UNIVERSITÀ DEGLI STUDI DI GENOVA

AREA RICERCA, TRASFERIMENTO TECNOLOGICO E TERZA MISSIONE

SERVIZIO PER IL TRASFERIMENTO TECNOLOGICO E DELLE CONOSCENZE

SETTORE VALORIZZAZIONE DELLA RICERCA, TRASFERIMENTO TECNOLOGICO E RAPPORTI CON LE IMPRESE

IL RETTORE

Vista la Legge 9 maggio 1989, n. 168 - Istituzione del Ministero dell'Università e della ricerca scientifica e tecnologica e ss.mm.ii;

Visto lo Statuto dell'Università degli Studi di Genova;

Visto il Regolamento Generale di Ateneo;

Visto il Regolamento di Ateneo per l'Amministrazione, la Finanza e la Contabilità;

VISTA la legge 7 agosto 1990, n. 241 recante "Nuove norme in materia di procedimento amministrativo e di diritto di accesso ai documenti amministrativi" pubblicata sulla Gazzetta Ufficiale n. 192 del 18/08/1990 e s.m.i.;

VISTO il Decreto del Presidente della Repubblica 28 dicembre 2000, n. 445 (Disposizioni legislative in materia di documentazione amministrativa) e s.m.i.;

VISTO il Decreto Direttoriale MUR n. 341 del 15/03/2022 di emanazione di un Avviso pubblico per la presentazione di Proposte di intervento per la creazione di "Partenariati estesi alle università, ai centri di ricerca, alle aziende per il finanziamento di progetti di ricerca di base" nell'ambito del Piano Nazionale di Ripresa e Resilienza, Missione 4 "Istruzione e ricerca" – Componente 2 "Dalla ricerca all'impresa" – Investimento 1.3, finanziato dall'Unione europea – NextGenerationEU";

VISTO il Decreto Direttoriale MUR n. 1553 dell'11/10/2022 di concessione del finanziamento del progetto Codice identificativo PE00000006, Acronimo MNESYS, Titolo "*A multiscale integrated approach to the study of the nervous system in health and disease*", registrato alla Corte dei Conti il 23/11/2022 al n. 2948 e relativi allegati;

CONSIDERATO che l'Università degli Studi di Genova è leader dello Spoke 6, dal titolo "*Neurodegeneration, trauma and stroke*";

CONSIDERATO che gli Spoke possono emanare - nell'ambito dei limiti e con le modalità previste dall'Avviso - "bandi a cascata" finalizzati alla concessione di finanziamenti a soggetti esterni per attività coerenti con il progetto approvato;

VISTA la delibera della seduta del 27 settembre 2023 con cui il Consiglio di Amministrazione dell'Università degli Studi di Genova ha approvato l'emanazione del bando a cascata per organismi di ricerca nell'ambito del Progetto MNESYS - "*A multiscale integrated approach to the study of the nervous system in health and disease* - PNRR M4C2 per lo Spoke 6;

VISTO il Decreto del Direttore Generale n. 5418 del 14 novembre 2023 di nomina del Responsabile

del Procedimento;

VISTO il Decreto del Rettore n. 5439 del 14 novembre 2023 e il Decreto Rettorale n. 5474 del 15 novembre 2023 di emanazione del Bando a cascata per il finanziamento di proposte di intervento per le attività di ricerca svolte da Organismi di Ricerca nell'ambito del programma di ricerca PE MNESYS "*A multiscale integrated approach to the study of the nervous system in health and disease*", per lo Spoke 6 dal titolo "*Neurodegeneration, trauma and stroke*", nell'ambito del PNRR, Missione 4, Componente 2, Investimento 1.3 – finanziato dall'Unione europea – NextGenerationEU (CUP D33C22001340002);

CONSIDERATO che alla data di scadenza per la presentazione delle proposte progettuali, fissata entro e non oltre il giorno 14 dicembre 2023, per la **Tematica B – "Cell- and microcircuit-level experimental multimodal probing and digital reconstruction of cortical human brain tissue: linking structure and function by in vitro multi-site and multi-scale recording techniques with in silico simulation"** era pervenuta a mezzo PEC all'indirizzo air3@pec.unige.it la seguente proposta:

PROPONENTE: Università degli Studi di Modena e Reggio Emilia
TITOLO PROPOSTA: FITS – (dys)Functional Information Transfer in ex vivo human brain tissue Samples: a multiscale investigation through in vitro and in silico approaches

TENUTO CONTO che la Responsabile del procedimento, Ing. Patrizia Cepollina, ha ritenuto ricevibile, ammissibile e conforme la proposta sopra citata;

CONSIDERATO che nel Bando è previsto che la valutazione di merito tecnico-scientifico dei progetti pervenuti sia affidata ad una Commissione composta da almeno tre esperti esterni al Partenariato, indipendenti e competenti dell'Area tematica dello Spoke;

VISTO il Decreto Rettorale n. 6114 del 20 dicembre 2023 con cui è stato emanato l'Avviso di manifestazione di interesse per la costituzione di un albo di esperti indipendenti a supporto della valutazione di merito dei progetti PNRR presentati sui bandi a cascata del progetto MNESYS – A multiscale integrated approach to the study of the nervous system in health and disease;

VISTO l'Estratto del Verbale della Riunione del 12 febbraio 2024 del Comitato Scientifico del programma di ricerca MNESYS "*A multiscale integrated approach to the study of the nervous system in health and disease*" che ha approvato la "Rosa di Candidati" per le Commissioni di Valutazione dei Bandi a cascata sul Programma MNESYS;

VISTO il Decreto del Rettore n. 855 del 20 febbraio 2024 con cui è costituito l'Albo a supporto delle valutazioni dei progetti presentati in risposta al bando pubblico per la selezione di proposte progettuali da finanziare nell'ambito delle attività di ricerca dello Spoke n. 6 di cui al programma di "*A multiscale integrated approach to the study of the nervous system in health and disease*" – MNESYS, a valere sulle risorse del Piano Nazionale di Ripresa e Resilienza (PNRR), Missione 4 "Istruzione e Ricerca", Componente 2 "Dalla ricerca all'impresa", linea di Investimento 1.3 "Creazione di Partenariati Estesi alle università, centri di ricerca, alle aziende per il finanziamento di progetti di ricerca di base";

VISTO il Decreto del Rettore n. 1131 5 marzo 2024 con cui è stata nominata la Commissione di valutazione delle proposte pervenute in risposta al bando a cascata di cui al D.R. n. 5439 del 14 novembre 2023, indicato nelle premesse del presente decreto;

ACQUISITO il verbale della Commissione di Valutazione della seduta del 16 aprile 2024 (Prot. n. 37982 del 07/05/2024);

VISTO il Decreto del Rettore n. 2286 del 10 maggio 2024 con cui è stata approvata la graduatoria di merito per la Tematica B – "Cell- and microcircuit-level experimental multimodal probing and digital reconstruction of cortical human brain tissue: linking structure and function by in vitro multi-site and multi-scale recording techniques with in silico simulation", di cui al bando a cascata di cui al Decreto del Rettore n. 5439 del 14 novembre 2023, indicato nelle premesse del presente decreto;

TENUTO CONTO che in data 14 maggio 2024 è stata inviata all'Università degli Studi di Modena e Reggio Emilia la comunicazione con prot. n. 41369 in cui si rendevano noti gli esiti della procedura e si richiedeva la documentazione propedeutica all'adozione del provvedimento di ammissione del finanziamento;

VISTO che in data 20 maggio 2024 con prot. n. 43926 la documentazione richiesta è stata ricevuta dall'Università degli Studi di Genova che l'ha ritenuta conforme a quanto previsto nel bando a cascata di cui al Decreto del Rettore n. 5439 del 14 novembre 2023 e il Decreto Rettorale n. 5474 del 15 novembre 2023, indicato nelle premesse del presente decreto,

DECRETA

ART. 1

L'ammissione a finanziamento del FITS – (dys)Functional Information Transfer in ex vivo human brain tissue Samples: a multiscale investigation through in vitro and in silico approaches per la **Tematica B – "Cell- and microcircuit-level experimental multimodal probing and digital reconstruction of cortical human brain tissue: linking structure and function by in vitro multi-site and multi-scale recording techniques with in silico simulation"** con Soggetto proponente l'Università degli Studi di Modena e Reggio Emilia – come rappresentato negli Allegati B e C alla proposta presentata con domanda di partecipazione prot. n. 73742 del 12 dicembre 2023.

ART. 2

L'entità dell'agevolazione concessa, a fondo perduto, ammonta a 149.793,14 euro complessivi come rappresentati nell'allegato C alla proposta presentata con domanda di partecipazione prot. n. 73742 del 12 dicembre 2023. L'agevolazione è pari al 100% dei costi di progetto trattandosi di attività di ricerca fondamentale per Organismi di Ricerca. L'agevolazione è concessa a valere sui fondi PNRR - Programma "*A multiscale integrated approach to the study of the nervous system in health and disease*" – MNESYS Codice PE00000006 a valere sulla Missione 4, Componente 2, Investimento 1.3, ai sensi del Decreto di concessione n. 1553 dell'11 ottobre 2022, registrato alla Corte dei Conti il 23/11/2022 n. 2948, iscritto al Bilancio di Ateneo sul progetto UGOV 100009-2022-TF-PNRR-

PE_MNESYS_BAC_DINOGMI.

ART. 3

Le attività, come indicate dettagliatamente nell'Allegato B alla domanda di finanziamento, dovranno essere avviate a partire dalla data di sottoscrizione del Contratto e concluse entro e non oltre 12 mesi, affinché siano rendicontate in tempo utile per consentire la chiusura del Programma PE MNESYS, il cui termine è attualmente previsto al 31 ottobre 2025.
Potrà essere valutata e concessa una sola proroga in presenza di ritardi dovuti a circostanze eccezionali e non dipendenti da scelte del Beneficiario esclusivamente nel caso in cui il MUR, a sua volta, proroghi il termine del Programma MNESYS.

ART. 4

Il presente atto sarà pubblicato sul sito UniGe https://unige.it/progetti-finanziati-dal-pnrr e laddove la normativa vigente lo richiede.
Il documento informatico originale sottoscritto con firma digitale sarà conservato presso l'Area Ricerca, Trasferimento Tecnologico e Terza Missione.

ALLEGATI:

Allegato B – Proposta progettuale
Allegato C – Piano economico-finanziario

IL RETTORE
Prof. Federico DELFINO
(documento firmato digitalmente)

ANNEX B

PE00000006
"A multiscale integrated approach to the study of the nervous system in health and disease"

MNESYS

SPOKE N. 6

Research proposal

Topic *b*: Cell- and microcircuit-level experimental multimodal probing and digital reconstruction of cortical human brain tissue: linking structure and function by *in vitro* multi-site and multi-scale recording techniques with *in silico* simulation.

FITS

(dys)**F**unctional **I**nformation **T**ransfer in *ex vivo* human brain tissue **S**amples: a multiscale investigation through *in vitro* and *in silico* approaches

- Name of the PIs' host institution for the project: **University of Modena and Reggio Emilia (UNIMORE)**
- Name of the Principal Investigators (PIs): **Prof. Dr. J. MAPELLI**
- Proposal duration in months: **12**

ROLE	***NAME***	***SURNAME***	***DEPT.***	***QUALIFICATION***	***YOUNG (<40)***	***F/M***
PI	*Jonathan*	*Mapelli*		*Associate Professor*	*No*	*M*

Co-PI	*Stefano*	*Meletti*		*Associate Professor*	*No*	*M*
Participant	*Giacomo*	*Pavesi*		*Associate Professor*	*No*	*M*
Participant	*Albertino*	*Bigiani*		*Full Professor*	*No*	*M*
Postdoc 1	*N/A*	*N/A*		*Assegnista(to be hired)*	*N/A*	*N/A*
Postdoc 2	*N/A*	*N/A*		*Assegnista(to be hired)*	*N/A*	*N/A*

ABSTRACT

The complexity of the human brain is poorly captured by animal tissue models or human pluripotent stem cells. While animal neurophysiology advanced basic Neuroscience, its translation to human brain disorders often fails. Organoids and stem cell cultures certainly match personalised genetic details, but unavoidably lack tissue cytoarchitectonics and microcircuitry realism. FITS uniquely combines cutting-edge electrophysiology, imaging, and in silico modelling with routine access to fresh human tissue samples, obtained from resective therapeutic neurosurgery. This novel route of investigation does recapitulate synaptic and network-level components of abnormal excitability and neurodegeneration, especially for hippocampal and cortical pathologies. Matching academic and clinical excellence, thanks to a unique geographical proximity between research labs and neurosurgery, FITS exploits advanced cell- and microcircuit-levels characterisation focusing on brain rhythms in health and diseases. By ultimately employing data to build accurate *in silico twins* of the microcircuits of interest, FITS closes a conceptual loop: from single-cell and (sub)cellular biophysical properties to (dys)functional network rhythms. Ultimately, the combined experimental and modelling characterisation will serve as a compact *fingerprint*, linking firing activity and electroresponsiveness across time-scales offering in future an (un)supervised identification of significant alterations associated to neurodegeneration such as neuronal dysplasia and epileptic activity. The electrophysiological data sets, the live and structural imaging data, and the models will lead to accurate computational descriptions of (dys)functional human cortical neurons and microcircuits, representing an additional perspective for personalised pharmacological screening and predictive medicine *in a dish*. FITS' multimodal combination of functional/structural data and *in silico* models will advance our knowledge and immensely boost scope and significance of neurophysiology, neurotechnologies, drug-screening, and mesoscopic *Brain Digital Twin reconstructions*.

RESEARCH PROPOSAL

Section a. State-of-the-art and objectives

Human cognitive abilities are unrivalled by those of any other mammal [1]. Differences in brain size, encephalization, neocortical thickening and specialisation of microcircuits [2,3] certainly contribute, besides genetic factors [4], to superior human cognitive performances. Ultimately however, **neuronal excitability** and **synaptic transmission** are the most relevant **building blocks underlying information representation, processing, and storage in health and disease** [5]. Then, given the vast number of (e.g. cortical) neurons and synapses, in the order of a million and trillion per cm^3, respectively [6], even **subtle differences in human (sub)cellular physiology - compared to other animals –** translate in a **dramatic boost in brain's operation and performance, with deep implications for our understanding of brain (dys)functions** [7].

Moreover, the sheer complexity of the human brain and the specific heterogeneity of its cellular and synaptic components, unveiled in comparative studies our team contributed to [8] (Fig. 1), **ultimately weaken the translational perspectives of current animal models of brain disorders.** While *in vitro* and *in vivo* animal studies are routinely featured in preclinical phases of neurotherapeutic drugs-development, they are often not sufficiently representative of disorders of the human nervous system. Failures become apparent during the clinical phases, after millions of euros have already been invested in trialling candidate molecules [9]. In the case of excitability disorders, **anti-epileptic drugs (AEDs) still fail in 30% of patients (i.e. drug resistance)**, despite today's availability of a third generation of compounds [10], and corresponding to **1.1+M patients** across the U.S., Japan and EU - and **23M patients worldwide**. While *in vitro* human stem cells reprogramming and cerebral organoids/spheroids have been proposed for an accurate genetic match, these preparations fail to recapitulate the microcircuit- and network-level dimensions of human brain tissue [11], which is key to capture inter-patient variability and *mesoscale* abnormalities of many brain disorders.

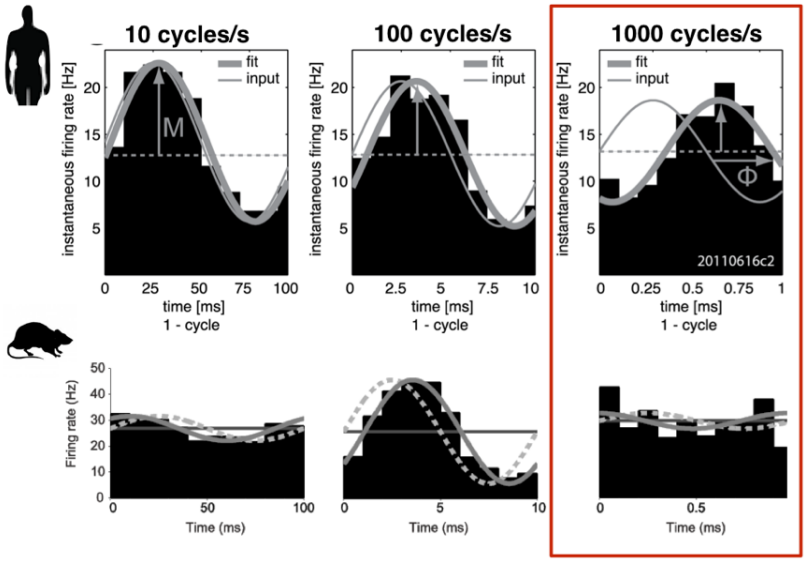

Figure 1: Results from our team [8] unveiled quantitative differences in excitability time scales: *human neurons relay much faster oscillatory inputs (up to 1000 cycles/s) than rodents,* as shown by spikes PSTHs.

Under these perspectives, **FITS targets both fundamental and translational research priorities of human brain tissue cell electrophysiology and cellular morphometric analysis**. This is possible by **direct access to the intact cytoarchitecture of *ex vivo* adult tissue samples**, obtained from therapeutic resective neurosurgeries in patients (Fig. 2).

FITS' main focus is on the mechanisms of brain rhythms in health [5,12,13] and diseases, such as epilepsy, Parkinson's, sleep disorders, and rhythm-based cognitive maladies.

Ultimately, **FITS aims at dissecting** neuronal excitability and dysfunctional network-level oscillations [14,15]. Given the project expected lifetime, FITS' ambition is restricted in view of the existence of **high-frequency epileptiform oscillations (60-100 cycles/s), fast ripples (260-600 cycles/s) and even faster oscillations (above 1000 cycles/s) recently described in epileptic patients** [15]. While these phenomena may predict ictogenesis [14], and intriguingly occur within the same bandwidth we had reported at single-cell level [8], they cannot yet be adopted as a biomarker (e.g. for operating future brain pacemakers and neuroprosthetics), without further mechanistic investigations.

By a multiscale approach, combining together single-cell, network electrophysiology and *in silico* modelling, **FITS' long-term goal is *linking brain (patho)physiological network rhythms and synchronisation to biophysical properties, upon a systematic and comparative characterization of the dynamical transfer function of human cortical and hippocampal cells***. Such an explicit link is possible by the **quantitative framework** *of "sparsely synchronised oscillations"*, reviewed in [12] (see also [16]).

FITS' hypothesis is that, when probed by accurate experimental protocols [8,16,17] and a multiscale approach, the **human cortical and hippocampal microcircuits reveal considerable differences from rodents'**. To accept or reject this hypothesis, FITS will gather experimental cellular evidence *in vitro* and explore network-level consequences by experiments and by realistic computer modelling and simulations.

FITS has 4 short-term objectives, designed to be Specific, Measurable, Achievable, and Time-realistic:

O1. optimise and standardise *ex vivo* acute/semi-organotypic human brain tissue samples **protocols for routine electrophys. experiments**, with comparison with standard rodent brain tissue;

O2. measure single-cell dynamical spiking response properties (in the Fourier domain) by patch-clamp, across cell types in temporal lobe structures, while reconstructing their morphology;

O3. incorporate all these data into ***in silico* multicompartmental mathematical models, to be** included in realistic 3-D cytoarchitectonic scaffolds, capturing cortical/hippocampal microcircuitry;

O4. validate *in silico "twin"* network activity against extensively measured observables in tissue slices, acquired by arrays of microelectrodes, for a first integrative step towards FITS' main goal.

Section b. Methodology

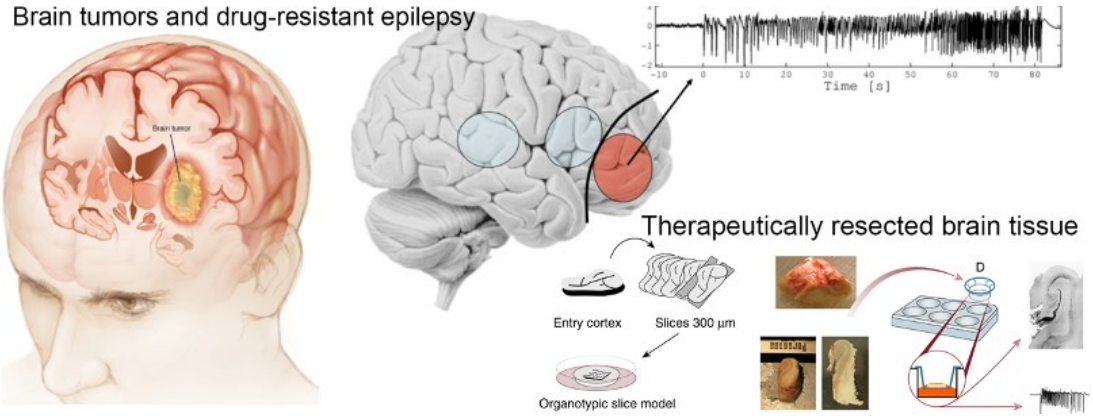

Figure 2: FITS' core: *access to human brain tissue is granted from routine resective neurosurgery.*

Developing routine cellular/network electrophysiological experiments, analysis and mathematical modelling, based on human brain tissue slices, is **at the frontiers of current research [18].** Due to human brain anatomy, during routine surgical treatment of drug-resistant epilepsies or brain tumours, the removal of healthy cerebral and hippocampal tissues is unavoidable to access the deeper structures of interest (e.g., the epileptic focus or the tumour) [19]. The neurosurgeon goes through healthy brain tissue when access to deep lesions must be gained (e.g. for non-superficial glioma, for tumours located in ventricular regions, for partly infiltrated regions, as well as for deep epileptic foci). Routinely, a portion of this tissue is sent to neuropathologists for morphological and histochemical analysis, while the rest is treated as biological waste.

We will then collect the small brain tissue samples (otherwise disposed) and use them in our labs (Fig. 2), as an ethically advantageous **opportunity**, currently **pursued only at a few excellence centres worldwide** (e.g., Vrije Univ. Medical Center of Amsterdam, Albert-Ludwigs-Univ. of Freiburg, Charite Medical Univ. of Berlin, Hôpitaux Univ. Pitié Salpêtrière of Paris, Centre Hospitalier Univ. Vaudois of Lausanne, Swedish Medical Centre/Allen Inst. of Seattle, Harborview Med. Centre of Washington state).

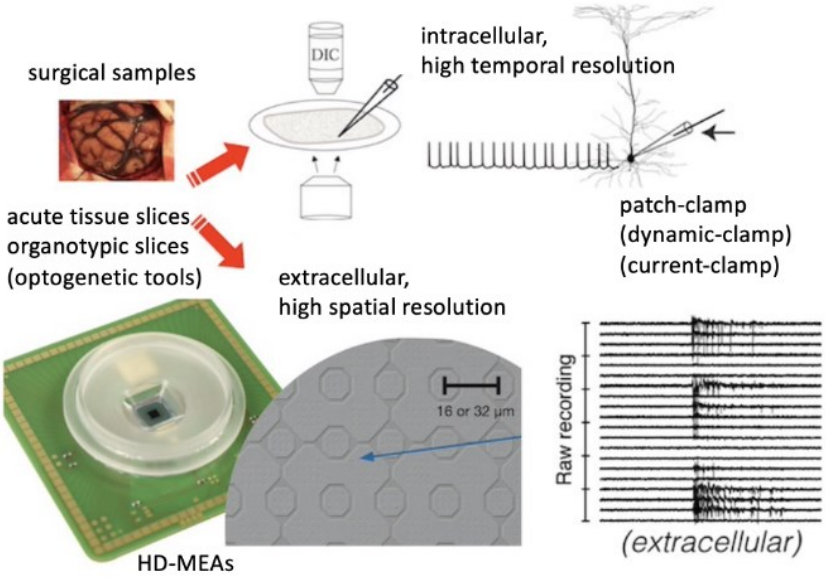

Figure 3: *Human brain tissue slices will be employed for intracellular (i.e. single-cell) and extracellular (i.e. network-level) electrophysiology, probing single-cell excitability, bandwidth, and transfer properties, as well as network-level excitability, rhythms as well as the spontaneous synchronisation.*

Fig. 3 sketches our methodology, using 1) brain tissue slices from humans; 2) differential-interference contrast (DIC) microscopy for guided whole-cell patch-clamp recordings and stimulation from the soma of cortical neurons; and 3) CMOS-based substrate-integrated microelectrode arrays (MEAs) for electrical recording/stimulation of network-level neuronal activity from (e.g.) 4225 individual sites.

Samples collected in the UNIMORE neurosurgery unit at the Baggiovara Hospital, will be immediately placed in a beaker filled with ice-cold artificial cerebrospinal fluid and transported to the experimental setups. Brain tissue will be sliced (300-350µm) by a vibratome, incubated and stored in an interface chamber until transfer to upright microscopes for patch-clamp. Slices will be also coupled to the surface of commercial (CMOS) substrate arrays microelectrodes (MEAs), recording multisite local field potentials and multiunit activity, under a variety of ionic (i.e. K+, Mg++, Ca++) and pharmacological manipulations (i.e. AMPAr/NMDAr agonists, GABAr antagonists), and delivering complex electrical stimuli and photoactivation. The latter will be generated by a PC and coupled via appropriate insulation electronics and wide-field light stimulators. Commercial AAV vectors, from commercial providers (e.g. VectorBuilder, AddGene, etc.) will be used for optogenetic transduction in CamK2a-expressing neurons.

With regards to patch-clamp, upright DIC microscopes will be employed to visually locate layer 2/3 and 5 cortical neurons (i.e. pyramidal, somatostatin-positive and parvalbumin-positive interneurons, to be further identified by immunohistochemistry a posteriori or tagged a priori by AAV vectors) as well as CA3 hippocampal neurons (i.e. thorny and a-thorny pyramidal cells, granule cells) in a submerged recording chamber. Recordings will be performed at physiological temperature, under continuous ACSF perfusion. Recordings and current injections will be performed with a single electrode by a patch-clamp amplifier, employing a linear non-parametric identification method for accurate on-line electrode compensation. Recorded signals and external signal-commands will be sampled at a 20kHz and 16-bit A/D resolution. Slices

will be then fixed for immunohistochemistry, and neuronal morphologies will be analysed under 2-photon microscopy and digitally reconstructed, confirming identity, and spatial localization and making it available for multicompartmental model optimisation and parameters best fit.

FITs is defined by 4 scientific work packages (WPs), designed to be risk-tolerant. Should e.g. the most severe risk occur to the backbone WP1 (i.e. limited access to human cortical tissue samples), WP2-4 would still progress - limited to hippocampal animal tissue - contributing to advance network physiology. Allowing project monitoring and interventions in case of unexpected delays, each WP carries a set of milestones. We report below only WPs' objectives, milestones, and timeline (in Months from the project start).

WP1 – Protocols refinements for viable human tissue electrophysiology and 2-photon morphometry

Task 1.1: optimising **tissue handling, AAV opsins transduction, and viability** for experiments; **Task 1.2:** refining biocytin **histochemistry for identification & morphological reconstruction**;
Milestones (with expected month, indicated) **1:** First routine recordings in human brain tissue slices (M2) **2:** First routine biocytin staining and morphological identification (M3)

WP2 – Dynamical transfer properties of principal neurons and interneurons

Task 2.1: Characterization of **pyramidal neurons**, by current- and conductance-clamp protocols; **Task 2.2:** Characterization of **fast-spiking GABAergic interneurons**, expressing somatostatin; **Task 2.3:** Characterization of **adapting GABAergic interneurons**, expressing parvalbumin;
Milestones **3:** Comparing current- & conductance-clamp in pyramidal neurons (rodents & humans) (M5) **4:** Dynamical transfer function for SOM+ interneurons in rodents (M5) **5:** Dynamical transfer function for SOM+ interneurons in humans (M5) **6:** Dynamical transfer function for PV+ interneurons in rodents (M7) **7:** Dynamical transfer function for PV+ interneurons in humans (M7)

WP3 – Optogenetic, pharmacological, ionic, and electrical manipulation of brain slices activity

Task 3.1: Robust local-field potential and multiunit recordings by MicroElectrode Arrays (MEAs) **Task 3.2:** Induction and characterization of spontaneous/epileptiform activity *ex vivo*
Milestones **10:** Successful recording of spontaneous or elicited LFP and multiunit activity (M10)

WP4 – *In silico* twin design and HPC computer simulation and comparison with data

Task 4.1: NEURONcore simulations and BluePyOpt parameters optimisation; **Task 4.2:** NEURONcore simulations of cortical and hippocampal scaffold, generating rhythms
Milestones **11:** First "release" of human pyramidal neuron models (M10) **12:** First "release" of network scaffold, generating spontaneous/evoked network activity (M12) **13:** Network-scale parameters selection for matching *in vitro* and *in silico* data (M12)

Deliverables (with month of delivery, indicated)

D1. Partial results dissemination at a workshop (M6)

D2. Report on Magnitude/Phase of cortical cells: human vs rodents, *in vitro* vs *in silico* (M10)

D3. Report on Magnitude/Phase of hippocampal cells: human vs rodents, *in vitro* vs *in silico* (M11)

D4. Report on Power spectra of network activity: human vs rodents, *in vitro* vs *in silico* (M12)

D5. Final results dissemination at a workshop & manuscript submission (M12)

References

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Section c. Available instrumentations and resources

- **4 x** patch-clamp fully-equipped electrophysiology setups: intracellular recordings, pair recordings, current-clamp, voltage-clamp electrophysiology, dynamic-clamp, horizontal pipette pullers, 2 x fresh-tissue vibratomes, organotypic slice culture incubators;
- **4 x** MEAs/CMOS high-density MEAs multisite extracellular electrophysiology setups (120-4225 substrate-integrated microelectrodes);
- **2 x** Wide-field LED optogenetic stimulators: active feedback photo-stimulator;
- Cell- and tissue-culture facilities: fully equipped L1/L2 labs with hoods, centrifuges, -80C fridges;
- **Two-photon** dedicated microscope, **Light-sheet** microscope; access to fluorescence microscopy facility (confocal and epifluorescence);
- On-site tissue lab at Neurosurgery unit (ospedale di Baggiovara).
- HPC + dedicated "in house" multicore workstations + privileged access to (Tier 1) HPC at CINECA: high-performance computing and (large) data-sets storage infrastructures;

- Extensive lab and office space for the newly (to be) recruited personnel.

Section d. GANTT diagram

N.	WP TITLE	YEAR 1											
		1	2	3	4	5	6	7	8	9	10	11	12
WP1	**Protocols refinements for viable human tissue electrophysiology and 2-photon morphometry**												
T1.1	Optimising tissue handling, AAV opsins transduction, and viability for experiments												
T1.2	Refining biocytin histochemistry for identification & morphological reconstruction												
	Deliverables						D1						D5
WP2	**Dynamical transfer properties of principal neurons and interneurons**												
T2.1	Characterization of pyramidal neurons, by current- & conductance-clamp protocols												
T2.2	Characterization of fast-spiking GABAergic interneurons, expressing somatostatin												
T2.3	Characterization of adapting GABAergic interneurons, expressing parvalbumin												
	Deliverables										D2	D3	
WP3	**Optogenetic, pharmacological, ionic, and electrical manipulation of brain slices activity**												
T3.1	Robust local-field potential and multiunit recordings by MicroElectrode Arrays												
T3.2	Induction and characterization of spontaneous/epileptiform activity ex vivo												
	Deliverables												D4, D5
WP4	**In silico twin design and HPC computer simulation and comparison with data**												
T4.1	NEURONcore simulations and BluePyOpt parameters optimisation												
T4.2	NEURONcore simulations of cortical and hippocampal scaffold, generating rhythms												
	Deliverables										D2	D3	D4, D5
	Milestones		1	2		3,4,5		6,7			10,11		12,13

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Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
Università di Genova
MNESYS

PERSONAL INFORMATION - JONATHAN MAPELLI

Researcher unique identifier: https://orcid.org/0000-0002-0381-1576

Date of birth: Oct 15th 1976 (47 y)

Nationality: Italian

URL for web site: https://www.nilab.unimore.it/

H-index: 22 (Google Scholar), 18 (Scopus); n = 42 "documenti Scopus"

ASN for "*Prima Fascia*": 05/D1 since 2023;

Research funding attraction: 1 M€

Patents: 2

EDUCATION

2006 University of Pavia (I), ***Doctorate in Physiology***

2002 University of Milan (I): ***Physics***

CURRENT POSITIONS

2018 – Dept. NEUBIOMET, UNIMORE (Modena), ***Associate Prof.*** **(BIO/09 - 05/D1, Physiology)**

PREVIOUS POSITIONS

2012 – 2018 Dept. NEUBIOMET, UNIMORE (Modena, I), ***Assistant Prof.*****(BIO/09 - 05/D1, Physiology)**

2011-2012 Fondazione C. Mondino IRCCS (Pavia, I)
Researcher

2007-2011 University of (Pavia, I), Dept Brain and Behavior **Post-Doc (D'Angelo's Lab)**

2006-2007 Non-Linear Spectr. Lab, Biophotonics lab (Florence, I) **Visiting researcher (Pavone's Lab)**

FELLOWSHIPS AND AWARDS

2004 "BeNeFri" PhD Programme in Neuroscience, Universities of Bern, Fribourg,Neuchatel (CH)

2010 Travel award to attend the IBRO Meeting (Florence 2010)

2011 Young researcher in Physiology (Italian Physiological Society)

2015 Cover of the scientific journal "Neurophotonics"

2015 Innovation grant (20,000 Euros) by the University of Milano Bicocca

SUPERVISION OF GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS

2012 – 2023 UNIMORE Supervision of 4 PhD students, 4 Post-Docs and 14 Undergrad. Students

2006 – 2014 UNIPV Supervision of 2 PhD students, 5 Undergraduate students

ORGANISATION OF SCIENTIFIC MEETINGS

2020 – 2023 Brain inspired computing workshop (BICW - Modena, Italy)

2014 International conference on Organic Electronic (ICOE 2014, Modena Italy)

INSTITUTIONAL RESPONSIBILITIES

2021 – UNIMORE, *Scientific Director of the "Centro Interdipartimentale per la stabulazione"*

2020 – UNIMORE, Departmental. Delegate for the dissemination

2021 – Member, "Commissione Interateneo for designing bachelor degree in Engineering for medical systems"
2023 – Member, "Commissione Interateneo for designing Master degree in Bioengineering for innovation in medicine"
2013 – UNIMORE, Neuroscience Area, Doctoral School, Faculty
2022 – TAN, Italian National PhD in Neuroscience, Doctoral School, Faculty

REVIEWING ACTIVITIES

2013 – Associate Editor for "*Frontiers in Cellular Neuroscience*" (open access)
2019 – Guest Associate Editor for "*International Journal of Molecular sciences*" (open access)
2016 – Special topic Editor for "*Frontiers in Neuroscience - Neural Tech.*" (open access)
2010 – Ad hoc reviewer for: iScience, Journal of Physiology, Scientific Reports, Brain, PLoS One, Frontiers in Cellular Neuroscience
2022 – 2023 ANR - France "Agence Nationale de la Recherche", Grant evaluator
2020 Regione Puglia, Grant evaluator
2017-2018 Cosyne symposium Salt Lake City (Utah, USA), Denver (Colorado, USA), external reviewer

MEMBERSHIPS OF SCIENTIFIC SOCIETIES

2010 – Italian Society of Physiology (SIF)
2008 – Federation Eur. Neurosci. Societies (FENS)
2007 – Italian Society of Neurosciences (SINS)

MAJOR COLLABORATIONS

Dr. M. Migliore National Research Council, Institute of Biophysics (Palermo, Italy)
Prof. Dr. V. Jirsa, University of Marseille (Marseille, France)
Prof. Dr. K. Friston, University College London (London, UK)
Prof. Dr. R. Van De Plas, TU Delft (Delft, The Netherlands)

Curriculum vitae of **MELETTI** Stefano
Researcher unique id. & webpage: 0000-0003-0334-539X (ORCiD)
personale.unimore.it/rubrica/dettaglio/smeletti
Citizenship, date of birth: Italian; 12 August 1969

EDUCATION

2018	Master in Management for Direction of Complex Health Facilities, UNIMORE, Italy
2002	PhD in applied physiology. Univ. of Bologna, Italy. (with Prof. Carlo Alberto Tassinari)
1996 - 2000	Clinical training in neurophysiology, epilepsy and sleep. Univ. of Bologna, Bologna, Italy
1999	Specialisation in Neurology. University of Bologna, Bologna, Italy.
1995	Doctor of Medicine and Surgery (MD). Univ. of Bologna, Medical School, Bologna, Italy

CURRENT POSITION(S)

2019 -	Director of Neurology & Neurophysiology, Azienda Ospedaliera-Universitaria Modena, Italy
2018 -	Director of Epilepsy Surgery Program, Azienda Ospedaliera-Universitaria Modena, Italy
2018 -	Director residency school of Neurology. University of Modena and Reggio-Emilia, Italy

PREVIOUS POSITIONS

2010 – 2017	Assistant professor of Neurology. University of Modena and Reggio-Emilia, Modena, Italy
2007 – 2010	Tenure-track researcher in Neurology. Univ. of Modena and Reggio-Emilia, Modena, Italy
2007 - 2019	Director of Epilepsy centre. Azienda Ospedaliera-Universitaria Modena, Modena, Italy
2004 – 2007	Consultant in Neurology, Azienda Ospedaliera-Universitaria Modena, Modena, Italy
2003 – 2006	Research lecturer. Department of Neurological Sciences, Univ. of Bologna, Bologna, Italy.

FELLOWSHIPS AND AWARDS

1999	Young Investigator Fellowship International Federation Of Clinical Neurophysiology
2002	Award for Culture And Scientific Merits Of The Italian League Against Epilepsy
2004	Award for Culture And Scientific Merits Of The Italian League Against Epilepsy
2018	Achievement of the eligibility to hold the position of full Professor in Neurology (ASN).

SUPERVISION OF GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS)

Supervision of 40 students for thesis in master's degree in Medicine and Surgery:
14 residents in Neurology;
11 PhD students;
8 Post-docs;

ORGANISATION OF SCIENTIFIC MEETINGS (last 2 years)

2023 Progetto masterclass in EEG. Corso residenziale 24-25 maggio Bologna, Italy.

2023 67° congresso società italiana di neurofisiologia clinica (SINC), Bergamo 17-20 maggio 2023.
2023 Membro del comitato scientifico: lo stato epilettico in Emilia Romagna. Bologna 13 gennaio 2023.
2022 Membro, comitato scientifico e relatore al corso webinar *Applicazioni del neuroimaging in epilessia*
2022 'Gray matters in status epilepticus'. 14th european epilepsy congress, 9-13 july 2022, Geneva (CH)
2022 Membro, comitato scientifico del corso *Aspetti clinici e neurofisiologici del mioclono*, Roma, Italy.
2021 Membro, comitato scient. e relatore al Corso di Video-EEG, Lega Italiana contro l'Epilessia, Catania

REVIEWING ACTIVITIES (present and last 3 years)
2022 - Associate editor for Frontiers in Neurology - Epilepsy section
2017 – Present: member of the Editorial Board of Epileptic Disorder
2016 – Present: Academic Editor, PlosOne

2023 Evaluation report for a PhD thesis, Università degli Studi Magna Graecia di Catanzaro
2022 Evaluation report for a PhD thesis, Università degli Studi di Pavia
2022 Evaluation report for a PhD thesis, Università Politecnica delle Marche
2021 Commissario esterno per il conferimento del titolo di dottore di ricerca, Università di Bologna

MEMBERSHIPS OF SCIENTIFIC SOCIETIES (if applicable)
2018 – European Academy of Neurology (EAN). Member of the Epilepsy panel board.
2021 – American Epilepsy Society (http://www.aes.org)
2000 – Italian Society of Neurology (SIN)
2000 – Italian Society of Neurophysiology (SINC). Faculty board of the society.
1998 – Intl. League Against Epilepsy (LICE), Chair ("neurophysiology" commission), faculty board

MAJOR COLLABORATIONS
Intl. research consortium: 'Identifying SUDEP risk: Sleep wakefulness modulation of central autonomic and respiratory networks', University College London; University of Melbourne; University of Geneva; Université De Lorraine; McGill University.

Intl. research consortium: 'Enhancing NeuroImaging and Genetics through MetaAnalysis(ENIGMA)-Epilepsy Working Group'. International coordinators S. Sisodiya, P. Thompson.

Intl. research agreement on Status Epilepticus Research Network between AOU Modena-UNIMORE and Christian Doppler Klinik, Paracelsus Medical Univ. of Salzburg (A), Prof. E. Trinka.

Curriculum vitae of **BIGIANI, Albertino**
Researcher identifier and webpage: ORCID 0000-0001-6987-488X (ORCiD)
www.researchgate.net/profile/Albertino-Bigiani
Citizenship, date of birth: Italian; 24 January 1959

EDUCATION

1991 – 1993 Postdoc, Prof. S.D. Roper, Dept. Anat. & Neurobio., Colorado State Univ., Fort Collins, USA
1991 PhD in Neuroscience, Inst. of Physiology, Univ. Pisa (I) (Prof. M. Pellegrino, Prof. S.D. Roper)

CURRENT POSITION

2005 – Full Prof. of Physiology, Dept. of Biomedical Sciences, Univ. Modena and Reggio Emilia (I)

PREVIOUS POSITIONS

2001 – 2005 Associate Prof. of Physiology, Dept. of Biomed. Sciences, Univ. Modena Reggio Emilia (I)
1993 – 1995 Visiting Ass. Prof., Dept. Anatomy & Neurobiology, Colorado State Univ, Fort Collins, USA
1992 – 2001 Assistant Professor of General Physiology, University of Modena and Reggio Emilia, Italy

FELLOWSHIPS AND AWARDS

1997 Italian CNR fellowship at Department of Physiology and Biophysics, Miami, USA
1991 Housing/travel Award, Association for Chemoreception Sciences (USA)
1987 Housing/travel Award, NATO Science Committee

ORGANISATION OF SCIENTIFIC MEETINGS

1998 Symposium Organiser: "Taste transduction", Eur. Chemorecept. Res. Org. (ECRO), Siena (I)

INSTITUTIONAL RESPONSIBILITIES

2013 – Coordinator, Technical Support Team, Dept Biomed. Sci, Univ. Modena & ReggioEmilia,
2008 – Coordinator, Physiology Section, Dept Biomed. Sci, Univ. Modena & ReggioEmilia,
2009 – 2012 Dean, Faculty of Pharmacy, University of Modena and Reggio Emilia, Modena, Italy
2008 – 2011 Deputy Director, Dept Biomed. Sci, University of Modena and Reggio Emilia, Modena, Italy

REVIEWING ACTIVITIES

2021 – Associate Editor for *Frontiers in Cellular Neuroscience*, section Cellular Neurophysiology
2019 – 2020 Guest Editor of the Special Issue "Salt Taste, Nutrition, and Health" for *Nutrients*
2020 – Section Editor for "Nutrition and Metabolism" of *Nutrients*
2008 – 2010 Board member of the European Chemoreception Research Organization (ECRO)
2005 – Reviewer, National Science Foundation, USA
2003 – Reviewer, EU, FP5 Program, Expert for Mid-term review
2002 – Reviewer, Philip Morris External Research Program, USA

MEMBERSHIPS OF SCIENTIFIC SOCIETIES

American Physiological Society (USA)
European Chemoreception Research Organization (ECRO)
Società Italiana di Fisiologia (Italian Society of Physiology)

Curriculum vitae of **Giacomo Pavesi**
Researcher identifier and webpage: ORCID : 0000-0002-9004-1775
https://personale.unimore.it/rubrica/dettaglio/gipavesi

Citizenship, date of birth: Italian; July, 14th 1966

EDUCATION
1996 Residency program at University of Verona, Verona Italy
1991 Doctor of Medicine and Surgery (MD). Univ. of Verona, Verona Italy

CURRENT POSITION(S)
2018 - Associate Professor of Neurosurgery, University of Modena and Reggio Emilia
2011 - Head of the Neurosurgical Department in Modena, Italy

PREVIOUS POSITIONS
2010 – 2011 Neurosurgeon at Neurosurgical Department in Padova, Italy

FELLOWSHIPS AND AWARDS
2005 Scholarship in Microsurgery, Department of Neurosurgery , Toolo Hospital, Helsinki University, Finland, prof. Juha Hernesniemi
1993 Scholarship in Vascular Neurosurgery, Presbyterian University Hospital, Pittsburgh (PA), Pittsburgh University, prof. Howard Yonas

ORGANISATION OF SCIENTIFIC MEETINGS (last 2 years)
2019: President of Fundamenta NeurochirurgicaV, Modena , Italy
2018: President of Fundamenta Neurochirurgica IV, Modena, Italy
2017: President of Fundamenta Neurochirurgica III, Modena, Italy
2016: President of Fundamenta Neurochirurgica II, Modena, Italy
2015: President of Fundamenta Neurochirurgica, Modena, Italy

MEMBERSHIPS OF SCIENTIFIC SOCIETIES (if applicable)
2018 – Member of the Italian Society for Neurosurgery

Appendix: All current grants, on-going, & submitted grant applications of the PI (Funding ID)

Mandatory information (does not count towards page limits)

Current grants (Please indicate "No funding" when applicable):

Project Title	*Funding source*	*Amount (Euros)*	*Period*	*Role of the PI*	*Relation to current proposal*
eBRAINS-Italy	PNRR-MUR	656'000	2022-25	Unit coordinator	Collections of human tissues for images
SMART-BRAIN	JTC-FLAGERA 2019	150'000	2021-24	PI	Reconstruction of human brain tissue through multimodal imaging
MSBFIINE	Italy-India Network of excellence	55'000	2022-25	Unit coordinator	Multiscale brain modeling
HUMAN-HIPPO	PRIN2022	110'000	2023-25	PI	Reconstruction of human hippocampus through advanced two-photon imaging

ALLEGATO C

TABELLA COSTI PERSONALE STANDARD				COSTO DEL PERSONALE		
FASCIA DI COSTO /LIVELLO	**NUMERO SOGGETTI**	**COSTO ORARIO vedi nota**	**MONTE ORE**			
Basso		31 €		- €		
Medio	**2**	48 €	500	24.000 €	4 MM	J + clinico
Alto	**1**	73 €	250	18.250 €	2 MM	Albertino
TOTALI	**3**		**750**	**42.250 €**		

COSTO ORARIO: si deve far riferimento al Decreto Interministeriale n. 116 del 24/1/2018

ALLEGATO C

BUDGET DI PROGETTO	COSTO DEL PERSONALE	OVERHEAD	Costi per servizi di Consulenza Specialistica	Costi per licenze direttamente imputabili al progetto	Costi per materiali e attrezzature direttamente imputabili al progetto	Costi per altre tipologie di spese direttamente imputabili al progetto	COSTO TOTALE
	42.250,00 €	6.337,50 €	0,00 €	0,00 €	28.000,00 €	73.205,64 €	149.793,14 €