JECN

Journal of Epilepsy and Clinical Neurophysiology

ISSN 1676-2649

Volume 25 | Number 1 | Year 2019

ABSTRACTS PRESENTED AT THE 6TH BRAINN CONGRESS BRAZILIAN INSTITUTE OF NEUROSCIENCE AND NEUROTECHNOLOGY (BRAINN-UNICAMP)

APRIL 1th TO 3th 2019 - CAMPINAS, SP, BRAZIL

J Epilepsy Clin Neurophysiol 2019; 25(1): 1-51

www.jecn.org

JECN Journal of Epilepsy and Clinical Neurophysiology

Órgão Oficial da Liga Brasileira de Epilepsia

Indexada no LILACS – Literatura Latino-americana e do Caribe em Ciências da Saúde

EXPEDIENTE

Editor Consultivo – Arthur Tadeu de Assis
Editora Executiva – Ana Carolina de Assis

Editora Administrativa – Atha Comunicação Editora
Contato – revistajecn@outlook.com

Ficha Catalográfica

Journal of Epilepsy and Clinical Neurophysiology (Revista de Epilepsia e Neurofisiologia Clínica) / Liga Brasileira de Epilepsia. – Vol. 23, n.3, jul 2019.

v.1, 1995 – JLBE: Jornal da Liga Brasileira de Epilepsia
v. 2 a 7 (n. 2, jun. 2001) Brazilian Journal of Epilepsy and Clinical Neurophysiology (Jornal Brasileiro de Epilepsia e Neurofisiologia Clínica)
Publicação trimestral.
ISSN 1676-2649

CDD: 616.8
CDU: 616.853(05)
616.8-092(05)
616.8-073(05)

Índice para Catálogo Sistemático:

Epilepsia – Periódicos – 616.853(05);
Neurofisiologia – Periódicos – 616.8-092(5);
Eletroencefalografia – Periódicos – 616.8-073(05);
Eletroneuromiologia – Periódicos – 616.8.073(05);
Neurologia – Fisiologia – Periódicos – 616.8-092(05).

Coordenação editorial, criação, diagramação, tradução e produção gráfica Atha Comunicação e Editora - E-mail: 1atha@uol.com.br

JECN Journal of Epilepsy and Clinical Neurophysiology

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JECN Journal of Epilepsy and Clinical Neurophysiology

ABSTRACTS PRESENTED AT THE 6TH BRAINN CONGRESS BRAZILIAN INSTITUTE OF NEUROSCIENCE AND NEUROTECHNOLOGY (BRAINN-UNICAMP)

APRIL 1TH TO 3TH 2019 - CAMPINAS, SP, BRAZIL

A BIOINFORMATICS METHOD DEVELOPED TO STUDY POLYGENIC RISKS IN WHOLE EXOME DATA FROM PATIENTS WITH DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHIES

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Introduction: Most common forms of epilepsy are polygenic [1–3]. However, to date, most genes identified to predispose different forms of epilepsy have a major effect and are transmitted in a monogenic fashion. This is especially true for the genes that have been identified in patients with developmental epilepsy encephalopathies (DEE). However, even when using large-scale genomic analysis in patients with DEE, only a minority of patients will have a major gene identified in genetic testing. Therefore, this work proposes the implementation of descriptive and predictive models of identifying polygenic risks to be applied to patients with DEE. **Materials and Methods**: We performed the variant call-set in data from whole exome sequencing of 122 patients with DEE as well as in 258 control samples from the BIPMed-WES control database (www.bipmed.org). In this initial work, we focused the identification of polygenic risks from 1259 candidate genes, selected based on their function in the central nervous system and the putative mechanisms involved in epilepsy. To construct the models, we first processed the variants, counting the alleles. For the model analysis, we use RapidMiner Studio (version 9.0.003) with the 'Auto Model' feature. To perform the functional annotation, we use the ConsensusPathDB [4]. We considered the following models in our analysis: Naive Bayes, Generalized Linear Model (with regularization), Logistic Regression, Deep Learning, Decision Tree (with automatic optimization), Random Forests (with automatic optimization), and Gradient Driven Trees (XGBoost) (with automatic optimization). We considered the models with AUC greater than 0.6 and variants with importance greater than 0.4. **Results**: We identified 43 genetic variants in 27 genes. We obtained 87 neighborhood-based enriched genes entries (NESTs), 5 enriched pathways, 124 enriched genetic ontology entries, and 1 enriched protein complex. The enriched pathways are: Axon guidance, NrCAM interactions, Developmental Biology, L1CAM interactions, and Signaling by ROBO receptors. The protein complex enriched in the gene pool is given by the physical interaction between the NRCAM (neuronal cell adhesion molecule) and NRP2 (neuropilin 2). **Discussion**: A polygenic effect is not exclusive to epilepsies, extending to other common disorders, in which many relatively rare variants with average risk interact in the disease predisposition [5–7]. Although polygenic inheritance is considered the mode of inheritance in the most common human disorders there are still major methodological challenges to identify these genetic variants [8,9]. **Conclusion**: We present a robust and straightforward method capable of identifying polygenic pathways which may be associated with disease predisposition in patients with DEE. Extrapolation of such a method is possible for other polygenic disorders. However, there are still limitations to be overcome, such as extending this type of analysis to a more agnostic approach, without the prior selection of candidate genes; and the establishment of validation methods, both statistical and function methods to test the reproducibility and validity of our results.

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USING EXPRESSION GENOME-WIDE ASSOCIATION STUDIES (EGWAS) TO IDENTIFY LOCI FOR MESIAL TEMPORAL LOBE EPILEPSY

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Introduction and Hypothesis:: Epilepsy is defined as a neurological disorder characterized by the permanent predisposition of the brain to generate spontaneous epileptic seizures. Temporal lobe epilepsy is the most common form of focal epilepsy in the adult population, accounting for approximately 40% of all cases of epilepsy in this population [1]. The understanding of the underlying mechanisms, including genetic predisposition, leading to epilepsy has grown rapidly in the last few decades; however, in complex inherited epilepsies, which are the most frequent forms, the genetic basis remains largely unknown. Mainly in focal epilepsies, the challenge of identifying susceptibility loci using genome-wide association studies (GWAS) has been unsuccessful [2]. Recent studies have integrated expression quantitative trait loci (eQTLs) data with GWAS in several complex diseases. Their findings demonstrated disease-associated variants are more likely to be eQTLs, affecting gene expression levels [3,4,5]. This approach can be used to improve our ability to discover genetic risk factors for mesial temporal lobe epilepsy (MTLE) and to enhance our understanding of its underlying biology. **Objective:** The aim of this research is to identify susceptibility loci for MTLE, using expression genome-wide association study (eGWAS). **Methods:** For the development of the project, GWAS data will be generated from a sample of 500 patients with MTLE and 500 controls, using a genomic SNP-array. In addition, genomic and gene expression data will be generated in surgical material from patients with MTLE (n = 70) and controls obtained from autopsy (n = 8) to perform an eQTL study. Subsequently, statistical analyzes will be performed to integrate GWAS and eQTL data to identify the susceptibility loci. **Relevance:** The literature has shown that by integrating gene expression data into association analysis is possible to increase sensitivity by incorporating functional data, which in turn reduces the number of multiple comparisons and statistical corrections that make it difficult to find positive results in GWAS.

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CIRCULATING CELL-FREE DNA METHYLATION AS A POTENTIAL PREDICTIVE AND PROGNOSTIC BIOMARKER IN NEUROLOGICAL DISEASES - MESIAL TEMPORAL LOBE EPILEPSY AND STROKE

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Introduction: Epilepsy and stroke are neurological diseases which represent public health problems. Stroke is the second leading cause of death worldwide and epilepsy affects more than 50 million people worldwide, with mesial temporal lobe epilepsy (MTLE) being the most frequent[1,2]. Diagnosis and prognosis of

patients with stroke and epilepsy is still a challenge since it is based on subjective clinical signs and symptoms[3,4]. Therefore, the identification of biomarkers for the diagnosis and establishment of prognosis becomes essential. Methylated cell-free circulating DNA (cfDNA) has recently emerged as a candidate for biomarker since it can be analyzed and quantified noninvasively[5]. **Materials and Methods:** Initially the work was divided into three phases, (1) isolate and quantify cfDNA present in plasma of patients with MTLE, stroke and controls; (2) sequencing the whole genome bisulphite (WGBS) of cfDNA isolated from patients and controls, and identifying the differentially methylated regions (DMRs) to be used as biomarkers; (3) to customize panels with DMRs to be used in an expanded sample of patients with stroke and MTLE to validate the potential biomarkers previously identified. More specifically the cohort of phases 1 and 2 are composed of 10 patients with medically refractory MTLE, 10 with patients with responsive MTLE, 10 patients in the acute phase of stroke, 10 in the chronic phase of stroke, and 10 control subjects. In phase 3, an independent cohort of 100 patients with MTLE, 100 with stroke and 100 controls will be included. **Results:** To date, we have completed the recruitment of 110 controls, 120 patients with MTLE, and part of the cohort of stroke patients (75 patients, being 35 in the acute phase and 40 chronic). For the investigation phase, MTLE patients were selected according to the most prevalent drug use, and the combination of two drugs, Carbamazepine and Clobazam, which was used by more than 30% of our patients, regardless of severity (responsive or refractory). The main phenotypic characteristics of the MTLE and stroke cohort were annotated to be subsequently grouped. Moreover, cfDNA extraction was standardized and our preliminary results by quantification in Quibit, although not significant, indicate that there is a modest increase in the total concentration (ng) of cfDNA in patients with refractory MTLE (29.4 ± 4.9) in relation to the responsive patients (25.1 ± 4.1) and controls (25.6 ± 4.2). In addition, we found an even greater increase in the concentration of cfDNA in patients with acute stroke (27.5 ± 6.8) when compared to chronic patients (16.8 ± 4.1). **Discussion:** The diagnosis of epilepsy and stroke is based on neurological history, electroencephalogram and neuroimaging findings[6]. However, there is still a significant challenge in diagnosis, since it still requires a certain degree of clinical expertise for the appropriated interpretation of these findings. In this context, it is evident that the identification of non-invasive diagnosis methods such as the use of biomarkers is urgently needed. Furthermore, the comparison of the methylation pattern of cfDNA between these two neurological conditions is of interest in the study of mechanisms of brain damage and plasticity. **Conclusion:** We recruited and characterized the complete cohort of patients with MTLE and controls, and a significant number of the stroke cohort as well. In addition, we standardized the cfDNA extraction method, and the quantification of the cfDNA samples already indicated the potential increase of cfDNA as a marker of severity for MTLE and stroke.

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MICROPROTEOMIC ANALYSIS OF THE HIPPOCAMPUS FROM PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY REVEALS MOLECULAR MECHANISMS RELATED TO DISEASE PROGRESSION

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Introduction: Mesial temporal lobe epilepsy (MTLE) is the most common form of epilepsy in adults, leading to refractory seizures in about 40% of patients, some of whom can benefit from epilepsy surgery. In most patients with MTLE, hippocampal sclerosis (HS) is identified in the pathological examination, which is usually resected during surgery [1]. We aim to evaluate whether there is any molecular progression in the HS lesion from patients with different ages of seizures onset by analyzing the protein expression in hippocampal dentate gyrus. **Materials and Methods:** Here we performed laser-microdissection to isolate the neurons from the hippocampal dentate gyrus (DG) of two groups of patients: G1 with less than 20 years of seizures onset (N=5), G2 with more than 20 years (N=5) and compared them with controls from autopsy (N=5). We used label-free microproteomics, and the analysis was performed at the RASR Laboratory, using an LTQ-Orbitrap Elite. All the MS^2 runs were in duplicate. For the bioinformatics analysis, we used ProteomeDiscoverer 2.2 software and DAVID database, as well as Reactome for enrichment analysis. We performed an ANOVA background-based statistical analysis and Benjamini-Hochberg correction test for multiple comparisons. **Results:** Overall, we identified 4000 protein groups. In the G1 we identified 133 differentially expressed proteins, and in the G2 we identified 114. The mainly differentially expressed proteins in both groups were up-regulated. Furthermore, only 40 proteins were found differently expressed in both groups of patients. **Discussion:** Our analysis clearly shows a remarkable difference in the enriched biological pathways and processes in the two groups of patients. In G1 we found major changes in transcription regulation, energy metabolism, and extracellular matrix reorganization; while, in G2 we found enrichment in programmed cell death, neurotransmission and receptors, and in disease-related pathways such as Alzheimer's and Parkinson's disease. In G2 we also found proteins related to drug resistance in epilepsy, such as ATP-binding cassette sub-family B member [2]. However, these were not identified as abnormally expressed in the G1 group. **Conclusion:** The present work reveals that there are remarkable differences in protein expression in tissue from patients with different disease duration, indicating that there is progression of the pathological lesion identified in patients with MTLE and HS over time.

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BRAVE – A COMPUTATIONAL SOLUTIONS FOR SHARING HUMAN GENOMICS DATA

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Introduction: Federated genomic databases have become widely popular among independent research laboratories to share their data faster than submitting it to centralized data servers. The Global Alliance for Genomics and Health (GA4GH) standardization efforts have influenced many organizations to implement the GA4GH guidelines for responsible human genomics data sharing [1]. However, there is no computational solution for sharing genomics data publicly available that offers all tools required for assisting research studies. To address this problem, we have created the BraVE project, a collection of software tools for human genomics data sharing and visualization. **Methods:** The BraVE application programming interface (API), based on the GA4GH Genomics API [2], exposes search system for genomic variant data through a secure internet protocol (HTTPS). Implementation server and data import tools were developed to host genomics data and to provide access via BraVE API. Implementation server stores data in non-relational databases (MongoDB) and exposes data through secure endpoints (REST). Importer tools support Variant Call Format (VCF) files with annotation data. We also developed a web application for researchers to search for variants and visualize data through a web browser. No individual data is stored in a database or exposed via API or showed at the web application. **Results:** We have used the BraVE computational solutions to share Brazilian Initiative on Precision Medicine (BIPMed) datasets. The web application hosting BIPMed data is available at https://bipmed.org/brave/. The search system supports multiple types of queries such as gene symbol (e.g., SCN1A), genomic range (e.g., 1:65000-70000), genomic position (e.g., 1:7737651) and dbSNP database ID (rs35735053). Queries can be mixed to get a customized collection of variants. Variant data reported by BraVE API contains genomic coordinate (chromosome and position), reference and alternative bases, dbSNP ID (when available), allele frequency, annotations such as gene symbol, HGVS nomenclature and clinical significance, and distributions of coverage and genotype quality. All tools and documentation are publicly available at https://github.com/bipmed/. **Discussion:** Sharing human genomics data has become an important task for any laboratory committed with open science initiatives and global research collaborations. The BraVE project provides all necessary tools

for responsibly sharing genomics data, allowing users to search for variants using the user-friendly web application and accessing data programmatically through secure API. Since no individual data is stored in the server or exposed, our computational solution can be used by independent research groups to host their own human genomics data locally or via public cloud computing services. **Conclusion:** Federated genomics databases diminish time and effort required for sharing data but require computational solutions for hosting, exposing, searching and interacting with these datasets over the internet. The BraVE project provides all necessary tools without compromising sensitive information such as individual data. Through secure internet protocols, advanced storage technologies and consistent API provided by BraVE project, we have succeeded to host BIPMed datasets.

Supported: FAPESP.

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TRANSCRIPTOMIC ANALYSIS OF SUBICULUM REGION IN ANIMAL MODEL OF MESIAL TEMPORAL LOBE EPILEPSY (MTLE) INDUCED BY PILOCARPINE

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Introduction: Temporal lobe epilepsy (TLE) is the most frequent type of epilepsy in adults and these patients usually are resistant to treatment. Among the different types of TLE, mesial temporal lobe epilepsy (MTLE) is the most frequent and it is characterized by damage in the mesial temporal structures, such as the hippocampus formation. Other structures belonging to the hippocampus formation, such as subiculum, dentate gyrus and enthorrinal cortex, are also altered in MTLE. The subiculum is an important structure because it forms the transition that connects the hippocampus with the enthorrinal cortex, which allows for high amplification and modulation of the neuronal response, and it is involved in the recovery of short-term memory and spatial memory codification. This study aims to understand the molecular changes that happen in the subiculum in the pilocarpine induced epilepsy experimental model. **Materials and Methods:** We used 4 control and 4 pilocarpine treated rats (CEMIB-UNICAMP) and performed Laser Capture Microdissection (LCM) using a Zeiss-PALM system. We extracted the subiculum from tissue sections using a surgical microscope (Zeiss), separating the dorsal (dSub) and ventral (vSub) parts. RNA was extracted using Trizol (Thermo) and libraries of cDNA were prepared using Truseq (Illumina) library preparation kit according to manufacturer instructions. For data analysis, we used two pilocarpine treatment samples and three control samples for alignment of reads to the Rat genome (STAR aligner) and statistics for differential gene expression with Deseq2 pipeline. Gene ontologies were analysed using the Metacore ® software. **Results:** A total of 25 differentially expressed genes were found ($p<0.05$) between the control dSub and pilocarpine dSub, and we found 4 up-regulated genes and 21 down-regulated genes in pilocarpine stimulation condition. The gene ontology analysis indicated cell adhesion and complement system in up-regulated genes, and translation initiation, ubiquinone metabolism and transcription HIF-1 targets in down-regulated genes. **Discussion:** The pathways enriched by up-regulated genes, such as cell adhesion and complement system, suggests that in the dorsal subiculum, 15 days after SE (silent phase), there may be a synaptic reorganization and cell death taking place. These observations mays indicate process involved in epileptogenesis. In addition the pathways enriched by down-regulated genes indicate a reduction in protein folding, however, a small number of genes indicate this phenomena. Further experiments are required to validate the present results. **Conclusion:** This study allows observing the differential expression of pathways in the dorsal subiculum region when comparing control and pilocarpine samples, showing changes in synaptic reorganization and a reduction in protein folding in this region. Therefore, through the present study, we are able to understand the role of subiculum in silent phase of epileptogenic process.

Support: FAPESP, CNpQ.

WHITE MATTER MICROSTRUCTURAL ALTERATIONS IN HUNTINGTON DISEASE

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Introduction: Although Huntington Disease (HD) symptoms have been explained mainly by degeneration in the caudate, putamen, globus pallidus, thalamus, and amygdala, there is considerable variability in age of onset, symptom severity, and rate of neurodegeneration progression between the affected individuals. Therefore, there has been an effort to comprehend the structural magnetic resonance imaging (MRI) alterations in HD. Imaging studies in patients with HD may help to determine differential vulnerability of CNS structures to the neurodegenerative process as well as to identify precisely when neurodegeneration starts, how it progresses and the associated triggers [1]. **Materials and Methods:** We obtained diffusion tensor imaging (DTI) (32 directions) acquired at 3.0T from 37 healthy volunteers and 36 patients (genetically confirmed), balanced for age ($p=0.9$) and gender ($p=0.9$). Patients underwent neurological (Unified Huntington's disease rating scale – UHDRS) and cognitive (Montreal cognitive assessment - MOCA) evaluations. Diffusion Tensor Images were processed with ExploreDTI/MATLAB-2014 (www.exploredti.com). Ten tracts [3 parts of the corpus callosum (CC), Corticospinal tract (CST), Inferior Fronto Occipital (IFO) tract, Inferior Longitudinal Fasciculus (ILF), dorsal and parahippocampal cingulum (PH-CINGULUM), uncinate and body of fornix (FORNIX)] were delineated by semi-automatic deterministic tractography to yield fractional anisotropy (FA). SPSS (software version 22 - https://www.ibm.com) was used for correlations, univariate, multivariate analyses and Chi-square test. **Results:** Multivariate analyses with Repeated-measures ANOVA for bilateral tracts revealed significant FA reduction mainly on cingulum and PH-cingulum ($p<0.004$, with Bonferroni correction). MANOVA of Corpus Callosum segments and FORNIX showed reduced FA values ($p<0.0125$ with Bonferroni correction) in patients with HD. While there was no significant correlation between FA values and CAG repeat expansion, we identified a significant correlation between UHDRS and CST (left $r=-0.575$, right $r=-0.45$, $p<0.005$), IFO (left $r=-0.51$, left $r=-0.58$, $p<0.002$) and left PH-CINGULUM ($r=-0.48$, $p=0.003$). In addition, there was a positive correlation between MOCA and FA values in PH-CINGULUM (left $r=0.54$, right $r=0.59$, $p<0.002$). **Discussion:** WM microstructural alterations were widespread, affecting midline and bilateral structures in patients with HD. The abnormal tracts are responsible for sensorimotor integration, motor control and planning, visuospatial function and emotional processing [2]. **Conclusion:** Prospective studies are underway in order to characterize how the pattern of WM alterations progresses over time.

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CHARACTERIZATION OF GUT MICROBIOME IN PATIENTS WITH DIFFERENT FORMS OF EPILEPSY AND AUTOIMMUNE ENCEPHALITIS USING METAGENOMIC ANALYSIS

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Introduction and Hypothesis:: Over time, man and microorganisms have co-evolved simultaneously to integrate a complex ecosystem [1]. The intestine is considered the largest reservoir of these microorganisms, and the colon reaches the maximum density of these germs [2,3]. Studies have shown that enteric microbiota plays a pivotal role in host physiology and immunity and acts as a key mediator in the central nervous system [4,5,6]. Such bidirectional signaling known as the gut-brain axis is achieved through metabolic and neurological pathways [7,8,9]. Epilepsy and Autoimmune Encephalitis (AE) are heterogeneous and disabling diseases that affect all ages and contribute to the global economic burden [10]. The main objective of this work is to characterize the composition of the intestinal microbiome in individuals with different forms of epilepsy as well as healthy controls [11,12]. Results could reveal novel insights related to clinical phenotype and drug resistance and could provide an alternative

therapeutic approach focused on molecular targets, fecal transplantation and probiotics. **Objective:** To determine if there are differences in gut microbiota composition among patients with different forms of epilepsy and autoimmune encephalitis. **Methods:** Fecal human DNA will be extracted and purified using the **FastDNA™ SPIN Kit for Feces** (MP Biomedicals) from a cohort of 180 individuals classified as follows: 30 patients with mesial temporal lobe epilepsy; 30 patients with genetic generalized epilepsy and 30 patients with autoimmune encephalitis. DNA yield and quality will be evaluated on 1% agarose gel electrophoresis and *Epoch Spectrophotometer system*. 16s ribosomal DNA sequencing will be performed in an Illumina MiSeq 2500 platform. Data analysis will be performed using QIIME, UPARSE, MOTHUR and DADA2 online bioinformatic tools workflow. Final results will be statistically validated and shared in a public database (www.bipmed.org). **Relevance:** The identification of new microbial communities capable of modulating and regulating different physiological processes related to the gut-brain axis may allow the development of alternative therapeutic strategies for the treatment of specific neurological conditions. In addition, the data generated in our study will constitute the first gene catalog of normal gut microbiota in the Brazilian population and may be used by any national or international research group interested in studying the intestinal microbiota in health and disease states.

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DIFFERENT PATTERN OF CIRCULATING MICRORNAS IN THE ACUTE AND CHRONIC PHASES OF ISCHEMIC STROKE

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Introduction: Stroke is one of the most common causes of death or disability worldwide [1,2]. Ischemic stroke (IS) is it the most frequent subtype, affecting almost 85% of patients. There are well established environmental risk-factors and comorbidities associated with IS; however, it is estimated that nearly 40% of patients with IS have no identifiable risks, which points to the role of genetic factors [2]. In addition, there are still some limitations in the current methods for the diagnosis and the establishment of prognosis in patients with IS, highlighting the need for the identification of non-invasive biomarkers of IS. Biomarkers are small molecules that will undergo some changes during the disease process [1]. Currently, biomarkers identified in easily assessable biofluids can aid in the diagnoses of several disorders, and in the area of oncology are becoming standard of care [1]. One such molecule is microRNA, small non-coding RNAs related to endogenous regulation of gene expression in different tissues. This study aims to identify circulating microRNAs which are candidates for biomarkers of disease and prognosis in the acute and chronic stages of IS. **Materials and Methods:** We evaluated 50 patients in the acute and chronic stages of IS and 50 controls. Blood samples were collected within 24 hours after the acute event (acute phase), as well as between 3 to 6 months after the acute event (chronic phase). Circulating microRNAs were obtained from plasma using the Mirvana-Paris® (Thermo Fischer, Inc) extraction kit. Sequencing libraries were prepared using the TruSeq® Small RNA Library Prep kit – RS-200-0048 (Illumina Inc) and small-RNA sequencing was performed in a Miseq®equipment (Illumina Inc). Reads were counted and microRNA expression was quantified in the different groups using HTSeqcount, DEseq2, and mirDeep software. **Results:** There are five microRNAs downregulated in patients (acute+chronic) as compared to controls; these are related to angiogenesis, regulation of transcription and regulation of cell proliferation. In addition, there are five microRNAs upregulated in the chronic stage of IS, which are related to regulation of angiogenesis, regulation of cell proliferation and regulation of cell-matrix adhesion. Three microRNAs are downregulated in the acute phase, and they are involved in the regulation of cholesterol homeostasis and regulation of lipoprotein particle clearance. **Discussion:** Overall our results show that there is an increased expression of microRNAs during the chronic stage of IS, which seems to be related to the recovery process [3]. By contrast, we observed a downregulation of microRNAs involved in lipid metabolism and stability in the acute phase of IS. **Conclusion:** We have identified a different microRNA-mediated gene-regulation signature in patients in the acute and chronic phases of IS. Further analysis are being carried out to investigate whether there are specific microRNAs related to the prognosis of patients with IS.

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EVALUATION OF RECONSTRUCTION METHODS OF COMPLEX SIGNAL IN MRI WITH A MULTI-CHANNEL COIL FOR THE QSM

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Introduction: The *QSM (Quantitative Susceptibility Mapping)* is a *MRI* technique with high potential in neurodegenerative studies [1-2]. In contrast to other techniques, it uses phase images in its processing, requiring a careful preprocessing [3-7]. Usually, magnitude and phase images acquired with a multi-coil receiver are automatically reconstructed by the scanner (AR). While it is a fast way to obtain the images, it could have noises on phase images related to the coils and other static sources (*offset phase*) that can con-

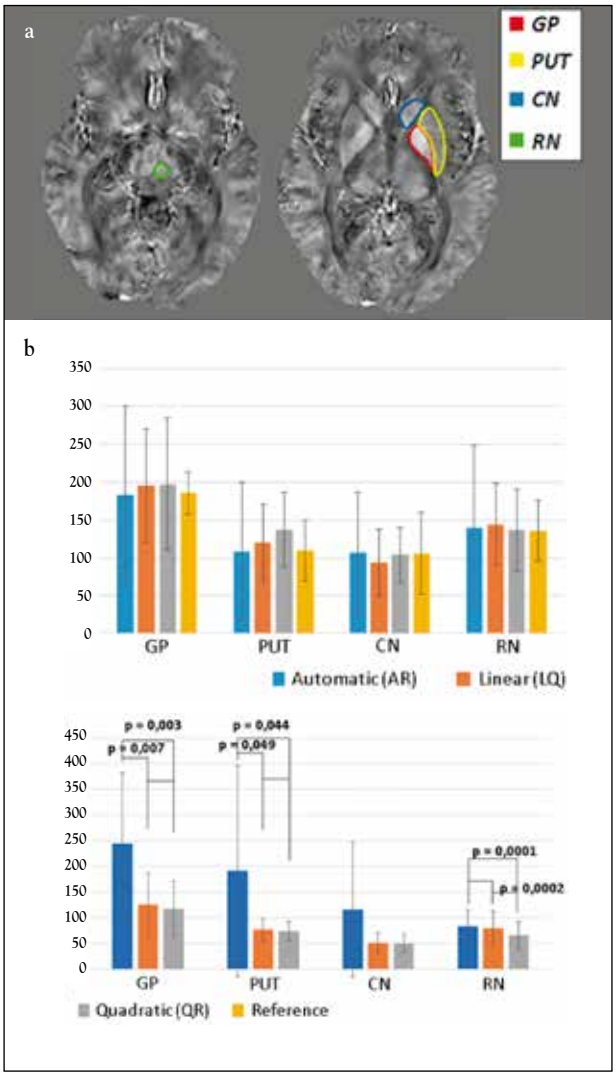

Figure 1. a) QSM processed with a quadratic ponderation, the four regions are outlined; b) Bar graphs of the susceptibility (left) and SD (right) across all subjects. Time processing for each method (mean values): AR:1h; LR: 1h50min; QR: 2h. p-values are shown only for those who had statistical significance on the SD graph.

tribute to undesirable artifacts in *QSM* [4-5]. Some reconstruction methods for the complex signal acquired with 32 channels were tested on this work, with the subtraction of the *offset phase*, and a linear (LR) and a quadratic (QR) ponderation of magnitude images. **Materials and Methods:** Images from 15 *postmortem* subjects without death by psychiatric, neurological or neurodegenerative disorder (51-87 years, 6 male and 2 female) were acquired with a multi-echo (first echo: 5ms; echo time: 4ms) 3D Gradient Echo sequence, with a 32-channels coil and a 7T MR scanner. Signal from each channel and the AR signal were acquired. Manual reconstruction (LR and QR) was made after the *offset* subtraction. *QSMs* were calculated for each method. Four regions (Globus Pallidus, GP; Caudate Nucleus, CN; Red Nucleus, RN; Putamen, PUT, Figure 1a), known to have relevant role on some neurodegenerative diseases (Parkinson's Disease, Alzheimer's Disease), were manually segmented for comparison between methods. **Results:** The bar graphs on Figure 1b (left) shows the susceptibility values (mean values) across all subjects. The graph on the right shows the Standard Deviation SD (higher SD results in lower uniformity) across all subjects, implying that the manually reconstructed methods resulted in higher uniformity. **Discussion:** Besides the fact that each region is heterogeneous, and hence, have a significative SD, another factor that could contribute to an increase in SD is the noise related to the *offset phase* and contributions from low sensibility from the coils. The signal from each coil enables the calculation and subtraction of the *offset phase*, thus eliminating undesirable signals. The magnitude ponderation helps to increase the signal from regions with more sensibility and decrease the signal from regions with poor sensibility. Also, it was observed that for two subjects, the AR method resulted in QSMs with negative susceptibility values on the segmented regions (which are known to have positive susceptibility), possibly due to errors during the phase unwrapping process. **Conclusion:** Although the LR and QR methods tested on this work are time costly in comparison to the AR method, they resulted in *QSMs* with higher uniformity and a significative artifact reduction, from the visual analysis of the maps.

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BEHAVIORAL CHANGES AND MULTIMODAL INTERACTION WITHIN A PERFORMATIVE SPACE: AN INTERDISCIPLINARY INVESTIGATION

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Introduction and Hypothesis: The aim of the project is to improve the efficacy of e-mocomu, a prototype technology previously developed and experimented at NICS (Interdisciplinary Nucleus of Sound Communication) [1, 2], thus establishing the important role of interactive environment in audio-visual-motor learning. Technology is as well a social instrument for equality, independently of age, race or, above all, disability [3]. For these reasons, a technology-driven shift in performative spaces needs to be undertaken on the basis of general theories on cognition, emotions, creativity, and music related neural activation, and should also engage the field of neuroscience to better understand the underlying mechanisms. In this research, we hypothesize that: A) Training with e-mocomu technology results in changes in cognitive control observable during improvisational sessions and measurable through the acquisition of functional Magnetic Resonance Imaging (fMRI), Heart Rate Variability (HRV), Electrodermal Activity (EDA). B) The audiovisual-motor learning generates and strengthens new sensorimotor maps based on cross-modal encoding thus increasing user's concentration, which can be assessed through fMRI. **Objective:** Measure the efficacy of e-mocomu technology by investigating the physiological, neurological and emotional processes that underlie the behavioral changes in the users, eventually developing a new and evolved prototype of Digital Musical Instrument (DMI) technology. **Methods:** We will test 15 healthy volunteers from Unicamp University, divided into three groups: Control Group (CG), Music Group (MG) and Exercise Group (EG). Each user will be asked to come regularly once a week for a period of 3 months, totaling 12 sessions per subject. During the experiment sessions of about 20 minutes, we will be recording the user's performance, data regarding the movements done by the user, and the length of the improvisation session. Subjects will interact within the performative space, observing their movement through a screen/wall in the orthostatic position or in the sitting position. We will collect and extract quantitative and qualitative data in the first session, the middle session, and the last session. Before and after the 12th sessions we will apply questionnaires on self-perceived performance, while during the 12th sessions we will collect HRV, EDA and the movement's data of each user. **Relevance:** The recent literature on related topics underscores the potential of a therapeutically-oriented technology which constitutes a currently developing novel field of study. In the last decade, the scientific community has shown considerable interest in the implementation of interactive spaces for therapeutic support [4]. Diverse technologies have been conceived and designed in order to couple the user's motion with sound production in a space where freedom of movements is considered critical for the subject's self-awareness.

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IDENTIFYING CIRCULATING BIOMARKERS IN PATIENTS WITH SYMPTOMATIC AND ASYMPTOMATIC CAROTID ARTERY STENOSIS: A PRELIMINARY REPORT

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Introduction: Stroke can occur due to an embolic blood clot formed by the rupture of an atherosclerotic plaque [1]. Therefore, the search for biomarkers related to plaque rupture could help the identification of patients with higher stroke risk. Circulating microRNAs, found in plasma microvesicles, exosomes and conjugated with lipoproteins, are non-coding RNAs molecules which are involved in the fine regulation of gene expression, and have been proposed as disease biomarkers for several conditions [2,3]. Thus, the main goal of this study is to investigate whether differences in microRNA profiles could be used as biomarkers to identify patients at a higher risk of atherosclerotic plaque rupture. **Materials and Methods:** We will study the profile of circulating microRNAs in patients with symptomatic and asymptomatic carotid stenosis in comparison to healthy controls. The total number of patients studied is 120, divided into the following groups: 30 with mild asymptomatic stenosis (MAS), 30 cardioembolic stroke patients with mild asymptomatic stenosis (CS-MAS), 30 with severe asymptomatic stenosis (SAS) and 30 with severe symptomatic stenosis (SSS). Peripheral blood has been collected from all patients for subsequent microRNA extraction and cDNA library preparation. MicroRNA expression will be studied using RNA-sequencing and subsequently analyzed using bioinformatics protocols. **Results:** Here we report the results of the phenotypic characterization of the cohort already collected, which is composed of 98 individuals. For the 30 MAS patients (mean age 60,7±9,1) the risk factors identified are hypertension (100%), smoking (60%), dyslipidemia (46%) and diabetes (46%). We have a cohort of 14 CS-MAS patients (mean age 64±9,8) the risk factors identified are hypertension (82%), smoking (54%), dyslipidemia (54%) and diabetes (30%). For the 29 SAS patients (mean age 68,1±9,2) the risk factors identified are hypertension (88%), smoking (56%), dyslipidemia (64%) and diabetes (48%). Finally, we have collected 25 SSS patients (mean age 72±10,2) the risk factors identified are smoking (85%), hypertension (76%), dyslipidemia (65%) and diabetes (45%). **Discussion:** Considering these preliminary results, all four groups have similar mean ages and risk factors, making them relevant cohorts for further comparisons. **Conclusion:** Here we present preliminary results of our study which is likely to aid in the identification of non-invasive biomarkers related to the formation, growth, and rupture of the atherosclerotic plaque.

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METABOLOMIC PROFILES OF PATIENTS WITH ISCHEMIC STROKE: SEARCHING FOR BIOMARKERS

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Introduction and Hypothesis: Stroke is caused by a blockage of the blood flow in the brain, resulting in neurological deficits [1]. Ischemic stroke (IS) is the most prevalent type as it affects almost 85% of all stroke patients [2]. Atherosclerosis of large vessels is one of the most frequent subtypes of IS, and it is mainly caused by an obstruction of large arteries due to thrombi formation derived from atherosclerotic plaques [1;3]. During IS there is the activation of several molecular mechanisms such as inflammation, excitotoxicity and cell death. Based on these processes of damage, as well as in tissue recovery rates, it is possible to classify IS in stages as acute, subacute and chronic [1]. The effects of ischemia on neural tissue worseness with the increase of the injured area, while tissue recoveries strategies, as vase recanalization, have a pivotal role to avoid the increase of ischemic events at the penumbra and to prevent further neural injuries [4]. Despite all clinical knowledge, there are no biomarkers to determine whether a given patient will follow the recanalization process, thus leading to clinical improvement, or he/she will get worse. One of the metabolomics techniques is the use of proton Nuclear Magnetic Resonance (^{1}H NMR), which is based on the absorption of radio wave frequencies by the molecule nucleus in the presence of a high magnetic field [5;6]. This allied with references in a databank and specific statistical strategies is one of the best ways to identify molecules present in a complex biological sample. **Objective:** The present study aims to determine the metabolomic profiles of plasma samples from patients in the acute and chronic stages of large vessels IS using ^{1}H NMR analysis. This information will be correlated with the NIH (National Institute of Health) Stroke Score variation, a measure of clinical evolution and prognosis. **Methods:** To determine the metabolic profiles of plasma samples we will use four groups of patients: twenty patients with large vessels IS at the acute stage; twenty patients with large vessels IS at the chronic stage; twenty asymptomatic patients with severe internal carotid artery stenosis; and twenty healthy individuals. This last group is composed from individuals over fifty years old, who do not present internal carotid artery stenosis, who had no stroke and no first-degree relatives with stroke. The samples will be diluted in deuterated water and analyzed in a 600 MHz NMR (^{1}H NMR, Bruker Inc). The metabolomic and metabonomic analyses will be performed using MestreNova and MetaboAnalyst software. **Relevance:** The present study may help to point to key metabolic pathways involved in the pathophysiological process of IS and to add-in to identification of biomarkers for prognosis in these patients.

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WHOLE GENOME DNA METHYLATION PATTERN IN HIPPOCAMPAL TISSUE OF PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY: A PROGRESS REPORT

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Introduction: Mesial temporal lobe epilepsy (MTLE) associated with hippocampal sclerosis is one of the most frequent and most severe types of epilepsy since many patients are refractory to antiepileptic drug treatment [1]. In these patients, a surgical procedure may be a therapeutic alternative, which includes the surgical resection of hippocampal tissue presenting with the histopathological hallmarks of mesial temporal sclerosis [2]. DNA methylation is the most studied epigenetic mechanism since it acts on gene regulation and may be reversible [3]. Thus, our main hypothesis is that the differences in gene expression identified in patients with MTLE may be caused, at least in part, by differentially methylated regions in the genome. In order to complement our hypothesis, we will integrate the methylome data with transcriptome and proteomics from the same patients, and compare it with the same data from autopsy controls. Therefore, we will be able to comprehend the patient as a unique biological organism, by molecular point of view, and not only by separate aspects. **Materials and Methods:** We selected ten patients with MTLE and five control individuals from an autopsy. The patients are organized in two groups: one with less than 20 years of disease (n = 5); and another with more than 20 years of disease duration (n = 5). Tissues from patients and autopsy were immediately frozen in liquid nitrogen until further use. Laser microdissection was performed to isolate the hippocampal *dentate gyrus*. DNA was extracted from the *dentate gyrus* using phenol-chloroform protocol [4] and quantified with *Qubit High Sensitivity (Thermo Fisher)*. Next, we performed the bisulfite conversion and the sequencing library construction using the *Pico Methyl-Seq Library Kit (Zymo Research)* for future whole genome sequencing (*Illumina Platform)*. The integration data will be performed, to start, with overlap of methylome, transcriptome and proteomics data. Then, we intend to establish a more robust protocol for this data integration. **Results:** All the tissues from the ten patients and five controls were microdissected. The phenol-chloroform protocol produced DNA with good quality but low quantity; however, we were able to optimize the protocol to obtain good DNA concentration in the whole genome sequencing libraries. **Discussion/Conclusions:** We believe that by integrating multiple modalities of omics data we will achieve a better understanding of the molecular mechanism involved in mesial temporal sclerosis.

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INVERSION EVENTS AND POSITIVE SELECTION ARE ASSOCIATED WITH GENOMIC ANCESTRY DEVIATIONS ON CHROMOSOME 8P23.1 AMONG BRAZILIAN INDIVIDUALS

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Introduction: genomes of admixed individuals encompass a mosaic of chromosomal tracts derived from different ancestral populations [1]. Since complex diseases can present multiple small allele effects, the manifestation of complex diseases in admixed populations depends on the combination of different ancestral tracts in their genomes. In this context, the application of precision medicine in admixed populations requires a detailed knowledge of ancestry tract distribution across each admixed genome. This distribution could be affected by genetic drift, natural selection or genomic inversion events. Global and local ancestries have been inferred in several admixed populations [1], but poorly studied in admixed Brazilian individuals. Therefore, we aim to describe the distribution of ancestry tracts and to identify deviations across the genome in admixed Brazilian individuals. **Materials and Methods:** We evaluated 264 individuals obtained within the scope of the Brazilian Initiative on Precision Medicine, and compared with the 1000 Genome Project dataset and additional 43 Native American samples. Genotyping calling was performed by SNP Array 6.0 platform (Affymetrix Inc.), and dataset filtering was performed by PLINK 1.9 software. Global and local ancestry was inferred by ADMIXTURE and RFMIX algorithms, respectively. We evaluated the presence of inversion for tracts featuring ancestry deviations by *invClust* package in R. Signals of selection were evaluated by five neutrality tests (|iHS|, |ΔiHH|, $|\Delta iHH_{derived}|$, XP-EHH, and PBS based on Hudson's Fst), which were combined in the Fisher Combined Score (FCS). **Results:** the sample presented an average of 76.9% of European ancestry, followed by 13.8% of sub-Saharan African, and 7% of Native-American ancestries. However, local ancestry revealed a decreased European ancestry (~30%), followed by an excess of Native American (~65%) ancestry on chromosome (chr) 8p23.1. In addition, we detected inversion events on chr. 8p23.1, as well as a signal of positive selection (under the 1% highest FCS values across the genome). **Discussion:** we explain ancestry deviation on chr. 8p23.1 by inversion events. However, we observed that Brazilian non-inverted haplotypes were more similar to Native American than European haplotypes, different than what was found for other admixed populations (Puerto Rican and Colombian individuals). This indicates

positive selection on chr 8p23.1, which was confirmed by our selection tests. Therefore, we hypothesize that a positive selection event has occurred under the Native American tract after admixture events in Brazilian individuals. Interesting, one gene (*PPP1R3B*) located on chr. 8p23.1 is related to diet and have already been associated with type 2 diabetes and obesity in admixed populations [2,3], which could be evidence of selection consequence on chr. 8p23.1 nowadays. **Conclusions:** Our results demonstrated that ancestry tract identification is crucial to the application of precision medicine and can generate relevant information about human health in the Brazilian population.

Supported: FAPESP.

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EXPLORING MULTI-OBJECTIVE OPTIMIZATION TO DEAL WITH MULTIPLE FEATURE EXTRACTIONS IN THE DETECTION OF EPILEPTIC SEIZURES

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Introduction: The high level of noise is one of the main challenges in data acquisition of epileptic seizures. Pre-processing and feature extraction are generally adopted, but there is no consensus on which features should be extracted [1]. This work relies on three alternatives for feature extraction [1] and proposes a multi-objective ensemble-based method that automatically finds and aggregates models with distinct influences of each feature extraction procedure, composing a single prediction. **Materials and Methods:** Three feature extraction procedures were applied to EEG recordings from 17 patients with labeled seizures [1]: (gph) synchronization graph-based features; (wlt) wavelet-based features; and (fou) Fourier transform-based features. The features of each extraction were considered as a group in the Group LASSO formulation [2], and this model was trained by MONISE [3] resorting to two strategies: (gl) consider the multinomial loss as conflicting with Group LASSO regularization; (mp) consider the multinomial loss as conflicting with the regularization for each group. The trained models are aggregated using three strategies: (wta) model selection; (elt) simple voting involving the 10 best models; (stk) using a meta-model which is synthesized taken as inputs the outputs of the generated models [3]. **Results:** We compared Group LASSO formulations with the models trained with regularized multinomial logistic regression for each procedure of feature extraction (fou, gph and wlt), to be aggregated by ensemble methods (wta, elt and stk). The results for all methods are depicted in Table 1. Those methods were evaluated using sensitivity (SEN), specificity (SPE) and latency to detect a seizure (LAT), and the values in Table 1 represent the average performance of each metric among all patients. **Discussion:** The results show the Fourier-based as the most robust feature extraction, with better performance for all criteria. Besides that, the gl formulation, that composes all procedures for feature extraction, was not capable of being competitive. However, when the regularization terms, one for each group, are considered as conflicting objectives under the multi-objective framework, the performance is recovered and even improved. **Conclusion:** Multi-objective optimization with a more general Group LASSO modeling (mp) was capable of better exploring multi-view approaches, overcoming the performance achieved by the best single procedure for feature extraction.

Table 1. Average values fo SEN, SPE and LAT metrics.

		SEN	SPE	LAT
fou	wta	0.833	0.953	2.634
	elt	0.826	0.951	2.810
	stk	0.853	0.935	2.029
gph	wta	0.783	0.857	3.130
	elt	0.775	0.863	3.739
	stk	0.735	0.886	3.995
wlt	wta	0.745	0.924	2.432
	elt	0.771	0.934	2.302
	stk	0.789	0.916	2.394
gl	wta	0.829	0.953	3.088
	elt	0.822	0.954	3.117
	stk	0.836	0.943	2.117
mp	wta	0.831	0.959	2.697
	elt	0.839	0.960	2.373
	stk	0.862	0.921	2.180

Supported: CNPq proc. #307228/2018-5, Fapesp proc. #2013/07559-3, and Fapesp proc. #2014/13533-0.

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FALL-RISK ASSESSMENT IN NEUROLOGICAL PATIENTS DURING HOSPITALIZATION AT THE HOSPITAL DA IRMANDADE DA SANTA CASA DE MISERICORDIA DE SÃO PAULO.

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Introduction: During hospitalization, falls are frequent with a negative effect on both, patients and institutions. [1] Bedridden patients are in greater risk for falling, as they present lack of physical conditioning and inadequate positioning and reduced mobility. Also, neurological disorders alter the perception of balance, muscle tone, protective reflexes, contributing to a greater risk of falls. [3] To evaluate the functional independence and the risk of falling, the Timed Up and Go (TUG) test is often used. **Materials and Methods:** During a three-month period, the TUG test was applied to the patients selected on the first day of the physical therapy evaluation. Participants were individuals with neurological abnormalities, who were indicated for physical therapy at Hospital Irmandade of Santa Casa de Misericórdia de São Paulo (HISCMSP). We excluded people with hearing disorders and orthopedic disabilities. The use of ancillary devices for gait and support from a physiotherapist, were allowed during the execution of the test, called in this study as TUG Modified (TUGM). **Results:** Time values below 10 seconds suggest independent individuals, between 10 and 19 seconds indicate low risk of falls, 20 and 29 seconds demonstrate a medium risk and a time score of 30 seconds or more are at high risk of falls.6 17 patients were included (9 male). Patients mean age was 59 years (min 27 - 80 max). Only one patient performed the test in less than 10 seconds, 9 patients took from 10 to 19 seconds and 5 patients ran between 20 to 29 seconds. One patient spent 30 seconds or more to complete the task. Three patients underwent the TUGM test. **Discussion:** There was no relation between pathology and time spent to perform the TUG. Patients who were older than the average study population, presented medium or high risk of fall, possibly because age is a predisposing risk factor for falls. In our study, three patients needed assistance to perform the test. It is known that individuals who need assistance to walk, have medium or high risk to fall. [4] Only one patient presented no risk for falls when performing the TUG test with a mean time of 9.79s. Similarly, only one patient demonstrated a high risk for falls during the TUG test, with a mean time of 49.94 s. It is also noted that there was no relation between fall risk and gender. Eight patients presented a good performance during the test. [5] **Conclusion:** Patients with neurological pathologies presented medium risk of falling, thus showing the importance of the early mobilization in the bed during hospitalization, diminishing weakness and muscle atrophy, and preventing falls.

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SEARCHING FOR BLOOD BIOMARKERS TO IMPROVE THE MANAGEMENT OF PATIENTS WITH EPILEPSY

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Introduction: Misdiagnosis of epilepsy occurs in about 25% of patients that

are refractory to antiepileptic drug (AED) therapy [1,2]. The identification of biomarkers for epilepsy could potentially improve diagnosis as well as treatment of these patients. Circulating microRNAs are good candidates to be biomarkers; these are small noncoding RNAs present in extracellular human body fluids including plasma or serum and have been already associated with the diagnosis of various diseases [3,4]. Therefore, the aims of this study are: i) to determine whether molecular signatures of circulating microRNAs could help to improve diagnosis of patients with epilepsy, including mesial temporal lobe epilepsy (MTLE), focal cortical dysplasia (FCD) and genetic generalized epilepsies (GGE) and ii) to identify and validate whether these could also be associated with response to AEDs. **Materials and Methods:** This study was divided into two phases: an initial discovery phase with 7 patients with MTLE who are responsive and 7 patients resistant to AED treatment, 7 patients with FCD, 7 patients with GGE and 7 control individuals. We determined plasma levels of circulating microRNAs using microRNA-sequencing. To further verify the power of these microRNAs to produce a specific molecular signature in different types of epilepsy we used a second independent validation cohort of 100 patients with MTLE and 200 healthy controls. In these individuals, we are quantifying candidate microRNAs by digital PCR.
Results:

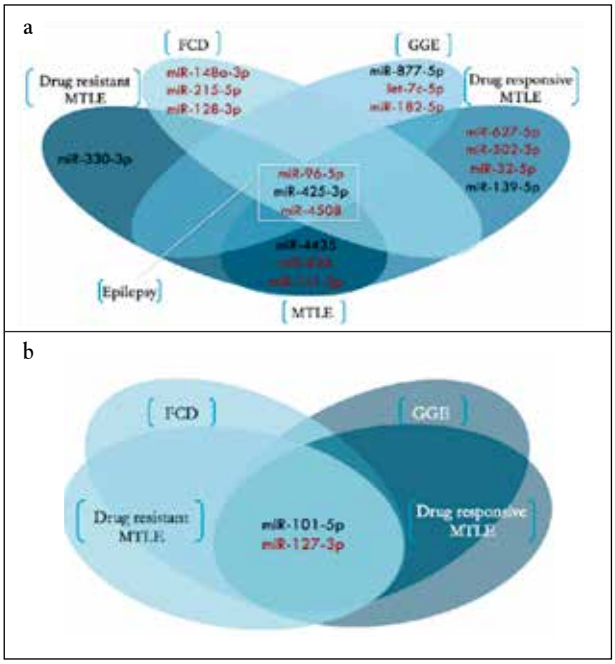

Figure 1. Venn diagram of differentially expressed circulating microRNAs (p-value < 0.01) found in the discovery phase. a) microRNAs associated with type-specific epilepsies. b) microRNAs associated with AED response. MicroRNAs highlighted in red were found upregulated and in black were downregulated. MTLE: mesial temporal lobe epilepsy; FCD: focal cortical dysplasia; GGE: genetic generalized epilepsy.

Discussion/Conclusion: To date, we identified 19 circulating microRNAs differentially expressed when comparing type-specific epilepsies with controls (Discovery phase, Fig.1). Comparing patients with drug-resistance and drug-responsive epilepsies, we identified two microRNAs - miR-101-5p and miR-127-3p that may be associated with AED response. Validation of these molecular signatures is underway. Although our data is still preliminary, we clearly show that there is a specific microRNA signature associated with different types of epilepsy, and therefore, circulating microRNAs could be used as non-invasive biomarkers to help improve the diagnosis of epilepsy. In addition, we have evidence that these could also be used to help predict response to AED therapy in patients with MTLE.

Supported: CEPID-FAPESP.

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REORGANIZATION OF FUNCTIONAL CONNECTIONS FOR A SEMANTIC VERBAL FLUENCY TASK

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Introduction: Semantic Verbal Fluency (SVF) is the process of word production according to a particular category or class. Damage to semantic processing is present in Alzheimer's diseases [1] and brain tumors [2]. There is extensive study on brain regions that activate during such process; however, how they are connected and their exact functional roles in the network remain divergent. Moreover, it is not still clear whether resting-state connectivity is simply recapitulated or reconfigured to perform the SVF task. Therefore, we used the functional magnetic resonance imaging (fMRI) based on the blood oxygen level dependent (BOLD) contrast to investigate the functional connectivity (FC) between regions involved in the performance of an SVF task, comparing to a resting-state condition, in healthy subjects. **Materials and Methods:** Images of sixteen healthy, right-handed subjects (age: 289 years, 9 men) were acquired in a 3T MRI scanner. For anatomical reference, T1-weighted GRE sequence was used (TR/TE=7/3 ms, flip angle=8°, matrix=240x240, FOV=240x240 mm^2, 180 1-mm slices). BOLD images were acquired with a 2D EPI sequence (TR/TE=2000/20 ms, flip angle=90°, matrix=80x80, FOV=240x240 mm^2, 31 4-mm slices, gap=0.5 mm). Task-based experiment consisted of six blocks of control (30s) intercalated with five blocks of task (30s). During task, a category was displayed and the participant should think about words belonging to such category. During control, months of the year were shown randomly and the participant should read them silently. Data analysis was done in SPM12 and Conn toolbox. Based on a previous meta-analysis [3] we chose seven SVF-related regions of interest in the left hemisphere: Angular Gyrus (AG), Superior Frontal Gyrus (SFG_BA6), Medial Frontal Gyrus (MFG_BA6), Inferior Frontal Gyrus (IFG_BA45 and IFG_BA47), posterior Medial Temporal Gyrus (pMTG) and Middle Frontal Gyrus (MidFG_BA9). An ROI-to-ROI FC analysis was performed using Pearson's correlation. Both conditions were compared by F-test ($p < 0.05$). **Results:** Individual and group activation maps showed responses predominantly in frontal, temporal and parietal regions. Comparing to resting-state, significant FC increase was observed in language-associated regions: pars orbitalis (IFG_BA47), pMTG, MidFG_BA9, and MFG_BA6. However, a significant

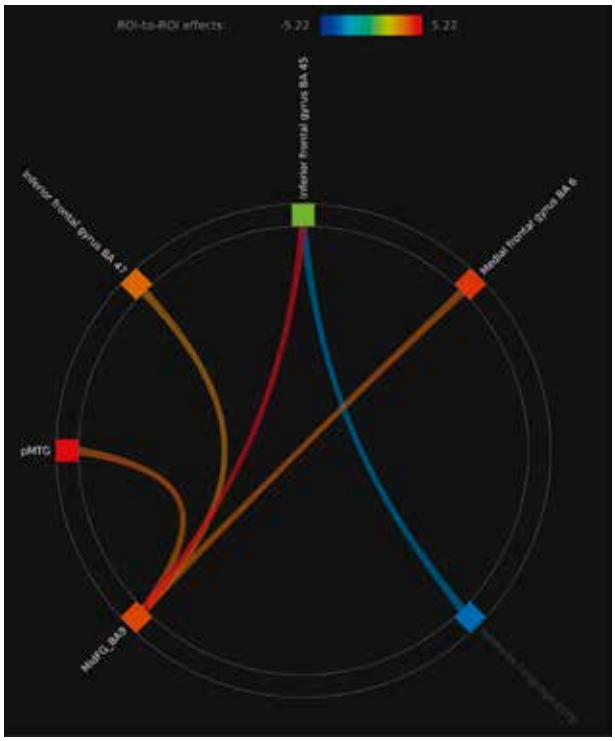

Figure 1. Functional Connectivity. ROI-to-ROI comparisons between task and rest (task > rest). Statistical threshold was $p < 0.05$ (FDR-corrected, one-sided positive).

decrease in FC between pSTG and IFG_BA45 was observed (Figure 1). **Discussion/ Conclusion:** We evaluated the semantic verbal fluency network in healthy controls comparing task performance with resting-state condition. As expected, significant FC increase in language-associated regions in frontal and temporal lobes was observed. However, the FC between two classical language regions (pSTG and IFG_BA45) decreased during task performance. Such results will guide future analysis of effective connectivity, which has been used to assess neural plasticity.

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RELIABILITY OF FAMILY REPORT FOR GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM

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Introduction: The Gross Motor Function Classification System - Expanded & Revised (GMFCS-E&R) is a standardized and validated method worldwidely used for describing the motor function abilities and their limitations of teenagers and children with cerebral palsy (CP). The GMFCS is based on voluntary movements emphasizing rolling, sitting, transfer of postures and mobility at home, school and community environments. The system is divided into 5 ordinal levels and each level is described across ages. The GMFCS Family Report Questionnaire (GMFCS-FR) is an option for family participation into CP motor mobility classification. The main objective of this study is to determine the reliability of GMFCS between parents or legal guardian and health care professionals (physiotherapists and neurologist) in a Brazilian population. In addition, compare the volunteers' classification of the motor abilities using the Gross Motor Function Measure (GMFM-66) and the Pediatric Evaluation of Disability Inventory (PEDI) with the results of the GMFCS. **Materials and Methods:** Two physiotherapists (P1 and P2) and a neurologist will take part in this study, classifying the GMFCS of each volunteer independently. P1 will read to the parents a Portuguese version of GMFCS-FR and ask them to classify their children under only one motor level. Also, P1 will apply the GMFM-66 in the study group while P2 will apply the PEDI with parents. Kappa index will be used to verify the interindividual concordance. **Results:** Results found until the moment revealed substantial levels of agreement between P1, and the neurologist (Kappa=1) and between P1 and the parents, (Kappa=1), with moderate agreement between P1 and P2 (Kappa=0,68) using the GMFCS-E&R and GMFCS-FR. The 8 volunteers with CP (from 2 until 10 years old) were classified with GMFCS and had following results:

Tabela 1.

N = 8	GMFCS	GMFM-66	PEDI – Functional Abilities Self-Care	PEDI – Functional Abilities Mobility	PEDI – Functional Abilities Social Function
1	I	100% within the expected for same age and motor level.	100% within the normality age interval for same age rate.	100% within the normality age interval for same age rate.	100% development delay for same age rate.
0	II	~~~	~~~	~~~	~~~
2	III	100% within the expected for same age and motor level.	100% development delay for same age rate.	100% development delay for same age rate.	100% within the normality age interval for same age rate.
2	IV	100% below to expected for same age and motor level.	100% development delay for same age rate.	100% development delay for same age rate.	50% within the normality age interval for same age rate. 50% below same age rate.
3	V	100% below to expected for same age and motor level.	100% development delay for same age rate.	100% development delay for same age rate.	100% development delay for same age rate.

Discussion: The use of GMFCS allowed to draw an evidence-based functional prognostication in children and teenagers with CP, providing parents and health care professionals with means to plan interventions. Tools as GMFM-66 and PEDI can be used for evaluate the development of these patients over the time. **Conclusion:** The good agreement until now in this study suggested that family and health care professionals reports of the GMFCS demonstrated a reliable method to define and measure gross motor functional abilities of children with CP.

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VALIDATION OF AN ALGORITHM FOR PREDICTING RESPONSE TO ANTIEPILEPTIC DRUG TREATMENT IN PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY.

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Introduction: Mesial temporal lobe epilepsy (MTLE) is the most common form of focal epilepsy in young adults. Approximately 40% of patients with MTLE are refractory to treatment with antiepileptic drugs (AEDs) and may be eligible for epilepsy surgery, which has a very good success rate. However, the long delay in recommending surgery for patients with AED-refractory MTLE can negatively impact the quality of care offered to these individuals. Recently, we proposed an algorithm to predict whether a patient with MTLE will be refractory to AED therapy. Using this approach, we were able to achieve an accuracy of 81.77% using 56 SNPs and the presence of hippocampal sclerosis (HS) (Silva-Alves et al. 2017). In the present study, we aim to replicate and validate this algorithm in an independent cohort. **Materials and Methods:** The replication cohort contains 253 patients with MTLE classified into two groups: 38 AED-responsive and 215 AED-refractory, based on the International League Against Epilepsy (ILAE) criteria. We genotyped the top ten most significant single nucleotide polymorphisms (SNPs) identified in our previous study, using the TaqMan™ and rhAmp™ real-time PCR system (Applied Biosystems, Foster City, CA, USA). **Results:** Based on the information derived from the genotypes of the 10 SNPs and the presence of HS we observed a 79.9 % of accuracy in predicting patients who are refractory to AED treatment, with a sensitivity of 92 %. **Discussion/ Conclusion:** We successfully validate our previous results in an independent cohort and demonstrated that by using only 10 SNPs it is possible to predict with high accuracy and sensitivity patients who are refractory to AED therapy. Thus, the possibility of using these genetic markers helps improving the quality of care offered to patients with MTLE.

Supported: FAPESP.

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ANATOMICAL CHANGES IN THE AGING BRAIN

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Introduction: Aging is a natural fact that causes brain changes in the amount of neurons, brain mass, volume and cortical thickness [1]. In this study, our main goal was to analyze the brain volume and cortical thickness changes in healthy aging comparing the results obtained by a recently proposed tool (Computational Anatomy Toolbox, CAT) [2] with the well-established FreeSurfer software. Materials and Methods: Data of 63 healthy volunteers (34 men, age: 18 - 70 years) were analyzed. Magnetic Resonance Imaging was acquired in a 3T Philips Achieva system at the HCFMRP-USP, using a 32-channel head coil dedicated to signal reception. T1-weighted high-resolution anatomical images were obtained for morphologic evaluation with the following parameters: TR/TE = 7/3 ms, flip angle (excitation) = 8°, matrix 240 x 240, FOV = 240 x 240 mm2, 160 1-mm-thick slices. For both CAT and FreeSurfer smoothing kernels of 15 mm were used prior to the estimation of vertex-specific GLM. Vertices in the medial wall were removed for CAT and FreeSurfer. Regarding their methods of analysis, CAT is a volume-based tool, while FreeSurfer is a surface-based tool. CAT computation time including pre-processing and surface analysis for an individual subject was about 1 hour. For FreeSurfer, minimal processing time

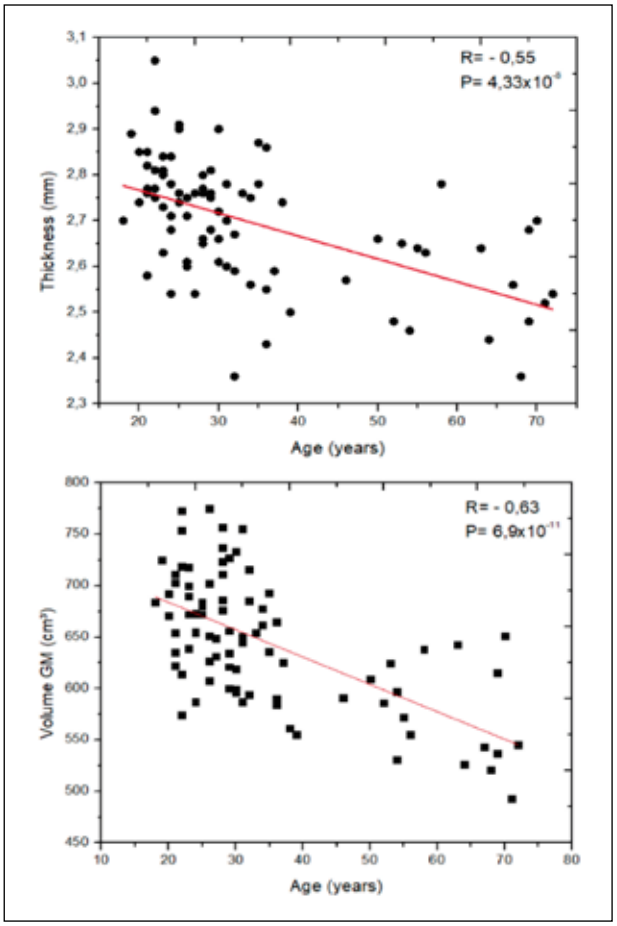

Figure 1. Relationship of cortical thickness and gray matter (GM) volume with age in healthy subjects. The measures were obtained with CAT. R is the Pearson's correlation coefficient.

per subject was 9.5 hours. Results: When comparing the measures of cortical thickness for different brain regions obtained with CAT and FreeSurfer, we observed correlations from medium to strong, significant ($p < 10\text{-}5$) for all regions, except for the right insula (Pearson's coefficient $R = 0.28$, $p > 0.05$). Using the results from CAT, we observed that gray matter (GM) volume and mean cortical thickness decrease with age (Figure 1), while cerebrospinal fluid volume increases with age. No alterations were observed for the white matter and total intracranial volumes. **Discussion:** The regional segmentation and measurements of cortical thickness obtained with CAT were satisfactory when compared with the FreeSurfer results. Such results are consistent with ones previously reported for heathy subjects and multiple sclerosis patients [3]. As expected, the values of cortical thickness and GM volume reduce with age [1]. **Conclusion:** Therefore, the CAT software can be used for such anatomical analysis of the brain, providing results very close to those of FreeSufer, including the structural changes of the brain observed in healthy aging.

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ARTIFICIAL INTELLIGENCE IN EDUCATION MEETS NEUROSCIENCE TO SUPPORT INDEPENDENT LEARNING FROM FILMS IN THE CONTEXT OF EPILEPSY TO OVERCOME SOCIAL EXCLUSION

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Introduction: Our research within the BRAINN project, as a part of the Education and Knowledge Dissemination Group, has explored the use of films to stimulate learning and reflection in contexts of overcoming social exclusion, with a particular focus on issues associated with the context of epilepsy. Previous work has focused on the development of a knowledge structure of epilepsy issues to serve as a basis for the construction of a system to support learning from audiovisuals in this context [1]. In addition, we have investigated the representation of epilepsy issues in film [2]. The next step involves the development of a computational framework to serve as a foundation for the construction of a system that can support several strategies of promoting learning from films in the context of epilepsy. This short paper presents the work that we have developed in this direction. **Materials and Methods:** In order to develop means for independent learning in this context that involves learning from films to overcome social exclusion of people with epilepsy, we have followed a methodology that combines techniques of Artificial Intelligence in Education with learning approaches that are based on constructivist theories [3] and with the use of films for learning [4]. This has led us to work on three fronts: first, the modeling of learning situations, which will take into account the video and knowledge structure of epilepsy issues previously developed [1]; second, the modeling of properties of the process of learning, which will serve as a basis for the system to construct a model of what has been learned by the learners from time to time during their interaction with learning situations; and third, the modeling of the opportunities for learning available in learning situations at each time, considering the characteristics of the course and state of the learning processes previously developed by the learners. **Results:** With regard to the first front, we have investigated issues related to the representation of the knowledge to be learned in films, to compose learning situations. With regard to the issue of assessing what has been learned (second front) our studies have shown that the focus should be the process by which the learners make meaning from the audiovisual content and narrative that constitute the film, as they construct a model of their comprehension. Finally, with regard to providing opportunities for further learning (third front), we have followed the ecological approach to visual perception and the theory of affordances [5], addressing the affordances of the film content and narrative for processes of making meaning from the film. **Conclusion:** This paper briefly describes our efforts to develop means for learning to overcome social exclusion in the context of epilepsy, taking advantage of technologies of Artificial Intelligence in Education to provide for independent and personalized learning in this context. Further work involves the precise definition of the models discussed above and the construction of a computational framework, addressing issues of representing learning situations centered on the use of films for learning about epilepsy (situation model), issues of monitoring and evaluating processes of learning from films (process model) and issues of adapting the opportunities for learning from films to the learners (model of affordances), in order to provide intelligent support for independent learning about epilepsy.

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IDENTIFICATION OF MUTATIONS ASSOCIATED WITH FOCAL CORTICAL DYSPLASIA USING NEXT GENERATION SEQUENCING

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Introduction: Malformations of cortical development (MCD), including focal cortical dysplasia (FCD), can cause epilepsy and are often associated with the occurrence of refractory seizures [1]. FCD is characterized by alterations in the cytoarchitecture also observed in other MCDs, such as tuberous sclerosis (TS) and hemimegaencephaly (HME) [2,3]. Recently, mosaic mutations were detected in TS, HME and FCD [4]; however, it is still unclear whether somatic mosaicism is indeed frequent in FCD [4]. **Materials and Methods:** Deep sequencing of the mTOR and GATOR pathway genes was performed on genomic DNA extracted from brain tissue resected by surgery (BTRS) and blood samples

of 12 patients with FCD. We performed capturing and enrichment with SeqCap EZ Choice Library (NimbleGen, Roche). Samples were sequenced following a 150bp paired-end protocol in a Miseq (Illumina), to achieve at least 600x of average coverage. We aligned sequences using BWA-MEM and performed realignment around SNPs and indels, quality recalibration and variant calling using the Genome Analysis Toolkit (GATK). We evaluated mosaicism using Mutect2, VarScan, and Strelka. Variants were classified as mosaic mutations when less than 10% of reads were not aligned to the human genome reference and are present only in BTRS. Variants were filtered prioritizing frameshift, missense, nonsense and splicing site mutations that were localized in coding regions or exon-intron boundaries. In addition, we also focused on variants not described previously or variants whose minor allele frequency (MAF) is < 0.01. Effect of variants was evaluated using Variant Effect Predictor (VEP). **Results:** We identified mosaic mutations in 67% of patients of our cohort (n=8/12). A total of 10 genes were affected by 11 mosaic mutations. Five mutations, two localized in *MTOR*, one in *DEPDC5, TSC2* and *RPTOR* gene, were already described in the literature. In addition, six mutations affecting *RPS6KA1, ULK1, MAPK3, PIK3CD, WDR59*, and *WDR24* were not previously reported in patients with FCD. These mutations were not found in the Exome Aggregation Consortium (ExAC) and in a Brazilian database of genomic variants (www.BIPMed.org). VEP classified all variants as probably damaging. **Discussion/Conclusion:** We identified somatic mutations in genes of the mTOR and GATOR pathways. Most of the mutations identified have never been described. Furthermore, somatic mutations in mTOR genes seem to be relatively common in patients with FCD since they are present in 67% subjects of our cohort. Interestingly, three patients studied had two potentially deleterious somatic mutations in genes of the mTOR pathway, supporting the 'two hits hypothesis' for FCD etiology. Additional experiments, including deep sequencing of a large number of patients and digital PCR, will be carried out to confirm these preliminary findings.

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FABRICATION OF GRAPHENE MEAS FOR NEUROSCIENCE STUDY

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Introduction: This paper describes the production of a new version of high-performance microelectrode arrays (MEAs) that can be used to explore in vitro neural networks. The goal is to produce MEAs with improved microelectrodes through the use of graphene, to enable accurate measurement of cell potentials and obtain images from neural cell cultures. Graphene has been gaining prominence as a MEA conductor for several applications because it combines the interesting features of flexibility and low noise to its other features of excellent electrical and thermal conductivity, mechanical and electrochemical stability, transferability, high mechanical strength (greater than 0.5 TPa), broad-spectrum transparency, and biocompatibility [1-4]. **Materials and Methods:** The MEAs were manufactured using direct write technology, without the need for photomask production, and comprised graphene microelectrodes and SU-8 insulation on a glass substrate. Graphene was grown by chemical vapor deposition on copper foil and then transferred to the substrate. We developed a method to utilize multi-level alignment for direct laser writing process. A direct write system (Heidelberg DWL66FS, Heidelberg, Germany) was used with a 405nm laser to pattern the MEA conductive region, as well as using modified SU-8 with a photoinitiator for exposure. The first prototype consists of a set of 60 circular microelectrodes (20 and 40 μm) distributed in an octagonal format, connected to square contact pads by the tracks. Fabrication steps can be subdivided into 4 basic parts, after the cleaning of the substrates: (1) formation of the conductor, and (2) insulation layers, both using lift – off, (3) transfer of graphene to form the electrodes, and (4) placement of a glass ring that surrounds the active region of MEA. **Results:** Results point out that the device yields satisfactory performance, close to standard commercial MEAs. We found that the graphene microelectrodes showed adequate sensitivity to noise, compatible with that obtained for the standard commercial MEA and is within the expected range [5]. Our MEA showed low noise, with amplitudes ranging from 5 to 10 μV. In addition, we have performed electrode tests: Cyclic Voltammetry (CV) and Impedance Spectroscopy (IS), which showed compatible responses to typical environments used in neuron studies. **Discussion:** The graphene MEAs experimentally exhibited adequate electrical specifications, with the electrode characterized using noise testing, CV and IS tests. The low amplitude of the noise observed from our microelectrodes is within the range found for commercial standard MEA (up to $\pm 10\,\mu$V). Regarding the CV test, resulting curves of our MEA allow to obtain the CIC (Charge Injection Capacity) of the microelectrodes. The mean amplitude is 0.7 mC/cm^2, which is higher than the amplitudes obtained for MEAs reported in the literature [2]. Finally, from EIS test it was possible to find the average impedance at 1 kHz for the electrodes herein. The obtained value was 5.2 kΩ, which is also compatible with commercial MEAs, since they exhibit levels between 30 and 400 kΩ. **Conclusion:** The present work confirmed that we have successfully fabricated a new type of MEA with the process developed herein, from the choice of the substrate to the definition of graphene patterns. The microelectrode response is within a suitable range that is comparable with commercial MEAs. Consequently, our device is biocompatible and is an interesting option for extracellular stimulation and neural activity recording.

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A BRAZILIAN DATASET DOMAIN ADAPTATION TO DIAGNOSE ALZHEIMER'S DISEASE AND SUBJECTS WITH COGNITIVE DEFICIT USING CONVOLUTIONAL NEURAL NETWORKS

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Introduction: Alzheimer's disease (AD) is a devastating type of dementia that affects millions of people around the world [1]. To date, there is no cure for Alzheimer's and its early-diagnosis has been a challenging task. The current techniques for image-based AD diagnosis have explored the structural information of Magnetic Resonance Imaging (MRI) [2]. Among these techniques, deep convolutional neural networks (CNN) is the most promising one. We aim to classify the different groups of AD diagnosis training a CNN on Alzheimer's Disease Neuroimaging Initiative [3] (ADNI) data and performing a domain adaptation by extending the analysis to a Brazilian dataset. **Materials and Methods:** The source domain dataset is composed of 582 T1-weighted MRI from ADNI, being distributed in 189 normal cohort (NC), 193 mild-cognitive impairment (MCI), and 200 AD balanced by gender and age. The target domain dataset is composed of 196 T1-weighted MRI acquired at HC (University of Campinas), being distributed in 78 NC, 67 MCI, and 51 AD. We pre-processed the data by rescaling it to isometric voxels, skull-stripping using CONSNet [4], brain registration using FLIRT [5], and intensity normalization. The slice selection of each MRI acquisition was performed in two steps. The first step started by choosing 80 slices going from the center slice of the coronal plane to the extremities. From these 80 slices, every second slice were selected, including the central slice. Then, each selected slice was used in the first channel of the CNN, while the remaining two channels were comprised of two other slices (jumping 3 slices) For example, if the position of a given slice for the first channel was 100, the position of the other two selected slices would be 104 and 108, respectively. The ResNet34 [6] model was adapted, by replacing the 3^d layer by three convolution layers, batch-normalization, dense layer, dropout, and another dense layer. We applied transfer-learning technique in the first layers, and then trained the added layers in the source domain. Finally, we fine-tuned from the second added convolutional layer to the remaining layers, in the target domain. The CNN was trained along 100 epochs in the source domain and 100 more epochs in the target domain, using

Table 1. Accuracy results from source to target domain adaptation.

Training set	Test accuracy (%) (NC vs MCI vs AD)	
	ADNI	Brazilian dataset
Source domain only (ADNI)	66.1	40
Target domain adaptation (Brazilian dataset)	39.82	53.75

2-fold cross-validation. **Results:** The proposed model achieved an accuracy of 66.1% while trained and tested on ADNI. However, this model reached an accuracy of 40% in the Brazilian dataset. On the other hand, the model that was fine-tuned with part of the Brazilian dataset showed an improvement of approximately 14% in the accuracy when tested only in the Brazilian dataset, but the test accuracy decreased on ADNI (Tab.1). **Discussion:** Domain adaptation strategy showed an increase in performance between source and target domains, which represents a real-world scenario. Demographic aspects seem to play a role, as observed by Farrer et al. [7], justifying the differences of accuracy between both domains. **Conclusion:** Classifying the different stages of AD is not a trivial task. Our results represent one import step in predicting the early-stage diagnostic of Alzheimer Disease and to the best of our knowledge, the first approach applied to a Brazilian dataset.

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INTERVENTION FOR VIRTUAL REALITY IN BALANCE, MOBILITY AND COGNITION IN ELDERLY

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Introduction: With the aging process, the elderly experience many difficulties that compromise a healthy aging. Virtual reality (VR) is proving to be an innovative method in the rehabilitation process, since it is a safe and feasible method, evidencing a significant improvement of the elderly's functionality. The objective of this study was to compare the evolution of balance, cognition and mobility factors in the elderly in a 5-month project linking the practice of physical activity (PA) with VR. **Materials and Methods:** GesturePuzzle software [1] was used to stimulate cognitive function, which a virtual Puzzle, where the user must fit the pieces in the correct position, by the gestural interaction through the Kinect device (gesture recognition sensor). Also, the RehabGesture [2] software was used to record the range of motion (ROM) of the shoulder joint before and after the interaction with the GesturePuzzle. The elderly need to perform different ROM to fit the puzzle correctly. Participated in the survey 21 elderly people, 16 women and 5 men, with an average age of 74 years old (SD ± 3,6). **Results:** Preliminary results from the VR and PA group show larger shoulder abduction movement and improved their functionality when considering the activities of daily living. This group (VR and PA) reduced the risk of falls by 50%, improved the memory by 33.3% (mean score) and attention by 17.7% while the group that performed only VR reduced the risk of falling by 33.3%, improved memory by 22.2% (mean score) and attention by 12.2%. **Discussion:** Functionality is strongly associated with independence and quality of elderly's life. Studies [3, 4] show that training aimed to improve gait, balance or cognitive function is efficient when associated with VR and may contribute to longevity and better quality of life. **Conclusion:** VR is an innovative method in the rehabilitation process because it is feasible. Therefore, it is fundamental to emphasize that this project intends to contribute to the rehabilitation and improvement of eldery's quality of life through VR therapy. According to the partial results, it is expected to improve the efficiency through VR solutions.

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HLA ALLELES AND CUTANEOUS HYPERSENSITIVITY TO CARBAMAZEPINE IN THE BRAZILIAN POPULATION

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Introduction and Hypothesis: The Human Leucocyte Antigen (HLA) genes are involved in susceptibility to inflammatory, infectious and autoimmune diseases. HLA genes are relevant in pharmacogenetics, as several of their alleles are associated with hypersensitivity to specific drugs, such as carbamazepine (CBZ), which is the most frequently administered first-line antiepileptic drug [1,2]. About 3% to 5% of the population is allergic to CBZ and is susceptible to a wide spectrum of adverse cutaneous clinical manifestations including extremely painful and life-threatening conditions [3]. We expect to find HLA alleles increasing the risk of adverse cutaneous reaction when CBZ is administrated. **Objective**: We aim to determine if there is a genetic association between CBZ-induced cutaneous adverse drug reactions and HLA variants in the Brazilian populations. **Methods**: This is a case-control study (30 patients with temporal lobe epilepsy with CBZ-induced cutaneous reactions manifestations and 100 CBZ-tolerant patients).The HLA genotyping will be performed using the Trusight HLA v2 Sequencing Panel (Illumina), which provides an assay to obtain ultrahigh resolution sequencing of 11 HLA Loci. DNA libraries will be loaded onto a MiSeq Sequencer (Illumina), and data will be analyzed with the TruSight HLA Assign 2.0 software. **Relevance:** Currently, there is a great interest in the study of cutaneous drug reaction to CBZ, since it is a widely used medication for the treatment of epilepsy and other neurological conditions. We sought to prevent CBZ-induced cutaneous adverse drug reactions by using HLA alleles identified as a risk factor to screen patients before administration of CBZ.

Supported: FAPESP.

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MOLECULES FROM SPIDER VENOM ARE POTENTIAL IMMUNOMODULATORS FOR TREATING BRAIN CANCER

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Introduction: The aim of this study was to investigate the immunomodulatory effect of the Phoneutria nigriventer spider venom (PnV) on macrophages, using xerographic glioblastoma and *in vitro* models; besides identifying the PnV-isolated molecule responsible for such effects. Immunotherapy has been considered an established antitumor approach, used alone or in combination with traditional treatments [1]. **Materials and Methods:** *In vivo*: NG97 cells were inoculated (s.c.) on the back of RAG$^{-/-}$ (B6129S7-Rag1tm1Mom) mice, female, 6-8-weeks-old (n = 5/group). After 7 days, the groups received: sterile saline (100 μl, i.p.), PnV (100 μg/Kg, i.p.), or Methotrexate (MTX – a positive control, 0.5 mg/Kg, i.m), every 48 h, for 14 days. After euthanasia, tumors were dissected for histopathology and immunohistochemistry (Iba-1). *In vitro:* bone marrow differentiated macrophages (C57BL6) were cultured in IMDM with 30% of L929 supernatant (source of M-CSF). Cells were pre-activated with IFN-γ (20 ng/mL, 48 h) and divided in six groups: control - without any treatment; PnV (14 μg/ml, 24 h) [2]; PnV-fractions (called F1, F2, F3; obtained using Amicon® filters; 1 μg/mL, 24 h); or Lipopolysaccharide (LPS - a positive control, 1μg/mL, 24 h). After treatments, macrophages were cocultivated with *Paracoccidioides brasiliensis* (Pb) or with glioblastoma (NG97) cells for 24 h. Pb phagocytosis (by colony forming unit count – CFU) and tumor cells viability (DAPI) were analyzed. **Results:** Tumor weight and volume of PnV- and MTX-treated animals were significantly lower, compared to control. Histopathological analysis showed extensive necrosis of PnV-tumors. Immunohistochemical revealed an increase in macrophages infiltrate in the PnV and MTX groups, compared to control tumors. However, flow cytometry showed that MTX induced M2-macrophages (IL-10 positive), whereas PnV decreased M2 cells. LPS- and PnV-stimulated macrophages strongly decreased tumor cells viability, compared to control. In addition, LPS- and PnV-stimulated macrophages presented an increased phagocytic capacity. F2 and F3-treated macrophages were more efficient than PnV or control cells. While LPS increased TNF-α, IL-6 and IL-10, PnV and fractions did not alter any cytokines. **Discussion:** Recent studies by our group have shown that PnV kills tumor cells in vitro in about 20%. However, mice treated with venom developed tumors 90% smaller than control animals, leading to the hypothesis that PnV could be fighting the tumor through immunomodulation. In fact, the present results demonstrated that tumors from PnV-treated mice presented a macrophages infiltrate, which was not observed in control. In addition, PnV-macrophages were more phagocytic and decreased the viability of tumor cells in vitro. Interestingly, compared with MTX and LPS, PnV induced

a different cytokine profile in macrophages, bringing up a possible mechanism of action that differs from classical anticancer drugs and immune cells activators. **Conclusion:** PnV acts on macrophage modulation, giving an opportunity for the development of a new potential anticancer immunotherapy for brain tumor.

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ANALYSIS OF THE INFLUENCE OF SPATIAL INFORMATION ON NIRS MEASUREMENTS

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Introduction and Hypothesis: Functional near-infrared spectroscopy (fNIRS) is a neuroimaging technique that employs near-infrared (NIR) light (~650-900 nm) to estimate hemoglobin concentration changes in tissue [1]. In the NIR region, light is more scattered than absorbed by tissue, thereby incident light in a volunteer's scalp can penetrate up to the brain cortex and come back to the scalp surface, bringing information from brain activity. Due to its main features, such as high temporal resolution, low cost, and portability, fNIRS has appeared as the main choice to investigate a variety of populations, from neonates to severely injured patients. However, fNIRS also presents some limitations. Currently, the main drawback of the technique is related to the low accuracy and reliability on positioning the optodes in the volunteer's head. In fact, it is not possible to guarantee that the optodes are measuring the desired brain region. The low spatial accuracy is even more critical to longitudinal measurements since one cannot always infer whether the signal changes are due to changes in the optodes' positioning or they are real biological changes. We hypothesized that improved reproducibility could be achieved by adding subject-specific spatial information to fNIRS measurements. **Objective:** The present project aims to improve the reliability of the fNIRS measurements by coupling the fNIRS system with a digitizer that can acquire spatial information of the optodes on the scalp. The integration between the two systems allows the localization of the optodes on the head surface prior to data acquisition, which can be used to register the optodes onto the spatial information of the real subject. **Methods:** Longitudinal fNIRS measurements have been performed during different days and during different times of the same day. Briefly, data from 10 healthy young volunteers at 5 different time points will be acquired during a finger tapping experiment. The finger tapping task is block designed, and it consists of 30 blocks. In each block, volunteers will tap their fingers for 2s followed by a random period of rest varying from 10 to 20s. Prior to the first day of experiments, we will acquire a structural MRI image of each subject so that the optodes can be registered onto the subject's structural space for posterior data analysis. The optical probe consists of 68 source-detector pairs (channels) at 3cm and 4 channels at 0.8cm to remove extra-cortical contributions. The experimental protocol was approved by the local ethical committee. **Relevance:** Over the last years, fNIRS has evolved from a promising and novel neuroimaging technique to the main choice of several researchers to investigate a variety of populations and brain diseases whose conditions limits other neuroimaging applications. More recently, wearable fNIRS systems have opened new directions on how scientists do neuroscience by allowing us to investigate the brain on unconstrained environments (outside the laboratory). Since each subject has its own anatomy, our project intends to improve NIRS spatial resolution, allowing to identify regions of interest more precisely, which may improve the accuracy of the technique.

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TRANSCRIPTOME INVESTIGATION ON THE MECHANISMS INVOLVED IN HIPPOCAMPAL SCLEROSIS ASSOCIATED WITH MESIAL TEMPORAL LOBE EPILEPSY

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Introduction: The most frequent neuroimage finding in mesial temporal lobe epilepsy (MTLE) patients is Mesial Temporal Sclerosis, that has hippocampal atrophy as one of its main components. The electrical stimulation of the perforant pathway for a period of 8 hours in awake rats reproduces hippocampal lesion with a morphology that resembles the human condition without the induction of an episode of status epilepticus (SE). In order for animals to survive such a long period of stimulation in this model it is necessary two days of 30 minutes preconditioning sessions by electrical stimulation of the perforant pathway. Therefore, the objective is to explore the biological processes, and the molecular components involved in the preconditioning of the hippocampus employing transcriptomic analysis of the different hippocampal sub-regions. **Materials and Methods:** Used 5 sham-control and 5 stimulated rats (CEMIB-UNICAMP) and performed the surgery to implant the electrodes. Microdissected the hippocampus (CA1, CA2, CA3 and Dentate Gyrus) using the PALM system (Zeiss) with glass pen membrane, colored in cresyl. Subsequently, we have done transcriptome analysis by high performance sequencing using the TruSeq Stranded mRNA LT (Illumina), and a HiSeq platform for the DG region, separated in a Dorsal DG and a Ventral DG. **Results:** A total of 2,423 genes were differentially expressed ($p<0,05$) when comparing the control DG with the stimulated DG, 908 genes were at the Dorsal region (DDG) and 459 were ventral region (VDG), and 528 genes at both regions. 659 genes in DDG were down regulated, and 777 up regulated. In the VDG, 525 genes were down regulated, and 462 up regulated. Genes analysis show GABAA receptors up-regulated in both groups, with exception of VDG GABRD, that is down-regulated, and down-regulation in GABAC receptors and cAMP in both groups at GABAergic synapses. However, gene analisys show Steroid biosynthesis pathway up regulated in VDG, and no different expression in DDG. **Discussion:** Differently expression when comparing VDG and DDG indicate different functions of dentate gyrus depending the region of the hippocampus. Both DDG and VDG presented differently expression genes related with inhibitory pathway, showing up regulation with GABAA receptors, and down regulation of genes in cAMP pathway, indicating an increase of inhibition. Only VDG had up regulation on Steroid biosynthesis, consisting in another indication of different function of VDG from DDG. **Conclusion:** This transcriptome data suggest different functions depending the region of DG, including different pathways and differents genes expression. Transcriptome data indicates a increase in inhibtion in the DG after pre-conditioning, a observation consistent with previous physiological data. Furthermore, there are still other regions to be studied.

TRANSCRIPTOME ANALYSIS OF RAT'S HIPPOCAMPAL CELL LAYERS

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Introduction: Anatomical and genetic studies have shown differences between the cellular layers of dentate gyrus (DG) and Ammon's horn (CA) in rat's hippocampus[1]. Extensive gene expression profiles have become an opportunity to explore the large heterogeneity of molecular mechanisms in different regions[2]. Thus, the present study explores expression datasets of hippocampal four layers (CA1, CA2, CA3, DG) for elucidating their distinctions. **Materials and Methods:** Rats (n=4) were euthanized and the brains processed for laser microdissected using Zeiss PALM LCM. All layers were bilaterally collected from hippocampus of each rat, total RNA was extracted, and libraries for RNA-Seq in Illumina Hiseq platform were prepared according to manufacturer instructions. Sequences were aligned, quantified and compared with the STAR Aligner/DESeq2 pipeline. Gene Onthologies were analyzed with the DAVID software. **Results:** A total of 3505 genes were differentially expressed ($p<0,05$) when comparing CA1 to CA2, 1704 genes were up-regulated and 1801 were down-regulated. Comparing CA1 to CA3, a total of 4527 genes were differentially expressed, 2273 genes were up-regulated and 2254 were down-regulated. Also, a total of 2063 genes were differentially expressed when comparing CA2 to CA3, 954 genes were up-regulated and 1109 were down-regulated. Furthermore, a total of 5676 genes were differentially expressed when comparing CA1 to DG, 2766 genes were up-regulated and 2910 were down-regulated. As well, comparing CA2 to DG, a total of 7311 genes were differentially expressed, 3724 genes were up-regulated and 3607 were down-regulated. In addition, a total

of 7401 genes were differentially expressed when comparing CA3 to DG, 3726 genes were up-regulated and 3675 were down-regulated. **Discussion:** Ammon's horn is composed predominantly by pyramidal neurons, where CA1 are the smallests neurons and CA2/CA3 the largests one. There are enrichment genes related to zinc-fingers and postsynaptic membrane receptors when comparing transcriptome data of smaller pyramidal neurons(CA1) to largests pyramidal neurons(CA2, CA3). Furthermore, CA2 and CA3 has different expressed genes in synaptic function, neurogenesis, ion channels and ion transport. On the other hand, granular neurons(DG) have upregulated genes associated to ribosome, spliceosome and intracellular signing when comparing to all pyramidal layers. However, genes connected to oxidative phosphorylation and energetic metabolism are downregulated in DG. The damage resistance of granular cells to insults like seizures, hypoxia and ischemia might be explained by enrichment genes related to intracellular signings for apoptosis regulation and neurogenesis[3]. Besides that, high levels of energetic metabolism enzymes on pyramidal cells are associated to sensibility for damage in neurons. **Conclusion:** RNA-Seq approach allow us to measure precisely the extend and the levels of transcripts. In this study, analysis of transcriptome profile shows in detail the complex heterogeneity in biological process and pathways of rat hippocampal layers.

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STUDYING THE WHOLE-GENOME DNA METHYLATION PATTERN IN PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY

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Introduction and Hypothesis: According to the World Health Organization epilepsy is one of the most common neurological diseases with about 50 million people affected worldwide [1,2]. Within this 50 million approximately 10% have juvenile myoclonic epilepsy (JME), which is characterized by the presence of myoclonic jerks with or without other types of generalized seizures. JME is the most common form of genetic generalized epilepsy (GGE) [3,4]. Current evidence points to a complex inheritance in most GGEs, and many candidate genes have been identified; however, most patients with JME do not have mutations in specific genes, raising the possibility that other factors may be involved in the predisposition to seizures in these patients [6]. Therefore, we hypothesize that there may be environmental factors that influence DNA methylation in patients with JME, leading to a distinct whole-genome methylation pattern in these patients. **Objective:** The main aim of this project is to determine the whole genome DNA methylation pattern of the patients with JME in comparison with control individuals. **Methods:** For this preliminary study will be analyzed three patients with JME and three controls subjects. All patients included in the study are prospectively followed at the University Hospital of UNICAMP according to a detailed research protocol that includes extensive clinical and neuroimaging evaluation. Patients will be selected after clinical confirmation and will be homogenized according to the age and type of antiepileptic drug used. Total genomic DNA will be extracted from the peripheral blood collected in EDTA tubes. Determination of the methylation pattern of the samples will be performed by the conversion of sodium bisulfite and subsequent whole genome sequencing (WGBS). We will determine differentially methylation regions (DMR) along the entire genome using bioinformatics algorithms. **Relevance:** This will be the first study seeking to identify DMR in the whole genome of patients with JME. Our results may help to better understand the role of epigenetic factors in determining predisposition to seizures.

Supported: FAPESP.

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METABOLOMIC ANALYSIS OF PLASMA FROM PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY: SEARCHING FOR BIOMARKERS OF DRUG RESISTANCE

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Introduction and Hypothesis: Mesial temporal lobe epilepsy (MTLE) stands out among the different types of epilepsy due to its prevalence and the high rate of resistance to the treatment with antiepileptic drugs (AEDs) [1]. Due to the complexity to predict which patients will be drug-resistant, alternative treatments to seizures, such as surgeries, may take many years to be indicated [2]. Thereby, the search for new biomarkers, capable of predicting this condition is necessary. The metabolomic approach has many advantages over other molecular techniques, such as greater proximity of the metabolites to the phenotype and high sensitivity and specificity in the detection of these analytes [3]. Therefore, the use of metabolomics to find biomarkers of drug resistance in patients with MTLE may allow us an earlier diagnosis of drug resistance and a more accurate and earlier indication of surgical intervention. **Objective:** We propose to analyze the plasma metabolic profile in patients with MTLE divided according to the response to pharmacological treatment. **Methods:** Patients with MTLE were divided into two groups according to their responsiveness to the pharmacological treatment. The plasma metabolic profile of both groups will be compared to control individuals by liquid-state NMR data acquisition combined with chemometric analysis. The obtained spectra from these groups will be processed using MestreNova and Matlab software and then analyzed using Metaboanalyst and the HMDB database to identify metabolites that may assist in an earlier diagnosis of drug response. **Relevance:** This study is relevant because it will generate a database using a high-reproducible molecular technique to find specific metabolites that may be present in patients with different responses to drug therapy. In addition, it may allow us to predict which patients will not respond to AEDs.

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AUTOMATIC DETECTION OF FOCAL CORTICAL DYSPLASIA IN CHILDREN WITH EPILEPSY

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Introduction: Focal cortical dysplasia (FCD) is the major cause of pharmacoresistant epilepsy in children. Surgical resection of the lesion, whenever possible, is the best option to achieve a better prognosis. [1] However, FCD has a wide morphological range that often makes it difficult to identify the lesions in magnetic resonance image (MRI). [2] This study aims to evaluate a post-processing protocol of MRI using voxel based morphometry (VBM) to improve the detection of FCD in pediatric patients with pharmacoresistant epilepsy. **Materials and Methods:** We selected 21 children with clinical diagnosis of pharmacoresistant epilepsy secondary to FCD followed in the Clinical Hospital of Unicamp. The images were acquired in a 3T MRI machine with volumetric T1-weighted sequences. We created an algorithm, using VBM, based on white e gray matter maps and compared the individual images of the patients with i) a group of 71 healthy pediatric subjects; ii) a group of age-matched healthy pediatric subjects (age +/- 2 years; 12-15 healthy subjects compared to each patient, according to the number of available controls in the age range). The clinical data was based in the pre-surgical investigation. **Results:** Comparing the patient's images with the complete pediatric control group, 12/21 (57%) individuals had sublobar concordance between the localization of the VBM map and the clinically defined epileptogenic zone. For the age-matched control group, 15/21 (71%) patients had sublobar concordance. Eleven patients (11/21; 52%) were submitted to surgery. Of those, 9 had VBM maps concordant with the surgical resection (with both complete pediatric control and age-matched control groups) and 5 (56%) became seizure-free. From the 2 patients with discordant VBM maps submitted to surgery, none became seizure free (0%). **Discussion:** The accuracy for the detection of the FCD increased with controls with age closer to each patient, despite the reduced number of individuals in the control group. This demonstrates that the structural differences of brains

of children with distinct ages can influence imaging analysis results. This work presented the importance of using a suitable group of control for the patient`s analysis and a better detection of the FCD. Also, the present VBM algorithm showed a high sensitivity to detect possible lesions concordant with the clinically defined FCD in children with pharmacoresistant epilepsy. Although the number of individuals submitted to surgery was small, none of the patients with discordant VBM maps became seizure-free, while more than half of those with concordant maps were seizure-free. **Conclusion:** The use of automatic VBM-based algorithm for the detection of FCD in children with pharmacoresistant epilepsy is a promising tool, especially with the use of age-matched controls as comparison. The evaluation of a higher number of individuals in a prospective study is necessary to validate the possible clinical utility of this algorithm of automatic detection of FCD in children with pharmacoresistant epilepsy.

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THE INFLUENCE OF DEPRESSIVE SYMPTOMS IN NEURONAL DAMAGE MEASURED BY PROTON MAGNETIC RESONANCE SPECTROSCOPY IN MESIAL TLE

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Introduction: Depressive symptoms (DS) are often found as a psychiatry comorbidity of mesial temporal lobe epilepsy (MTLE) [1]. However, just few studies have addressed the pathophysiology of MTLE with DS using neuroimaging tools [2,3]. The mechanisms and extent of alterations underlying the comorbidity remain poorly understood. Our study aimed to investigate hippocampal neuronal damage in patients in mesial temporal lobe epilepsy (MTLE) with or without hippocampal sclerosis (HS) associated with DS using noninvasive metabolic quantification. **Materials and Methods:** We measured ipsi- and contralateral hippocampal N-acetylaspartate ratios to creatine (NAA/Cr), a marker of neuronal dysfunction, using proton magnetic resonance spectroscopy (1H-MRS) from 79 MTLE patients (age median [range] 35[19-64] years, 37 with DS, 42 without DS) and 50 controls (age 47 [19-64] years, 4 with DS, 46 without DS). We used the Beck Depression Inventory (BDI) and the structured clinical interview for DSM-IV to assess DS. We performed analysis of covariance using the presence of DS (yes, no) and HS side (MRI-negative, right-HS, left-HS) as main effects, and age and seizure frequency as nuisance covariates, followed by simple effects analysis, when appropriate. A Sidak or FDR-corrected $p<0.05$ was set as significant. **Results:** We found a significant effect of HS ($F_{3,119}=4.16$, $p=0.008$) but no effect of DS on ipsilateral NAA/Cr ($F_{1,119}=0.001$, $p=0.97$). Post-hoc Sidak-corrected comparisons showed reduced NAA/Cr in HS-left compared to controls ($p=0.004$). After inspection of interaction graphs, we conducted simple effects analysis on the interaction term. Considering only individuals without DS, we found significantly reduced ipsilateral NAA/Cr in left-HS ($p=0.001$) compared to controls. Regarding DS-positive individuals, ipsilateral NAA/Cr was reduced in both left- ($p=0.025$) and right-HS ($p=0.031$) compared to controls. Similarly, contralateral NAA/Cr showed a significant effect of HS side ($F_{3,119}=2,69$, $p=0.049$), and no effect of DS ($F_{1,119}=0.03$, $p=0.86$). Post-hoc analysis showed contralateral NAA/Cr reduction in left-HS ($p=0.044$). Simple effects showed that contralateral NAA/Cr is reduced only in left-HS compared to controls ($p=0.019$) when there is DS diagnosis. **Discussion:** Our finding of broader neuronal dysfunction in patients with HS and DS indicate common or additive pathological changes. Indeed, the association of MTLE and DS is likely bidirectional, i.e., one may lead to the other [4]. Moreover, our results corroborate data on more impaired neural mechanisms in left-sided HS [5]. A previous report showed that hippocampal metabolic alterations (measured by a map of Cr/NAA abnormality) correlated with depression scores in MTLE but failed to show NAA differences regarding side of HS and depression [6]. Differences in scales used to evaluate DS, population background and epilepsy syndromes included may account for discrepancies. Nevertheless, our findings might help to bridge the underlying dysfunctions of MTLE with DS. **Conclusion:** Left-HS showed more intense and bilateral evidence of neuronal damage than the other MTLE groups, while right-HS had only ipsilateral changes in the presence of DS. The presence of DS alone did not influence NAA/Cr levels. However, DS seems to have an additional effect, worsening NAA/Cr reductions bilaterally in left-HS and ipsilaterally in right-HS patients.

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Financial: CNPq and FAPESP.

GRAY MATTER AND WHITE MATTER ATROPHY IN CHILDREN WITH PHARMACORESISTANT EPILEPSY SECONDARY TO FOCAL CORTICAL DYSPLASIA

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Introduction: Focal cortical dysplasias (FCDs) are the most common cause of pharmacoresistent epilepsy in children.[1] These patients often present cognitive and behavioral morbidity.[2] Structural damage away from the FCD may be associated with these comorbidities.[3] In this context, this study aims to evaluate the presence and patterns of individual alterations in gray (GM) and white matter (WM) in children with epilepsy secondary to focal cortical dysplasia. **Materials and Methods:** We selected 21 consecutive children with pharmacoresistant epilepsy secondary to FCD followed in the Clinical Hospital of Unicamp. The images acquired in a 3T MRI machine with volumetric T1-weighted sequences were processed using voxel based morphometry (VBM) analysis. The individual GM and WM maps of each patient was compared with a control group composed by 71 healthy pediatric controls in order to look for increased or decreased volume. **Results:** 20/21 (95%) had WM atrophy with the following patterns: diffuse justacortical (n=16), diffuse in deep WM (n=3), periatrial (n=2), corpus callosum (n=1) and cerebellum (n=2). Only 11/21 (52%) patients showed GM atrophy and in all it had a localized pattern outside the area of the FCD including pre-central gyrus (n=2), occipital region (n=3), temporal region (n=1), basal ganglia (n=1) and cerebellum (n=5). There was no difference of the age of seizure onset between patients with or without GM atrophy (two-sample T-test, p=0.358). There was no difference of seizure control after epilepsy surgery between patients with or without GM atrophy (Fisher exact test, p=1) or with diffuse or localized WM atrophy (Fisher exact test, p=0.454). **Discussion:** Subtle GM and WM atrophy occurs in children with epilepsy secondary to FCD and it may be associated with the cognitive and neuropsychiatry comorbidities. The patterns of GM and WM abnormalities are different in these patients and, possibly, distinct causes, such as poor seizure control and cerebral insults during the neurodevelopment. **Conclusion:** Children with pharmacoresistant epilepsy secondary to FCD have diffuse brain WM atrophy and less frequent localized GM atrophy.

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A STATISTICAL METHOD FOR DETECTION OF COPY NUMBER VARIATION USING NEXT-GENERATION SEQUENCING DATA

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Introduction and Hypothesis: Epilepsy is a group of disorders characterized by recurrent seizures and is one of the most common neurological conditions [1]. Genetic factors are believed to be play a role in approximately 80% of patients with epilepsy [2]. Recent advances in genomic technologies led to a fast improvement in our understanding of epilepsy genetics [1]. In particular, a type of genetic variation, copy number variations (CNVs), have contributed to elucidating the etiology of in several patients with epilepsy [1]. CNVs are deletions and duplications of stretches of DNA ranging from 1 kilobase to an entire chromosome that can be a source of normal genomic variation but can also be causes of diseases [3]. The platform of choice to detect CNVs has traditionally been SNP arrays [4]. Over the last few years, next-generation sequencing (NGS) has evolved into a popular strategy for genotyping and it is desirable to exploit these data also to detect CNVs [4]. Several methods have

been proposed to detect CNVs from NGS data, each one with its advantages and limitations. Though there has been great progress, none of the currently available methods have resulted in a satisfactory comprehensively detection of CNVs [5]. **Objective:** The main goal of this project is to develop a statistical method for CNV detection from NGS data informed by whole exome sequencing (WES) and panel sequencing data. **Method:** We have previously generated data from a large group of subjects studied on different platforms, such as SNP array and panel sequencing or SNP array and WES. These data allow us to assess the possibility of using either panel or WES to detect CNVs. We propose to use this combined data to calibrate a model developed to perform this task. Also, thinking about the fact that copy number events may be associated with population-specific factors, we can use data on subjects from the cohort of reference individuals form the Brazilian population available at the Brazilian Initiate on Precision Medicine (BIPMed) databases (www.bipmed.org). More specifically, we aim to propose estimators for LRR and BAF adapted for data generated through WES/Panel experiments designed specifically for neurological disorders. **Relevance:** SNP array data is still the gold standard for CNV detection, however, its precision is low [4, 5]. The most relevant advantages of detecting CNVs from SNP array data is higher coverage and lower cost. However, there are disadvantages such as the low resolution of breakpoints and the limitation of being capable of detecting only sequences already know and expected variations [6]. The own nature of SNP array experiments based on previously designed probes imposes the impossibility of discovering new variants. Nowadays, there is an increasing demand for statistical methods and computational tools that fill up these gaps of information. A good method for CNV detection from NGS data will contribute, particularly in the context of precision medicine, for diagnostic and prognostic purposes, and to increase treatment efficiency.

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COGNITIVE TEST PREDICTION FOR ALZHEIMER'S DISEASE PROGRESSION WITH MULTI-TASK LEARNING

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Introduction: In the domain of research related to Alzheimer's Disease (AD), the use of cognitive scores impacts on drug trials, assessments of the severity of symptoms, the progressive deterioration of functional ability, and deficiencies in memory [1]. Multi-Task Learning (MTL) is a Machine Learning approach that learns several tasks simultaneously while estimating how learning one task can benefit other tasks. This contrasts with a learning method being applied to each task individually, Single-Task Learning (STL). In this work we applied MTL to predict cognitive tests scores from fMRI scans, also estimating how each region-of-interest (ROI) from one test relates to all other tests. **Materials and Methods:** We used a dataset collected by the Alzheimer's Disease Neuroimaging Initiative (ADNI) and pre-processed as described in [1]. The subjects are the same for all tests and can be categorized in three groups: cognitively normal, mild cognitive impairment and Alzheimer's disease. Each ROI in the brain corresponds to a group of covariates in the Group LASSO regularization [2]. We want to predict 5 cognitive measures: Rey Auditory Verbal Learning Test (RAVLT) Total score (TOTAL), RAVTL 30 minutes delay score (T30), RAVLT recognition score (RECOG), Mini Mental State Exam score (MMSE), and Alzheimer's Disease Assessment Scale cognitive total score (ADAS). To this end, we propose GAMTL, an MTL method that is not only able to learn tasks simultaneously using the Group LASSO regularization, but can also estimate an asymmetric transference between tasks for each group of covariates. We considered the LASSO [3] and Group LASSO [2] as STL contenders; MT-SGL [1] as MTL contender, and GAMTL. All hyper parameters were selected by means of a cross-validation procedure using NMSE as metric. We run each method 30 times. **Results:** Table 1 shows the mean and standard deviation of NMSE for all 30 runs of each method. **Discussion:** In Table 1 we can see that our proposal (GAMTL) achieves the best competitive predictive performance among the contenders. Matrices in Figures 1 and 2 contain in their element (i, j) how much task i influences task j. For instance, in Figure 1 we see the relationship between tasks considering ROI Left Inferior Lateral Ventricle (#49), and In Figure 2 we see different influences among tasks in ROI Corpus Callosum Posterior (#88). This asymmetric structure is not possible with the existing methods that consider the Group LASSO regularization. **Conclusion:** GAMTL presents a good performance in terms of Cognitive Test Score prediction while estimating an asymmetric transference structure between tasks in a way that each ROI has its own relationship matrix between all tests. This leads to an easy interpretation of the relationship between tasks, where we can choose which ROIs we are going to analyze.

Table 1. mean and standard deviation of NMSE of all methods on ADNI dataset.

Method	NMSE
LASSO	0.787 (0.000)
Group LASSO	1.005 (0.262)
MT-SGL	0.809 (0.000)
GAMTL	0.774 (0.001)

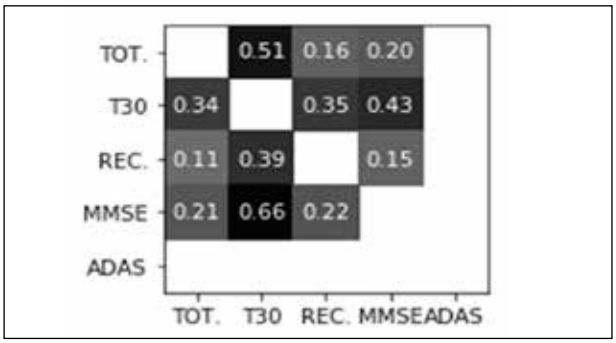

Figure 1. Relationship of ROI #49.

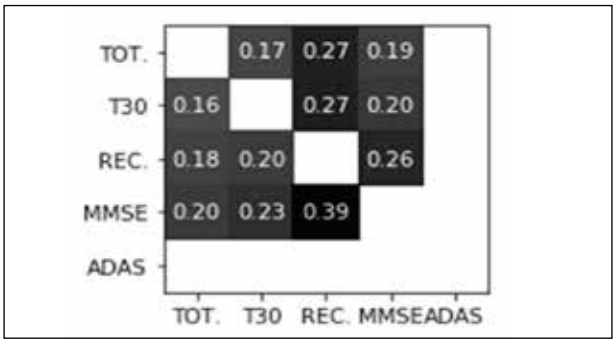

Figure 2. Relationship of ROI #88.

Supported: CNPq, proc. #141881/2015-1 and proc. #307228/2018-5, Fapesp, proc. # 2013/07559-3.

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SPECTRAL CHARACTERISTICS OF LOCAL FIELD POTENTIALS AS BIOMARKERS TO CLINICAL SUBTYPES OF PARKINSON'S DISEASE

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Introduction: Deep brain stimulation (DBS) emerges as a promising therapy for treating Parkinson's disease (PD) motor symptoms when drug treatment is no more efficient [1]. Yet, distinctive stimulation protocols for clinical subtypes of Parkinson's disease (tremor dominant [TD], akinetic-rigid [AR], and undetermined) is still missing, mainly due to the lack of electrophysiological (EP) biomarkers that better describe the underlying phenomena. In the present work, we investigated spectral features of local field potentials (LFP) from the

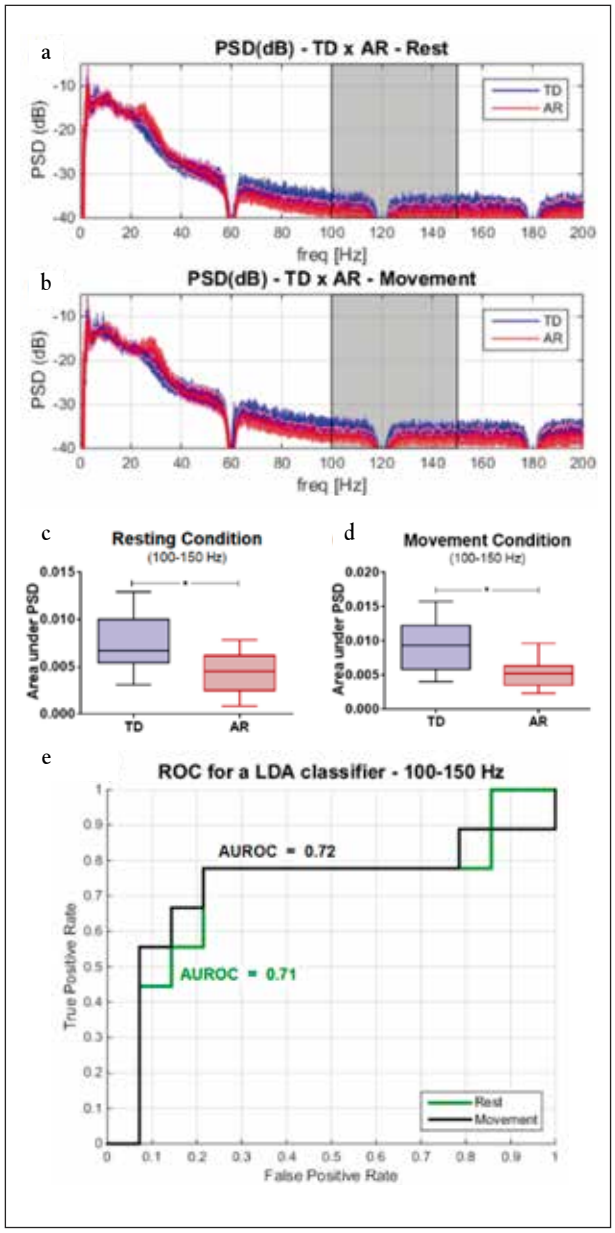

Figure 1. Periodogram for TD and AR groups for rest (a) and active (b) arm movement. Box plot for the best discriminating band (100-150 Hz) in rest (c) and movement (d). (e) ROC curves for rest and active arm movement.

subthalamic nucleus (STN) for the discrimination of TD and AR subtypes. **Materials and Methods:** PD subtypes were defined by Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores. 60 s of LFP were recorded intraoperatively from 1 MOhm macroelectrodes inserted in the sensorimotor part and digitally stored for off-line analyses (LeadPoint - Minneapolis - USA) from 23 distinct brain hemispheres (14 AR and 9 TD) in rest and active arm movement. Signals were downsampled (1 kHz), band-pass filtered (2-400 Hz) and z-score normalized. The power spectrum density (PSD) was estimated by Welch method for each PD's group (Figure 1). The mean power for electroencephalogram frequency bands was estimated. Classification scheme was performance by leave-one-out cross validation. Linear discriminant analysis (LDA) and receiver operating characteristics (ROC) curves were used for evaluating average classification accuracy. **Results:** Figure 1 illustrates PSD for TD and AR subtypes in rest (A) and movement (B). The best discriminating band 100-150 Hz (shaded in gray in Figure 1A and B) has shown higher values for TD in both resting and movement conditions (Figure 1C and D). TD vs. AR during resting condition yielded to F1-score=0.78, accuracy=0.83±0.17 and area under the ROC (AUROC) curve of 0.71. TD vs. AR during movement resulted in F1-score=0.71, accuracy=0.78±0.22 and AUROC of 0.72 (Figure E). **Conclusion:** LFP with higher frequency components are more effective in discriminating TD and AR subtypes of PD. These findings may contribute to future efficient and distinctive DBS protocols for specific clinical subtypes.

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INVESTIGATION OF THE CANDIDATE LOCUS AT CHROMOSOME 2Q24.3/*SCN1A* GENE IN MESIAL TEMPORAL LOBE EPILEPSY

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Introduction and Hypothesis: Mesial temporal lobe epilepsy (MTLE) is the most common form of focal epilepsy in the adult population, and most cases are refractory to treatment with antiepileptic drugs. MTLE is a genetically complex disease for which the identification of predisposing genes is, for the most part, still elusive. Recent genomic association studies discovered a few genomic regions that could harbor genetic variants which predispose to MTLE, of which stands out the locus on the chromosome (ch) 2q24.3. Multiple association studies detected signs indicating a significant association at this locus [1,2]. Interestingly, the *SCN1A* gene is in this same location. Mutations in *SCN1A* have been extensively associated with monogenic forms of epilepsy, especially in the developmental encephalopathies. In addition, at this same chromosomal location, other genes encode ion channel subunits and can be considered good candidates for MTLE. Therefore, this project aims to look deeper into the locus at ch 2q24.3 in patients with MTLE by target next-generation sequencing. With this strategy, combined with extensive bioinformatics, statistic and *in silico* predictions, we expect to better clarify the role of the candidate region ch 2q24.3 in MTLE; thus, contributing to the ongoing worldwide collaborative studies to unravel the genetics of the complex epilepsies. **Objective:** This study is divided into two main objectives: i) Build a gene panel to capture and sequence, by next-generation sequencing, the candidate region on ch 2q24.3/*SCN1A* in over 300 patients with MTLE, as well as in controls; ii) Analyze the obtained data with bioinformatics tools, *in silico* functional analyses and statistical tests in order to identify genetic variants putatively related to MTLE. **Methods:** MiSeq target Next-Generation Sequencing (Illumina, San Diego, California, United States) will be used for sequencing the candidate region on ch 2q24.3/SCN1A. The obtained data will be aligned using the Burrows-Wheeler Aligner algorithm. Variants will be detected by the Genome Analysis Toolkit and identified using the Variant Effect Predictor. **Relevance:** When completed, our results will help to elucidate the molecular mechanisms underlying MTLE. Furthermore, our work could be also relevant for the development of better treatments, prevention, early diagnosis, identification of risk factor and for genetic counseling of patients with MTLE patients.

Supported: FAPESP.

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SPECTRAL CHARACTERISTICS FROM LOCAL FIELD POTENTIALS DISTINGUISH RESTING FROM MOVEMENT CONDITION

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Introduction: Deep Brain Stimulation (DBS) is regarded as an effective method for treating motor symptoms of Parkinson's Disease (PD) [1]. The lack of electrophysiological (EP) data, however, prevents improvements in its therapeutic effects, such as developing a closed-loop control system that would provide different stimulation strategies for rest and movement conditions, getting closer to reality of patients' daily routine. To accomplish this task, this work aims to identify local field potentials (LFP) spectral features from the subthalamic

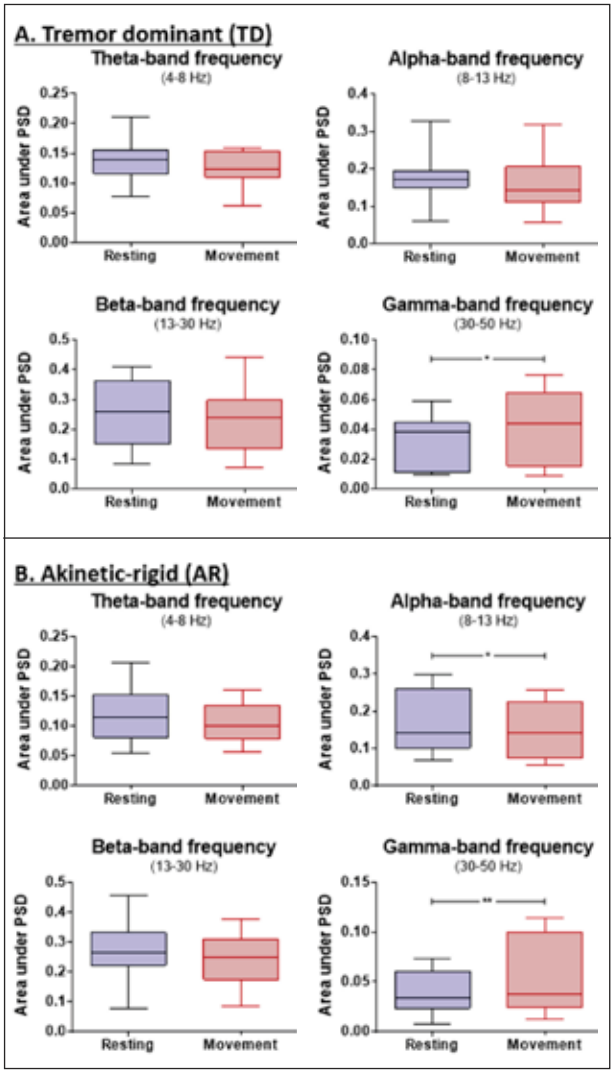

Figure 1. The area under the PSD for the subtypes TD (A) and AR (B) grouped in rest (blue) and movement (red) conditions, for each EEG frequency bands.

nucleus (STN) able to distinguish resting from movement condition. **Materials and Methods:** Intraoperative 60 s of STN LFPs were recorded from 23 distinct brain hemispheres from 14 Akinetic-rigid (AR) and 9 tremor-dominant (TD) PD patients, in rest and active arm movement. Signals were downsampled (1 kHz), band-pass filtered (2-400 Hz) and z-score normalized. The power spectrum density (PSD) was estimated by the Welch method. The area defined by the PSD for classic EEG frequency bands (theta 4-8 Hz; alpha 8-13 Hz; beta 13-30 Hz; gamma 30-50 Hz) were calculated. Resting *vs.* movement conditions were compared using paired *t*-test, first in AR and TD subtypes and then considering all subjects without differentiating subtypes. **Results:** Gamma band showed significantly higher values for movement (Figure 1) in both TD and AR subtypes ($p=0.024$ and $p=0.009$, respectively). The other frequency bands yielded higher values for resting for both TD and AR subtypes (alpha band AR, $p=0.025$). These differences between resting *vs.* movement were highlighted when considering the entire cohort (mean±SD; theta: 0.13±0.04 *vs.* 0.12±0.03, $p=0.07$; alpha: 0.17±0.07 *vs.* 0.15±0.07, $p=0.007$; beta: 0.26±0.10 *vs.* 0.24±0.09, $p=0.04$; gamma 0.036±0.019 *vs.* 0.048±0.031, $p=0.0003$). **Discussion and Conclusion:** Resting and movement conditions showed different EP signatures on specific LFP frequency bands. The results suggest these spectral characteristics could be used as biomarkers for the investigation of the underlying EP mechanisms driving PD and for developing future DBS closed-loop control system.

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ASSESSMENT OF OVERLAPPING IN CORTICAL MOTOR MAPS OF HAND MUSCLES RELATED TO THE GRIP MOVEMENT USING TRANSCRANIAL MAGNETIC STIMULATION

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Introduction and Hypothesis: Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that has been widely used to obtain functional maps of the human motor cortex for pre-surgical planning and motor control studies. A coil placed externally over the primary motor cortex (M1) produces magnetic pulses that induce electric fields in cortical tissue causing depolarization of neurons. The action potentials result in a motor evoked potential (MEP) in the target muscle. The MEP amplitude and TMS pulse application site define together a region over the head to obtain a response of the desired muscle. This procedure is called motor mapping and is used to delimit areas of a target muscle representation on the cortical surface [1]. Published studies suggest different methodologies for calculating motor maps and different areas of cortical representations for single, target muscles commonly stimulated with TMS [2] [3]. However, a TMS pulse causes simultaneous contraction of adjacent muscles group [4]. Yet, the cortical representation of the overlapping maps of hand and forearm muscles is still unclear [3]. The manual grip is an interesting movement which requires concurrent recruitment of the hand's flexor pollicis brevis (FPB) and abductor digiti minimi (ADM) muscles and the forearm muscle flexor carpi radialis (FCR). Therefore, we hypothesize that when the TMS is targeted to one particular muscle mentioned above, there may be an extensive coactivation of the muscles participating in the manual grip movement. **Objective:** The goal of the project is to evaluate the degree of overlap between the cortical representations of ADM, FRC and FPB muscles, in order to understand the coactivation of the target and adjacent muscles elicited by TMS. **Methods:** The data processing of a neuronavigated TMS experiment will be done with SignalHunter software (https://github.com/biomaglab/signalhunter), written in Matlab (Mathworks Inc., EUA). The TMS experiment was performed in 10 healthy volunteers. Previously, an MRI of the volunteer was obtained, and latter imported to the InVesalius Navigator [5]. Electrodes were placed in the FPB, ADM and FCR muscles and the TMS coil placed tangentially to the scalp. Three single TMS pulses with 110% and 120% of resting motor threshold intensity were applied at 20 points around the maximum stimulation site (hotspot). The MEPs of each muscle were obtained simultaneously. MEP amplitude and latency were extracted and combined with the stimulation coordinates in the SignalHunter software. The data analysis will be done in TMSmap [6], a graphical interface software that creates 3D maps of cortical representations and calculates mapping parameters such as areas, volume, center of gravity, hotspot and overlapping degree between cortical representations. The SignalHunter exported data will be used in TMSmap to create the cortical motor maps of ADM, FPB, and FCR muscles. Therefore, the percentage of intersection between the maps of these three muscles will provide a degree of overlap from the muscles involved in manual gripping. **Relevance:** Evaluate the degree of overlap of cortical motor representation associated with a movement can bring a new perspective to understand the mechanisms involved with movement control. If motor maps show a high degree of overlap and coactivation between adjacent muscles, it may be possible to define common regions of activation of particular muscle groups. On the other hand, searching for areas with a lower level of overlap, which results in a lower coactivation of adjacent muscles, can allow a more specific study of the muscle of interest.

Support: FAPESP (GPT fellowship and CEPID Neuromat), CNPq and CAPES.

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AMYOTROPHIC LATERAL SCLEROSIS MUTATION SCREENING OF BRAZILIAN PATIENTS USING NEW GENERATION SEQUENCING

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Introduction and Hypothesis: Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disorder of motor neurons leading to severe muscle weakness and atrophy [1]. Typically, death due to respiratory paralysis occurs in 3

to 5 years after onset. Only about 5-10% of ALS cases are familial with a Mendelian pattern of inheritance with the most prevalent genes being SOD1, C9orf72, FUS e TARDBP [2]. Because of that broad methods of screening are necessary so prophylactic and gene-specific approaches can be used. **Objective:** This study aims to unravel new mutations sites on patients that don't have a solid diagnose due to the uncommon phenotype as well as correlate some genes that have not been associated with ALS which can cause concomitantly some other disease or increase the risk of developing ALS in Brazilian control case groups. **Methods:** Around fifty samples from familial cases of ALS collected on Hospital de Clínicas da Unicamp were sent for exome analysis and the output is going to be analyzed using a validated pipeline available on Varstation. The results and the sequencing are going to be validated using the Sanger method. **Relevance:** Due to our peculiar ethnic composition, which includes Amerindians, Blacks and Caucasians and the presence of mutations in some families which are only present here, e.g. VAPB and the lack of clinical studies [3], the search for new mutations and deep analysis of NGS data are required to better understand how this disease takes form here.

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ANALYSIS OF VISUAL STIMULATION BY LED AND MONITOR FOR BCI-SSVEP SYSTEMS

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Introduction: Brain-computer interfaces (BCI) are systems capable of establishing a direct communication between the human brain and computers. A popular BCI approach is based on steady state visually evoked potentials (SSVEP), which employs visual stimuli that flickers at a specific frequency to evoke a defined electrical activity in the visual cortex [1]. In this study, we have developed two visual stimulation systems: (1) by light emitting diode (LED), feeding it by a sine and square waveforms, and (2) monitor. The brain activity was registered using electroencephalography (EEG). **Materials and Methods:** The frequencies and intensity of LEDs were controlled by an Arduino Mega. The sine waves were generated mapping a sine function from the mathematic library and modulated in a PWM (pulse-width modulation) signal output, then it was filtered by an external low-pass filter before feeding the LED. The square waves were generated by switching the output (HIGH/LOW) of the digital pins. These systems could work with four green LEDs, which glowed at independent frequencies in the range of 1–100 Hz. Also, a 15-inch monitor was used to design four square-shaped stimuli that flickered between black and white colors following a sine-wave function, the monitor can only project with precision frequencies sub-multiples of its 60 Hz refresh rate [2]. A female subject was exposed to each stimulus for 12 seconds. The electric circuit was carefully electromagnetically isolated as the dry electrodes are very sensitive to electromagnetic interference. The data was collected with 16 dry electrodes on scalp [1], and our analysis focused on the Oz electrode positioned in the visual cortex. The signal was filtered by the Common Average Reference (CAR) to reduce noise interference. **Results:** Table 1 presents the signal-to-noise ratio (SNR) observed in the acquired brain signals. The negative values represent the signal immerses in noise.

Table 1. SNR in dB.

	6 Hz	10 Hz	15 Hz	20 Hz	40 Hz	70 Hz	80 Hz	90 Hz
LED (square wave)	2.78	4.41	9.09	2.65	10.85	16.82	14.63	10.39
LED (sine wave)	3.64	1.00	5.32	4.95	8.12	14.70	11.28	7.69
Monitor	6.65	-5.66	-2.73	2.11	-	-	-	-

Discussion: Results show that all developed stimulators were capable of evoking potentials with precision and accuracy enough to be detected by an EEG, being stimulation options for BCI-SSVEP to work fine. The signals collected when the subject was stimulated by the green LEDs presented great SNR for all the frequencies, being better than the signals obtained with the monitor system, mainly for 10 and 15 Hz. Both the feeding waves of the LEDs showed similar results. The subject did not complain about visual fatigue for any of the scenarios. **Conclusion:** Our experiment showed a preliminary comparison between LEDs frequencies and feeding wave, besides a test with a monitor to evoke visually a subject. The results tend to indicate that the signal collected with the LEDs present more intense evoked potentials than those obtained with the monitor. Moreover, the LEDs are a more versatile form of stimulation by allowing more frequency values.

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AUTOMATIC IDENTIFICATION OF POOR-QUALITY SPECTRA IN MR SPECTROSCOPIC IMAGING (^{1}H-MRSI) BASED ON SPECTRAL QUALITY CRITERIA AND CSF CONCENTRATION

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Introduction: Magnetic resonance spectroscopy (MRS) is a non-invasive technique widely used for studying cerebral metabolic changes in neurodegenerative diseases and other diseases that affect the brain [1]. Nevertheless, the accurate measurement of brain metabolite concentrations is still problematic and challenging, especially for multi-voxel MR spectroscopy (^{1}H-MRSI) acquisitions, due to the presence of artifacts and cerebrospinal fluid (CSF) contamination [2]. In this abstract, we present a pipeline for ^{1}H-MRSI acquisitions that allows automatic identification of a subset of poor-quality spectra, using spectral quality criteria and analysis of CSF concentration. **Materials and Methods:** Spectra of 80 subjects on a 3T MR scanner, ^{1}H-MRSI acquisitions from supraventricular superior region (Volume of interest (VOI) ≈ 100.52 x 84.74 x 16 mm; 208 spectra) and mask brain tissues segmentation by Freesurfer [3]. First, the quantification of metabolites concentrations was obtained by TARQUIN software [4] separately for each spectrum of the MRSI acquisition. Then, three spectral quality criteria: Signal-to-noise ratio (SNR), full width at half-maximum (FWHM) and Cramér-Rao lower bounds (CRLB) [2], were computed. Second, the VOI of acquired spectra was registered to the masks of segmented tissue and the percentage of CSF in each voxel of the VOI was computed. Based on the spectral quality criteria and on the CSF concentrations, a subset of poor quality spectra was identified. The proposed pipeline is implemented in Python/Numpy and will be made available as an open-source toolbox on GitHub. **Results:** As the criteria for poor-quality spectra identification, we used the following threshold values: SNR > 10; FWHM < 10 and CRLB < 50 [2]. Regarding CSF contamination, spectra acquired in a region with more than 30% of CSF concentration was considered contaminated (Figure 1).

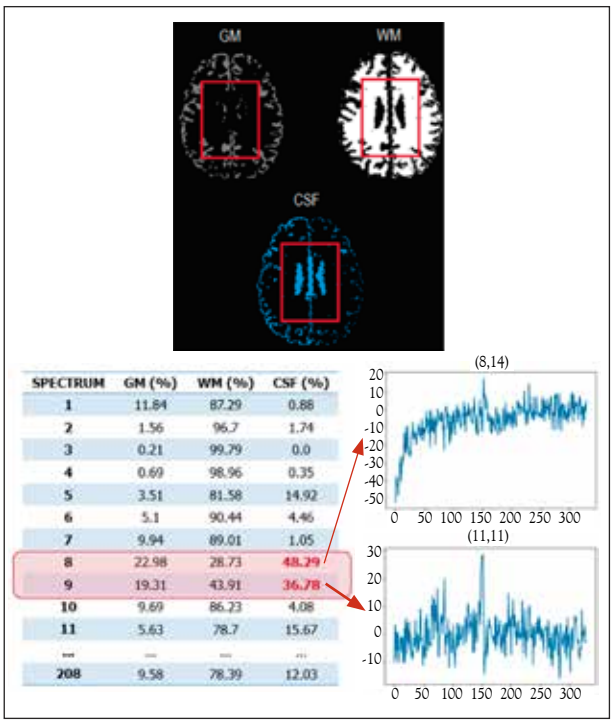

Figure 1. Left: VOI from supraventricular superior region and the percentage of brain tissues contained in each voxel and the identification of some spectra with high concentration of CSF. Right: visualization of the contaminated spectra.

Conclusion / Discussion: Our experiments showed the possibility of identification of a subset of poor-quality spectra, based on spectral quality criteria and CSF concentration. Until now, there is no agreement among experts on what exactly defines a good spectrum, and the key point is to choose threshold values for spectral quality metrics (SNR, FWHM and CRLB) and for CSF contamination (percentage of CSF). These threshold values might differ depending on the type of the clinical studies and thus, must be thoroughly investigated.

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DEFAULT MODE NETWORK CONNECTIVITY ASYMMETRY IN MCI COMPARED TO HEALTHY AGING INDIVIDUALS

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Introduction: Disruption in Default Mode Network (DMN) functional connectivity (FC) is commonly found in Alzheimer´s Disease (AD), but studies in MCI have showed conflicting results (normal, hyper or hypoconnectivity) and one of the possible reasons may be the difference regarding AD pathophysiology status in MCI subjects. We compared DMN FC in MCI subjects considering the AT(N) classification and divided subjects in suspected non-Alzheimer's pathophysiology (SNAP), AD continuum (A+) and normal AD biomarkers (N). **Materials and Methods:** We recruited 106 volunteers (74 MCI and 32 controls). We classified subgroups based on CSF amyloid-β, total tau and phosphorylated tau results. MCI with altered Aβ were considered A+ (n=40); with t-tau or/and p-tau alterations with normal Aβ were considered SNAP (21) and individuals with normal biomarkers were considered N(13). All subjects underwent MRI in a 3T scanner. To first identify the DMN, we placed a seed in the posterior cingulate cortex of 50 control subjects generating one spatial map for each one. The resultant DMN mask, which was an average of the 32 maps of controls, was subdivided in 8 non-contiguous regions (PCC, medial frontal, right and left temporal, parietal and hippocampus). Connectivity of these regions were obtained. **Results:** A multivariate analysis of covariance were performed, using age as covariates. We found significant differences ($p<0,05$, corrected) in Right-hippocampus, Right-temporal and PCC between controls and all AT(N) subcategories. Right parietal was different only in SNAP and A+. An inspection of the means scores shown lower connectivity in Right subparts of DMN in MCI and higher connectivity in PCC compared to controls. **Discussion:** Our hypothesis that AT(N) profile would be able to differentiate MCI subtypes was not confirmed, what can indicate that clinical aspects would be more relevant than biomarkers profile in this sample concerning DMN connectivity. It would be interesting to evaluate other neural networks, as well as structural brain measures. We also found higher connectivity in PCC in relation to controls, what could be considered a compensatory mechanism. **Conclusion:** We found a lower connectivity in right subparts of DMN and a higher in PCC in MCI individuals compared to controls, independent of AT(N) status. These findings were not expected and could imply that the different pathologic processes in MCI has similar outcomes on connectivity. Interestingly, we found patterns of hypo and hyperconnectivity in DMN of all MCI subgroups and, in addition, a right-left asymmetry in the studied DMN subparts.

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ASSESSING THE QUALITY OF CORPUS CALLOSUM SEGMENTATIONS USING A CNN

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Introduction: The corpus callosum (CC) is the greatest white matter bundle in the brain, and is related with important diseases, being studied using mainly magnetic resonance imaging (MRI). CC segmentation in MRI is a common step for performing analysis and is usually done by automatic segmentation methods. Since such studies use large MRI datasets and automatic segmentation methods are prone to errors, there is a necessity of assessing CC segmentation results before using them in any analysis. This control is done by visual inspection, and correction if necessary, in a one-to-one basis. In this work, we propose an automatic quality control framework that separates correct from incorrect CC segmentations using convolutional neural networks (CNN). **Materials and Methods:** T1-weighted images of 252 subjects were acquired on a Philips scanner Achieva 3T at University of Campinas. From each volume, only the middle slice was used and a 123x74 region around the CC was cropped. Manual CC segmentation was performed by a specialist for 150 subjects. For the 102 remaining subjects, the Max-Tree[1] was used to create a pool of incorrect segmentations for training the model. Therefore, a correct/incorrect CC segmentation dataset was generated with a 159/93 ratio respectively (Some manual segmentations were incorrect and some Max-Tree resulted correct). A gaussian filter ($\sigma=2$) was applied over all the binary masks for smoothing them. A pre-trained ResNet18 CNN[2] was used to learn the classification among correct and incorrect classes. The convolutional feature extractor part of the CNN was preserved unchanged while the last max-pooling and fully connected layers were removed and changed by three fully connected layers with two interleaved dropout layers. Only these last layers were trained using fine-tuning. The inputs for the three channels of the CNN were arranged as follows: original T1, T1 weighted by the mask; and the mask (Fig.1). 85% of the dataset was used for training the model along 10 epochs using cross entropy, Adam optimizer and early stop regularization. Finally, the 15% remaining data was used for testing. **Results:** After 5 epochs, the model underwent overfitting, getting 92% of test accuracy (Figure 2). **Discussion:** Results showed it is possible to train a CNN to distinguish between correct and incorrect CC segmentations. Transfer learning was effective in adapting the model with few epochs. The overfitting can be explained by the data distribution (bias toward correct segmentation class). **Conclusion:** This work presented a CNN for automatic classification of CC segmentations into correct/incorrect classes. In the future, more realistic incorrect segmentations will be included.

Figure 1. Input channels (T1 image, T1 image weighted by smoothed mask and smoothed mask).

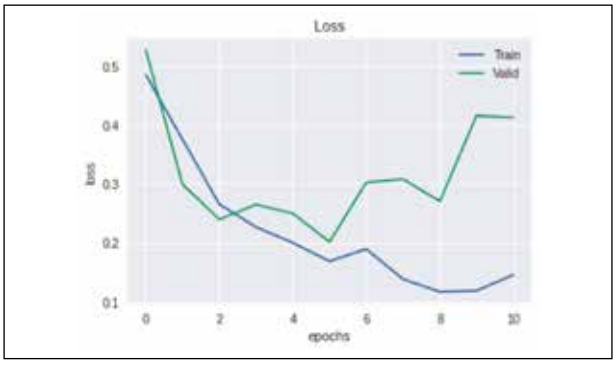

Figure 2. Loss along 10 epochs for train and validation sets.

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EPILEPSY AND EMPREGABILITY: BARRIERS AND DIFFICULTIES ANALYZED THROUGH THE GROUNDED THEORY

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Introduction and Hypothesis: According to the International League Against Epilepsy (ILAE), epilepsy is a chronic brain disease [3] and by consequence has the same impact as other chronic diseases. Besides of the physiological impacts, the diagnosis and the stigmatizing characteristics of the epilepsy affects directly the social and occupational life of the individual [4]. Considering social factors such as preconception and stigma and its impacts, the active Brazilian population with epilepsy may face difficulties in inserting themselves into work contexts and, by consequence, the diagnosis can affect not only the individual's quality of life but can also has a big economic impact [8]. In Brazil, about 50% of the adults with epilepsy are unemployed and there's a gap in Brazilian law referring to the protection of work rights of people with epilepsy, being fundamental to think about strategies to include this group of people into job market [2];[5]. Thus, it is necessary to carry out a study that can be used as a scientific basis to ensure the insertion and permanence of the person with epilepsy in the job market. Investigating methods that could certify an effective qualitative result, the Grounded Theory methodology has been chosen to this study. **Objective:** The objective of this study is to develop a theory based on data (Grounded Theory) about the empregability process of the person with epilepsy in the job market, searching to identify the barriers and difficulties faced by the patient. The study intends to analyze the biopsychosocial factors that surrounds the relation of the person with epilepsy at the job market, in owe to build a work that could be used as support for the development of public politics. **Methods:** The methodology used for the construction of the study is the Grounded Theory methodology, also known as theory based on data. Consists in a flexible systematics for data collection that uses inductive data to construct analytical categories through an interaction process with the data itself [1]. Material: formal semi structured interviews will be used as instrument to collect the data, during the literature review process the instrument will be constructed (Figure 1.). The interviews will not trespass 15 minutes. Subjects: groups of people, over 18 years old, that permeate the biopsychosocial reality of the person with epilepsy in its specific relation to the labor market. Example: patients, family, work colleagues, recruiters, doctors. Sample number: Under 100 subjects.

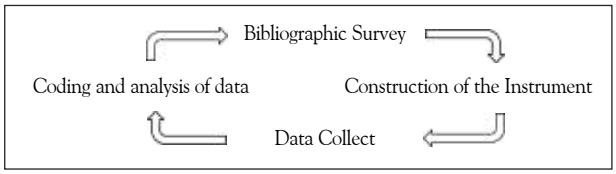

Figure 1. Visual representation of data construction, application and analysis.

Relevance: Considering that there's a gap in Brazilian's law to protect the constitutional work right of the person with epilepsy, in order to think of ways to include the person with epilepsy in the labor market, the present study will demonstrate its relevance by collecting and analyzing data that could be used to construct an instrument as a basis to future public politics.

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MODULAR STRUCTURE IN C. *ELEGANS* NEURAL NETWORK AND ITS RESPONSE TO EXTERNAL LOCALIZED STIMULI

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Introduction: In this work we probe the community structure of the neural electrical junction network of the C. *elegans* using the partially forced Kuramoto model of synchronization [1]. We aim to understand how the network responds to external localized stimuli and which modules are more affected when a specific group of neurons, that can be a functional, anatomical or topological module, is stimulated. We use two different metrics to characterize the overall behavior of the network under a localized stimulus: the synchronization of neurons within and between modules, as measured by the usual Kuramoto order parameter, and the phase velocity-velocity correlation inter neurons. We want to investigate the set of parameters that leads the network to global induced synchronization and highly correlated behavior, where the network responds as a whole, or to a globally uncorrelated state, where neurons do not react to each other. **Materials and Methods:** Neurons were described as Kuramoto oscillators,

$$\dot{\phi}_i = \omega_i - \sigma - F\delta_{i,C} sin\phi_i + \frac{\lambda}{k_i}\sum_{j=1}^{N} A_{ij}\, sin(\phi_j - \phi_i)$$

with $i = 1,\ldots,N$, where N is the number of neurons, is the natural frequency of neuron i taken from a Gaussian distribution with zero average, λ is the internal coupling strength, is the adjacency matrix of internal connections, is the degree of node i, F and σ are respectively the amplitude and frequency of the external stimulus, and C specifies the subgroup of oscillators being stimulated. We defined if and zero otherwise. The weighted electrical junction (EJ) network has 248 neurons and 511 electrical synapses. We used a hierarchical algorithm to detect community structure, which provided 3 modules with modularity $Q = 0.44$. The neurons were also anatomically classified as belonging to 10 ganglia and divided by their functionality, classified by their types (motor, inter and sensory neurons). We stimulated the largest topological module, the anatomical ganglion C and the functional group of sensory neurons. **Results:** Stimulation of neurons of the largest topological module induced strong anti-correlation in the velocity fluctuations of the neurons of the other modules, which kept their original state of spontaneous sync for moderate values of λ. The response of the network to stimulation of ganglion C was quite different, displaying two distinct regions with large parameter intervals of almost complete uncorrelated behavior (small λ) and complete correlated behavior (large λ). Effective sync of ganglion C with F requires large values of λ. Finally, the response of the network to sensory neurons stimulation led to induced sync for small λ, while the other two functional classes showed spontaneous sync. Many sets of neurons displayed strong anti-correlation. **Discussion:** Topological modules do not contain purely anatomical groups or functional classes. Stimulating different classes of neurons lead to very different responses. Anti-correlation seems to be associated with small inter-module sync while positive correlations implies larger sync. **Conclusion:** Our results corroborate previous studies [2-4] and show the complexity of the brain's neuronal wiring and function. The modular structure hinders full synchronization, protecting the system from seizures. Responses to stimuli applied to functional or topological modules are more coherent than those applied to anatomical sets (ganglia).

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BRAIN STRUCTURAL CONNECTIVITY IN THE AID OF LOCATION OF THE EPILEPTOGENIC FOCUS

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Introduction: Epilepsy is a neurological disorder characterized by excessive and abnormal electrical discharges in the brain cortex. These discharges propagate trough the brain and can be detected by Electroencephalogram (EEG) technique in the scalp. Localization of the epileptogenic focus is a mandatory step in patients to be submitted to surgery; however, it is a hard task in cases with several spike patterns in the EEG at the scalp. In this study, we propose the use of the brain structural connectivity information obtained by magnetic resonance imaging (MRI) to help in the localization of the electric source generating epileptiform discharges in patients with epilepsy. **Materials and Methods:** Prospectively, four males and two women patients (aged 20-47 years) successful submitted to epilepsy surgery were selected with scalp-EEG and MRI data available. Multiple spikes from several electrodes in only one hemisphere were marked by a specialist, suggesting focal epilepsy for a better validation of our approach. Anatomical and diffusion weighted magnetic resonance images

were used to estimate the connectivity matrix using FSL software and MRtrix3 tools. Electrodes positions (from 11 to 29 electrodes, depending on the patient) were defined based on the labels of the brain Atlas Destrieux. Percentage of discharges in each electrode obtained in the EEG were modeled as a linear combination of the electrical source activities and structural connectivity in the labels of the chosen Atlas. Spatial distribution of the electrical activity was estimated after matrix inversion and compared to the resected region in the surgery. **Results:** Estimated electrical activity was focused in one cortical area for each patient, even when two or more channels had registered a high frequency of spikes.

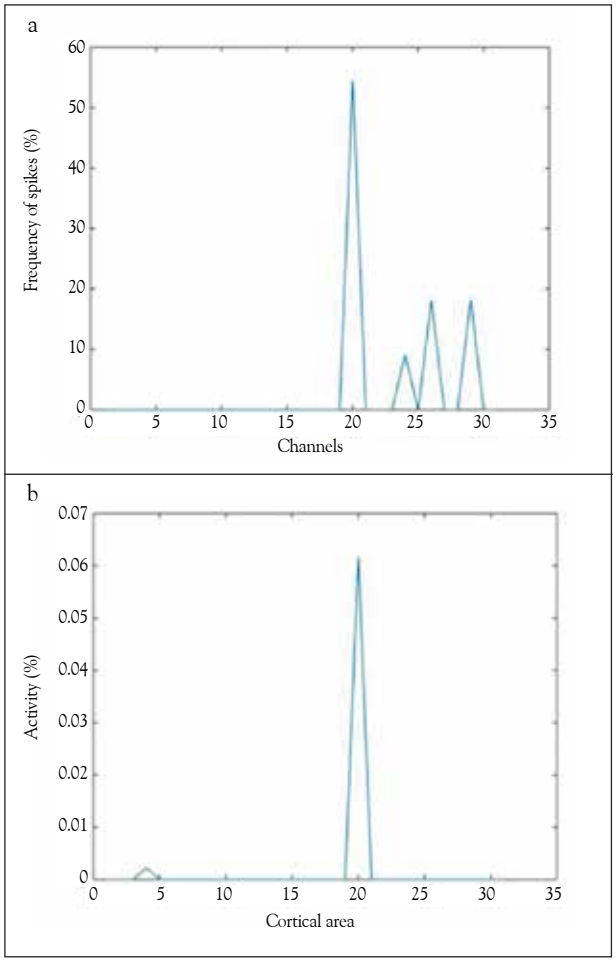

Figure 1. (a) percentage of spikes per electrode. (b) Activity of the cortical area.

The indicated area was associated to the electrodes with spike closer to the resected region in three patients. In the other patient, the estimated electrical activity was focused in the occipital area in correspondence to the prior EEG data, notwithstanding the frontal lobe was operated. In tree patients, the estimated electrical activity was at the same lobe of the surgery. **Discussion:** The spikes observed in different electrodes can be an evolution of the electrical propagation coming from a common region, whose possible explanation can be given by the structural connectivity. Our approach reduced the number of "suspect" electrodes, helping the medical work. **Conclusion:** The assessment of white matter tracts connecting several brain regions can provide useful information about the main electrical paths in the brain affecting the voltage distribution over the head during an epileptic discharge. However, it is still necessary to process more data in order to a complete validation of our simple linear model.

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DESIGN OF A FOREARM PROSTHESIS USING 3D PRINTING SCAN

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Introduction: Forearm congenital malformation and amputation imply in a huge impact in life quality, difficulty on daily routine and social inclusion. The main causes of transradial upper limb amputation in Brazil are associated to disease's sequelae, as also work and traffic accident. Despite of the high prosthetics technology available in the market concerning myoelectric based control, a functional, light and inexpensive option is stills missing to attend user's requirements. On the other hand, the available open source models, 3D printing technologies and cheap microcontrollers can provide an interesting alternative, requiring an integrative approach. In this work, we present a forearm prototype for a harmonious connection with an open-source myoelectric hand (OpenBionics) and the forearm stump aiming to increase user's functional and aesthetic satisfaction, enabling a greater self-sufficiency for patients of forearm prostheses. **Materials and Methods:** a whole portable and low cost setup was designed and implemented as shown in Fig. 1A. Volunteers – unilateral congenital deficient or unilateral amputees - are positioned in front of Microsoft Kinect®, forming a radius of approximately 500mm to scan the forearm stump circularly. The same procedure is repeated for the healthy arm of the patient when applicable. Using the Skanect® software, it is possible to transform the Kinect® device into a low-cost 3D scanner, capable of capturing the stump structure as also and the health arm anthropometric characteristics in a few minutes. An intermediate step, very important after scanning, is the conversion of this cloud of points, except in STL format, into a solid type format. Thus, we can perform the modeling and detailing of the prosthesis as we can see in Fig. 1C. The proposed setup allows creating a 3D meshing structure of the scanned parts as also its manipulation for designing new structures from acquired data (Figure 1B). **Results:** Fig. 1A shows the scanner implemented setup. Fig. 1B shows a mesh structure obtained from Skanect® and a preliminary proposal for prosthesis coupling on a forearm stump (Figure 1C).

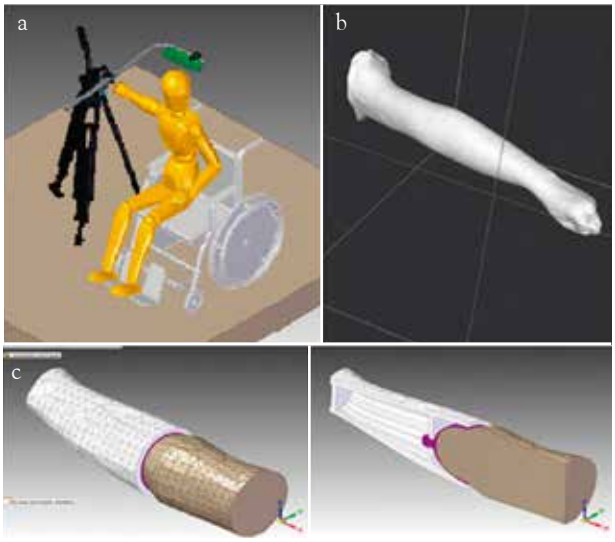

Figure 1.

Discussion/ Conclusions: This work presented a low cost portable setup for scanning upper limbs aiming to design a forearm coupling structure from stump and low cost open source myoelectric hands. Preliminary results suggest the success of the proposed approach, being the next step devoted for design and performance evaluation with amputee volunteers.

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ASSESSMENT OF CEREBRAL BLOOD FLOW FOR THE DIAGNOSIS OF THE PRECLINICAL PHASE OF THE ALZHEIMER'S DISEASE

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Introduction: Alzheimer's disease (AD) is an irreversible neurodegenerative disease that causes cognitive impairment and progresses to dementia [1]. One of the prevailing hypothesis about AD etiology is that diminished perfusion in specific areas contributes to the deflagration of the process that leads to the disease, and may be detected years before clinical features of AD are apparent [2]. Our main goal in this study is to assess cerebral blood flow (CBF) of healthy controls (CDR 0), patients with mild cognitive impairment (MCI, CDR 0.5) and mild AD (CDR 1) using pseudocontinuous Arterial Spin Labeling (pCASL). **Materials and Methods:** Data of nine healthy controls, five AD and six MCI patients, totalizing twenty subjects (age: 79 ± 8 male) were acquired in a 3T MRI scanner. 2D pCASL images were acquired using an EPI sequence with the following parameters: flip angle = 90°, matrix = 80x80, FOV = 240x240 mm^2, number of slices = 20, slice thickness = 5 mm, repetition time (TR) = 4 s, echo time (TE) = 14 ms, labeling time (LT) = 1650 ms and post-labeling delay (PLD) = 1525 ms. For anatomical reference, T1-weighted images were acquired using a GRE sequence with the following parameters: TR/TE = 7/3 ms, flip angle = 8°, matrix = 240x240, FOV=240x240 mm^2, number of slices = 160, slice thickness = 1mm. Data was processed and analyzed using MATLAB routines and SPM12 toolbox. Preprocessing included motion correction and spatial smoothing of pCASL images. Sinc-subtraction was used to obtain perfusion maps. CBF was quantified using the General Kinect Model and parameters recommend by previous studies [3]. **Results:** CBF in gray matter was lower in patients compared to healthy controls, but no difference was observed between MCI and mild AD patients. CBF values were 37 ± 17 mL/100g·min for AD, 38 ± 10 mL/100g·min for MCI, and 45 ± 10 mL/100g·min for healthy age-matched controls. **Discussion and Conclusion:** Gray matter hypoperfusion in AD and MCI groups was observed, indicating that blood flow changes are present in patients with MCI even before the clinical symptoms of AD. Such result is consistent with the thesis that MCI is a preclinical phase of AD and patients may be treated to slow the progression of the disease. Future analysis will consider a greater number of participants and regional quantification of CBF.

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DEEP VOLUMETRIC CONSENSUS HIPPOCAMPUS SEGMENTATION

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Introduction: Information about the hippocampus is important in the diagnosis and treatment of diseases such as epilepsy and Alzheimer's disease. The state-of-the-art in segmentation for many years consisted of slow methods with around 90% overlap (DICE Coefficient). Recently, some works have been published using Deep Learning [2]. This work applies Deep Learning to achieve a fast and reliable segmentation of the hippocampus. **Materials and Methods:** The main private dataset used on this work was collected at HC-UNICAMP. It contains 214 Montreal Neurological Institute (MNI) space registered, T1-weighted, MRI acquisitions, separated in a hold-out strategy of 80/10/10. Our method consists of using three 2D fully convolutional neural networks (FCNNs) for each MRI orientation. Each FCNN has an improved UNet based architecture, with the addition of residual connections, batch normalization and removal of bias. The encoder of the network is initialized with VGG11 [1] weights. Training is performed on 32x32 patches centered around the hippocampus border, 20% of them originating from random areas. Each patch and its two nearest neighbors are used as a 3-channels input. Random intensity, noise and affine augmentation are used. Hyperparameters were selected after a grid search study. As a post-processing step, volumes predicted from each orientation are summed in a majority voting strategy. The two (or one) largest connected volumes are selected as the final segmentation. Final prediction is performed on 160x160 center crops. **Results:** Training takes on average 12 hours on a Titan X GPU. Our method achieved 96.3% DICE in our test set, while a state-of-the-art method [2] achieved 86.24%. Our masks (green) were also qualitatively compared with [2] (yellow) in a third-party public dataset, CC-359 [3] (Fig.2). Prediction takes around 15 seconds per volume. A performance comparison of our FCNNs in each orientation and the consensus was also done (Fig.1). **Discussion:** The consensus strategy improved performance in comparison to each orientation individually. Each listed modification on the UNet architecture improved DICE in the test set by around 1%, and prevented previously observed overfitting, allowing for the method to be competitive with other state-of-the-art methods in a different dataset (Fig.2). **Conclusion:** We achieved state-of-the-art fast results. We showed that a consensus approach can improve performance of 2D slice prediction methods, and that the UNet architecture can be improved. However, more validation in other datasets is necessary.

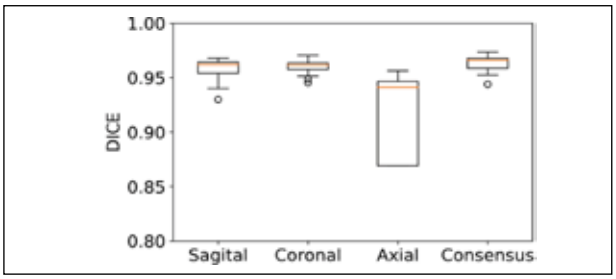

Figure 1. DICE when using each orientation alone and when using the consensus of all three orientations.

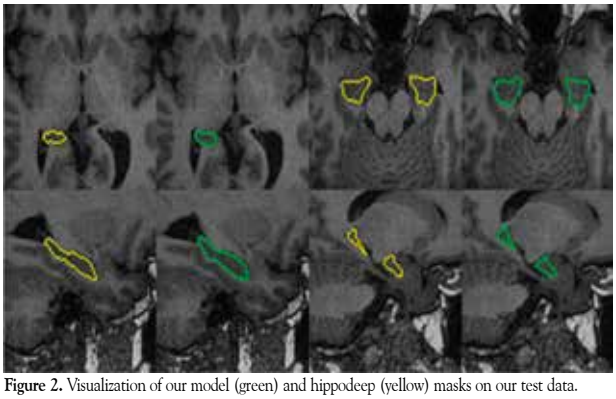

Figure 2. Visualization of our model (green) and hippodeep (yellow) masks on our test data.

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INTEGRATING A FRIENDLY INTERFACE FOR FUNCTIONAL CONNECTIVITY ANALYSIS WITH EEG OPENBCI® DEVICE FOR REMOTE REAL-TIME PROCESSING

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Introduction: A graph consists in a large collection of connected nodes that can represent the associations of any quantity: people, computers, biological cells, etc [1]. In neuroscience, the brain functional connectivity (FC) aims to capture the observational similarity between different brain regions and has contributed to the diagnosis of relevant pathologies such as Parkinson, Alzheimer and depression [2]. More recently, EEG-based Brain Computer Interfaces (BCIs) have been proposed to investigate brain functioning using FC in a better temporal detailed framework. To accomplish this task and to take advantage of the currently EEG best low cost technology, this work provides an integration, in terms of real-time processing, from EEG signals acquired by OpenBCI® hardware [3] with a friendly Java-based interface for evaluating functional connectivity from a remote device by means of HTTP protocol . **Methods:** We developed a NodeJS-based service [4] that get signals from OpenBCI® and designed a Java-based interface for getting data from txt files or data buffer in execution time, using HTTP protocol. The interface can run in notebooks, desktops, smartphones or any other remote device. The developed interface allows the user to set: a) the use of common average reference (CAR) spatial filter; (b) the updating graph rate, i.e., data samples for each time window; c) the number of overlapping samples between consecutive windows; d) Pearson's threshold correlation between the

electrodes for defining the FC connections. Four graph measures can be evaluated by our interface using the GraphStream toolbox [5]: node degree, clustering coefficient, eigenvector centrality and betweenness centrality. The results with the desired metrics can be exported to a text file. Figure 1 shows a integrate scheme of the proposal (A) and the Java-based interface (B).

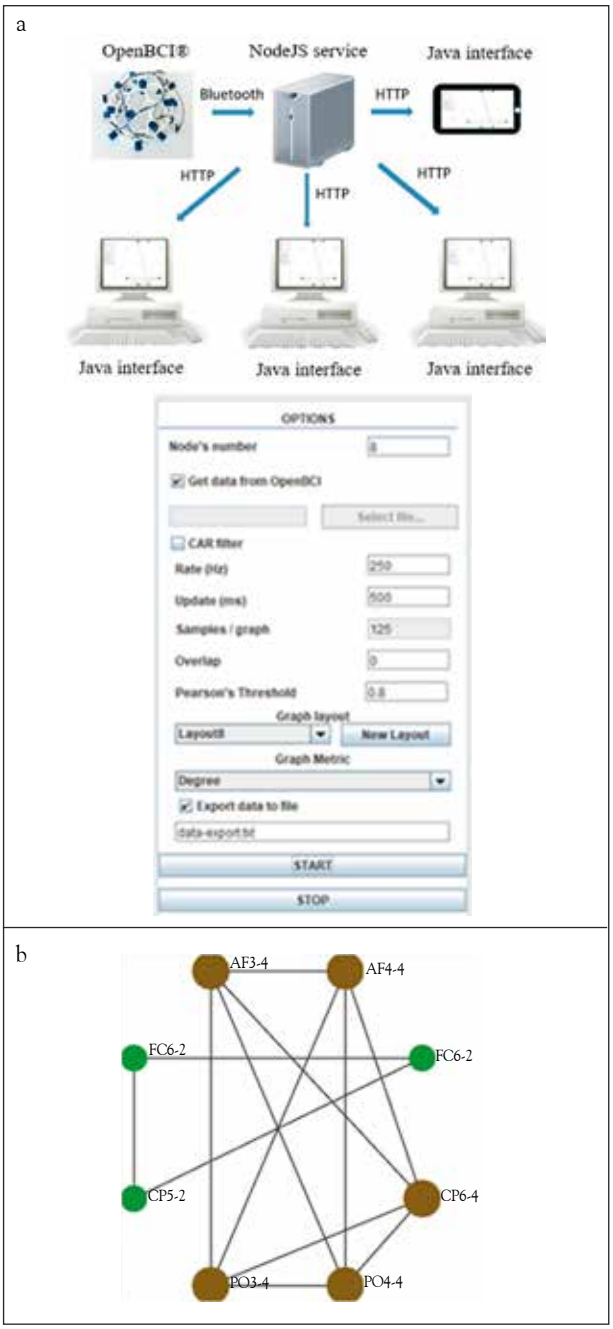

Figure 1. (a) The integration between components. The Open BCI hardware, NodeJS-based service and devices with the Java-based interface; b) Java-based interface.

Relevance: This work presents a service to consume data from the low cost OpenBCI EEG acquisition hardware and a friendly graphical interface for functional connectivity analysis. The service will allows an easy integration between OpenBCI® hardware and other applications, providing a powerful framework for FC remote analysis in real-time.

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EPILEPSY AND EMPREGABILITY: A BIOPSYCHOSOCIAL ANALYSIS ABOUT THE IMPACT OF THE DIAGNOSIS TO THE INDIVIDUAL IN THE WORK CONTEXT

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Introduction: Through a biopsychosocial analysis of the patient with epilepsy, a deterioration in the quality of life and the impact of the diagnosis on work activities are detected [11]. The relation between epilepsy and work has been studied in Brazil over eighteen years, considering work a determining factor in the individual's quality of life [2]. To the person with epilepsy, however, the work context is surrounded by situations that difficult the insertion or permanency of this individual in a formal job and previous studies [8];[6], point to factors that influence in the empregability process of the person with epilepsy, through a literature review this study has analyzed the principal factors that can affect the relation between epilepsy and work and consequently difficults the insertion or maintenance of the person with epilepsy in the job market. Materials and Methods: The construction of this work was based on a literature review about the theme, including previous works that have considered one or more biopsychosocial event in the individual with epilepsy's life. To this study 11 works were included. Results: The results found in the 5 emerged categories were divided by topics considering the biopsychosocial factors that were analyzed to this work: the diagnosis, adverse effects of medication, uncontrolled seizures, psychosocial aspects and work and quality of life. Discussion: According to some authors [3];[6];[13], the initial diagnosis is filled with doubts about the seizures, the treatment and fear of people's reaction; revealing the diagnosis of epilepsy increases the anxiety. Adverse effects of medication: some medicine such as the Fenobarbital can affect the cognitive functions of the individual such as other medication that can harm short term memories and attention [1]. Uncontrolled seizures: Previous studies [7];[9];[11] point that being refractory of the medical treatment can cause feelings of shame, dependency and guilty. Psychosocial aspects: patients with epilepsy tend to live psychosocial problems [5] in similar areas such as emotional and interpersonal adjustment [4];[12]. Work and quality of life: As reported by [4] work is considered determining factor to the individual's quality of life , considering a large number of people with epilepsy unemployed is possible to detect lower levels of quality of life in this group of people [8]. Conclusion: About 3 million people in Brazil are diagnosed with epilepsy and 50% of them are unemployed, so 1,5 million Brazilians aren't generate charges for the State. There's a need of dealing with the disease as a public health issue and in Brazil there is no public policy to guarantee the work rights of the person with epilepsy, what leads to the importance of studying the relation between epilepsy and work in order to create an instrument that could be used as a basis to the construction of public politics to guarantee the job rights of the person with epilepsy.

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SUB-CONVULSIVE DOSES OF PENTYLENETETRAZOL MODIFY THE ZEBRAFISH LARVAE BEHAVIOR

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Introduction: Zebrafish (*Danio rerio*) is recognized as a model of acute seizures (1). However, there is no indication in the literature whether zebrafish can become chronically epileptic or about the impact of sub-convulsive doses in the zebrafish brain. A chronical seizure model in zebrafish offers new opportunities of investigation given its advantages for cellular, molecular and drug screening studies, thus contributing to improve the currently knowledge about the mechanisms of epileptogenesis. Previous study of our group showed that the adult zebrafish did not present spontaneous seizures

or behavior modifications after sub-convulsive doses of pentylenetetrazole (PTZ). In the present study, our main aim was to investigate the impact of sub-convulsive doses of PTZ on the zebrafish immature brain. **Materials and Methods:** This study was approved by the Ethics Committee on Animal Use (CEUA) of UNICAMP #4426-1, #4660-1. Wild-type zebrafish larvae at 5 days post-fertilization (dpf) were separated in Control Group (CTL) and Pentylenetetrazole Group (PTZ). Animals from PTZ group were exposed to sub-convulsive doses of PTZ at 7.5 mM for 2 minutes over four weeks (once a day, Monday to Friday). Behavior and molecular profiles were assessed immediately after the first exposure to PTZ (5 dpf) and later at 9, 16 and 23 dpf (n = 25, each group). Animals from CTL were handled in the same way but in PTZ-free water. Behavior analysis were recorded by the Danio Vision equipment and analyzed with EthoVision software for quantification of velocity and distance traveled. To investigate the sensitization of the immature brain during the PTZ-sub-convulsive treatment, we exposed the zebrafish to convulsive doses of PTZ at 15mM and evaluated latency and number of seizures, which were examined by a double-blind experiment. Statistical comparisons were carried out by unpaired t-test and one-way ANOVA with Tukey's correction (GraphPad Prism v 7.0). **Results:** Our results showed that sub-convulsive doses of PTZ significantly modified the behavior of animals, which presented an increased swimming activity; Distance (mm) 5dpf PTZ vs 5dpf CTL (191.975 ± 13.72 vs 87.519 ± 15.47, p = 0.0001); 9dpf PTZ vs 9dpf CTL (174.381 ± 19.33 vs 56.595 ± 20.66, p = 0.0023); 16dpf PTZ vs 16dpf CTL (136.604 ± 23.84 vs 21.938 ± 6.113, p = 0.0004); Velocity (mm/s) 5dpf PTZ vs 5dpf CTL (1,602 ± 0.1145 vs 0.730 ± 0.1291, p = 0.0001); 9dpf PTZ vs 9dpf CTL (1.455 ± 0.1613 vs 0.472 ± 0.1725, p = 0.0023); 16dpf PTZ vs 16dpf CTL (1.140 ± 0.199 vs 0.183 ± 0.0519, p = 0.0004). The sub-convulsive PTZ-treatment was able to increase the brains response in comparison to CTL when both groups were exposed to the 15mM PTZ treatment. The PTZ group present a greater number of seizures: 5dpf PTZ vs 5dpf CTL (3,167 ± 0,4156 vs 3 ± 0,3947, p = 0.7725); 9dpf PTZ vs 9dpf CTL (3,167 ± 0,465 vs 1,875 ± 0,2112, p = 0.0149); 16dpf PTZ vs 16dpf CTL (5,292 ± 0,4564 vs 3 ± 0,2331, p < 0.0001). No difference was found in latency for both groups. **Discussion:** The PTZ sub-convulsive treatment during the zebrafish development was able to increase its swimming activity compared to the CTL group in all ages investigated. Besides, the sub-convulsive doses of PTZ become the zebrafish brain more sensitive to the PTZ 15mM. **Conclusion:** Although the zebrafish had become more responsive to the PTZ-evoked seizure, no indication was obtained that the impact was not sufficient to make it chronically epileptic. These results, added to our previous results in adults, may indicate that zebrafish can be resistant to become epileptic, shedding new lights into the epilepsy research.

Support: FAPESP 2014/15640-8, CEPID-BRAINN 2013/07559-3 and CAPES.

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TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) REDUCES BLOOD PRESSURE AND IMPROVES AUTONOMIC MODULATION IN RESISTANT HYPERTENSIVE PATIENTS: A RANDOMIZED CLINICAL TRIAL.

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Introduction: The pathophysiology of resistant hypertension (RH) is multifactorial, with sympathetic hyperactivity, being considered a major cause of treatment refractoriness. Invasive therapies have been developed for the treatment of RH, however, sympathetic hyperactivity still remains a challenge for the control of blood pressure (BP) levels. The possibility of using brain stimulation techniques, such as non-invasive transcranialdirect current stimulation (tDCS) in the cerebral cortex in the RH may be promising, but still poorly studied. Thus, the aim was to evaluate the effects of a tDCS or SHAM session (20 min) on hemodynamic and autonomic modulation of RH and non-RH (hypertension stage 1 and 2) patients. **Materials and Methods:** Patients RH (n = 14) and non-RH (n = 13) were randomly assigned to the SHAM and tDCS sessions. Hemodynamic Finometer®; the amplification index (AIx) by aplanation tonometry; and the autonomic modulation (Fast Fourrier Transform) were evaluated before, during stimulation with tDCS or SHAM, immediately after (30 minutes) and during the 24 hours after the sessions (only ambulatory BP monitoring, ABPM). **Results:** Hemodynamic variables of the non-RH patients were not acutely altered, except for the decrease in peripheral vascular resistance (PVR) (Δ= -1696.51±204.65 dyn.s/cm^5). In addition, in the same group, a decrease in the augmentation index was observed (AIx, Δ= -6.7±3.01%). Sympathetic modulation was reduced (LF band = -61.47%) an decrease vagal modulation (HF band= +38.09%) in non-RH patients after tDCS. Such acute changes led to reductions in BP levels assessed by ABPM. Thus RH patients, systolic BP (Δ= -23±7mmHg) and diastolic (Δ= -20±11mmHg), as well as cardiac output (Δ= -1.62±0.84L/min), PVR (Δ= -3356±1522 dyn.s/cm^5), Central systolic BP and AIx were reduced shortly after tDCS. As possible mechanisms of this BP regulation in the RH group, was observed a reduction in sympathetic cardiac modulation (LF band -68.81%) and vascular sympathetic modulation (LF band of SBP = -50.09%), as well as an expressive increase in vagal modulation (HF band = 97.33%) and spontaneous baroreflex (LF alpha = 39.95%). Such acute changes led to reductions in BP levels assessed by ABPM. **Discussion:** This study aimed to evaluate the use of tDCS in an acute session in order to reduce BP levels in individuals with RH. Thus, previous studies investigating the effects of tDCS on improving the state of psychic depression and on the performance of athletes demonstrated a reduction in cortical sympathetic modulation after tDCS, decrease pressure levels and increased vagal modulation, as well as in normotensive individuals. Thus, these findings support the present investigation of decrease arterial pressure levels after the ABPM, such as responses were associated with changes in the central control mechanism, which was observed by the attenuation of the sympathetic hyperactivity, as well as the improvement of the sympatho-vagal balance in the RH group. **Conclusion:** The data suggests that tDCS was able to promote expressive reductions of BP in RHpatients, possibly caused by the reduction of sympathetic modulation and increased vagal modulation, promoting reductions in PVR and cardiac output in these subjects.

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VOXEL-BASED MORPHOMETRY AND SURFACE-BASED MORPHOMETRY IN UNILATERAL, BILATERAL AND NEGATIVE TEMPORAL LOBE EPILEPSY

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Introduction: Temporal lobe epilepsy (TLE) is the most common focal epilepsy in adults. Patients with TLE may present not only refractory seizures but also different levels of cognitive impairment and psychiatric disorders. These outcomes seem to be influenced by etiology and lesion side. In this study, we aim to identify abnormalities of brain surface and grey matter atrophy in patients with TLE and unilateral or bilateral hippocampus sclerosis (HS) or negative MRI using surface-based morphometry (SBM) [1,2] and voxel-based morphometry (VBM) [3]. **Materials and Methods:** we acquired T1-weighted MRI images from 142 patients and 167 control subjects using a 3T Philips Achieva scanner. Patients were separated into four groups according to presence and side of structure abnormalities in visual analyses (37 left (LTLE), 34 right (RTLE), 24 bilateral TLE (BIL-TLE) and 47 negative (NEG-TLE)). Patients and controls were paired for sex (p=0.85) and age (p=0.1). We run SBM and VBM analyses using the CAT12 toolbox/SPM12 (http://www.neuro.uni-jena.de/cat/). The images underwent normalization, segmention and smoothing. Afterwards, we extracted cortical thickness, gyrification index, cortical complexity and sulcal depth parameters through SBM analyses and volumetric grey matter maps through VBM. Group comparisons were performed with separated ANOVA's for each parameter, using sex and age as covariates (p<0.05, with Bonferroni correction). **Results:** GM alterations were observed in the four groups mainly in the bilateral and LTLE. While volumetric GM atrophy clearly characterized each of the 4 groups, the analyses of surface parameters (thickness, gyrification, cortical complexity and sulcal depth) revealed scattered clusters (with increase or reduction), compared to controls. No significant GM alterations were identified in the NEG-group. On the contrary, BIL-group presented bilateral limbic GM atrophy, associated

with reduced cortical complexity and sulcal depth in the temporal lobes. LTLE group showed ipsilateral limbic and cerebellar GM atrophy, associated with reduced thickness in some areas besides increased cortical complexity and sulcal depth in other regions. RTLE presented ipsilateral limbic GM atrophy, with fewer alterations in cortical thickness and reduced gyrification of the ipsilateral insula. **Discussion:** as expected, VBM showed unilateral or bilateral GM atrophy in the mesial temporal regions according to lesion side and no atrophy in NEG-TLE. Meanwhile, SBM presented a diversified complex of abnormalities in which each patient group revealed its own pattern of significant findings. Among the four groups, BIL-TLE and LTLE seemed to present more severe abnormalities while NEG-TLE showed lesser areas of alterations. This difference may be related to etiology and disease severity. **Conclusion:** a comprehensive analysis of GM reinforces that the negative impact of hippocampal sclerosis extends beyond the temporal lobe, mainly in those with bilateral atrophy. While the NEG-group presented fewer alterations, LTLE and BIL-group were severely affected in different aspects of surface complexity.

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CASE REPORT: MANDALAS OF EMOTIONS TO IMPROVE COPING FOR A PATIENT WITH EPILEPSY AND CAREGIVER

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Introduction: The Mandalas of Emotions are based on theoretical precepts of TCM such as the five colors (green, red, yellow, white and black) and five emotions with their negative and positive aspects (anxiety/understanding, agitation/compassion, concern/gratitude, sadness/joy, fear/courage) [1]. Through the approach of each of these emotions and represented by the colors of mandalas, the purpose of this study is to enable reflection and work the emotions of people with epilepsy and their families, as part of a PhD project. **Materials and Methods:** Recruitment took place at the Neurology Outpatient Clinic of a teaching hospital, with the approval of the Ethics Committee (64276116.4.0000.5404), upon request of the telephone contact of people with epilepsy and relatives. The six biweekly meetings from 10:30 a.m. to 12:00 p.m. between August and October 2017 enabled each of the five mandalas and their associated emotions to work. Participants received a notebook explaining the method, colored cards to form the mandalas and pages for the daily record of the application of the method. The technique was applied by two nurses and a psychology student, with the distance support of the doctor who created the Mandalas of Emotions technique. At each encounter, one of the five emotions and their polarities (eg, anxiety and understanding) were explained. The participants were asked to close their eyes and, for 8 minutes, reflect on the questions: "(i) Have you felt this (the emotion)? (ii) How often? (iii) Do you remember any situation? (iv) How did you react? (v) Do you think you could have reacted differently? In what way?". After this period, the participants shared about their reflection and new perspectives on the emotions. **Results:** Of the 30 people invited, twelve confirmed their presence, four attended and two people concluded the six sessions, one person with epilepsy and his mother. The mandalas aroused emotions related to periods of great clinical, family and personal instability: the postoperative period of the removal of a tumor in the brain, which triggered epilepsy; to the period of a month in which the patient, then pregnant, was in coma after falling due to the epileptic crisis, causing the loss of the baby; but also related to the separation of the husband and the return to the house of his mother. The mother, in turn, reported several emotions due to her daughter's clinical condition. At each session, participants also demonstrated the progressive development of strategies to deal with emotions, in order to allow a new vision and better coping. **Discussion:** The sessions and the registration in the notebook, mediated by the mandalas, allowed the reflection on traumatic situations experienced by the patient with epilepsy and his relative, in order to make possible the awareness about the emotions. **Conclusion:** Such an exercise gave a detachment between emotion and individual, greater self-knowledge and empowerment over emotions, and better mastery over its effect on decision-making and interpersonal relationships.

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SEGMENTING ISCHEMIC STROKE LESION ON PERFUSION DATA USING DEEP LEARNING

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Introduction: Ischemic stroke lesion is the consequence of oxygen and nutrients lacking in the brain tissue due to an obstruction in the blood flow. The definition of the permanent ischemic stroke lesion region in early stages is important as it can help doctors to choose the best treatment for each specific case [1]. However, this definition is challenging since current imaging techniques cannot show contrast on the future lesion extent. On the other hand, we have tools such as Deep Learning algorithms that are capable, given the correct circumstances, of evidencing implicit information within the data. This work aims to investigate if it is possible to train a Convolutional Neural Network to predict the extension of a permanent ischemic stroke lesion from perfusion images. **Materials and Methods:** The dataset from ISLES Challenge [2] is composed of raw perfusion images (PWI), Perfusion Maps (CBV, CBF, MTT, TTP, TMAX), and ADC maps from 63 patients. It comprises also all lesions segmentations masks (ground-truth). The images were acquired during the ischemic stroke acute stage (within 8 hours of the stroke) and the ground-truth was manually drawn on T2 or FLAIR after the stabilization of the stroke lesion. We processed the dataset to resize the voxels (2.5x2.5x6 mm) and to patch all images to ensure standardization and data balancing. We then have tried two Convolutional Neural Networks (CNN) architectures, V-Net [3] and U-Net [4], on perfusion MRI data. Both architectures were tested in several different combinations (varying depth, number of channels, data combinations, voxel interpolation sizes, and 2D and 3D versions) in order to achieve the best performance. **Results:** As a quantitative analysis, the DICE coefficient was evaluated on the validation subset for different CNN architectures and image combinations (Table 1). The best achieved DICE was 0,560 using a 2D U-Net and Perfusion maps as input. A qualitative analysis was also performed, comparing the ground-truth and the predicted segmentation shape on sample slices (Fig.1). The agreement of predict extent versus the manual annotation varied a lot, among slices and subjects. **Discussion:** Both Deep Learning architectures, V-Net and U-Net, presented good performances in this task when using only perfusion maps. State-of-the-art methods present an average DICE around 0,58 [5]. Furthermore, the 2D versions of the CNNs performed better than the 3D version, probably because 3D versions requires a larger dataset, and the U-Net always performed better than the V-Net in this particular problem. **Conclusion:** Even considering the training with a short database, the CNNs were able to find the extension of most lesions, mistaken only for very small lesions and on the lesions borders. This results show that these CNNs are suitable for Ischemic Stroke Lesion Segmentation on perfusion MRI.

Table 1. Comparison of architecture and data combinations: average DICE value for V-Net and U-Net on PWI and Perfusion Maps.

Data	CNN	DICE	CNN	DICE
PWI	U-NET 3D	0.357	V-NET 3D	0.203
P Maps	U-NET 3D	0.518	V-NET 3D	0.479
PWI	U-NET 2D	0.429	-	-
P Maps	U-NET 2D	0.560	-	-

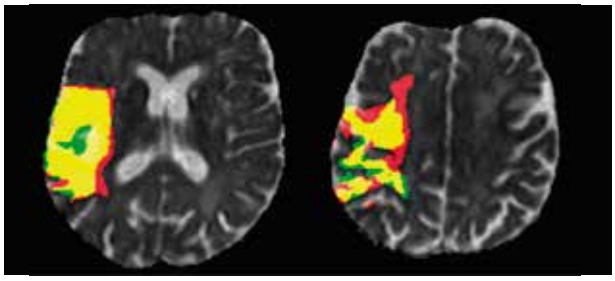

Figure 1. Ischemic stroke lesion segmentation example over ADC map in two different slices of the same subject. Correct prediction in yellow, false negatives in green, and false positives in red.

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DEBIASING THE PREDICTION OF GENERAL INTELLIGENCE: CONFOUNDERS REMOVAL THROUGH ADVERSARIAL LEARNING

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Introduction: Machine learning allows the prediction of general intelligence, or g, from neuroimaging. While it might perform well, it is often biased due to exogenous factors, such as height, weight, age and gender, which are moderately correlated to intelligence, and the disentangling of such factors often benefits the neuroscientific understanding of the neural bases of intelligence. We present an approach based on adversarial network learning [1] as an alternative to the linear regression-based removal of confounders. **Materials and Methods:** Data were provided [in part] by the Human Connectome Project (HCP), WU-Minn Consortium (1U54MH091657); and by the McDonnell Center for Systems Neuroscience at WUSTL [2]. We obtained g and other factor estimates with R package "psych" as described in [3] from 1159 subjects from the HCP 1200 data release. We obtained regional Freesurfer surface area estimates of 68 cortical regions obtained from 812 subjects using the "recon2" reconstruction method. 786 subjects had complete imaging, intelligence and demographic data, and were eligible for further analyses. Our network consists of three fully-connected subnetworks: a coder (C), a predictor (P) and an adversary (A) branch in parallel. Inputs to P and A network are the outputs of the C network. We built and trained our network in Flux [4], written in Julia [5]. C consists of a hidden layer receiving regional area estimates as inputs while both P and A consist of a hidden layer and an ouput layer. We used ELU activation thoroughly, except for the output layers. We optimize C and P networks to predict intelligence factors and to not predict confounder factors, using the loss of A rectified for R-squared below zero, weighted by a constant , which we estimated empirically during testing. We performed standardization of inputs in-place during training, avoiding leakage. We ran epochs to optimize A in between epochs to optimize C and P networks, for a total of 20 epochs. The objective is to obtain the best prediction of intelligence possible while diluting away any information about confounders, e.g. brain volume or handedness. P predicts g, crystallized ability, processing speed, visuospatial ability and memory factors as described in [3], as these are positively correlated to g and help stabilize the model. We performed 10-fold cross-validation repeated 100 times. For each training run, we used a holdout set composed of 20% of the training data to determine early stopping. Due to kinship in the HCP data, we decided to separate folds based on family IDs, and not subjects. **Results:** We obtained a R^2=0.066 for the prediction of g, while the best prediction for confounders averaged R^2= -0.46, regarding brain volume, which is intrinsically linked to brain surface area. Across repetitions, the R^2 for the confounders did not ever reach a positive value. In another experiment where we did not control for confounders (effectively setting), we reached a R^2=0.089, while the optimal performance for A reached R^2=0.670, for the prediction of brain volume. **Discussion:** We successfully removed the effects of confounder from regional surface area estimates, including total brain volume, as we attested comparing the R^2 for A when controlling for and when affording confounders. We reached a relatively low R^2 in comparison to the literature, though we cannot be sure other results are not biased through the ineffective removal of confounds. Our method is trained end-to-end and does not restrict the hypotheses on the functional relationship between confounders and variables of interest. **Conclusion:** We present a method for the removal of confounds in predictive tasks, with an exemplary application to the prediction of g from regional surface area estimates. We attest that regional area plays a role, albeit small, in explaining unique g variance, in respect to confounding phenotypes. This method will benefit projects employing data from different scanners, acquisition sequences, populations and many other confounders.

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EFFECTS OF SILDENAFIL (VIAGRA®, PFIZER) ON THE INFLAMMATORY PROFILE IN PARKINSON'S DISEASE

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Introduction: This study analyzes the inflammatory profile (systemic and in the brain) in a murine model of Parkinson's disease (PD) chronically treated with the phosphodiesterase 5 Inhibitor (PDE5-I), sildenafil (Viagra ®, Pfizer), which promotes cGMP accumulation. PDE5-Is have been shown to modulate the neuroinflammation, and their use in the treatment of neurodegenerative diseases has been proposed [1, 2]. However, although there is a vast literature on multiple sclerosis, little has been demonstrated about PDE5-Is effects on PD. **Materials and Methods:** The Parkinsonian model was reproduced in C57B1/6 mice treated with Rotenone (ROT; 1 mg/kg, s.c.) for 14 days; during the first 5 days, mice also received Lipopolysaccharide (LPS; 0.2 mg/kg, i.p.). Animals were divided into five groups (n = 5 per group): Disease - no treatment; Preventive - treated with sildenafil (Viagra®, 10 mg/kg, s.c.) for 21 days, starting 7 days before the first ROT injection; Therapeutic - received sildenafil for 7 days, starting 7 days after the first ROT injection; one group (sildenafil control) did not received ROT/LPS (no disease), but was treated with sildenafil for 21 days; and one last group (Naïve) did not receive ROT or any treatment. Animals were clinically evaluated by motor/behavior record through Rotarod and open field tests; after euthanasia, brains were dissected for immunofluorescence (Iba1 and GFAP – measured by integrated optical density); plasma was collected to detect IL-1β and IL-10 cytokines by ELISA; and T-cells were isolated from the spleen for flow cytometry. The experiments were done in triplicate. All data were statistically compared between the groups using ANOVA/Bonferroni. **Results:** Rotarod showed that ROT/LPS induced significant motor impairment, compared to Naïve. Both Preventive and Therapeutic sildenafil groups showed no difference in motor capacity. ROT/LPS induced an increase in IL-1β levels, while did not change IL-10, compared to Naïve. Preventive (but not Therapeutic) sildenafil significantly decreased IL-1β and increased IL-10, compared to Naïve and Disease groups. T-cell analysis showed that ROT/LPS did not alter the percentage of Th1, but reduced Treg cells, compared to Naïve. Both Preventive and Therapeutic sildenafil significantly reduced Th1; and Preventive sildenafil increased Treg, compared to the Disease group. Immunofluorescence of brain slices showed that Preventive and Therapeutic sildenafil increased GFAP and Iba-1, compared to the Disease group. No differences were detected between Sildenafil and Naïve control groups. **Discussion:** Sildenafil induced a clinical improvement in this model, associated with a modulation of inflammatory/immunological systemic parameters to an anti-inflammatory profile. However, sildenafil treatment aggravated neuroinflammation (increased Iba1 and GFAP intensity in the brain). Although some studies suggest that the accumulation of cGMP induced by PDE5-I is a promising therapeutic strategy for PD [3], it is important to be cautious. **Conclusion:** The study contributed to a better understanding of the sildenafil effects on a murine PD model. Experiments are underway to respond whether the aggravation of neuroinflammation induced by sildenafil can be reproduced in other PD-models and whether there may be any clinically relevant correlation.

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NANOPARTICLES TO NEURONAL CELLS GROWTH ORIENTATION

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Introduction: This experimental method consists of a new approach to demonstrate how static magnetic field, SMF, and magnetic nanoparticles, MNPs, attached to neuronal cells can be exploited to manipulate neuronal cells. The static magnetic field is applied to stimulate targeted cells in the field's direction for directing their orientational growth. Degenerative neural diseases after accidents are important matters in neuroscience field. Physical stimulus for neuronal growth and development can be achieved with tensile force [1-3]. Particles under a magnetic field force can provide physical guidance for neuronal regeneration [4,5]. **Materials and Methods:** The nanoparticles functionalization was made with less expensive biomaterial, than genomic DNA. The particles were homemade, they are biocompatible. A biocompatible test of the MNPs was developed to investigate the particles toxicology. The magnetic field was applied with different magnets, the higher SMF was from neodymium magnets, which the value was 26 Gauss. This methodology is less costly than others found in the

literature. Influence of particles' concentration and field`s intensity was analyzed to determine the optimum values for higher oriented growth, processing the images data obtained using electronic microscopy. The different solutions were prepared to 9 Petri dishes to each experiment. The concentration of MNPs varied from 0.01 mg/ml to 0.9 mg/ml. The time intervals of observation were 24h, 48h, 72h, 96h, 120h, 144h, 168h, 192h, 264h images were taken from all time intervals. For each observation time, 2 parameters were varied: concentration of the MNPs in the media and the intensity of the applied MF. The cells behavior was observed and analyzed using optical microscope. The data were processed and analysed with data mining techniques, with the software Damicore, a set of algorithms of knowledge discovery in data bases, KDD. The Fig. 1 ilustrates the diagram of experimental and methods procedures.

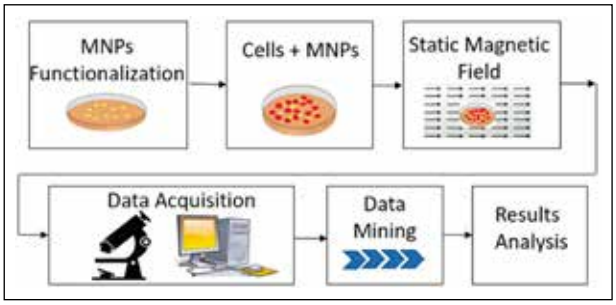

Figure 1. The functional diagram of the experimental procedure.

Results: In this work, it was observed that concentrations above 0.9 mg/ml could be toxic to the cells. Such high concentrations of MNPs can kill the cells approximately in 24 hours, which confirms previous works observations. From the experiments it was observed that the group of cells which obtained a greater growth in the radial direction was the group with 0.01 mg / ml of concentration of MNPs, which is the medium value of concentration. The applied magnetic field, for these groups, with a greater growth, had value of field of 26 Gauss. **Discussion:** Higher directed growth of neuronal cells with MNPs was observed from qualitative and quantitative evaluation of images data, obtained in the experiments. Consistent and reliable results were achieved using data mining technique. This result can be explained by the fact that there is an optimum concentration of nanoparticles, which, when encapsulated and functionalized, are even more likely to grow towards the magnetic field direction, since the cells are linked to the particles. **Conclusion:** The results recorded through images that were processed and analyzed. The present work will allow cells growth to form tissues in faster and oriented way, regenerate nerve terminals to avoid amputation, spinal column repair, skin, organs tissue, therapies for recovery of neurodegenerative diseases.

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HYPOTHALAMUS SEGMENTATION FROM MRI USING CONVOLUTIONAL NEURAL NETWORKS

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Introduction: Hypothalamus is a small structure of the brain with important role in sleep, appetite, body temperature regulation and emotion. However, hypothalamic morphological landmarks are not always clear and manual segmentation can become variable, leading to inconsistent data on literature[1]. In this work we investigate the possibility to train a convolutional neural network (CNN) to segment the hypothalamus with minimal user interaction. To the best of our knowledge, this is the first work using CNN for hypothalamus segmentation. **Materials and Methods:** We used 177 MR T1-weighted images (dimensions of 240x240x180) acquired from HC at UNICAMP from healthy subjects, splitting the dataset into 80% for training/validation and 20% for testing. Subjects used for training/validation were not used for testing. The proposed method is composed by 5 steps (Fig.1): (1) Dataset Organization: Hypothalamus is a small region of the brain. In order to prevent data unbalance on training, we cropped these slices into 60x60 pixels around the hypothalamus, using a user provided seed. (2) Normalization: Image intensity standardization (between 0 and 1) and normalization to zero mean and unit variance. (3) Data augmentation: By translation and rotation. (4) U-net [2] classification (5) Threshold binarization: Classification returns a probability image, by thresholding it we have the final segmentation. The method was applied on all views of brain, i.e., we trained three different models (axial, sagittal and coronal). As ground truth, we used manual segmentation of hypothalamus. **Results:** Our final test achieved dice coefficient of 0.787, 0.781 and 0.747, for axial, sagittal and coronal models, respectively (Table 1) when compared with the specialists manual segmentation.

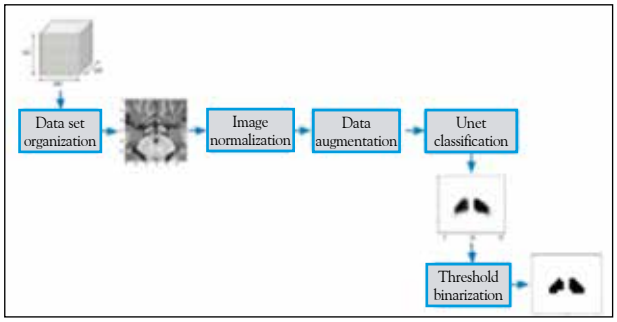

Figure 1. Proposed method fluxogram.

Table 1. Final results dor each model (axial, sagittal and coronal).

	Axial	Sagittal	Coronal
Dice	0.787	0.781	0.747
Precision	0.785	0.804	0.825
Recall	0.809	0.778	0.703

Discussion: Currently on the literature, most of hypothalamus segmentation is done via atlas or manually. On [3], it was reported an intraclass correlation (ICC) of 0.78 and 0.82 between three raters. To the best of our knowledge, this is the first work to perform a semi-automatic segmentation, decreasing the variation risks and time of manual segmentation. **Conclusion:** We presented an automatic method for hypothalamus segmentation using convolutional neural networks and minimal user input. The proposed method obtained good results, compatible with ICC on manual segmentations. For future work, we plan to improve the method results creating a consensus voting between all three networks and transform it into a fully automatic method, developing an algorithm to find the 60x60 patches automatically.

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BILATERAL AND LEFT HIPPOCAMPAL ATROPHY SEVERELY DISRUPT FUNCTIONAL CONNECTIVITY IN TEMPORAL LOBE EPILEPSY

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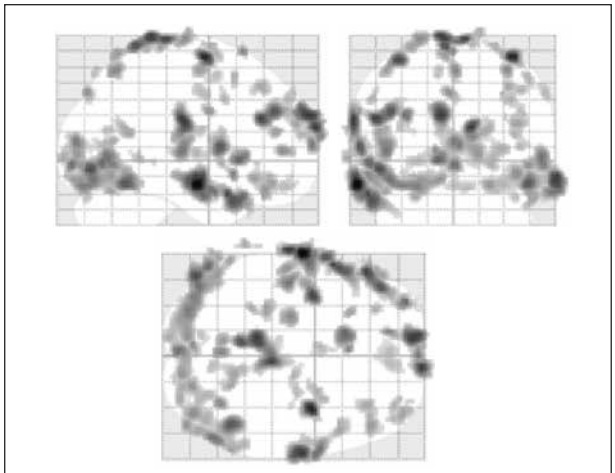
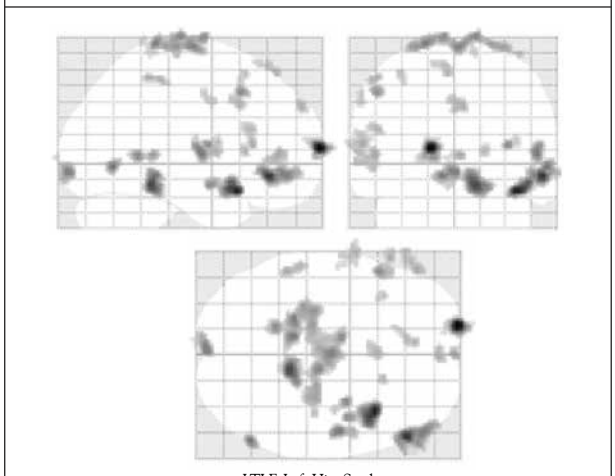
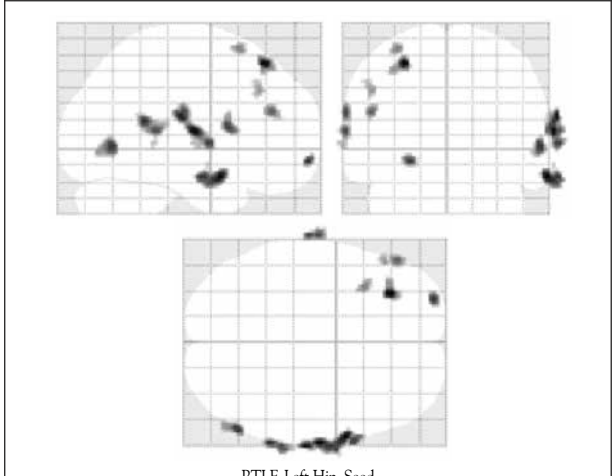
Introduction: Although functional connectivity (FC) studies in temporal lobe epilepsy (TLE) have revealed alterations in brain resting state (RS) networks (mainly in the Default Mode Network (DMN)), fewer studies have investigated the impact of unilateral and bilateral hippocampal sclerosis (HS) on FC [1]. Our objective was to compare patterns of connectivity dysfunction in patients without HS (NEG-TLE), right (RTLE) and left HS (LTLE), and bilateral HS (BIL-TLE). **Materials and Methods:** Resting-state fMRI (and 3D T1weighted) were acquired on 3T-PHILIPS from 145 patients (80 women, median age 52) and 153 controls (82 women, median age 52), balanced for age (p=0.19) and gender (p=0.44). Patients were separated in 45 LTLE, 43 RTLE, 22 BIL-TLE, 35 NEG-TLE. We used a seed-based approach running on UF2C/SPM12/MATLAB2017 (https://www.lniunicamp.com/uf2c) (https://www.fil.ion.ucl.ac.uk/spm/) to extract FC maps from DMN (0,-51,21), right hippocampus (29,-



BIL-TLE-Left Hip. Seed



LTLE-Left Hip. Seed



RTLE-Left Hip. Seed

Figure 1.

11,-19) and left hippocampus (-29,-11,-19) based on BOLD time-series [2]. Statistical comparisons of maps between patients and controls were performed with SPM12 (minimum T-statistic of 3). Clinical data were analyzed with SPSS 20. **Results:** While NEG-TLE group presented few areas of abnormal FC, there was a widespread pattern of altered FC, mainly on BIL-TLE and LTLE groups (mostly on connectivity derived from left hippocampus and right hippocampus). RTLE group presented alterations of DMN maps and abnormal FC associated with seed in the right hippocampus. On the contrary, LTLE group showed extensive dysfunction for seeds in ipsilateral and contralateral hippocampi, and restricted alteration of DMN. **Discussion:** Bilateral and left hippocampus sclerosis have a more widespread pattern of alterations. This is probably due, first, to bilateral lesion condition of BIL-TLE and to dominant pattern of left brain hemisphere. Following this analysis, patients without HS, as expected, seem to present preserved FC. Finally, left and right HS have an ipsilateral worse network pattern, probably secondary to the disruption caused by this major lesion. **Conclusion:** As BIL-TLE and LTLE groups present a similar pattern with severe damage, compromising not only the ipsilateral but also the contralateral networks, we hypothesize that left HS associates with dysfunction of FC. NEG-TLE showed limited areas of dysfunction and RTLE a more ipsilateral pattern of abnormalities (associated with seed in the ipsilateral hippocampus).

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WHAT ARE THE DIFFERENCES AND MEANINGS OF THE DESIGNATION OF CHRONIC DISEASES?

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Introduction: Social prejudice is a set of negative beliefs and attitudes that are directly associated with a particular characteristic of the individual, and may awaken attitudes towards some visible or non-visible characteristics [1], being related to social categorization [2]. Fear and anguish caused by prejudice may be the most important factors that cause psychological distress in the individual [3]. This study will be conducted through the constructivist approach called the Grounded Theory, in which "the relevant data is detailed, focused and complete. This strategy reveals the opinions, feelings, intentions and actions of the participants, as well as the contexts and structures of their lives" [4]. **Materials and Methods:** The quanti-qualitative methodology will include the application of a questionnaire to collect sociodemographic data and the preference for each diseases: Epilepsy, Dementia, Schizophrenia, Depression, HIV/AIDS, Diabetes, Hypertension and Leprosy; whether using the adjective (eg, epileptic) or the term "person with" (eg, person with epilepsy). To elucidate the reason for this choice, we will use the Grounded Theory. The steps for the construction of Grounded Theory are important for the eligibility of this theory, divided into: definition of research purpose, data collection and complementary methods, open coding, focused coding, theoretical coding, saturation, memos, and Grounded Theory writing. **Relevance:** Engagement in social problems is little explored within the area of prejudice awakened by the negative social burden that certain terminologies can bring to the individual. Two major issues can be raised with this debate. The first is the social burden that brings the forms of these specific linguistic behaviors. And the second is the conception that the use of terminologies that have a negative social burden can lead to disease-related prejudice.

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TISSUE REACTION TO THE NEURAL PROBES IMPLANTED INTO THE RAT BRAIN: A TRANSCRIPTOME ANALYSIS

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Introduction: Brain probes are important tools for understanding the nervous system. They allow evaluating the electrical activity of single neurons and its relation with the subject behavior. Since neural probes need to be positioned within tens of micrometers of the neurons of interest, they are necessarily invasive devices. As it happens with any foreign material that is implanted into the body, the tissue reaction process starts with the attempt to clean up the site and eliminate the threat of the invader [1]. If the threat persists, a chronic inflammatory process ensues, with the attempt to shield the affected area from the surrounding tissue. This shielding, which in the brain consists of a capsule formed predominantly by astrocytes, gradually decreases the quality of the recorded neuronal signals [1,2]. This study evaluates the transcriptome of the tissue response to the neural probes designed and fabricated by the BRAINN research groups, comparing it with the

tissue response to other recording devices implanted into the brain. **Materials and Methods:** Stereotaxic surgery for implantation of recording neural probes was performed in Fischer 344 male rats. Rats received recording neural probes developed in Brainn projects, or commercial silicon probes, or stainless steel micro wires. Recording probes were implanted into the dentate gyrus of the hippocampus (AP -3.0; L ±2.0; V -3.5). After a period of 2 or 28 days, rats were euthanized and the brains were removed. Laser microdissection of the regions proximal to probe implantation was carried out and the material was subjected to transcriptome analysis by RNA-seq using Illumina HiSeq platform. Neural tissue was also analyzed with immunofluorescence labeling for markers for foreign body reaction astrocyte marker (GFAP) and microglia marker (CD68), and for neuronal marker (NeuN). All procedures were approved by the Ethics Committee for Animal Research at the Unicamp (protocol 4438-1). **Results:** Transcriptome analysis of the neural tissue 2 days after surgery showed 8000 differentially expressed genes among control and implanted groups. Between implanted groups, there are 798 differentially expressed genes in the tissue surrounding the BRAINN probe compared to the tissue surrounding the stainless steel micro wire electrode. Two days after surgery, the tissue surrounding the probes is disorganized and immunostaining for CD68 around the probe sites reveals reactive microglia. **Discussion:** Our data show that probes implanted into the brain lead to an acute reaction with drastic changes in gene expression. The differentially expressed genes are involved in different pathways mainly in those related to immune response. **Conclusion:** Our preliminary data show that probes implanted into the brain lead to an acute reaction with drastic changes in gene expression. Furthermore, different probe materials induced different tissue responses.

Financial support: Fapesp.

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CLINICAL EFFECTS OF PHYSIOTHERAPY PLUS VIRTUAL REHABILITATION PROGRAM ON CHRONIC ISCHEMIC STROKE

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Introduction: Post-stroke patients may present cognitive, psychological, social and motor impairments, with gait and upper limb deficiencies being the most frequent. More than 80% of patients have impaired upper limb function, and about 25% remain dependent for walking after the acute phase.[1] Virtual rehabilitation (VR) seems to be a tool with significant potential in neuroplasticity, optimizing the recovery process of some post-stroke patients.[2] This study aimed to analyze the effects of VR as an adjunctive tool to conventional physiotherapeutic treatment in post-stroke patients in chronic phase (> 6 months). **Materials and Methods:** 24 selected individuals were submitted to a clinical evaluation, resulting in a total sample of 14 patients (randomized in control group, with conventional physiotherapy (CPt), and experimental group, CPt plus VR). We used as motor variables: the Fugl-Meyer Assessment (FMA), Berg Balance Scale (BBS) and Timed Up and Go Test (TUG); and as a cognitive variable: Montreal Cognitive Assessment (MoCA). Subjects were evaluated before and after a 6-week treatment period (2 sessions/week). Resting state functional magnetic resonance imaging (rs-fMRI) (3T PHILIPS® Achieva, 3x3x3mm^3 voxel, gap, FOV = 240x240x117mm^3, TR / TE = 2000 / 30ms, flip angle = 90 °, 180 volumes) were also acquired before and after treatment, in order to evaluate possible connectivity differences in default mode network (DMN) intra-group, using UF^{2}C tool for SPM/Matlab and SPM12 (paired t-test)[3]. **Results:** To identify statistical relevance among the clinical variables from the comparison of intra-group means, we submitted the data to the t-student test for paired samples, (significant value when $p < 0.05$). Both groups demonstrated clinical improvements, but the experimental group presented relevant improvements in FMA ($p = 0.04$) and BBS ($p = 0.01$), with a large effect size (Cohen, 1988) in both variables (0.52 and 0.66, respectively). We also performed an analysis of the means obtained in the isolated FMA scores for upper limb and lower limb, observing that the evaluation of lower limb for the experimental group obtained more relevant results ($p = 0.02$; effect size = 0.76). No significant changes were observed in DMN analysis in rs-fMRI for both groups. **Discussion:** The clinical data observed in the FMA and BBS corroborate the results of previous similar studies: although individuals in conventional treatments obtain functional gains, the treatment using VR as an adjuvant tool may potentiate their recovery. In a previous study developed by our group, post-stroke patients with motor symptoms had decreased motor connectivity and a reduction in the number of functional networks.[4] The functioning of these networks and their impairments may help in understanding how physical recovery occurs in certain patients and not in others. **Conclusion:** In general, we verified that physiotherapy and VR are able to change clinical parameters for chronic stroke patients, although the use of VR protocol suggests optimization of functional recovery. The size of the sample (< 30 patients) is a limitation for the study, mainly for the complex analysis of rs-fMRI. Clinical improvements were perceptible in both groups, reaffirming the use of VR as a rehabilitation or physiotherapy tool and not as an isolated protocol.

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DEVELOPMENT OF A HYBRID WEARABLE GLOVE-LIKE ORTHOSIS FOR THE FOREARM USING TENDON-DRIVEN SYSTEM AND FUNCTIONAL ELECTRICAL STIMULATION (FES), TO HELP PEOPLE WITH DIFFICULTY TO MOVE THEIR HANDS – PARTIAL RESULTS.

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Introduction: This work is a preliminary result concerning the creation of a hybrid wearable glove-like orthosis for the forearm using tendon-driven system and functional electrical stimulation (FES). It is aimed to help people who had suffered from stroke or spinal cord injury (SCI), and present difficulties in hand movements. The final purpose is to devise an orthosis with the advantages of FES, a rehabilitative technology, and the advantages of an exoskeleton, an assistive technology. The project is still in progress, and therefore in what follows is presented the first stage of the project, the development of the glove orthosis with the tendon-driven system. **Materials and Methods:** To start the development of the glove-like orthosis for the forearm, it was decided to implement a scheme similar to [1]. After selected the materials, glove, Bowden cable system and cable, tendon actuator mechanism (developed by [3]), and motor (a Dynamixel motor), it was developed the glove-like orthosis setup, as represented in Fig. 1. The configuration is able to move a set of fingers composed of the index finger and middle finger, allowing flexion and extension movements. Furthermore, it allows adaptive grasping (the fingers can adapt to the objetc's surface). In order to assess the functioning and performance of the system assembled, it was used an armband capable of reading electromyography (EMG) signals (the Myo armband [2]), a program developed in the MatLab® environment, and a small size USB communication converter that enables to control and to operate the motor with the computer (U2D2) (as seen in Fig. 2).

Figure 1. First prototype of the glove-like orthosis for the forearm.

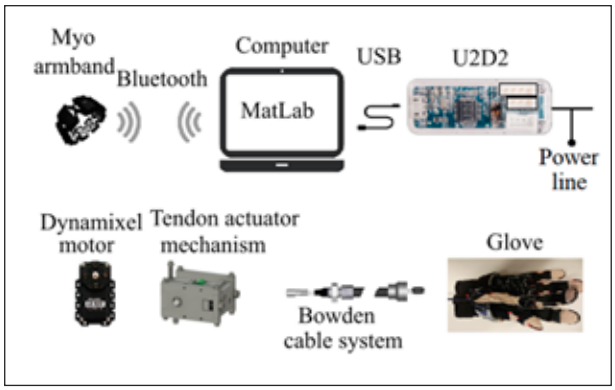

Figure 2. Block diagram of the system configuration for tests.

Results: The Myo armband placed on the forearm provided EMG signals employed to drive the motor responsible for winding and unwinding the cable that performs the flexion and extension movements of the hand. As the user sustains a contraction of flexion, or extension, the glove keeps closing, or opening, for as long as the user sustains the contractions. In the absence of user's contractions, the motor is stopped. The whole system performed as expected. **Discussion:** With the EMG signals provided by the Myo armband was possible to control the flexion and extension movements of the set of fingers. Moreover, using a single tendon actuator mechanism, is possible to execute both flexion and extension movements, and thus reduce the number of motors used in the project. **Conclusion:** With the first stage of the prototype achieved, the second step is to replicate the driven system to the thumb finger, and start implementing the hybrid control strategy with FES, which is ongoing.

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AUTONOMOUS MOVEMENT ASSISTANT TO WHEELCHAIR USERS BASED ON ARTIFICIAL NEURAL NETWORKS

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Introduction and Hypothesis: People with a physical disability represent 1.3% of Brazilian population, according to the National Health's Research [1]. Wheelchair users face huge challenges doing everyday tasks, such as crossing a corridor or avoiding an obstacle [2], and assistive technologies are developed to turn these activities easier. Assistive Robotics is the robotics' area that studies and develops methods and techniques aiming at the recovering of the abilities lost with the deficiency. Artificial intelligence techniques may be used to help in the user's welfare. **Objective:** This project focus on the development of an autonomous system able to assist a wheelchair's user in executing hard maneuvers. An artificial neural network (ANN) is responsible to command the autonomous movement sending the directional movement to the wheelchair, while a neural network based shared control sets its angular and linear velocity. **Methods:** To perform this autonomous movement, a mobile robot with physical dimensions of a real wheelchair will be simulated using the V-REP simulation framework [3], and an ultrasonic sensor array composed by eight frontal sonars and eight rear sonars will provide the environment data. The obstacles distances returned by the sonar array are arranged in a manner to activate or deactivate influence zones. Those zones are the input data of the ANN while the output is represented by the directional commands. To train this ANN we will perform multiple executions in different maps on V-REP, storing the inputs given by the user and the corresponding output data. Those data are processed and compose a dataset to do the supervised training of a multilayer perceptron ANN. When the user is in a complicated situation, he/she can send a command to the wheelchair to activate the autonomous movement ANN, producing a directional command sequence able to carry the patient to a safe place, without obstacles in front of him, where he can control the wheelchair again. Figure 1 shows the related system structure. **Relevance:** This technique provides a solution independent of a global map to execute a path planning, based only in the local obstacles detected by the wheelchair. The zonal approach reduces

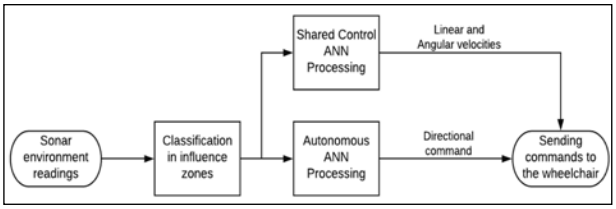

Figure 1. Flowchart representing each system stages. The first stage is the sonar environment reading, followed by the zonal classification. The data will be processed by two artificial neural networks that provides the movement executed by the wheelchair.

the number of inputs, reducing the time for training the ANN and makes it capable to have a fast data processing. The firsts experiments made in the V-REP simulator show that the simulated robot is capable to learn movements such as obstacle avoidance and backing up to exit from a narrow passage. This system is important to aid people that have strong motor disabilities, helping to bring back their autonomy in executing daily activities.

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EFFECT OF SINGLE-SESSION TDCS IN ACUTE STROKE PATIENTS: A RANDOMIZED SHAM-CONTROLLED SAFETY STUDY.

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Introduction and Hypothesis: Stroke is the primary cause of morbidity and the third cause of mortality (50,000 deaths per year) in industrialized countries. Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation (NIBS) technique which has experienced significant growth in recent years. Studies show that tDCS can effectively modulate (up- or down-regulate) cortical excitability of targeted brain regions, pointing out its potential therapeutic value for the treatment of different diseases, such as cognitive and motor disorders in stroke [1]. However, the tDCS still have several opened questions that need to be addressed so that the technique can reach its full potential. In the present work, we aim to evaluate the tDCS's application safety as well as better understand the impact of tDCS on increasing brain plasticity during the acute phase after stroke. **Objective:** The main aim of this randomized controlled trial is, therefore, twofold. First, we aim to show that tDCS session during the acute phase after stroke is safe to the patient. Second, we intend to elucidate the impact of tDCS sessions on inducing brain plasticity by combining two complementary neuroimaging techniques: functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS). **Methods:** This is a prospective, randomized, placebo-controlled, double-blind, single-center study over a period of 6 months. Each patient included will participate in four visits. Visit 1 (V1): inclusion and baseline assessment visit. Patients who fulfill all the inclusion and non-inclusion criteria and who have signed informed consent will be included in the study. During this visit, we aim to perform all clinical and functional evaluations. Patients will also complete all clinical scales and self-evaluation questionnaires. Furthermore, blood samples will be taken in order to carry out biochemical analyses. Visit 2 (V2): single session of tDCS (2 mA for 20 min) or placebo visits. During these visits, before the cortical stimulation (real or placebo), all functional and clinical data will be collected. fNIRS data will be acquired before, simultaneously, and after the stimulation. We will also perform fMRI scans before and after the stimulation. The order of the placebo and anodal tDCS visits will be randomized. The visits 1 and 2 will be 1or 2 days apart. Visit 3 (V3): after 1 month of stimulation. All functional and clinical data will be collected. Visit 4 (V4): after 6 months of stimulation. All the functional and clinical data will be collected. **Relevance:** The question of the best therapeutic window in which noninvasive brain stimulation (NIBS) could potentiate the plastic changes for motor recovery after a stroke is still not fully understood. Most of the previous NIBS studies included patients in the chronic phase of recovery and very few in the subacute or acute phase. Thus, our project aims to investigate the role of tDCS in the acute phase of stroke, with emphasis on patient safety and tolerability.

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IDENTIFICATION OF THE GENETIC BASIS OF FAMILIAL MESIAL TEMPORAL LOBE EPILEPSY

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Introduction: Mesial temporal lobe epilepsy (MTLE) constitutes the most frequent focal epilepsy in the adult population [1], and it is characterized by epileptic discharges originated from the mesial structures of the temporal lobe. MTLE is also frequently associated with histological abnormalities in the mesial temporal structures, such as the hippocampus, also known as mesial temporal sclerosis (MTS) [2]. Although MTLE +MTS were classically considered as sporadic, in which environmental factors seemed to play a more relevant role, our group previously identified a familial form of MTLE+MTS (FMTLE+MTS) with autosomal dominant inheritance and linked to a candidate locus in the chromosome (ch) 18p11.31 [3]. Using state-of-the-art techniques, we aimed to study further this family (F-10) to identify the causative genetic variants located in the ch18p region and/or in other regions of the whole human exome. **Materials and Methods:** Peripheral blood DNA from all participants in the study was previously collected, and it is part of our biobank. All patients in the study were diagnosed as having FMTLE+MTS, based on clinical and encephalographic exams, according to International League Against Epilepsy (ILAE) defined criteria. Patients are prospectively followed, and all clinical, neuroimaging and inclusion/exclusion characterization have been previously described by our group [4]. Whole exome sequencing (WES) was carried out in 9 members of the F-10 family, using the TruSeq Exome Enrichment Kit in an Illumina Hi Seq 2500 platform. Small Nucleotide Variants (SNVs) and Insertions/Deletions (*InDels*) discovery pipelines were followed according to the *Genome Analysis Toolkit* guideline [5]. Genome-Wide Human SNP Array 6.0 microarray chips were also carried out for 25 members of the F-10 family. A simple comparison of variants presence/absence was carried out for the affected and non-affected groups and Variant Effect Predictor (VEP) tool [6] was used to select and further validate the variants which could be associated to the FMTLE. **Results:** WES data analysis showed 1808 SNVs and more than 1000 *InDels* segregating only with the affected members. After VEP filtering for greater deleterious impact, and Maximum Allele Frequency (MAF) < 5%, 3 SNVs (rs77251052, rs537005361 and rs72666050) and 1 deletion (ch8:23114758-23114759) remained. We also applied a filter exclusively for the 18p11.31 haplotype and confirmed the segregation of an SNV (rs79570056). Microarray analysis data showed 319 SNVs segregating between both groups, and, after filtering, 2 SNVs remained (rs11230701and rs11821008). **Discussion:** In this study, we could not confirm the segregation of the haplotype 18p11.31 previously associated with the FMTLE in the F-10. Also, WES and Microarray experiments did not show any coincident SNVs. These differences found between this study and the 2012 study and between the microarray and WES experiments might be related to the techniques used and the number of individuals sampled. Nonetheless, some SNVs with greater deleterious implications were found associated with FMTLE in affected individuals, including one previously associated with this family – at *LINC00667* gene. This gene codes for a long-non-coding RNA that shows expression in neural tissue, from development to adulthood and has been previously associated with cell cycle control [7]. **Conclusion:** Our study shows that SNVs with great deleterious potential are segregating in the affected individuals of F-10. At this point it is still unclear whether these variants are causal elements or could be acting as a modifier of the phenotype in the F-10. Additional studies are being carried-out in order to better clarify the issue.

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ALTERNATIVE ODOMETRY METHODS FOR THE AUTOMATION OF A WHEELCHAIR

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Introduction: This research evaluates different methods for wheelchair odometry other than those based only on encoders. Odometry is important since it gives an estimation of the location of a vehicle. Thus, odometry is relevant for the automation of mobile robots and vehicles such as wheelchairs. An encoder is a sensor coupled to a wheel that counts pulses while the wheel spins. The number of pulses gives a hint on how much the wheel has displaced and, therefore, on how much the vehicle has moved. However, wheel slip may jeopardize the measurement once the encoder counts pulses even when the vehicle has not dislocated. New techniques have emerged, such as Visual Odometry [1], that uses cameras to estimate movements through space. This work uses the methods of Laser Odometry proposed in [2] and [3] with two different laser sensors and the Visual Odometry given by the *ZED Stereo Camera*. **Materials and Methods:** The algorithms evaluated here intend to estimate the linear and angular velocities of the wheelchair based on a method called scan matching [2]. Fig. 1 shows the sensors attached to the wheelchairs. The experiments were made in both static and dynamic environments. They were also made inside the Electrical and Computer Engineering building of Unicamp (indoor environment). Static environments are those were everything is stationary, i.e., nothing in the environment moves as time passes. Dynamic environments are the opposite of static environments. One experiment was made using the *rf2odom* [2] algorithm and two of the laser sensors in a dynamic environment. Two experiments were made using the *HectorSlam* [3] algorithm and two of the laser sensors in a dynamic environment. Finally, two experiments were made using the Visual Odometry given by the *ZED Stereo Camera*, one in a static and the other one in dynamic environment. It was collected position measurements in all experiments. **Results:** It was shown that position measurements given by *rf2odom* algorithm were not good at all using both laser sensors. Using *HectorSlam* algorithm together with *RPLidar A2* laser sensor

Figure 1. a) RP Lidar A2 and Sick Tim 551 laser. b) ZED Stereo Camera.

also does not provide good measurements as it was show in the two experiments taken. *HectorSlam* used together with *Sick Tim 551* laser sensor provides better results as it was observed a small error in the first experiment (but not small in the second experiment). Visual Odometry from the *ZED Stereo Camera* works well in static environments but poorly in dynamic environments. **Discussion:** The present work shows that for indoor and dynamic environments the best proposal is to use the *HectorSlam* algorithm together with the *Sick Tim 551* laser sensor. However, it does not work well for all the cases. Besides that, the *Sick Tim 551* laser price is around 2,500 dollars while the *RPLidar A2* laser costs 600 dollars. The *ZED Camera* costs 450 dollars and the GPU board from *Nvidia* needed process the camera's data costs around 500 dollars. **Conclusion:** The methods using laser or visual odometry still have unsatisfactory performance considering their higher costs. The use of encoders together with IMUs provides cheap and sufficiently good odometry. This combination is a work that will be developed by the authors.

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EEG CLASSIFICATION USING ACOUSTIC STIMULI FROM CHAOTIC SYSTEM CIRCUITS

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Introduction: The use of Electroencephalography (EEG) to assess the

influence of sound, consisting mainly of music and random distributions, over brain activity is not novel [1]. The nonlinear EEG methods of characterization [2] aroused the question of how would the brain respond to exposure to this kind of dynamic. This study aimed to use voltage derived from chaotic systems as acoustic stimuli and compare the obtained accuracy of classification between stimuli and rest classes in EEG recordings. **Materials and Methods:** 32 healthy volunteers (23.6 ± 4.77) participated following the presented experimental protocol of sound exposure (Table 1). The implemented circuits were Chen, Unstable dissipative (UDS), two attractors of Rössler System: chaos and limit cycle (Rossler*), along with pink noise, which is commonly used as the reference for neutral sound. EEGs were recorded using g.USBamp with 16 Sahara dry electrodes positioned according to Figure 1, stimulation was presented through Sennheiser CX 300-II Earbuds. Experiments were approved by the local ethics committee. **Results:** Figure 2 shows a box plot for the classification accuracy distribution using a least square classifier and a Leave M Out cross-validation scheme (70% of trials for training and 30% for test) with 100 repetitions. The mean spectral powers in classical EEG rhythms (Delta, Theta, Alpha, Beta and Gamma) were used as attributes for classification (5 power features by 16 electrodes) of the stimulus vs. rest condition. **Discussion:** It was found high inter-subject variability, ranging from 82% of accuracy in the best case overall (Participants number 1&3 using Rössler Chaotic System stimulus) to 51% (Participant 30, using Pink Noise stimulus). **Conclusion:** The present work confirmed that both deterministic and random audio stimuli can be discriminated from rest state based on EEG behavior. However, a further statistical comparison is still required for determining the significance on the generative model and dynamics on such process, which outlines a natural perspective of this work.

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Table 1. Timeline of the experiment.

EEC recording			EEC recording			EEC recording			EEC recording			EEC recording	
30 sec	30 sec	10 sec	30 sec	30 sec	10 sec	30 sec	30 sec	10 sec	30 sec	30 sec	10 sec	30 sec	30 sec
Rest	Rössler	Pause	Rest	Chen	Pause	Rest	UDS	Pause	Rest	Rössler*	Pause	Rest	Pink noise
Block (Performed 5 times using an aleatory pattern of stimuli distribution)													

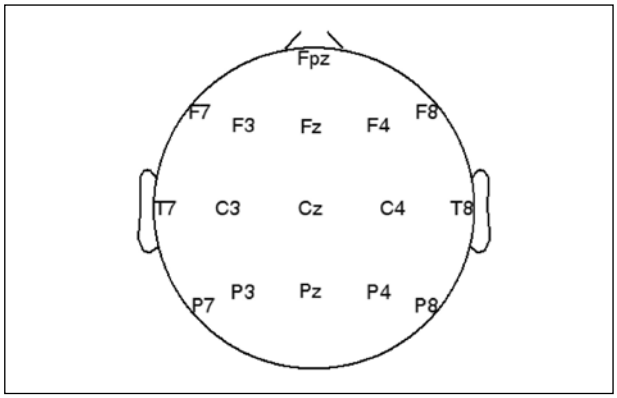

Figure 1. Electrode configuration.

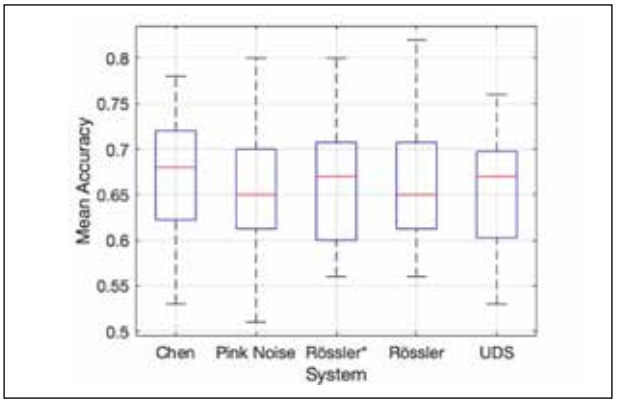

Figure 2. Classification Accuracy obtained for the 32 volunteers.

IMPROVEMENT OF FORCE CONTROL INDUCED BY VIBROTACTILE STIMULATION DOES NOT DEPEND ON THE MOTOR LATERALIZATION

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Introduction: Motor control studies have shown that an optimal level of vibrotactile stimulation improves motor performance. This improvement is associated with an increased excitability of cutaneous mechanoreceptors. The increased sensory inflow to the spinal cord would reduce the synaptic noise to motor neurons, thereby decreasing the variability of the motor output. It is known that motor lateralization reflects asymmetries in the processing of sensory information by the neural circuits that control hand movement [1]. Here we will investigate whether the motor lateralization of healthy subjects would influence the enhancement of force control caused by vibrotactile stimulation. **Materials and Methods:** Eleven right-handed healthy young participants (N=11, 9 males, 29±4 yr) performed a visually guided force-matching task, which consisted of abductions of the index fingers of non-dominant (ND) and dominant (D) hands (independently). The target contraction was set to 5% of the maximal voluntary contraction (MVC) measured in each hand. During isometric contractions, vibrotactile stimulation (freq=175Hz) was applied to the proximal phalanx of the index finger. Six intensities of stimuli (from 0 to 1.5G peak to peak) were presented in a random order after 4s of the task onset. The experimental protocol was performed in separate blocks, each consisting of five trials of 30s in each hand. We evaluated force variability (coefficient of variation, CoV) and the relative power of force spectrum in two frequency bands (0-5Hz and 7-12Hz). The optimal vibration (OV) was considered when the subject produced the best performance (lowest force variability) in the force control task. A two-way analysis of variance with repeated measures and Bonferroni's *post hoc* tests compared data between vibration conditions (control and OV) and hand dominance (ND and D). **Results:** Force steadiness was similar for the ND and D hand, with no significant effect of lateral dominance on the force CoV ($p=0.482$). Since no significant interaction was found ($p=0.202$), the decrease in the force CoV with OV ($p<0.001$) was independent of the hand. For the force power in 0-5Hz and 7-12Hz bands there were significant effects of vibration ($p=0.007$ and $p=0.012$) and hand ($p=0.025$ and $p=0.003$). Force power spectrum shifted to higher frequencies with OV, and the power in the low-frequency band (common drive, 0-5Hz) was greater in ND than in D case, while in the 7-12Hz band (physiological tremor) the power was greater in D than ND case. **Discussion:** The results showed that OV significantly decreases force CoV irrespective of putative lateral asymmetries, which result in the lateral dominance (or motor lateralization). We hypothesize that in our experiment the proprioceptive asymmetry between hands was occluded by visuomotor corrective feedback and, thus, no interlimb discrepancy was found [2]. The observed shift of power to higher frequencies with OV, which is associated to an increased Ia afferent activity [3], would be due to the effect of cutaneous afferents on the presynaptic inhibition of Ia afferent terminals [4]. As to the effect of hand in the force power spectrum, the higher power in physiological tremor band (7-12Hz) in the D case can be explained by asymmetries in spinal excitability [5], which might also reflect a greater involvement of Ia afferents. **Conclusion:** Irrespective of lateral asymmetries in cortical and spinal levels, improvement on motor performance induced by vibrotactile stimuli does not depend on the lateral dominance of the subjects.

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DEVELOPMENT OF A NOVEL SMART CRUTCHES BASED EXOSKELETON

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Introduction and Hypothesis: Exoskeletons usage have numerous advantages over wheelchairs, for patients that suffer from stroke, spinal cord injury, muscle weakness and other neurological or musculature disorders [1]. Prolonged use of wheelchairs can cause urinary problems, poor blood flow and bruising in lower extremities. Also, stairs and bumps can easily limit wheelchairs locomotion in city environments [2]. The before mentioned problems can be avoided with the use of foot mobile platforms [3]. Providing an easy to use and intuitive Human Exoskeleton Interface (HEI) encourage patient to use this kind of foot mobile platforms [1]. Designed to improve the capabilities of the system, the HEI is projected to have different approaches to estimate the user's intent, which will be developed throughout the different stages of the project. Moreover, the HEI will be able to perform a path-planning giving the pose of each step and crutches position. Also, the path should satisfy a static walking while the user will able to agree or modify the path-planning while the system will check for the viability of the path. Therefore, the user will be able to walk through rough terrains. **Objective:** Develop an exoskeleton platform in multiple stages allowing incremental progress along the project. Build an exoskeleton system capable of walk and navigate flat and sloped floors, stairs and rough terrains. While achieving a novelty HEI for enhancing the human-machine linkage, an intuitive system will allow certain exoskeletons to achieve far better results during activities

Figure 1.

of the daily living. **Methods:** As starting point a base structure without the actuators is built (Fig.1), the structure will be use for collecting kinematics and dynamics data of the exoskeleton, crutches and patient while gait. The before mentioned data will be collected with rotatory sensors at the joints, inertial measurement units in the exoskeleton and crutches and a motion capture system. Second stage consists in building the actual exoskeleton with high torque DC motors and added with smart crutches [4]. The latter will function also as part of the HEI. Through next stages a laser-pointing technique will be implemented as part of the path-planning in order to choose and modify paths. Furthermore, a Virtual Reality headset for a more engaging interface, and depth sensor will enable mapping the surrounding. **Relevance:** Robotic exoskeletons field has vastly expanded over last decades. Advances in motor and battery manufacturing technologies have reduced prices and increased the viability of exoskeleton prototypes. Although most of current exoskeleton have very intuitive interface, they have quite limited the exoskeleton capabilities because of control weaknesses or the interface itself. There are still areas in HEIs to be developed.

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CEREBELLAR INVOLVEMENT IN HEREDITARY SPASTIC PARAPLEGIAS

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Introduction: Hereditary spastic paraplegias (HSP) are a heterogeneous group of neurodegenerative disorders characterized clinically by slowly progressive lower limb weakness and spasticity. Corticospinal tract is the key target of damage in the disease, but other structures are also involved. Little is known about cerebellar involvement in HSP. **Objective**: to identify cerebellar abnormalities in the most frequent subtypes of pure (HSP-SPG4) and complicated HSP (HSP-SPG11). **Methods**: We recruited 14 patients with HSP-SPG4 (8 men; mean age 48.9 ± 12.3 years), 14 with HSP-SPG11 (7 men; mean age 27.5 ± 5.1 years) and 26 healthy age and gender-matched controls (14 men; mean age 38.5 ± 14.8 years). Image acquisition was performed in a 3T MRI scanner and T1-weighted structural 3D images were assessed by the Spatially Unbiased Atlas Template (SUIT)-SPM12-toolbox. GM cerebellar volumes were compared between groups via voxel-based morphometry (VBM). Statistical analyses were performed in SPM12 using analysis of variance and FWE-corrected p-values<0.05. **Results**: Mean disease duration for patients with HSP-SPG4 and HSP-SPG11 were 19 ± 11.2 and 12.2 ± 6.9, respectively. Four patients with HSP-SPG11 had clinically evident ataxia. We failed to identify cerebellar GM atrophy in the HSP-SPG4 group. In contrast, patients with HSP-SPG11 had cerebellar volumetric reduction at both lobules VI and right sided crus I in comparison to healthy-controls. **Conclusion**: Cerebellum is affected in HSP-SPG11, but not HSP-SPG4. Lobules VI look particularly vulnerable. Such difference helps to understand the phenotypic differences between both diseases. **Keywords:** HSP, MRI, SUIT, cerebellum, SPRS, VBM.

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A HYBRID CONTROL STRATEGY USING TENDON-DRIVEN SYSTEM AND FUNCTIONAL ELECTRICAL STIMULATION FOR ACTUATION OF A WEARABLE GLOVE-LIKE ORTHOSIS FOR THE FOREARM

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Introduction and Hypothesis: Hand orthoses which provide grasping by only using tendon-driven system are considered assistive technologies. On the other hand, when only functional electrical stimulation (FES) is applied for this purpose, it is considered as rehabilitative technology. However, the extended use of FES rapidly causes fatigue in the muscles of the hand [1], whereas orthosis using tendon-driven system can be used for long periods of time. As a means to deal with the limitation of FES and at the same time use the advantage of orthosis with tendon-driven system, a hybrid control strategy is proposed. The idea is to create a device that integrates both technologies, providing a FES-based rehabilitative approach combined to the tendon-driven system that is capable of reducing the muscle fatigue. **Objective:** Fig. 1 shows a generic waveform of FES, with ramp up and ramp down (transient phases related to the increase and fall of current excitation, mimicking how muscles are normally recruited and released from function in voluntary contraction, respectively), and a period of time window, between t_1 and t_2, in which the stimulation is kept constant by using FES. The aim of the proposed hybrid control strategy is trying to reduce the use of FES applied for providing grasping via muscular contraction between t_1 and t_2, while the device uses the system actuation of the orthosis for keeping the grasp. **Methods:** In order to apply the hybrid strategy, Fig. 2 contains a self-explanatory block diagram with the logic of the hybrid control strategy. As the surface electromyography (sEMG) can be influenced by the use of FES, a solution to this problem is to apply a optical fiber force myography (FMG) sensor [2]. **Relevance:** The main contributions of this project are the development of a low-cost rehabilitation device for using in activities of daily living (ADL) and for home therapy, as well as trying to guarantee the use of the orthosis without causing fatigue to the muscles of the hand.

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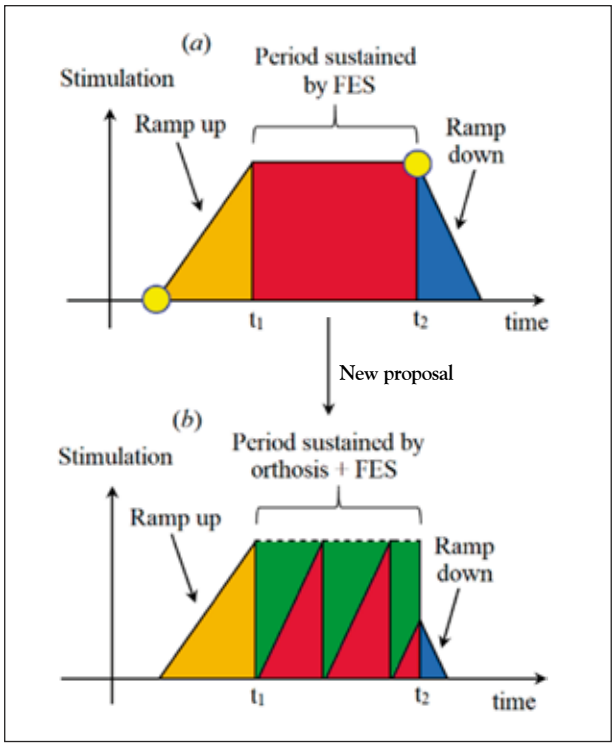

Figure 1. (a) Generic waveform of FES, and (b) the new proposed waveform for FES + tendon-driven orthosis.

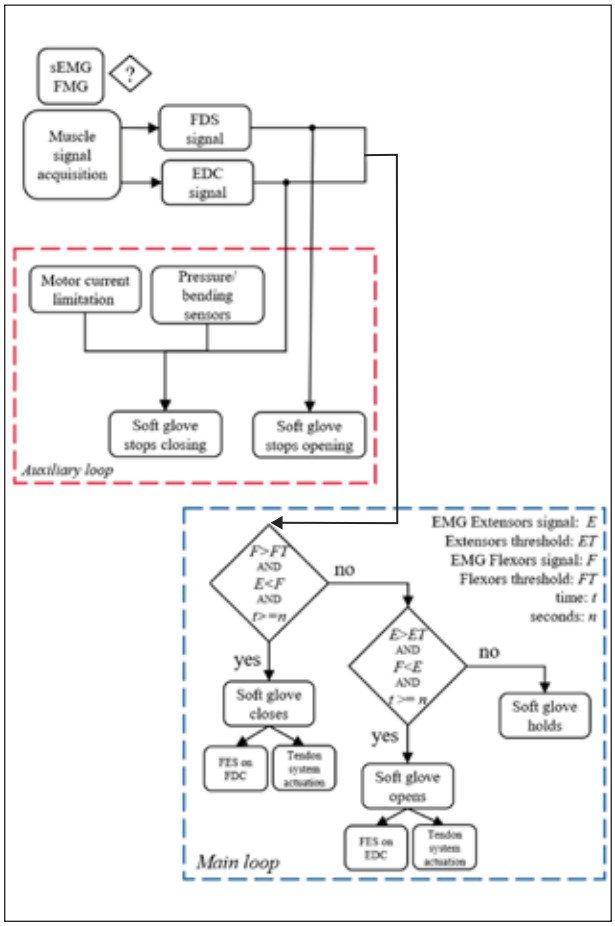

Figure 2. Block diagram for hybrid control strategy.

STUDY ABOUT EEG SIGNAL PROCESSING AND ANALYSIS AND APPLICATION TO EEG DATA FROM EPILEPSY PATIENTS

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Introduction and Hypothesis: Electroencephalography (EEG) is the gold standard exam for diagnosing epilepsy. Usually, a trained neurologist examines the EEG exam, searching for specific patterns. However, nowadays most EEG exams are digital, and can be easily processed and analyzed using computer techniques, ranging from standard digital signal processing to machine learning methods. Particularly, EEG data can be analyzed to provide information about the brain functional connectivity of the patient and how it is changing over time. The hypothesis of this work is that EEG exams analyzed in such a way may reveal information not detectable in a visual inspection. **Objective:** To process and analyze EEG data from epilepsy patients, obtained simultaneously with fMRI data (during EEG-fMRI exams). **Methods:** EEG data from the EEG-fMRI database of the Neuroimage Laboratory at UNICAMP will be used. The data were acquired for other projects, previously approved by the Ethics Committee of UNICAMP. The EEG signals will be first processed and analyzed with standard Fourier analysis. Later, functional connectivity analyses will be performed. Different similarity measures to compute the connectivity will be explored, such as Pearson's correlation, space-time recurrences [1] and motifs [2]. **Relevance:** Epilepsy may cause cognitive and behavioral disfunctions; epilepsy patients have a death rate 2-3 times higher than the general population and may suffer from social-related disfunctions as well (e.g. overprotecting familiars) [3]. All these problems (and many others) add up as obstacles for individuals with epilepsy to have a normal life. Therefore, treating the disfunction as efficiently as possible, and providing them all conditions necessary to live a normal life is a social matter. Understanding what is generating some types of crisis is also an issue, as it is estimated that one third of epilepsy types don't have a known cause, which complicates the diagnosis and treatment of some epilepsy syndromes that require precise information about them. The analysis of electrical waves and of how EEG-based functional connectivity evolves over time for this type of patients may be helpful to understand more about the epilepsy crises, for it is known that specific rhythms (such as the α waves) are related to specific brain states. Last, but not least, this work may shed light on the propagation mechanism of epilepsy crises, and hopefully, help to delimitate epileptogenic zones.

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INDICATION OF LEFT FRONTAL INVOLVEMENT IN HANDS MI RESPONSE MEASURED WITH EEG

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Introduction: Motor imagery (MI) is a commonly explored strategy in brain-computer interfaces (BCIs) [1]. Although its electroencephalography (EEG) response has been reported as event-related desynchronizations (ERDs) in the contralateral motor cortex to the MI performance in the μ band [1], there is still no optimum established manner of designing an MI-BCI; besides, such systems usually suffer from a large inter and intra-subject variability [2]. Therefore, a more in-depth knowledge of possible MI common patterns amongst subjects could endorse the currently available techniques for MI classification. In this study, our goal was to investigate the stability of electrodes ranked by a feature selection filter over several MI sessions for healthy subjects. **Materials and Methods:** EEG data from 10 healthy subjects were acquired at 256 Hz with the g.tec® amplifier connected to a 16 dry-electrodes' cap. All participants underwent 12 MI sessions, without feedback. Each session was divided in five 2-minutes runs; also, each run encompassed four 6-seconds blocks of right and left hands MI. These tasks were randomly assigned to avoid stimulus habituation, and alternated with rest blocks. Preprocessing steps included filtering in the μ band, a common average reference filter for general artifacts removal and an independent component analysis-based method for further removing eye blinking artifacts [3]. Furthermore, we calculated the signals' power difference between an MI block and its previous rest block, associating it as an indicative of the ERD occurrence. These values were then

assigned to a Fisher filter to rank the best suitable electrodes for distinguishing between the MI tasks. **Results and Discussion:** Fig. 1 displays a scalp map of the most recurrent electrodes across the MI sessions for two representative subjects (A and B) and for the group average (C). The larger and closer to red the circle around a given electrode, the more often that channel was ranked amongst the four most useful for distinguishing between left and right hands MI, at a given session. Our results suggest that the F3 electrode was of high relevance for all subjects. Moreover, electrodes C3 and C4, commonly reported as containing the MI ERD response, were not necessarily among the most relevant channels for all subjects, as represented by their minor circles in Fig. 1C. Given its anatomical location, the F3 activity might be linked to the premotor area's outputs for the primary motor cortex regarding motor action planning.

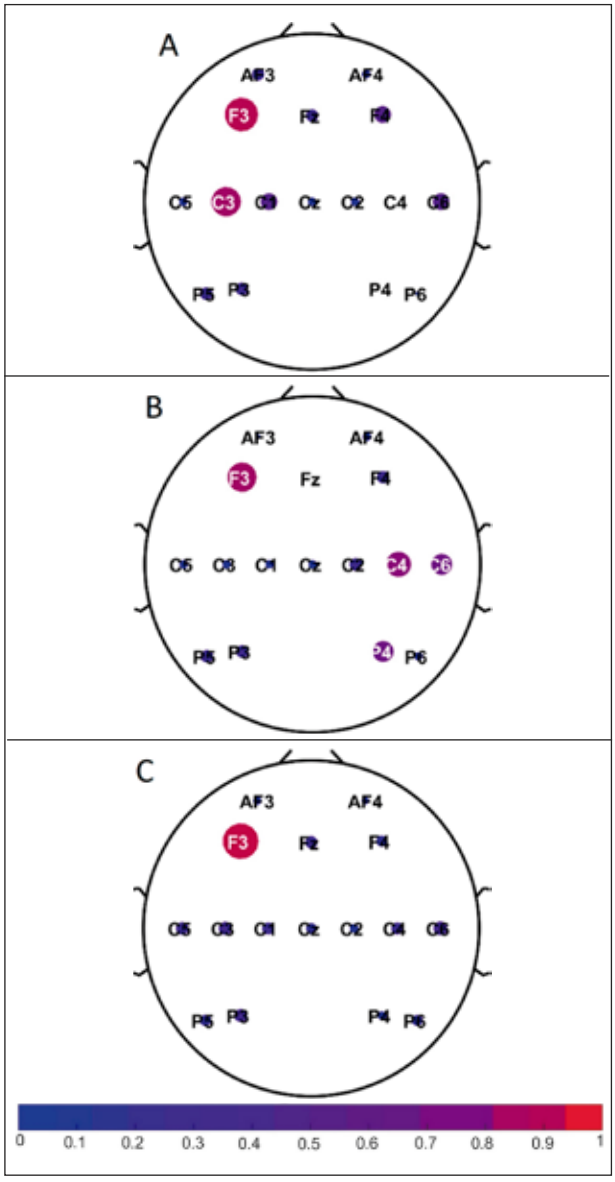

Figure 1. Mapping of a given electrode's recurrence according to the Fisher criterion for distinguishing between hands MI tasks. (A) and (B) display representative subjects, whereas (C) shows the group average result.

Conclusion: Future studies may benefit from including information from F3, not just the primary motor cortex (i.e., C3, Cz and C4), and even further exploring its response to better understand its dynamical EEG behavior during hands MI, as well as its possible implications for MI-BCI designing.

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DEPRESSIVE DISORDER IS ASSOCIATED WITH REDUCED CORTICAL THICKNESS IN WOMEN WITH TEMPORAL LOBE EPILEPSY

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Introduction: Major Depressive Disorder (MDD) has a high prevalence in patients with mesial temporal lobe epilepsy (MTLE)[1], especially in women, carrying significant morbidity. The frontal-limbic model of MDD[2] is well established, however, there are no structured studies with neuroimaging and clinical analysis including patients with epilepsy and this psychiatric comorbidity. This study aimed to investigate the cortical thickness (CT) abnormalities associated with MDD in women with MTLE and hippocampal atrophy (HA). **Materials and Methods:** We included 50 MTLE patients (left MTLE, n=20; right MTLE, n=30), 41 healthy controls, and 15 patients with MDD (without epilepsy, MDD-only). All patients and controls included were females. MTLE patients were subdivided into two groups: MTLE-MDD-Neg (23 patients without MDD) and MTLE+MDD (27 patients with MDD). The four groups were balanced for age (p=0.28). For some analysis, we subdivided the MTLE+MDD group into MTLE+MDD-MILD (n=9) and MTLE+MDD-MODERATE-SEVERE (n=18). All participants underwent a high-resolution volumetric T1-weighted MRI in a 3T scanner. We used FreeSurfer 6.0 for CT analyses. All participants were submitted to a clinical psychological evaluation through the Structured Clinical Interview for DSM-IV (SCID-IV) and completed the Beck Depression Inventory (BDI). We performed correlations and multivariate analysis (corrected for multiple comparisons) with SPSS. **Results:** Initially, we performed a statistical correlation analysis among the 68 CT regions (34 ipsilateral/34 contralateral) with the BDI scores in the group MDD-only. We found, in this first step, significant correlations between BDI and CT in 14 areas in frontal and temporal regions ($p<0.05$, $r>-0.5$). We selected these 14 CT areas as the basis for the next group's analysis. After multivariate analysis including these 14 areas, we observed a thinner CT in the ipsilateral-lateral-orbitofrontal gyrus (p=0.028) and in the ipsilateral-fusiform gyrus (p=0.023) in MTLE-MDD--MODERATE-SEVERE group when compared to the MTLE-MDD-Neg. We also found a reduced CT in the contralateral-superior-frontal gyrus (p=0.015) in the MTLE-MDD-MODERATE-SEVERE group when compared to the MTLE-MDD-MILD. In addition, the contralateral-superior-frontal gyrus was thinner (p=0.042) in the MTLE-MDD-MODERATE-SEVERE when compared to MDD-only group. **Conclusion:** Our findings showed several areas with reduced CT associated with MDD in women with MTLE, suggesting a network of fronto-temporal cortical thinning associated to the co-occurrence and intensity of depressive symptoms in women with epilepsy.

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ALZHEIMER'S DISEASE PREDICTION ON EARLY STAGES COMBINING TEXTUAL AND VISUAL DATA USING TRANSFER LEARNING, SUPPORT VECTOR MACHINE, RANDOM FOREST AND NAIVE BAYES

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Introduction and Hypothesis: In the medical field, the efficient prediction of the Alzheimer's Disease (AD) is one of the most challenging issues. This challenge is compounded when the method is focused on the early stages (i.e. prodromal). The Clinical Dementia Rating (CDR) is a well-known scale that attempts to state the dementia level, starting from 0 (no dementia) up to 3 (severe AD). Computational methods use scales such as the CDR to support doctors by predicting and classifying the AD level based on imaging and cognitive tests. Recent advances in the computational field show that the combination of multiples modalities may aid the prediction of AD through the detection of Mild Cognitive Impairment (MCI). **Objective:** In this work, we propose a multimodal and multi-projection computational method for the prodromal classification of the Alzheimer's Disease using a small number of samples. It combines Convolutional Neural Network, Random Forest, Naive Bayes, Support Vector Machine techniques and committees' concepts. **Method:** To reach our

objective, we employed the following method: First, we retrieved 416 samples (textual + imaging) from the OASIS-1 Dataset [1]. These 3D images were then split to obtain three brain projections (sagittal, coronal and axial). Due to the lack of information on textual data (CDR missing), a number of samples were removed to comply with the criteria proposed by Duarte et al [2] in their preprocessing step. After preprocessing, two separate flows were conceived for each type of data: 1) *textual*: Random Forest and Naive Bayes classifiers were applied to the processed textual data, thus obtaining two different predictions for each sample; 2) *imaging*: A Convolutional Neural Network (CNN) using the Transfer Learning (TL) concept was applied with a pretrained ImageNet using only the six first layers of a VGG19 architecture. The final matrices of TL-CNN were inserted to a Support Vector Machine to obtain predictions related to each brain projection. Since in the final process we ended up with three responses for imaging and two for textual data, three committees (Majority Voting, False-Positive Priori, and Super Learner) were used to combine these brain projections and the textual data. An arbitration process further combines these three outputs into a single final prediction. **Relevance:** The relevance of this work lies in addressing three main challenges: Firstly, the work with small datasets poses a challenge to the training step in approaches based on artificial intelligence (which usually require a large number of samples); Secondly, it is simply harder to discriminate the disease in its prodromal stages than in the later stages; Finally, the combination of multi-projection and multi-modalities to gather different patterns of the same patient.

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SMART HOME CONTROL USING FACIAL EXPRESSIONS

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Introduction: Brazil has an average of 6 to 8 thousand new cases of spinal cord trauma (SCT) annually [1]. The victims of SCT often need the help of caregivers or family members in daily tasks. Smart Homes afford automatic control of devices present in the residential environment, and can offer greater autonomy and quality of life for these people. In this context, this work presents the development of a software solution that allows controlling devices of a Smart Home through a natural interface, using expressions and facial movements. **Materials and Methods:** We developed the software on the Python programming language and used a regular low-cost webcam to capture facial expressions and facial movements. The OpenCV library, based on the Viola Jones classifier [2], identifies the user's movements and facial expressions. When identified a smile, the software starts up and displays the menus containing all Smart Home devices. Then a centroid of the user's face is calculated, and it displays a virtual joystick on the screen, with pre-defined width and height parameters. In this joystick, the central area is neutral and sends no commands to the interface. So, to send commands, the user must position the nose on the Up, Down, Left and Right area, as can be seen in Fig.1. Additionally, a simulated Smart Home environment for experimentation using the V-REP software [3] was created. We performed usability experiments using 12 volunteers with no deficiency to test the ease of use and control aspects of the task. The volunteers used the interface freely for ambiance, and soon after they should turn on the lights of one of the rooms of the environment and simulate and close one of the doors of this same environment, using the developed interface. **Results:** The users answered a questionnaire expressing the level of difficulty in accomplishing the task. Thus, 66.7% considered the interface to be a very easy to use, 25% considered it easy to use and 8.3% considered the interface regular, no user specified the level very difficult. In addition, users were asked about the feeling of full control in the task, 54.5% answered that they felt high control, 36.4% expressed that they felt control in a mean, in most cases, dealing with some unexpected situations, and only 9.1% of users did not feel in control of the interface tested. **Discussion:** There are software dedicated to the control of smart homes available in the market, some based on voice, others based on touchscreen surfaces. Thus, not all interfaces can be controlled by people with stroke and other diseases, the interface based on movements and natural facial expressions, allows this audience to control the environment in which they are inserted in. **Conclusion:** The usability tests performed showed that the interface was robust and easy to use. Moreover, this project showed a low-cost solution that people with disabilities can use, offering greater autonomy and quality of life, to control the devices of a Smart Home, with security and reliability.

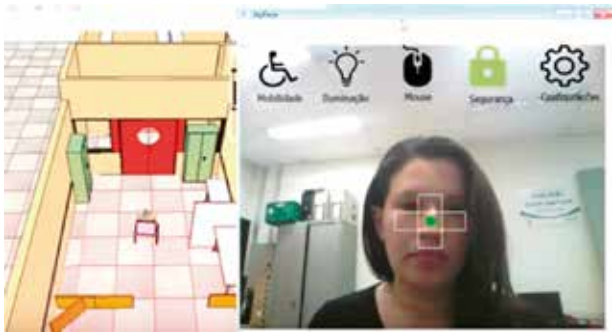

Figure 1. Smart Home control.

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IMPLEMENTATION ON RASPBERRY PI OF A BCI BASED ON SSVEP: PRELIMINARY ANALYSIS

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Introduction: Brain-Computer Interface (BCI) is a system capable of converting brain signals directly into commands. A usual approach to conceive a BCI is based on Steady State Visually Evoked Potentials (SSVEP) [1], which explores the fact that when a user focuses on a scintillating stimulus at a specific frequency, the firing of the neurons of the occipital cortex go into sync mode, increasing brain activity in this same frequency. The objective of this paper is present the signal processing module of a BCI-SSVEP using Python language on the Raspberry PI. **Materials and Methods:** In this study, we have used the brain signals acquired from two health volunteers. The brain activity was registered at 256 Hz by electroencephalography using 16 dry electrodes [2]. The visual stimuli blinked on a monitor at four frequencies: 6, 10, 12 and 15 Hz. The database used was composed of 8 replicates of 12 seconds for each frequency, totaling 32 trials for each volunteer. The signal processing was performed in three stages: preprocessing, feature extraction and classification. In the preprocessing, the signal of 12 s was windowed in 3 s and filtered by Common Average Reference technique (CAR), in order to eliminate noises and artifacts. The feature extraction was operated by Fast Fourier Transform (FFT) and the linear classifier (least squares method) was trained with 78% of the samples, which were randomly selected, and validated with the remaining 22%. The hit rate was evaluated with a 20-fold cross-validation method. **Results:** Table 1 presents the performance of BCI-SSVEP applying FFT and linear classifier for the two subjects.

Table 1. Average hit rates for each frequency of the two subjects.

	Average Accuracy (%)				
Subject	6 Hz	10 Hz	12 Hz	15 Hz	Mean ± Standard deviation
1	85.71%	92.86%	85.71%	92.85%	89.29 ± 3.57%
2	72.86%	95.00%	87.86%	95.71%	87.86 ± 9.19%

Discussion: The results show that the feature extraction by the FFT and the linear classifier can be applied successfully to discriminate the evoked frequencies of a BCI-SSVEP for both subjects tested. The mean hit rate of identification of frequencies was always higher than 72% and the average accuracy of the BCI was close to 90%, for both subjects. We also observed a best performance for the frequencies 10 and 15 Hz, probably because the frequencies 6 and 12 Hz are harmonics. **Conclusion:** The implementation of the signal processing module of a BCI-SSVEP in Python language, using Raspberry PI was concluded

with success, obtaining a satisfactory accuracy in the test with the signals from two volunteers. The advantage of using Raspberry PI is the mobility, low cost and open source platform. As future work, we plan to incorporate more signal processing techniques and make the system online.

Support: CNPq, Fapesp and UFOP.

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THE INCREASE OF AXIAL DIFFUSIVITY IN GENU OF CORPUS CALLOSUM IS DISTINGUISHED IN MCI PATIENTS WHO PROGRESSED TO AD

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Introduction: The corpus callosum (CC) is the brain's primary conduit for interhemispheric transfer and integration of information. Alterations in white matter (WM) in the CC has been observed in several disorders including Alzheimer's disease (AD), indicating a possible biomarker of brain circuitry integrity [1]. WM changes are well-documented in AD and its prodromal stages, including mild cognitive impairment (MCI). However, the pattern and underlying mechanism of these changes remain unclear. Diffusion tensor imaging (DTI) is recommended as a sensitive method to explore whole brain WM alterations at an asymptomatic stage of the disease [2]. We aimed to verify if the diffusion parameters in CC structures may distinguished patients with MCI who progressed to AD. **Materials and Methods:** We included in our study 59 patients, over 55 years of age, who where underwent to an exam of MRI in a 3T scanner. All patients were followed for 14 months approximately. Individuals who progressed to a clinical diagnosis of AD dementia were considered converters (MCI-C, n=10); those who remained with a diagnosis of MCI were considered to be stable (non-converters) (MCI-NC, n=49). We used an automated segmentation method – MultiAtlas [3], which evaluates DTI measures (fractional anisotropy [FA], radial [RD] and axial [aD] diffusivity) to verify WM integrity in the body, splenium, and in the genu of the CC. We performed a generalized linear model of repeated measures (corrected for multiple comparisons) with SPSS. **Results:** We only found a significant increase of aD in the Genu of the CC in the group of individuals who converted to AD ($F(1, 38) = 10.78$, $p=0.002$, partial $n^2= 0.22$). **Discussion:** The evidence base gathered by DTI investigations in the last decade has helped to better define the pathological cascade underlying AD. Our results show that the measure of aD, which evaluates axonal injury in the genu-CC can differentiate MCI patients who converted to AD. We observed that patients who progressed had higher aD than those who maintained MCI, showing that this measure could be used as a possible biomarker of disease evolution. **Conclusion:** The present work may confirm that diffusivity parameters, especially in aD, can be efficient of differentiating the MCI-C from the MCI-NC in the Genu-CC, also confirming that the CC region is very important and it is linked to AD pathology.

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DETECTION OF OUTLIERS IN MAGNETIC RESONANCE SPECTROSCOPY IMAGING WITH A NOISE-SENSITIVE CLUSTERING METHOD

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Introduction: Magnetic Resonance Spectroscopic Imaging (MRSI) is a method used to analyze the concentration of metabolites in the brain from the frequency signals. This information combined with MR images can support diagnostics and treatments of diseases such as epilepsy and brain tumors [1]. However, some factors can affect the quality of the spectra and invalidate the analysis. Usually, metrics such as signal-to-noise ratio (SNR), full width at half maximum (FWHM) and Cramér-Rao lower bounds (CRLB) are used to evaluate the quality of the spectra. However, these metrics need threshold values to set whether a spectrum is noise or not and there is no consensus among experts on these values. This work aims to identify patterns in spectra indicating which ones tend to be noise using a machine learning method. **Materials and Methods:** MRSI of one healthy subject was acquired from the supraventricular posterior region (VOI size ≈ 100.52 x 84.74 x 16 mm; grid of 16 x 13 spectra) (Fig. 1). The detection of outliers was done by means of the density-based clustering algorithm DBSCAN [2] due to its noise-sensitive property of marking as outliers spectra that lie in low-density regions, which are considered noise. Since the corpus callosum is in the central region of the VOI, it is expected that valid spectra become a unique group because of the homogeneity of the pure white matter spectra. On the other hand, noisy spectra are expected to be identified as outliers and located in the VOI boundaries. **Results:** The distance function used by DBSCAN was Pearson correlation and the parameters epsilon and minimum of samples were 0.1 and 15, respectively. The result presented in Fig. 2a corresponds to the brain region highlighted in the yellow rectangle of Fig. 1. White pixels are a single cluster of valid spectra and black pixels are noise. In addition, some valid and noisy spectra automatically classified by the clustering result are shown in Fig. 2b. It corresponds to the region highlighted in Fig. 2a. Spectra in black are interpreted as noise and spectra in red are taken as valid information. **Discussion:** The result has a spatial coherence considering the proximity of the valid spectra in the image space and the expected location of the corpus callosum. Also, the method found a single cluster of valid spectra. This corroborates the apparent homogeneous appearance of the pure white matter spectra. Besides that, the visual evaluation of the classification in the plotting of the spectra confirms that the method reached consistent results. **Conclusion:** The automatic detection of valid spectra in MRSI is important because it highlights some relevant information for the specialist. The proposed method found patterns in spectra with spatial coherence. This contributes to support future analysis since the technique can be considered a valid preprocessing step to properly filter outliers. A comparison of these results with the commonly used quality metrics will be part of the next steps of the research.

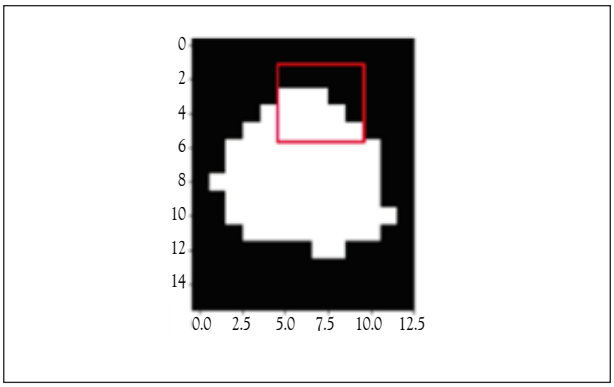

Figure 1.

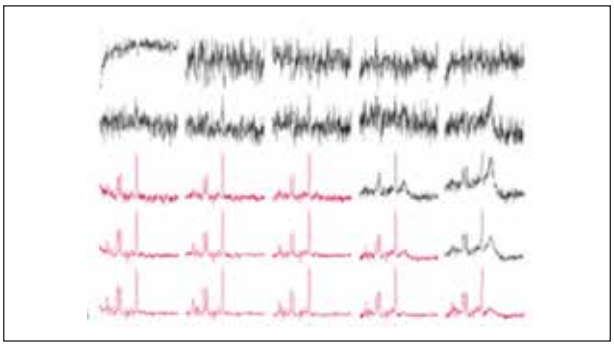

Figure 1. Clustering result produced by DBSCAN and a sample of valid and noisy spectra.

Supported: Fapesp and CNPq.

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ANALYSIS OF MRSI QUANTIFICATION USING A BICLUSTERING TECHNIQUE

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Introduction: Magnetic Resonance Spectroscopic Imaging (MRSI) is a technique that has been used to estimate the concentration of metabolites from frequency spectra, providing additional information for Magnetic Resonance Imaging (MRI) techniques. The task of determining the concentrations is called quantification and usually handles 34 different metabolites, being able to support the definition of tumor type and grade [1]. For more accuracy, the analysis must include more than one metabolite concentration at once, thus characterizing a hard task for a human expert. Therefore, our proposal aims to enrich this analysis using biclustering techniques to mine combinations of similar metabolite concentrations in a subgroup of spectra. **Materials and Methods:** MRSI of two healthy subjects was acquired from the supraventricular posterior region (VOI size ≈ 100.52 x 84.74 x 16 mm; grid of 16 x 13 spectra) (Fig. 1). Quantifications of these MRSI were obtained by the TARQUIN software [2]. Although the quantification produces real numbers, we decided to work with binary datasets, highlighting the high concentration of metabolites in the spectra. For that, each metabolite concentration was normalized to zero mean and unit standard deviation. Afterward, values above a standard deviation of the mean were set to 1, thus indicating high concentration, otherwise were set to 0. We used an enumerative and very efficient biclustering algorithm called In-Close2 [3] to mine all maximal biclusters of 1's in these two binary datasets. Therefore, the algorithm obtained biclusters composed of a subgroup of metabolites with high concentrations in a subgroup of spectra. **Results:** We used the following criteria to consider a bicluster as being significant: a bicluster must have at least two metabolites with a high concentration among a list of three that are considered the most important ones - NAA, Cr, and Glx. Biclusters are presented in the spatial image domain (the two rectangular grids of Fig. 2 correspond to the brain region highlighted in the yellow rectangle of Fig. 1) and each black or white small square box corresponds to a spectrum of MRSI (a white box means that the spectrum belongs to the bicluster; otherwise it does not belong). In both examples, the two biclusters contain the metabolites Cr, NAA, TNAA, TCho, and TCr. **Discussion:** The results suggest that there is coherence between the biclusters and the image space of the brain because the clustered spectra are spatially contiguous. Notice that the spatial information of the spectra was not included as input to the method. Also, these two examples, that have a subgroup of metabolites in common and a similar location in the grid spectra show that the biclustering technique can automatically find meaningful patterns involving multiple subjects. **Conclusion:** The results show that this technique is appropriate to provide enhanced information for MRSI analysis. Usually, most of the studies reduce the number of metabolites to facilitate the manual inspection of the results. However, resorting to biclustering, we can easily see all metabolites that follow the same pattern in a specific region of the brain. This kind of analysis can help the specialists mine other metabolites that are potentially relevant, for instance, being highly correlated with brain diseases.

Supported: Fapesp and CNPq.

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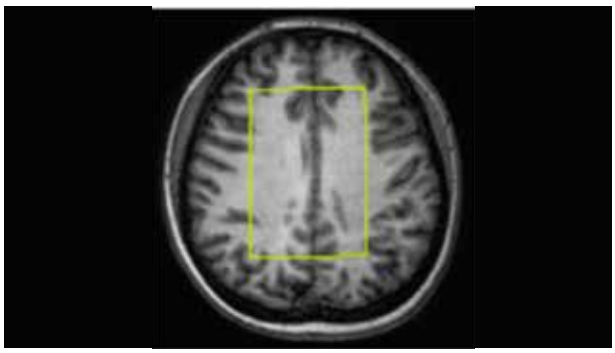

Figure 2. Example of the grid spectra localization (yellow rectangle).

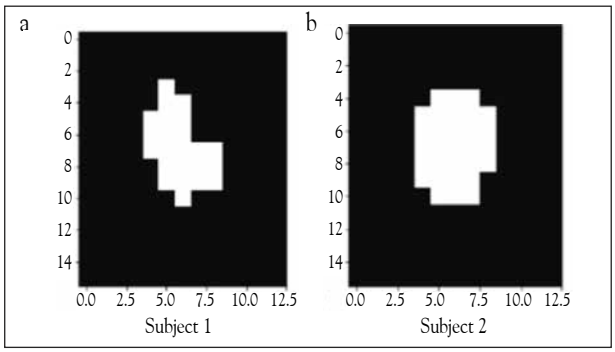

Figure 2. Samples of biclusters located in grid spectra.

USING ARTIFICIAL INTELLIGENCE FOR SEIZURE RECOGNITION IN EPILEPTIC PILOCARPINE-INDUCED RATS

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Introduction and Hypothesis: Epilepsy is a chronic neurological disorder characterized by recurrent spontaneous seizures [1]. Animal models are widely used and contribute significantly to understand this disorder. Seizures induced by pilocarpine has been one of the most widely used epilepsy models [2][5]. The detection of epileptic seizures is of great importance for the improvement in the quality of life of epileptic patients and artificial intelligence (AI) is increasingly having a more important role in seizures detection and prediction [3] [4]. **Objective:** The main purpose of the present study is to develop an efficient artificial neural network (ANN) model that might be able to identify behavioral seizures patterns from video recordings of rats having pilocarpine-induced seizures. **Methods:** Video-monitoring records of male Wistar rats kept at CEMIB vivarium of the University of Campinas (UNICAMP), from the project "Multimodal investigation of epileptogenesis - emphasis on the incorporation of new models and new tools" (FAPESP - 2011/50680 -2) will be the target source for the ANN. The rats were kept under controlled lighting conditions with 12 hour/cycle (light/dark), food and water access throughout the observation period. Two groups were set: rats showing seizures and not showing seizures. All animals were monitored 48 hours, 15 days for 1 month. Video recordings (TV-IP301 from TRENDnet) were conducted 24 hours/day for 8 months. Behavioral analysis of spontaneous seizures comprised classical parameters: direct visual inspection by trained observers plus recording with digital video-monitoring system. Seizures stages were evaluated according to the Racine Scale. Videos of both groups were evaluated to identify and discriminate between *status epilepticus* (SE) or not. The videos were pre-processed in order to achieve a dimensionality reduction before be loaded into an AI model comprised by a Convolutional Neural Network (CNN-LSTM), an architecture specialized in image recognition, followed by a Long Short-Term Memory Network, a neural network specialized in learn sequence patterns such as time series data. The model is able to learn, at the same time, patterns from 2D images (video frames), and from the third dimension, the time, thus detecting behavioral patterns associated with seizure events. **Relevance:** Build an accurate Artificial Intelligence model able to learn and then recognize behavioral patterns associated with epileptic seizures from video records might automate a very demanding and time-consuming process, reducing costs and finally, accelerate epilepsy researches.

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CHARACTERIZATION OF HEALTHY SUBJECTS AND STROKE PATIENTS USING TEXTURE ANALYSIS OF BRAIN MR IMAGES

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Introduction and Hypothesis: The magnetic resonance imaging (MRI) technique is nowadays one of the most widely used methods for conducting *in vivo* studies of the human body and its pathologies in a noninvasive way. As the MR exams become routine in several hospitals, the problem of how to extract relevant information

from the enormous amounts of generated data arises. Several pathologies in the brain can be characterized, among other factors, by a change in the affected tissue. Precise detection of the lesion range, or of an alteration in a tissue, is critical for surgery or for diagnosis. Texture analysis is a technique for processing and analyzing digital images, which consists in extracting values from the gray level distribution of the image. This technique can be applied for efficient image classification based on a reduced number of parameters, or to detect subtle variations in the gray level distribution. The hypothesis of this work is that a set of texture measures from different brain regions can be used to characterize and differentiate populations. **Objective:** The main goal of this work is to characterize healthy individuals and stroke patients using texture parameters extracted from structural brain regions of MR images. As secondary goals, we have: 1) Verify the texture parameters distribution among different brain regions and on stroke lesions; 2) Investigate different similarity measures to compose brain networks based on texture parameters; 3) Verify the viability of using texture-based brain networks to characterize the subject groups studied. **Methods:** An atlas will be used to perform the parcellation of the structural MR images in order to obtains the brain regions. Using the co-occurrence matrix method, the texture parameters will be extracted. These will allow to identify relations between different brain regions. Through graph theory, those relations will be used to generate a texture-based brain network. The brain networks of healthy individuals and stroke patients will be compared to search for differences between them. **Relevance:** There is an increasing volume of medical images data being acquired. Texture analysis aims to reduce the data amount of an image to a few parameters. In brain MR images, these parameters could be more easily used to characterize a patient population. To this moment, there is no work investigating the viability of using texture parameters to compose brain networks that can characterize groups of individuals, therefore this is an original work.

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MODIFIED ANTERIOR TEMPORAL LOBECTOMY (MATL): SEIZURE CONTROL AND POSTOPERATIVE OUTCOMES

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Introduction: This study aims to evaluate the efficiency and safety of a novel technique for the surgical treatment of temporal lobe epilepsy (TLE) secondary to hippocampal sclerosis (HS). This approach, so-called modified anterior temporal lobectomy (mATL), is based on a transsylvian resection of the temporal pole (TP) followed by an amygdalohippocampectomy using limen insula as a landmark [1]. **Materials and Methods:** A total of 62 patients with HS submitted to mATL were enrolled. Patients performed pre- and postoperative DTI, Engel's classification, and postoperative Humphrey perimetry. Mixed-models analysis was applied for comparisons between pre- and postoperative tractographies of the inferior fronto-occipital fasciculus (IFOF) and optic radiations (RO), controlling for patient's age at image acquisition. Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), number of voxels and number of streamlines were compared between pre- and postoperative tractographies. Other variables were analyzed semi-quantitatively. **Results:** After a mean follow-up of 33.73 ± 18.14 months, forty-nine patients (79.03%) achieved Engel class I, of whom 39 patients (62.09%) were Engel class IA. Considering both sides together, there was no statistically significant change of both IFOF and OR tractographies postoperatively. Analyzing the right and left hemispheres separately, there was only a slight but significant decrease in the AD of the right IFOF after surgery, with no significant differences regarding other tractographic variables. Reliable perimetry was obtained in 25 patients, of whom 17 patients (68%) exhibited no visual field defect (VFD), six patients (24%) showed quadrantanopia, and two patients (8%) showed incomplete hemianopia. There were no deaths or permanent motor deficits postoperatively. **Discussion:** The mATL showed a rewarding seizure control that suggests the major participation of TP in the epileptogenic zone associated with HS. Respecting the limen insula as the posterior limit to resect the TP caused minimal damage against the temporal stem (TS). Moreover, perimetric outcomes and the absence of major postoperative complications confirmed the safety of this approach. **Conclusion:** The mATL showed a rate of seizure-free comparable to the standard anterior temporal lobectomy, with a relative preservation of TS components and an incidence of VFD similar to selective approaches. Patients with refractory HS can benefit from a less extensive temporal lobectomy with no prejudice of seizure control and postoperative complications.

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A CASE STUDY OF BRAIN CHANGES IN A STROKE PATIENT AFTER A VIRTUAL REALITY REHABILITATION PROTOCOL

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Introduction: Virtual reality (VR) has been vastly used as an option for rehabilitation of functional disabilities in stroke patients. VR provides more freedom for therapy execution, which can be performed at home with remote assistance from the therapist; it is associated with a greater commitment from the patient; and allows the control of the feedback given to the patient. This study aims to investigate the brain changes after VR rehabilitation of the arm, in a chronic stroke patient, based on the VR Rehabilitation Gaming System (RGS) [1]. **Materials and Methods:** A female chronic (2 years post ictus) stroke patient, aged 50, underwent 24 VR rehabilitation sessions (1 hour long, twice a week). The patient was evaluated at 3 time points throughout therapy: before the 1st session, after 12 sessions and after 24 sessions. Evaluation consisted of acquisition of 2 magnetic resonance (MR) images (a T1-weighted anatomic and a resting-state functional image) together with functional and neuropsychological assessments. MR data were used to analyze brain connectivity changes throughout the 3 time points. For this, a graph was defined from a 264 regions' atlas [2]. The time series of each ROI was determined using the average of the 27 neighboring voxels to the coordinates defined in the atlas. A 264×264 connectivity matrix was obtained by means of the Pearson correlation between each pair of ROIs. The matrix was binarized using a threshold considering the 20% stronger correlation values as 1 and the others as 0. Variations of degree, clustering coefficient and betweenness centrality were evaluated among the 3 time points, as well as the evolution of clinical variables. **Results:** There was a greater variation of the analyzed metrics in the lesion region. The degree of the lesion area relative to the whole brain was 0.86% at the 1st moment and 1,35% at the 3rd moment. Betweenness centrality, which is a measure of how important a region is for information flow in the network, increased by 50% from the 1st to the 3rd time points in the lesion area. The Fugl-Meyer scale, which measures patient's functionality, had a 13-point increase in motor function and 23-point increase in the overall score. **Discussion:** The variation of the graph metrics analyzed was higher in the lesion region, and the clinical variables showed an improvement in the patient's motor function. Both results correlate with the patient's arm function improvement seen during the sessions. More importantly, the betweenness centrality measure seems to have accompanied the changes in functionality assessed with the Fugl-Meyer scale. This measure may be related to neuroplasticity occurring in the lesion region due to rehabilitation. **Conclusion:** The graph measures assessed in this study seem to be related to the functionality improvement of the patient, and may be an indication of neuroplasticity occurring in the lesion region due to rehabilitation. However, a study including more patients is needed to determine the extent of the relation between the connectivity graph metrics and the RV rehabilitation therapy.

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NON-RIGID REGISTRATION FOR NEUROANATOMY ATLAS

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Introduction: A neuroanatomy atlas consists in a reference frame, where every relevant structure is outlined and labeled with its anatomical name. Common applications are comparison, classification and finding patterns of neuroanatomical data [1]. Automatically labeling of neuroanatomical structures is an important application for medical education. Instead of a challenging neuroana-

tomy segmentation algorithm, we proposed to co-register an individual 3D T1 MRI image onto the MNI152 template space and converted the coordinates of this normalized space to the Tailarach one, which is still used to locate the brain structures. This study aims to develop a non-rigid registration algorithm for this purpose. **Materials and Methods:** Coarse affine co-registration followed by a local deformation was our paradigm. As we had already implemented an affine MMI (maximization of mutual information) co-registration algorithm [2], our focus was the second part. According to the comparison studies of non-linear deformations conducted in [3], we applied the Free-Form Deformation (FFD) approach. B- Spline functions were used to allow local deformations, which are a desired characteristic for local non-rigid registration [4][5]. As optimization algorithm, we used the Quasi-Newton. The mean of square error (MSE) was applied for evaluating the convergence of the numerical procedure. A prototype was implemented with MATLAB software. For testing, we co-registered a sagital slice T1 MRI volume (Fig. a) with its FFD deformed version (Fig. b), and the axial slice (Fig. c) with a slice of the MNI152 T1 in almost the same brain location (Fig. d). **Results:** In the first test, the co-registration algorithm almost precisely co-registered two volumes. Visually the differences were the colored regions highlighted in Fig (e), while in the second test the results were not expected (Fig. f). **Discussion:** The results of the first experiment confirm the viability of the implemented algorithm in co-registering images of the same

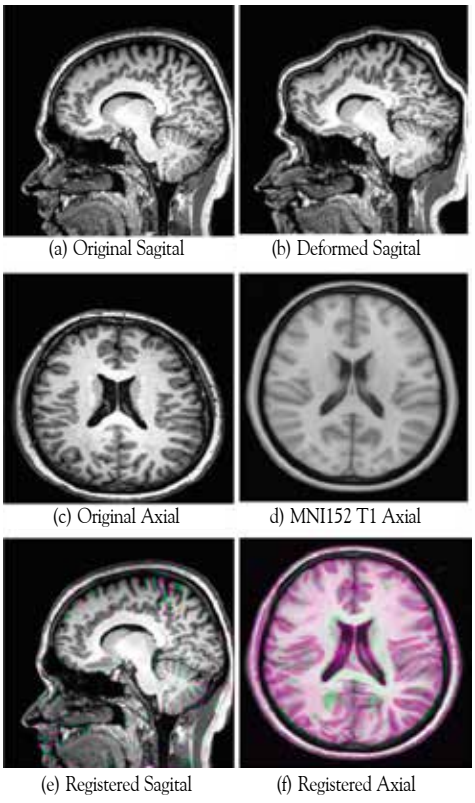

Figure 1. Clustering result produced by DBSCAN and a sample of valid and noisy spectra.

modality scanned with the same device, even when the slices are different [5]. The second experiment shows us, however, that the algorithm is not appropriate for the purpose of co-registering a T1 MRI volume with the average MNI152 T1 volume [6]. It is necessary to choose another metric that is independent from the characteristic intensity range of each scanner [3] [4]. **Conclusion:** Other metrics should be evaluated for accomplishing our purpose. The strong candidate is the mutual information.

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A COMPUTER SIMULATION STUDY ON THE EFFECTS OF AMYOTROPHIC LATERAL SCLEROSIS PROGRESSION ON EXCITATORY POSTSYNAPTIC POTENTIALS AND INTERSPIKE INTERVAL VARIABILITY OF SPINAL MOTOR NEURONS

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Introduction: Spinal motor neurons (MNs) receive a plethora of synaptic inputs from descending commands (supraspinal centers) and sensory afferents. Excitatory postsynaptic potentials (EPSPs) and interspike interval (ISI) variability are frequently used to study the influences of presynaptic inputs on the dendritic processing in MNs. In the present study, we investigated how intrinsic properties of MNs change synaptic excitability and integration in different stages of ALS progression, namely the hyperexcitability, normal excitability, and hypoexcitability [1]. **Materials and Methods:** Two-compartment FF-type MN models were designed in NEURON simulator and coded in Python programming language. The models were parameterized so as to represent the electrophysiological properties of spinal MNs during different stages of ALS [2]. Synaptic conductances were modeled as an alpha function (to peak). The stochastic discharge of MN models was produced by injecting homogeneous stochastic point process. The relation between standard deviation (STD) of ISIs and the mean ISI was calculated for different mean firing rates. Simulation durations were , and differential equations were solved using a backward Euler method with a time step of . **Results:** In the reference model (non-pathological condition), EPSP amplitude, dendritic area, maximum slow potassium conductance (), and persistent inward conductance (PIC) were , , 16 and 0.65, respectively. During ALS progression, EPSP amplitudes were: in hyperexcitability, in hypoexcitability, and in normal excitability (frequency-to-current, f-I, relation was similar to the reference model). The slopes of linear fits of the relations between ISI STD and mean ISI were in the reference model, in the hyperexcitability, in hypoexcitability and in normal excitability. **Discussion:** EPSP amplitude was higher in the hyperexcitable model probably due to the decrease in dendritic area. In the normal excitability condition, which is observed during ALS progression, the EPSP was lower than the reference value, thereby suggesting that albeit the MN had a similar f-I gain, its excitability to synaptic inputs was reduced due to the increase in the dendritic area. At hypoexcitability, the EPSP amplitude decreased by that is similar to the reduction reported in [1]. In the latter case, there was a lower increase in the dendritic area as compared to the normal excitability condition. The analysis of ISIs showed that in the hyperexcitable condition the MN had lower discharge variability, while in the normal excitability condition the variability was higher than the reference model. The higher variability in the normal excitability condition can be explained by an increase in membrane time constant. **Conclusion:** Here we show that synaptic efficacy (as estimated by EPSP amplitude) and ISI variability change during ALS progression and are notably different from the non-pathological condition.

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INVOLVEMENT OF 5HT1A RECEPTORS IN THE MANAGEMENT OF NEUROPATHIC PAIN BY CHRONIC CONSTRUCTION OF THE CIATIC NERVE AFTER TREATMENT WITH LASERTHERAPY

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Introduction and Hypothesis: The patients with neuropathic pain (DN) present spontaneous pain, allodynia and hyperalgesia and usually do not respond well to a great variety of therapies, many times they present comorbidities like depression, anxiety, psychological problems and sleep disturbance which leads to a worsening of quality of life [1,2,3]. Lasertherapy is a non-invasive device which has few contraindications and low cost, studies show positive results of lasertherapy in reducing DN, however its mechanisms of action at the supraspinatus level remain obscure in the literature. The hypothesis of this work is the involvement of 5HT1A receptors in dorsolateral periaqueductal gray matter (PAGd.l) in the management of DN after

treatment with lasertherapy. **Objective:** The objective of this study was to identify the influence of the 5HT1A receptor in the PAGd.l in mice treated by lasertherapy after chronic constriction of the sciatic nerve (CCI). **Methods:** Male mice were submitted to the CCI [4] and cannula implant [5]; after five days they received infusion of 5HT1A receptor antagonist drug intra PAGd.l and treated with lasertherapy, with the intensities of 0 J/cm^2 and 50 J/ cm^2 [6] in acute condition. The thermic hyperalgesia was evaluated by the hot plate test and the mechanical stimulation by the monofilament aesthesiometer. The animals were divided into 4 groups containing 6 animals per group: CCI+ VEICULO+ LASER 50 J/cm^2; CCI+ VEICULO+ LASER 0 J/cm^2; CCI+ ANTAGONISTA 5HT1A+ LASER 50 J/cm^2; CCI+ ANTAGONISTA 5HT1A+ LASER 50 J/cm^2. **Result:** After the CCI it was observed a significant reduction in the nociceptive threshold in all groups, evaluated by the mechanical hyperalgesia test (p<0,001) and thermic test (p<0,001). However, after the application of lasertherapy only in the CCI + VEICULO + LASER 50 J/cm^2 group it was detected the antinociceptive effect through the hot plate test (p<0,001) and Von Frey test (p<0,001) the antinociceptive effect lasted to the antinociceptive effect lasted until the fifth hour in comparison with the other groups. The groups CCI + VEICULO + LASERTHRAPY 0 J / cm^2; CCI + ANTAGONISTA 5HT1A + LASERTHERAPY 50 J / cm^2; 5HT1A + LASERTHERAPY 50 J / cm^2 remained with reduced nociceptive threshold after treatment with lasertherapy, where the antagonist of 5HT1A prevented the analgesic effect of lasertherapy and the lasertherapy applied in the intensity of 0J / cm^2 had no effect on the nociceptive threshold. **Discussion:** [7] Andrade ALM et al. showed in their study that lasertherapy producesthe increase of β-endorphin and reduces effectively the neuropathic pain, byusing higher fluencies of 20 and 40 J/cm^2 These findings corroborate with ourstudies, being that the lasertherapy produced the antinociceptive effect in group CCI + VEICULO + LASERTHERAPY 50J/cm^2 .**Relevance:** Although there is evidence pointing to the beneficial effect of lasertherapy in clinical practice, basic experimental research is essential to explain the mechanisms involved in the analgesic effect provided by lasertherapy, strengthening evidence-based practice. **Conclusion:** In view of the above, we can suggest the involvement of 5HT1A receptors located in the PAGd.l antinociceptive effect provided by laser therapy in animals submitted to CCI.

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THE IMPACT OF GRAVE'S DISEASE HYPERTHYROIDISM ON GREY MATTER ATROPHY

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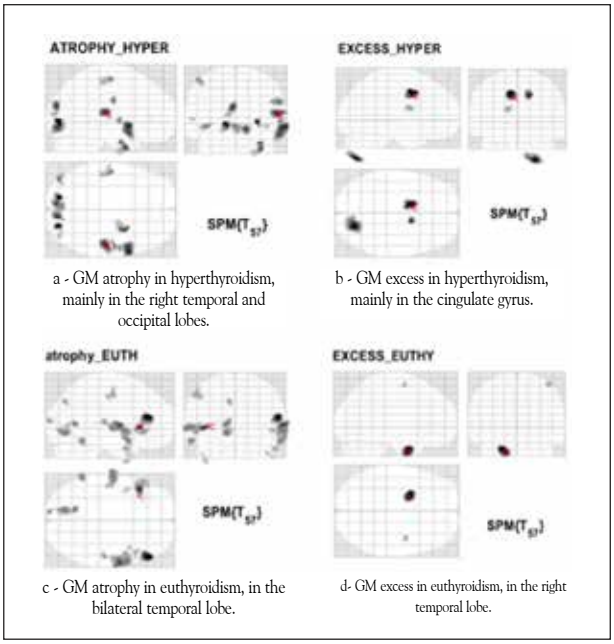
Introduction: Graves' disease is an autoimmune disease associated with the state of thyrotoxicity [1] and cognitive dysfunction, such as memory deficits [2]. Unfortunately, the endocrine mechanism behind this process is still not clear in the literature. Here, we investigated the relationship between Graves' disease and grey matter atrophy, using Voxel-based Morphometry. **Materials and Methods:** We acquired high-resolution T1-weighted MRI images from 35 patients and 24 control subjects using a 3T scanner. Patients were separated into two groups according to the presence of active hyperthyroidism (15) or euthyroidism (20). We run VBM analyses using the standard protocol with CAT12 toolbox/SPM12 (http://www.neuro.uni-jena.de/cat/). The images underwent normalization, segmentation and smoothing. Afterwards, we extracted volumetric grey matter maps through and performed group comparisons ANOVA (p<0.001, uncorrected for multiple comparisons). **Results:** GM atrophy was observed in the two groups (Figures A/C, slightly more widespread in patients with hyperthyroidism) mainly in bilateral frontoparietal and in the temporal lobe, compared to controls. On the contrary, the excess of GM (Figures B/D), was mainly identified in the cingulate gyrus in the hyperthyroidism and temporal lobe of euthyroid patients. **Discussion:** Despite the different clinical and laboratory manifestations of the two groups, volumes of GM marked



a - GM atrophy in hyperthyroidism, mainly in the right temporal and occipital lobes.

b - GM excess in hyperthyroidism, mainly in the cingulate gyrus.

c - GM atrophy in euthyroidism, in the bilateral temporal lobe.

d- GM excess in euthyroidism, in the right temporal lobe.

Figure 1.

with atrophy were similar and widespread. Besides, in the two groups, we identified GM excess, mainly in patients with hyperthyroidism. **Conclusion:** A comprehensive analysis of GM reinforces the negative impact of Grave's disease on brain atrophy, which persists even after resolution of thyrotoxicity.

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COGNITIVE DEFICITS IN FAST KINDLING OF BASOLATERAL AMYGDALA ARE ASSOCIATED WITH ENHANCED THETA-GAMMA PHASE-AMPLITUDE COUPLING DURING REM SLEEP

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Introduction: Morphofunctional changes in limbic structures are classically followed with cognitive deficits in Temporal Lobe Epilepsy (TLE) patients. Previous studies [1] revealed that during slow-wave sleep (SWS) pathological events such as fast ripples and IEDs (interictal epileptiform discharges) gradually replace physiological events, such as Sharpwave Ripples (SWR). This replacement may be necessary for cognitive impairments observed in TLE since SWRs are fundamental for information transfer during memory consolidation. REM (rapid eye movement) sleep also plays an essential role in mnemonic processes, facilitating synaptic plasticity events and coordinating distant brain regions by coupling different oscillations, such as theta and gamma. However, alterations in REM sleep neuronal dynamics during epileptogenesis are poorly investigated. We tested the hypothesis that memory deficit during epileptogenesis can be associated with dysfunctions on rhythmic coordination during REM sleep. **Materials and Methods:** Adult male Wistar rats were submitted to a rapid kindling protocol (RK) on basolateral amygdala (BLA), allowing evaluation of electrophysiological changes during the epileptogenic process. Electrodes were implanted for the local field potentials (LFP) recording in CA1 and medial prefrontal cortex (mPFC), as well stimulation electrodes in BLA for both kindling (KD, n = 8) and control (CT, n = 5) groups. The RK protocols were performed during 3 days, applying 10 trains of 50 Hz stimulations with 10 seconds duration. Object recognition tasks were performed before and after the RK to evaluate cognitive impairment through discrimination index (DI). Sleep recordings were performed daily after the object recognition or kindling stimulation, assessing the incidence of electrophysiological events as hippocampal IEDs and SWR and cortical delta-waves and spindles during non-REM (NREM) sleep. We evaluated theta and gamma oscillations during REM sleep through power density and phase-amplitude

comodulation analysis. All protocols were approved by the Ethics Committee on Animal Use of FMRP (#016/2016). **Results:** We observed impairment on object recognition task after RK (DI before and after RK for KD group: 0.68±0.08 and 0.51±0.02, p = 0.024; CT group: 0.73±0.02 and 0.66±0.03, p = 0.936; *Mann-Whitney Test*). During REM sleep an average reduction of 7,32±0.40% theta power was observed when compared to control (CI: [-8,11; -6,57]), and an increase of theta and low-gamma comodulation after kindling application (54.1±11.3 %, 48.3±9.6 % and 58.3±15.6 % increase of Modulation Index (MI) in KD group compared to CT during three stimulation days). We observed a negative correlation (r = -0.55, p = 0.03) between average MI values and the average after-discharge duration (AD) induced by RK. During NREM sleep the IEDs incidence increased along kindling application (*tau* = 0.83, *Mann-Kendall*; p < 0.001, *z-test*) while SWR presented a decrease (*tau* = -0.70, p < 0.01, *z-test*). Alteration on hippocampal-cortical coupling was also observed, with delta events occurring 0.27±0.09 s faster after IEDs when compared to ripples (CI: [-0.43; -0.10]). **Discussion:** Our results suggest that electrophysiological alterations during REM sleep are related to memory impairment. Correlation between MI and AD suggest that epilepsy may hijack learning mechanisms such as theta-gamma comodulation, complementing findings observed during NREM sleep in epileptic patients [2].**Conclusion:** Our findings expand the comprehension of electrophysiological changes in sleep during kindling, suggesting possible mechanisms for epileptogenesis and memory deficits in TLE.

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COMPUTATIONAL MODELING OF BIOPHYSICAL CHANGES IN MOTOR AXONS CAUSED BY CHARCOT-MARIE-TOOTH TYPE 1A

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Introduction and Hypothesis: The Charcot-Marie-Tooth type Ia (CMT1A) disease is characterized by changes in the conduction velocity (CV) of motor and sensory nerves, with a uniform reduction of approximately 20m/s. This feature is not observed in demyelinating diseases such as multiple sclerosis, Guillan-Barré syndrome, and other peripheral neuropathies [1]. In the affected axons, the original myelin sheath that covers the internodes is lost and replaced by one or more internodes of smaller length, with some regions remaining demyelinated [2]. Also, there is a redistribution of the Na^+ and K^+ ionic channels in these regions [3]. The knowledge of the biophysical properties of nerve conduction combined with the tools of computational neuroscience provide an interesting environment to examine the CV of the nerve impulse after changes in the structure of the myelin sheath caused by CMT1A. In this vein, it is possible to test the hypothesis of whether the reduction in the CV of nerve axons affected by CMT1A is related to the uniform demyelination pattern. **Objective :** To develop a computational model that represents the morphological and electrophysiological properties observed in motor axons in the CMT1A. Additionally, the study is aimed at evaluating how the properties of nerve axons altered by the disease influence CV. **Methods:** The computational model will be developed in the NEURON simulator, using Python programming language [4]. Differential equations will be solved using a backward Euler method with a fixed time step of 10μs. Two neurons will be modeled: i) the reference model, which represents a non-pathological condition without demyelination, and ii) a model with morphological and electrophysiological properties of CMT1A. The neuron model encompasses isopotential sections connected through a coupling conductance so as to form a branched and wrapped cable with properties that can vary along its length. Each neuron will be divided into compartments that represent the neuron soma and axon. The axon will be divided into the node of Ranvier and internode region, the latter being subdivided into paranode and internode itself. In the regions without myelin, Na^+ and K^+ ionic channels will be included following the formalism of Hodgkin and Huxley [5], but with varying distributions among different simulations. The different distributions will be adopted to investigate the role of ionic channel distribution in axon CV. **Relevance:** CMT1A is an inherited disease that impacts the life of millions of people around the world and has no cure yet [6]. The use of tools such as mathematical and computational models can help to understand the mechanisms responsible for the onset and progression of this neurodegenerative disease, which affects both motor and sensory neurons. The model that will be developed and used in the present project is expected to be biologically plausible, and it will represent the known anatomical and electrophysiological data from humans and animal models. In addition, the model will contribute to the understanding of mechanisms operating at the molecular and cellular levels regarding the shortening of the internodes and its consequences to the CV of action potentials. The model will also allow us to test new biophysical changes that are going to be discovered in the future.

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POST-STROKE SEIZURES: A VOXEL BASED MORPHOMETRY ANALYSES REVEALING LIMBIC ATROPHY

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Introduction: The incidence of seizures after stroke is around 10% and is more prevalent in hemorrhagic than ischemic stroke (10-20% X 2-14%). Despite the negative impact in the quality of life, the etiopathology of PSE is still unclear.[1] Here we evaluated grey matter atrophy of twenty-six patients with PSE comparing to thirty free-seizures controls using Voxel-based morphometry (VBM). **Materials and Methods:** Patients (n=26) and controls (n=30) were balanced in terms of age (p= 0.5) and sex (p=0.4). The 3D-T1 weighted images were segmented with VBM, using standard protocol with CAT12/SPM-12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), running on Matlab2014.T-tests were performed with SPM12 to determine areas with GM atrophy, with Bonferroni correction for multiple comparisons. Clinical information was analyzed with SPSS23. **Results:** The average of the time between stroke and the first seizure was 1.4 years, being 65% (n=17) classified as late-onset PSE, occurring after more than one week[2]; 84% (n=22) corresponds to large vessels occlusions and 16% (n=4) lacunar lesions due to small vessels disease. Atrophy was identified in the cerebellum, thalamus, frontal lobe, parahippocampal gyrus and hippocampus as we can see in the figure 1.

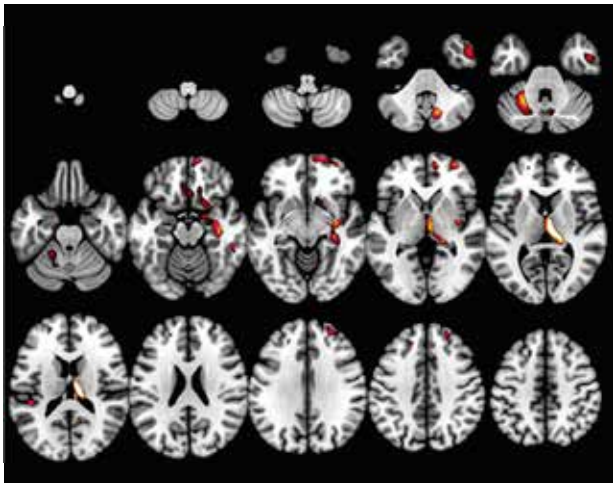

Figure 1. Gray Matter Atrophy.

Discussion: By combining patients with large and small lesions in PSE (and comparing with patients without seizures), we identified significant atrophy in the limbic region, which is highly associated with epileptogenesis. **Conclusion:** Future researches with neuroimage resources could be useful in the development of diagnostics, finding biomarkers for stroke epileptogenesis, helping to predict patients that will come with PSE.

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VISUAL ANALYTICS APPROACH FOR TRACTOGRAPHY ROI SEEDING

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Introduction: With a goal of increasing the trust in the assessment of the cerebral neuronal connectivity, we propose a visual analytics environment, in which a doctor together with a machine can improve the reproducibility of a tractography. Instead of the well-known pruning approach [3], we advocated a constructive approach from which an expert could be made aware of any uncertainties along the fiber tracking. This may enhance the safety of an intra-operative procedure and the prognostics of functional deficits caused by the resection of abnormal tissues. **Materials and Methods:** The diffusion-tensor (DT) streamline based tractography [1] was applied in the reconstruction of each fiber from the major eigenvectors of the diffusion tensor data. The tract of interest seeds were drawn, as a ROI, based on co-registered T1-weighted magnetic resonance images, color-coded fractional anisotropy map and superquadric tensorial glyphs [2]. At interactive rates, the user can visualize and assess the reconstructed fibers, and redraw the seed regions. For evaluating our approach, we planned to reconstruct 54 pairs of pre- and post-operative temporal lobe tracts (uncinate fasciculus (UF), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), arcuate fasciculus (AF), optic radiations (OR)) of patients that underwent neurosurgery. **Results:** Based on the neuroanatomy we devised procedures to reconstruct the listed tracts. Up to now, 12 out of 54 pairs have tracts reconstructed. For illustration, we present the ROI seeds and the corresponding reconstructed pre- and post-operative IFOF of a male 44 years old patient in figure 1. **Discussion:** Although we have not yet reconstructed the tracts of all test volumes, the preliminary results show that an accurate lineation of seed regions on the basis of co-registered anatomical and diffusion data improves tract specificity and facilitates its reproducibility. Without performing several pruning operations, common in most available software, our proposal provides better insights into the individual anatomy of the fibers. Nevertheless, as expected, the DTI-based tractography failed in handling fibers of complex topology and non-linear geometry. We had, for example, problems in reconstructing corticospinal tracts and cingula. **Conclusion:** We presented a new approach for ROI seeding that avoid time-consuming traditional preprocessing of the whole brain tractography. To ensure the quality and reliability of visualized fibers, further work in the reconstruction of complex fibers is still required.

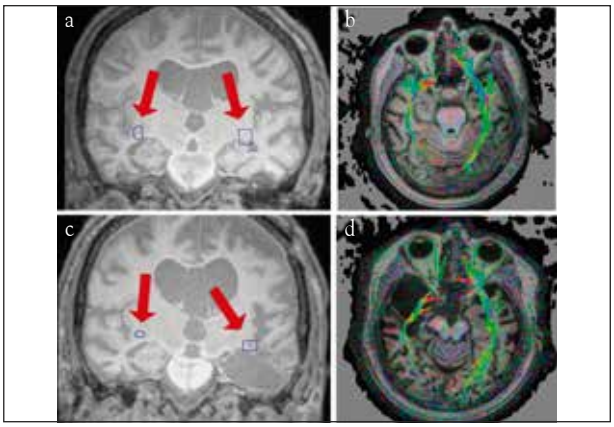

Figure 1. Pre-operative co-registered images: (a) ROI seed draw location (b) IFOF final tracts. Post-operative co-registered images: (c) ROI seed draw location (d) IFOF final tracts and visualization of the resected area.

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