Fondazione Giovanni Celeghin

Bando di Ricerca 2019 - 2020

1. GENERAL INFORMATIONS

"Neuro-Imaging studies of Oncological patients for Planning outcome and surgery"
(Neuro-Onco Plan)

DEPARTMENTS	Department of Neuroscience (DNS), Engineering Information (DEI), Internal Medicine (DIMED), University of Padova, Azienda Ospedaliera Padova (AOP)
PRINCIPAL INVESTIGATOR	Maurizio Corbetta, 03/02/1961
DURATION OF THE PROJECT	24 months
BUDGET	142.000 €

2. PLAN OF THE RESEARCH

1. ABSTRACT

Background. Brain surgery is one of the most daring and complex acts of medicine. Surgery improves the outcome of brain tumors, but is often fraught with neurological complications. Notwithstanding important advances in intra-operative techniques and neuroimaging, most procedures are still performed with little regard to the underlying structural and functional organization of the patient's brain. In fact, the main strategy to preserve function, i.e. intra-cortical stimulation, is based on pioneering studies performed more than 70 years ago by Wilder Penfield at the Montreal Neurological Institute. **Description of the project**. By taking advantage of a hybrid PET/MR system available at the University Hospital of Padova, patients with a clinical diagnosis of glioma (n=50, ~20% low grade) eligible for neurosurgery will be evaluated at three different time points: (T1) ~1-week prior to surgery; (T2) follow up at 1 month before the pharmacological treatment; (T3) follow up at 4 months after the pharmacological treatment. The patients will be also evaluated with an extensive neuropsychological assessment at the same time points. **Main aims and expected results.** The main goal of this project is to create a new strategy for brain surgery based on a deeper understanding of the effects of the tumor on the surrounding and distant brain tissue, as well as on behavior. First, we plan to carry out simultaneous metabolic and structural/functional MRI studies on a longitudinal cohort of patients with brain tumors studied pre- and post-surgery (1-week, 1 month). Next, we plan to develop a sensitive behavioral and outcome

assessment to describe tumor and surgery related deficits. Thirdly, brain imaging variables and behavioral outcome will be related using state-of-the-art machine learning methods that 'select' the most important neuroimaging features for behavioral prediction of deficits post-surgery and long-term outcome. These features will be used in a new neuro-navigation protocol as part of clinical care. Through these studies, we will acquire fundamental new information on the effects of tumors on the physiology, anatomy, and vascular systems of the brain.

RIASSUNTO

Background. La neurochirurgia rappresenta uno degli atti più audaci e complessi della medicina. La chirurgia migliora la prognosi dei tumori cerebrali, tuttavia è spesso fonte di complicanze neurologiche. Nonostante le notevoli innovazioni nelle tecniche intraoperatorie e di neuroimmagine, molte procedure non tengono ancora abbastanza in considerazione le strutture sottostanti e l'organizzazione funzionale del cervello del paziente. Infatti, la strategia principale per preservare le funzioni cognitive, ovvero la stimolazione intra-corticale, si basa sugli studi pionieristici eseguiti più di 70 anni fa da Wilder Penfield al Montreal Neurological Institute. **Descrizione del progetto**. Sfruttuando il sistema combinato PET/MR disponibile presso l'Azienda Ospedaliera Universitaria di Padova, pazienti con diagnosi clinica di glioma (n=50, ~20% di basso grado) candidati a intervento di neurochirurgia saranno valutati a tre differenti time points: (T1) al massimo una settimana prima della chirurgia; (T2) follow up a un mese prima del trattamento farmacologico; (T3) follow up a 3 mesi dal trattamento farmacologico. I pazienti saranno inoltre valutati tramite un esteso esame neuropsicologico agli stessi time points. **Obiettivi e risultati attesi.** L'obiettivo principale del progetto consiste nel creare una nuova strategia chirurgica basata su una comprensione più specifica degli effetti del tumore sia sul tessuto cerebrale circostante e distante, sia sul comportamento. Primariamente, pianifichiamo di acquisire simultaneamente esami MRI metabolici, strutturali e funzionali su un gruppo di pazienti con tumore cerebrale, studiandoli prima e dopo la chirurgia (a una settimana e a un mese). Successivamente, ci proponiamo di sviluppare una valutazione funzionale abbastanza sensibile da rilevare I disturbi secondari al tumore e alla chirurgia. Infine, le variabili di neuroimmagine e le misure comportamentali saranno correlate tramite metodi di machine learning, che permetteranno di selezionare la caratteristiche di neuroimmagine più importanti per predire i disturbi funzionali post-chirurgici e a lungo termine. Queste variabili potranno essere usate nel futuro in un nuovo sistema di neuro-navigazione come parte della pratica clinica. Attraverso questi studi, acquisiremo nuove fondamentali conoscenze sugli effetti dei tumori sulla fisiologia, l'anatomia e il sistema di vascolarizzazione del cervello.

2. BACKGROUND AND RATIONALE

In Europe and US, the incidence of brain tumors has been estimated around 1-10/100.000, of which about 80% are high grade (malignant). Around 10-40% of patients with a non-primary brain tumor also develops brain metastasis. Surgery for brain tumors is one of the most daring acts of medicine, yet it is still performed around the world using a strategy that was developed more than 70 years ago by the pioneer neurosurgeon Wilder Penfield [1]. Penfield developed a method for electrically stimulating the exposed cortex near the tumor that allowed him to localize 'centers' of the brain specialized for movement, language, and sensation. This 'functional electrical mapping' approach allows sparing of regions of the brain important for movement, speech, or sensation. However, only a minority of brain regions is involved in these functions. Most times surgery involves associative cortex for which no standard functional mapping is currently available. Accordingly, most deficits post-surgery are not easily detected with a standard neurological examination, but involve 'cognitive' impairment. Yet sensitive neuropsychological measures are not routinely used to track

clinical outcome. Therefore, a first major gap in knowledge is the lack of reliable tools to monitor function of associative cortex beyond motor and language functions, and sensitive neuropsychological tests to detect cognitive deficits in brain tumors.

The traditional electrical stimulation mapping strategy has been integrated with more novel methods including intraoperative EEG, motor evoked potentials, and on-line assessment of cognitive functions during awake surgery. The development of structural brain imaging, first Computerized Tomography (CT) scans, then Magnetic Resonance Imaging (MRI), has allowed the anatomical localization of the tumor in vivo. Finally, functional MRI (fMRI) and Diffusion Tensor imaging (DTI) have been increasingly used preoperatively to map functional cortical regions and their structural connections. This array of multi-modal information is integrated in 'neuro-navigation' systems for the surgeon to view through computer monitors in the operating room. Imaging-guided surgery, currently state-of-the-art, is thought to improve survival by maximizing the volume of resection while minimizing neurological disability. Unfortunately, the scientific evidence for the efficacy of imaging-guided surgery is mixed. While individual studies support its efficacy in maximizing resection and outcome [2, 3], a recent meta-analysis of different techniques shows that image-guided surgery (including intra-operative MRI; 5-ALA; DTI) does not increase the rate of patients who have complete tumor resection on post-operative MRI [4]. A second major gap in knowledge, therefore, is lack of understanding of which biological variables are important for planning the most complete resection with the least possible neurological disability. characterized by a complex alteration of the tissue physiology. Tumors not only structurally displace normal brain tissue, but also cause disruption of blood-brain barrier, vascular auto-regulation, coupling between blood flow and neuronal activity. Finally, they also cause true alterations of neuronal activity and functional organization, both near the lesion and in distant areas. In low-grade gliomas, we can also expect significant degree of functional reorganization, presumably with displacement of white matter tracts and connected cortical regions, as well as remapping of function. Finally, the individual variability in brain organization interacts with the tumor. Brain systems are organized in structural and functional networks whose organization, determines brain function. Therefore, a more complete understanding of the biological variables that influence outcome must involve multi-modal imaging of both tumor biology and brain organization.

Sophisticated multi-modal imaging is not enough unless we have a sensitive way to measure outcome in our patients. Behavioral impairment post-resection rarely involves basic sensory-motor-language functions given surgeons' awareness of primary regions of the brain. However, damage to association cortex and underlying white matter pathways is a different matter. In evaluating patients with brain tumors is necessary a sensitive behavioral battery to measure patients' deficits and quality of life, both short-term after surgery, but also long-term as patients undergo chemo- and radio-therapy, both known to have a negative impact on cognitive functions [5].

The challenge of this project is to develop an entirely novel approach to brain surgery that takes in account the functional and structural organization of the brain and the biology of the tumor to improve outcome using advanced mathematical methods and sophisticated computer models.

References

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3. PRELIMINARY RESULTS

Behavioral and neuropsychological profile

Several studies have been conducted to characterize the consequences of brain tumors on cognitive functions. All studies suggest the importance of an extensive and shared neuropsychological protocol in pre and post-operative stage [6-7-8]. However, no study has defined thus far the profile of cognitive deficits in brain tumors while taking in account the specific neurological nature of this pathology, and the effect of surgery. One of the goals of this project is to develop a sensitive neuropsychological battery, able to pick up subtle cognitive deficits in brain tumors both before and after surgery.

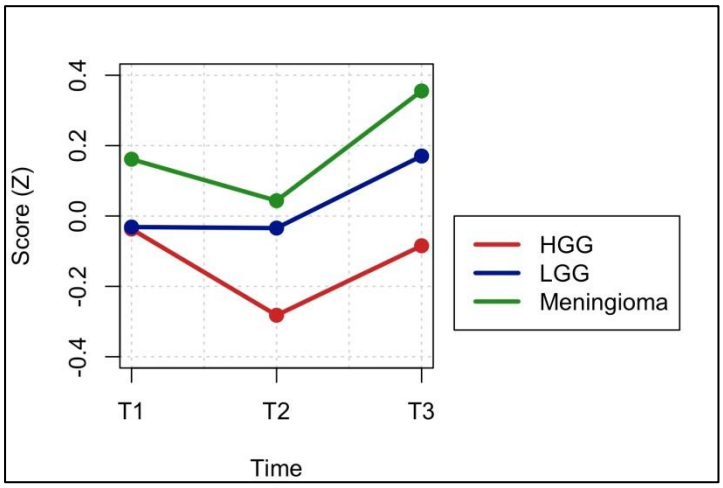

Fig. 1: the trend of cognitive performance of a group of brain tumor patients through different time points: (T1) pre-surgery; (T2) post-surgery); (T3) 1 month follow up

In the last two years, we have run a series of pilot projects in which we have compared the performance of a group of brain tumor patients (glioma and meningioma, n=80) and first-time stroke patients (n=133). The results show that although both groups of patients show similar deficits, each pathology is characterized by a specific cognitive profile. Specifically, brain tumor patients tend to have fewer sensory, motor, or language deficits, and more memory, executive, and attention deficits. Therefore, high level cognitive deficits are those we shall focus on when evaluating brain tumor patients pre- and post-surgery.

We have also run pilot studies on trying to define the impact of surgery and long-term outcome. In a group (n=50) of brain tumor patients (meningioma, glioma), we analyzed behavioral data at three different time points: pre-surgical, post-surgical and one month follow up. We found a global worsening of the cognitive scores in the immediate post-operative stage, with a subsequent recovery at one-month follow-up (Fig. 1). Again, the most sensitive scores were related to memory and attention. Therefore, to assess whether surgery has caused deficits it is important to focus on these domains. Moreover, these functions are those that we shall focus on in our attempt to link neuropsychological deficits to biological variables of the tumor, or in examining mechanisms of recovery of function.

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Preliminary imaging analysis

A fundamental step that may improve the ability to resect more aggressively and protect neurological function is mapping of the functional organization of the brain, and its alterations in tumors. To map the functional organization of the brain in tumors, we will implement the method of resting state fMRI (R-fMRI) based on the temporal correlation of the blood oxygenation level dependent (BOLD) signal between brain regions (functional connectivity, FC). The PI (Dr. Corbetta) has pioneered this method for the study of functional brain systems in healthy and stroke subjects. In particular, his team has developed a technique for the automatic classification of every region of the brain in one of several functional networks. The advantage as compared to standard task fMRI is that we can localize all networks at once, not just those involved in a task. Recent work shows that R-fMRI detects the distortion of functional networks induced by tumors, hence providing a potential functional guide during surgery. We have begun to combine these two sets of information in tumor patients. Fig.2 shows a patient with a high-grade glioma in the frontal lobe in which we have simultaneously acquired structural/functional information, and combined these sets of images to study the relative sparing of tissue near the tumor for resection. The first row shows that a region in medial frontal cortex that is apparently damaged on structural images (T2wFLAIR) maintains a healthy level of functional connectivity (red arrow) with posterior parietal regions when studied with R-fMRI. This region belongs to a brain network, the default mode network, involved in memory function. The second row shows that this region maintains a normal glucose metabolism (FDG-PET) indicating its viability. There is a nice correspondence between normal metabolism and normal synchronization, a topic barely investigated even in healthy subjects. Therefore, it is apparent that a resection based on only the FLAIR signal, a common approach in current neurosurgical techniques, would remove a normal brain area potentially causing a memory impairment.

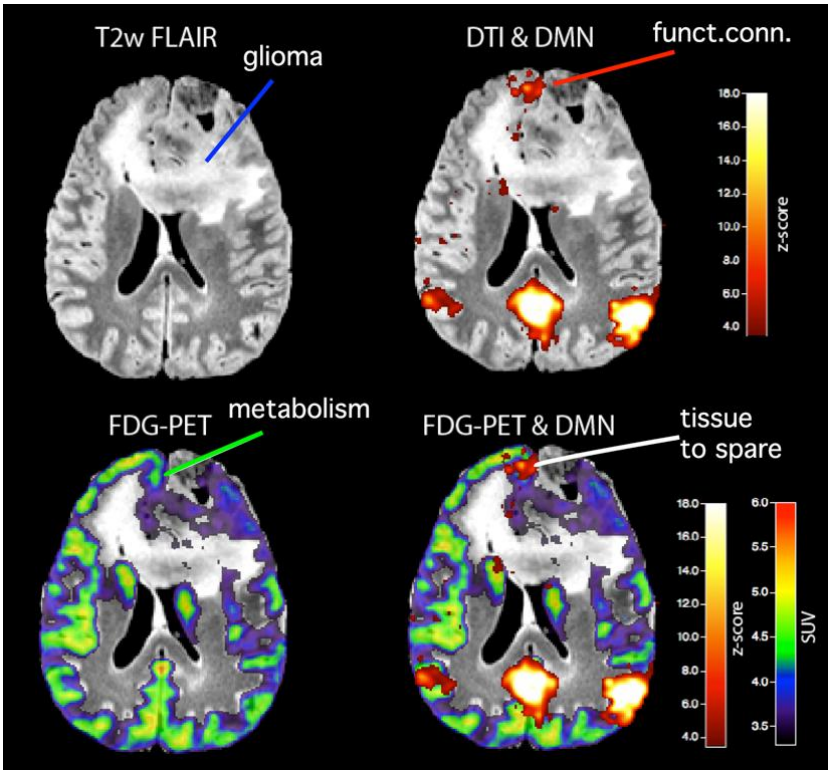


Fig. 2: Multimodal imaging of brain tumors tags healthy tissue. Top (L) Anatomy (T2wFLAIR): glioma; (R): regions of connectivity (DTI&DMN), note healthy tissue (red line) near tumor; Bottom (L): Glucose metabolism (FDG-PET): connected tissue is metabolically normal (green line); (R) multi-modal fusion in neuro-navigator identify tissue to spare (white line).

During the last year we investigated how the presence of high-grade gliomas modifies brain connectivity and how those changes can be related to tissue metabolism and perfusion by means of simultaneous multimodal PET-MRI acquisitions. In glioma treatment the gross total resection is associated with better outcome and prolonged survival, but the benefits of a larger neurosurgical resection needs to be balanced against the risk of significantly altering the patient quality of life by inflicting deficits in areas of eloquent cortex, one of the aims of our study was to delve deeper into the relationship between the fluid attenuated inversion recovery (FLAIR) hyperintensities, which are typically employed to define regions of brain tumors amenable to resection, and the regional

connectivity and the underlying metabolism and perfusion. In pilot studies, we are discovering that, as compared with the contralateral normal region, the FLAIR hyperintense area is highly heterogeneous both metabolically and functionally. In particular, the centre of high-grade gliomas has either a very high or low (necrotic) phosphorylation core surrounded by regions of either high or low FDG delivery. fMRI connectivity shares the same heterogeneity pattern, with areas of concurrent increased local functional connectivity and phosphorylation. In contrast to these findings, we also observed normal fMRI and metabolic activity in regions of abnormal FLAIR. These preliminary results suggest that brain connectivity is significantly affected by the presence of gliomas. and that tumors surgery may benefit from a more precise definition of the functional and metabolic signals in regions of abnormal FLAIR signal.

4. SPECIFIC AIMS AND EXPECTED RESULTS

Our strategy is to develop first multi-modal imaging of brain tumors, specifically looking at the impact of the tumor on the structural and functional organization of the brain. Next, we will use these multi-modal data sets to select features that are highly predictive of good neurological outcome post-surgery. MRI is nowadays the most widely approved methodology to study brain tumors but presents a number of limitations concerning grading and definition of the real extent of the pathology. Using an integrated 3T PET/MRI system, able to simultaneously acquire dynamic PET and MRI images, we will be able to integrate the advantages of both methodologies with the possibility of depicting simultaneously structural changes (morphologic sequences and DTI), basal functional changes (BOLD default mode network), functional activation changes (AS labeling, BOLD task positive network) and changes in metabolic rate of glucose pre- and post-surgery, and to correlate these measures with behavioral outcomes.
To develop multi-modal imaging of brain tumors, we plan to take advantage of the new Siemens Biograph hybrid PET/MR, a state-of-the-art imaging device able to acquire dynamic PET and MRI sequences. We will measure the tumor and its effects on the brain's structural and functional organization by acquiring: (a) structural data about the lesion (e.g. volume, edema, shape, pathology post-op), (b) distortion of structural connectivity measured with DTI; (c) alterations of functional connectivity measured with R-fMRI; (d) blood perfusion and volume with DSC-MRI, and (e) glucose metabolism with 18F-FDG PET and amino acid consumption using 18F-FET.

Aim 1: To implement multi-modal imaging of brain tumors and connectivity, and related neuro-navigation. We will measure using the Biograph hybrid PET/MR system structural (T1w, Flair, T2*, T1w gadolinium enhanced), diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), resting state fMRI (R-fMRI), and fluoro-deoxyglucose (FDG) metabolism or amino acid consumption (18FFET) pre-operatively (T1=~1 week prior to surgery), post-operatively (T2=~1-month post-surgery) and at follow up (T3=~4 months post-surgery). The main result will be to integrate R-fMRI, DTI, CBF/CBV, and FDG (or FET) maps in the neuro-navigation system of the operating rooms in the Neurosurgery Unit of Padua University Hospital.

Aim 2: To develop a sensitive behavioral assessment for measuring cognitive performance, outcome, and quality of life in brain tumors, and measure the impact of lesion location. We will develop a neuropsychological battery and test the same group of patients at 1 week pre-, 1 week post-, 1 month post-, and 3 months post-surgery.

Expected results: outcome in brain tumors is strongly related to cognitive disability. Yet, cognitive testing is not routinely used to assess the effects of brain surgery. Our hypothesis is that deficits of memory, attention, and executive functions will be more likely than deficits of sensation, motor,

and language functions. This is consistent with our preliminary results and clinical experience that visible neurological complications rarely occur post-surgery. Tumors/resections affecting the white matter, especially regions of convergence of many white matter tracts, will lead to more severe cognitive deficits than tumors/resection affecting the cortex. Gliomas, as they extend in the white matter, may cause deficits of communication between brain regions that support associative functions (e.g. memory, attention, executive function), rather than more localized sensory, motor, or language functions. This is consistent with our recent observation in stroke. Damage to the white matter was associated with deficits in multiple domains as compared to more specific deficits after cortical damage. Moreover, cognitive deficits are much less dependent on damage of specific cortical regions, but more dependent on the functional integration between brain regions (Siegel et al. 2016). As a result, functional connectivity measures, rather than structural measures, are more related to cognitive outcome. Finally, tumors, in contrast to stroke, can grow for many months and years in a person's brain thus presumably leading to re-organization of connections, especially in low-grade tumors. Therefore, the effect of white matter damage should be stronger for high- than low-grade gliomas. The results of the analysis will provide statistical maps that will show at the population level which structures (gray, white matter) are more related to different kinds of deficits (attention, memory, executive, etc.)

Aim 3: To relate tumor variables and behavioral outcome to structural, functional, and metabolic metrics of brain organization.

Expected results: the effects of the tumor on the functional/metabolic organization of the brain are unknown. Hence an important first goal is to clarify the relationships between different imaging signals. Do regions with altered T2w-FLAIR signal, which are used by surgeons as a guide to resection, always show evidence of neural dysfunction as indexed by low glucose metabolism and disrupted functional connectivity? Our preliminary evidence, based on a few cases run thus far (e.g. Fig.3), clearly show some regions with abnormal FLAIR signal that have normal metabolism and normal functional connectivity with structurally normal distant regions. This result alone, if confirmed, would be of high significance as it strongly suggests that T2w- FLAIR signals is not enough to guide surgery, and that neuro-navigation based on a more complete imaging assessment should lead to safer surgery. It is also not clear how the biology of the tumor distorts the normal connectivity, perfusion, and metabolic of near (perilesional) and remote regions. We need this information to develop imaging biomarkers to predict behavioral outcome. To make the project focused we plan to examine two sets of connections: interhemispheric and perilesional functional connections. Inter-hemispheric connections have been shown in stroke to be highly predictive of neurological deficits acutely and chronically. Perilesional connections, especially their interactions with distant structurally normal regions, are also predictive in stroke, and may be particularly important to predict post-surgery deficits as their presence may render the perilesional cortex especially vulnerable to surgical damage. Specifically, we predict that perilesional connectivity will be more normal in low-grade than high-grade gliomas since the latter do not allow a reorganization of connections. Similarly, for metabolic parameters, we will focus on changes in metabolism/blood flow, both perilesionally and contralesionally. Tumor variables (volume, edema, cellularity, genetic make-up, metabolism) will relate preoperatively to abnormal functional connections of affected brain networks (inter-hemispheric decrements, intra-hemispheric increments) and decreased contralateral glucose metabolism. High grade gliomas will presumably cause more dramatic alterations of functional connectivity and glucose metabolism than low-grade gliomas that allow for a reorganization of connections/function. Specifically, abnormal perilesional connectivity will be associated with more neurological impairment post-operatively. High-grade gliomas will cause stronger alterations of perilesional connectivity than low-grade gliomas.

Future perspectives

In summary, the main outcome of this project will be an enhanced description of the behavioral deficits caused by tumors, and a more sensitive monitoring of the behavioral effects of surgery. The multi-modal neuroimaging pre-surgery may improve the surgical approach, and provide new information for the diagnosis of tumors, e.g. separating tumors with worse or better outcome. The comparison of multi-modal imaging features before and after surgery will provide novel information on the mechanisms of recovery of function.

There are several important future developments. First, if neuroimaging variables will confirm the heterogeneity of the FLAIR hyperintensities, then a clinical trial may evaluate the safety and efficacy of surgery when using multi-modal imaging for neuro-navigation. Second, it may be possible to relate our imaging phenotypes to genetic and immunological information that are currently used for tumor subtyping. Genetic modifications found in brain tumors are beginning to be used for chemotherapy and radiotherapy selection, by adding information from multimodal imaging we may be able to increase their predictive value.

This project has wide ranging implications for the health of the Veneto Region. One major impact is the improvement of neurosurgical planning and clinical outcome at Padova University Hospital. Since Padova is one of the two hubs of the regional health system, and neurosurgery is highly centralized and attracts a lot of patients outside of the Region, this project will provide the whole regional and national health system new tools for improving the lives of patients affected by brain tumors. The two milestones: (a) behavioral battery, and (b) imaging metrics related to outcome, could be used also to track the effectiveness of standard and novel oncological treatments at Istituto Oncologico Veneto (IOV) where treatment typically begin 1-month post-surgery.

5. HUMAN RESOURCES

- **Prof. Maurizio Corbetta**, PI, is the Director of the Clinica Neurologica, Professor and Chair of Neurology, and Funding Director of the Padua Neuroscience Center. The center is dedicated to the study of brain networks in health and disease. The PI has 30 yrs. experience in neuroimaging, and pioneered some of the first neuroimaging studies of human cognition. He has extensive experience in studying patients with focal brain lesions, especially stroke and TBI. The study of brain tumors is a new direction for the PI. The PI will be responsible for the overall direction of the project. He will spend 10% of his time on the project.
- **Prof. Domenico d'Avella** is Professor and Chair of Neurosurgery. His expertise is brain trauma, brain tumors, and pediatric neurosurgery. He will be one of the neuro-surgeons involved in the study. He will coordinate surgical care for the patients treated as part of this study. Percent effort: 10%.
- **Dr. Franco Chioffi,** Director UOC Neurosurgery. Dr. Chioffi is the new Chief of the Neurosurgery Unit of the Padova University Hospital. He has specific experience in brain tumor surgery and neuro-navigation. Percent effort: 10%
- **Prof. Alessandra Bertoldo** is Associate Professor in Bioengineering with specific expertise in brain imaging signals including PET, fMRI, and perfusion. She will be responsible for acquisition and analysis of PET, fMRI and blood flow data collected. She has worked for the last year on optimizing the sequences of the Biograph including multi-band and multi-echo. She will facilitate the development of a rapid analysis pipeline, and she will be involved in data analysis, interpretation and reporting of results. Percent effort: 10%.
- **Prof. Diego Cecchin**, Associate Professor of Nuclear Medicine, is responsible for the Biograph PET/MR system at the Hospital. Prof. Cecchin will be responsible for the PET/MR instrument and will coordinate all phases of the studies (injection of radiopharmaceuticals, quality check,

acquisition of scans of the patients). He will be also involved in data analysis including pre-processing: reconstruction, and elaboration of PET dynamic data, and post-processing: statistical analysis, parcellation, inference. Finally, he will be involved in data interpretation and reporting. Percent effort: 10%.

- **Prof. Chiara Briani** is an Associate Professor of Neurology, and will function as the clinical neurologist for the study. She runs the neuro-oncology clinic in Padova. She will follow up the patients from a clinical standpoint, and answer any clinical question that the patients or their families may have. Percent effort: 5%
- **Dr. Mariagiulia Anglani** is a Staff Neuroradiologist of the University Hospital of Padua. She is responsible for lesion diagnosis and segmentation. Percent effort: 5%
- **Dr. Alessandro Salvalaggio** is a neurologist, currently a PhD student of the Padova Neuroscience Center. He is responsible for patient selection and follow up. He is also involved in lesion segmentation and image analysis, specifically to the question of multi-modal imaging pre-surgery and long-term outcome. Percent effort: 20%
- **Dr. Marco Castellaro** is a bioengineer, currently working as one of the post-doctoral fellows of the Padova Neuroscience Center. He's running some of the pilot studies, and he will be involved in supervising scanning, data pre- and postprocessing, and statistical analyses. Percent effort: 20%

- **Dr. Erica Silvestri** is a bioengineer working with Prof. Bertoldo at Department of Engineering Information (DEI) as post-doctoral fellow. She will be involved in scanning the patients, data pre- and postprocessing, and statistical analyses. She will focus on the pre-surgery description of the tumors based on multi-modal imaging. Her percent effort will be 100% percent for 2 years, and her salary is requested on this grant beginning January 2020.
- **Dr. Silvia Facchini** is a PhD student in Neuropsychology, who will complete her training in October 2019. She will be involved in patient enrollment, development of the neuropsychological analyses, and the correlation with multi-modal imaging. Her effort will be 100% for 2 years, and we request her salary on this grant beginning January 2020.

Partnership

- **Prof. Alessandro Della Puppa** is the director of Neurosurgery at the University Hospital of Firenze. His practice focuses on oncology, vascular, and functional surgery (awake). He will be involved as a collaborator in recruiting additional patients from the Florence Neurosurgery Unit. Percent effort: 10%.

6. METHODS

Subjects

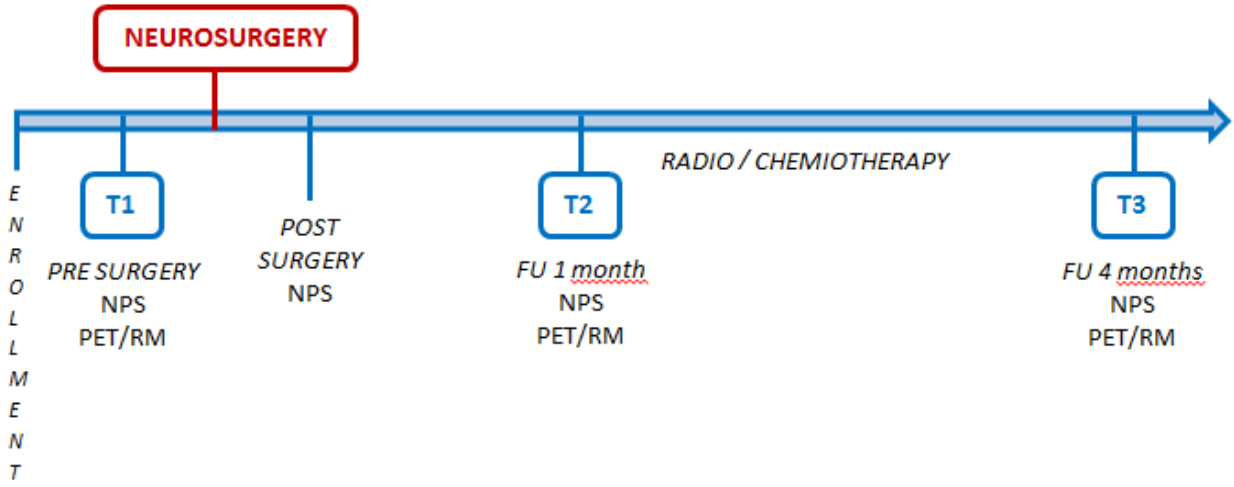
Patients with a clinical diagnosis of glioma. Exclusion criteria: metastases, recurrences, age under 18, history of neurological or psychiatric disorders, history of prior brain surgery, presence of other medical conditions that preclude active participation in research and/or may alter the interpretation of the behavioral/imaging studies, inability to maintain wakefulness during testing and insufficient knowledge of the Italian language.

Time line of research protocol

(T1) 1-week prior to surgery: neuropsychological battery and PET/MRI acquisition. One week after surgery and prior to discharge patients will repeat the same behavioral evaluation. The pre-surgery evaluation serves to obtain a behavioral baseline and neuroimaging data for tumor classification, neuro-navigation, and potentially outcome prediction. The post-surgery behavioral evaluation serves to document post-surgery deficits.

(T2) follow up at 1 month: same neuropsychological battery and 2nd PET/MRI acquisition imaging protocol. This assessment will serve to document behavioral and neuroimaging changes related to re-organization of function/recovery.

(T3) follow up at 4 months: same neuropsychological battery and 3rd PET/MRI acquisition imaging after radiotherapy and chemotherapy and physical /cognitive rehabilitation. This examination will evaluate the effects of therapies on neuronal plasticity and remodeling possibly allowing a better modulation and time scheduling of pharmacological treatment and rehabilitation.



Behavioral assessment

An extensive neuropsychological battery will be administered covering different cognitive domains, including: the Oxford Cognitive Screen (OCS; Demeyere et al. 2015) a brief screening tool composed of tasks on language, visual attention, spatial neglect, praxis abilities, visual and verbal memory, calculation, number reading and executive functions; some subtests of the Esame Neuropsicologico Breve 2 (ENB-II, Mondini et al. 2011): the Trail-Making-Test, forms A and B (selective attention and switching ability), Verbal fluency, Prose memory immediate and delay recall, Interference memory test; the Boston Naming Test (visual naming); the forward and backward Digit span and the Corsi block-tapping test (short-term and working memory) and the Purdue Pegboard Test for manual dexterity and motor speed.

The emotional status and the health related quality of life will be also evaluated using HADS (for depression and anxiety) and QLQC30 (a specific instrument used in neuro-oncology to evaluate the impact of the disease on different life areas).

Imaging assessment

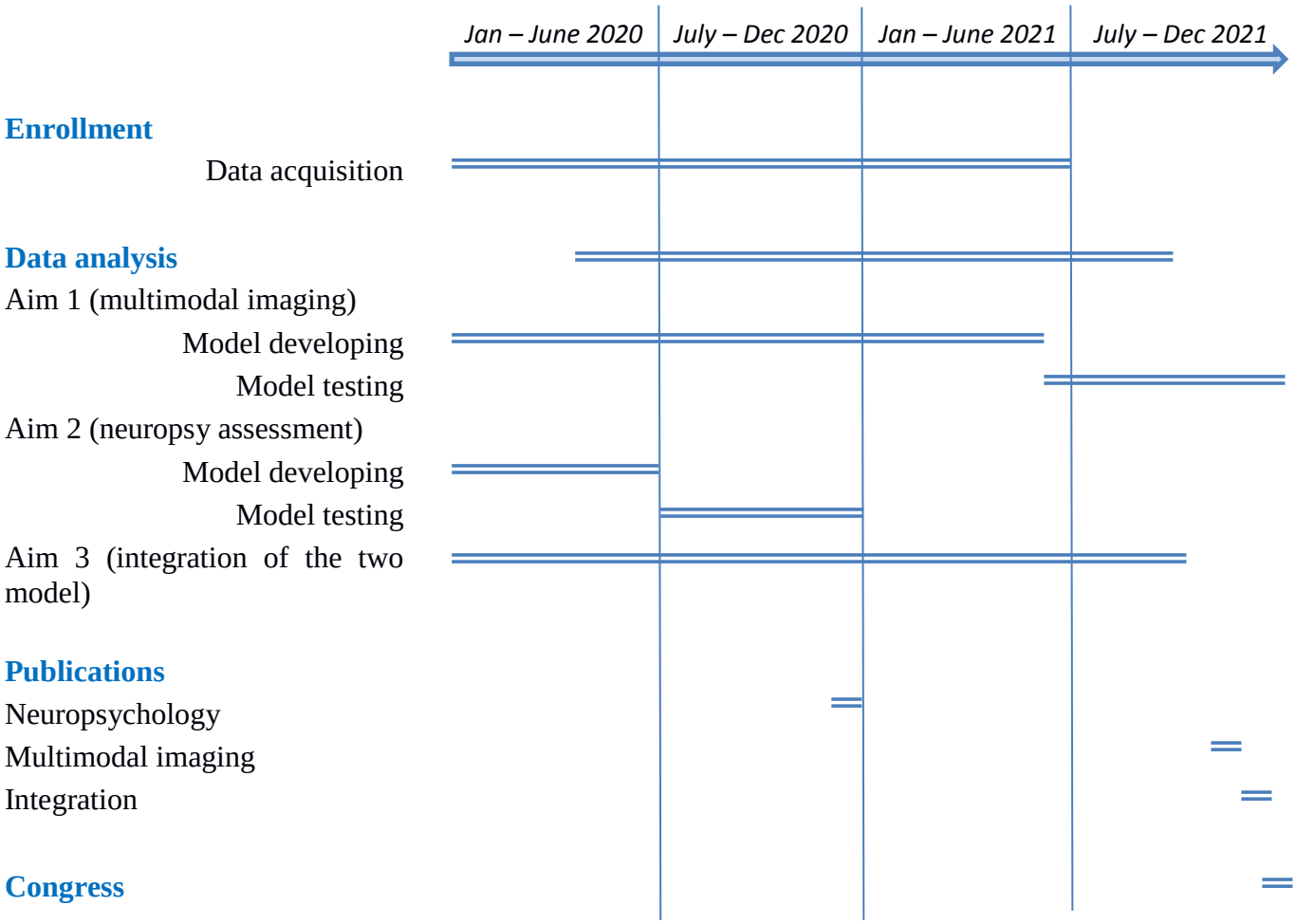
At T1, T2, T3 patients will undergo a PET/MRI scan to measure:
1. Structural information with T1 Volumetric, Flair Volumetric, Diffusion tractography, T2 Axial
2. Functional connectivity using R-fMRI
3. Blood flow and alteration of neurovascular coupling with DSCMRI
4. Glucose metabolism (or amino acid consumption) measured with PET sequentially acquired

PET will be acquired simultaneously (not sequentially) to MRI sequences.

Post-processing imaging data

Cortical segmentation with Freesurfer on T1 images; for fMRI: coregistration, motion correction, field inhomogeneity correction, removal of nuisance regressor, etc.; for PET: motion correction, coregistration, partial volume effect correction. Lesion segmentation will be done manually.

Plan of the activities



3. BUDGET

Consumables	Computer storage	€ 4000
Personnel	*Erica Silvestri* – senior post-doc 30.000/anno x 2 anni (bioengineer: scanning the patients, data pre- and postprocessing and statistical analyses) *Silvia Facchini* – junior post-doc 27.000/anno x 2 anni (neuropsychologist: patient enrollment, development of the neuropsychological analyses and the correlation with multi-modal imaging)	€ 114.000
External services	Processing PNC (Padua Neuroscience Centre – University of Padova)	€ 11.900
Travel expenses	Congress at the end of the project	€ 7100
Others (papers)	Publications	€ 5000
TOT		€ 142.000

4. INFORMATION ABOUT PRINCIPAL INVESTIGATOR AND RESEARCH TEAM

Principal Investigator: Prof. Maurizio Corbetta

Personal informations:

Date of birth: February 3, 1961
Place of birth: Como, Italy
Citizenship: Italian & US

Curriculum vitae:

Education:

- 1993-1996 Residency in Neurology, Barnes Hospital, Washington University School of Medicine Research (no final grade is given)
- 1992-1993 Internship in Internal Medicine, Jewish Hospital, Washington University School of Medicine (no final grade is given)
- 1990-1992 Fellowship in Neuroimaging Barnes Hospital, Washington University School of Medicine, St. Louis, MO (no final grade is given)
- 1986-1990 Residency in Neurology, Institute of Neurology, University of Verona, Italy (30/30 cum laude)
- 1979-1985 M.D. Summa cum laude, University of Pavia School of Medicine, Italy

Academic Positions:

- 2015-present Chair of Neurology, Director Clinica Neurologica, Azienda Ospedaliera Padova, Italy
- 2015-present Professor of Neurology, Department of Neuroscience, University of Padua, Italy

- 2011-2016 Chief, Division of Neuro-Rehabilitation, Department of Neurology
- 2005-2016 Norman J. Stupp Chair Professor of Neurology
- 2014-present Professor of Biomedical Engineering
- 2005-present Professor of Neurology, Radiology, Neuroscience, Washington University School of Medicine, St. Louis, MO
- 2002-2016 Director of Stroke and Brain Injury Rehabilitation, The Rehabilitation Institute of St. Louis
- 2001-2005 Associate Professor in Neurology, Radiology, Anatomy, and Neurobiology, Washington University School of Medicine, St. Louis, MO
- 1997-2001 Assistant Professor of Neurobiology, Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO
- 1997-2001 Assistant Professor in Radiology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO
- 1996-2001 Assistant Professor in Neurology, Department of Neurology and Neurological Surgery, Washington University School of Medicine, St. Louis, MO
- 1990-1996 Instructor in Neurology, Department of Neurology and Neurological Surgery, Washington University School of Medicine, St. Louis, MO

Other professional experiences:

Clinical Activities:

- 2015-present Director Neurology Unit, Clinica Neurologica Azienda Ospedaliera Padova
- 1996-2015 Weekly outpatient clinic specialized in Stroke, TBI, and Cognitive Neurology
- 2001-2015 Attending Physician, TRISL (4 weeks/year): responsible physician for stroke and TBI rehabilitation unit. Patient care, and Residents & Fellows education.
- 1996-2001 Attending Physician, Barnes-Jewish Hospital (4 weeks/year): responsible physician of stroke unit and consultant Neuro-ICU. Patient care & Resident & Fellow education.

Teaching Activities:

- Cattedra di Neurologia, Scuola di Medicina, Università di Padova (2016-present)
- Lecturer in Resident's Teaching Series, PMR Residents (2001-2016)
- Clinical Neuroscience Lecture Series, Neurology Residents WUMS (1996-2015)
- Lecturer in Clinical Neurosciences course 2nd year medical school (1996-2015)
- Lecturer in Neuroscience course 1st year medical school (1996-2015)

Publications

Official H index: 84
Total Publications at 01/09/2019: 201

Selected Publications:

- Baldassarre A, Metcalf NV, Shulman GL, Corbetta M. Brain networks' functional connectivity separates aphasic deficits in stroke.Neurology. 2019 Jan 8;92(2):e125-e135.
- Griffis JC, Metcalf NV, Corbetta M, Shulman GL. Structural Disconnections Explain Brain Network Dysfunction after Stroke. Cell Reports, 2019, 28(10):2527-2540.
- Suweis S, Tu C, Rocha RP, Zampieri S, Zorzi M, Corbetta M. Brain controllability: Not a slam dunk yet. Neuroimage. 2019, 200: 552-555.

- Karolis VR, Corbetta M, Thiebaut de Schotten M. The architecture of functional lateralisation and its relationship to callosal connectivity in the human brain. Nature Communications, 2019, 29;10(1):1417.
- Patel GH, Sestieri C, Corbetta M. The evolution of the temporoparietal junction and posterior superior temporal sulcus. Cortex, 2019, 118: 38-50.
- Corbetta M, Siegel JS, Shulman GL. On the low dimensionality of behavioral deficits and alterations of brain network connectivity after focal injury. Cortex. 2018 Oct;107:229-237. doi: 10.1016/j.cortex.2017.12.017. Epub 2018 Jan 2. Review.
- Siegel, J.S., G.L. Shulman, and M. Corbetta, Measuring functional connectivity in stroke: Approaches and considerations. J Cereb Blood Flow Metab, 2017. 37(8): p. 2665-2678.
- Ramsey, L.E., et al., Normalization of network connectivity in hemispatial neglect recovery. Ann Neurol, 2016. 80(1): p. 127-41.
- Siegel, J.S., et al., Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. Proc Natl Acad Sci U S A, 2016.
- Corbetta, M., et al., Common behavioral clusters and subcortical anatomy in stroke. Neuron, 2015. 85(5): p. 927-41.
- Baldassarre, A., et al., Large-scale changes in network interactions as a physiological signature of spatial neglect. Brain, 2014. 137(Pt 12): p. 3267-83.

Abstracts of the research group about the topic

- Castellaro M., Silvestri E., Bisio M., Metcalf N., Palombit A., Facchini S., Monai E., De Pellegrin S., Baro V., Briani C., Cagnin A., D'Avella D., Della Puppa A., Cecchin D., Bertoldo A., Corbetta M. (2019). Multimodal molecular and functional imaging for a better description of glioma heterogeneity. 49th congress of Società Italiana di Neurologia, Rome, Italy,
- Silvestri E., Castellaro M., Palombit A., Facchini S., Monai E., D'Avella D., Della Puppa A., Cecchin D., Corbetta M., Bertoldo A. (2019). Simultaneous PET/MRI to detect brain tumour metabolic and functional heterogeneity. ISMRM 27th Annual Meeting 2019, Montreal, Canada.
- Silvestri E., Moretto M., Castellaro M., Facchini S., Monai E., D'Avella D., Della Puppa A., Cecchin D., Corbetta M., Bertoldo A. (2019). A whole brain approach to study altered functional connectivity in gliomas. OHBM 25th Annual Meeting 2019, Roma, Italia.
- Facchini S, Zangrossi A, Zannin M, Bisogno AL, D'avella D, Della Puppa A, Anglani M, Semenza C, Corbetta M. "Contrasting and comparing the cognitive profile of brain tumors and stroke: definition of a specific and sensitive neuropsychological battery", XXIII Congresso nazionale e corso residenziale AINO (Associazione Italiana Neuro-Oncologia), 2019, Udine.
- Facchini S, Zangrossi A, Tarantino V, De Pellegrin S, D'avella D, Vallesi A, Della Puppa A, Semenza C, Corbetta M. "Cognitive outcome of patients with brain tumor: the importance of follow-up evaluation. Preliminary data of a longitudinal study", XXII Congresso nazionale e corso residenziale AINO (Associazione Italiana Neuro-Oncologia), Mantova, 2018
- Silvestri E., Castellaro M., Palombit A., Bisio M., Facchini S., Monai E., Cecchin D., D'Avella D., Corbetta M., Bertoldo A. (2018). Multi-modal connectivity mapping of brain tumours using 18-Fluoro-deoxyglucose (FDG) PET and structural-functional MRI. 6th Biennial Conference on Resting State and Brain Connectivity, 2018, Montreal, Canada.

Projects

- **FC-Neuro Progetto Strategico University of Padova** (01/10/2015 – 30/09/2020)
  Maurizio Corbetta, PI
  University of Padova $500,000

- **National Institute of Neurological Disorders (NINDS)** NS095741 (30/09/2015 – 30/06/2016)
  Maurizio Corbetta, PI
  Stroke, Brain Networks, and Behavior $558,553/year for 5 years
  The goal of this grant is to understand the relationship between stroke, behavioral deficits and recovery, and structural/functional correlates of focal damage.

- **FLAG-ERA JTC** (2017-2020)
  Maurizio Corbetta, PI EUR 290,000
  Alterations of functional connectivity in the human brain after focal lesion and cognitive function: empirical and modeling studies (Brain-Synch HIT)

- **Progetto Dipartimenti di Eccellenza Italian Ministry of Research (MIUR)** 01/05//2018-30/04/2023
  Maurizio Corbetta, PI EUR 8,000,000
  Neuro-DIP: Precision Neuroinformatics in Clinical Neuroscience

Collaborations

1. NIH grant: Gustavo Deco, Pompeu Fabra Barcelona; Michel Thiebaut de Schotten, Sorbonne, ParisER.
2. ERA FLAG: Andrea Brovelli, U.Marseilles; Rainer Goebel, Maastricht University
3. ETN (European Training Network): Andreas Engel, U.Hamburg with other 20 researchers throughout Europe.

5. SUPPLEMENTARY INFORMATION

Prof. Alessandro Della Puppa, Director of UOC Neurosurgery at University of Firenze, will contribute to the enrollment of patients, which will be studied with the same RMN and neuropsychological protocol (Support Letter attached).

Struttura Organizzativo Dipartimentale Complessa a direzione Universitaria
NEUROCHIRURGIA
Azienda Ospedaliera Universitaria Careggi
Dipartimento NEUROFARBA – Università degli studi di Firenze

Firenze, 2 September 2019

Object: Grant Fondazione Celeghin

Dear Maurizio,

I am very pleased to participate to the project you are submitting to the Fondazione Celeghin. The project is focused on the development of new multi-modal imaging in brain tumors, through the integration of PET/RM data with behavioral assessments longitudinally as a measure of the functional impact of the lesion, and as a possible new way to neuro-navigate the lesions prior to surgery. This innovative project has the potential to create new ways for the diagnosis, outcome prediction, and surgical treatment of brain tumors. Specifically, the correlation of tumor variables and behavioral outcome with structural, functional, and metabolic metrics of brain organization may lead to more accurate diagnosis and long-term outcome prediction, as well as the development of more accurate hence safer neuro-navigation of brain tumors.

My role in the project will be to sustain the enrollment with patients of the Careggi Hospital in Florence where I direct the Neurosurgery Department, and the execution of RMN and neuropsychological assessment on these patients.

With kind regards,

Prof. Alessandro Della Puppa

Chair
Neurosurgery
Department NEUROFARBA
University Hospital of Careggi
School of Medicine
University of Florence
FLORENCE

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