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Neurosurgery planning in rodents using a magnetic resonance imaging assisted framework to target experimentally defined networks

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ABSTRACT

Background and objective: Meaningful targeting of brain structures is required in a number of experimental designs in neuroscience. Current technological developments as high density electrode arrays for parallel electrophysiological recordings and optogenetic tools that allow fine control of activity in specific cell populations provide powerful tools to investigate brain physio-pathology. However, to extract the maximum yield from these fine developments, increased precision, reproducibility and cost-efficiency in experimental procedures is also required.

Methods: We introduce here a framework based on magnetic resonance imaging (MRI) and digitized brain atlases to produce customizable 3D-environments for brain navigation. It allows the use of individualized anatomical and/or functional information from multiple MRI modalities to assist experimental neurosurgery planning and *in vivo* tissue processing.

Results: As a proof of concept we show three examples of experimental designs facilitated by the presented framework, with extraordinary applicability in neuroscience.

Conclusions: The obtained results illustrate its feasibility for identifying and selecting functionally and/or anatomically connected neuronal population *in vivo* and directing electrode implantations to targeted nodes in the intricate system of brain networks.

1. Introduction

Neurosurgical methods for precise targeting of brain nuclei are necessary to many experimental designs in current neuroscience. For instance, multiple electrophysiological recordings (from tens to hundreds of locations) are now possible with silicon probe technology. Simultaneous recording from multiple brain targets is fundamental to unveil the rules of information coding in such a system which implements a

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highly distributed and parallel processing. These technologies can be applied both *in vivo* and *in vitro* in live tissue. For *in vitro* recordings, the preparation of brain slices containing interconnected neuronal populations is critically limited by the lack of specific information on fibers trajectory. Thus, cutting brain tissue commonly results in the dissection of most, if not all, long-range axonal connections. Another example of current interest in neuroscience is the electric microstimulation of deep brain structures. This technique is being investigated in preclinical settings to uncover their functional principles and exploit their full clinical possibilities [1–13]. Stereotaxic neurosurgery is particularly relevant to deep brain stimulation since the precise location of the stimulated cell population will determine the functional outcome [14,15].

There are two leading procedures for targeting specific brain structures. The first one is an atlas-guided technique based on the combination of an anatomical atlas with a stereotaxic frame. The main drawbacks of this method are the lack of three-dimensional information for the electrode insertion, the inaccuracy due to biological variability in size and shape among subjects, and the lack of specific atlases for all animal species and particular ages (for instance, from development to aging). Although inter-individual variation is reduced in experimental animals [16], especially in those lissencephalic as rats and mice [17], the lack of three-dimensional information and age and species-specific atlases hampers the precision in many experimental designs.

The second methodology is based on magnetic resonance imaging (MRI) guidance. This approach brings as major advantage the possibility to apply personalized surgical procedures and coordinates in three dimensions [18]. The inherent disadvantage of this approach is the utilization of two different devices, the imaging system and the stereotaxic frame, using consequently, two different reference systems. This problem has been solved in the past by recognizing in the images several tissue landmarks and using their relative position to determine the brain orientation in the stereotaxic frame [19]. Alternatively, recent work has exploited the idea of placing external landmarks, such as bars or cannula filled with paramagnetic material [16,20]. These landmarks are easily detectable in the MR image and are used to obtain the transformation parameters between the two reference systems. Regardless of the strategy, both reference systems need to be registered [21]. The process of obtaining the transformation parameters for the registration can be done manually or automatically by means of cost-function algorithms, and several registration strategies can be found in recently published papers [22–26].

In the case of rat brain region-wise studies, most solutions assume as a *de facto* model the anatomical atlas developed by G. Paxinos and C. Watson in 1982 [27]. For instance, Schwarz et al. [28], Cai et al. [29] or Hjornevik et al. [30] developed their respective rat brain atlases taking as reference the Paxinos and Watson model. In [30] it was possible to combine the developed rat brain atlas with both Positron Emission Tomography (PET) and MRI, but involving manual coregistration. Schwarz and collaborators [28] presented a framework for functional MRI (fMRI) whereby it was possible to register automatically anatomical and functional images to a digital version of the Paxinos and Watson rat brain atlas. Besides the version of Schwarz et al., other digitalizations of Paxinos and Watson atlas attempt to improve the label coregistration accuracy using Principal Components Analysis [29,31].

Another interesting approach is presented by the Allen Developing Mouse Brain Atlas [32]. Its tool elegantly provides a characterization of gene expression in the brain beginning with mid-gestation to aging, in conjunction with an online database and annotated reference atlases.

Other methods involve spatial normalizations to a common stereotaxic space [33]. The current trend is given by whole brain registrations, as they allow inter-subject studies and extends the research to a higher level by giving the possibility to compare among populations. Such direction is followed in Schweinhardt et al. [34], who used the SPM software package (SPM99, Wellcome Department of Cognitive Neurology, London, United Kingdom) to implement an approach to register functional MR images to a rat brain template based upon anatomical landmarks present in T2-weighted images. Anatomical correspondences in the two image spaces were identified and used in a label-based affine spatial transformation. However, this forces to identify as many anatomical landmarks as possible to achieve a better approximation. This method relies on the biological observation that the skull shape and size of rat brain are essentially the same as long as their weights are within certain range [19].

In this work we are presenting a virtual space to assist sophisticated experimental designs and surgery planning in rodents using functional and anatomical information extracted from MRI, in addition to general cartographic information provided by an integrated brain atlas. Importantly, experimental designs can be planned based on both, average group-level imaging results or individualized results for specific subjects. Imaging data used to guide electrode implantations, orientation of brain slicing for *in vitro* experiments or complex surgeries in general, include functional MRI (fMRI), diffusion tensor imaging (DTI) and manganese enhanced MRI (MEMRI), just to mention some examples. The possibilities opened by the developed framework for the study of rat brain circuits *in vivo* are illustrated, as a proof of concept, in three examples of functional and anatomical connectivity experiments based on electric stimulation-driven fMRI and MEMRI neuronal tract-tracing.

2. Materials and methods

All computational procedures have been written using MATLAB R2009b (The Mathworks, Inc., Natwick, MA, USA). The FSL (FMRIB Centre, Oxford, United Kingdom) and SPM (SPM8, Wellcome Department of Cognitive Neurology, London, United Kingdom) packages have been used for preprocessing and statistical analysis. All experiments were approved by the local authorities (IN-CSIC) and were performed in accordance with Spanish (law 32/2007) and European regulations (EU directive 86/609, EU decree 2001-486).

2.1. *Electric stimulation functional MRI*

Urethane anesthetized (1.3 g/kg) Sprague-Dawley rats (250–300 g) were implanted with platinum-iridium electrodes