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Research article

A multimodal imaging-guided software for access to primate brains

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ABSTRACT

Background: Imaging-guided access to the brain has become a routine procedure for various research and clinical applications, including drug administration, neurophysiological recording, and sampling tissue. Therefore, open-source software is required to handle such datasets in these specific applications.

New methods: Here, we proposed an open-source tool utilizing different imaging modalities for automating the steps to access the brain. This tool provides means for easily calculating the co-ordination of the area of interest concerning a specific point of entry. The source and documentation are available at this link.

Results: We have used this software for three different applications: electrophysiological recording, drug infusion in the nonhuman primate brain, and guided biopsy procedure in the human brain. We performed a neural recording of two monkeys' prefrontal cortex and inferior temporal cortex using this software in submillimeter resolution. We also applied our procedure for infusion in the putamen and caudate nuclei in both hemispheres of another group of rhesus monkeys with histological proof in one animal. More so, we validated this software in the human subjects that underwent biopsy surgery with the commercial software used in human biopsy surgery.

Comparison with existing methods: Our software uses different imaging modalities by co-registering them. This will provide structural details of the skull and brain tissue. We can calculate each brain region's coordination at the point of entry by re-slicing the images. Atlas-based image segmentation were implemented in our software. Three mentioned applications of our software in neuroscience will be further discussed in this paper.

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[1] Same amount of contribution.

Conclusion: In our procedure, working with different imaging modalities provides a precise estimation of the specific region in the brain related to the location of implants or stereotaxic frames. There is no limitation to using metal implants in this procedure.

1. Introduction

During intracranial interventions, guided access to specific brain regions is crucial in both research and clinical applications. Because of individual anatomical differences among subjects in primates [1], the need to use approaches for gaining more precision in performing surgeries and electrophysiological recordings is clear [2]. In animal studies such as rodents and non-human primate's traditional surgeries, brain atlases released from several animals were used in accessing the desired brain area [3-8]. After the experiment, post-mortem autopsies were used to validate the accuracy of accessing the target, with the obvious disadvantage of sacrificing the subject during the procedure (e.g. Ref. [9]). With the advent and prevalence of imaging technologies, pre-and post--validations are more easily conducted in vivo using different imaging procedures. Nonetheless, the goal of pinpointing the target location and/or guiding the procedure at hand still exists. During the surgeries for pharmacological drug manipulation, cell therapy, and gen delivery procedures, researchers need to know where the injecting cannula is following in the stereotaxic coordination or in the reference frame in which injecting cannula is displacing [10,11]. Although, the imaging techniques were used to guide the track of cannula penetration based on brain atlases [10,11], a software to calculate the precise track of penetration is highly needed in these surgeries. Similar requirements exist in the human biopsy, deep brain stimulation, and ablation surgeries. In all these procedures, reaching high levels of precision is highly favorable and most naturally ensures the reliability of procedures and the resulting findings.

In the chronic electrophysiological recording, electrodes proceed in the brain, then some implants including recording chambers are placed on the skull over the area of interest, which provides safety and support for the recording media [1,10,12–16]. The precise location of penetrated electrodes has to be defined based on the coordination of the recording chamber. One way is to put several markers in the chamber's coordination during MR imaging. The track of markers shows the path of electrode penetration in the MR images [1]. Using this method, the imaging should take place only after the surgery, which will result in the metal implants shadowing the region of interest during the imaging procedure [12–16]. So the software which overlays MRI and CT data to have detailed information on the bone and the brain tissue in a stereotaxic frame and calculates the angle and depth of penetration at each point of entry is highly applicable in chronic electrophysiological recording. Although there are commercially available software packages in the clinic, most of them are pricy and unavailable to some researchers. Some notable attempts have been made to increase the accuracy of surgeries by developing such software for the calculation of the track of penetration [1,12–16]. The statistical parametric mapping (SPM) toolbox is a general-purpose application. It needs to be customized for primate surgeries. Two other options, namely pyElectrode and SPLASh were the specific available tools for monkey studies. ClearPoint is another software used for gen delivery in primates' brain [17]. It is needed to have a precise view of both the brain tissue and implants on the skull or surgery stereotactic frame. Recently, color-labeled brain atlases have been released, which determine the region of interest very easily [18–24]. Atlas-based image
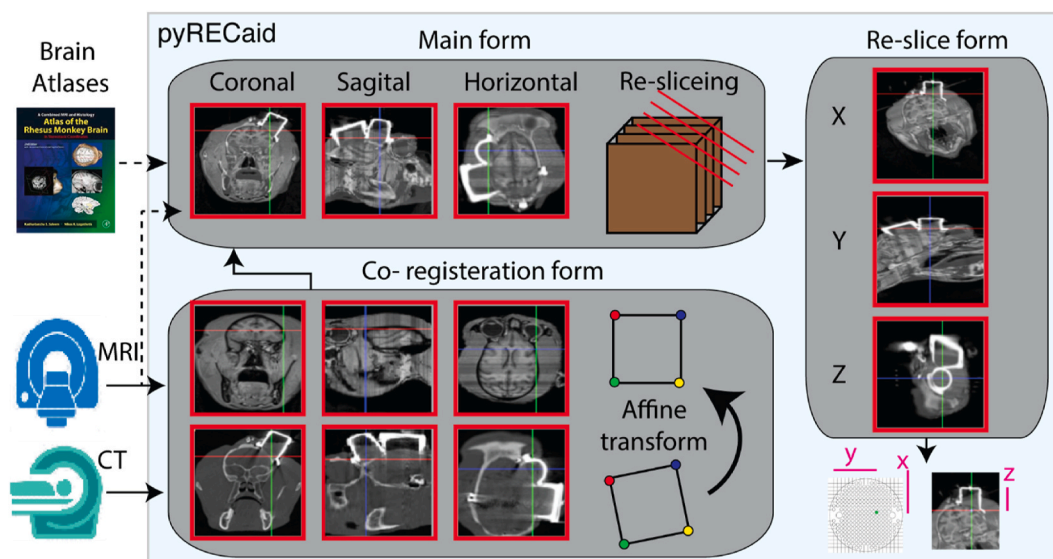

Fig. 1. The diagram of pyRECaid software. The software involves three main functional forms. The image data including MRI or CT were imported in both main and co-registration forms. In co-registration, images series were overlayed over each other by automated or manual procedures, and the results were sent to the main form. re-slicing images were extracted from image data in the main form. In the re-slice form, the precise information of the brain region will be present in any new coordination system.

segmentation on the image data of animals/humans is possible using these brain atlases. None of above-mentioned programs used different image modalities or atlas-based image segmentation. The present work offers a user-friendly solution using viable python 3.6 stacks for addressing these requirements in basic neuroscience and clinical setting.

2. Methods and materials

2.1. Requirements for image guided access to the brain

We have developed and successfully tested a helpful open-source software, available at the link. Our software can be used for imaging-based localized intracranial access, applicable to both chamber-free and chamber-based to a desired intracranial target (Fig. 1). The software provides tools for both handling different imaging modalities and looking into the brain in the desired direction. By co-registering of MRI and CT imaging modalities into a single coordinate system, it provided a useful tool for monkey/human brain surgeries as shown in Fig. 1. The tool offers features for re-sliced image series along the desired angle in the orientation of the recording chambers or a track for accessing the specific brain region as represented in Fig. 1. This ability calculates the angle and depth of insertion from a specified point on the skull to a certain target within the brain tissue. It is possible to add a chamber/marker to the image series for some applications of the tool. These features will provide all the necessities for image-guided access to any brain region.

2.1.1. pyRECaid software environment

All the requirements for a free install of the software are available in our GitHub link. All python repositories (PyPI and conda channels) as described in the guidelines of the GitHub can be installed freely. The software is thoroughly tested for the Ubuntu 16, 18, 20, Windows 10, and Mac platforms. Figure S1 depicts the application's main form, with different areas named in the caption. The user manual is available in the supplementary text and on GitHub. In the following, some relevant points regarding the application's design are explained, which we hope would help possible future developers to better understand the workings of the software.

2.1.2. Load image to pyRECaid forms

Raw image data of both MR and CT images must be in DICOM (Digital Imaging and Communications in Medicine) or NIFTI (Neuroimaging Informatics Technology Initiative) standard formats. DICOM file format is a series of data sets prefaced by header meta-information about the data collection setting [25]. Header tag information was used to classify series within each directory using the Pydicom library dataset object [26]. For handling the loading of such files, we used a 3rd-party python binding for Grassroots DICOM (GDCM) library (accessible on conda clinical graphics repository), which provided routines for easy decompression of images compressed with different protocols. The files within the directory are then grouped according to DICOM header information. NIFTI file format was used in clinical imaging and data were saved in a three-dimensional structure with a smaller header size and memory. Nibabel library is employed to handle NIFTI file formats. After selecting a specific folder to be opened by using "Load Folder" you will see the image series being loaded according to their ID. The series taken together during MR or CT imaging are grouped as a single entry in the list. After selecting one series from the list click on "Load" to read and transfer the series to the view panels.

Based on the patient orientation, the attribute of the DICOM/NIFTI format is read and placed in the panel for each orientation respectively, "Coronal", "Sagittal" and "Horizontal". In the cases, where the original image size doesn't fit the image box, linear interpolation from OpenCV was used for each panel. Instead of referring to different axes or planes by the abstract Cartesian coordinate, we adopted the more descriptive terminology of ML (Medial-Lateral), AP (Anterior-Posterior), and Depth similar to monkey brain atlases [7]. If the direction of images is not correct in panels the orientation can be changed to the correct way by "flip" and "swap" options. It is recommended to perform MR imaging before surgery using an MR-compatible imaging adaptor and CT imaging after surgery by chronic implants [27]. This procedure provides a stereotaxic coordinated view of MRI data and satisfactory results in co-registration as it helps to have the same reference frame for MR images and brain atlases [28]. For navigating along with different panels, when the operator rolls through each panel, a color line (see panels in Figure S1 e-g) gives a hint of the position of each plane in the panels (AP-depth or coronal, ML-depth or sagittal, and ML-AP or transverse/horizontal). When navigating in the image panel, the location is presented at the top-left of each panel. These values are distances from zero point, and the coordination of zero point after loading new data is the first image slice. It is possible to set a specific point as the new zero point. This reference point can be set based on brain atlases [28] or relative to extrinsic markers placed in the ear connector of the imaging adaptor [27]. The coordination values will be transformed using the new reference for comparative purposes by different brain atlases.

2.1.3. Co-registration of two image modalities

Each imaging modality shows the specific aspects of the biological sample, CT images are good at representing high-density tissues (skull + implants) and MR images are better at showing details of the soft tissue (brain). In the context of medical imaging, co-registration refers to the spatial integration of different imaging modalities into the same coordinate system. Different methods exist for this purpose, for example, with regard to the use of global or local, intrinsic (anatomical) or extrinsic (external markers introduced into the image space) information, and the criteria for the final fusion of the two series (how the integrated corresponding point in the result is decided based on the input) [29]. Imaging modalities differ in terms of their resolution (resolution viewed as raw points for height, width, and the number of slices) and the scale of the images produced which is inherently a technical issue. Here we adopted a manual procedure based on intrinsic or extrinsic local landmarks. Such manual matching of the CT and MR image series is previously shown to significantly enhance the precision of imaging-guided procedures [30]. A proper choice of a matching point is

completely essential for the quality of the result. For more details about the proper choice of intrinsic features and landmarks for co-registration, see Ref. [31] and also [29]. Our software provides the possibility of using CT images taken after surgery to determine the location of the chronic chamber.

Figure S2 depicts the Co-registration form of the application along with an example. The co-registration form will be opened by the related button in the main form. In the first step, two series (MR/CT) are loaded along with one another. The form includes three rows of image series. In this software, we provided two procedures for co-registration Manual and automated. The manual co-registration is based on spatial shift and rotation transformations in both image modalities. Automated co-registration is based on affine transformation to fit the second-row series on the first one. The result of co-registration is presented in the third row in the co-registration form in Figure S2. The affine transformation performs rotation, scaling, and the shift together. To estimate the affine transformation matrix, we need to manually landmark four points in each modality. For the sake of the resolution-difference problem, during the process, a hard-coded distance of 1 mm has been considered and the two series are made to conform to this distance. The missing values are interpolated by Spline using the Ndimage package. To remove insignificant probable noises caused by interpolation, the images are normalized to the 0–1 range, then a threshold is applied and points below the threshold are removed from the result. Also, to make better use of the advantages of each imaging utility, for each point in the resulting final series, the modality with maximum contrast is taken, resulting in bone-tissue information by the CT and brain-tissue information by the MR image series. It should be considered that the transformation was performed for the second image and there is no transformation or interpolation on the first image modality.

2.1.4. Change the coordination toward desired framework

Usually, the main form shows the images in the standard coordination. While entering the electrodes or tubes in the brain tissue is done in specific coordination related to the implant on the skull or stereotaxic surgery frame. Then, we need to find the region of interest in the new coordination. Re-slicing allows changing the coordination of images in a specific direction. Figure S3 depicts the Re-slicing form of the application. We can follow the track of penetration in 3 orthogonal panels in the re-slices form. The user can send over a point in the main form to the corresponding coordinates in the resliced view, which can be of assistance in determining the target. Upon running an instance of the program, the user interface by default drives the user to open a previously saved project or to start a new one by reading a series of MR and CT images from a selected directory. It is also possible to place a marker chronic access site with the desired size, location, and orientation. By inserting a marker, the user can acquire the target point and the required insertion angle from any point bound by the marker.

2.1.5. Atlas-based segmentation of image series

Recently high-resolution 3D brain atlases based on MRI imaging and histology were released for both humans [18,19] and monkey [20-24]. It is needed to register brain atlases on the image series of human/animal under study in order to locate the region of interest based on brain atlases. Similar to co-registration, segmentation refers to the spatial integration of different imaging modalities into the same coordinate system and similar methods exist for segmentation too. Figure S4 depicts the segmentation form of the application along with an example. The segmentation form will be opened by a related button in the main form. The segmentation form is similar to the co-registration form and includes three rows of image series. The first series belongs to brain atlases. The second series is the MR image of the subject under study. In this software, we provided two procedures for segmentations Manual and automated. The manual segmentation is based on spatial shift and rotation transformations in both image modalities. This type of segmentation doesn't work in most cases because of structural differences between animals. Automated segmentation is based on affine transformation to fit the second-row series on the first one (brain atlases). The result of segmentation is presented in the color-labeled area (if the used brain atlases are color-labeled) in the third row in the segmentation form in Figure S4. We used a 3D color labeled atlases of monkeys got published recently in this figure [24].

2.2. Acute neurophysiological recording

For neural recording experiments were performed on two adult male rhesus monkeys (Macaque mulatta). All the procedures such as surgeries, postoperative care, behavior studies, and management conditions were strictly in accord with NIH guidelines for the care and use of laboratory animals and the internal regulations on animal care issued by the IPM SCS committee for ethics. We obtained MR imaging (3.0 T MRI scanner; GE Healthcare) of monkeys. Custom-designed implants were fixed on the skull of animals for recording from both the prefrontal and temporal areas (for more detail, [27]). After surgery, CT imaging (Somatom Spirit; Siemens) was performed.

2.3. Pharmacological manipulation

Pharmacological manipulation procedures were performed on fourteen adult rhesus monkeys (Macaque mulatta) model of Parkinson diseases. All the procedures such as surgeries, postoperative care, behavior studies, and management conditions were strictly in accord with NIH guidelines for the care and use of laboratory animals and the internal regulations on animal care issued by the Royan institute committee for ethics. We obtained MR imaging (3.0 T MRI scanner; Siemens) of monkeys in MRI compatible adaptor. The locations of cell transplantation were determined based on the stereotactic reference frame.

2.4. Histology of monkey brain

The histological processing was performed to detect two specific cell markers Stem 121(Human specific cell marker) and Tyrosine hydroxylase (TH, dopaminergic neuron marker). The monkey brain was harvested six months after the last injection. All histological processing (section cutting and staining) was done in the Royan institute. The brain was removed and saved in a fixative solution with 10% formalin for three months at 4 °C. Tissue processing was done and representative areas were embedded in the paraffin blocks. Serial sections (40 µm thick) were cut on a sliding microtome sagittally through the putamen and caudate nuclei. Sections were processed for Stem121 and TH stains (Fig. 4d).

2.5. Human biopsy surgery

The head scan of MR and CT images were taken before the surgery. The head of the patient was fixed in a surgical stereotaxic frame (Leksell Stereotactic System, Elekta) in the same situations for both CT imaging and surgery. Using computer-assisted imaging the track of insertion of the sampling needle was determined by the neurosurgeon.
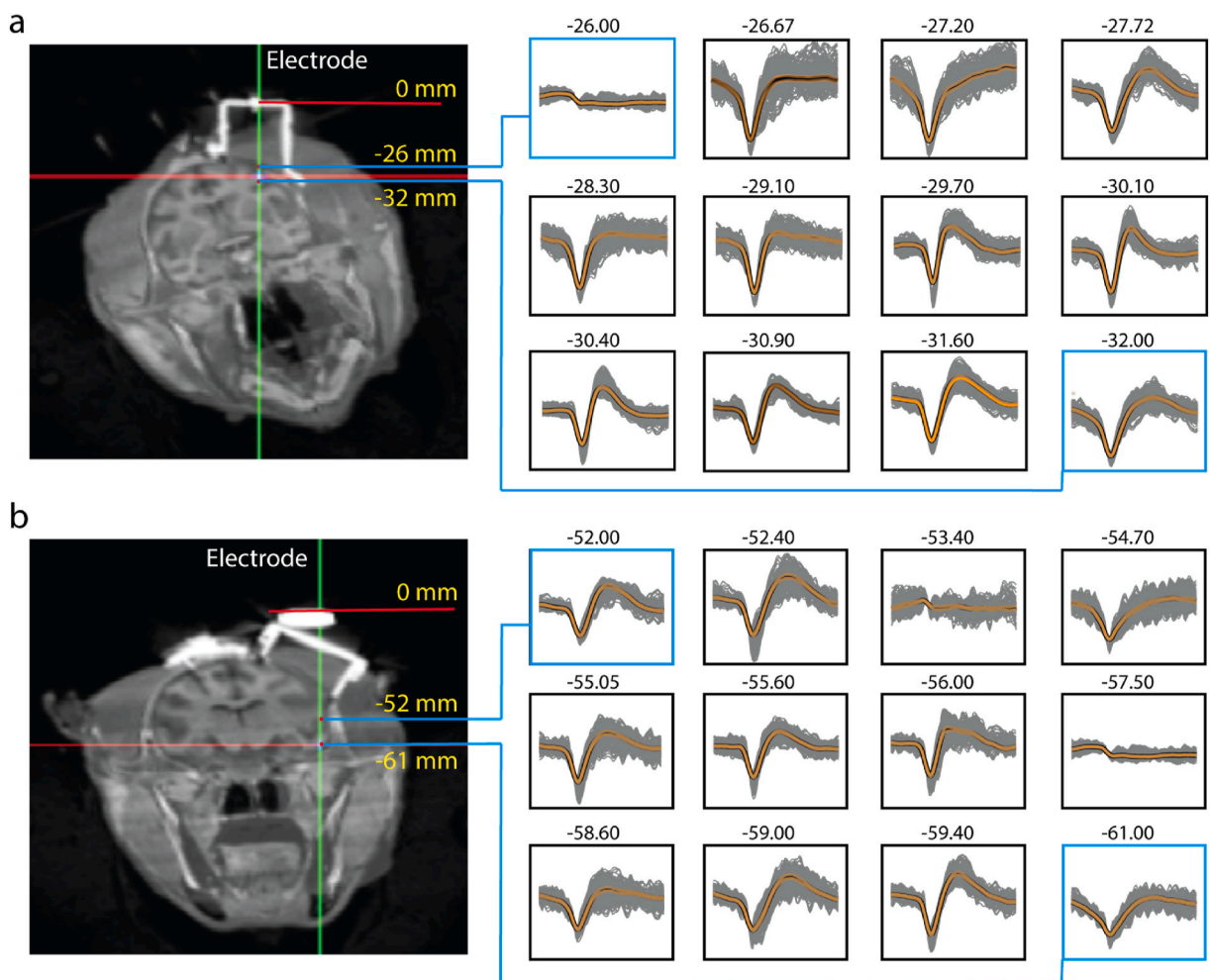

Fig. 2. The quality of pyRECaid application for Electrophysiological recording. The quality of neural data recording using pyRECaid software was evaluated after spike sorting in different depths for two recording chambers. a) In this panel the image coordination has changed over a chamber located on the prefrontal cortex. The panels in right show the quality of spiking activity was recorded. The yellowish line shows the sorted spikes in each panel. The distances were calculated from the top of the chamber for different depths: from −26 mm to −32 mm. The depth for each panel was written on the top of the panel. b) In this panel the image coordination has changed over the chamber located over the IT cortex. In this chamber, it is needed to penetrate electrodes in the angled view over the chamber. Similar to (a), right panels show the evaluation of software by recording in different depths. The distances were calculated form the base of manipulator in different depths: −52 mm to −61 mm.

3. Results

The pyRECaid software was designed and developed as an open-source tool for imaging-guided brain access, considering the existing needs for non-commercial options. We have used this software in three different applications: electrophysiological recording, pharmacological drug infusion in nonhuman primates, and biopsy sampling in humans. We proposed this software as a straightforward method for determining the location of electrodes during recording in two monkeys in different brain areas. Moreover, we have tested the software for targeting six regions in the subcortical areas in the brain of fourteen monkeys. Also, in collaboration with Shohadaye Tajrish Hospital, we have cross-validated the software in biopsy sampling of human subjects. Our experience with testing applications of this software in the ongoing projects was satisfactory and the intended functionalities were good at serving our purpose. Since the subjects of the mentioned experiments are currently under study, we cannot offer histological affirmations but electrophysiological results from typical targets show the compliance of the application in targeting these areas. We have illuminated our software's capability and precision in determining the target area by the quality of recording in the electrophysiological recording. In the pharmacological manipulation, the recovery of animal performance compared to control groups shows the effectiveness of our manipulation. Moreover, PET scan imaging showed the representation of implanted cells in the target area (the result of this project is under publishing by our collaborator elsewhere). Our application in the biopsy surgery on humans was complementary to commercially available software in the hospital and validated by neurosurgeons.

3.1. Electrophysiological recording in nonhuman primates

Electrophysiological recording were performed on two adult male rhesus monkeys (Macaque mulatta) in two different areas prefrontal and temporal areas (for more detail, [27]). MR imaging of monkeys was done before surgery. Custom-designed implants were fixed on the skull of animals for recording. After surgery, CT imaging was performed. Both image modalities were imported into the pyRECaid software in the co-registration form. As MR images were given by MR compatible stereotaxic frame, we transformed CT image series on the coordination of MR images by co-registration option (points on both ears and eyes were used as landmarks in automated co-registration). In one monkey two separate chambers were implanted on the skull to record the prefrontal cortex and inferior temporal cortex (IT) (Fig. 2(a,b), Figure S4 shows neural recording from the second monkey). For each chamber, all the data was re-sliced to the chamber's coordination in two different re-slice forms. The re-slice on the prefrontal chamber was done by angle
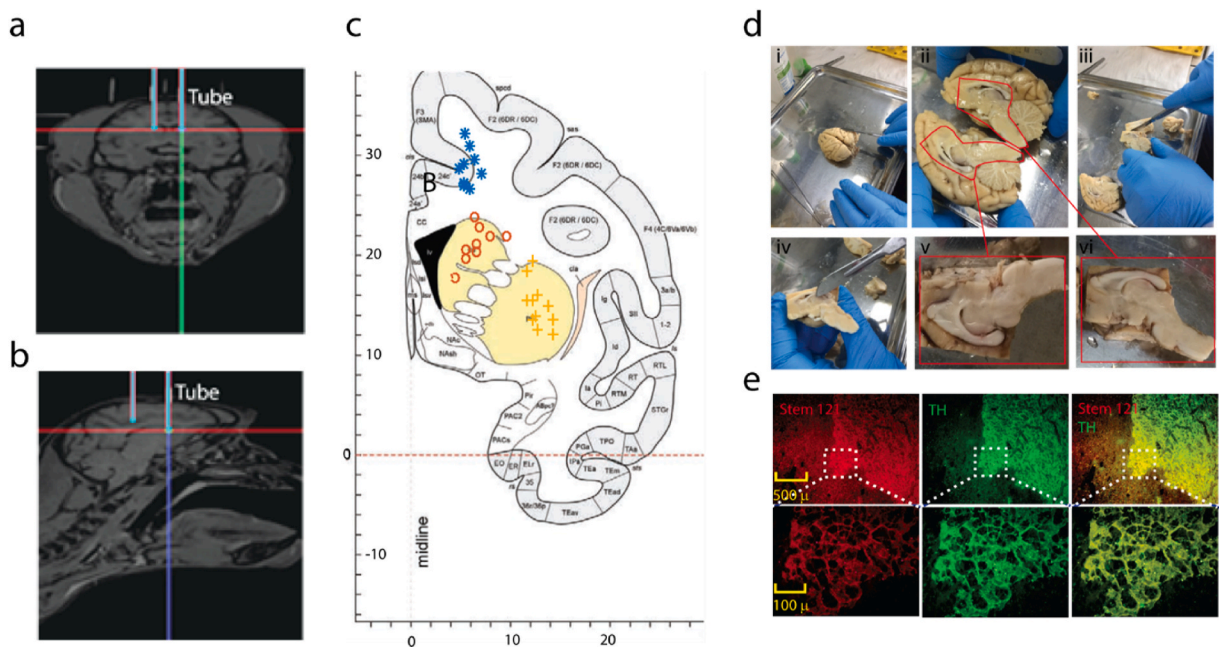

Fig. 3. Pharmacological manipulation using pyRECaid software. The infusion cannula was inserted in six different locations of basal ganglia in two hemispheres. a) This panel shows the coronal section of cannula penetration to reach the posterior part of the caudate nucleus in both hemispheres. b) This panel shows the sagittal section of cannula penetration in order to reach the putamen and caudate in the left hemispheres. c) This panel shows the coordination for infusion in the putamen (+), anterior (o) and posterior (*) part of caudate. The coordination of all animals in one hemisphere was placed on the atlas's coordination. d) Histology procedure for one animal in cell transplantation experiment. i-iv) Extracting putamen and caudate area from hole brain tissue. v-vi) Extracted target area (containing caudate and putamen) for left (v) and right (vi) hemispheres. e) Immunofluorescence staining of extracted target area. Representative images of double staining for the human cell marker Stem-121 (red) and a dopaminergic marker Tyrosine hydroxylase (TH, green) after six month of cell transplantation surgery. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(AP = 0°, ML = 25°, DV = 0°) parallel to the chamber direction (Fig. 2a). The re-slice on the IT chamber was done by angle (AP = −6°, ML = 7°, DV = 0°) perpendicular to the manipulator's base (Fig. 2b). Then, the projects were saved to recover for different recording sessions for each recording day separately. The estimated location by our software was cross-validated by neural recording in different depths. Electrophysiological evidence for the location of recording in different depths is shown in Fig. 2. The existence of neural activity in the target location is verified visually and audibly by the experimenter [32]. The quality of neural data was evaluated after spike sorting in different depths. We used the fixed threshold, 4 mv, for spike detection in all panels in Fig. 2. By changing the depth of the electrode, based on the structure of gray and white matter, the pattern of spiking activity has been confirmed with <0.1 mm accuracy.

3.2. Pharmacological manipulation of primate's brains

The pyRECaid software was used for drug manipulation in anesthetized animals. The acute infusion procedure is similar to electrophysiological recording where the injecting cannula is instead of recording electrodes. The location of injection can be verified by recording the neural activity of the target location using custom-made injectrodes [33]. We tested our software in the anesthetized monkeys (n = 14) within the stereotaxic frame (Toos BioResearch co. Iran). Using the stereotaxic coordination, the infusion cannula was inserted in six different locations of basal ganglia in two hemispheres for each monkey (Fig. 3a–c, Table 1). The region of interest and the direction of penetrations were determined using the pyRECaid software. Table 1 reported the coordination of specific locations in all animals. We transplanted human dopaminergic progenitor cells in the putamen and caudate of the animal model of Parkinson's disease. After six months of follow-up, we performed histological analysis to evaluate the maintenance and maturation of transplanted cells in the targeted putamen and caudate areas (Fig. 3d) with Stem121 and TH staining (Fig. 3e). Our results rebuild those specific human markers, (Stem 121) and dopaminergic specific marker (TH), which were co-expressed in transplanted cells directly in the targeted areas (Fig. 3e). The follow-up behavioral examinations showed increased animal performance after surgery and treatment. Also, the SPECT- CT scan shows the location of transplanted cells in the location of basal ganglia after transplantation (the result of this project is under publishing by our collaborator elsewhere).

3.3. Human biopsy pre-surgical planning

In dealing with certain types of brain tumors, the suggested medical procedure is to take a sample of the tumor for pathological examination. This procedure is usually performed by neurosurgeons in an image-guided operation using commercial software (Inomed, Germany). Our software was verified in one patient after surgery. The head scan of MR and CT images were taken before the surgery. The head of the patient was fixed in a surgical stereotaxic frame (Leksell Stereotactic System, Elekta) in the same situations for both CT imaging and surgery. Using computer-assisted imaging the track of insertion of the sampling needle was determined by the neurosurgeon. In this procedure, the CT image with the Leksell frame is the reference, and calculations were done based on that (Fig. 4a–d). The neurosurgeon determined the location of the tumor in the MR image relative to the AC-PC (Anterior Commissure and Posterior Commissure) line (Fig. 4c). We used co-registration to combine both image modalities. Then, the re-slices option was used for recalculation of track for insertion biopsy probe in a direction parallel to AC- PC line (Fig. 4d). Our software was tested and has shown satisfactory submillimeter accuracy compared to commercial software (Inomed, Germany).

4. Concluding remarks and suggestions

Highly targeted pharmacological or electrophysiological interventions in the brain require carefully conducted steps for

Table 1
The precise location in putamen and caudate in pharmacological manipulation. The value of coordination for fourteen monkeys are in millimeter relative to ear bar line. Sub (subject's abbreviated name), M/F (gender). AP (anterior-posterior axis), ML (Medio lateral axis), DV (Depth in brain in dorsal-ventral axis).

| Sub	M/F	Posterior Putamen			Anterior Caudate			Posterior Caudate		
		AP	ML	DV	AP	ML	DV	AP	ML	DV
Os	M	32.5	±5	25	34	±9.5	17	29.5	±13	21
Ar	M	20	±5.6	24.5	21.5	±10	16.2	15.3	±15.5	19
Sh	M	19.5	±6	24	24	±10.5	19.5	19.5	±12	20
Sa	M	19.5	±5	14.5	21	±8	8.5	17.5	±12	11
Ta	M	11	±5.5	19.5	14.5	±7	13.5	7	±14	12
Ak	M	17.5	±6.5	31	20	±9	21.5	16	±13.5	24
Ka	M	21	±5.5	28.5	23	±10	20.5	16.5	±14	21.5
Pa	F	20.5	±5	23.5	22.5	±9	19.5	16	±14	19
Ce	M	15.5	±5.5	26.5	19	±9	17	15.5	±11.5	22
Pn	F	19.5	±6	29	21.45	±9	21	15.6	±13.5	25
Ga	M	22.5	±5	14	25.5	±6.5	8.5	20.5	±12	8.5
Gha	F	17	±6	27	20	±8	22	16	±12.3	25
Sh	M	21	±6.5	25	24	±8	17.5	18	±12.5	22
Ay	F	18	±5	21.5	21	±9	16.5	16	±12.5	18
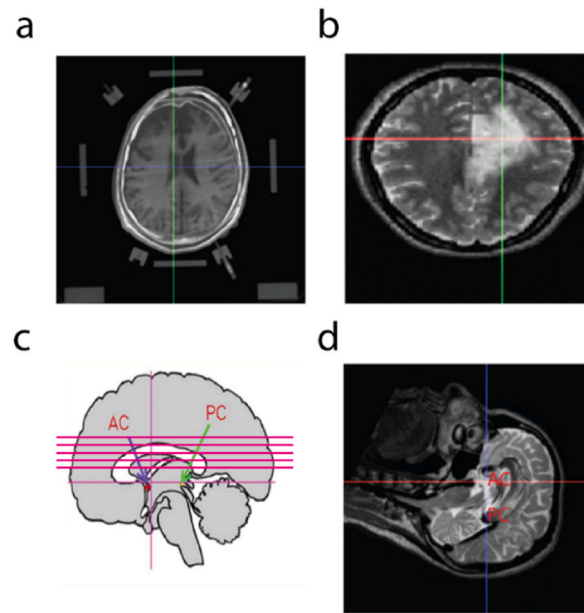
Fig. 4. Planning human biopsy surgery using pyRECaid software. The software was verified in one patient after surgery compared to available commercial software (Inomed, Germany). a) Co-registration result for human data. CT imaging was done by surgical stereotaxic frame. b) The location of the tumor tissue in the MR image was located related to AC-PC line. c) Re-slice images over AC_PC line. d) The sagittal view of re-sliced image series parallel to AC-PC line.

ascertaining their accuracy. In a typical setting, imaging provides a terrain map, guides the procedure, and finally validates the results. Automation in the form of a utility program is appealing at first glance. Although there is software like the SPM toolbox, our platform was optimized for providing access to brain regions in specific approaches. At the time we started this work, two options, namely pyElectrode and SPLASh were the specific available tools for monkey studies. Considering their acceptance as reflected in the citation rate of the two tools, this does not mean that they are considered the go-to options. None of this software has proposed different modality co-registration. Our protocol provides a precise view of both the brain tissue and implants on the skull. SPLASh (Stereotactic PLAnning Software), was developed to be a Linux-only add-on to the cross-platform Caret (Computerized anatomical reconstruction toolkit) workbench [34] of the Human Connectome Project. Although Caret is now replaced by Connectome Workbench, SPLASh is not compatible with this new platform. The other available option, pyElectrode dates back to 2013 and is developed in python 2.x and therefore, did not lend itself to upgrades with the mainstream python development. This utility although open-sourced, offered only DICOM/NIFTI viewing, chamber positioning, and electrode routing functionalities but performed MR images by implants, and made shadows on the underneath region of interest. We proposed the co-registration option to overcome this problem. Our software also provides atlas-based image segmentation which is not implemented in these software yet. We conclude by inviting others to share their views and suggestion with the authors or to directly change the source code to best suit their needs. For the sake of the continuing development of the program, we tried our best to have a reasonably well-grained object-oriented approach in the context of a python application to the development and modularity.

4.1. Suggestions for further developments

At the end, we would like to propose some features for further development of the presented tool to be implemented by others or by the authors themselves.

1. Fully automatic co-registration

In our software, the image registration was performed by four landmarks in both modalities by affine transform. An automated procedure for finding landmarks will be prepared for the next versions.

2. Chamber grid feature

The traditional chambers used for chronic access to the brain are usually used via a grid of equidistant holes through which electrodes can be inserted. A grid feature can be added to the software to better simulate chamber-based recordings.

3. 3D reconstruction

Attempts can be made to add a 3-dimensional perspective view to the software, similar to that in many commercial software. This way, users feel more comfortable in selecting a point for making measurements or inserting a chamber.

4. Addition of a logger

During a session, the coordinates of the targeted points and the angles and depths used for their targeting can be logged for later retrievals and documentations.

5. Addition of other image modalities

In our software, the image registration now works with MR and CT image series. Adding PET image modality in the co-registration form can provide more applications for the software that handles PET image data.

Declarations

Author contribution statement

Ehsan Rezayat and Mohammad-Reza A. Dehaqani - Conceived and designed the experiments and Analyzed and interpreted the data.

Pouya Narimani, Hamed Heidari-Gorji and Farzad Shayanfar: Contributed analysis tools and prepared the proposed software.

Ehsan Rezayat and Jalaledin Noroozi: Performed the experiments of application 1 (nonhuman primate electrophysiology recording).

Ebrahim Shahbazi and Ehsan Rezayat: Performed the experiments of application 2 (nonhuman primate cell transplantation and histology confirmation).

Abolhasan Ertiaei and Ehsan Rezayat: Performed the experiments of application 3 (human biopsy surgery evaluation).

Ehsan Rezayat, Farzad Shayanfar, Pouya Narimani and Mohammad-Reza A. Dehaqani wrote the paper.

Data availability statement

The code is available on GitHub.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2022.e12675.

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