16.9

Note: Values are mean ± SD; B: baseline, F: follow-up.