Resting state and task related fMRI in small cell lung cancer patients

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***Abstract*- Prophylactic cranial irradiation (PCI) is a standard treatment technique for small cell lung cancer patients. However, there is evidence that this technique may contribute to neurocognitive deficits. Therefore the study of anatomical and functional connectivity in patients undergoing PCI as well as their neurocognitive functionality, depending on the type of disease and the phase of treatment and time of clinical examination, is of considerable interest. In this context, we investigate whether there are any differentiations in brain function during resting state and task-related functional magnetic resonance imaging (fMRI) in patients with cancer before PCI compared to healthy subjects. During a finger tapping task, the brain regions that were activated bilaterally for both groups are consistent with previous studies. During rest, the Default Mode Network (DMN) was identified in both groups. The preliminary results presented herein are subject to further investigation with larger patient and control group.**

I. Introduction

Cancer remains one of the most serious plagues for public health nowadays, despite the undeniable progress made in cancer research and treatment. Scientific research undertakes initiatives at various levels, not only in order to save lives, but also in order to improve the quality of life of cancer patients. Medical imaging contributes to the comprehension of the neuropsychological basis of the disease, providing better presymptomatic diagnosis and dynamic adaptation and personalization of treatment. Especially for cancer patients suffering from limited and extensive stage small cell lung cancer (SCLC), prophylactic cranial irradiation (PCI) has become a standard of care systemic treatment [1]. With recent increases in mean overall survival and an increased number of longer-term survivors, the potential contribution of PCI to the development of neurocognitive deficits is becoming more clearly defined [2]. Although application of PCI in certain types of cancer has considerably increased life expectancy, it is avoided in many cases because of its potential negative effect on cognitive functions such as frontal lobe executive functions, motor coordination and memory [3].

Due to the progress of science and technology, functional and structural imaging constitutes the cornerstone of the study of cerebral operation in-vivo. Specifically, Magnetic Resonance Imaging (MRI) can distinguish tumors, inflammatory lesions, and other pathologies from the normal brain anatomy while it is also useful for the diagnosis of demyelinating disorders. Functional Magnetic Resonance Imaging (fMRI) measures the haemodynamic response related to neural activity in the brain. Recently, during rest, functional imaging studies have shown that multiple cortical brain regions are functionally linked forming resting-state networks [4]. This finding led to the hypothesis that these regions constitute a network supporting a default mode of brain function. This high level of functional connectivity within resting-state networks suggests the existence of direct neuroanatomical connections between these functionally linked brain regions to facilitate the ongoing interregional neuronal communication, as has been recently shown for some of these networks [5].

Recent studies have stressed out the significance of the feasibility of using resting state networks and functional connectivity, as well as DTI parameters for the characterization of the complex patterns of neural and behavioral consequences of cancer, treatment and brain injury [6], [7], [8]. Advanced MR imaging modalities, have significantly improved our understanding of the physiopathology of brain tumors and have provided invaluable additional information for treatment planning and monitoring of treatment results [9].

Based on the aforementioned and due to the widespread use of: a) conventional magnetic resonance imaging (MRI) in clinical practice and increasing use of advanced MRI techniques in clinical research b) PCI, as anticancer and in particular preventive for metastases treatment, aiming at developing patient welfare-focused therapy strategies, we present herein part of our ongoing work regarding the study of MRI and fMRI imaging data collected from SCLC patients undertaking PCI and patients with metastatic brain disease undertaking therapeutic cranial irradiation, before and after the radiation treatment. Our overall scope is to investigate anatomical and functional connectivity in

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patients with SCLC as well as their neurocognitive functionality, depending on the type of disease and the phase of treatment and time of clinical examination. Our goal in the present study is to report if there are any differentiations in brain function during resting state and task-related fMRI in SCLC patients before PCI compared to the healthy group. To our best knowledge, there do not exist any studies regarding the characteristics of fMRI resting state networks in cancer patients of this type.

II. METHODS

A. Acquisition

MRI acquisition. 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. Foam pads and headphones were used to reduce head motion and scanner noise.

Volumetric sequences. 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.

Rs-fMRI sequence. Functional MRI data were acquired while subjects were lying quietly in the scanner with eyes closed. Whole brain rs-fMRI was performed using a gradient echo planar imaging sequence (TR = 2000 msec / TE = 30 msec, flip angle = 90). For maximum consistency, all subjects were instructed to close their eyes throughout the rs-fMRI sequence, relax, but to remain awake and motionless as much as possible during the data acquisition.

The finger tapping task consisted a block design with two conditions, sequential tapping and rest. Participants were instructed to tap the fingers of their right hand sequentially at a standard pace, starting with the thumb and finishing with the little finger. During the rest condition they were instructed to keep their eyes closed and stay calm. Each block had duration of 30 s and a 2 s verbal prompt at the beginning with the words tap and rest respectively. Each run included four repetitions of each tapping condition and five repetitions of the rest condition. The same design was repeated for the left hand for each participant.

B. Participants

Five healthy participants (two male, age range 45-65 years) and four SCLC patients (one male, age range 45-65 years) before PCI treatment participated in the study. All participants were native Greek speakers, right-handed (self reported), 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. All participants provided written informed consent and the study was approved by the appropriate research ethics committee.

C. Preprocessing and data analysis

Task-related fMRI data

The preprocessing steps and the analysis were carried out with FEAT (FMRI Expert Analysis Tool, v. 5.63), which is a tool of FSL (FMRIB's Software Library, version 5.0; www.fMRIb.ox.ac.uk/fsl). Functional data were realigned to correct for motion (MCFLIRT) [10]. Non-brain structures were extracted using BET [11]. A high-pass filtering was implemented to remove low-frequency drifts (60 s cutoff) and images were spatially smoothed using a Gaussian kernel of 6 mm full width at half maximum and grand-mean scaled to ensure that the comparison between groups will be carried out properly. After pre-processing the median functional image was aligned to the high-resolution T1-weighted image using a rigid body transformation [10], [12] and then registered to the T1 MNI152 template using affine as well as non-linear transformations.

The fMRI data from all the participants were analyzed at first level using FILM (FMRIB's Improved Linear Model) [13]. The contrasts of interest were left-tapping vs. baseline and right-tapping vs. baseline. Following this, higher-level analysis was conducted in order to investigate for group differences and group mean using fixed effects analysis due to the limited number of subjects. We used two-sample unpaired t-tests because of the fact that in this stage the two groups have different number of subjects. To obtain better results of the observed differences, we kept only those voxels with significant ($p<0.05$) effect.

Resting state fMRI data

Resting state fMRI data were analyzed using the MELODIC FSL tool. The data were decomposed into 110 independent components and analyzed using multi-session temporal concatenation group ICA. Model order was estimated using the Laplace approximation to the Bayesian evidence for a probabilistic principal component model. The aim of this work was to focus on the DMN which was visually identified based on previous studies [14], [15].

The spatial map of the DMN from the multi-session temporal concatenation group ICA was used to generate subject-specific versions of the DMN's spatial map, and associated timeseries, using dual regression [16]. First, for each subject, the group-average spatial map of the DMN was regressed onto the subject's 4D space-time dataset. This resulted in a set of subject-specific timeseries, one per group-level spatial map. Next, those timeseries were regressed into the same 4D dataset, resulting in a subject-specific spatial map of the DMN, one per group-level spatial map. Subsequently, using FSL's randomize permutation-testing tool, we performed nonparametric permutation tests (5000 permutations) in order to test for significant group differences in the DMN. Finally, to control the probability of false activations we performed a family-wise error correction (FWE) using a threshold of $p<0.05$ [17].

III. Results

Task-related fMRI data

For the healthy group, the areas of the brain significantly activated during the left tapping task, were the premotor cortex, primary somatosensory cortex and primary motor cortex of the right hemisphere. For the patient group, we observed activations in the right premotor and primary somatosensory cortices as well as the left cerebellum (Fig. 1, 2).

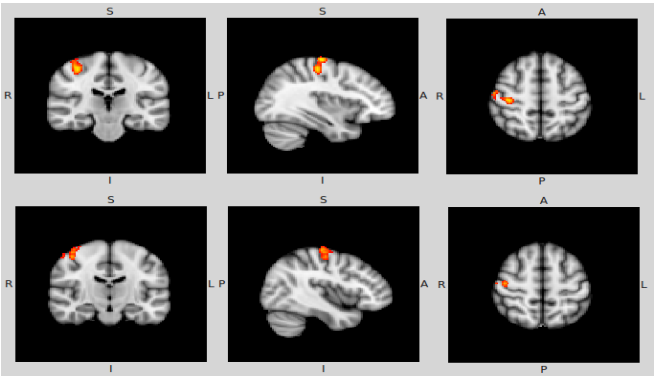

Fig. 1. Group activations in healthy subjects (top images) and SCLC patients (bottom images) for the left tapping task. .

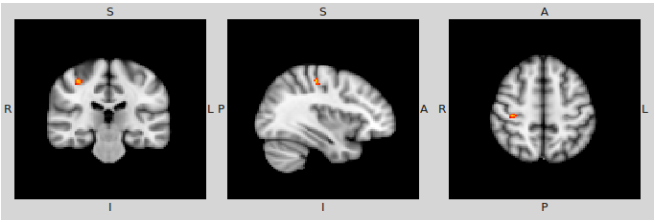

Fig. 2. Comparison between the control and patient groups for the left tapping task.

The right tapping task for the control group excibited activations in the primary motor cortex, the corticospinal tract, the premotor cortex, the superior parietal lobule and the primary somatosensory cortex. In the patient group the activation was mainly restricted to the left premotor and left primary somatosensory cortices (Fig. 3, 4).

Resting state fMRI data

For the healthy group, significant activations were reported in the DMN which includes the medial prefrontal cortex (MPFC), the medial temporal lobes (MTLs) and the posterior cingulate cortex (PCC). On the other hand, for the patient group the identified DMN was a part of the DMN that was observed for the healthy group (Fig. 5, 6).

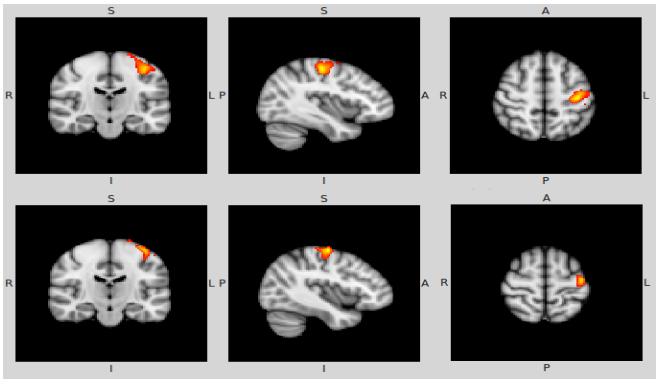

Fig. 3. Group activations in healthy subjects (top images) and SCLC patient (bottom images) for the right tapping task.

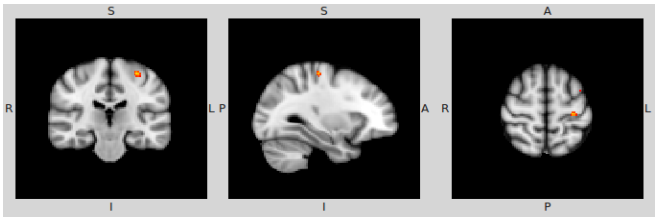

Fig. 4. Comparison between the control and patient groups for the right tapping task.

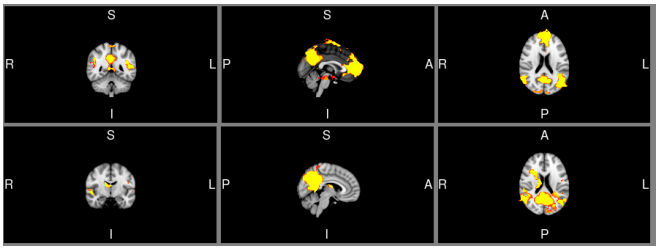

Fig. 5. Default Mode Network in healthy group (top images) and patient group (bottom images).

IV. Discussion and Conclusion

The aim of this paper was to explore the brain areas that are activated in both control and patient groups after a sequential tapping task as well as to identify the DMN and investigate potential activation differences between groups. As with prior studies of simple motor paradigms, the primary motor network, including primary motor cortex, premotor cortex, and primary somatosensory cortex were activated bilaterally in healthy subjects during the tapping task. Similar activations were reported in the patient group. During rsfMRI, the DMN was observed in the healthy group and in the patient group. Comparison between the two groups in both rest and task conditions may reveal small differences of activation in the prefrontal cortex, which is subject to further investigation. This analysis is on-going as the number of the participants is currently increased, a fact that will ensure improved robustness and potential verification of the aforementioned preliminary findings.

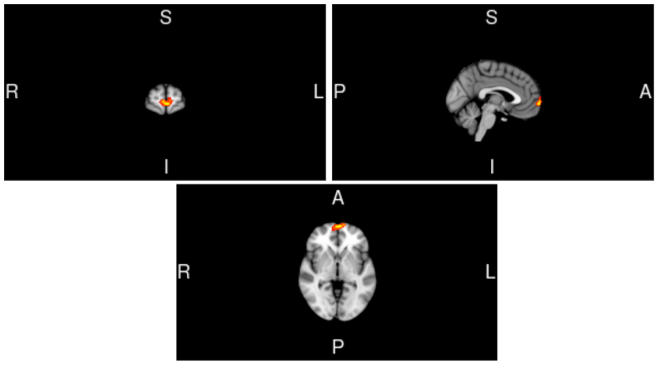

Fig. 7. Comparison of the DMN map between healthy and patient groups.

In the near future, brain areas which are functionally and anatomically connected will be studied, in both healthy subjects and SCLC patients. These networks will be studied also in cancer patients for the first time to our best knowledge. Moreover, this study will be extended to investigate the various stages of treatment and disease.The main target group of this consists of cancer patients having the dilemma of following or not therapeutic procedures that may significantly improve life expectancy while may also negatively affect their neurocognitive abilities.

The main scope of our work is based on unanswered questions raised by its fundamental objectives: “How are brain functions in cancer patients being affected as the disease and the therapeutic procedure progress?”, “Are there any underlying mechanisms affecting brain functions in the above cases that could be identified before even symptoms are clinically evident?” In the near future, newly collected experimental data will be analyzed, yielding additional insight on the aforementioned issues.

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