Author's response to reviews

Title: Changes in neuronal activation patterns in response to androgen deprivation therapy: A Pilot study.

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Author's response to reviews: see over
We thank the reviewers for their time and thoughtful review of the manuscript. We have responded to each comment below and incorporated responses into the text. In addition, the Journal Editor requested that we address the clinical relevance of the findings. We have added some information regarding the clinical relevance in the last section (second to last paragraph) of the discussion section. We hope the reviewers will find the changes satisfactory. The manuscript is much improved with these revisions.

First Reviewer

Major Compulsory Revisions

1. Please specify what is the limit of detection of fMRI changes in activation based on the sample size using a yardstick that the average reader can understand (e.g. effect size, power, etc).

We have added some statements to the text, that will hope will help readers appreciate both the statistical power of fMRI as well as the limitations. For ease of review we have also pasted the information below. Also, Table 2 contains the p values for the brain regions that demonstrated a significant change over time and as designated in the bottom half of the table the group and time comparisons. We have added the p value for Figure one which was previously missing. Generally speaking fMRI studies are somewhat similar to behavioral data with regard to power such that many things can affect the power to detect differences between groups. In particular, although a large sample size is always desired, more observations (i.e. images) per person can increase power as well as repeated observations (i.e. repeat scans like the present study with pre-post) and controlling (i.e. matching) for variables of interest that are thought to exert effects on the outcome variable of interest such as cognitive processing (i.e. age, education).

Additional factors affecting power can include the paradigm design, the resultant hemodynamic response and MRI strength and set-up (Friston et al 1999 – Multisubject fMRI studies and conjunction analysis. Neuroimage 10:385). Block designed paradigms as we used in the present study are generally regarded as having good statistical power (Liu TT: Efficiency, power, and entropy in event-related fMRI with multiple trial types. Part II: design of experiments. Neuroimage 21:401 2004)

Specifically with regard to our data, the variance in the BOLD signal for our study, for most brain regions across all paradigms was about 1% of the total signal. Given the design of our paradigms this would allow us to detect a 0.5% increase in signal (task-associated activation) with about 50% power and 0.75% change with > 80% power in individual subjects. Review of clusters of significant task-associated activation within individual subjects revealed, as expected from the simplistic prior power calculation, signal changes ranged 0.25-1.0% of the signal.

Minor Essential Revisions

Abstract

1. Please include number of subjects and controls.
We have added the final analysis number to the abstract.

2. Please indicate that controls were matched and on what variables.
Controls and ADT patients were matched for age within four years and education within two years. This has been added to the text.

3. In results please comment on the encoding task results as well.
There are no behavioral indices of ‘encoding’. During the encoding phase, participants view the quick time movie of the complex environment and are told they will be tested on the information following the encoding period. As all participants are given a full practice session, using a different environment than the actual fMRI session, the participants are fully aware of the type of testing they will undergo after the encoding session. For example, if you were to undergo a task in which you heard a list of words and then were subsequently asked to indicate on another list of words which words were in the original list. The first part (hearing the words) is considered encoding and the second part indicating which words are new or old is considered recognition. Similarly for our spatial task, the first part - viewing the environment is considered encoding and the second part - indicating the correct or incorrect spatial layout is considered recognition. There is no behavioral data to report for the encoding section. Neuroimaging data during the encoding scans is included throughout the manuscript.

Background
4. Please add a ref. for sentence 1, para. 3 on p. 3.
We have added a reference.

Methods
5. Please add a statement about sample size (likely here a convenience sample in a substudy of a larger study, so no formal calculations were done).
We did not conduct a formal power analysis. However, it is not unusual for studies involving both functional neuroimaging and patients with clinical conditions, with repeat assessments to have sample sizes in the range of 5 – 15 patients. (See for example Bookheimer et al. (2000) examined APOE4 positive and negative and the final sample (scanned twice) was 7 in each group; Wishart et al. (2004) N=10 Multiple Sclerosis patients; Saykin et al. (1999) N=9 Alzheimer’s patients & N=6 controls; Amiez et al. (2008) patients with brain tumors N=4; Brown et al. (1998) N=6 breast cancer patients, Wagner et al. (2004) N=10 breast cancer patients. See also (McDonald BC, Saykin AJ, Ahles TA. Brain Imaging Investigation of Chemotherapy-Induced Neurocognitive Changes. In: Meyers CA, Perry JR, editors. Cancer and Cognition. New York: Cambridge; 2008. p 19-32.) for a review of neuroimaging studies in cancer.
We have made attempts to acknowledge the small sample size in the discussion and presumably the reviewers and readers can appreciate the complexity of coordinating functional neuroimaging studies in temporal sequence with ongoing clinical treatment. In addition, we have titled the manuscript with “pilot study” to indicate that we acknowledge these results can only be considered preliminary in recognition of the small sample size.

Results
6. No p-values are provided to allow us to contextualize fMRI changes in neuronal activation (i.e. are they significant even if observed to be different).
Table 2 contains the p values for the brain regions that demonstrated a significant change over time, and as designated in the bottom half of the table the group and time comparisons. We have added the p value for Figure one which was previously missing.

7. Were activation differences seen in all patients compared to controls, or only some?
Similar to data analysis of non-image data, the general linear model (GLM) analyses for imaging data included group membership as a factor. Figure 1 depicts the group average decline in the ADT group. Table 2 details the p values and spatial extent (Area in cm3) of the brain regions that declined in the ADT group compared to baseline and compared to the controls. Figure 2 depicts the change from baseline for each individual
subject. Readers may refer to Figure 2 to appreciate the standardized Z score for change for each individual subject.

8. Please add handedness of the patients. Did this affect results? 
We did not select or exclude participants due to handedness. However, all participants were right handed. We have added that information to the text.

Discussion
9. The sample is highly educated. Please comment on the impact of this on findings. 
Although the range of education levels (12 - 21 years) is large, the average is somewhat high (17 years) which corresponds to one year of school beyond the college degree. It is possible this may have affected results, particularly since some studies have found a correlation with education and the mental rotation task. However, it is not at all unusual for research studies to have samples in which the education level is higher than the general population as there is a greater likelihood for higher educated individuals to volunteer for studies. Thus, our results are not likely to be different from other research studies. We have added a statement about education level at the end of the discussion section.

10. The sex differences on mental rotation are somewhat conflicting in published studies. The authors seem to suggest prior studies have found consistent results, which is not the case. 
The reviewer is correct in noting that we have simplified the numerous studies concerning mental rotation and of course not all studies support a sex difference. Nonetheless, this study only involved men. We have added some information that further balances this statement.

11. Generally well written. Limitations need a bit of expansion especially with the small sample size. 
We have added some additional information on aspects of the study (e.g. prospective) and context with regard to other neuroimaging studies involving cancer patients. See last paragraph discussion section.

Tables are fine
Figure 1 - better labelling of the illustration is necessary, in terms of anatomic description in the legend and use of arrows in the figure. 
We have edited the figures and added some additional information and p values to the figure legends.

Second Reviewer.

Major compulsory revisions: 
The only major concern that I have about this report in its current form is the question of the extent to which the study radiologists were blinded to treatment assignment. I am not a neuroradiologist so I hasten to add that these concerns may be irrelevant (ie there may be little in the way of subjective interpretation of the findings of fMRI studies) however it would seem reasonable to design a study such as this with blinding of the reading radiologist to treatment assignment. If this study was performed with that methodology it should be more clearly stated, and if not, there should be some more acknowledgement and discussion of what I believe to be a reasonable methodological critique.

The reviewer has noted an important consideration in the methodology. Although it is
not feasible to have a study in which men with prostate cancer without metastases and biochemical relapse (rising PSA following local therapy) are randomized to no treatment, we did make attempts to control for other factors. Radiology technicians who were responsible for scanning the participants were blind to condition and only subject numbers identified imaging data. PB who performed the image analysis was also blind to condition and image analysis steps are operator independent. We have added this information to the methods section.