ANNUAL REPORT

Second year - PhD Program in Sciences & Medical Biotechnology
University of Piemonte Orientale "Amedeo Avogadro", Novara

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PART 1: Scientific activity

PART 2: Didactic and educational activities

PART 1: Scientific activity

Project title:

MULTIMODAL STUDY OF EPILEPTOGENIC NETWORKS IN EPILEPSY

Scientific background

Epilepsy is one of the most common serious brain disorders characterized by recurrent seizures. In Italy 30000 new cases are diagnosed each year, with an incidence higher in infants and elderly people. Epilepsy has negative effects on quality of life, function, and increases risk of mortality despite available treatments (Duncan et al., 2006). It is drug-resistant in about one-third of cases. Despite past and current research, the pathophysiology of many forms of epilepsy remains partly obscure.

The epilepsy syndromes can be subdivided into focal and generalized types depending on whether seizures arise from a localized brain area or show widespread involvement of both hemispheres from the outset. The most common type of generalized epilepsy, idiopathic generalized epilepsy (IGE) is, for the most part, considered to have a genetic basis. Focal epilepsies, in contrast, more often arise from an abnormal focal anatomic substrate such as hippocampal sclerosis or an area of cortical dysgenesis. Temporal lobe epilepsy (TLE) is the most common focal epilepsy.

The current understanding of the pathophysiology of epilepsies relies on the "system hypothesis" that goes beyond the classical dichotomy between focal and generalized epilepsy: some types of epilepsy may depend on the susceptibility to epileptogenic factors within a specific brain system (Avanzini et al., 2012). The ideal model of "system epilepsy" is epileptic photosensitivity, an exaggerated neural response to visual stimuli that may involve even distant areas as the primary motor cortex (M1). Its most elementary and common form is the photoparoxysmal response (PPR) to intermittent light stimulation (ILS).

Unravelling how the epileptogenic process is affecting the brain networks in photosensitivity and other forms of epilepsy will invaluably advance our understanding of the pathophysiology of epilepsy and will lead to development of improved therapeutic perspectives.

The epileptogenesis is a complex dynamic process that progressively alters neuronal excitability, establishes critical interconnections and requires intricate structural changes before the first spontaneous seizure occurs (Pitkanen and Lukasiuk, 2011). In addition, during epileptogenesis may occur maladaptive plastic processes ('pathological plasticity'). It begins after the occurrence of an insult (eg. traumatic brain injury or stroke), or even during the insult (prolonged febrile seizure, status epilepticus, or encephalitis). Changes at the molecular level (B) ultimately translate into an unbalance between excitatory and inhibitory neural circuits leading to cortical hyperexcitability in specific networks (A).

(A) Clinical neurophysiology provides extremely valuable methods to study the brain processes non-invasively and with the highest temporal resolution. In this project we will use single, paired and repetitive transcranial magnetic stimulation (TMS) (1) and quantitative analysis of visual evoked potentials (VEPs) (2). (1) TMS is a well-established, safe, painless and non-expensive neurophysiologic method for non-invasive

measurement of brain network excitability (Badawy et al., 2014). This relies on several physiologic variables, which, over the past 25 years, proved much informative in terms of both physiology and disease in epilepsy (Badawy et al., 2014). Furthermore, a variety of TMS protocols have been developed to probe mechanisms of synaptic plasticity in the intact human brain. Plasticity induced by TMS can be modulated by pharmacological interventions, targeting ion channels, or neurotransmitters (Hamada et al., 2012; Strigaro et al., 2014).

(2) Single and paired flash visual evoked potentials (F-VEPs) provide specific information on the excitability properties of the visual system. Modern equipment and simplified measures render this an easy test, with statistical validity (Cantello et al., 2011). VEPs contain gamma high frequency oscillations (HFOs) around 120 Hz that are an emerging epileptogenic marker in epilepsy (Zijlmans et al., 2012).

(B) Molecular changes can include alterations in gene-expression patterns, intracellular signalling and synaptic function (Pitkanen and Lukasiuk, 2011). The latter is regulated by different neuropeptides along with classic neurotransmitters (Kovac and Walker, 2013). Ghrelin is a novel neuropeptide (Kojima et al., 1999) which has a primary role in metabolism and stimulates the release of growth hormone by the pituitary gland (Kovac and Walker, 2013). Ghrelin circulates in the bloodstream in two forms: acylated ghrelin (AG) and unacylated ghrelin (UAG). Interestingly, recent studies performed in vitro or in animal models of epilepsy demonstrated a clear anticonvulsant and neuroprotective action of ghrelin (Portelli et al., 2012). Thus, an impairment of ghrelin signalling could be involved in the pathophysiology of some forms of epilepsy, drug resistance and pathological plasticity, opening new treatment strategies.

Rationale of the study

To increase understanding into the specific networks involved in the pathophysiology of different types of epilepsy, we propose a multimodal approach involving extensive neurophysiological studies on patients with epilepsy. First, we will study patients with photosensitive IGEs since they represent a “model” of system epilepsy. Later, we will focus on patients with different syndromes of generalized and focal epilepsy. We aim to define specific neurophysiological phenotypes which may be the expression of unique molecular alterations and translate the findings into clinically useful parameters. Further investigation into the pathophysiology of these diseases would increase understanding into the ictogenesis of human epilepsies and the neural networks involved and eventually open new therapeutic targets.

Subjects and Methods

Patients with epilepsy will be recruited from the Epilepsy Clinic at the Department of Neurology, ″Maggiore della Carità″ Hospital of Novara. The diagnosis of epilepsy will be made on the basis of the clinical history, imaging, and electroencephalography (EEG) findings by two experienced epileptologists not involved in the present study, according to the ILAE criteria.

Healthy volunteers matched for age, sex and BMI will be recruited as controls. All neurophysiological tests will take place in the afternoon, between 14.00 and 17.00 and will be performed according to the published safety guidelines (Rossi et al., 2009).

Neurophysiological study

Several neurophysiological measures will be used to investigate different epileptogenic networks, including measures of brain functional connectivity (1), motor cortex synaptic plasticity (2) and visual system excitability (3).

1. Brain functional connectivity:

Paired TMS technique allows investigation of time-related changes in functional connectivity between the primary motor cortex and other cortical areas (Ferbert et al., 1992; Civardi et al., 2001; Strigaro et al., 2015c) and explores with high temporal resolution various epileptogenic networks. In particular, the visuomotor and interhemispheric connectivity have been considered.

Visuomotor connectivity: in order to study the pathophysiology of PPR, we first proposed a novel paired TMS method to study the time course of visual inputs on M1 in healthy subjects (Strigaro et al., 2015c). Conditioning stimuli delivered to the occipital region (V1) suppressed M1 activity while the subject was at rest, while it reversed into facilitation in the context of a visuomotor reaction task. Then we applied this novel protocol to study the pathophysiology of photosensitive epilepsy (see results).

To this aim we studied a total of 21 adult patients with IGE referred to the epilepsy clinic of the University Department of Neurology, Novara, Italy: 11 had IGE with PPR and 10 had IGE without PPR. The connection between V1 and M1 was assessed in resting participants by delivering a conditioning stimulus (CS) over the phosphene hotspot of the visual cortex (intensity 90% phosphene threshold, PT) followed at random interstimulus intervals (ISIs; 15, 18, 21, 24, 27, 30, 35 and 40 msec) by a test stimulus (TS) over the left motor cortex to elicit a motor evoked potential (MEP) of ~1 mV from the right first dorsal interosseous muscle.

Interhemispheric connectivity: we designed a study to examine the excitability of interhemispheric connections in patients with focal and generalized epilepsy. We measured the interhemispheric inhibition (IHI) both from left-to-right and from right-to-left M1s (Ferbert et al., 1992; Avanzino et al., 2014). A CS was given to one hemisphere 10 ms (short latency IHI, SIHI) or 50 ms (long latency IHI, LIHI) before a TS delivered to the other side (Ni et al., 2009). The TS and the CS were adjusted to produce an MEP with a peak-to-peak amplitude of ~1 mV (CS1mV; TS1mV) (Ni et al., 2009).

2) Motor cortex synaptic plasticity

Abnormal cortical plasticity has been hypothesized to play a crucial role in the pathogenesis of epilepsies. To study the motor cortical plasticity we used paired associative stimulation (PAS).When a repetitive electrical stimulus to the median nerve is paired with a TMS pulse over the controlateral motor cortex at an ISI of 21.5–25 ms, a long term potentiation (LTP)-like synaptic plasticity is induced in the

corticospinal system. We thus investigated the motor cortex LTP-like synaptic plasticity by means of PAS in patients with juvenile myoclonic epilepsy (JME), the most common IGE.

Twelve adult patients with JME were compared with 13 healthy subjects of similar age and sex. PAS consisted of 180 electrical stimuli of the right median nerve paired with a single TMS over the hotspot of right abductor pollicis brevis (APB) at an ISI of 25 ms (PAS25). We measured motor evoked potentials (MEPs) before and after each intervention for up to 30 min.

3) High frequency oscillations (HFOs)

We will assess the visual system excitability of photosensitive patients with IGE with the F-VEPs. We will study 19 photosensitive patients with IGE showing a PPR. Twenty-two normal subjects of similar age and sex will act as controls. We will record F-VEPs from occipital electrodes and we will measure HFOs by digitally filtering raw VEPs from 75 to 175 Hz (Butterworth type, 12 dB/octave) yielding the "high-frequency" VEP. This procedure has been applied in previous studies (Heinrich et al. 2001). Amplitude values will be measured as the vertical distance between a positive and the following negative peaks. The background signal, the number and the latency of the negative peaks and related amplitudes will be recorded.

Molecular study

Fasting AG and UAG levels in all subjects and circulating drug levels in patients were evaluated at 8.00-8.30 a.m. following an overnight fasting. Blood plasma samples for AG e UAG measures were collected in tubes containing EDTA and a protease inhibitor (pepstatin A 10µM), centrifuged at 3000 rpm for 15 min (temperature = 4°C), then supernatans were stored at -20°C. Samples for AG determination were also added of 1mM of p-hydroxymercuribenzoic acid (PHMB) to prevent AG degradation by protease, acidified by the addition of 1N HCl, then stored at -80°C. AG and UAG levels, expressed in pg/ml, were measured separately by ELISA kits in according to the manufacturer's instructions (BioVendor - Laboratorni Medicina a.s., Brno, Czech Republic). Sensitivity was 0.8 pg/ml and 0.6 pg/ml for AG and UAG, respectively. This part was performed in collaboration with the Laboratory of Pediatrics, University of Piemonte Orientale.

Results

Neurophysiological study

1) Brain functional connectivity:

Visuomotor connectivity (Strigaro et al., 2015d)*:* In healthy subjects, a CS over V1 suppressed M1 at ISIs between 18 and 40 msec. Similar effects occurred in IGE patients without a PPR. This was not true in PPR-positive IGE patients, in whom this type of physiologic inhibition was significantly ($p < 0.05$) reduced (Figure 1).

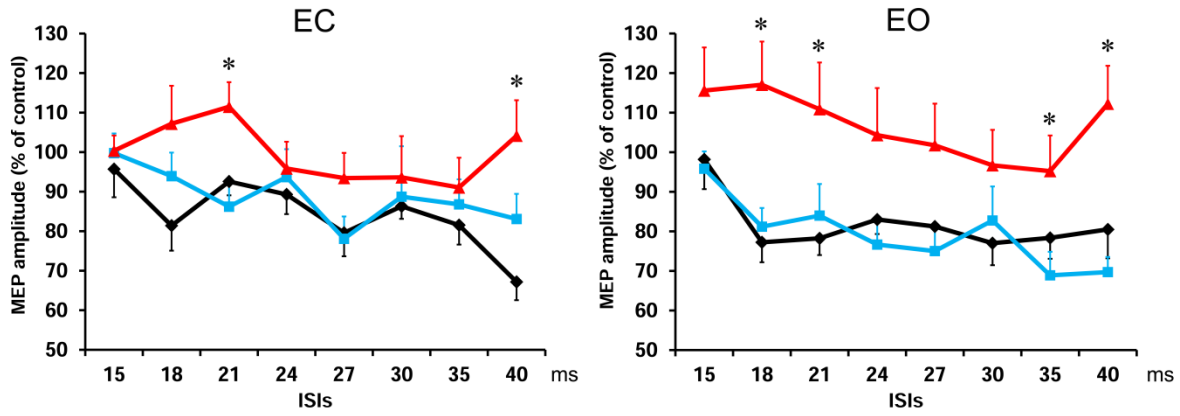

Figure 1.

Effects of a conditioning stimulus (CS, 90% phosphene threshold), at different eye states (EC, eyes closed; EO, eyes open) on the test MEP, in subjects at rest. Red line: IGE + PPR patients. Blue line: IGE-PPR patients. Black line: healthy subjects. Amplitude of MEPs (mV) is normalized and expressed as a percentage of control. Errors bars indicate SEM. Asterisks indicate a p-value <0.05 on separate ANOVAs exploring ISIs.

Altered excitability in V1-frontal connections at rest is not the only factor that contributes to the PPR. A second factor is likely to be hyperexcitability of the visual cortex in response to the flickering light (Strigaro et al., 2012). Paired VEP studies (Cantello et al., 2011) show that this relies on a mechanism of defective inhibition in the visual system, whose time course would fit some of the most "activating" ILS frequencies, such as 16 and 20 Hz (Strigaro et al., 2012). We suggest that this abnormal V1 excitability, coupled with defective control over V1 inputs to frontal cortex produces the PPR. Thus the paradoxical facilitation of EEG activity evoked over central area that is seen in PPR-positive patients with the paired VEP technique would be caused by a combination of reduced inhibition between stimuli in V1 coupled with excess spread of activation to frontal central areas.

Interhemispheric connectivity (Strigaro et al., in preparation): to our knowledge, this is the first study evaluating interhemispheric inhibition using paired pulse TMS in patients with focal and generalized epilepsy. We found that patients with focal epilepsies have a bilateral defective interhemispheric inhibition at short and long ISIs, even though this was present in patients with IGE and healthy individuals. When patients were stratified according to the lateralization of the epileptic focus, the interhemispheric inhibition at long ISI (= 50 ms) appeared to be defective only when the CS was on the focal hemisphere. Thus, the ability of the focal hemisphere to inhibit the motor cortex of the non-focal hemisphere is impaired. We suggest that these alterations may underlie the spread of the epileptic discharge and the secondary generalization of seizures in focal epilepsies.

2) Motor cortex synaptic plasticity (Strigaro et al., 2015b):

In healthy subjects the PAS25 protocol was followed by a significant increase of the MEP amplitude ($p < 0.001$). On the contrary, in patients with JME, the MEP amplitude did not change (Figure 2). We suggest three possible mechanisms involved in the disruption of the motor cortical plasticity in patients with JME: (1) A pathological form of plasticity may occur during epileptogenesis leading into an unbalance between excitatory and inhibitory neural circuits in specific networks, i.e. the motor cortex. In fact, a close relation between LTP and epileptogenesis was recently demonstrated in models of hippocampal epilepsy (Lopantsev et al., 2009). In this view, abnormal cortical plasticity may be the neurophysiological background for the development of myoclonus in JME. (2) Seizures themselves have a significant and lasting impact on the brain in animal models of epilepsy, leading to structural and functional alterations of neuronal circuits which may be accompanied by declining cognitive and behavioural functions, as already recognized in JME. The background of these manifestations might include an impairment of cortical plasticity. (3) The antiepileptic treatment itself may induce long lasting changes in cortical plasticity.

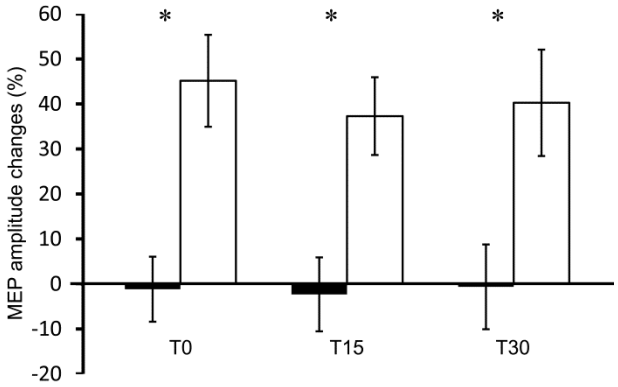

Figure 2

Grand average of normalized MEPs at T0, T15 and T30 to baseline in patients (black) and controls (white). Asterisks indicate a significant difference ($p < 0.05$).

3) High frequency oscillations (HFOs):

We are currently investigating the visual HFOs in photosensitive patients with IGE. We are finishing the recruitment of the participants. Preliminary data have been presented as oral communication at the national congress of the Italian League Against Epilepsy (see below) and showed that patients with photosensitivity had larger HFO amplitude than healthy controls. HFOs may represent a useful biomarker of visual hyperexcitability in epilepsy.

Molecular study

Results of this part have already been shown in the scientific report in 2014 (Varrasi et al., 2014). For further developments, I applied to the Fondazione Cariplo's grant 2015 with a project titled "The role of ghrelin signalling in the regulation of cortical excitability and plasticity in patients with epilepsy" (see below).

Conclusions

1. An overactive functional connection between the primary visual and primary motor cortex, as studied by TMS, may contribute to the pathogenesis of PPR, a key feature of photosensitive idiopathic epilepsies. An excess response of M1 to visual inputs may underlie the fast spread of epileptic activity from posterior to anterior areas of the brain and the origin of the abnormal epileptic motor phenomenon, such as myoclonus.
2. Defective motor cortex plasticity is likely involved in the pathogenesis of JME and may be primarily involved in the pathogenesis of myoclonus in this frequent form of epilepsy.

References

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GRANTS

- Principal investigator, Fondazione Cariplo's call for proposals "Biomedical research conducted by young researchers 2015" with a project titled "The role of ghrelin signalling in the regulation of cortical excitability and plasticity in patients with epilepsy". *Submitted in April 2015.*
- Participation to the call "*Aldo Fasolo award 2015*" for the best PhD research in Neuroscience. University of Turin. Italy. *Submitted in September 2015.*

CONGRESSES AND TRAVEL GRANTS

- 15th European Congress on Clinical Neurophysiology, September 30 – October 3, 2015, Brno, Czech Republic.
- 38° National Congress of the Italian League Against Epilepsy, June 10-12, 2015, Genova, Italy. Travel grant for authors of the best selected orals.
- 60° National Congress of the Italian Society of Clinical Neurophysiology, May 21-23, 2015, Verona, Italy.
- Riunione policentrica in Epilettologia, January 29-30, 2015, Roma, Italy

ORAL COMMUNICATIONS

- "*Strategie terapeutiche alternative al Valproato nelle adolescenti e donne in età fertile*". Regional meeting of the Italian League Against Epilepsy. September 11, 2015, Novara, Italy.
- *"Variability in response to 1 Hz repetitive TMS*". 15th European Congress on Clinical Neurophysiology, September 30 – October 3, 2015, Brno, Czech Republic.
- "*High frequency oscillations in the visual system of photosensitive epilepsies*". 38° National Congress of the Italian League Against Epilepsy, June 10-12, 2015, Genova, Italy.
- "*Visuo-motor connectivity in photosensitive epilepsies*". 60° National Congress of the Italian Society of Clinical Neurophysiology, May 21-23, 2015, Verona, Italy.

POSTERS

15th European Congress on Clinical Neurophysiology, September 30 – October 3, 2015, Brno, Czech Republic:

- **Strigaro G,** Falletta L, Matino E, Tondo G, Lunardon C, Pizzamiglio C, Varrasi C, Cantello R. *Visuo-motor connectivity in photosensitive epilepsies. Poster.*
- Tondo G, **Strigaro G**, Cerino A, Falletta L, Matino E, Varrasi C, Cantello R. *Impaired visual inhibition in migraine with aura. Poster.*

- Pizzamiglio C, **Strigaro G**, Falletta L, Matino E, Tondo G, Varrasi C, Cantello R. *Defective motor cortex plasticity in juvenile myoclonic epilepsy. Poster.*

60° National Congress of the Italian Society of Clinical Neurophysiology, May 21-23, 2015, Verona, Italy:

- **Strigaro G**, Hamada M, Cantello R, Rothwell JC. *Variability in response to 1 Hz repetitive TMS. Poster.*

1st International Brain Stimulation Conference, March 2 - 4, 2015, Singapore:

- **Strigaro G**, Hamada M, Cantello R, Rothwell JC. *Variability in response to 1 Hz repetitive TMS. Poster.*

38° National Congress of the Italian League Against Epilepsy, June 10-12, 2015, Genova, Italy:

- Naldi A, Tondo G, **Strigaro G**, Varrasi C, Cantello R. *Esordio di MELAS con crisi allucinatorie complesse: video EEG. Poster.*
- Tondo G, **Strigaro G**, Zacchetti G, Matino E, Falletta L, Varrasi C, Giordano M, Cantello R. *Epilessia farmacoresistente, ritardo mentale e dermatite atopica in un paziente con duplicazione 13q12.3. Poster.*
- Lunardon C, **Strigaro G**, Pizzamiglio C, Matino E, Falletta L, Tondo G, Carecchio M, Mula M, Varrasi C, Cantello R. *Epilessia, ritardo mentale e atassia in una paziente con delezione 6q22.1-22.31. Poster.*

XLVI Meeting of the Italian Neurological Society, October 10-13, 2015, Genova, Italy:

- Pizzamiglio C, **Strigaro G**, Falletta L, Cerino A, Tondo G, Varrasi C, Cantello R. *Abnormal motor cortex plasticity in juvenile myoclonic epilepsy. Poster. Accepted.*

PUBLICATIONS (2015)

1. **Strigaro G**, Falletta L, Varrasi C, Rothwell JC, Cantello R. Overactive visuomotor connections underlie the photoparoxysmal response. A TMS study. *Epilepsia.* 2015. doi: 10.1111/epi.13190.
2. **Strigaro G**, Falletta L, Cerino A, Pizzamiglio C, Tondo G, Varrasi C, Cantello R. Abnormal motor cortex plasticity in juvenile myoclonic epilepsy. *Seizure.* 2015;30:101-5.
3. **Strigaro G**, Cerino A, Falletta L, Mittino D, Comi C, Varrasi C, Cantello R. Impaired visual inhibition in migraine with aura. *Clin Neurophysiol.* 2015;126(10):1988-93.
4. **Strigaro G**, Ruge D, Chen JC, Marshall L, Desikan M, Cantello R, Rothwell JC. Visuomotor functional connectivity: a TMS study. *J Physiol.* 2015;593(10):2365-77.
5. **Strigaro G**, Mayer I, Chen JC, Cantello R, Rothwell JC. Transcranial Direct Current Stimulation Effects on Single and Paired Flash Visual Evoked Potentials. *Clin EEG Neurosci.* 2015;46(3):208-13.
6. Vecchio D, Varrasi C, **Strigaro G**, Cantello R. Thalamic hemiataxia. *Int J Emerg Ment Health* 2015,17:137. DOI: 10.4172/1522-4821.1000137.

PART 2: Didactic and educational activities

- Seminars and lessons of the PhD Program at the University of Piemonte Orientale, Novara
- Weekly seminars and "Journal club" at the Department of Neurology, University of Piemonte Orientale, Novara.
- In 2015 supervision of the experimental work and the thesis of 1 medical student.
- April 7– June 26, 2015 – Course on *"Chirurgia dell'Epilessia: percorso diagnostico - terapeutico dalla selezione del paziente all'intervento chirurgico"*. Centro per la chirurgia dell'epilessia "Claudio Munari", Department of Neuroscience, Ospedale Niguarda Ca' Granda, Milano, Italy.
- From October 2014, teaching appointments at the "Course of clinical neurology" of the School of Physiotherapy (10 hours) and School of Medicine (4 hours), University of Piemonte Orientale, Novara.

September 25, 2015 Gionata Strigaro