HyperProbe

Project title: Transforming brain surgery by advancing functional-guided neuronavigational imaging

Project acronym: HyperProbe

Grant Agreement: 101071040

Call identifier: HORIZON-EIC-2021-PATHFINDERCHALLENGES-01

D2.1 Definition of the essential features of the system for the prototype device

Lead partner:	EMO
Author(s):	Domenico Alfieri, Lorenzo Targetti, Duccio Rossi degl'Innocenti, Luca Giannoni, Camilla Bonaudo, Bruno Montcel, Thiebaud Picart, Pietro Ricci, Francesco Pavone
Work Package:	WP2
Due date:	Month 27
Actual delivery date:	31/01/2025
Type:	R
Dissemination level:	PU

Funded by the European Union

European Innovation Council

Tables of contents

1. Introduction 3
2. Medical need 3
2.1 Pre-operative localization of the tumor mass and definition of the brain functional areas in the proximity of the tumor. 3
2.2 Intraoperative guiding and navigating standard procedures 3
2.3 Glioma identification and classification 4
3. System requirements (prototype features) 4
3.1. Illuminating system 4
3.2. Detection system 6
3.3. Image processing, storage and timing features 6
3.4. Safety features 6
3.4.1. Basic safety and essential requirements 6
3.4.2. Usability requirements 7
3.4.3. Environment and indication of use features 7
4. Conclusion 7

Abbreviations

FOV Field of View

WD Working distance

Disclaimer

1. Introduction

High-grade gliomas are tumors of the glial cells, found in the brain and spinal cord. Glial cells support neurons, or nerves, in the central nervous system. These tumors are fast-growing and spread quickly through brain tissue, which makes them hard to treat. Gliomas are the most frequent primary brain tumors, and they are classified by their location and by how they appear when examined under a microscope. Classifying the tumor helps determine how the disease will progress and helps identify the best therapeutic strategy. Gliomas might present very fragmented margins, and healthy perilesional tissue can be infiltrated by cancer cells, making it difficult to define precisely the volume of tissues that must be removed to avoid recurrences. The initial treatment of high-grade glioma usually involves surgically removing the tumor without hindering the brain's functions. The amount of tumor that can be removed is determined by its size, depth, and location with respect to the functional areas of the brain. The standard approach is to remove as much of the tumor as possible while sparing areas controlling critical functions such as speech or movement.

2. Medical need

The fundamental aspects connected to the surgical removal of gliomas are the following:

2.1 Pre-operative localization of the tumor mass and definition of the brain functional areas in the proximity of the tumor.

Standard Practice: The standard procedure is to perform a whole-brain MRI examination including perfusion and metabolic MRI and functional MRI (fMRI) before the operation to locate the tumor mass and define the functional areas in its proximity planning. Functional areas must be avoided at the time of surgery to optimize clinical outcome of oncological patients, based on the principle of the 'onco-functional balance'. These functional data improve surgical planning and the extent of surgical resection, broaden surgical indications for lesions in classically eloquent areas, and reduce intraoperative duration, which may ultimately improve functional outcome and tumor control (in terms of Overall Survival_OS_ and Progression Free Survival_PFS). (MR-DTI) before surgery. MR-DTI is an advanced magnetic resonance modality that uses the Brownian motion of water molecules to provide data for images. This cutting-edge neuroimaging technique allows exploration of the intricate architecture of the brain. DTI enables the visualization of neural pathways and subcortical white matter fiber tracts, therefore highlighting connectivity, making it a helpful tool for understanding brain anatomy, function, and pathology.
Another preoperative method for mapping cortical functional areas is the Navigated Transcranial Magnetic Stimulation (nTMS), one modality that allows for highly accurate, image-guided, non-invasive stimulation of the brain, thus allowing for differentiation between eloquent and non-eloquent cortical regions.

2.2 Intraoperative guiding and navigating standard procedures

Standard Practice: Surgeons usually use a surgical navigation system (i.e. Medtronic Stealth Station S8) integrated with a microscope (i.e. Zeiss900) or, in some situations, with an exoscope (i.e. Olimpus Exoscope Orbeye 4k), depending on the surgeon's preference and the characteristics of the surgical procedure and approach. The MRI images obtained before surgery are imported and displayed in the field of view of the microscope and used by the surgeon during surgery to localize the tumor mass and avoid functional areas, integrating the previously mentioned information acquired during the surgical planning.
Challenge: Brain shift is a brain deformation caused by several factors indirectly related to surgery, including gravity, head position, fluid drainage, use of hyperosmotic drugs, changes in intracranial pressure, and swelling of brain tissue. It is also directly affected by surgical

Funded by the European Union
European Innovation Council

intervention, i.e., tissue retraction and tumor resection. Brain shift can be patient-specific and highly non-linear, significantly impacting the usefulness of preoperative imaging for neuronavigational systems. During surgery, it is necessary to verify the distribution of functional areas because they may have delocalized along with the parenchyma during resection, compared with what was established with preoperative analysis (brain shift). This is performed by applying electrical stimulation and observing patient behavior in awake surgery, or alterations during recording of intraoperative monitoring signanls, such as Motor Evoked (MEPs) and SomatoSensorial Evoked Potentials (SSEPs) during procedures under general anesthesia.

Medical Need: A real-time functional image of the brain's area of interest would improve precision and speed during surgery and allow the patient to be anesthetized/benefiting from a functional adaptive image, although the evaluation of patient's behavior is not possible under general anesthesia.

2.3 Glioma identification and classification

Standard Practice: Actual standard procedures require labeling tumoral tissue with fluorescence dyes to be revealed during operation, such as fluorescein and 5ALA.

Intraoperatively, the patient may be given indocyanine green, a fluorophore injected intravenously that, visualized through an infrared camera, can highlight blood vessels and detect bleeding and control the patency of arterial or venous structures during either oncological or vascular surgical procedures.

Once tumoral tissue is removed, remoted histological analysis is performed to determine the tumor grade.

Challenge: Such a method has shortcomings: fluorescein sodium is a low quantum efficiency dye; on the contrary, the 5ALA is a metabolic dye, whose intracellular uptake makes it more specific but less sensitive and very expensive.

Furthermore, the fluorescence technique fails to provide detailed images of the tumor borders when presenting ragged edges. Moreover, it is not relevant to identify tumor-infiltrated parenchyma around the tumor bulk. Therefore, these techniques lack sensitivity.

Tumor grading is based on histological and molecular data (available around 10 days after the surgery). Knowing the tumor grade preoperatively or intraoperatively is not mandatory as, independently of the grade, the glioma resection aims to achieve a maximal safe result.

However, it is helpful to have the perioperative confirmation of the diagnosis of glioma. For example, in those rare cases in which the tumor is a lymphoma, and therefore, surgery is not useful. According to certain surgeons, having real-time indication of the potential grade of the tumor could lead to adopting different surgical approaches.

Medical Need: To have a label-free image of the tumor and adjacent parenchyma with a higher degree of sensitivity and specificity. To have a label-free imaging of blood vessels and blood perfusion. To have a real-time indication of certain biomarkers, such as iron content and lipid concentration, to support tumor grading during the intervention. However, such biomarkers are not officially recognized and accepted as tumor indicators.

3. System requirements (prototype features)

We aim to develop the HyperProbe device that provide real-time (msec) and high spatial resolution (mm) brain tissue images at a relatively large number of wavelengths (20) in the UV-visible and NIR range, during neurosurgery and in parallel with cortical/subcortical stimulation.

3.1. Illuminating system

The multispectral illumination system is LED based and is composed of at least of 20 wavelengths in visible and NIR range, appropriately selected to identify biomarkers of interest, detect hemodynamics and the variation of oxidized cytochrome-C-oxidase (oxCCO).

Starting from the wavelengths emitted by the LEDs available in the USHIO SMBB model, which are available in the range 365 nm up to 1750 nm, a Montecarlo simulations were performed to identify the number and which wavelengths should be used to monitor hemodynamics and oxCCO. The set of 4 wavelengths to monitor the hemodynamics are [470 490 590 620] nm while the set of 5 wavelengths to monitor oxCCO are [550 590 620 780 810] nm.

From the analysis of data (images acquired at different wavelengths) acquired with HyperProbe 1 on brain tumor tissues (biopsies) collected during surgical operations for the resection of brain tumors of different grade published in https://doi.org/10.1117/1.JBO.29.9.093508, an illumination system containing the set of 14 wavelengths should be implemented, identified in [540 550 555 565 580 595 610 625 700 740 820 845 865 895] nm, should provide the same tumor grade classification ability achieved with all wavelengths used with HyperProbe1.

Aggregating the requirements of both needs the illumination system that can monitor hemodynamics, oxCCO and classify a tumor grade must contain the set at least of 20 wavelengths composed as follows, [470 490 540 550 555 565 580 590 595 610 620 625 700 740 780 810 820 845 865 895] nm, and for each wavelength emitted a spectral width of 5 nm, the same spectral spacing used with HyperProbe 1.1, and an emitted optical power of at least 10 mW for single wavelength to have a good signal to noise ratio.

Considering that filtering LEDs to obtain narrow spectral lines, which in some cases do not coincide with the central emission wavelengths where the power is maximum, may generate too low emission for our purposes, that the cost of the filters could be high if the characteristic are custom made, and that it is not possible to predict the impact of the degradation on the processing results of the developed unmixing algorithm due to the emission shape and spectral width of the LEDs, we will design and implement an illumination system with USHIO SMBB LEDs that best cover the spectra between 510 and 900 nm, as shown in the Figure 1, to which are added the wavelengths at 470 and 490 for functional imaging, and possibly other wavelengths between 365 and 450 nm both to excite fluorescence and where the absorption of hemoglobin is high in case is useful for our analysis.

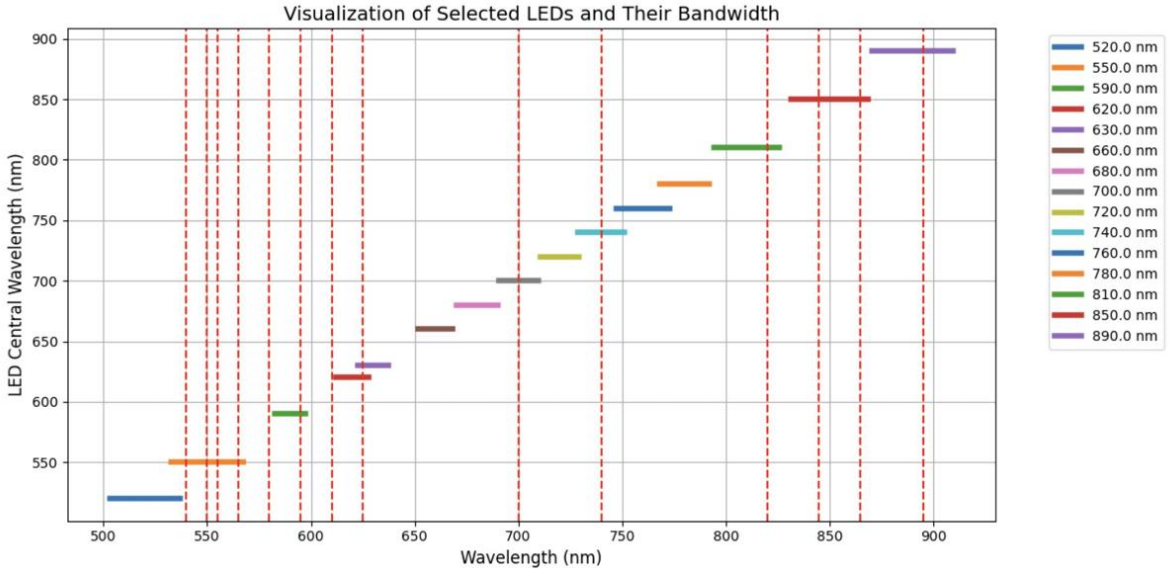

Figure 1. Subset of LEDs that allows to cover as best as possible the full 510-900 nm range.

Therefore, the set of initial wavelengths of the illumination system based on LED USHIO are [470, 490, 520, 550, 590, 620, 630, 660, 680, 700, 720, 740, 760, 780, 810, 850, 890] nm.

During the validation phase following the design, the appropriate changes to the lighting system will be evaluated and made with the aim of resolving any degradations that make the unmixing algorithm inconclusive and allowing efficient functional imaging.

3.2. Detection system

The detection system will be based on the camera with is equipped HyperProbe 1.1, because the characteristics of the “pco.panda 4.2 bi cMOS” camera are suitable for collecting the reflectance signal as reported in the deliverable D.1.1 - Lab system development (HyperProbe1).

A custom achromatic objective lens must be optically designed to adapt the spectral requirements (broad detection spectrum at least 450-900 nm), the Field Of View (FOV) requirements (at least 10x10 cm) and the distance requirements (at least 15 cm) in order to reduce optically aberrations and distortions which can induce degradations on images due at requirements regarding the width of the acquired spectra, FOV and work distance.

The illumination and detection system will be equipped with cross polarizing filters to reduce specular reflections.

3.3. Image processing, storage and timing features

Considering that the detection system could be acquire 21 images at a time, including the dark image for subsequent conditioning, and PCO camera which has the sensor with resolution 2048 x 2048 pixel a 16 bit, each images cube composed from the acquired images is around 176 MB, the prototype will be managed through a software that will coordinate the timing of lighting and acquisition, retrieve data from the camera and take care of saving the images. The images will then be transferred to the image analysis partners of the project to be processed and fine-tune the unmixing algorithm. The acquisition time for each wavelength will depend on the optical power that the lighting system will emit and on the number of LEDs required for the analysis. As example, for functional imaging, which requires the acquisition of 7 wavelengths, a frame rate of at least 5 Hz is required, the acquisition time will be around 25 ms.

3.4. Safety features

The main safety requirements related to the prototype that will be designed and integrated during the activities of WP2 are described in the following.

3.4.1. Basic safety and essential requirements

During the design we will take into consideration the requirements of the standards applicable to the medical device.

We consider the requirements of the IEC 60601-1: general requirements for basic safety and essential requirements, concerning:

- Legibility of marking
- Durability of marking test
- Limitation of voltage, current or energy
- Leakage current and patient auxiliary currents
- Resistance to heat
- Mechanical hazards associated with surfaces, corner or edges
- Instability hazards
- Acoustic energy
- Excessive temperature in MD equipment
- Mechanical strength

in addition to specific hazardous situations and single fault conditions.

We consider the CEI EN 60601-1-2: Electromagnetic compatibility - Requirements and tests, to ensure that the device does not affect other devices, and its performance is not affected by electromagnetic disturbances generated by other devices in the environment in which it is used.

We consider the CEI EN 60601-2-57:2012: Medical electrical equipment/Part 2-57: Particular requirements for the basic safety and essential performance of non-laser light source equipment intended for therapeutic, diagnostic, monitoring and cosmetic/aesthetic use, to evaluate the photobiological risk of the system and whether we need and can implement risk control measures already in the design phase.

We need to perform type tests to demonstrate compliance with safety requirements of the system and draft risk management documentation, because are required by the ethics committees in order to give a positive opinion to the observational study for the evaluation of the system performance in the hospitals involved in the project.

3.4.2. Usability requirements

The prototype will be equipped with the proper labelling to warn of residual risks identified during the design and system integration activity and with regard to warnings for its correct and safe use. The optical head will be positioned on a servo-assisted robotic arm to facilitate the stable positioning of the optical head in front of the sample to be acquired, acquire the images of interest and position the optical head outside the operating space to allow the continuation of the surgical intervention. The base of the servo-assisted robotic arm must have a space to accommodate the computer and its peripherals, on which the software runs for managing and controlling the optical head and saving the images.

3.4.3. Environment and indication of use features

The working distance of the optical head being 15 cm indicates that the prototype will be used in the sterile area of the surgical room. Therefore, the prototype must be completely wrapped with sterilizer bags to guarantee its sterility, the part of the optical head where the light comes out and the distal part of the objective must be covered with a sterilizable optical polymer cover that does not perturb the illumination light and acquisition system guaranteeing the sterility of the entire prototype. The sterilizable optical polymeric covers will be sterilized according to the Hospital standards where the prototype will be used.

4. Conclusion

The main purpose of this project consists of creating a prototype tool (HyperProbe) to optimize the surgical excision of brain lesions, respecting functional boundaries, integrating dynamic and optical information about tumor /healthy tissue. This ambitious project aimes at providing new highlight in the context of modern Neurosurgery to achieve the maximal safe resection, a maximal recognition of pathological tissue, and at the same time a maximal functional preservation of higher cognitive functions, to grant high quality of life to our patients.