

Effects of Androgen Deprivation on Cerebral Morphometry in Prostate Cancer Patients – An Exploratory Study

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Abstract

Background: Androgen deprivation therapy (ADT) is a common treatment for non-metastatic, low-risk prostate cancer, but a potential side effect of ADT is impaired brain functioning. Previous work with functional magnetic resonance imaging (MRI) demonstrated altered prefrontal cortical activations in cognitive control, with undetectable changes in behavioral performance. Given the utility of brain imaging in identifying the potentially deleterious effects of ADT on brain functions, the current study examined the effects of ADT on cerebral structures using high resolution MRI and voxel-based morphometry (VBM).

Methods: High resolution T1 weighted image of the whole brain were acquired at baseline and six months after ADT for 12 prostate cancer patients and 12 demographically matched non-exposed control participants imaged at the same time points. Brain images were segmented into gray matter, white matter and cerebral ventricles using the VBM toolbox as implemented in Statistical Parametric Mapping 8.

Results: Compared to baseline scan, prostate cancer patients undergoing ADT showed decreased gray matter volume in frontopolar cortex, dorsolateral prefrontal cortex and primary motor cortex, whereas the non-exposed control participants did not show such changes. In addition, the decrease in gray matter volume of the primary motor cortex showed a significant correlation with longer reaction time to target detection in a working memory task.

Conclusions: ADT can affect cerebral gray matter volumes in prostate cancer patients. If replicated, these results may facilitate future studies of cognitive function and quality of life in men receiving ADT, and can also help clinicians weigh the benefits and risks of hormonal therapy in the treatment of prostate cancer.

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Introduction

Prostate cancer is the most common non-skin cancer in American men. Almost half of all patients with prostate cancer will receive androgen deprivation therapy (ADT) over the course of their illness [1,2]. Although ADT has documented efficacy in the treatment of metastatic prostate cancer, ADT is also given to patients with non-metastatic prostate cancer, as neoadjuvant and adjuvant treatment and in patients who have a rising PSA level after definitive therapy. Evidence suggests that ADT can improve

the survival of patients with non-metastatic prostate cancer with poor prognostic features, but no consensus exists regarding indications for or duration of ADT in the patients with lower-risk disease [3]. Despite this uncertainty, use of ADT has become more prevalent in the U.S. in recent years, accounting for most of price-adjusted growth in Medicare spending related to prostate cancer [4].

Common side effects of ADT include fatigue, decreased sexual function, gynecomastia, osteoporosis, and changes in metabolism, and the negative impact of these adverse effects on quality of life

has been studied extensively [5]. It remains unclear, however, whether or to what extent ADT influences cognitive function, a major determinant of quality of life in these mostly elderly patients. Both observational and randomized studies support an association between androgens and cognitive function [6–10], and studies have suggested a protective effect of testosterone against age-related decline in cognitive function, including the development of dementia in men. Conversely, the effects of ADT on cognitive function in patients with prostate cancer remain unclear, with reports suggesting no effect [11], impaired function [12–14], and a mixed effect with patients showing an improved performance on some tests and a deterioration on others [15].

Magnetic resonance imaging (MRI) provides a non-invasive method to measure brain structures and activations. Investigators have used MRI and other imaging methods to evaluate the effects of chemotherapy and hormonal therapy on brain structures and functions in patients with breast cancer [16–19]. Prior work of 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 altered prefrontal cortical activation during cognitive control [20]. These and other findings suggested the utility of brain imaging to detect the effects of hormonal therapy on brain structures and functions before the manifestation of cognitive and behavioral effects.

In this context, the current study uses structural MRI to evaluate changes in cerebral gray matters among prostate cancer patients who receive ADT, compared with patients who do not receive the treatment.

Materials and Methods

Participants and Clinical Profiles

Patients were recruited from the Medical Oncology and Urology Clinics at the VA Connecticut Healthcare System. Potential candidates were identified at the bi-monthly Genito-Urinary Tumor Board, or during their routine clinic visits, and offered to participate in the study. Eighteen men who had non-metastatic, biopsy proven prostate cancer and who were prescribed ADT—either as adjuvant treatment or because of biochemical recurrence after prostatectomy or radiotherapy—were recruited to participate in the study. ADT consisted of medical castration with a luteinizing hormone releasing hormone agonist (Goserelin 10.8 mg subcutaneously every 90 days) after a lead-in period for 2 weeks with bicalutamide 50 mg daily. During the same time interval, 18 age-matched individuals with non-metastatic prostate cancer who were undergoing radiotherapy or had prostatectomy and had never been treated with ADT were enrolled as non-exposed control participants. Exclusion criteria included: currently active second malignancy; Eastern Cooperative Oncology Group (ECOG) Performance Status >1; any significant cardiovascular conditions (e.g., New York Heart Association (NYHA) Class III or IV congestive heart failure, recent myocardial infarction, unstable angina, pacemaker); or hepatic (e.g., liver cirrhosis Child-Pugh B or C), renal, or neurological disease. Patients who had a diagnosis of axis-I psychiatric or substance (excluding nicotine) use disorders [21], and patients receiving any investigational agents, were excluded. A score of less than 27 out of 30 on the mini-mental state examination (MMSE) was another exclusion criterion [22]. All participants underwent a health questionnaire interview to ensure eligibility for fMRI prior to the study.

Written informed consent was obtained in accordance to institutional guidelines and procedures approved by the Yale Human Investigation Committee and the Human Investigation

Table 1. Patient characteristics and quality of life rating.

Group	ADT; n = 12	Control; n = 12
Age	69.1±5.6 years	65.5±6.6 years
Education	9 th grade: 1	9 th grade: 1
	High School/GED: 3	High School/GED: 3
	College 1–3 years: 3	College 1–3 years: 2
	College graduate: 2	College graduate: 3
	Post-graduate: 3	Post-graduate: 3
MMSE	29.1±1.1	29.5±0.7
Cancer staging	Stage 1: 0	Stage 1: 1
	Stage 2: 10	Stage 2: 9
	Stage 3: 2	Stage 3: 2
Local therapy	Radiation 100%	Radiation 33.3%
	Surgery 0%	Surgery 58.3%
	Surgery+Radiation 0%	Surgery+Radiation 8.3%
QOL at baseline	116±25	128±18
QOL of life at 6 months	111±23	124±21
Testosterone at 6 months	0.16±0.11 ng/ml	2.88±1.01 ng/ml

Note: ADT: Androgen Deprivation Therapy; GED: General Education Development Test; MMSE: Mini Mental State Examination; QOL: FACT-P quality of life score; there is no difference between groups in age ($t=2.080$, $p=0.166$, two-sided two-sample t test); there is no difference between groups in MMSE score ($t=2.101$, $p=0.273$, two-sided two-sample t test); Staging follows the current guidelines of the 2010 American Joint Committee on Cancer (AJCC); there is also no difference across the two time points in the change of QOL between groups ($F=0.015$, $p=0.905$, interaction, repeated measures analysis of variance).

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Subcommittee of the Veterans Affairs (VA) Connecticut Health Care System. Of the original study population, 12 ADT and 12 control participants completed the structural brain scans both at baseline and 6 months (after treatment) (**Table 1**).

Working Memory: N-back Task

Working memory is a form of short-term memory that allows individuals to hold and manipulate information in mind in order to do complex tasks such as comprehension, reasoning, and learning. A behavioral paradigm widely used to study working memory is the N-back task. In the N-back task, participants view a series of letters and respond to a letter (a target) that matches the previous letter (“1-back”) or the letter two time steps back (“2-back”). Thus, to detect the target, participants need to hold the memory of the letters that appear consecutively for a period of time. In “0-back” trials, participants simply respond to a pre-designated target letter. Zero-, 1- and 2- back trials are run in different blocks and both the accuracy rate (percentage of the target letters correctly identified) and the reaction time (RT) of correct trials are used as indices of performance. A higher accuracy rate and shorter RT represents better working memory.

Our participants performed an N-back working memory task outside the scanner at baseline and 6 months following treatment. Participants responded to a series of letters presented at a rate of 1 every 2 s (stimulus duration = 500 ms). Fifteen phonologically distinct letters served as stimuli (A, B, C, D, E, F, G, H, K, M, N, P, S, W, X), with three blocks in the task, differing in working memory load. Each subject performed 3 sessions of the N-back task, with each session comprising 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 “load” for that block (5 s) and contained 24 trials, with one-third of them representing targets. Correct response rate and reaction time of correct trials were recorded for each block and averaged for the each load condition for analyses.

Subjective Assessment of Quality of Life

As a general assessment of overall status, participants completed standardized Quality-of-Life-Questionnaires (QOL) for prostate cancer patients (Fact-P[®]) at baseline and again at 6 months [23].

Imaging Protocol

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 mm³ 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°.

Voxel-based Morphometry (VBM)

The aim of VBM is to identify differences in the local composition of brain tissue and its association with behavioral and cognitive measures, while discounting large scale differences in gross anatomy and position. This can be achieved by spatially normalizing individuals’ structural images to the same stereotactic space, segmenting the normalized images into distinct brain tissues, smoothing the gray-matter images, and performing a statistical test to localize significant associations between anatomical and behavioral measures [24].

Voxel-based morphometry was performed using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) packaged in Statistical Parametric Mapping 8 (Wellcome Department of Imaging Neuroscience, University College London, U.K.). T₁-images were first co-registered to the Montreal Neurological Institute or MNI template space (1.5 mm³ isotropic voxels) using a multiple stage affine transformation, during which the 12 parameters of interest were estimated. Co-registration started with a coarse affine registration using mean square differences, followed by a fine affine registration using mutual information. In this step, coefficients of the basis functions that minimize the residual square difference (between individual image and the template) were estimated. Tissue probability maps constructed from 471 healthy subjects were used in affine transformation. After affine transformation, T₁-images were corrected for intensity bias field (kernel size FWHM = 60 mm) and a local means denoising filter [25] with default parameter 1 was applied, to account for intensity variations (inhomogeneity) and noise caused by different positions of cranial structures within MRI coil. The images were then segmented into cerebrospinal fluid, gray and white-matters, using an adaptive maximum a posteriori method [26] with k-means initializations, as implemented in VBM8, generating tissue class (including gray matter or GM) maps.

In segmentation, partial volume estimation was performed with default parameter 5, with a simplified mixed model of at most two tissue types [27]. Segmented and the initially registered tissue class maps were normalized using Dartel [28], a fast diffeomorphic image registration algorithm of SPM. As a high-dimensional non-linear spatial normalization method, Dartel generates mathematically consistent inverse spatial transformations. We used the standard Dartel template in MNI space, constructed from 550 healthy subjects of the IXI-database (<http://www.brain-development.org/>), to drive the Dartel normalization. Normalized

GM maps were modulated to obtain the absolute volume of GM tissue corrected for individual brain sizes. Finally, the GM maps were smoothed by convolving with an isotropic Gaussian kernel. Smoothing helps to compensate for the inexact nature of spatial normalization and reduces the number of statistical comparisons (thus making the correction for multiple comparisons less severe); however, it reduces the accuracy of localization. Most VBM studies used a kernel size of FWHM = 12 mm. We used a smaller kernel size of FWHM = 8 mm to achieve localization accuracy.

In group analyses, we compared the cerebral gray matter volume at baseline and after treatment, for both the ADT and non-exposed group, using paired-sample t test. We also derived the gray matter volumes of the regions of interest for individual participants and correlated these measurements with changes in performance on the working memory task.

Results

Quality of Life Scores

No statistically significant differences between ADT and control patients were found in QOL scores at baseline, or with regard to change over 6 months using the FACT-P[®] questionnaire (**Table 1**).

Performance in N-back Task

As shown in Table 2, the results of N-back task performance scores indicated that the correct response rate decreased with increasing memory load for both ADT and non-exposed participants. We conducted two-way repeated measures ANOVA separately for 0-, 1-, and 2- back data. The results indicated indistinguishable N-back task performance between the two groups across the two time points.

Voxel-based Morphometry

Paired sample t-tests were used for voxel-wise comparison between gray matter volumes at the two time points, for both the ADT and control group. The results showed decreased gray matter volumes for the ADT group but not the control group in the primary motor cortex ($x = -48, y = -10, z = 37, 185$ voxels, $Z = 4.02$), frontopolar cortex ($x = 23, y = 51, z = 4, 158$ voxels, $Z = 3.91$), and dorsolateral prefrontal cortex ($x = -42, y = 38, z = 27, 192$ voxels, $Z = 3.67$), $p < 0.001$, uncorrected, as shown in **Figure 1**. A flexible factorial analysis of variance with time point as a within-subject factor confirmed that the gray matter volumes in the primary motor and dorsolateral prefrontal cortices were significantly lower 6 months after ADT, when compared to baseline, in the ADT group in contrast with the control group ($p < 0.05$, small volume correction for family-wise error of multiple comparisons).

We extracted the gray matter volume of these two regions of interest for all patients and correlated these changes in cerebral gray matter volume to changes in performance in the N-back task (**Figure 2 upper panel**). The results showed that a decrease in the gray matter volume of the primary motor cortex correlated with prolonged reaction time to target detection during the zero-back condition in the ADT group ($p < 0.0042, \rho = -0.7832$, Spearman regression, **Figure 2 lower panel**). The gray matter change of the primary motor cortex and dorsolateral prefrontal cortex did not correlate with the change in accuracy or reaction time in the one- or two- back condition, for the ADT or control group (all p 's > 0.107).

Table 2. Performance in the N-back working memory task.

	0-back (correct %)	0-back (RT, ms)	1-back (correct %)	1-back (RT, ms)	2-back (correct %)	2-back (RT, ms)
ADT_B	98±3	593±116	82±13	669±153	62±16	765±153
ADT_F	97±5	569±103	85±12	720±181	64±18	805±189
Control_B	99±1	494±89	89±12	575±109	77±15	719±138
Control_F	99±2	563±70	88±4	659±125	82±9	745±116
P value*	0.79	0.19	0.50	0.19	0.55	0.78

Note: B: baseline; F: follow-up; RT= reaction time of correct trials;

*P value of the group by time interaction in repeated measures analysis of variance.

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Discussion

Studies of traditional neurocognitive testing without brain imaging have shown variable effects of ADT on cognitive function. In the current study, we observed a decrease in gray matter volumes in frontal and prefrontal cortical structures associated with the use of ADT. The decrease in gray matter volume of the primary motor cortex correlated with increased response time – suggesting processing insufficiency – during target detection in the N-back task. These results are consistent with our previous study that showed ADT-induced altered medial prefrontal cortical activation during cognitive control [20], and with the study by

Cherrier and colleagues, which showed ADT-induced changes in parieto-occipital activation during spatial memory [29]. Our patients were matched by age and level of education, and all assessments were performed either before or at least 3 months after any surgery or radiation treatment to minimize any impact of treatment-related symptoms. Together, these results suggest that androgen deprivation may have a deleterious impact on cerebral structures and functions that are not evident using traditional behavioral tests [30].

Previous studies have shown that regional sex differences in gray matter volume are associated with sex hormones in the developing human brain [31]. Corrected for age, global gray matter volume

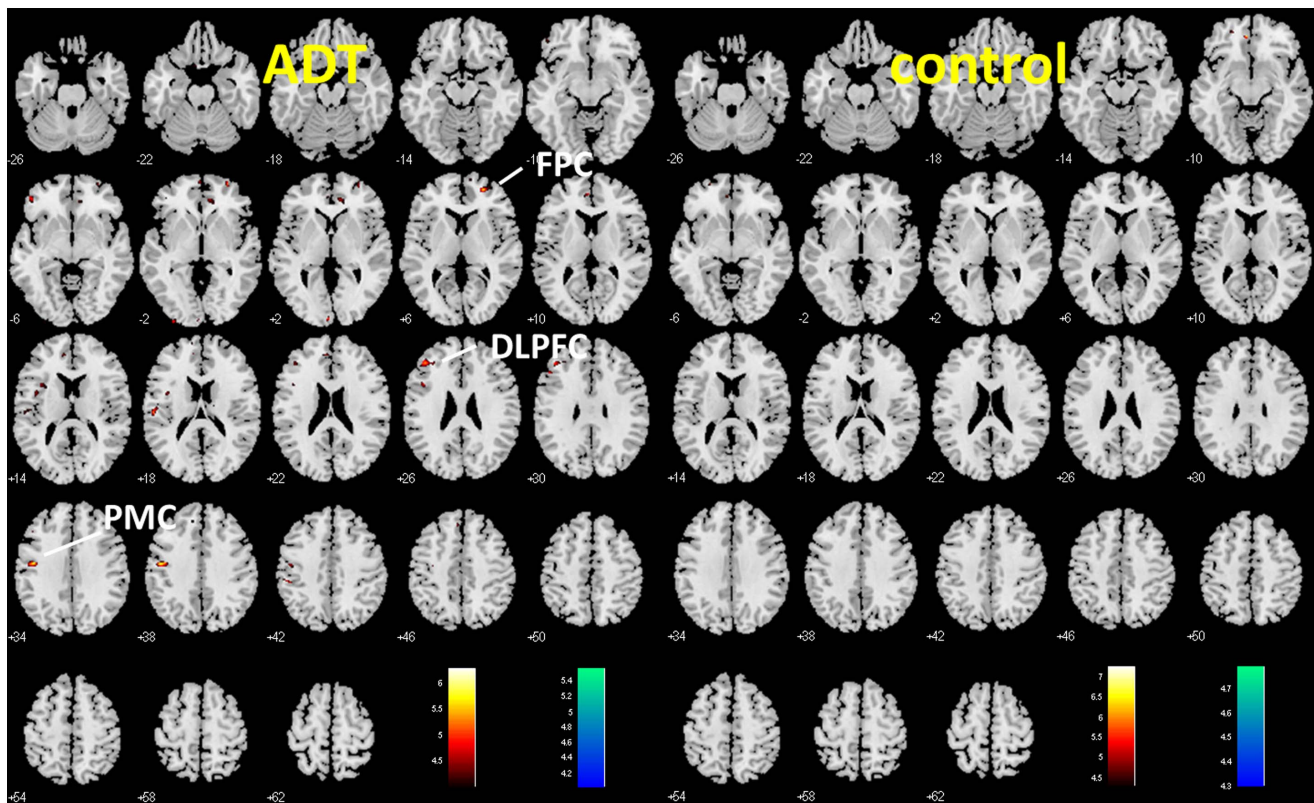


Figure 1. Changes in cerebral gray matter volumes in frontal cortices as demonstrated by voxel-based morphometry. Voxelwise paired t test between baseline and 6 months for ADT (patients who received 6 months of androgen deprivation therapy) and Control (patients who did not receive any hormonal therapy) group, at $p < 0.001$, uncorrected. The difference in gray matter volume, as reflected by a map of T values (color bar), is shown here on a structural brain image in axial sections, from $z = -26$ to $z = +62$, with adjacent sections 4 mm apart. Warm color: baseline $>$ 6 months; Cool color: 6 months $>$ baseline. Neurological orientation: Right (R) = right. ADT but not control patients showed decreased gray matter volume in the primary motor cortex (PMC), frontopolar cortex (FPC), and dorsolateral prefrontal cortex (DLPFC).
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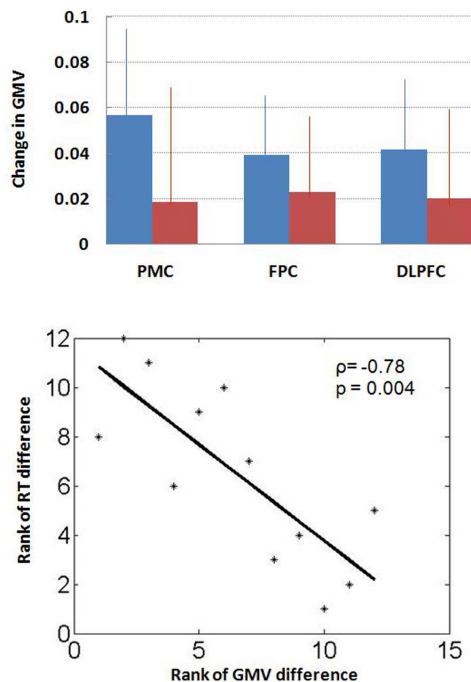


Figure 2. Changes (mean \pm s.d.) in Gray matter volume (GMV) for the three regions of interest: primary motor cortex (PMc), frontopolar cortex (FPC), and dorsolateral prefrontal cortex (DLPFC), for the ADT (blue) and control (red) group (upper panel). A decrease in the GMV of the PMc correlated with prolonged reaction time to target detection during the zero-back condition in the ADT group (lower panel). Because of the small sample size, we used a Spearman regression for correlation ($p < 0.0042$, $\rho = -0.7832$). The result of Pearson regression was also significant: $p < 0.0049$. doi:10.1371/journal.pone.0072032.g002

was negatively associated with estradiol levels in girls, and positively with testosterone levels in boys [32]. Cerebral morphometric analysis suggested that gray matter development in certain brain regions is associated with sexual maturation and that pubertal hormones might have organizational effects on the developing human brain [33]. Children with Klinefelter syndrome who did not receive testosterone replacement therapy showed decreased total gray and white matter volumes [34]. Adults with Klinefelter syndrome also had a significant reduction of left temporal lobe volume and increased ventricular volume, which was inversely correlated with cognitive function [35]. In contrast, boys with familial male precocious puberty and early excessive androgen secretion were characterized by increased gray matter volume in several cortical and subcortical structures [36].

Data in adults also support the modulatory effects of androgen on cerebral cortical activities [37–41] and gray and white matter

volume [34,42]. A higher level of free testosterone was associated with greater cerebral blood flow in the hippocampus and prefrontal cortices in elderly men [37], and testosterone replacement therapy increased cerebral blood perfusion in the midbrain and prefrontal cortex in hypogonadal men [37]. In healthy women, administration of testosterone increased ventral striatal responses to reward [39].

Neuroimaging studies have reported differences in regional brain activations in neurological or psychiatric patients even when they performed at a level equal to their demographically-matched control participants. We argued earlier that these performance-independent changes in brain activities cannot be accounted for by effort or motivation, and potentially represent a correlate specific to the cerebral pathologies [20]. Here we demonstrate that androgen deprivation also alters cerebral morphometry. Since motivation or effort is highly unlikely to change cerebral morphometry within the time frame of the current experiment, these results provide additional evidence for potential side effects of ADT on the central nervous system. Nonetheless, we did not observe differences in the subjective report of quality of life or behavioral performance during the working memory task. More studies are thus required to thoroughly evaluate the overt impact of these functional and structural changes of the brain as a result of ADT.

A few limitations of our study need to be considered. First, the study involved a small sample size of 12 ADT and 12 control participants; thus, the results should be considered preliminary with the need for replication in future work. Second, the duration of observation is relatively short in the current cohort. Future studies should address whether the functional and structural differences associated with ADT worsen over time.

Conclusion

Androgen deprivation for 6 months leads to structural brain changes in prostate cancer patients. Such changes are associated with prolonged reaction time to target detection in an N-back working memory task. The clinical implications of these changes are not known and warrant future study.

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Author Contributions

Conceived and designed the experiments: HHC EU MR JC C-SRL. Performed the experiments: HHC SH EU. Analyzed the data: JI SZ C-SRL. Wrote the paper: HHC MR JC C-SRL. Read and approved the final manuscript: HHC SH JI EU SZ MR JC C-SRL.

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