I. Introduction

Performing neuroimaging on awake and freely moving animals could bridge the gap between preclinical and clinical studies in neuroscience and even pave the way to a powerful association of behavior studies and real time neuroimaging. To overcome anesthesia's potential biases on brain processes, approaches have been developed, mainly focusing on micro-PET devices [1], [2]. Although offering a real potential to image awake rodents, these techniques limit the field of exploration for the animal, which prevents the opening to most behavioral studies. The MAPSSIC project proposes a complementary approach aiming to locally measure the uptake of PET radiotracers in targeted brain structures using a wireless implantable microprobe [3] while the animal remains freely moving. This probe is capable of detecting β^+ particles before their annihilation, taking advantage of their limited range in brain tissues (less than 2mm, for ^{11}C), allowing to study exclusively the structures of interest. Compared to the micro-PET approach, this device offers a total autonomy to the rodent during behavior studies. We first describe the overall structure of this probe before presenting Monte Carlo simulations of an *in vivo* imaging acquisition. This study aims to determine the ability of the device to report the uptake and quantify the specific signal in a structure of interest based on local measurements using established kinetic models.

II. Material & Methods

Device description: The probe relies on two 14700 µm × 610 µm × 200 µm CMOS Monolithic Active Pixel Sensors (MAPS) glued back to back, containing 128 × 16, 50 µm × 30 µm binary pixels readout using an adjustable rolling-shutter. The probe is mounted on a µ-PCB card and the digital signal is forwarded through a flex cable to a micro controller carried by the animal on a backpack. The wireless communication to a remote computer is ensured by a radio frequencies module (figure 1).

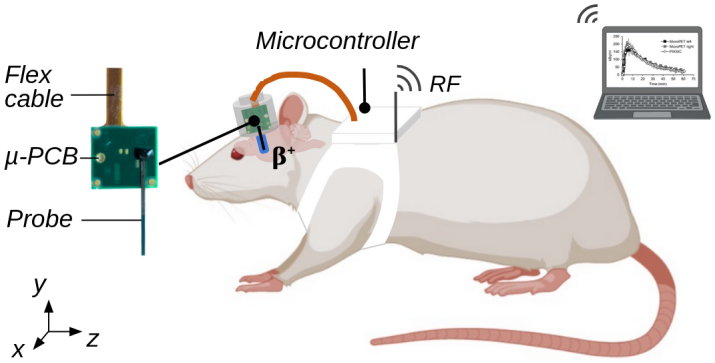

Fig. 1: Schematic view of the MAPSSIC device worn by a rat with the probe, the µ-PCB card, the micro controller and RF module communicating with a remote computer

Monte Carlo study: In order to confirm the ability of the probe to record kinetic and spatial information in an *in vivo* environment, we simulated a neuroimaging acquisition using [^{11}C]Raclopride, a radiotracer antagonist of D_2 dopamine receptors commonly used for research on schizophrenia and addictions, disorders that could benefit from behavior neuroimaging studies. A whole body anatomical rat phantom [4] was used with voxels of 100 µm sides in the skull area. Two silicon parallelepiped, simulating the probes, of dimensions 0.45 mm × 9.5 mm × 0.65 mm (xyz) were inserted in the striatum (probe 1), structure of interest in our study, and in the cerebellum (probe 2), structure used as a reference for the non-specific signal. Simulations were run applying [^{11}C]Raclopride time-activity curves (TACs) of anesthetized rats, corresponding to a bolus injection of 9 MBq. These TACs were generated from one hour long dynamic micro-PET acquisitions performed on 3 rats using regions of interests (ROI) for different structures of the rat anatomy. Alternative TACs of the striatum were also generated in order to simulate decreases of 5 % to 30 % of the Binding Potential (BP_{ND}) using the Simplified Reference Tissue Model (SRTM) [5] with the cerebellum used as the reference region. This was done in order to assess the capacity of the probe to accurately quantify variations in BP_{ND} consistently with micro-PET techniques.

III. Results

Approximately 30 minutes after the start of the simulated acquisition, 89 % of events recorded in the probe 1, result from direct detection of positrons (76 % for probe 2). Moreover, the harderian glands, known for being an important source of noise in [^{11}C]Raclopride micro-PET procedures, contribute to less than 1 % of the total events measured. More than 93 % of the probe 1 signal is contained in the first 2 millimeters surrounding the probe as shown in figure 2.A displaying the emission position of the detected particles. This proves that the signal provided by the device is based on local information as expected.

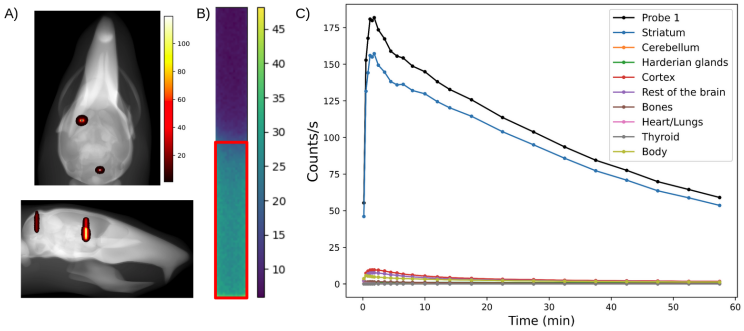

Fig. 2: A) Heat map showing axial (top) and sagittal (bottom) views of the source positions of the detected particles, B) simulated image of 1 min. integration, 27 min. after the injection and the ROI used to study the striatum (red box), C) Simulated count rates in the ROI (black line) and organs contributions (colored lines), during a one hour acquisition.

Figures 2.B shows an image of counts recorded by the probe 1 over 1 minute. The difference in counts between the top and the bottom halves of the image corresponds to the cortex-implanted and the striatum-implanted parts of the probe, respectively. The spatial information provided by this image was used to identify a ROI to study the striatum uptake. Figure 2.C shows the signal recorded over one hour in the ROI and the contribution of each organ. Table I shows the BP_{ND} used as input to the simulations (derived from micro-PET TACs) and the BP_{ND} calculated using the probe simulated data. The BP_{ND} calculated using the probe data is around 22 % lower to the one used as input, due to the volume of the cerebellum being larger compared to the striatum. This can easily be corrected using effective volumes or a correction factor in the future. Nevertheless, the calculated decrease of BP_{ND} is actually consistent with the input showing an error of less than 4 % which demonstrates the capacity of the MAPSSIC probe to quantify variations of the specific signal.

Input BP_{ND}	Measured BP_{ND}	Error on BP_{ND}	Input BP_{ND} variation	Measured BP_{ND} variation
3.0941	2.3919	22.7 %	0 %	-
2.9394	2.2769	22.5 %	- 5 %	- 4.81 %
2.7847	2.1611	22.4 %	- 10 %	- 9.65 %
2.6300	2.0442	22.3 %	- 15 %	- 14.54 %
2.4753	1.9283	22.1 %	- 20 %	- 19.38 %
2.3206	1.8109	22.0 %	- 25 %	- 24.29 %
2.1659	1.6936	21.8 %	- 30 %	- 29.19 %

TABLE I: Comparative table of the BP_{ND} used as input for the simulation and the BP_{ND} measured on simulated probe data.

IV. Conclusion

We developed a probe dedicated to behavior neuroimaging applications based on the local measurement of β^+ radiotracers uptake.

First results from Monte Carlo simulations of an *in vivo* neuroimaging procedure confirm the relevance of information that the probe can provide. Spatial information allowed to explore a first image segmentation approach that has proven to be efficient in targeting specific brain structures and quantifying variations of the BP_{ND}, which allows the opening to longitudinal and comparative behavior neuroimaging studies. The MAPSSIC project is currently undergoing rapid developments as newly manufactured probes have successfully undergone physical tests and are scheduled for biological validation on rodents. This validation is planned based on comparisons with the micro-PET which is the gold standard.

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