Advanced neuroimaging techniques in the clinical routine: A comprehensive MRI case study.

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Abstract

Neuroimaging with Magnetic Resonance Imaging (MRI) is one of the most useful tools available to study the human brain in vivo. Several techniques provide insights into the human brain's structure, function, and connectivity. The aim of this study is to showcase the feasibility of employing advanced neuroimaging techniques within the clinical routine in a patient with a neurological disorder. An 83 years old male patient with right motor aphasia and somatosensory impairment underwent a clinical and advanced neuroimaging MRI protocol with 3D-T1, FLAIR, diffusion weighted and tensor imaging, and resting state functional MRI. Advanced neuroimaging postprocessing was employed to perform cortical and subcortical brain segmentation, white matter fibers tractography, and functional connectivity (FC). These analyses revealed an impairment of the left posterior insular cortex that showed low cortical grey matter volume, high restriction in diffusivity maps, and an increased FC as a compensation mechanism. The results pointed towards a left insular cortex stroke and the patient was then admitted to neurology for hospitalization. This amalgamation of cuttingedge technology with clinical practice underscores the pivotal role of neuroimaging in the contemporary management of neurological disorders, heralding a new era of precision medicine tailored to individual patient profiles.

INTRODUCTION

Neuroimaging techniques have revolutionized our understanding and diagnosis of neurological disorders by providing unprecedented insights into the structure, function, and connectivity of the human brain. In the clinical environment, the integration of advanced imaging modalities has significantly enhanced the precision and efficacy of diagnostic assessments, treatment planning, and monitoring of neurological conditions. These techniques encompass a diverse array of methodologies, ranging from traditional structural imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) to dynamic functional imaging techniques like functional MRI (fMRI) [1,2]. Leveraging the principles of physics, mathematics, and neuroscience, neuroimaging in clinical settings enables clinicians to visualize pathological changes, localize lesions, elucidate neural circuitry dysfunction, and evaluate treatment responses with unprecedented accuracy and specificity [3,4].

Opensource neuroimaging software packages like FreeSurfer [5] and SPM [6] have enabled researchers worldwide to conduct brain studies to characterize brain structure and function in healthy subjects and patients with several neurodegenerative diseases. These tools have also increased the reproducibility of results, particularly when combined with publicly available datasets [7]. The automated processing methods in current neuroimaging tools require MRI scans acquired with high isotropic resolution (typically 1 mm) to minimize errors in threedimensional (3D) analyses such as segmentation or registration [8,9]. For this reason, most modern research neuroimaging studies include a structural MRI acquisition that requires high spatial resolution and MR contrast. T1-weighted scan acquired with the ubiquitous 3D magnetization prepared rapid gradient echo (MPRAGE) pulse sequence fulfills these requirements [10,11].

Segmentation of cortical and subcortical regions from 3D T1-weighted structural brain MRI scans is a crucial task in neuroimaging analysis, aiding in the study and diagnosis of various neurological disorders such as Alzheimer's disease and epilepsy. AdaBoost, an ensemble learning method, has emerged as a powerful tool for automating this process with high accuracy and efficiency, especially in the segmentation of the hippocampus [12]. The application of AdaBoost for hippocampus segmentation offers several advantages, including its adaptability to different imaging protocols and its ability to handle complex patterns in the MRI data.

Regarding structural MRI techniques, Diffusion tensor imaging (DTI) has emerged as a valuable technique in MRI, offering unique insights into the microstructural organization of white matter fibers in the human brain. In the clinical setting, DTI provides clinicians with a powerful tool for investigating neurological disorders, assessing disease progression, and monitoring treatment response [2,13]. One of the primary applications of DTI in the clinical environment is the assessment of white matter abnormalities in various neurological conditions, including traumatic brain injury, stroke,

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multiple sclerosis, and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [14]. Changes in diffusion parameters, such as fractional anisotropy (FA) and mean diffusivity (MD), can serve as biomarkers for axonal injury, demyelination, and neurodegeneration, aiding in the diagnosis and prognosis of these disorders [15]. Along with structural MRI, functional connectivity (FC) analysis using fMRI has emerged as a powerful tool for investigating the functional organization of the human brain in both health and disease [16]. In the clinical environment, FC holds great promise for elucidating the underlying neurobiological mechanisms of various neurological and psychiatric disorders, aiding in diagnosis, treatment planning, and monitoring of therapeutic interventions [17]. FC enables the assessment of temporal correlations between different brain regions, providing insights into the intrinsic functional networks that support cognitive, emotional, and sensory processes. By analyzing the coherence of spontaneous lowfrequency fluctuations in blood oxygen level dependent (BOLD) signals, FC and generally fMRI offer a noninvasive means to map functional connections within the brain and identify aberrant patterns associated with neurological conditions such as Alzheimer's disease, schizophrenia, Parkinson's disease, depression, and epilepsy [18,19]. For this reason, in the clinical setting, fMRI is employed to investigate alterations in FC associated with disease progression, cognitive decline, response to pharmacological treatments, and neurorehabilitation [20].
Neuroimaging studies linked the insula and cingulate cortices to interoceptive awareness [21]. Specifically, the anterior insular cortex has been considered as a hub that encodes and represents interoceptive information, and for this reason, it has also been defined as an interoceptive cortex [22]. From a microstructural point of view, the insula has a reciprocal neural link with the anterior cingulate cortex (ACC), which is related to physiological information and provides autonomic responses [21]. These regions are functionally linked within the salience network (SN), namely, a brain network critically involved in integrating highly processed sensory information with visceral, autonomic, and hedonic markers, to guide the own behavior [23]. This study aims to showcase the feasibility of employing advanced neuroimaging techniques within the clinical routine in a patient with a neurological disorder.

MATERIALS AND METHODS

Case Description and MRI Acquisition

An 83 yearsold male patient admitted to the emergency department underwent a neurological evaluation at "San Leonardo" hospital (Castellammare di Stabia, Italy), in order to investigate a motor aphasia and a right motor hemisyndrome he complained about. He presented motor rigidity (mainly in the lower limbs), lack of balance, and postural instability. MRI was acquired on a Magnetom Sola 1.5T scanner (Siemens Healthcare, Erlangen, Germany) and reviewed by an expert neuroradiologist (A.T). Informed written consent was obtained from the patient. A 16-channel head coil was employed with the following structural and functional MRI sequences:

- 3D T1-Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE), voxel size 1 × 1 × 1 mm3, Field of View (FOV) 256 × 256 mm, TR/TE/TI = 2300/2.64/900 ms.
- Diffusion tensor imaging (DTI), voxel size 1.5 × 1.5 × 4 mm3, TR/TE = 4400/77 ms, bvalue = 1000, 12 directions, acquisition time 1 minute and 19 seconds
- Resting state fMRI, sequence Echo Planar Imaging-Gradient Echo (EPI-GRE), voxel-size 2 × 2 × 3 mm3, TR/TE = 2000/50 ms, 125 measurements, bandwidth: 1796 Hz.

Data Analysis

For structural image processing, the parcellations of morphological T1-weighted 3D images of HC and the patient were performed with the FreeSurfer v7.1 toolkit [24]. Briefly, this processing includes spatial inhomogeneity correction, non-linear noise reduction, skull stripping, subcortical segmentation, intensity normalization, surface generation, topology correction, surface inflation, registration to a spherical atlas, and thickness calculation [25]. Consequently, the result was normalized by the ratio with the estimated total intracranial volume (eTIV). For structural images, to test differences in brain volume the following cortical and subcortical regions were selected: hippocampal, amygdala, ventricles, thalamus, basal ganglia, whole brain volume, and temporal cortex. These variables were contrasted against a normative population of 385 healthy control subjects provided by the NeuGRID2 consortium. All values are normalized on total intracranial volume.
DTI images were preprocessed with Syngo.via software (Siemens Healthineers, Germany) with a pipeline that provides denoising, eddy current correction, T1 coregistration, and deterministic fiber tractography reconstruction. Fractional anisotropy (FA), apparent diffusion coefficient (ADC), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) values were calculated for each tract.
Regarding functional image processing, resting state fMRI data were analyzed with functional connectivity toolbox (CONN) [26]. Functional and anatomical data were preprocessed using a flexible preprocessing pipeline [27] including realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation and MNI space normalization, and smoothing. Functional data were realigned using the SPM realign & unwarp procedure [28], where all scans were coregistered to a reference image (first scan of the first session). Temporal misalignment between different slices of the functional data (acquired in interleaved Siemens order) was corrected following SPM slice timing correction (STC) procedure [29], using sinc temporal interpolation to resample each slice BOLD timeseries to a common mid acquisition time. Functional

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and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure using SPM unified segmentation and normalization algorithm [30] with the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 8 mm full width half maximum (FWHM). In addition, functional data were denoised using a standard denoising pipeline including the regression of potential confounding effects characterized by white matter and CSF timeseries, motion parameters, and their firstorder derivatives, followed by bandpass frequency filtering of the BOLD timeseries [31] between 0.008 Hz and 0.09 Hz.

Seed based connectivity maps (SBC) and ROI-to-ROI connectivity matrices were estimated characterizing the patterns of functional connectivity with 138 HPC-ICA networks [26] and Harvard-Oxford atlas ROIs. FC strength was represented by Fisher-transformed bivariate correlation coefficients from a weighted general linear model (weighted-GLM), defined separately for each pair of seed and target areas, modelling the association between their BOLD signal timeseries.

RESULTS

MRI of the brain showed multiple areas of chronic vascular disease in the FLAIR sequence and hyperintensities in the DWI b1000 sequence located in the left insular cortex with related hypointensity in the ADC map. Freesurfer structural analysis revealed a regular value of total grey matter volume of 511986 mm3 contrasted in a normative dataset made of 385 ADNI healthy elderly controls (Figure 1), while the volume of the left insular cortex is lower than the right one (6075 mm3 vs 6770 mm3).

Besides the hyperintensity in left insular cortex from clinical DWI b-1000, the analysis of DTI and deterministic fiber tractography showed a regular representation of white matter tracts and regular values in the FA map. While MD, RD, AD and ADC maps of the left insular cortex showed lower values compared to the right one (Figure 2).

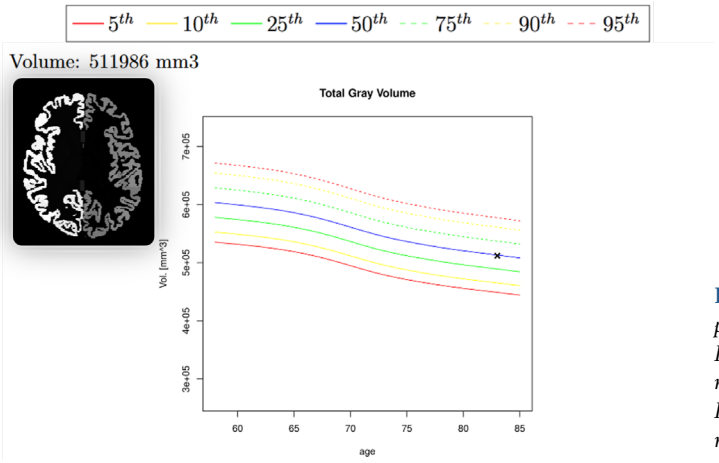

Figure 1. *Total grey matter volume of the patient; every colored line represents the Prediction Percentile of a normative dataset made of 385 ADNI healthy elderly controls. In this graph, the biomarker of the patient is represented by a black cross.*

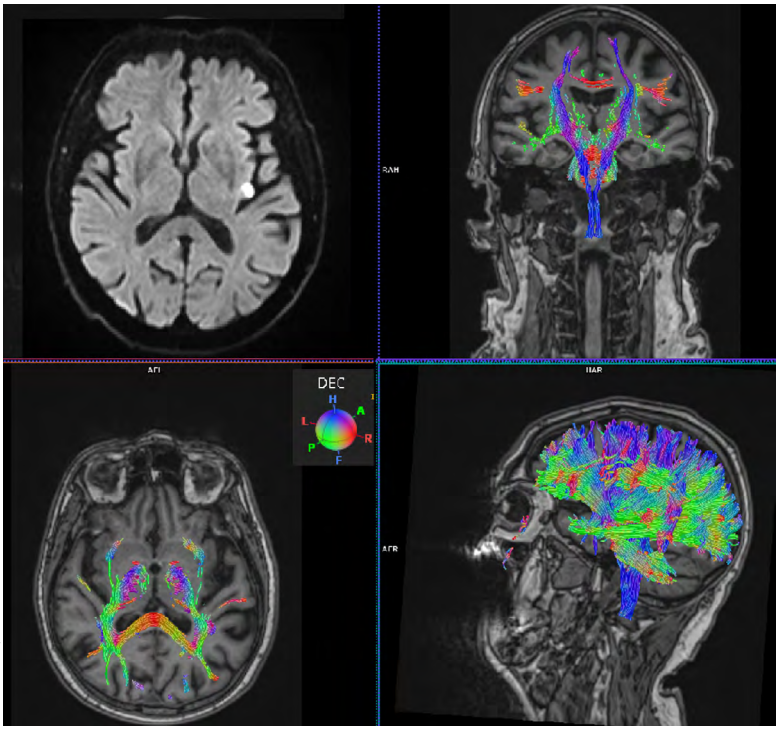

Figure 2. *DWI b-1000 image in top left side. Fiber tractography from DTI acquisition on a 3D-T1 MRI se-quence in top right and bottom side.*

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Regarding FC analysis, for each voxel, a separate GLM was estimated, with first level connectivity measures at this voxel as dependent variables. SBC using the left insular cortex as seed showed an increased FC with the right parahippocampal gyrus, subcallosal cortex, right insular cortex, left central opercular cortex, posterior cingulate gyrus, left pre and postcentral gyrus, and right middle frontal gyrus (Figure 3). While SBC using right insular cortex as seed showed an increased FC with bilateral parahippocampal gyrus, left insular cortex, right frontal pole, left and right precentral gyrus, left inferior frontal gyrus, and lateral occipital cortex (Figure 4).

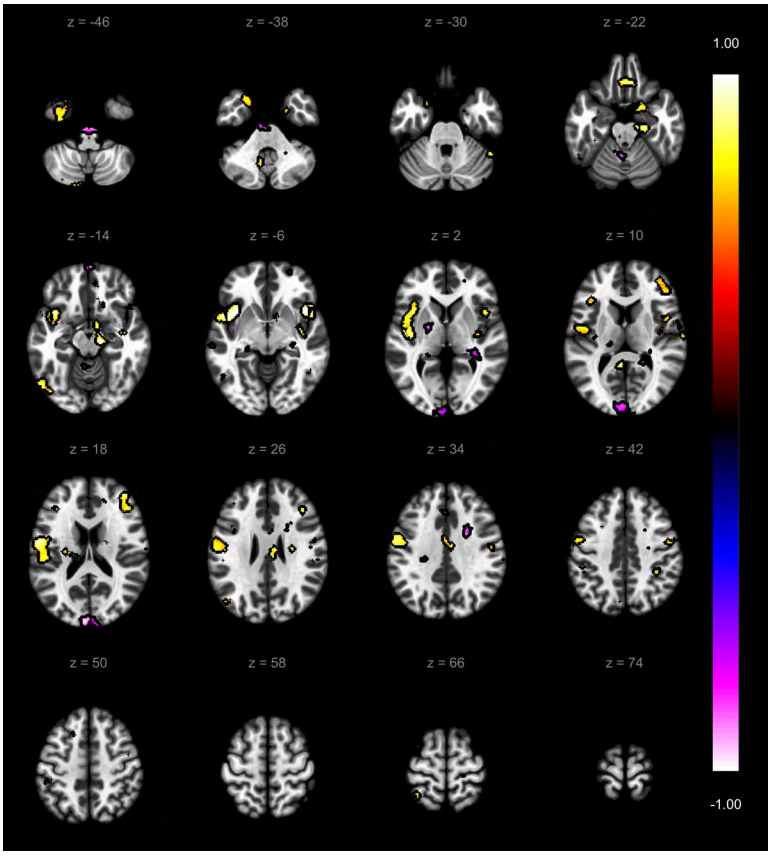

Figure 3. *left insular cortex seed-based connectivity (SBC) map that shows increased FC between left in-sular cortex and brain regions.*

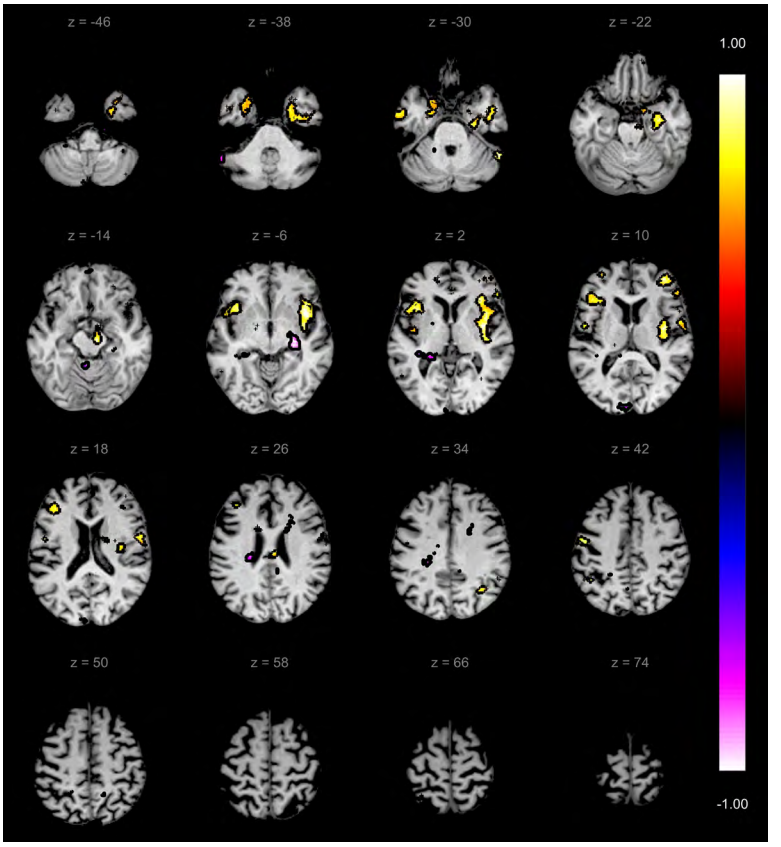

Figure 4. *right insular cortex seed-based connectivity (SBC) map that shows increased FC between right insular cortex and brain regions.*

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DISCUSSION

Our study presents a detailed investigation into the use of advanced neuroimaging techniques to diagnose and understand neurological conditions [32,33], with a focus on a patient with a left insular cortex stroke. The insula is involved in somatosensory functions and contributes to interoceptive processing. Moreover, the posterior insular cortex is a site of convergence of interoceptive and limbic system inputs [34]. Relevant to the central networks involved in learning are the neural connections of the rostral agranular insular cortex with the amygdala and hippocampal formation [35].

Freesurfer analysis revealed a regular value of total grey matter volume but when it focused on the volume of left and right insular cortex a sensitive decrease in volume was found in the left insular cortex compared to the right one. Decreased cortical volume, as observed in this case study, reflects the structural impact of stroke on the brain tissue. Cortical atrophy in the stroke is a manifestation of the loss of neuronal and glial cells due to ischemia. In the context of the insular cortex, this reduction in volume can significantly affect the brain's functional integration, given the insula's involvement in a wide array of motor and somatosensory processes [36].

Diffusion restriction, observed through DWI and ADC maps, is indicative of cytotoxic edema, which typically occurs in acute stroke. This restriction reflects the cellular response to ischemia, where water movement is hindered within the cell due to energy failure and subsequent ionic pump dysfunction. In the case of the insular cortex, diffusion restriction highlights the acute phase of the stroke, revealing the area of ischemic damage within this region's dense neural network. The findings of diffusion restriction in this area are consistent with literature that characterizes the acute responses of brain tissue to ischemic stroke [37]. While the normal representation of DTI and fiber tracts in the external capsula reflects the integrity of underlying white matter since the stroke is confined only in the insular cortex which is composed only of grey matter. The integration of diffusion restriction and decreased cortical volume findings underscore the comprehensive damage that an insular cortex stroke can inflict, from acute cellular changes to subacute or longterm structural alterations. These neuroimaging markers not only facilitate the localization and characterization of the stroke but also offer insights into the potential clinical outcomes and rehabilitation strategies [38,39].

Our results also showed increased FC in both the left and right insular cortex in SBC. The question of whether the insular cortex can show a pattern of higher functional connectivity when structurally damaged is intriguing and counterintuitive, given that structural damage often leads to decreased functionality or connectivity. The brain's ability to reorganize itself by forming new neural connections is well documented. Following structural damage, such as a stroke or traumatic brain injury, the brain often seeks to compensate for lost functions or to optimize remaining functionalities. This can lead to increased functional connectivity as part of the compensatory neuroplastic changes [40]. The insular cortex, with its diverse roles in emotional processing, autonomic control, and interoception, may thus exhibit enhanced connectivity with other brain areas in an attempt to maintain or recover its broad range of functions [41]. Structural damage may also reduce inhibitory signaling within the brain's networks, potentially leading to an increase in functional connectivity. This is because the loss of inhibitory control can allow previously suppressed connections to become more active, manifesting as increased connectivity [42].

The brain's response to damage often involves rerouting information through alternative pathways or recruiting additional regions to support the affected functions. This adaptation can appear as increased functional connectivity, reflecting the brain's effort to adapt to the impairment [43]. Specifically, regarding the insular cortex, evidence suggests that its structural damage can lead to altered connectivity patterns, potentially increasing in certain conditions as the brain adapts. This has implications for understanding recovery and rehabilitation processes [41,42].

FC contributes to the development of personalized therapeutic strategies and facilitates the evaluation of treatment efficacy over time [44]. Furthermore, FC MRI holds potential for predicting clinical outcomes, stratifying patient populations based on neurobiological profiles, and guiding interventions aimed at modulating dysfunctional brain networks. These networks could also be investigated with DTI which improves our understanding of brain connectivity and network dynamics in health and disease. By mapping the structural connectivity of the brain, DTI contributes to the elucidation of neural circuits underlying cognitive functions, emotional processing, and sensorimotor integration [45].

This amalgamation of cutting edge technology with clinical practice underscores the pivotal role of neuroimaging in the contemporary management of neurological disorders, heralding a new era of precision medicine tailored to individual patient profiles. As we delve deeper into the intricacies of these neuroimaging modalities, we unravel the complexities of the human brain and pave the way for innovative strategies in diagnosis, prognosis, and therapeutic interventions, thereby reshaping the landscape of clinical neuroscience.

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