SUBMISSION FORM OF PROPOSALS FOR DOCTORAL RESEARCH PROJECTS

Objective of the Doctoral Programme in Health Sciences and Technologies

The objective of the new interdepartmental Doctoral Programme in Health Sciences and Technologies is to train the next generation of leaders in industrial, clinical, and academic research. Our goal is to develop an organic research programme at the interface between engineering and medicine, which is inspired by the quantitative and integrative approach of physical sciences, and by the latest development in biomedical research, drive the development and clinical translation of disruptive health technologies.
The doctoral training programme will prepare students in conducting research which:
- Extend the comprehension of how human physiology and pathology work in term of physical and chemical mechanisms, and how these mechanisms respond when perturbed by external factors such as therapies, changes in life style, and environmental factors;
- Develop new technologies that by leveraging on this mechanistic understanding pursue a wide spectrum of applications relevant to human health, including prevention, diagnosis, prognosis, treatment, and rehabilitation.

Procedural aspects on the submission of proposals for doctoral research projects

Every year the PhD process will start with the submission of proposals for doctoral research projects. Each proposal must be submitted jointly by two supervisors, one providing the clinical expertise, the other the technological expertise. The Project Selection Committee will select a number of projects that is three times the number of available scholarships and should be distributed in similar proportion between medical-led or technology-led proposals. The resulting list of projects will be included in the call for student applications that the Executive Committee will compile soon after. Each student, depending on their degree, will be able to apply only for a sub-set of projects; among them each student will be allowed to select three projects, and name them in order of preference; however, in some cases it might not be possible to satisfy all requests, and some students might be offered a research project different from those they selected.

Doctoral training program

In order to be admitted to the selection, a student needs a five-year higher education degree, which includes at least one module for each of the following disciplines: mathematics, physics, computer science, biology, physiology, and anatomy.

Max number of proposals for each member of the Academic Board: 3 (three)
Max number of selected projects for each member of the Academic Board: 2 (two)
Max number of selected projects for 2019: 12 (twelve)

Title of the project

Developing models of schizotypal neurocognitive mechanisms: an integrative use of machine learning, EEG and neurostimulation

Student's degree (you can choose more than one, if needed)

Yes/Not	Cultural area
Yes	Medicine, biology, or related disciplines
Not	Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines

Student's skills (you can fill more than one field, if needed)

Cultural area	Skills
Medicine, biology, or related disciplines	Past experience with:

	- experimental setup including write-up of accurate Psychophysics script (knowledge of dedicated programs such as Eprime, Presentation or Matlab Psychtoolbox; - EEG setup and cap montage; - EEG data processing (knowledge of M/EEG analysis packages such as BrainVision Analyzer, EEGLab, SPM or Fieldtrip) - Neurostimulation tools such as Transcranial Magnetic Stimulation (TMS)
Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines	

Tutors (2, from different cultural areas and with at least 1 from the Academic Board)

Cultural area	Name & Surname	Department
Medicine, biology, or related disciplines	Vincenzo Romei	Department of Psychology
Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines	Stefano Diciotti	Department of Electrical, Electronic, and Information Engineering "Guglielmo Marconi"

Research project

	Synthetic description
Summary (max 1000 chars)	This research project will provide a novel approach for the investigation of early biomarkers of psychosis, aimed at tailored plans for prevention in the healthy population at risk and interventions in the psychiatric population. A key aspect concerns the study of the neurophysiological underpinnings accounting for individual differences along the schizotypy axis. According to the continuum hypothesis, sensory and attention performance, known to be altered in schizophrenia, will be tested in people with low and high levels of schizotypy. An integration of machine learning, dense EEG signal analysis and innovative neurostimulation protocols will be implemented to test the fronto-parietal functional disconnection hypothesis: machine learning will aim at decoding composite biomarkers best predicting levels of schizotypy, neurostimulation will aim at modulating plasticity of long-range connectivity, dense EEG oscillatory signal analysis will inform Machine Learning and Neurostimulation.
Objectives (max 1000 chars + max 5 relevant references)	A primary goal of the research is to develop predictive models that best account for neurocognitive profiles associated with schizotypy – a personality trait pertaining to the same dimensional continuum as schizophrenia [1]. To this aim, machine learning tools will be developed [2] to identify reliable composite biomarkers best predicting high-schizotypy with a risk of developing psychotic symptoms, hence improving the predictive (schizotypy) and diagnostic (schizophrenia) work-up potential at a single subject level. Finally, the composite biomarkers will inform biologically-inspired neurostimulation protocols [3-5] aimed at individually-tailored interventions. Specifically, the role of functional connections and alpha oscillations along the fronto-parietal network will be investigated and neurostimulation implemented to induce plastic changes of the

	composite biomarkers. The degree of degraded oscillatory activity of the functional network will be predictive of the level of neurostimulation efficacy setting the boundaries of intervention at the individual level to re-establish neural and behavioural functional patterns. References *[1] Ferri F, Venskus A, Fotia F, Cooke J, Romei V. (2018) Higher proneness to multisensory illusions is driven by reduced temporal sensitivity in people with high schizotypal traits. Conscious Cogn. 65, 263-270.* *[2] Ciulli S, Citi L, Salvadori E, Valenti R, Poggesi A, Inzitari D, Mascalchi M, Toschi N, Pantoni L, Diciotti S. (2016). Prediction of Impaired Performance in Trail Making Test in MCI Patients With Small Vessel Disease Using DTI Data. IEEE J Biomed Health Inform. 20,1026-1033.* *[3] Romei V, Thut G, Silvanto J. (2016a) Information-Based Approaches of Noninvasive Transcranial Brain Stimulation. Trends Neurosci. 39, 782-795.* *[4] Romei V, Chiappini E, Hibbard PB, Avenanti A. (2016b). Empowering Reentrant Projections from V5 to V1 Boosts Sensitivity to Motion. Curr Biol. 26, 2155-2160.* *[5] Chiappini E, Silvanto J, Hibbard PB, Avenanti A, Romei V. (2018). Strengthening functionally specific neural pathways with transcranial brain stimulation. Curr Biol. 28, R735-R736.*
Rationale and scientific background y (max 2000 chars+ max 5 relevant references)	Perceptual and cognitive dysfunctions are considered core features of schizophrenia. Attentional anomalies have also been spotted in individuals with accentuated schizotypal characteristics, that seem analogous but more attenuated than those found in schizophrenia. These results suggest the existence of altered top-down attention processes that enable voluntary control, inhibition and selection of the relevant stimuli [1]. Although the crucial role of posterior alpha oscillations in attention processes has been widely investigated and largely confirmed, the exact functional mechanism linking different alpha parameters to attention selection remains the object of diverse interpretations. Numerous investigations were able to associate the modulation of posterior alpha amplitude with attention selection processes, acting as a mechanism able to filter and select relevant information (e.g., [2]). While these observations refer to posterior brain areas, enhanced synchronization between low-level visual cortex and higher-level brain regions was observed in the alpha band contralateral to the cued location, whereas in the ipsilateral hemisphere a decreased synchronization was measured. This mechanism is thought to enhance processing of the stimuli at the attended location. These fluctuations in the alpha band phase synchrony were associated with the activation of frontal and parietal areas (as measured through fMRI), whose intrinsic connectivity pointed to the activation of the fronto-parietal network [3]. Recent EEG studies investigating alpha band oscillations in schizotypy individuals have unveiled a systematic increase in alpha amplitude together with a decrease in its frequency [4] while TMS-EEG studies have revealed a reduced fronto-to-parietal connectivity associated with cognitive dysfunctions in schizophrenia [5]. References *[1] Fuggetta G, Bennett MA, Duke PA. (2015). An electrophysiological insight into visual attention mechanisms underlying schizotypy. Biol Psychol. 109, 206-221.* *[2] Thut G, Nietzel A, Brandt SA, Pascual-Leone A. (2006). Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. J Neurosci. 2006 Sep 13;26(37):9494-502.*

	[3] Sadaghiani S, Scheeringa R, Lehongre K, Morillon B, Giraud AL, D'Esposito M, Kleinschmidt A. (2012). a-band phase synchrony is related to activity in the fronto-parietal adaptive control network. J Neurosci. 32,14305-14310. *[4] Fuggetta G, Bennett MA, Duke PA, Young AM. (2014). Quantitative electroencephalography as a biomarker for proneness toward developing psychosis. Schizophr Res. 153, 68-77.* *[5] Ferrarelli F, Riedner BA, Peterson MJ, Tononi G. (2015). Altered prefrontal activity and connectivity predict different cognitive deficits in schizophrenia. Hum Brain Mapp. 36, 4539-4552.*
Preliminary results if existing (max 1000 chars+ max 5 relevant references)	Preliminary findings on a group of 20 participants with low-schizotypy (LS) and 20 with high-schizotypy (HS) scores have shown both impaired behavior in a visual attention task and altered resting alpha oscillations in the HS group [1]. Specifically, the HS group has shown no gain in performance for items attended to the left hemifield. Accordingly, resting alpha frequency was significantly reduced in the contralateral right hemisphere. Importantly, reduced connectivity as measured through the phase-lag index [2] in the right fronto-parietal network within the alpha range was found in the HS group. On the other hand, EEG data collected on the general population (N=20) during the same attention task [3] has unveiled the crucial role played by alpha amplitude and its frequency in controlling stimulus processing at the attended location. Correct responses were associated to alpha amplitude suppression and higher frequency in the hemisphere contralateral to the attended location, along with an increase of alpha amplitude in the ipsilateral hemisphere. References *[1] Di Gregorio F, Trajcovic J, Roperti C, Romei V. Electrophysiological correlates of perceptual asymmetries in schizotypy. Conference Communication: OHBM, 9-13 June 2019. Rome (submitted).* *[2] Stam CJ, Nolte G, Daffertshofer A.(2007) Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum Brain Mapp. 28, 1178-93.* *[3] Romei V. Model-based vs. model-free mechanisms of conscious perception. Conference Communication. Presentation at the symposium: Neural Oscillations in Perceptual and Attentional sampling. OHBM, 9-13 June 2019 Rome (submitted).*
Research project including methodology (max 5000 chars)	**Hypotheses** According to the scientific background and preliminary results and in line with the research objectives, the project will be testing the following hypotheses: 1. **Behaviour:** The HS group will achieve weaker performance on visuo-spatial attention tasks compared to the LS group. especially over the left hemifield. 2. **EEG correlates:** The HS group will show EEG alterations in the alpha band preceding voluntary attention focusing towards the left hemifield, possibly concerning reduced functional connectivity from frontal to parietal (spatial) and occipital (visual) areas in the right hemisphere within the alpha frequency range. Specifically, the hypothesis is that a reduced inter-areal alpha synchronization and thus the inability of anterior regions to supervise the orienting of attention by parietal areas will fail to control the cortical excitability of lower-level visual cortex to functionally map the to-be-attended location. This will in turn have consequences on the optimal functioning of the local occipital alpha, with the reduction of flexible fine-tuning of alpha peak frequency and amplitude in the visual cortex generally observed during voluntary attention control.

3. **Machine Learning:** A predictive model can be developed able to identify, at the single subject level, composite biomarkers accounting for the degree of the individual schizotypal trait.
4. **Causal manipulation:** The introduction of a novel neurostimulation protocol named cortico-cortical paired associative stimulation (ccPAS) (e.g., [1]) will manipulate inadequate fronto-parietal communication during attention control, through the enhancement of cortico-cortical plasticity of the targeted network, by increasing long-range alpha synchronization and achieving optimal fronto-parietal information transmission to fine-tune control of visual cortical regions. As a result of the plasticity of the synaptic connections, this intervention will improve attention control, with net perceptual gain especially in the HS group.

Materials and methods

In order to test the proposed research hypothesis, the Schizotypal Personality Questionnaire (SPQ) [2] will be administered to a cohort of 500 students. The distribution of scores will be divided into deciles with the first decile representing the participants rated as LS and the tenth decile representing the participants rated as HS. A total of around 100 participants (50 in each group) will be enrolled.

64 channels easy-cap electrodes connected to a TMS-compatible EEG amplifier (BrainAmp, Germany) will measure neural activity at rest and concurrently during task execution. The task consists of a visuospatial attention cueing paradigm.

Signal analysis includes source localization of cortical generators involved during endogenous visual attention control and will focus on phase- and time- locking measures [3] between individual cortical sources, as well as analysis of alpha amplitude and peak frequency modulations in the visual cortex associated with successful attention control. All this information will be fed into a machine learning system able to classify a single subject into a predefined group (i.e., LS and HS group), making use of the out-of-sample error, a measure of how accurately an algorithm is able to predict values for unseen data. While a number of studies have applied machine learning techniques to brain computer interfaces (BCI) using EEG data, very few studies for schizophrenia (e.g., [4]) and no studies for schizotypy have approached the investigation of HS trait using a machine learning scenario. Analysing the information through machine learning techniques can 1) improve the diagnostic and prognostic potential upon single subject examination and 2) discover composite biomarkers for the HS profile.

In order to casually test the functional relevance of the inter-areal feedback connectivity in the alpha range in attention control, its direct modulation will be achieved using ccPAS in combination with EEG. Based on the principle of Hebbian plasticity, the parameters of the ccPAS protocol will be tailored to each individual in order to modulate the fronto-to-parietal network by pairing pre-to-post-synaptic interstimulus intervals to match and speed-up the length of each individual alpha cycle. According to the communication through coherence framework [5] this timing and stimulus directionality will mimic and thus favour functional and adaptive plastic changes in the alpha range, ultimately resulting in improved attention performance. The paradigm is thought to enhance the functional connectivity within the alpha range along the fronto-parietal network and to positively impact attention control. Pr-e vs. post-ccPAS EEG and behavioural recordings will allow causal direct estimation of the predictive model value, together with the electrophysiological and behavioral effects of neuromodulation.

References

	[1] Romei V, Chiappini E, Hibbard PB, Avenanti A. (2016). Empowering Reentrant Projections from V5 to V1 Boosts Sensitivity to Motion. Curr Biol. 26, 2155-2160. *[2] Raine A. (1991). The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr Bull. 17, 555-64.* *[3] Stam CJ, Nolte G, Daffertshofer A.(2007) Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum Brain Mapp. 28, 1178-93.* *[4] Ince NF, Goksu F, Pellizzer G, Tewfik A, Stephane M. (2008). Selection of spectro-temporal patterns in multichannel MEG with support vector machines for schizophrenia classification. Conf Proc IEEE Eng Med Biol Soc.* *[5] Fries P. (2015). Rhythms for Cognition: Communication through Coherence. Neuron. 88, 220-235.*
Innovation potential (scientific and/or technological) (max 1000 chars)	The research will enable to create and directly test a novel integrative and coherent model able to learn composite biomarkers (that take into consideration both local and large scale alpha oscillatory mechanisms and their interactions) accounting for efficient attention control shown to be deficient in HS and schizophrenia. Moreover, the research will make use of a novel neurostimulation paradigm that has the potential of enhancing oscillatory-specific synchrony across different cortical areas, thus enhancing cortico-cortical connectivity to optimise the mechanisms of communication through coherence. This in turn will allow the predictive model to test the extent of the effective impact of the ccPAS intervention on the composite biomarker associated with the group definition. If the hypotheses are confirmed, this novel paradigm could be successfully implemented in the clinical setting and expanded to various research areas interested in exploring the functionality of long-distance synchrony in human cognition.
Expected results and applications to human pathology and therapy (max 1000 chars)	a) preliminary results in the general population pinpoint to a functional role of posterior alpha frequency coding for perceptual accuracy, and anterior-to-posterior alpha synchrony coding for perceptual confidence; importantly, lack of flexibility for adaptive changes in alpha peak frequency and amplitude over visual areas might account for attention deficit in schizotypy; b) integration of such measurements in a machine learning context would enable the identification of potential composite biomarkers for the schizotypy type able to reliably quantify an individual's level of schizotypy, indicating a possible higher risk of developing psychiatric symptoms; c) neurostimulation is expected to enhance alpha synchronization and boost effective communication between cortical regions involved in attention control. Post stimulation performance fed back into machine learning context will quantify and qualify the impact of the treatment; d) according to the schizotypy-schizophrenia continuum framework, the paradigm has the potential of representing a valid, non-pharmacological and non-invasive treatment of attention deficits in schizophrenia.

Available resources for the project

	Synthetic description
Research environment (labs involved, background, and location)	- Laboratory of Biomedical Engineering (LBE Bologna), Department of Electrical, Electronic, and Information Engineering "Guglielmo Marconi", Bologna. - Laboratory of Biomedical Engineering (LBE Cesena), Department of Electrical, Electronic, and Information Engineering "Guglielmo Marconi", Cesena.

	- Center for research and studies in Cognitive Neuroscience (CsrNC), Department of Psychology, Cesena. The Ph.D. student will have all the possibility to successfully accomplish this project within the above-mentioned laboratories, which offer all resources (high performance CPUs and GPU), dedicated and qualified staff and facilities (EEG and TMS equipment) needed to effectively realize this project.
Main equipment (facilities and location)	- High performance workstations (40 virtual CPUs, 192 GB RAM, >30 TB disk space, Linux operating system) (LBE Bologna) - High performance GPU (NVIDIA Titan X) (LBE Bologna) - two 64 channels TMS-compatible EEG systems (BrainAmp and Actichamp) (CsrNC, Cesena). - 1 monophasic dual coil TMS Magstim; two biphasic super rapid TMS Magstim (CsrNC, Cesena).
Additional funding (title, amount, start date, duration)	Bial Foundation (Grant n. 204/2018) awarded to Vincenzo Romei. Title: Boosting Working Memory capacity by strengthening the oscillatory functional fronto-parietal pathway Amount: € 47000,00. Start date: March 2019 Duration: 18 Months. The MathWorks Inc. grant awarded to Stefano Diciotti. Title: Biomedical Signal Processing and Imaging with MATLAB and Simulink Amount: € 28501,00 Start date: September 2017

International collaborations for the project (also in view of the Student's secondment)

	Project	**Location and team**
#1	Bayesian Deep Learning for Alzheimer's conversion prediction in Mild Cognitive Impairment subjects	School of Computer Science and Electronic Engineering (CSEE), University of Essex, Colchester,UK Dr. Luca Citi (Reader)
#2	Boosting Working Memory capacity by strengthening the oscillatory functional fronto-parietal pathway	Department of Psychology, Ludwig-Maximilian-University Munich, Germany Prof. Paul Sauseng
#3		