UNIVERSITY OF PADOVA
DEPARTMENT OF INFORMATION ENGINEERING (DEI)

Ph.D. School in Information Engineering
Section: Bioengineering

Ph.D. Candidate: Ilaria Mazzonetto

Cycle: XXX

Supervisor name: Prof. Alessandra Bertoldo

Thesis title: EEG source reconstruction accuracy and integration of simultaneous EEG-fMRI resting state data.

Priority research grant: Scholarship from Department of Neurosciences, founded by the European Research Council Starting Grant LEX-MEA n° 313692 (FP7/2007-2013) to Prof. Antonino Vallesi. Project theme: "Life Experience Modulation of Executive Function Asymmetries".

Three-year report

1. Education

1.1 Courses organized within the department for PhD students

- Applied Machine Learning in Biomedicine, Prof. E. Grisan
- Bayesian Machine Learning, Prof. G.M. Di Nunzio
- Mathematical modelling of Cell Biology, Prof. M. Pedersen
- Statistical Methods, Prof. L. Finesso

1.2 Schools

- Magnetic Resonance Techniques in Multiple Sclerosis – 18° advanced course. March 19th-20th 2015, Milano, Italy.
- Statistical Parametric Mapping (SPM) Short Course. May 13th-16th 2015, UCL Institute of Neurology, London, UK.
- Educational Courses OHBM 2016, Annual meeting. June 26th, 2016, Geneva, Switzerland.
- Educational Courses OHBM 2017, Annual meeting. June 25th, 2017, Vancouver, Canada.

1.3 Workshops

- Images of the Mind: new frontiers in brain imaging Advanced (f)MRI statistical methods and their applications. April 9th - 10th 2015, Milano, Italy.

1.4 Seminars

- Brain-Machine-Interface (BMI) in Complete Paralysis, Stroke and Neuropsychiatric Disorders. November 5th, 2014, Padova.
- Conference on statistics in neuroimaging. January 15th, 2015, Padova.
- Non-linear dynamical analysis of electrophysiological data (EMG and EEG). February 17th, 2015, Padova.
- Learning with Computational Regularization. March 27th, 2015, Padova.
- Computational modeling in cognitive neuroscience: from neurons to robots. April 1st, 2015, Padova.
- Oscillations and synchrony in brain dynamics. May 12th, 2015, Padova.

- Executive functions: from neural bases to cognitive training. May 19th, 2015, Padova.
- Recent Advances in ERP Estimation and Classification. July 3rd, 2015 Padova.
- From Scalp to the Cortex: the High-spatial resolution EEG as neuroimaging tool. July 7th, 2015, Padova.
- New perspectives in multiple testing 80 years after Bonferroni. October 9th, 2015, Padova.
- The use of input function in PET kinetics modelling. December 2nd, 2016, MD. Paolo Zanotti Fregonara, DEI Padova.
- If you talk to a man in a language he understands, that goes to his head. If you talk to him in his language, that goes to his heart. December 15th, 2016, Prof. Albert Costa, Padova.
- Neuroscience Day @ DEI. February 2nd, 2016, Padova.
- Long-range functional interactions in the resting state human brain. June 8th, 2016, Prof. Dante Mantini, Padova.
- Personalized whole brain simulations reveal candidate mechanisms of neural computation. July 7th, 2016, Prof. Petra Ritter, Padova.
- Detecting large-scale brain networks using high-density EEG. September 19th, 2016, Prof. Dante Mantini, Padova.
- Networks: Brain, Health, and Society. September 29th, 2016, Prof. Maurizio Corbetta, Padova.
- Networks cerebrali e comportamento, January 17th, 2017, Prof. Maurizio Corbetta, Padova.
- Consciousness: From Theory to Practice. May 18th,2017, Prof. Giulio Tononi, Padova.
- Il meccanismo specchio, May 30th, 2017, Prof. Giacomo Rizzolati, Padova.
- Learning by Nature: How to Build Soft Robots. June 4th, 2017, Prof. Barbara Mazzolai, Padova.

1.5 International conferences

- 22nd Annual Meeting of the Organization for Human Brain Mapping (OHBM). June 26th - 30th 2016, Geneva Switzerland.
- 5th biennial conference on resting state data and brain connectivity 2016. September 21st - 23rd 2016, Vienna, Austria.
- 23nd Annual Meeting of the Organization for Human Brain Mapping (OHBM). June 26th - 29th 2017, Vancouver, Canada.
- BrainModes 2016, Coordinated brain activity: foundations and applications. December 1st - 2nd 2016, Brussels, Belgium.
- Cognitive Neuroscience of Executive Functions (CNEF). September 28th – 30th, 2017. Padova, Italy.

1.6 National conferences

- 7th Annual Meeting of International Society for Magnetic Resonance in Medicine (ISMRM) Italian Chapter, February 4th – 5th 2016, Bologna, Italy.

1.7 Teaching activities (as Tutor Junior)

- Providing support and one-to-one assistance in MATLAB laboratories for the classes of:
  - Biological Signal Processing course 16/17, Padova, DEI (10 hours, March 2017 – July 2017)
  - Bioengineering Laboratory course 16/17, Padova, DEI (3 hours, March 2017 – July 2017)
- Frontal lectures on fMRI artifact removal from the EEG data and filtering in EEG analysis for Bioengineering Laboratory course (3 hours, March 2017 – July 2017).
- Correlator activity for the master thesis:

– "Metodi per l'integrazione dell'informazione EEG nell'analisi fMRI in resting state" by Raffaele Giordano

1.8 Mobility action

- October 4th – December 21st, 2016: Visiting Scholar at the Faculty of Kinesiology and Rehabilitation Sciences (KU Leuven, Belgium) to work on EEG source localization techniques under the supervision of Prof. Dr. Dante Mantini.

2. Research

The research activities carried out in this three-year PhD programme are related to the analysis and integration of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) data acquired during both task and resting state conditions.

All data were collected within the "LEX-MEA" project (PI: Prof. Antonino Vallesi) at the University Hospital of Padova. MRI images were acquired with 3T Ingenia Philips whole body scanner equipped with a 32-channel head-coil of Neuroradiology Unit, EEG were recording using BrainAmp amplifiers from 64 Ag/AgCl electrodes that were mounted on an elastic cap (EASYCAP GmbH) according to the extended 10-20 system. For the multimodal acquisition, an MR-compatible system of EEG with the same properties was used.

At the beginning, most of the activities were conducted on EEG and fMRI task-related dataset.
EEG analyses were performed on three different dataset. The first dataset consisted of 54 subjects who were required to perform verbal and spatial task-switching paradigms ([J1]), the second one of 54 subjects involved in verbal and spatial monitoring tasks ([C2],[J3]), and the last of 23 subjects performing a cued task switching paradigm ([J2]). After preprocessing, cortical EEG source imaging on the individual ERPs were performed. Since these steps were conducted with several software, an automatic algorithm for their interfacing was developed, if not yet available.
The fMRI dataset consisted of 23 subjects who were required to respond to the onset of a target that followed a neutral warning signal. The acquisition protocol includes structural images, namely T1w and T2w, 40 minutes equivalent to 4 sessions of task-related fMRI, and two spin-echo EPI images for each session with reversed phase encoding directions. During this study, the PhD programme was devoted to preprocess and process structural and functional data with state-of-the-art approaches. Particular attention was paid on motion artefact correction as well as high-pass filtering of functional data. fMRI data were then modelled using trial-by-trial Kullback-Leibler divergence (DKL) between the posterior and the prior probability of the target onset. The latter could be estimated based on how the experimental paradigm was designed. Preliminary network analysis between regions whose activity was significantly modulated by DKL were also conducted ([C8]).
At the same time, to test whether leftward structural grey matter asymmetries was able to predict inter-individual differences in the Stroop test performances, 111 subjects, for whom Stroop test scores and T1 images were available, were analyzed. Laterality Indices (LI) for the surface thickness and for the area of each vertex in each participant were computed. The correlation of these LI measures with the result on Stroop test was assessed at each vertex by means of general linear models at the whole-brain level ([J5]).
This first part of the activity was aimed to acquire the methodology for the preprocessing for Event Related Potentials (ERPs) analysis and source reconstruction of task-related EEG data, a needed background for the following step of integration with fMRI data.

Then, the PhD programme dealt with the integration of EEG-fMRI. Dataset consisted of 22 subjects. In this study, 60 minutes of simultaneous EEG-fMRI were acquired, followed by a structural T1w image. Despite previous study, structural T2w and spin-echo EPI images could not be acquired because these sequences were not compatible with the used EEG system. Simultaneous acquisition

included 7 minutes of resting state and 53 minutes, equivalent to 5 sessions, of task-related activity in which subjects were asked to monitor sequences of images. Constraint on the amount of radio frequency energy in a given time and the requirement of a TR not higher than 2 s forced the use of a voxel size bigger than what is currently present in the fMRI literature. This, combined with the lack of T2w and spin-echo EPI images, required particular attention during the coregistration of functional data to the template.

The fMRI data were preprocessed and subjects with excessive head movement were discarded. After MRI artefact removal, EEG underwent standard preprocessing and ERPs were obtained. The relationship between the ERP and the fMRI responses was investigated using the integration-by-prediction method. This method, which was developed for event-related designs, in this study was adapted to a block design. For the integration analysis, the ERP components that were found to be associated with the monitoring process in the conventional analyses were considered ([C3], [C9], [J4]).

Resting state simultaneous acquisition was used to analyse the scalp distribution of the EEG spectral correlates of fMRI Resting State Networks (RSNs) and, especially, how the interplay between different EEG frequency bands is related to BOLD fluctuations within distinct RSNs. Since in this study EEG signal is not averaged in time as in the ERPs analysis, the preprocessing steps previously used were only partially followed. Most of the activity in this part of PhD programme were spent to delineate an ad hoc pipeline for an aggressive artefact removal. Preprocessed fMRI underwent a group Independent Component Analysis and a subsequent dual regression step, in order to obtain RSNs maps and timecourses for each subjects. For each subject and channel, the RSN timecourse was correlated to the different band power time series to assess EEG-fMRI relationship. Mass-univariate analysis applied at different levels allowed to identify some putative specific spatio-spectral fingerprints of distinct subcomponent of the Default Mode Network, one of the most studied RSNs.

However, to infer about anatomical localization of these spatio-spectral fingerprints, the same analysis should be conducted at the source space.

From literature, 64 channels seem not to be enough to ensure an effective source localization; therefore, a simulation study to investigate the accuracy of source localization across different brain regions, depending on EEG sensors density, was performed ([C7]). To do this, standard 256-channel positions were spatially subsampled to 32, 64 and 128 channels, respectively, with electrodes positioned according to a standard EEG montage and source localization was solved with a state-of-the-art approach. The template structural magnetic resonance image was segmented in 12 tissue classes and based on that a realistic head model, where each tissue was assigned a specific conductivity value, was built. Locations of the dipoles, corresponding to brain sources, were derived by discretizing the grey matter with a regular 2 mm grid and the leadfield matrix was then calculated. The simulated EEG potentials were obtained by forward projection of each source to scalp sensors using the leadfield matrix with additive Gaussian noise of 10% SNR. For each dipole and each electrode montage inverse solution was obtained and performances of source reconstruction were quantified by means of different metrics.

Meanwhile, a systematic examination of test-retest reliability for resting state EEG spectral metrics at both the scalp and the cortical level was carried out ([C5], [MS1]). The usefulness of these metrics for automatic rsEEG-based biometric identification was also assessed.

Dataset consisted of resting state EEG activity in 45 volunteers in two 5-minute, eyes-closed resting-state sessions separated by 15-22 months. After preprocessing step, a source-based spectral analysis was performed to compute both classical and more complex spectral metrics at both the scalp and the cortical level. An extensive set of experimental tests using different correlation coefficients were carried out to assess systematically the test-retest reliability of the spectral metrics. Moreover, by using several scalp- and cortex-derived rsEEG spectral metrics as biometric features as well as different distance metrics, the accuracy of different classification algorithms in identifying participants across sessions, was also assessed.

The research activity of this PhD programme was carried out under the supervision of Prof. Alessandra Bertoldo. At closure of the PhD programme, a PhD thesis with title: "EEG source reconstruction accuracy and integration of simultaneous EEG-fMRI resting state data" was composed.

3. Publications

3.1 Publications in international journals

[J1] Capizzi M., Ambrosini E., Arbula S., Mazzonetto I., Vallesi A. (2016). Electrophysiological Evidence for Domain-general Processes in Task-switching. Front Hum Neurosci. 10:124. Doi: 10.3389/fnhum.2016.00124

[J2] Tarantino V., Mazzonetto I., Vallesi A. (2016). Electrophysiological correlates of the cognitive control processes underpinning mixing and switching costs. Brain Res, 1646, 160–173. Doi: 10.1016/j.brainres.2016.05.048

[J3] Capizzi M., Ambrosini E., Arbula S., Mazzonetto I., Vallesi A. (2016) Testing the domain-general nature of monitoring in spatial and verbal cognitive domains. Neuropsychologia, 89, 83-95. Doi: 10.1016/j.neuropsychologia.2016.05.032

[J4] Tarantino V., Mazzonetto I., Formica S., Causin F., Vallesi A. (2017). The neural bases of event monitoring across domains: a simultaneous ERP-fMRI study. Front Hum Neurosci, 11, 376. Doi: 10.3389/fnhum.2017.00376

[J5] Vallesi A*., Mazzonetto I*., Ambrosini E., Babcock L., Capizzi M., Arbula S., Tarantino V., Semenza C., Bertoldo A. (2017). Hemispheric asymmetries in the posterior inferior temporal cortex underlie verbal Stroop performance. Behavioural Brain Research. Doi: 10.1016/j.bbr.2017.08.024, *co-author

3.2 Manuscripts in preparation

[MS1] Ambrosini A., Mazzonetto I., Vallesi A. Test-retest reliability for resting-state EEG spectral metrics. To be submitted to Neuroimage.

3.3 Publications in international conferences

3.3.1 Abstracts

[C1] Tonietto M., Mazzonetto I., Monaco S., Calabrese M., Castellaro M., Bertoldo A. Effective and functional connectivity in the motor cortex are sensitive to disability in MS. OHBM 2015, June 14th - 18th, 2015, Honolulu, Hawaii, USA.

[C2] Capizzi M., Ambrosini E., Arbula S., Mazzonetto I., Vallesi A. (2016). Assessing the Role of Cognitive Domain in Monitoring Processes: An Event-Related Potential Study. International Meeting of Psychonomic Society 2016, May 5th - 8th, 2016, Granada, Spain.

[C3] Tarantino I., Formica S., Mazzonetto I., Vallesi A. (2016). The neural bases of sustained and transient event monitoring: an ERP-fMRI study. Third International Conference of the European Society for Cognitive and Affective Neuroscience, June 23rd - 26th, 2016, Porto, Portugal.

[C4] Mazzonetto I., Ambrosini E., Vallesi A., Bertoldo A., Vallesi A. (2016). A study on the link between source-based spectral metrics and BOLD signal at rest. Fifth biennial conference on resting state and brain connectivity 2016, September 21st - 23rd, 2016, Vienna, Austria.

[C5] Ambrosini E., Mazzonetto I., Vallesi A. (2016). Test-retest reliability for resting-state EEG spectral metrics. Fifth biennial conference on resting state and brain connectivity 2016, September 21st – 23rd , 2016, Vienna, Austria.

[C6] Vallesi A., Mazzonetto I., (2016). Left-ward structural asymmetry in visual word form area favors verbal Stroop performance. Society for NeuroScience 2016, November 12nd – 16th, 2016, San Diego, USA.

[C7] Mazzonetto I., Liu Q., Bertoldo A., Mantini D. (2017). To what extent does the EEG montage density impact on the accuracy of source localization? OHBM 2017, June 25th – 29th, 2017, Vancouver, Canada.

[C8] Visalli A., Capizzi M., Mazzonetto I., Vallesi A. (2017). Neural representations of model updating and surprise of temporal expectations: an fMRI study. ESCOP 2017, September 3rd -6th , 2017, Postdam, Germany.

[C9] Tarantino I., Mazzonetto I., Vallesi A. (2017). Sustained and transient neural correlates of cognitive control. CNEF 2017, September 28th-30th, 2017, Padova, Italy.

Date: 28/09/2017

Signature of PhD student: Ilenia Mazzonetto

Signature of Supervisor: