Brain Functional Connectivity in Small Cell Lung Cancer Population after Chemotherapy Treatment: an ICA fMRI Study

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Abstract. Previous neurocognitive assessments in Small Cell Lung Cancer (SCLC) population, highlight the presence of neurocognitive impairments (mainly in attention processing and executive functioning) in this type of cancer. The majority of these studies, associate these deficits with the Prophylactic Cranial Irradiation (PCI) that patients undergo in order to avoid brain metastasis. However, there is not much evidence exploring cognitive impairments induced by chemotherapy in SCLC patients. For this reason, we aimed to investigate the underlying processes that may potentially affect cognition by examining brain functional connectivity in nineteen SCLC patients after chemotherapy treatment, while additionally including fourteen healthy participants as control group. Independent Component Analysis (ICA) is a functional connectivity measure aiming to unravel the temporal correlation between brain regions, which are called brain networks. We focused on two brain networks related to the aforementioned cognitive functions, the Default Mode Network (DMN) and the Task-Positive Network (TPN). Permutation tests were performed between the two groups to assess the differences and control for familywise errors in the statistical parametric maps. ICA analysis showed functional connectivity disruptions within both of the investigated networks. These results, propose a detrimental effect of chemotherapy on brain functioning in the SCLC population.

1. Introduction

Small Cell Lung Cancer (SCLC) is an aggressive form of lung cancer with a high tendency to develop brain metastases. For this reason, the standard therapeutic schema includes (1) platinum-based chemotherapy and (2) Prophylactic Cranial Irradiation (PCI). Despite the effective role of PCI in reducing the incidence of brain metastases, there is evidence from previous neurocognitive assessments [1] that highlight the presence of neurocognitive impairments associated with PCI in the SCLC population.

On the other hand, there is literature supporting the existence of those impairments even before PCI treatment, mainly as a result of chemotherapy treatment [2]. Furthermore, a recent resting-state fMRI study [3] using ROI-to-ROI and Seed-to-voxel analyses, found disrupted functional connectivity within
the Default Mode Network (DMN) and the Task-Positive Network (TPN) in the SCLC patients after chemotherapy treatment. These networks are associated with working memory and executive functions.

The scope of the current study is to investigate potential functional connectivity alterations within the aforementioned networks using Independent Component Analysis (ICA) in SCLC patients after chemotherapy treatment.

2. Methods

2.1. Acquisition

2.1.1. MRI acquisition. Whole brain MRI 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.

2.1.2. 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 mm³ 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 mm³ reconstructed voxel size.

2.1.3. 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.

2.2. Participants

Thirteen healthy participants and nineteen SCLC patients after chemotherapy 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.

2.3. Preprocessing and data analysis

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) [4]. Non-brain structures were extracted using BET [5]. A high-pass filtering was implemented to remove low-frequency drifts (100 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 preprocessing the median functional image was aligned to the high-resolution T1-weighted image using a rigid body transformation [4] and then registered to the T1 MNI152 template using affine as well as non-linear transformations with a warp resolution of 10 mm.

Data analysis was carried out using the MELODIC FSL tool. The data were decomposed into 49 independent components and analyzed using multi-session temporal concatenation group ICA.
order was estimated using the Laplace approximation to the Bayesian evidence for a probabilistic principal component model. The 49 components were used to generate subject-specific versions of all spatial maps, and associated timeseries, using a regression technique called dual regression. First, for each subject, the group-average spatial maps were regressed onto the subject's 4D space-time dataset (spatial regression). 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 (temporal regression), resulting in a subject-specific spatial correlation maps. The scope of the current study was to focus on two spatial maps (components) representing the DMN and the TPN which were visually identified. After setting a specific design matrix for cross-subject modelling, nonparametric permutation tests (5000 permutations) were performed using FSL's randomize permutation-testing tool, in order to estimate the DMN and TPN spatial maps of each group and test for statistically significant differences between groups in these networks. Finally, to control the probability of false activations we performed a family-wise error correction (FWE) using a threshold of p<0.05.

3. Results

Comparisons between groups revealed lower functional connectivity in the SCLC group in both the DMN and the TPN.

Specifically, the DMN map showed lower connectivity in the patient group in the middle temporal gyrus, the right inferior parietal lobule, the pars triangularis of the inferior frontal gyrus, the anterior division of the cingulate gyrus, the paracingulate gyrus, the frontal pole, the left superior temporal gyrus and the superior frontal gyrus (figure 1).

Similarly, the TPN map showed lower connectivity in the patient group in the left inferior parietal lobule, the primary somatosensory cortex, the secondary somatosensory cortex, the primary auditory cortex, the lateral occipital cortex and the anterior insula (figure 2).

4. Discussion

In this study we document brain functional connectivity disruptions regarding the two most prominent networks, the DMN and the TPN in a cohort of SCLC patients after chemotherapy treatment. Our findings are in line with a recent resting-state fMRI study in SCLC population [3] showing inefficient functional integration of the DMN. In addition, we reported lower strength of functional connectivity in the inferior parietal lobule (IPL), a component of the temporal-parietal-limbic neural network that plays an important role in various cognitive functions [6]. Furthermore, we found less connectivity in the inferior frontal gyrus, a brain region that is involved in a variety of decision-making and cognitive
control processes [7]. Together these findings provide evidence that disruptions within the DMN may be related to attention deficits in the SCLC after chemotherapy.

As TPN has been shown to be involved in working memory, executive function and attention tasks, changes within this network may provide information regarding the impact of chemotherapy on cognitive functioning. Among the regions that were functionally disrupted within the TPN in the SCLC group, our analyses revealed an interesting finding. We found less connectivity in the anterior insula (figure 3), a limbic region that plays a critical role in high-level cognitive control as well as working memory and attentional processes [8].

Figure 3. Statistically significant lower functional connectivity in the anterior insula.

5. Conclusion

The current study suggests an overall cognitive deterioration in the SCLC after chemotherapy treatment that could be characterized by the disrupted functional connectivity within the DMN and the TPN. Future studies should explore how these alterations are related to cognitive performance, cancer itself and age.

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