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Research at the Medical Imaging Laboratory, CIBERSAM CB07/09/0031

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ABSTRACT – The Medical Imaging Laboratory is a research group within the Hospital General Universitario Gregorio Marañón. The main research line of the group is focused towards the development and exploitation of medical imaging techniques, including the development of new processing tools for image analysis in clinical and preclinical research. The group has a multi-disciplinary profile and a priority for translational research topics, derived from real problems faced by the clinical specialists. One of the main research areas is the development of technologies for molecular imaging, some of which have been transferred to the industry and are now among the top products of the market. These systems include high-resolution PET, CT and PET-CT. Over the last years the group has developed several software tools to enable quantification of multimodal brain images using morphometric and functional data. Some research applications of these hardware and software tools are illustrated in the paper.

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Resources

The Medical Imaging Laboratory was created in the early 90' as a small group embedded in the general research Department of the Hospital General Universitario Gregorio Marañón at Madrid. Parallel to the enormous expansion in the field of medical imaging, during the past decade the group underwent an exponential growth in human resources (from less than 5 to 35) and technical means. The facilities of the Neuroimaging Research Laboratory include a space of 350 m2 that include offices, electronic workshop, and animal imaging laboratory. The most significant facilities are molecular imaging scanners of several modalities, for preclinical use (high resolution CT, PET, MRI, SPECT, and Optical Imaging). Funding during the last six years has come from more than 30 national or international research projects granted to the group, from public or private programs, as well as from technology transfers to the industry.

Research

The main research line of the group is focused towards the development and exploitation of medical imaging techniques, including the development of new processing tools for image analysis in clinical and preclinical research. The group has a noticeable multi-disciplinary profile and its location within the Hospital warrants an excellent connection with clinicians and ensures a higher priority for translational research topics, derived from real problems faced by the clinical specialists. The multi-disciplinary composition of the group allows for a rapid validation of the results obtained in the research projects, also facilitating the technology transfer to industry. Some of the main research topics of the group in the field of neuroimaging are presented below.

High resolution imaging of laboratory small animals

Molecular imaging techniques applied to animal models are an excellent tool to study pathological processes. One of the main research areas in our group is the development of technologies for molecular imaging, some of which have been transferred to the industry and are now among the top products of the market. These systems include high-resolution positron emission scanners (PET) computerized tomography scanners (CT) and its combination (PET-CT) (Figure 1), nowadays one of the most useful tools for biomedical research in the area of molecular imaging[1,2]. PET enables the monitoring of biochemical processes "in vivo" at a molecular level. This technique has multiple applications in the development of new drugs, in the study of human diseases on animal models or in the characterization of the genomic expression and phenotypical changes caused by genetic manipulation (transgenic, knock-out or knock-in animals).

An ongoing imaging project deals with the cerebral damage produced by the new "design" drugs (MDMA, methamphetamine). The main objective of the study is to combine PET and CT techniques to evaluate the damage to serotonergic neurons and to determine whether there is damage to dopaminergic neurons, taking into account factors such as sex, type of drug and dosage scheme. The two substances selected were MDMA and methamphetamine, the former with a clear preference for the serotonergic system and perhaps for the dopaminergic system; and the latter with a preference for the dopaminergic system[3]. With the help of high-resolution animal PET-CT we can correlate serotoninergic and dopaminergic changes with changes in brain function and with its exact location in the brain. Furthermore, the study aims to determine to what extent the neurons may recover from the damage induced by MDMA.

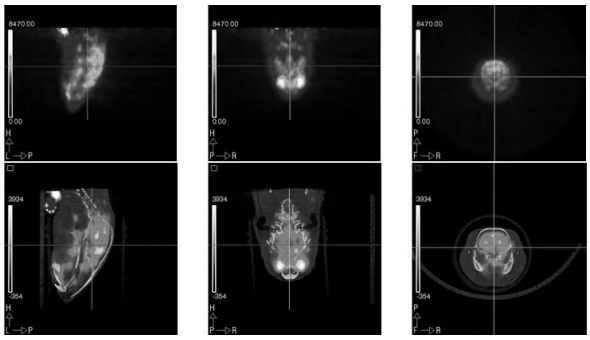

Figure 1. An illustration of molecular imaging. Triplanar view of an 18F-FDG PET rat study fused with a CT of the same animal. Images were acquired with the VrPET/CT, a system developed in our group.

Brain Imaging quantification

Over the last years the group has developed several software tools to enable quantification of multimodal brain images using morphometric and functional data. One of these software tools is based on the Talairach proportional grid system[4,5]. Using this tool we can benefit from the anatomical information of structural images to quantify functional images that have poor spatial resolution, like such as PET or perfusion (cerebral blood volume) scans (Figure 2).

The Talairach quantification tool is an application of the Talairach proportional grid system[6], used as a method for semiautomatic segmentation and analysis of MRI and functional images (PET, or Cerebral Blood Volume maps obtained by MR Perfusion weighted images). The method can be described as a multimodal application where the anatomical information of the MRI is used to build the Talairach grid and a co-registered functional image is superimposed on the same grid. By doing so, the Talairach-normalized tessellation of the brain is directly extended to functional images, allow-

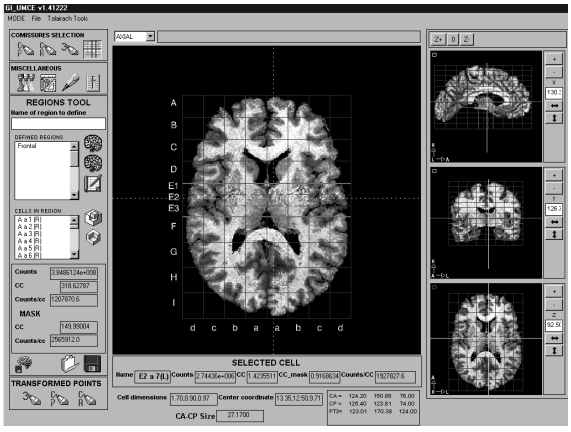

Figure 2. A screenshot of the software tool developed for volumetric and functional quantification of brain images. The triplanar view shows a Talairach grid built upon an MRI and a co-registered PET superimposed for quantification. For each of the 1,065 cells of the grid, volume and metabolic data is obtained for each brain tissue (total or WM, GM, CSF separately).

ing for a convenient regional analysis of volume and activity rates of brain structures, defined in the Talairach Atlas as sets of cells. This procedure requires minimal manipulation of brain geometry, thus fully preserving individual brain morphology. The brain standardization proposed in the Talairach grid system begins with a reorientation centered on the anterior and posterior commissures and the inter-hemispheric plane as the vertical axis, followed by a piecewise linear transformation that produces a tessellation of the brain into a 3D grid of 1,056 cells representing homologous brain regions across subjects. This subdivision of the brain according to the Talairach grid system allowed us to use it as the basis for a segmentation method for inter-subject comparisons, by defining brain regions of interest (ROI) as sets of 3D volume grid cells or 'boxels'. Following this procedure for defining ROI's we have been identified over 20 brain regions, from which we can obtain volume data for each tissue (Gray Matter, White Matter, and CSF), metabolic activity (PET) or perfusion (cerebral blood volume), for the whole brain parenchyma or separately for each tissue. Using this tool, we obtain data for more than 400 anatomical and functional variables[4,5]. This software have been used in numerous publications related to structural and functional alterations of psychiatric patients.

Effect of spatial normalization on voxel-wise studies

In pathologic brains with morphological alterations, the process of spatial normalization, as performed by Statistical Parametric Mapping (SPM) methods, may introduce a confounding effect in the measurement of functional (metabolic) activity data. We have investigated the effect of the spatial normalization of PET images, using MRI and PET studies of schizophrenic patients and controls[7]. Using the Talairach-based segmentation tool mentioned above, and manual segmentation, we measured regional metabolic activity in the untransformed brains and after their spatial normalization. We observed that the spatial normalization has little effect for large ROIs, such as the main brain lobes, even in brains showing pronounced morphological abnormalities. However, smaller structures as the caudate nucleus show a considerable change in metabolic activity values after normalization. This normalization bias is much larger in patients than in controls, and may lead to artifactual differences between both groups if the data are assessed by means of voxel-wise methods (SPM). We concluded that spatial normalization of the PET images of pathologic brains may introduce a potential source of error that should be taken into account in the analysis of functional data, in particular, when studying small brain nuclei as the caudate[7].

Neuroimaging studies in neurogical and mental diseases

In the field of medical imaging, the neurogical and mental diseases are one of the most typical examples of problems which require a multidisciplinary approach. Following a multimodality strategy to describe structural and functional brain alterations, in our research group we make use of the following techniques: structural imaging (MR, CT), for volumetric and morphometric studies; magnetic resonance spectroscopy (MRS), for measurements of some neural metabolites (N-acetil-

aspartate, creatine, choline, mio-inositol); perfusion, to measure microvascularization of cerebral tissue; diffusion tensor imaging, for measurements of White Matter anisotropy and tractography; and PET imaging using 18F-FDG as tracer, for measurement of glucose metabolism as a marker of neuronal activity.

Schizophrenia

The interest of quantitative data extracted from the neuroimaging studies in schizophrenia derives from multiple previous findings of groups of schizophrenic patients who show functional and structural brain alterations (e.g., atrophy of frontal cortex), sometimes related to clinical manifestations (predominating symptoms, evolution, pharmacological response) or to treatment. To generate accurate quantitative data, we measure the volume of the main brain lobes and their tissues (WM, GM and CSF), exploring the structural alterations detectable in chronic and recent onset patients. Among the key findings in our studies, we have found significant clinical and biological differences between treatment resistant and non treatment resistant schizophrenia patients[8]. These differences included greater clinical severity in the treatment resistant sample at baseline, and different baseline anatomical (volumetric) and electrophysiological (response to P300) parameters, together with longitudinal changes in cerebral volumes after treatment with atypical neuroleptics. The structural differences showed a significant degree of sensitivity and specificity, which supports the existence of a distinct subgroup of patients with marked frontal deficits and a poorer response to treatment within the spectrum of schizophrenia[8].

Alzheimer's disease

An early diagnosis of AD and its discrimination against other types of dementias (Lewy, fronto-temporal) are key issues to establish the appropriate treatment, the prognosis and a forecast of the forthcoming social needs of the patient. To achieve an earlier and more reliable diagnosis, a combined used of several imaging techniques have been proposed, with the aim of detecting early changes associated with the disease. In order to detect structural and functional alterations, 18F-FDG PET images are used in combination with four MRI techniques: 1) Anatomical image sequences T1 and T2, for volumetric measurements; 2) spectroscopic studies, to assess the biochemical changes in neurological metabolite markers such as N-acetyl-aspartate, Choline, and Creatine; 3) perfusion studies, to assess the functionality of parenchymal microvasculature and 4) DTI studies, to asses the integrity of white matter tracts. Preliminary results show lower volumes of GM and less blood volume flow in the temporal lobe of patients with severe dementia symptoms compared with patients with mild dementia, suggesting that we can distinguish between different degrees of cognitive impairment at early stages of AD[9].

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