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Tract-based Spatial Statistics and fMRI Analysis in Patients with Small Cell Lung Cancer before Prophylactic Cranial Irradiation

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Abstract. Prophylactic cranial irradiation (PCI) is known to increase life expectancy to a significant degree in Small Cell Lung Cancer (SCLC) patients. The overall scope of this research is to investigate changes in structural and functional connectivity between SCLC patients and controls before and after PCI treatment. In the current study specifically we use diffusion tensor imaging (DTI) and functional Magnetic Resonance (fMRI) to identify potential alterations in white matter structure and brain function respectively, in SCLC patients before PCI compared to healthy participants. The results in DTI analysis have showed lower fractional anisotropy (FA) and higher eigenvalues in white matter regions in the patient group. Similarly, in fMRI analysis a lower level of activation in the primary somatosensory cortex was reported. The results presented herein are subject to further investigation with larger patient and control groups.

1. Introduction

Prophylactic cranial irradiation (PCI) is a standard method to prevent metastatic tumors in the brain for small cell lung cancer patients. Despite the fact that PCI prolongs life expectancy, negative effects (such as chemotherapy) in various cognitive functions have been reported [1].

In order to discriminate those effects, Diffusion Tensor Imaging (DTI) has been applied. DTI can detect white matter (WM) lesions [2] by measuring the diffusion of water molecules in the brain. The most common parameters of this technique are mean diffusivity (MD) and fractional anisotropy (FA), which define the magnitude of diffusion and the preferential directionality of water diffusion along the white matter tracts, respectively [3].

Additionally, functional Magnetic Resonance Imaging (fMRI) technique has been implemented in order to determine the null hypothesis of neurocognitive impairments. fMRI measures brain activity by detecting changes in the local oxygenation of blood. In the current study, we employed two fMRI techniques; task-related and resting state fMRI. During rest, several brain regions are functionally connected thus forming resting-state networks. These networks are of great importance for the characterization of the complex patterns of neural and behavioural consequences of cancer.

In the present study, having a larger sample size and more statistical power than in previous attempts [4], [5], [6], [7] we sought to examine for potential differentiations by comparing SCLC patients with normal controls using DTI as well as fMRI techniques.

2. Methods

Thirteen healthy participants and seventeen SCLC patients before PCI treatment participated in the study. All participants had complete response to initial treatment (chemotherapy with or without chest radiotherapy), without any brain metastases shown, met the standard MRI safety criteria and had no history of diagnosed neurological disorder, major psychiatric disorder or treatment with psychotropic medication, including substance misuse. Whole brain MRI, DTI and fMRI data were collected on a Philips 3.0T scanner (Achieva; Philips, Best, The Netherlands) at the Radiology Research Unity, Medical Imaging Department, Evgenidion Hospital, National and Kapodistrian University, Athens, Greece using an 8-channel SENSE head coil used for radiofrequency reception of the nuclear magnetic resonance signals. Foam pads and headphones were used to reduce head motion and scanner noise. Anatomical imaging was performed with T1-weighted 3D sagittal acquisition (1.0-mm-thick slices, 0 mm slice gap, TE = 4.6 msec/TR = 15 msec, FOV = 256, and 1.0 x 1.0 x 1.0 mm^3 reconstructed voxel size, and T2 Fluid Attenuated Inversion Recovery (FLAIR) acquisition (1.0-mm-thick slices, 0 mm slice gap, TE = 4.6 msec/TR = 15 msec, FOV = 256, and a 1.0 x 1.0 x 1.0 mm^3 reconstructed voxel size.

All data were preprocessed and analyzed using FSL (FMRIB's Software Library, version 5.0;www.fMRIb.ox.ac.uk/fsl) [8]. Images from the whole dataset were initially brain-extracted using BET (Brain Extraction Tool) [8].

DTI data set was corrected for stretches and shears induced by eddy currents in the gradient coils and simple head motions by using affine transformation. A diffusion tensor model was fitted on the data to determine the level of anisotropy for each voxel independently. Fractional anisotropy, $\lambda 1$, $\lambda 2$ and $\lambda 3$ maps were generated using FDT-FMRIB's Diffusion Toolbox [9]. The FA was calculated and plotted in a single FA map for each subject. Voxel-wise statistical analysis of the FA data was performed using TBSS implemented in FSL [10]. TBSS analysis was also applied to the $\lambda 1$, $\lambda 2$ and $\lambda 3$ maps, as well as in MD.

fMRI data were realigned for motion correction (MCFLIRT) [11]. A high-pass filtering was implemented (60 s cutoff) and images were spatially smoothed using a Gaussian kernel of 6 mm full width at half maximum. Artefacts were removed using MELODIC (Independent Component Analysis-ICA tool in FSL). The median functional image was aligned to the high-resolution T1-weighted image using a rigid body transformation [11] and then registered to the T1 MNI152 template using affine as well as non-linear transformations with a warp resolution of 10mm. First level analysis was conducted using FILM (FMRIB's Improved Linear Model) [12]. The contrasts of interest were left-tapping vs. baseline and right-tapping vs. baseline. Group comparisons were conducted using mixed effects (ME) analysis. Finally, two-sample unpaired t-tests were accomplished in order to estimate each group's cross-subject variability separately ($p<0.05$).

Resting state fMRI data were decomposed into 42 independent components and analyzed using multi-session temporal concatenation group ICA (MELODIC FSL tool). Model order was estimated using the Laplace approximation to the Bayesian evidence for a probabilistic principal component model. For each subject, the group-average spatial maps were regressed onto the subject's 4D space-time dataset (spatial regression) using a regression technique called dual regression. A set of subject-specific timeseries were created, one per group-level spatial map. Those timeseries were regressed into the same 4D dataset, resulting in a subject-specific spatial correlation maps. The component representing the default mode network (DMN) was identified visually [13]. Group comparisons were conducted in this network by performing nonparametric permutation tests (5000 permutations) using FSL's randomize permutation-testing tool. Additionally, to control the probability of false activations, a family-wise error correction (FWE) was performed using a threshold of $p<0.05$.

3. Results

Results from DTI analysis report that brain regions within the centrum semiovale WM, the cerebellum as well as the fornix may represent lower FA in SCLC patients compared to controls (voxelwise thresholding uncorrected for multiple comparisons, $t>3$, $p<0.05$). Furthermore, TBSS analysis showed that regions with FA reductions were accompanied by increased λ1, λ2, λ3 and MD (figure 1).

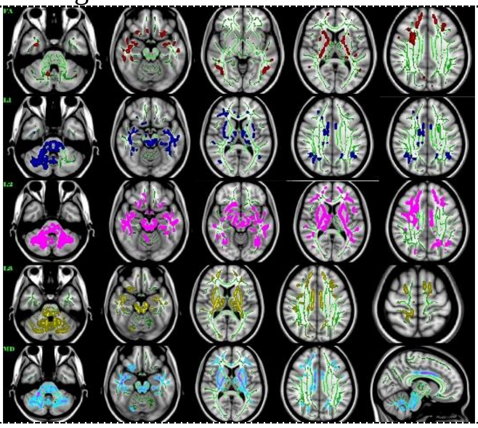

Figure 1. Significant differences, where patient FA is lower than control FA, are visualized with red coloring and the increase of λ1, λ2, λ3 and MD are visualized with blue, purple, yellow and cool respectively. Mean FA skeleton is presented in green color. The first row shows differences in FA, the second in λ1, the third in λ2, the fourth in λ3 and the last row in MD.

Results from task-related fMRI analysis showed common activations in both patients and healthy controls (including the premotor cortex, the primary motor cortex, the primary somatosensory cortex and the corticospinal tract) during the left and right tapping task. Additionally, when comparing the two groups, the healthy participants showed a significantly higher level of activation in the left as well as right primary somatosensory cortex (figure 2). Resting state fMRI analysis results showed that for both groups the DMN was significantly activated (figure 3).

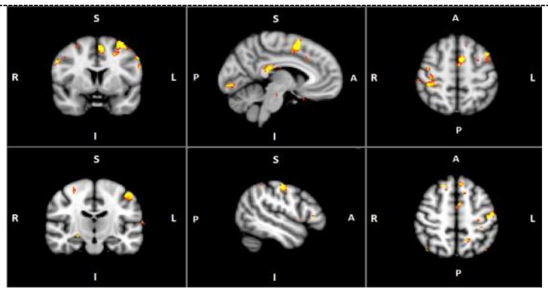

Figure 2. Comparison between the control and patient groups for the left tapping (top images) and the right tapping (bottom images).

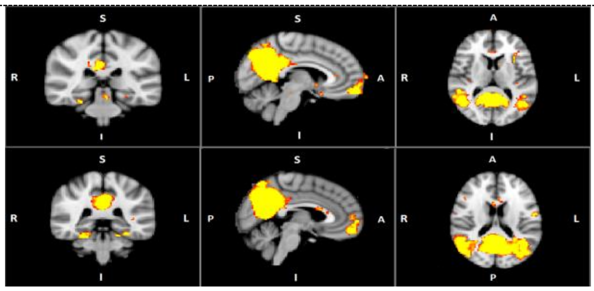

Figure 3. Default Mode Network in healthy group (top images) and patient group (bottom images).

4. Discussion and Conclusion

In this study, we found some WM tract damages in patients with SCLC before PCI treatment. The results show decreased FA in the centrum semiovale WM, the cerebellum and the fornix. Furthermore, three eigenvectors of the diffusion tensor and the MD were analyzed. λ2 and λ3 were increased while λ1 and MD revealed smaller changes. In terms of fMRI analysis, when comparing the two groups, the healthy participants showed a significantly higher level of activation in the left and right primary somatosensory cortex. Moreover, during rs-fMRI, the DMN was identified in both groups.

As this research is ongoing, anatomical and functional connectivity in healthy subjects and patients with small cell lung cancer [4], [5], [6], [7] depending on the type of disease and the phase of treatment and time of clinical examination, will be studied. Study of cognitive functionality of patients with SCLC will be conducted with imaging and clinical examination. The effects of radiation (PCI) both at anatomical as well as functional levels in the brain will be consequently assessed. Efforts are being made to increase the number of participants at different stages of disease and treatment which is a difficult task taking into consideration the significant percentage of mortality of this specific type of cancer patients.

5. References

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