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MARCH 27th TO 29th 2017 - CAMPINAS, SP, BRAZIL

PART I

J Epilepsy Clin Neurophysiol 2017; 23(2): 37-72

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Keppra® levetiracetam

- ***Keppra®*** *é o* ***único FAE*** *considerado* ***nível A*** *de evidência para o* ***tratamento de crises focais****, em terapia adjuvante, pelos guidelines da* ***ILAE*****, em pediatria*[1]
- ***Keppra®*** *solução oral, em terapia adjuvante, se mostrou bem tolerado no tratamento* ***de crises focais em crianças a partir de 1 mês de idade, crises mioclônicas (incluindo epilepsia mioclônica juvenil) a partir de 12 anos*** *e em crises tônico-clônicas primariamente generalizadas a* ***partir dos 6 anos de idade***[2,3,4,5]

**International League Against Epilepsy*

CONTRAINDICAÇÃO: Hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **INTERAÇÃO MEDICAMENTOSA:** Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam.

Referência Bibliográfica: 1. Wilmshurst JM, Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. - Epilepsia. 2015 Aug; 56(8): 1185-97. **2.** Berkovic; Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy – Neurology 2007; 69: 1751–1760. **3.** Piña Garza; Adjunctive levetiracetam in infants and young children with refractory partial-onset seizures - Epilepsia, 50(5): 1141-1149, 2009. **4.** Noachtar et al.; Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures - Neurology. 2008 Feb 19; 70(8): 607-16. **5.** Glauser; Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures - Neurology. 2006 Jun 13; 66(11): 1654-60.

Keppra® (levetiracetam). **Apresentação**: Frasco de vidro âmbar contendo 150 mL de solução oral (100 mg/mL), acompanhado de uma seringa de 3 mL para administração. **Indicações**: é indicado como monoterapia para o tratamento de crises parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia. Keppra® também é indicado como terapia adjuvante no tratamento de: - crises convulsivas parciais em adultos, crianças e bebês a partir de 1 mês de idade, com epilepsia; - crises convulsivas mioclônicas em adultos e adolescentes a partir dos 12 anos, com epilepsia mioclônica juvenil; - crises convulsivas tônico-clônicas primárias generalizadas em adultos e crianças com mais de 6 anos de idade, com epilepsia idiopática generalizada. **Contraindicações**: Hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **Cuidados e Advertências**: para informações completas de advertências, vide bula do produto. A administração de Keppra® em pacientes com comprometimento renal poderá necessitar de um ajuste da dose. Foram notificados suicídio, tentativa de suicídio e ideias e comportamento suicida em pacientes tratados com levetiracetam. *Gravidez*: categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. Levetiracetam é excretado no leite humano materno. **Keppra®** é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas. *Interações medicamentosas (vide bula completa do produto)*: Dados indicam que levetiracetam não influencia as concentrações séricas de medicamentos antiepilépticos existentes (fenitoína, carbamazepina, ácido valproico, fenobarbital, lamotrigina, gabapentina e primidona) e que estes medicamentos antiepilépticos não influenciam a farmacocinética de levetiracetam. A probenecida (500 mg quatro vezes ao dia), um agente bloqueador da secreção tubular renal, mostrou inibir a depuração renal do metabólito primário, mas não a do levetiracetam. Contudo, a concentração deste metabólito permanece baixa. Levetiracetam 1000 mg por dia não influenciou a farmacocinética dos contraceptivos orais (etinilestradiol e levonorgestrel). Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam. A extensão de absorção do levetiracetam não sofreu qualquer alteração com a ingestão de alimentos, mas a taxa de absorção diminuiu ligeiramente. Não estão disponíveis dados sobre a interação do levetiracetam com o álcool. *Reações Adversas*: para informações completas de reações adversas, vide bula do produto. Os eventos adversos mais comumente reportados nos estudos clínicos foram astenia, fadiga, dor de cabeça e sonolência. Adicionalmente às reações adversas relatadas durante os estudos clínicos, as seguintes reações adversas foram reportadas na experiência pós-comercialização, além de outras mencionadas na bula completa do produto: comportamento anormal, raiva, ataque de pânico, ansiedade, estado de confusão, alucinação, distúrbios psicóticos, suicídio, tentativa de suicídio e ideação suicida, parestesia, coreoatetose, discinesia, letargia. **Posologia**: A dose inicial recomendada para monoterapia no tratamento de crises parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia, é de 250 mg (2,5 mL) duas vezes ao dia, a qual poderá ser aumentada para uma dose terapêutica inicial de 500 mg (5 mL) duas vezes ao dia, após duas semanas. A dose máxima é de 1500 mg (15 mL) duas vezes ao dia. Nos casos de terapia adjuvante, para adultos e crianças acima de 12 anos e com peso igual ou superior a 50 kg, a dose terapêutica inicial é de 500 mg/duas vezes ao dia (5 mL/duas vezes ao dia). Esta dose poderá ser iniciada no primeiro dia de tratamento, a dose diária poderá ser aumentada até o máximo de 1500 mg/duas vezes ao dia (15 mL/duas vezes ao dia). Ainda nos casos de terapia adjuvante, para adolescentes, crianças e bebês a partir dos 6 meses com peso inferior a 50 kg a dose terapêutica inicial é de 10 mg/kg (0,1 mL/kg) duas vezes ao dia, a dose pode ser aumentada até 30 mg/kg (0,3 mL/kg) duas vezes ao dia. A alteração das doses não deve exceder aumentos ou reduções de 10 mg/kg (0,1 mL/kg) duas vezes ao dia, a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A posologia em crianças com peso igual ou superior a 50 kg é igual à dos adultos. Nos casos de terapia adjuvante para bebês com mais de 1 mês e menos de 6 meses de idade a dose terapêutica inicial é de 7 mg/kg (0,07 mL/kg) duas vezes ao dia, a dose pode ser aumentada para um máximo de 21 mg/kg (0,21 mL/kg) duas vezes ao dia. A alteração das doses não deve exceder aumentos ou reduções de 7 mg/kg (0,07 mL/kg) duas vezes ao dia a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A solução oral é a forma farmacêutica ideal para uso em bebês. **USO ADULTO E PEDIÁTRICO ACIMA DE 01 MÊS DE IDADE. USO ORAL. VENDA SOB PRESCRIÇÃO MÉDICA – SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.** Para maiores informações, consulte a bula completa do produto. (0302040021R8 Rev. Agosto 2015). www.ucb-biopharma.com.br **Reg. MS – 1.2361.0083**

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JECN Journal of Epilepsy and Clinical Neurophysiology

O BRAINN Congress é um encontro que visa reunir pesquisadores e estudantes (graduação e pós-graduação) que trabalham em neurociência, neurotecnologia e áreas afins. O principal objetivo é promover comunicação e colaborações mais fortes, a fim de alcançar padrões de pesquisa de alta qualidade.

O Congresso é uma iniciativa do projeto BRAINN (*Brazilian Institute of Neuroscience and Neurotechnology*), que é um Centro de Pesquisa, Inovação e Disseminação (RIDC) da Fundação de Pesquisa de São Paulo (FAPESP). O BRAINN congrega pesquisadores de muitas áreas (neurologia, física, engenharia elétrica, psicologia, entre outros), provenientes principalmente da Universidade de Campinas - UNICAMP e do Centro de Tecnologia da Informação Renato Archer, que é um centro federal de pesquisa e desenvolvimento; mas também de outras instituições brasileiras, como Universidade Federal do ABC, Universidade Federal de São Paulo, Pontifícia Universidade Católica do Rio Grande do Sul, entre outras; bem como algumas instituições estrangeiras, como a Universidade de Montreal e University College London, entre outras.

Como o próprio nome indica o projeto BRAINN concentra-se na pesquisa científica básica em neurociência, juntamente com o desenvolvimento de tecnologias que podem auxiliar no diagnóstico, prognóstico e tratamento de doenças neurológicas, principalmente, mas não restrito a, epilepsia e acidente vascular cerebral.

Nesta edição do *Journal of Epilepsy and Clinical Neurophysiology* estamos iniciando a publicação da primeira parte dos resumos do 4th BRAINN Congress de 2017. Haverá a publicação da segunda e última parte na próxima edição da revista.

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PART I

THE ROLE OF MIR-221 AND HSP90AB1 GENE IN SEIZURES IN THE ZEBRAFISH IMMATURE BRAIN

M. C. S. Nunes[1], W. Souza[2], V. H. S. Zago[1], R. A. Oliveira[1], A. S. Vieira*, A. H. B. Matos[3], C. S. Rocha[2], B. Carvalho[4], I. Lopes-Cendes[2], C. V. Maurer-Morelli[1]

[1]Zebrafish Laboratory; [2]Biostatistics and Computational Biology Laboratory; [3]Molecular Genetics Laboratory, Department of Medical Genetics, School of Medical Sciences, UNICAMP; [4] Department of Statistics, Institute of Mathematics, Statistics and Scientific Computing- UNICAMP and Brazilian Institute of Neuroscience and Neurotechnology, BRAINN.

Introduction: MicroRNAs (miRNAs) have been recognized as key molecules underlying seizures as well as associated with epileptogenesis[1]. In order to unravel molecular mechanisms, zebrafish has been successfully used by researchers as an animal model for genetic studies for a while[2]. This study aimed to integrate miRNA and mRNA transcript profiles by applying massive sequencing approach in order to identify molecular mechanisms underlying seizures in the zebrafish seizure model. **Materials and Methods:** Zebrafish larvae at 7 days post fertilization were divided into three experimental groups: CTL - animals exposed to bath medium for 3 hours (n=3); AS - acute seizure, animals exposed to pentylenetetrazol (PTZ) for 20 minutes (n=2) and *SE* - status epilepticus–like, animals exposed to PTZ for 3 hours (n=3). Each sample (n) was composed by pooling 20 larva heads. Total RNA was extracted, and validated mRNA and miRNA libraries (*Illumina TruSeq Stranded mRNA LT* and *TruSeq Small RNA Sample*) were achieved followed by high throughput screening (*Illumina HiSeq 2500*). Bioinformatics analyses were first performed to filter the mRNA and miRNA differentially expressed on the samples ($p<0.01$), and secondly to perform an integrated analysis to cross the data between a determined miRNA and their targets. In our analyses, we utilized the public databases miRBase (mirbase.org) and TargetScanFish (targetscan.org). **Results:** We previously reported the miRNAs differentially expressed[3] for each comparison (CTL *vs* SE; CTL *vs* AS and AS *vs* SE). For each miRNA, we selected one target gene that exhibited an inverse correlation regarding expression. Here we highlight the microRNA *mir-221* that is differentially expressed in the SE *vs* AS comparison and its target, the *hsp90ab1*gene. **Discussion:** A recent article reported *mir-221* as an important miRNA in pro-epileptogenic processes in the human brain [1]. Interesting, this microRNA is orthologous in humans and zebrafish. We chose the orthologue gene, *hsp90ab1*, as a target for *mir-221* since both are inversely expressed. In the literature, this gene is related to the mTOR signaling pathway, important to the gene expression regulation of the GABAergic and glutamatergic receptors, neuroinflammation, antiepileptic drugs resistance, and morphine addiction. **Conclusion:** In this work, we performed an integrated analysis of miRNA and mRNA massive profiles in zebrafish brain after two protocols of PTZ-induced seizures. We highlighted the *mir-221* and its target gene *hsp90ab1* due to its possible importance in epilepsy. The following steps will be performing real-time PCR for independent validation, and to perform in-situ hybridization in order to localize these molecules in the zebrafish brain. By using the zebrafish model, we hope to increase the understanding of the molecular mechanisms underlying seizures and provide targets that are potentially therapeutic for seizures.

References: [1] Cattani, et al. Epilepsia. 2016; [2] Dodd, et al. Human Molecular Genetics. 2000; [3] Zago, et al. JECN. 2015;22(3):94.

AGING EFFECTS ON FUNCTIONAL BRAIN CONNECTIVITY BY MAGNETIC RESONANCE IMAGING

J. P. S. Silva[1], R. F. Leoni[2], A. C. dos Santos[2]

[1]Inbrain Lab, Department of Physics, FFCLRP, University of São Paulo, Ribeirão Preto, Brazil; [2]Department of Medical Clinic, FMRP, University of Sao Paulo, Ribeirao Preto, Brazil.

Introduction: Recently, the effects of aging on human brain tissue, mainly how changes in brain functionality happen through time have been extensively discussed1. However, there is still no agreement on which brain regions have altered Functional Connectivity (FC) and how it is related with healthy aging. Therefore, this study aims to investigate the Resting State Networks (RSNs) and FC in healthy aging using functional Magnetic Resonance Imaging (fMRI). Materials and Methods: Twenty subjects were included in this study: ten healthy young (6M/4F, mean age = 24.2±3.2 years) and ten healthy elderly (4M/6F, mean age = 60.2±8.3 years). Images were acquired in a Philips Achieva 3T System, using a 32-channel head coil for signal reception. For anatomical reference, images were acquired using a 3D T1-weighted GRE sequence, with the following parameters: TR/TE = 7/3 ms, flip angle = 8°, matrix = 240 x 240, FOV = 240 x 240 mm², 160 1-mm slices. For functional evaluation at resting state, images based on BOLD contrast were acquired using a 2D EPI sequence, with the following parameters: TR/TE = 2000/20 ms, flip angle = 90°, matrix = 80 x 80, FOV = 240 x 240 mm2, 31 4-mm slices, gap = 0.5 mm, number of dynamics = 200. Images were processed using own routines developed in MATLAB (MathWorks, Natick, MA) and SPM12 routines. Group ICA of fMRI Toolbox (GIFT) was used to assess the spatial distribution of RSNs. T-tests corrected for multiple comparisons were used to show differences in RSNs maps between subject groups (p-FDR < 0.05), and Dice similarity coefficients were calculated to assess the similarity between maps. For FC evaluation, fMRI data was analyzed within the Conn toolbox considering all brain regions in Harvard-Oxford atlas as seeds. Results: Statistical parametric maps from both groups showed the following RSNs: default mode network, visual, auditory and left executive control. However, a voxel-wise analysis comparing RSNs maps between groups showed differences in spatial distribution. Alterations in FC were observed in healthy aging, mainly between regions involved in memory, planning, attention, visual processing and language (Figure 1).

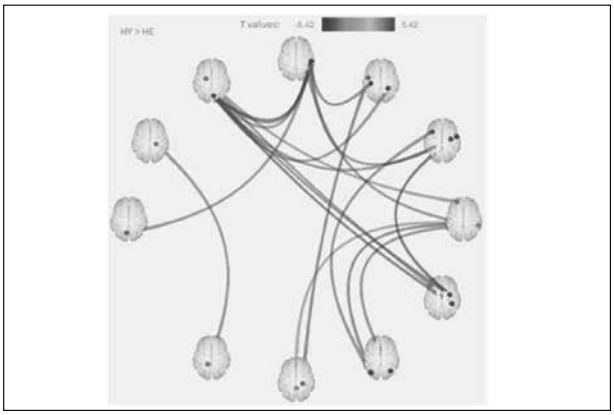

Figure 1. Red and blue lines show, respectively, higher and lower correlations for the young group compared to the elderly group. Statistical threshold was set at $p < 0.05$ (FDR-corrected).

Discussion: RSNs maps were more spread in elderly, showing that, with aging, the brain may recruit new areas as a form of compensation, leading to a loss of expertise2. **Conclusion:** So far, the results of the present study indicate a significant alteration of FC and differences in spatial distribution of RSNs in healthy aging. Further analysis and greater group sizes with allow more understanding on the relationship between aging and changes in brain functionality.

References: [1] Ferreira LK, et al. Neurosci Biobehav Rev. 2013;37(3):384-400; [2] Sala-Llonch et al. Front. Psychol. 2015;6(663).

PROTEOMIC PROFILE FROM DORSAL AND VENTRAL DENTATE GYRUS FROM THE CLASSIC PILOCARPINE MODEL OF MTLE

A. M. Canto[1], A. H. B. Matos[1], B. B. Ayoama[1], A. S. Vieira[2], R. Glioli[3], I. Lopes Cendes[1]

[1]Genetics Dept., FCM, UNICAMP, BRAINN; [2] Biology Institute, UNICAMP; [3] CEMIB, UNICAMP.

Introduction: Mesial Temporal Lobe Epilepsy (MTLE) is the most common type of severe epilepsy in adults and it is characterized by histopathological abnormalities in the mesial temporal lobe structures[1]. The dentate gyrus (DG) is an integral portion of the larger functional brain system called hippocampal formation. Thus, there are numerous features of the DG that make it unique in a neuroanatomical and functional way. The hippocampal formation is also subdivided into dorsal and ventral portions in rodents, which are described having distinct and specific functions in the brain[2]. The pilocarpine model is a classical chemoconvulsant model to MTLE that presents many characteristics similar to those found in patients[3]. Therefore, we propose to study the proteome from the cell bodies of the dorsal (dDG) and ventral (vDG) dentate gyrus of the hippocampal formation obtained from epileptic rats induced with pilocarpine. **Materials and Methods:** Wistar rats (8 weeks old) received a 320mg/kg of pilocarpine (n=5, i.p.). The status epilepticus (SE) was observed during 4 h and the diazepam (4mg/kg) was administrated to stop the seizures. The animals were video-monitored 24h during 15 days. With the frozen tissue PEN slides (polyethylene naphthalate) were properly made for laser-microdissection (Zeiss). After the microdissection process the protein was extracted using 8M urea, digested with trypsin and de-salted with SepPack C18 columns. The proteins were analyzed using a LTQ-Orbitrap from CeTICS – Butantan Institute, SP, and label-free quantitation was performed. The proteins were analyzed with the MaxQuant and R software. **Results:** We identified a total of 507 proteins in the dDG of which 76 were differentially expressed in the epilepsy model. We found 439 proteins in the vDG of which 40 were differentially expressed. Interestingly, we found that enriched biological pathways and the proteomic profile were different between the dDG and vDG. **Discussion:** For the dDG we found changes in proteins related to energy metabolism, such as the Glycolisis and gluconeogenisis pathways and Ca^{2+} signaling, while in the vDG we identified protein changes in signal transduction involving the mTORC2, which is related to many biological processes such as cellular metabolism and cytoskeleton properties and the transformation of Schawnn cells in neurofibromatosis type 1. **Conclusion:** Here we show remarkable differences in protein expression among different sub-regions of the DG of the classic pilocarpine model of MTLE. The proteins identified can indicate anew molecular mechanism potentially involved in epileptogenesis. Furthermore, our results have important implications for future studies of epileptogenesis in animal models and how these translate to knowledge about epilepsy in patients.

References: [1] Blumcke et al. Epilepsy Res. 1999;36(2-3):205-23; [2] Strange, et al. Nature reviews. 2014;15:655–69; Buzsáki, Moser. Nature Neurosci. 2013;16:130-38; [3] Turski, et al. Behav Brain Res. 1993;9:315-35. **Support:** FAPESP – CEPID/BRAINN

PROTEOMIC ANALYSIS OF THE SUBICULUM REGION OF THE HIPPOCAMPUS IN ANIMALS WITH TEMPORAL LOBE EPILEPSY INDUCED BY PILOCARPINE

B. B. Aoyama[1], A. M. Canto[1], A. H. B. Matos[1], A. Vieira[2], B. S. Carvalho[3], R.Glioli[4], I. Lopes-Cendes[1]

[1]Department of Medical Genetics, School of Medical Sciences; [2]Department of Structural and Functional Biology, Institute of Biology; [3]Department of Statistics, Institute of Mathematics, Statistics and Computer Sciences; University of Campinas, UNICAMP; and the Brazilian Institute of Neuroscience and Neurotechnology, BRAINN, Campinas, SP, Brazil; [4]Multidisciplinary Center for Biological Investigation,CEMIB; University of Campinas, UNICAMP, Campinas, SP, Brazil.

Introduction: Temporal lobe epilepsy (TLE) is the most frequent type of epilepsy in adults and these patients usually do not respond well to clinical 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. This structure is situated in the cortical area of the mesial temporal lobe and its function is related with memory formation and emotional control. In the anatomical aspect of rodents, the hippocampus is divided in ventral and dorsal regions. 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 involved in the recovered short-term memory and spatial memory codification. This study aims to understand the molecular role of the subiculum in MTLE in the classical model of pilocarpine induced epilepsy. For this purpose, we used laser capture microdissection (LCM) to isolate cells of the subiculum, which were subsequently used for proteomics studies. **Materials and Methods:** We used 5 sham-control and 5 treated rats (CEMIB-UNICAMP) and performed LCM (Zeiss). We extracted the subiculum from the brain tissue using a surgical microscope (Zeiss).Then we extracted the proteins using 8M Urea and performed in-solution digestion with trypsin. The quantification was made using Qubit Protein Assay Kit (Thermo) and for the de-salting we used C18 SepPack columns (Waters). The samples were analyzed using an LTQ-Orbitrap from CeTICS/ Butantan and the bioinformatics analyzes will be performed with the MaxQuant and R softwares. **Results:** We were able to obtain around 8.8μg of protein from dorsal controls, 23μg from ventral controls, 4.5μg from dorsal pilocarpine treatment and 12.5μg from ventral pilocarpine treatment. As this study still is under way, we expect to find distinct protein expression patterns and biological pathway from the dorsal and ventral portions of the subiculum. **Discussion/Conclusion:** LCM is an extremely important tool to isolate cell populations allowing these distinct regions to be correctly analyzed. Moreover, the mass spectrometry analyzes will show us the differential expressed proteins comparing controls with pilocarpine treated animals, as well as regional differences in the subiculum.

Support: CEPID-FAPESP, CNpQ.

VARIANTS OF EEG FUNCTIONAL BRAIN CONNECTIVITY EVALUATION METHODS FOR BCI MOTOR IMAGERY CLASSIFICATION

P. G. Rodrigues[1,4], C. A. Stefano Filho[2,4], R. Attux[3,4], G. Castellano[2,4], D. C. Soriano[1,4]

[1]CECS, UFABC; [2]Neurophysics Group, IFGW, UNICAMP; [3]FEEC, UNICAMP; [4]Brazilian Institute of Neuroscience and Neurotechnology, BRAINN, Campinas, SP, Brazil.

Introduction: Brain-computer interfaces (BCIs) not only provide alternative means for controlling assistive devices, but also allow means for a better understanding of neuronal mechanisms underlying different cognitive tasks. This work presents a BCI performance comparison between two different approaches for feature generation, based on brain functional connectivity. Connectivity was represented by an adjacency matrix (**A**), built by considering similarities between all pairs of electrodes under BCI motor imagery (MI) tasks recorded by EEG. **Materials and Methods:** A four-command motor imagery database containing training and testing datasets for nine subjects (BCI competition IV – dataset 2a[1]) was analyzed. Functional connectivity was estimated by considering two different similarity measures between the electrodes for obtaining **A**: 1) Pearson correlation; 2) Space-Time recurrence (STr) counting. Feature extraction was performed considering classical graph metrics: degree, clustering coefficient, betweenness and eigenvector centralities. A least squares (LS) classifier was used and the classification error was obtained based on training and testing datasets as defined in[1]. **Results:** Table 1 shows the classification error for the best pair and also all classes using Pearson correlation and the space-time recurrences. **Discussion and Conclusion:** The results show that it is possible to use spatial recurrences between electrodes over a time window to compute similarity in order to obtain the adjacency matrix. However, it can be noted that different approaches can lead to possibly different pair of best classes for the same subject. In addition to that, the STr approach exhibited the best performance considering the mean among all subjects using all tasks ($p = 0.006$ – paired t-test) and can be considered a relevant alternative for measuring similarity.

Table 1. Classification performance for the best pair of classes and for all classes considering Pearson correlation and STr similarity measures. Classes: 1: left hand; 2: right hand; 3: feet; 4: tongue; $\mu \pm \sigma$: mean ± standard deviation. Graph edges were defined by a correlation threshold (ρ) or by a distance threshold (ε) and counting threshold (ψ) for STr.

	Pearson Correlation (ρ = 0.78)		Space-Time Recurrence (ε, ψ) = (1.3, 0.5)	
Subject	Best Pair (x/y) - error	All Classes	Best Pair (x/y) - error	All Classes
S1	(1/4) – 0.201	0.552	(2/4) – 0.146	0.507
S2	(1/2) – 0.424	0.715	(1/3) – 0.389	0.632
S3	(1/4) – 0.306	0.559	(2/4) – 0.153	0.483
S4	(2/3) – 0.368	0.590	(1/3) – 0.292	0.601
S5	(2/4) – 0.451	0.719	(2/3) – 0.410	0.722
S6	(3/4) – 0.410	0.729	(1/4) – 0.403	0.691
S7	(2/4) – 0.389	0.733	(3/4) – 0.278	0.629
S8	(1/4) – 0.306	0.649	(1/2) – 0.188	0.504
S9	(3/4) – 0.285	0.587	(1/4) – 0.153	0.517
$\mu \pm \sigma$	-	0.648±0.077	-	0.587±0.088

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GA4GHCLIENT: ACCESSING FEDERATED GENOMIC DATABASES THROUGH GA4GH

W. Souza[1], B. S. Carvalho[2], C. Rocha[1], I. Lopes-Cendes[1]

[1]Department of Medical Genetics, School of Medical Sciences; [2]Department of Statistics, Institute of Mathematics, Statistics and Computer Science; University of Campinas, UNICAMP, Campinas, SP, Brazil and the Brazilian Institute of Neuroscience and Neurotechnology,BRAINN, Campinas, SP, Brazil.

Introduction: Federated databases consist in using local resources for hosting data instead of submitting data to centralized data servers[1]. This concept facilitates sharing genomic data with restricted access to sensitive information such as individuals' information. It also avoids legal issues associated to data protection. Hosting data locally leads to difficulties in data integration from different databases because each provider may implement its own non-standard interface for publishing data. The Global Alliance for Genomics and Health (GA4GH) was formed to help accelerate the potential of genomic medicine to advance human health. They developed data model schemas and application program interfaces (APIs) for genomic data. These APIs are specifically designed to allow for standardized genomics data exchange. There are server-side implementations of these APIs for hosting genomic data via the Internet. Due to the lack of software for retrieving information from GA4GH-based data servers, we developed the GA4GHclient for accessing these federated data servers and retrieving genomic data through the GA4GH APIs. GA4GHclient provides a graphical web interface for easy data interaction and programming libraries for integrative data analysis development. **Materials and Methods:** The GA4GH API schemas are developed continuously to address many issues regarding genomic and clinical data sharing. We used the latest version of these schemas for retrieving variant genomic and sequence alignment data from GA4GH-based data servers. We implemented our software in R programming language using Bioconductor packages for manipulating API data[2]. The web-based user interface was designed to show general data while omitting sensitive data such as patient information. We tested our software package by retrieving genomic data from 1000 Genomes Project, Ensembl, BRCA Exchange and the Brazilian Initiative on Precision Medicine (BIPMed). **Results:** We developed GA4GHclient, a Bioconductor package that provides easy access to GA4GH-based public data servers. Our package provides programming tools for integrating genomic data from different databases. The programming framework contain tools for converting retrieved data to common file formats such as VCF. GA4GHclient also provides a graphical web application for interacting with genomics data with search engine by gene name and genomic location.**Discussion:** Federated genomic databases that use the GA4GH API implementations combined with the GA4GHclient package open new opportunities for integrating genomic data from thousands of individuals. GA4GHclient's graphical interface allows interacting with GA4GH-based databases. The graphical interface is also useful for making available genomic databases with restricted access to anonymous users. **Conclusion:** We developed GA4GHclient, a Bioconductor package that provides programmatic access to GA4GH-based databases and a user-friendly web interface. The GA4GHclient package is freely available at https://github.com/labbcb/GA4GHclient.

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SOMATIC MUTATIONS ARE ABUNDANT IN FOCAL CORTICAL DYSPLASIA

V.S. de Almeida[1], S.H. Avansini[1], M. Borges[1], M.G. Mazutti[1], F.R. Torres[1], F. Rogerio[2], B.S. Carvalho[3], F. Cendes[4], I. Lopes-Cendes[1]

[1]Department of Medical Genetics, School of Medical Sciences; [2]Department of Anatomical Pathology, School of Medical Sciences;[3]Department of Statistics, Institute of Mathematics, Statistics and Scientific Computing, IMECC; [4] Department of Neurology, School of Medical Sciences; University of Campinas, UNICAMP, Campinas, SP, Brazil and the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, SP, Brazil.

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 cytoarchitecture also observed in other MDCs, such as in Tuberous Sclerosis (TS) and Hemimegaencephaly (HME)[2,3]. Recently, mosaic mutations were detected in TS, HME and rare cases of FCD[4]; however, it is still unclear whether somatic mosaicism is indeed frequent in FCD[4]. **Materials and Methods:** Deep whole exome sequencing was performed on genomic DNA extracted from brain tissue resected by surgery (BTRS) and blood samples of six patients with FCD. We performed capturing and enrichment with Nextera® Expanded Kit (Illumina®). Samples were sequenced following a 200bp paired-end protocol in a Hiseq2500 (Illumina®) to achieve at least 200x 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 mosaicisms using Mutect2. Variants were classified as mosaic mutations when less than 20% of reads are not aligned to 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 in 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 a total of seven mosaic mutations in BTRS, including three variants in genes belonging to mTOR pathway (*PIK3R3, AKT2* and *IRS1*), and four variants localized in genes belonging to Tau pathway (*NDUFA2, GRIN1, LRP1* and *CAPN1*). All patients sequenced had two or more somatic mutations in these previously described genes. **Discussion/Conclusion:** Somatic mutations were identified in genes with functional roles and expression in the central nervous system. Somatic mutations were abundant in FCD tissue and were detected in all samples examined.

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INVESTIGATING A POLYGENIC EFFECT IN GENOMIC DATA OF PATIENTS WITH CHILDHOOD EPILEPTIC ENCEPHALOPATHIES

H.T. Moraes[1], B.S. Carvalho[2], I. Lopes-Cendes[1]

[1]Department of Medical Genetics, School of Medical Sciences; [2]Department of Statistics, Institute of Mathematics, Statistics and Computer Science; University of Campinas, UNICAMP, Campinas, SP, Brazil and the Brazilian Institute of Neuroscience and Neurotechnology, BRAINN, Campinas, SP, Brazil.

Introduction: Childhood epileptic encephalopathies (CEEs) is a group of severe epilepsies that are resistant to drug treatment and associated with delayed neuropsychological, motor and cognitive development (Guerreiro et al., 2000; McTague et al., 2016). The diagnosis of CEE is still based on clinical criteria and electroencephalogram results and the etiology remains unknown in most patients. With the progress of molecular studies, in the last five years new mutations associated with CEE have been described (Gonsales et al., 2015). However, a significant portion of the patients still do not have a major genetic variant identified (assuming a monogenic inheritance

model) even after whole human exome sequencing (Berkovic et al., 2015). Thus, the main objective of this work is to apply new analytical paradigms to identify and investigate genetic changes following complex inheritance models. **Methods:** We will use whole exome sequencing data from a large cohort of CEE patient. The preparation of the exoma libraries will follow protocol recommended by SureSelectXT Target Enrichment System for Illumina Paired-End Sequencing Library kit (Agilent Technologies) and will be sequenced on Illumina Hiseq 2500. After the identification and annotation of the variants we will apply algorithms that allow us to consider a polygenic and cumulative effect on genes in the same or different molecular pathways, but with potential additive effect in the phenotype. **Results**: This is still an ongoing study and we expect that at the end of our work, we will have applied and tested the original hypothesis that cases of CEE can be caused by mutations with small individual effects, occurring in several genes of a common pathway or in pathways that may converge to a major final effect on the phenotype. **Discussion/Conclusions:** This work has the potential to change the entire analytical paradigm currently used in the molecular diagnosis of CEEs leading to valuable information about the etiology and molecular diagnosis of these severe forms of epilepsy.

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CONTROLLING A GAME USING A BCI-SSVEP WITH FOUR COMMANDS

H. M. A. Leite[1,2], S. N. Carvalho[2], T. B. S. Costa[1], R. Attux[1], H. H. Hornung[3], D. S. Arantes[1]

[1]FEEC; UNICAMP; [2]ICEA, UFOP; [3]IC, UNICAMP.

Introduction: BCI (Brain-Computer Interface) is an important modality of Human-Computer Interaction, since it expands the interaction possibilities of people with disabilities[1]. SSVEP (Steady-State Visually Evoked Potentials) is a BCI paradigm that allows the generation of commands through visual stimuli that flicker at different frequencies[2], each one related with a specific command. In this abstract, we discuss a game with four commands controlled by BCI-SSVEP. This game is intended to teach the use of BCI-SSVEP to possible users who will need to manipulate this technology, so that they gradually gain confidence and ability before interacting with more complex applications, such as controlling a wheelchair or manipulating a prosthesis. **Materials and Methods:** A game whose goal is to collect coins distributed by a board has been developed in Unity3D. The game has four movement commands that allow a ball to move across the board to collect the coins. The movement commands of the ball are related to four visual stimuli that blink at frequencies: 6 Hz (left), 10 Hz (right), 12 Hz (down) and 15 Hz (up). These frequencies were chosen as multiples of the monitor refresh rate to ensure the accuracy of the stimulus. The stimuli consist of black and white squares positioned in the center region of the left, right, top and bottom ends of the screen. The brain signal was monitored by an electroencephalography (EEG) device using 16 dry electrodes positioned at O1, O2, Oz, POz, Pz, PO4, PO3, PO8, PO7, P2, P1, Cz, C1, C2, CPz, FCz, according to the 10-10 system. An experimental study has been conducted with 2 healthy subjects to analyze their interactions with the game. Each volunteer played four matches with the task of collecting four coins in a maximum of two minutes. A questionnaire regarding their perception about the game was applied. Both subjects were informed about the experiment and agreed to the approved consent form (Ethics Committee of UNICAMP, 791/2010 CAAE 0617.0.146.000-10). **Results:** Both subjects successfully managed to control the game through BCI-SSVEP. Considering four matches, subject 1 collected an average of 3.75 ± 0.50 coins, collecting all the coins in three of the four matches. Subject 2 collected an average of 2.25 ± 0.96 coins, collecting all coins in only one of the four matches. Subjects reported that the control of ball movement in the game was intuitive. Despite the need for a continued concentration on the visual stimuli, neither of the subjects reported fatigue caused by the game. However, subject 2 reported that his eyes watered. Subjects did not report discomfort about the use of the EEG cap. Considering the hit rate calculated with training data, subject 1 has an information transfer rate (ITR) of 60 bits/min and subject 2 has an ITR of 13.53 bits/min. However, during the game, the transition times to change command and the distraction caused by interaction with the game tend to reduce the hit rate and consequently the ITR. **Discussion:** The results show that both subjects adapted satisfactorily to the control of the game, and showed that it is possible to achieve the goal of the game, which was to collect the four coins distributed by the scenario. During the experiment, it was possible to perceive that the users were motivated to collect all the coins and that there was a bit of frustration when this goal was not achieved. We believe that for training applications this motivation is important as it encourages the subject to maintain concentration and increases their abilities with BCI controls. **Conclusion:** A game controlled by BCI-SSVEP has been developed and tested with two subjects. The results have shown that the control of four commands proved to be efficient, causing minimal discomfort to the user. However, a more detailed experimental study should be conducted before the game is made available to the training and conditioning stage of BCI-SSVEP applications.

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CORPUS CALLOSUM FRACTIONAL ANISOTROPY VALUES WITH SIGNIFICANT STATISTICAL DIFFERENCES DUE TO DISTINCT DTI-BASED PARCELLATION METHODS

G. S. Cover, M. P. Bento, L. Rittner

MICLab – Medical Image Computing Laboratory, School of Electrical and Computer Engineering (FEEC), UNICAMP.

Introduction: The Corpus Callosum (CC) is a set of neural fibers in the cerebral cortex, responsible for connecting both hemispheres of the brain and facilitating interhemispheric communication. The CC is the structure with the largest amount of white matter in the brain, CC changes present a correlation not only with age and gender but also with different stages of neurodegenerative diseases. To facilitate the study of specific portions, the CC is usually parceled into smaller regions, also known as its parcellation. These divisions are based on differences in function or histological composition, information that is not available through anatomical magnetic resonance imaging (MRI) techniques. Diffusion tensor imaging (DTI), an MRI modality, provides new information useful for the CC study when compared to anatomical MRI. This work implements and compares three parcellation approaches on DT images through the fractional anisotropy (FA) measurement, to verify if there are statistically significant differences between them. **Materials and Methods:** Our image database was composed by DT images from 150 subjects obtained in the axial plane (2.0 mm thickness, 1.0 x 1.0 mm, 32 directions) at Hospital de Clínicas of UNICAMP. As a pre-processing step, the CC is initially segmented in the midsagittal slice using the FA map weighted by the projection of the DTI's main eigenvector[1]. After its segmentation, the CC is then parcellated in five regions with three distinct methods: Witelson[2], Hofer & Frahm[3] and the Watershed[1]. To verify statistically significant differences between all methods, the mean FA scalar map derived from the DT image, that represents the degree of anisotropy of water diffusion for each parcellated region, is computed. Furthermore, the analysis of variance (ANOVA) for repeated measures was also obtained to compare all parcellated region results. **Results:** The obtained parcellation (Figura1) was evaluated for 150 subjects, with FA mean results (Figura 2) within all five regions. **Discussion:** The final CC parcellation presented the ANOVA for repeated measures of $p < 0.05$ to the first and fifth parcellated regions among all three methods. **Conclusion:** Although all methods parcellated the CC in five regions, the first and fifth regions seemed to be statistically different.

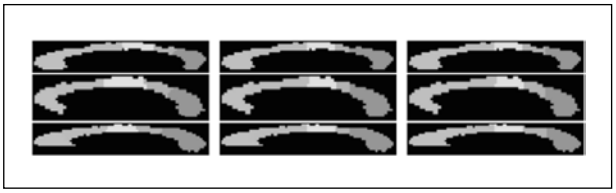

Figure 1. CC parcellation results in three distinct subjects (lines) using parcellation method: Watershed (column 1), Hofer & Frahm (column 2) and Witelson (column 3).

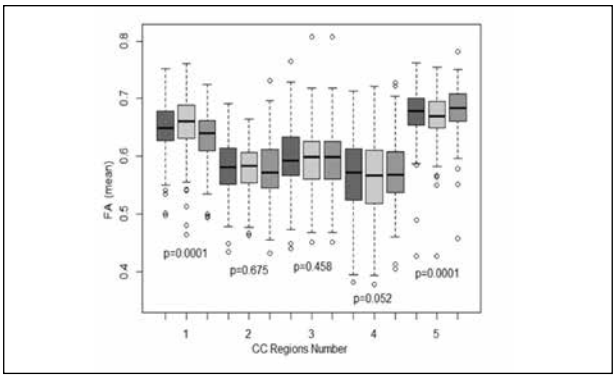

Figure 2. Mean FA results for Witelson (red), Hofer & Frahm (yellow) and Watershed (blue) parcellation method.

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UPGRADING OF A CLINICAL GAMMA-CAMERA FOR HIGH RESOLUTION BRAIN PERFUSION SPECT IMAGING OF RATS AND MICE

J. Mejia[1], A. Miranda[1], M. de Barboza[1], L. de Oliveira[1], E. Sales[1], O. Galvis-Alonso[2], F. Cabral[1]

[1]Hospital Israelita Albert Einstein, São Paulo, SP; [2]Departamento de Biologia Molecular, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, SP.

Introduction: Preclinical molecular imaging techniques allow the assessment of the functionality of internal organs of small animals and the response to an experimental protocol, at different time points, in vivo. With this, the quality of the results is improved and the cost of the experiment is reduced. In this work, we developed and characterized an updated version of an electromechanical device to upgrade a clinical gamma-camera[1], standardized an appropriate imaging protocol and applied the system to obtain high resolution brain perfusion SPECT images of mice and rats. **Materials and Methods:** A retired GE Systems Discovery VH gamma-camera was installed in our preclinical molecular imaging laboratory. We built an updated version of the miniSPECT device, including hardware and software subsystems. The hardware subsystem allows the study of different size animals, from mice to large rats. Projections are obtained using single pinhole collimators. Three different diameters and materials were tested, as well as double and triple pinhole collimators. Tomographic images are obtained using a locally developed software tool based on the OSEM algorithm[2]. To image brain perfusion of normal and stroke mice and rats, animals were injected with 110 to 370 MBq of ^{99m}Tc-HMPAO. Forty projections of 45 secs were determined as an appropriate set, using 1.0- or 1.5-mm diameter collimators. Tomographic images were reconstructed with 10 iterations, 4 subsets and a 1.5-voxel smoothing kernel between iterations. **Results:** Three different configurations were defined for different size animals, given magnifications of 9.5×, 7.1× or 5.6×. Spatial resolution for those configurations varies from 0.45 to 1.5 mm, as determined using Jaszczak microphantoms. Acquisition and reconstruction times are around 30 mins each, which is appropriate for a routine setup. The system was validated by obtaining brain perfusion images of normal and stroke mice and rats, and comparing them with TTC-stained histological slices. **Discussion:** Adapting already existing or retired instrumentation [3] for alternative purposes opens the opportunity to apply molecular imaging techniques to assess the effect of experimental protocols with a reduced cost investment. Depending on the desired image characteristics, good quality images can be obtained, if compared with the ones obtained with the specific-purpose commercially available instruments. In this work, we used ^{99m}Tc as imaging agent, which emits gamma-rays at 140 keV. However, other radioactive elements can be used, as ^{201}Tl, ^{67}Ga, ^{123}I or ^{188}Re, which emit at energies below 200 keV, and whose use depends on the development of appropriate radiopharmaceuticals or animal models of disease. Finally, the implemented solution can be applied in several areas besides Neurology, as Cardiology or Nephrology. **Conclusion:** We have developed an electromechanical upgrading device for a retired gamma-camera, which allows us to obtain high resolution tomographic SPECT images of organs of laboratory animals. The device was used to image brain perfusion in normal and stroke animals. However, it can be applied in other areas depending on the available radiopharmaceutical or the animal model to be studied. In any case, this kind of solution can reduce studies duration and number of animals used in experimental protocols, in accordance with ethical guidelines.

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SOCIAL IDENTITY AND THE REPRESENTATION OF EPILEPSY IN CINEMA

F. S. Gutiyama[1], F. N. Akhras[2]

[1]Multimedia Dept., IA, UNICAMP; [2]Multimedia Dept., IA, UNICAMP.

Introduction: This study is an analysis of epilepsy representation in occidental films made since 2005, which continues the studies started by Kersons[1], who analyzed the representation of seizures in more than a hundred movies comparing them to the seizures and epilepsy classification of International League Against Epilepsy (ILAE). Throughout our analysis, we realized that previous studies related to cinema did not explore the question of alterity, identity, and social representation of the person with epilepsy, and for this reason to contribute to the research in this field, we seek to bring this new bias to the theme. **Materials and Methods:** Our selection of movies was determined by relevance of the type of production, to develop a comparative between different audiovisual languages from three fictional films (*Requiem, The Exorcism of Emily Rose* and *Electricity*) and three documentary films (*Zach, A seizure by Nathan Jones and Illegal*). As apparatuses to develop a new methodology of analysis, we have applied to studies in sociology, medical anthropology, and cultural studies. Based on the biopolitical vision of Michel Foucault[2], we developed this methodology to analyze the cited films, which consisted of the following steps: a contextual survey of the type of production; analysis of the script's discourse and how it approaches to the theme; analysis of the representation of the crisis of epilepsy; and analysis of the relationships between the characters and social institutions represented or involved. **Results:** The fictional films still portray epilepsy in a stigmatized way, even when they attempt to break with this type of prevailing social gaze through questioning us about medicinal treatments and religious beliefs. The classic documentary films still explore a humanitarian vision that portrays people with epilepsy as different from the rest of society, even those made with the participation of associations that fight for the recognition of epilepsy. The loss of body control is an intense image to which camera looks away. Although, there is the independent production *A seizure by Nathan Jones*, produced by himself who has epilepsy, portrays the manifestation of the crisis as a daily experience, and it creates space for a new type of look and new subjectivity. **Discussion:** Cinema allows us to look at and analyze our social reality, and through it we identify the roles of social institutions, the body as an extension of the subject's identity, and the perception about oneself. In a diachronic way, the occidental representation of epilepsy shifted from the perceptions of spiritual possession to the bodily medical perceptions, per our cultural context. And today the discussions about corporality and the self-consciousness of the own identity gain strength, just as the questions about the forms of power that regulate our habits, our culture, and our way of being raised by Foucault[2] are reflected in the films, and it gives space for the expression of new subjectivities; and within our theme, it questions us about what it is to be healthy and how the speech of social institutions standardizes the reality of those who have epilepsy. **Conclusion:** Through the analysis we conclude that the stigma of epilepsy remains predominantly represented, and consequently, it remains present in our social reality, likewise we recognize the cinema as a re-reading of our society, how it is defended by Pierre Sorlin[3].As we see, we must to review the way people with epilepsy are approached by social institutions in a general way, especially the approaches of the institutions of medical and educational systems, and family, and we have to analyze if the discourses reproduced by them respect the subjectivity and identity of people with epilepsy.

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FREQUENCY OF MICROREARRANGEMENTS ON PATIENTS WITH EPILEPTIC ENCEPHALOPATHIES AND RELATED PHENOTYPES

C. M. Toledo[1], M.C Gonsalez[1], C. V. Soler[1], I. Lopes-Cendes[1]

[1] Dept. of Medical Genetics, School of Medical Sciences, University of Campinas-UNICAMP, Campinas, SP, Brazil; and the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, SP, Brazil.

Introduction: The aim of this study was to assess the frequency of copy number variations (CNV) in patients with Childhood Epileptic Encephalopathies (CEE)[1], including patients with Dravet and Doose Syndromes, as well as related phenotypes, such as Generalized Epilepsy with Febrile Seizures Plus (GEFS+). Copy number variations account for microrearrangements in the DNA, being either deletions or duplications of a segment, in this case, in the target gene. The target gene chosen was *SCN1A*, one of the most prominent genes in the analysis of epileptic disorders and with high frequency of point mutations found in patients with CEE. **Materials and Methods:** The chosen method was Multiplex Ligation Probe Amplification (MLPA), one of the main techniques used to assess CNVs in a specific gene. A total of 98 patients were evaluated, 92 of which had one of the CEEs and 7 of which were diagnosed with GEFS+. We choose to study related phenotypes, such as GEFS+ spectrum, in order to determine if CNVs account for a broader spectrum of childhood epileptic disorders. The results obtained in the experiments were interpreted using the program Coffalyser. **Results:** Out of the 98 patients analyzed, mutations were found in three patients: two deletions and one duplication. One of the deletions was found in a patient with CEE (on exon 2), and the other on a patient with GEFS+/borderline Dravet Syndrome (on exons 21 to 26). In addition, a the duplication, a preliminary result that needs to be confirmed, was found in a patient with CEEs, but the standout aspect of this duplication is that it was present in the promoter region of *SCN1A* , as well as on exons 4 and 6. These alterations account for a frequency of 3% of structural abnormalities in the group of patients analyzed. **Discussion:** Although the frequency of CNVs found is smaller than that of point mutations, its significance lies on the fact that these alterations were found on patients without detected point mutations, indicating that this assessment alongside standard sequencing methods will provide a broader and more accurate picture of genetic alterations in *SCN1A* in patients with CEEs and GEFS+. The deletions are predicted to alter protein function[3], specially in the case of the 5 exon deletion found in the GEFS+ patient. On the other hand, the duplication in the promoter region, if present in tandem, could implicate in the loss of binding sites of gene expression regulators, which would impair the function of the HB exon.
Conclusion: This research indicates that performing structural analysis is fundamental in order to have a deeper understanding of the role of *SCN1A* alterations in patients with phenotypes associated with the CEEs.

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ALTERED CONNECTIVITY OF LANGUAGE-RELATED AREAS IN HIGH-FUNCTIONING AUTISM

B.M. Campos[1], A. Pereira[2], TM. Lopes[1], L.F.L. Pegoraro[3], F. Cendes[1]

[1]Neuroimaging Lab., FCM, UNICAMP; [2]Pediatrics Dept., PUC-Rio Grande do Sul, [3]Psychiatry Dept., FCM, UNICAMP.

Introduction: High-functioning autism (HFA) represents a complex neurodevelopmental condition characterized by deficits in communication and social behaviors but with normal global IQ[1]. We studied the functional connectivity at rest in known areas associated with language function, exploring the human communication systems (gestural/facial, verbal and writing). **Materials and Methods:** We included 29 controls and 22 young patients with HFA. An anatomical (T1WI) and the resting state fMRI of all volunteers were included. The analysis was fully performed with UF^{2}C-Toolbox and is briefly described as: dynamics realignment, co-registration, normalization, smoothing, regression for 6 head motion parameters and WM/CSF average series, detrend and band-pass filter[2]. On the first level analysis, we generated individual matrices based on the pair-wise correlation of the BOLD time series from eight left hemisphere cubic (1 cm^3) ROIs: Wernicke's area (WA); Heschl's gyrus; ant. sup. temporal gyrus; ant. mid. temporal gyrus (AMTG); Broca's area; ant./mid. fusiform gyrus (face form area [FFA]); post. fusiform gyrus (visual word form area [VWFA]); and the temporal pole. In the second level analysis, we applied an ANCOVA to compare groups (ROI level, alpha=0.05 FDR-corrected, gender as covariate). **Results:** We found two ROIs pairs with reduced FC in HFA: AMTG with WA and FFA with VWFA (Figure 1). **Discussion:** The Wernicke's area is accepted as a critical association area for speech comprehension and in part for production. Other studies indicated that the AMTG is also involved in comprehension. The FC reduction between these regions could indicate that the deficits in verbal communication skills in HFA may be related, with other factors, to a wrong semantic process and a lower cooperation between these areas. VWFA is associated to visual aspects of graphemes, useful for reading abilities requiring orthographic and phonological aspects, as well as semantic components. The VWFA is also related to a more complex language aspect: the mental inference from facial expressions of emotion. In the same direction, FFA is associated to the visual aspect of the faces recognition. Considering that people with HFA have impaired recognition of facial expressions, we could speculate that both regions need to be hemodynamically communicative for adequate performance of reading and emotional interpretation (and interaction) of facial expressions[3,4].
Conclusion: Our results suggest that the language impairment in HFA patients could be related to decreased FC within associative language areas. These findings reinforce the idea that hemodynamic pattern among brain regions ion the rest condition may reflect the dysfunctional behaviors.

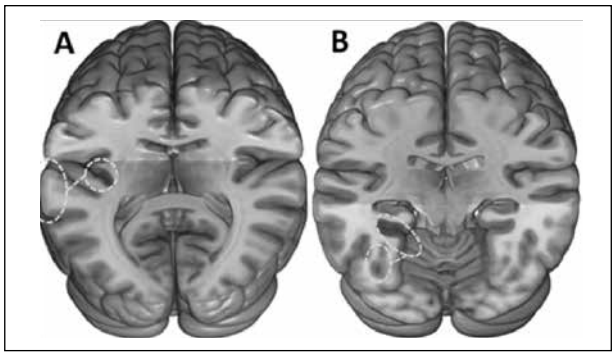

Figure 1. Pairs of ROIs with reduced FC in HFA. A) in blue the AMTG and in green the WA. B) in red the FFA and in orange the VWFA.

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IDENTIFICATION OF THE GENETIC BASIS RELATED TO FAMILIAL MESIAL TEMPORAL LOBE EPILEPSY

M. C. P. Athié[1], R. Secolin[1], M.E. Morita[2], C. Maurer-Morelli[1], M. Alvim[2], C.Y. Yasuda[2], F. Cendes[3], I. Lopes-Cendes[2]

[1]Department of Medical Genetics; [2]Department of Neurology; School of Medical Sciences, University of Campinas – UNICAMP, Campinas, SP, Brazil; and the Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, SP, Brazil.

Introduction: Mesial temporal lobe epilepsy (MTLE) constitutes the most frequent focal epilepsy in the adult population 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). Although MTLE +MTS were classically considered as sporadic forms of epilepsies in which environmental factors seemed to play a more relevant role, we identified a familial form of MTLE+MTS (FMTLE+MTS) with clear autosomal dominant inheritance presenting a candidate locus on chromosome (ch) 18p11.31. Currently we are developing additional studies in order to identify the genetic variants related to the FMTLE+MTS locus. **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 previously diagnosed as having FMTLE+MTS, based on clinical and encephalographic exams, according to International League Against Epilepsy (ILAE) defined criteria. Patients are being prospectively followed and all clinical, neuroimaging and inclusion/exclusion characterization have been previously described by our group[1]. Whole exome sequencing has been carried out in the family known to be linked to ch 18p as well as in additional families, using TruSeq Exome Enrichment Kit in an Illumina Hi Seq 2500 platform. Sequencing data is currently being submitted to bioinformatics packages for genetic elements prospection, such as SNVs, CNVs, exon skipping and transposable elements. Exome data will be validated in all samples by 1) allelic discrimination qPCR 2) Genome-Wide

Human SNP Array 6.0 *microarray* chips for CNVs; 3) Sanger sequencing for exon skipping and insertion of transposable elements. Validated genetic elements will be further studied in functional experiments involving induced pluripotent stem cells (iPSC) cultures obtained from patients and non-related healthy controls. In addition, we will use' biopsy punches' fibroblasts in order to identify possible morphological, cellular connection and gene expression alterations. Human fibroblasts transformation into iPSCs and neural precursor will follow protocols specific to the generation of telencephalic neural precursors, especially hippocampus granular cells[2]. **Results:** With these approaches, we aim to identify strong genetic candidates for FMTLE+MTS that will be submitted to functional validation in FMTLE iPSCs cultures in order to confirm their role in the development of this type of familial epilepsy. **Discussion:** The recent revolution in molecular biology techniques allows us to tackle complex diseases presenting clear genetic origin with different, yet sensitive approaches in a more dynamic and complete form. This way, this project was designed to integrate all data already available about FMTLE+MTS individuals and also to collect new genetic information, in an attempt to unequivocally identify the genetic variants responsible for FMTLE+MTS. **Conclusion:** The data collected in the present project might be crucial for the development of less invasive and more efficient therapies for FMTLE patients and also, improve our knowledge of neural excitability control mechanisms.

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POSTURAL EFFECTS ELICITED BY MUSCLE VIBRATION FACILITATES GAIT INITIATION IN PEOPLE WITH PARKINSON'S DISEASE AND FREEZING OF GAIT

M. P. Pereira[1], P. H. S. Pelicioni[2,3], L. T. B. Gobbi[1]

[1]Posture and Locomotion Studies Laboratory, UNESP-Rio Claro; [2]Neuroscience Research Australia, UNSW (Sydney), [3]School of Public Healthy and Community Medicine, UNSW-Sydney.

Introduction: People with Parkinson's disease (PD) and more so those who experience Freezing of Gait (FOG) show gait initiation deficits: hypometric and slower postural adjustments, slower first step and movement execution (entire task: postural adjustments + step)[1,2]. FOG+ have an impaired weight-shifting ability, mainly in the anterior-posterior (AP) direction[3]. Therefore, the aim of this study was to investigate the effects of muscle vibration (a wearable device able to induce postural adjustments and to reduce FOG severity[4,5] on gait initiation in FOG+. **Materials and Methods:** Nine FOG+, 9 PD patients without FOG (NFOG) and 11 healthy elderly performed gait initiation with and without muscle vibration applied simultaneously on the tibialis anterior, rectus femoris and trapezius superior, in order to shift the body forward (a required postural adjustment during gait initiation). The first step, anticipatory postural adjustment (APA) characteristics, and the center-of-mass (CoM) behavior were assessed by an optoelectronic system (Optotrack Certus [NDI®]). **Results:** FOG+ showed an impaired gait initiation performance (slower step velocity, slower task completion time and reduced AP-CoM displacement during APA compared to other two groups. Muscle vibration reduced APA duration ($F_{(2,26)}=6.40$, $p=0.017$) andthe speed of task completion ($F_{(2,26)}=8.25$, $p=0.007$) in all groups. Additionally, as expected, vibration elicited a CoM forward displacement before the movement onset ($F_{(2,26)}=16.12$, $p<0.01$) and reduced the CoM A-P displacement during APA in all groups ($F_{(2,26)}=46.50$, $p<0.01$) . Both PD groups showed step adaptations with the use of vibration: while FOG+ reduced the first step length ($p<0.01$), NFOG took a longer time to execute the first step ($p=0.01$). No effects on step width and CoM mediolateral displacement were found. **Discussion:** Vibration replaced the voluntary anterior CoM shift expected during APA, thereby reducing the APA duration. As a result, a faster movement execution was observed in all groups with the use of vibration. We believe that healthy elderly could process the new motor plan elicited by vibration in a faster way than other groups, since no adaptions in step were found for this group. On the other hand, although both PD groups used different strategies, they needed to adapt the first step as a result of adaptations elicited by vibration: NFOG needed more time to process the new motor plan (increasing the step time). In a different way, FOG+ executed a more conservative strategy with the use of vibration (reducing the step length). Since no mediolateral adaptations (step with and CoM displacement) were observed, we do not believe that vibration elicited an unstable situation. **Conclusion:** The present work confirmed that muscle vibration may be an interesting and safe tool to reduce gait initiation deficits in PD and specially in FOG+.

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DECREASED B-GALACTOSIDASE ACTIVITY IN THE ZEBRAFISH MODEL FOR GM1 GANGLIOSIDOSIS

M. B. Baptista[1*], E. Moro [2*],C. V. Maurer-Morelli[1], C. E. Steiner[1]

[1]Zebrafish Laboratory, Department of Medical Genetics, FCM, UNICAMP; [2]Lysosomalstorage disease modeling group, Department of Molecular Medicine, University of Padova.

Introduction: GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by mutations in the *GLB1* gene, which leads to the deficiency of β-galactosidase. This decreased enzymatic activity results in a GM1 ganglioside deposition that cause a severe neurodegeneration and clinical phenotype with coarse facial features, gingival hypertrophy, corneal clouding, hepatosplenomegaly, skeletal dysostosis, psychomotor regression[1,2]. Currently, there are no effective treatments for this disease. Zebrafish is a powerful tool to model human diseases but there is no study investigating GM1 gangliosidosis in this animal model[3]. In this study, we investigated the main features of zebrafish larvae after targeting the *glb1* gene by Morpholino Antisense Oligonucleotide (MO). **Materials and Methods:** Animals were maintained according to standard procedures[4]. Embryos of zebrafish at one to four-stage cells were microinjected with MO to target the *glb1* gene or with corresponding mismatch control at 1,75 ng. The *glb1* MOs were designed to block translation (Gene Tools, LLC). Morphological features were observed by visual inspection under a stereomicroscope (Nikon compound microscope with ViCo superconfocal system), and β-galactosidase activity was achieved by X-gal (5-bromo-4-chloro-3-indolyl β-D-galactopyranoside) *in situ* test[5] performed in zebrafish larvae at 48, 72 and 96 hpf. This study was approved by the Animal Ethical Committee of UNICAMP #3092-1. **Results:** After 48 hours post fertilization (hpf) zebrafish larvae presented coarse facial features, and differentiated yolk extension, as well as tail malformation. The X-gal test showed that the β-galactosidase in morphant larvae was reduced compared to the control groups (no microinjected or mismatch control groups). We did not observe enzymatic activity in the lens, yolk and central nervous system, probably due to a gradual decrease of the MO efficiency after 96 hpf. **Discussion:** It is possible to consider that the facial features in the microinjected zebrafish embryos were subtle but with suggestive correspondence to the facial coarse features found in patients with GM1 gangliosidosis[1], while the tail malformation results from the cell apoptosis, which may have been caused by the deposition of the GM1 ganglioside. Phenotype evaluation showed that the yolk extension was different from those observed in controls, and this may be associated to the importance of the β-galactosidase in the yolk degradation during embryogenesis[5]. Finally, the X-gal test showed that the enzymatic activity was reduced in embryos microinjected with MO targeting the *glb1* gene. **Conclusion:** The present work showed that the zebrafish can be an animal model for GM1 gangliosidosis studies since we found reduced β-galactosidase activity in *glb1*-morphant larvae that was sufficient to lead to a phenotype similar to that observed in patients. We hope this *glb1*-morphant model can contribute for a better understanding of the physiopathology of this disease.

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VALPROATE ACID INFLUENCE IN THE CORTICAL SURFACE OF EPILEPSY'S PATIENTS BRAIN STRUCTURES

G. Wertheimer, A. C. Coan, C. L. Yasuda, F. Cendes[1]

[1]Department of Neurology, University of Campinas-UNICAMP, and the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, São Paulo, Brazil.

Introduction: Macro and micro-structural abnormalities are common findings in epilepsy. However, the pathogenesis and associated factors of these changes are not fully understood. Recent studies found an association of valproate acid

(VPA) with brain atrophy independent of the seizure type. VPA is a commonly used anti-epileptic drug (AED) for focal and generalized epilepsies. This study aims to analyze the involvement of VPA in brain atrophy observed in epilepsy patients. **Materials and Methods:** Patients followed in our epilepsy service had their medical charts analyzed for VPA use during their treatment. MRI images were post-processed with the FreeSurfer program to determine the cortical thickness, volume and surface of brain structures. A control group (n=50) was included for comparison.Patients were divided according with VPA use in two groups: a) never used VPA, but used other AEDs (VPA-, n=21) and b) were currently taking VPA when the MRI was taken (VPA+, n=13). Patients with major structural abnormalities were excluded from the analyses. The Student t-test was used for statistical analysis. **Results:** We found that patients currently taking VPA (VPA+) had increase brain surface in the temporal-parietal region when compared to patients that had never taken the drug (VPA-) and to healthy controls. The group taking AEDs, but that had never used VPA, showed decrease in brain surface when compared to the VPA+ group (Table). **Discussion:** The results show increased brain surface areas in patients currently taking VPA when compared to healthy controls and patients that never used AED. Cortical surface areas are usually increased in regions with reduced cortical thickness because of the consequent increase in sulcation of the cortical mantle. The temporal-parietal regions affected may be related to the effects of VPA in cognition and behavior.**Conclusion:** The present work showed a possible link between VPA use and areas of increased cortical surface. More studies are necessary to better understand the relation between this AED and the changes in brain structure.

Table. Areas of significant changes between patients' groups and controls.

Changes in VPA+ patients compared to VPA-patients*	Changes in VPA+ patients compared to controls*	Changes in VPA- patients compared to controls*
↑ LH Cuneus(surface)	↑ LH Cuneus (surface)	= LH Cuneus (surface)
↑ RH Parietal superior (surface)	↑ RH Parietal superior (surface)	= RH Parietal superior (surface)
↑ RH Entorrinal (surface volume volume)	= RH Entorrinal (surface and volume)	↓ RH Entorrinal (surface and volume)

*T-Test with two samples, p<0,05. LH: left hemisphere; RH: right hemisphere.

WHITE MATTER TRACTS INTEGRITY IN CHILDREN WITH FOCAL CORTICAL DYSPLASIA

S. V. Gouvêa[1], E. Ghizoni[2], B. M. de Campos[2], S. Appenzeller[3], F. Cendes[2], A. C. Coan[4]

[1] Graduation program, School of Medical Sciences - UNICAMP, Campinas-SP, Brazil; [2]Neuroimaging Laboratory, Department of Neurology, School of Medical Sciences, UNICAMP, Campinas-SP, Brazil; [3]Department of Rheumatology, School of Medical Sciences, UNICAMP, Campinas-SP, Brazil; [4]Child Neurology Service, Department of Neurology, School of Medical Sciences, UNICAMP, Campinas-SP, Brazil.

Introduction: Studies of adults with epilepsy and focal cortical dysplasias (FCDs) show abnormalities of white matter tracts; however, the pattern of white matter tracts abnormalities in children with epilepsy and FCD remains unknown[1]. We aimed to evaluate the integrity of white matter tracts in children with pharmacoresistant epilepsy secondary to FCD. More specifically, we investigated alterations in tracts with different patterns of maturation across lifespan. **Materials and Methods:** We analyzed diffusion tensor imaging (DTI) acquired in a 3 Tesla MRI of 14 patients (13 ± 4 years, 10 female) and 29 age and sex-matched controls (13 ± 4 years, 17 female). The cortical spinal tract (CST), as an important source of projection fibers, and the corpus callosum (CC), as the main commissural fiber tract, were selected for the present studyImages were processed and analyzed using the software *ExploreDTI* with semiautomatic deterministic method to obtain average fractional anisotropy (FA), axial (AD), radial (RD) and mean (MD) diffusivity. Statistical analysis was performed with SPSS 24. **Results:**Compared with controls, patients with FCD presented increase of MD and RD in the genu of the CC (Two sample T-test, MD: p<0.001; RD: p=0.03) and increase of FA (p=0.011) and MD (p=0.046) in the splenium of the CC. Differently, patients presented decrease of MD (p=0.009), AD (p<0.001) and RD (p=0.02) in the CST ipsilateral to the FCD. **Discussion:** Children with epilepsy and FCD have abnormalities in white matter tracts. These abnormalities differ between CC and CST, with the first showing increase in FA and other diffusivities and the later showing decreased diffusivities. These tracts have similar patterns of maturation in normal children: FA showing progressive increase and, MD, progressive decrease[1,2]. **Conclusion:** Therefore, our findings suggest that abnormalities of white matter tracts observed in children with FCD can be secondary to impairment of normal maturational process.

Table 1. Comparison between the results of the present study with the literature[1,2].

Anatomic region	Parameter	Patients with FCD in comparison with healthy controls	Literature
Corpus Callosum	FA	-	Progressive increase with age
	MD	Increased	*
	AD	-	*
	RD	Increased	Progressive decrease with age
Cortical Spinal Tract	FA	-	Progressive increase with age
	MD	decreased (ipsilateral to the FCD)	Progressive decrease with age
	AD	decreased (ipsilateral to the FCD)	Progressive decrease with age
	RD	decreased (ipsilateral to the FCD)	Progressive decrease with age

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POWER SPECTRAL DENSITY OR FUNCTIONAL CONNECTIVITY INDICES? A COMPARATIVE STUDY REGARDING FEATURE SELECTION FOR MOTOR IMAGERY-BASED BRAIN-COMPUTER INTERFACES

C. A. Stefano Filho[1], R. Attux[2], G. Castellano[1]

[1]Neurophysics Group, IFGW, UNICAMP; [2]Dept of Automation and Control, FEEC, UNICAMP

Introduction: In this study, a multi-layer perceptron (MLP) neural network was used to classify fist MI tasks from electroencephalography (EEG) data. The classifier's performance was analyzed regarding the use of distinct features, as well as different feature selection (FS) approaches. **Materials and Methods:** All 64 channels EEG data were provided by an open online database[1] containing records of 109 healthy subjects, from which data from only ten were analyzed. An estimate of the power spectral density (PSD) in two bands of interest (mu and beta) and elements from a functional connectivity matrix (FCM) were tested as features for the classifier. The FCM was estimated using the motifs method[2]. Pre-processing included using a common average reference (CAR) filter. FS was done in one of three ways: (1) a wrapper was designed to add new features from a single electrode, until no improvement in classification accuracy could be observed after four consecutive iterations. This approach was only used for the PSD inputs, as using it with elements from the 64 x 64 FCM would take too much processing time. The other two forms of FS were tested for the two types of inputs, and combined with the wrapper described in (1): (2) Pearson's and (3) Fisher's filters[3]. A total of 10 runs were done for each subject, with data from left and right fists MI being randomly assigned as training, validation and testing ensembles. Validation error was used as a criterion for defining the architecture of the MLP to be used on the test data. **Results:** Table 1 displays average results in the form (mean ± standard deviation). Standard deviation was calculated considering only variations across subjects. **Discussion:** As expected, the use of filters for FS significantly increased classification accuracy rates. Average results increased 12% when the PSD was used as feature for the classifier with Pearson's filter (Table 1). Using Fisher's filter also increased accuracy, but to a lesser extent (mu band). Classification

Table 1. Average classification accuracy results between all ten subjects for different types of input features.

Frequency band	Classification accuracy (%)					
	PSD			FCM elements		
	(1)	(2)	(3)	(1)	(2)	(3)
Mu	70 ± 11	82 ± 8	76 ± 11	-	72 ± 7	69 ± 12
Beta	62 ± 7	67 ± 12	73 ± 14	-	79 ± 6	73 ± 9

rates for the mu band using FCM elements were comparable to using (1). On the other hand, in the beta band, FCM elements provided the best rates when Pearson's filter was used, and an equal average value to PSD features with Fisher's filter. However, in both cases, the standard deviation for FCM features was considerably smaller, indicating that this method can produce more accurate results across subjects. **Conclusion:** The present work confirmed that the use of FS filters can significantly increase classification accuracy rates. Also, we found that even though MI-BCI studies have focused on extracting features mainly from the mu band, connectivity patterns were more distinguishable in the beta band. This indicates that there may be non-straightforward relations between the manner event related synchronizations and desynchronizations alter functional connectivity in the brain across distinct frequency bands that can be recorded with EEG. Better generalization remarks may be achieved after further data analysis, such as increasing the subjects' sample and investigating other frequency bands.

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COMPARISON OF 2D AND 3D CO-OCCURRENCE MATRICES FOR EVALUATION OF TEXTURE PARAMETERS FROM BRAIN MR IMAGES OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

J. P. O. P. Santos[1], L. Rittner[2], S. Appenzeller[3], G. Castellano[1]

[1]Neurophysics Group, IFGW, UNICAMP; [2]Dept. of Computing and Automation, FEEC, UNICAMP; [3]Dept. of Medical Clinics, FCM, UNICAMP.

Introduction: Texture analysis using a co-occurrence matrix (COM)[1] has been widely applied to MR images[2]. However, most studies use 2D COMs, despite the fact that MR images are inherently 3D. In this work, we developed a 3D method to compute a COM. We applied both the 2D and 3D methods to extract and compare texture values from hippocampi of systemic lupus erythematosus (SLE) patients and healthy subjects (control group)[3]. We expect that the 3D method should produce parameter values more discriminating than those from the 2D method, given the 3D nature of MRI. **Materials and Methods:** 25 SLE patients and 25 controls participated in this study. Images were acquired with a 3T MRI scanner (Phillips). Corresponding hippocampi masks were obtained using FreeSurfer (surfer.nmr.mgh.harvard.edu). 2D and 3D COMs were computed for every subject, for distances of 1 to 5 pixels, and 11 texture parameters were extracted from each COM: Uniformity (U), Contrast (C), Correlation (COR), Entropy (E), Variance (V), Homogeneity (H), Sum Average (SA), Sum Variance (SV), Sum Entropy (SE), Difference Variance (DV), Difference Entropy (DE). The parameters were compared between groups, through a qualitative and through a statistical analysis using a t-test, uncorrected and then Bonferroni corrected for multiple comparisons. **Results:** Qualitatively, we found that there is indeed a slight difference in the mean value of each texture parameter between groups. The difference is more apparent in the 3D method than in the 2D one, as expected. However, when including the standard deviation in the comparison, the parameter distributions overlap each other by a significant amount. Figure 1 shows an example of the mean values of the DE parameter obtained overall, where error bars represent the standard deviation. The statistical analysis showed significant differences ($p < 0.05$) for the following parameters: 2D – U (distances 1 to 3), H, E, SA, SE, DE (distances 1 to 5); 3D – Cor, H, DE (distances 1 to 5), SA (distances 1, 2); but these differences disappear ($p > 0.05$) when Bonferroni corrected. **Discussion:** The results found are probably due to the extra dimension added to the 3D method. We know, indeed, that the methods do not compute the exact same thing: the 3D COM uses all 26 possible directions corresponding to the 3D neighbors of a cube to find the co-occurrences, whilst the 2D uses the eight possible directions corresponding to the 2D neighbors of a square, in each 2D slice of the 3D image, and then uses a weighted average of each slice parameter for the 3D image. Thus, not only we have different results between groups but also between methods. **Conclusion:** The present work confirmed that it is, indeed, possible to use a 3D COM method for texture analysis of MR images, and showed some indication that this is better than a 2D method, since the differences seem more significant. While the standard deviation leaves little room for a more definitive and objective saying on the matter, we can assume that a more sophisticated work (using more images of each kind, and other kinds of masks) could help us in the future.

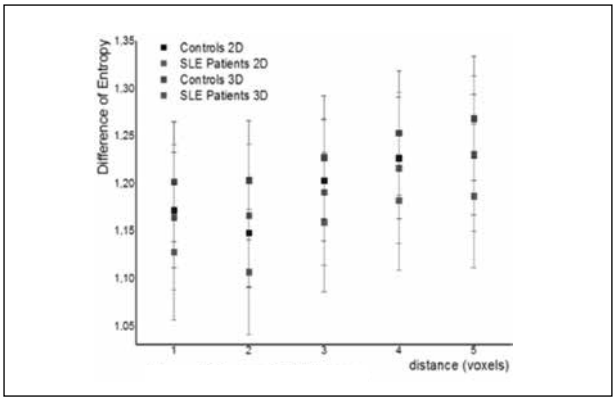

Figure 1. DE versus COM distance.

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ZIKV INFECTION INDUCES SYNTHESIS OF CARDIAC GLYCOSIDES AT GLIOBLASTOMA CELLS

E. O. Lima[1], T. M. Guerreiro[1], C. F. O. R. Mello[1], D. N. Oliveira[1], D. Machado[2], M. Lancelloti[2], R. R. Catharino[1]

[1]Innovare Laboratory, FCM, UNICAMP; [2]Laboratory of Biotechnology, FCF, UNICAMP.

Introduction: The recent outbreak of Zika virus (ZIKV) has been matter of concern, mainly due to the increasing number of cases of microcephaly in newborns, associated with ZIKV infection[1]. Recent studies have shown that ZIKV-infected progenitor neuronal cells present morphological abnormalities, as well as increased rates of cell death[2], which may be indicators of microcephaly causes[3]. Taking into account that ZIKV presents tropism for brain cells, especially cells with high multiplication rates, how would glioblastoma (GBM) cells behave under ZIKV infection? GBM are the most common and malignant brain tumor in adults, presenting extreme chemoresistance and high morbidity and mortality rates[4]. Interfering with the survival of GBM cells would be quite interesting for cancer management in the future. Therefore, this study aimed at analyzing the metabolomic profile of human neural cancer cells under ZIKV infection *in vitro*.**Materials and Methods:** Human malignant M059J glioblastoma cells (GBM) were infected with Zika virus, Brazilian strain, and analyzed at 24 and 48 hours post-infection (hpi). Microscopic evaluation was performed using optical microscopy. For the metabolomics study, both control and infected cell cultures were submitted to MALDI-MSI analysis. Mass spectrometry data were submitted to PLS-DA statistical analysis, which allowed electing distinct biomarkers for each studied group; the elected molecules were identified based on MS/MS fragmentation profile and semi-quantification through images. **Results:** Microscopic images showed that the GBM-ZIKV 24hpi group presented slight cytopathic effects, whilst GBM-ZIKV 48hpi group showed pyknotic nuclei and pronounced cell death compared with the GBM-CT groups. Mass spectrometry analysis allowed identifying two glycosphingolipids, and one eicosanoid for 24hpi and 48hpi GBM-CT groups, respectively. For GBM-ZIKV groups, 24hpi cells showed endogenous cardiac glycosides like Digoxin, Lanatoside-C and 2"-oxovoruscharin, as well as HMG-CoA. Differently, the elected biomarker for GBM-ZIKV 48hpi group was the sphingolipid sphingofungin E. **Discussion:** Although sphingofungin E represents an attempt to survive and impair replication[5], malignant glioblastoma cells were susceptible to ZIKV infection, what was observed through cell death over infection time, as cited previously[4,6]. The cytopathic effect may be related to cardiac glycosides synthesized under ZIKV infection. Cardiac glycosides are natural Na^+/K^+-ATPase pump inhibitors and recent reports suggests that they present anticancer properties, as antiproliferative and apoptotic effects[7,8]. In addition, the identification of HMG-CoA shows a possible biochemical pathway for cardiac endogenous glycosides synthesis, as previously suggested[9]. **Conclusion:** The current research points out to unprecedented metabolic changes during GBM-ZIKV infection, which may bring light to cancer management. Therefore, the present study suggests that genetically engineered ZIKV could be a potential new strategy for fighting against neural cancer through induction of endogenous cardiac glycosides synthesis.

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SYMBOL DIGIT MODALITIES TEST AND EFFECTIVE CONNECTIVITY OF INFORMATION PROCESSING SPEED

P.H.R.da Silva[1], C.T. Spedo[2], R.F. Leoni[1]

[1] Department of Physics, FFCLRP, University of Sao Paulo, Ribeirao Preto, Brazil; [2]Department of Neuroscience and Behavior Sciences, FMRP, University of Sao Paulo, Brazil.

Introduction: The evaluation of the Effective Connectivity is relevant for neurological diseases, such as Multiple Sclerosis (MS), since its assessment over time may indicate the occurrence of adaptive neuroplasticity[1]. Therefore, this study aims to investigate, in healthy volunteers, the effective connectivity between regions activated during the performance of an adapted version of the Symbol Digit Modalities Test (SDMT), an international gold standard for screening of Information Processing Speed (IPS) of MS patients. **Materials and Methods:** Eight right-handed controls were recruited and underwent a cognitive evaluation with an oral version of the SDMT before image acquisition. MRI was acquired in a 3T Philips Achieva System. BOLD images were acquired with a 2D EPI sequence. The experiment consisted of six 30-second blocks of control, intercalated with five 30-second blocks of task (SDMT). During the task blocks, a symbol was displayed every 2 seconds, and the participant was asked to associate the number corresponding to the displayed symbol based on a response key. During the control blocks, a number was displayed every 2 seconds, and the participant was asked to silently read the number displayed. In the SPM12 software, after the usual preprocessing, statistical maps were obtained using a voxel-wise GLM with a boxcar regressor convolved with a canonical hemodynamic response function (p-FWE < 0.05). Dynamic causal modeling considering two hypothesized models of network structures for IPS was implemented and Bayesian Inference was applied between the two models for comparison. **Results:** Activations were observed in the frontoparietal network and occipital cortex for the individual and group analysis. Highest evidence for a system architecture featured the lingual gyrus in a serial position between cuneus and two parallel regions (precuneus and superior parietal lobule), from which information, modulated by the SDMT task, converges onto the inferior frontal gyrus, cerebellum and finally bifurcates into right and left middle frontal gyri. **Discussion:** The IPS system identified in meta-analysis studies demonstrated robust activation in our experiments, showing that our SDMT adaptation is consistent, despite methodological differences and different sample sizes. Functional architecture of IPS and the effective connectivity within it have been studied with hypothetical and preliminary network structure models. Studies with other models will be needed to better delineate the functionality of each core that makes up the network and its role within the IPS task. **Conclusion:** Preliminary data show activations in the frontoparietal network and occipital cortex as observed in previous studies[2,3]. A likely network model with areas involving IPS was obtained and may serve as a reference for future investigations of this cognitive process in MS. We are still testing other possible networks, and more data is being acquired to improve our statistics.

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IMPAIRED SALIENCE NETWORK IN SCHIZOPHRENIA: AN ARTERIAL SPIN LABELING STUDY

I. A. F. Oliveira[1], R. F. Leoni[2]

[1]Inbrain Lab, Department of Physics, FFCLRP, USP, Ribeirao Preto, Brazil.

Introduction: Schizophrenia is a significant mental disorder which affects practically the whole-brain structure as well as several functions[1]. The insular cortex is one of the brain regions that show consistent abnormalities in both structural and functional neuroimaging studies of schizophrenia. The Salience Network (SN) is anchored in the right Anterior Insula (rAI) and dorsal Anterior Cingulate Cortex (dACC) and has predominant limbic and subcortical components. The SN is involved in behavioral salient events and is important for initiation of cognitive control, maintenance and complementation of task sets, and the coordination of behavioral responses[2]and an important question is how its nodes interact. One theory is that the dACC provides the earliest cortical signal of behaviorally salient events, such as errors. Alternatively, the anterior right insula (aRI. In the present study, we used pseudocontinuous ASL to investigate the hole of the SN in schizophrenic patients.

Materials and Methods: Fifty-six young adults (28 healthy; 28 schizophrenic) participated in the study. All participants gave written consent after being informed about the experimental procedures. Patients were recruited at the Clinical Hospital of Ribeirao Preto, and the inclusion criteria were both genders, age between 18 and 45 years, and schizophrenic diagnosis in treatment with the presence of positive or negative symptoms (score equal or greater than 4 in any item of PANSS – *The Positive and Negative Syndrome Scale*) evaluated by a trained psychiatrist. Imaging was performed on a 3T Philips System. Resting-state ASL images were obtained using a 2D single-shot EPI sequence with the following parameter: TR/TE = 4000/14 ms, FA = 90°, FOV = 240 x 240 mm^2, matrix = 160 x160, 20 5-mm slices, label duration = 1650 ms, post-labeling delay = 1525, 50 control/label pairs. For anatomical reference, a 3DT1 GRE was acquired with the following parameters: TR/TE= 7/3.2 ms, FA = 8°, matrix = 240 x 240, FOV = 240x240 mm^2, 160 1-mm slices. Data processing was performed using Statistical Parametric Mapping (SPM12). For ASL images we use based batch scripts available in ASL toolbox (ASLtbx), and connectivity measures were obtained using CONN toolbox. A seed-to-ROI approach was used to acquire the Pearson's correlation coefficients between regions of SN (ACC; AI; rPFC, rostral Pre-Frontal Cortex; and SMG, Supramarginal Gyrus). A two sample Welch t-test with Sidak correction for multiple comparisons was used to compare correlation coefficients and connectivity strengths between groups. We treat the correlation coefficient as connectivity between two regions, and the connectivity strength as a network property of each region. **Results:** Compared to healthy controls, significant reduced connectivity within SN was observed in schizophrenia, more specifically in the connections between: ACC and right AI, ACC and right rPFC, left AI and bilateral SMG, right AI and bilateral rPFC, right AI and left SMG. Also, significant reduced connectivity strength was observed for all SN regions in the schizophrenic group. **Discussion:** Our results are consistent with previews studies using BOLD-fMRI, which showed presence of dysconnectivity within SN[3]. Functional and structural observations suggest that insular dysfunction may diminish the capacity of individuals to discriminate between self-generated and external information. ACC and AI connections are important for mental life, since they are involved in cognitive, affective and behavioral situations[4]. Moreover, SMG is involved in controlling empathy towards people. All of these functions have been associated with schizophrenia. **Conclusion:** In summary, disrupted functional connectivity is observed within the salience network in schizophrenia using an arterial spin labeling approach. Next, we will assess resting perfusion in these regions, and investigate if there is a relationship with the impaired connectivity.

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COMPARISON OF INFLUENCE OF ACQUISITION PARAMETERS IN DTI INDICES FOR 8-CHANNEL AND 32-CHANNEL HEAD COILS: A FIBER PHANTOM STUDY

E. M. Souza[1,2,3,4], E. T. Costa[1,2], G. Castellano[3,4]

[1]Biomedical Engineering Department, FEEC, UNICAMP, Campinas, Brazil; [2]Biomedical Engineering Center, UNICAMP, Campinas, Brazil; [3]Neurophysics Group, IFGW, UNICAMP, Campinas, Brazil; [4]Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, Brazil.

Introduction: Diffusion tensor images (DTI) have many applications in neurology and other areas of medicine. However, the measured signal is susceptible to the influence of noise and artifacts, being thus important to check if these factors do not compromise the parameters calculated from the images. Given that there is no standard quality control routine for these kind of images[1], the main goal of this work was to evaluate how the Diffusion Tensor Imaging indices (DTIi) are related to imaging acquisition parameters for an 8-channel and a 32-channel head coil. The study was performed using an in-house developed anisotropic diffusion phantom. **Materials and Methods:** An anisotropic diffusion phantom was built and DTI acquisitions were performed in the 3T Philips Achieva MRI scanner using an 8 and a 32-channel head coil. The phantom had 3 Dyneema fiber bundles, each with a different fiber diameter (0.25, 0.35 and 0.40 mm). The diameter of bundles was 74.90, 75.48 and 75.62 mm,

respectively. For each coil, the following acquisition parameters were varied, one at a time: b-value, echo time (TE), number of averages (NSA), Sensitivity Encoding factor (SENSE), voxel size and the number of directions of diffusion gradients (NDGD). For each acquisition, the DTIi calculated were: mean diffusivity (MD), fractional anisotropy (FA), relative anisotropy (RA), volume ratio (VR), sphericity (C_S), linearity (C_L) and planarity (C_P). Coefficients of Variation (CV) and correlations were evaluated for each DTIi. **Results:** We found correlation between DTIi and acquisition parameters for both coils tested. The most correlated acquisition parameters (with DTIi) were NDGD, followed by b and NSA, for the 8-channel coil and the lowest diameter fiber bundle of the phantom. The DTIi that seemed most susceptible to acquisition parameter changes were FA, C_S and C_P. The highest CV value was found for C_S, C_L and C_P, when NSA was changed, for the 32-channel coil. **Discussion:** The relation between acquisition parameters and DTIi is not yet well-defined, and neither are the causes. However, it was found that the acquisition parameters that most influence DTIi were the parameters related to diffusion-weighting, for the 8-channel head coil. Also, the DTIi with largest CV were those related to geometry. Possibly, the higher number of channels in the 32-channel head coil tends to improve the SNR, reducing image noise and geometric distortions effects. The higher number of channels also reduces distortions due to voxel size variation. **Conclusion:** The findings suggest that DTIi are susceptible to acquisition parameters' variations, which must be considered when clinical and research protocols are developed or modified, as well as when data obtained from different protocols or scanners are compared.

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ELDERLY CAREGIVERS WITH CHRONIC PAIN: BETTER OR WORSE COGNITIVE PERFORMANCE?

M. Terassi[1], A.C. Ottaviani[1], E.S. Rossetti [1], T.S. Alexandre[2], P. Hortense[3], SCI. Pavarini[2]

[1]Programa de Pós-Graduação em Enfermagem, UFSCar; 2Departamento de Gerontologia, UFSCar; 3Departamento de Enfermagem, UFSCar.

Introduction: Taking the responsibility of caring of a elderly family member can modify the routine of life of the caregiver, increasing the workload and being susceptible to the onset of pain[1]. Chronic pain can interfere the cognitive process causing memory deficits, concentration, attention and reduced response time[2]. The aim of this study was to verify the cognitive performance of elderly caregivers with chronic pain and absence of pain using the Addenbrooke Cognitive Examination - Revised (ACE-R). **Materials and Methods:** This is a descriptive, exploratory research, with a quantitative approach and cross-sectional design. The study was carried out in the city of São Carlos, Brazil, with people aged 60 years and over, who were caring for another elderly person at home. The final sample included 320 elderly caregivers, allocated to two groups: one group with chronic pain (n = 187) and one group with no pain (n = 133). To evaluate the pain was used the Multidimensional Pain Rating Scale (EMADOR) and for the cognitive performance the Cognitive Exam of Addenbrooke - Revised (ACE-R). The research was approved by the Ethics Committee and all ethical precepts were preserved **Results:** The mean age of the study population was 69.4 years, with a predominance of females (76.2%). Regarding education, the majority of the elderly reported 1 to 4 years of study and it was observed that the group with chronic pain presented a better level of schooling, with lower rates of illiteracy when compared to the group without pain. Regarding cognition, the group of caregivers with absence of pain had worse cognitive results, with a total average of 61.3 points, when compared to the group with chronic pain that obtained a mean of 64.6 points, but without statistically significant results (p = 0.209), data that diverge from the literature. The group with absence of pain obtained worse results in all cognitive domains of the ACE-R instrument. Regarding pain, 58.4% of the elderly reported pain for more than six months. The most prevalent sites were the lumbar region (58.8%) and the lower limbs (58.8%). **Discussion:** In the present study it was not possible to observe a statistical difference in the cognitive domains between the groups, and the group of caregivers with chronic pain presented better scores. These data diverge from the literature, which reports that elderly people with chronic pain presenting worse performance in cognition[3]. Since these are elderly caregivers, a specific population, it is recommended that new studies be performed with this population. **Conclusion:** The present study allowed to know the sociodemographic profile of the elderly caregivers and to compare the cognitive alterations in the elderly with chronic pain and absence of pain, noting statistically significant differences.

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A STUDY IN WEARABLE TECHNOLOGY WITH PRESSURE TRANSDUCTION FOR USES IN NEUROLOGIC REHABILITATION TREATMENT FOR HAND SENSORY LOSS.

F. L. Conrado, J. H. Clarici, M. A. Cotta

Laboratório de Nano e Biossistemas – Instituto de Física Gleb Wataghin – Universidade Estadual de Campinas.

Introduction: This research consists on developing technology that could help neurologic rehabilitation using the concept of neuroplasticity, which is the ability of the central nervous system (CNS) to respond to intrinsic and extrinsic stimuli by reorganizing its structure, functions and connections. This brain change is visible, for example, in the sensorimotor cortex in Braille readers[1]. Currently, neuroplasticity is known to be crucial forneurological rehabilitation. The goal of this research is the development of wearable equipments to be used in the rehabilitation of patients with somatosensory loss. The equipment replaces the tactile response by a visual response using sensors that transduce the pressure made on them into electric signals. The major project consist on gloves with sensors at the fingertips. The project is still ongoing, with the first prototype finalized and a second, improved version in progress. **Materials and Methods:** In this research, we focused specifically in loss of hand sensation. For that, we used piezoelectric materials to create sensors which drive Light Emitting Diodes (LED) depending on the pressure applied to them. We intend to create an equipment that will be light and independent of an electrical outlet, so that the patient could wear it in daily activities and not necessarily during rehabilitation sessions. We believe that, with the constant use of the equipment, the user can adapt to the visual stimulus, slowly regaining arm and hand sensibility and strength control, while reestablishing the neural connection between the CNS and the sensory nerves. **Discussion:** Our main obstacle was to find pressure sensors that could be used in our project. The material should be small, light and flexible so it could be placed in the regions where pressure is applied, with no discomfort to the user. The feedback given by the sensors needed to be immediate and stable, because any kind of variance could hinder patient development. Thus, the material also needed to present good repeatability and reproducibility. The commercial product that best fitted our expectations was the sensor named Flexiforce A101, produced by Tekscan. The product consists in a small circular piezoelectric material that changes resistance according to the pressure exercised on it. Using the Flexiforce A101 sensors, two prototypes were created. **Results:** The prototypes were created to be used in generic hand movements and exercises, consisting in a glove with a Flexiforce A101 sensor at each of the fingertips. For each finger, there is a high luminosity LED; its intensity varies with the pressure exercised at the fingertip (sensor area). The equipment has a circuit near the wrist and is powered by a common 3V watch battery. For the second prototype, a microcontroller will improve the battery use and the sensor feedback. RGB LEDs will provide color instead of intensity as the feedback signal. Also, conductive wires will be sewn to the glove to replace the metal wires used in the first version of the equipment, to improve the comfort for the patient. **Conclusion:** The initial tests showed that the prototypes provide immediate feedback with good precision. The feedback signal does not vary over time and the battery charge lasts enough for daily tasks. The equipment does not capture very light touch, but it can be recalibrated as the patient sensibility evolves. The second prototype brings improvements on the circuit and layout, as well as to the patient's comfort.

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STUDY OF THE CORTICAL CONNECTIVITY IN ALTERED STATES OF CONSCIOUSNESS: MEDITATION

T.G. Toutain[1,2,3,4], J. A.M. Porto[1,4], A. F. Baptista[2,4], H. F.Japyassú[3,4], R. S. Rosário [1,4], J. G. V. Miranda[1,4]

[1] Núcleo de Inovação Tecnológica em Reabilitação, NITRE; [2] Núcleo de Estudos em Saúde e Funcionalidade, NESF; [3]Núcleo de Etologia e Evolução, NuEVo; [4]Universidade Federal da Bahia, UFBA.

Introduction: Although meditation is known for changing the consciousness's state[1], little is known about the dynamics of the changes in brain connectivity. Here we analyse functional networks of brain dynamics[2] (Time Varying Graph – TVG – (Figure 1)), comparing cortical activity and stability during meditation (MD) and relaxation (RL), considering experienced meditators of two groups, Raja Yoga (RY - from Brahma Kumaris) and Gurdjieff (GD), both from Salvador – Bahia/Brazil. Understanding the function features of the meditation state in time domain can help in a deeper understanding of the mechanisms that make thispracticea powerful tool in promoting health and well-being. **Materials and Methods:** This study included 16 experienced meditators from RY (n=8) and GD (n=8). EEG data were recorded with BrainNet BNT 36, using 30 electrodes (International 10-10 system)[3]. We used NuPrep Waves Gel® to improve the conductivity and Contact-Cream® to fix the electrodes on scalp. The sample rate was 600 Hz, electrode reference in Cz, and the impedance was between 0 and 5 Ω. **Protocol**: Base Line (BL) - 5 minutes; RL - 6 minutes and 12 minutes of traditional meditation (RY or GD) with eyes closed. Only one run was done for each subject. Data were analyzed through TVG, using *motifs synchronization*[4]. The study was approved by the Ethics and Research Committee of Health Sciences Institute of Federal University of Bahia. **Results:** According to[4] the time electrodes remain synchronous is measured by the weighted degree (kp) of the added static network of individuals TVG. Results show kp increase during meditation (Wilcoxon paired p=0.044). This is mainly due to Gurdjieff meditators (T-Test p=0.031), since Raja Yoga meditators do not show changes in brain dynamic connectivity (Wilcoxon paired p=0.484). This difference can be view in Figure 2. Meditation also increased cortical stability (measured as the coefficient of variation of the clustering coefficient in time, T-Test, p=0.024), meaning that the topology of the network's brain stabilizes during meditation for both groups. **Discussion:** Previous studies with EEG and fMRI have indicated that meditation and relaxation are associated with different brain dynamics[5] for quantitative EEG and fMRI. However, in experienced meditators, these states can be similar[6]. The result found in RY group is probably due the intention of the meditation and way of life. The GD group does exercise regularly with synchronized movements and use deep relaxation in their meditative practice. **Conclusion:** The present study confirmed that MD and RL are different, in the Gurdjieff group, but these results aren't the same for Raja Yoga group.In MD state, analyzed by agglomeration coefficient, the cortical topology keeps more stable than RL state does.

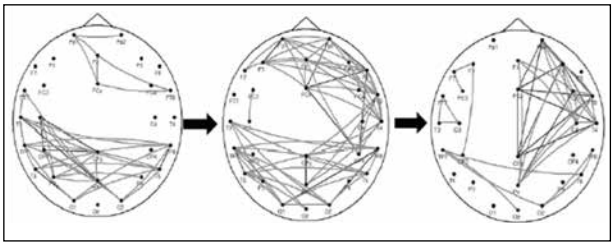

Figure 1. TVG. Edges represents synchronization between electrodes. Green lines indicate arrows (directed synchronization), and blue lines edges (undirected synchronization).

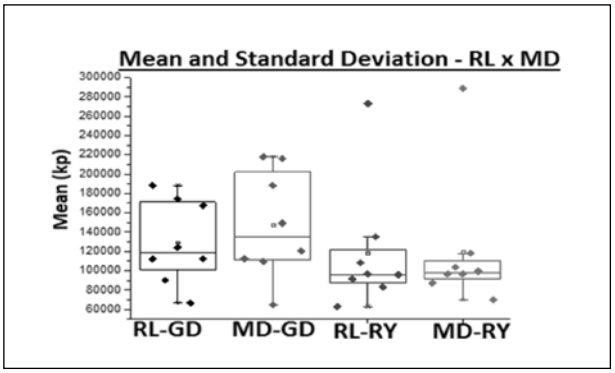

Figure 1. Differences in Kp of relaxation (RL) and meditation (MD). Values are expressed as mean and dispersion values. GD: Gurdjieff, RY: Raja Yoga. Each point represents a subject.

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IDENTIFICATION OF PUTATIVE PATHOGENIC CNVS IN A LARGE COHORT OF PATIENTS WITH INTRACEREBRAL HEMORRHAGE

A. Donatti[1], R. Secolin[1], F. R. Torres[1], L. E. Ferreira[2], M. Maccarone[3], P. H.C. França[2], V. Nagel[2], M. Mancuso[3], N. L. Cabral[2], B. S. Carvalho[4], D. Woo[5], I. Lopes-Cendes[1]

[1]Department of MedicalGenetics, School of Medical Sciences, University of Campinas, UNICAMP, and the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, SP, Brazil; [2]Department of Medicine, Regional University of Joinville - UNIVILLE, Joinville, SC, Brazil; [3]Department of Experimental and Clinical Medicine, Neurological Institute, University of Pisa, Pisa, Italy; [4]Department of Statistics, Institute of Mathematics, Statistics and Scientific Computing, University of Campinas , UNICAMP, SP, Brazil; [5]Department of Neurology and Rehabilitation Medicine, College of Medicine, University of Cincinnati, Cincinnati, OH, USA.

Introduction: Intracerebral hemorrhage (ICH), although less frequent than ischemic stroke, has a higher mortality rate. Several studies have demonstrated evidence of genetic factors influencing ICH. Copy number variations (CNVs) are common structural mutations, which have been identified as causing changes in gene expression, thus potentially leading to disease. The aim of this study is to identify putative pathogenic CNVs in patients with ICH. **Materials and Methods:** We performed microarray-based genotyping of SNPs (*Genome-Wide Human SNP Array* 6.0; Affymetrix Inc.) to identify CNVs present in patients with ICH. The cohort is composed of individuals with a minimum age of 50, divided into two groups: 1053 patients with ICH and 781 healthy individuals. Patients were ascertained in four centers: University of Joinville, Brazil; University of Pisa, Italy; Massachusetts General Hospital, USA and University of Cincinnati, USA. CNV calls were performed by two algorithms, Affymetrix APT Copy Number tool and PennCNV; only CNVs identified in both were recorded. In addition, we only considered CNVs containing more than 25 markers, in order to avoid short variations that could interfere in our analysis. We determined CNV frequency by PLINK, and in an initial analysis, considered only CNVs present exclusively in patients. These were subsequently analyzed by GProfiler and METACORE™ software in order to identify the main pathways related to the phenotype. **Results:** Overall, we identified 866 CNVs among cases. Individual CNVs identified were present at a low frequency, with a maximum of 12 patients with the same CNV. GProfiler and METACORE™ software identified four potential genes related to Ras, MAPK and Ephrin signaling pathways (p-values=1.57e-2; p-value=5.026e-8) within these CNVs: *CDC42*, *EFNA1*, *EFNA3* and *SHC1*. **Discussion:** Those genes are described as related to blood coagulation, regulation of blood vessel endothelial cell migration, angiogenesis and MAPK cascade.Further analyses are important to better elucidate these pathways and their genetic influence on stroke. **Conclusion:** Copy number variants may identify additional genes of interest to ICH risk.

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A COMPREHENSIVE ANALYSIS OF MISSENSE MUTATIONS IN *SCN1A* IN PATIENTS WITH DRAVET SYNDROME IMPROVES INTERPRETATION OF CLINICALLY RELEVANT VARIANTS

M. C. Gonsales[1], M. A. Montenegro[2], P. Preto[2],M. M. Guerreiro[2], A.C. Coan[2], M. P. Quast[3], B. S. Carvalho[3], I. Lopes-Cendes[1]

[1]Departments of Medical Genetics; [2]Neurology, School of Medical Sciences, [3]Department ofStatistics, Institute of Mathematics, Statistics and Computer Science, University of Campinas, UNICAMP; and the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, SP, Brazil.

Introduction: The *SCN1A* gene is currently considered one of the most relevant epilepsy-related genes in the clinical setting, with the majority of mutations identified in patients with Dravet syndrome (DS)[1]. However, interpreting the clinical significance of genetic variants found in molecular tests can be challenging, particularly for variants of unknown significance such as missense mutations. In order to access the rate of success in the classification of missense variants, we evaluated algorithms to predict functional effects of *SCN1A* missense mutations in patients with DS reported in the literature as well as mutations identified in our own molecular studies.**Materials and Methods:** We carried out a comprehensive meta-analysis of previously described *SCN1A* mutations in patients with DS, as well as data generated in our laboratory, and assessed the use of ten different computer algorithms to predict deleterious effects of

amino acid changes resulting from missense mutations. Initially, each algorithm was tested individually; subsequently, we developed an ensemble classifier to obtain more reliable prediction, by using a combination of scores obtained in five prediction algorithms. Furthermore, we evaluated whether amino acid changes are predominant in specific protein regions by performing a permutation test. **Results:** A total of 780 potentially deleterious nucleotide variants in patients with DS were compiled from the literature, in addition to those identified in our laboratory. Of these, 45.3% (353/780) are missense mutations. *In silico* analysis of the deleterious effect of the 353 *SCN1A* missense variants showed that the majority (57.5%) are predicted as deleterious by all ten algorithms individually. In addition, almost all amino acid changes (92.6%) are considered deleterious by more than half of the algorithms tested. Our classifier combining multiple prediction scores presented high accuracy (0.8873), sensitivity (0.8379) and specificity (0.9191). Moreover, we found a predominance of amino acid changes in the voltage sensor segment (S4), the pore forming region (S5-S6) and adjacent subunit S6 ($p<0.05$). **Discussion:** We observed that the most frequent type of *SCN1A* mutations in DS patients is missense, confirming that such class of mutations is frequent in patients with severe phenotypes and not only present in patients with more mild clinical presentations, such as typical GEFS+ as previously proposed. One important issue that we aimed to address was the problematic interpretation of the prediction test results. Therefore, we used multiple algorithms to improve success rates of prediction analysis and successfully obtained consistent results for most alterations. **Conclusion:** In conclusion, we were able to correctly ascertain putative pathogenic effect in the vast majority of missense mutations in *SCN1A* found in patients with DS, thus minimizing the inconvenience of inconclusive reports in the molecular diagnosis of patients with this severe form of epilepsy. The combined score created for testing functional changes in *SCN1A* was highly sensitive and specific to discriminate pathogenic changes and can be used in the clinical setting.

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INVESTIGATION OF THE INFLUENCE OF SUBJECTS' TRAINING IN THE PERFORMANCE OF AN MI-BASED BCI USING DIFFERENT FEATURE SETS

A.C. Buzzi[1,2], C. A. Stefano Filho[1,2] ,G. Castellano[1,2]

[1]Neurophysics Group, IFGW, UNICAMP, Campinas, Brazil; [2]Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, São Paulo, SP, Brazil.

Introduction: The main goal of this work was to analyze and test which features generate the best performance results of a motor imagery (MI) based brain computer interface (BCI) using an LDA classifier. Furthermore, we aimed to investigate whether subjects' training improved the results, as pointed out by some studies[1].**Materials and Methods:** Six volunteers (mean age 22 ± 3, 2 men) participated in this study, approved by the Ethics Committee of Unicamp. Two acquisition paradigms were used, one with 10s-blocks and another with 6s-blocks, both alternating rest blocks with blocks of motor imagery of the right (RH) and left hand (LH). The 10s and 6s paradigms had 170s and 240s of duration for each trial, respectively. Data were obtained through EEG with 16 dry electrodes (g.USBamp and g.SAHARA, from g.tec). All routines were implemented in Matlab. Features consisted of the amplitude of the Fourier transform within specific bands (μ: 8 to 12Hz, β: 12-30Hz). We used the LDA classifier and the "*leave one out*" method for training/testing. We tested3 feature sets that differed in the considered band (μ; β; μ and β). Finally, two acquisitions were made with each subject, one without training and the second one week later, after the subject had trained for 7 days, 4 minutes a day. **Results:** We found that for both paradigms, the best classification results were for sets 1 and 2, which consider only one of the bands (μ or β) (Table 1). Also, in general, classification accuracy worsened with training. The paradigm with 6s-blocks had worse performance than the 10s', especially for the set with both bands (Set 3). **Discussion:** Data acquisition was always performed with the 10s paradigm before the 6s', so fatigue may be a reason why performance worsened in the 6s' paradigm. The worse results after training were unexpected, but the difference between the results with and without training is 2%, which is within the standard deviation. The worse results obtained with both bands were also unexpected. This indicates that isolated bands are more discriminant for these tasks, at least, using an LDA. **Conclusion:** The present work confirmed that MI is not an easy task, even with subject training for a week, as several external and internal factors may influence the subject's performance. Increasing the number of subjects may lead to more robust results.

Table 1. Classification rate obtained for the 6s and 10s-blocks paradigms, with and without training, for each of the 3 feature sets. Numbers indicate mean value (between subjects and acquisitions) ± standard deviation.

Set (band)	Block of 6s - Without Training	Block of 6s - With Training	Block of 10s - Without Training	Block of 10s - With Training
1 (μ)	61±8	60±8	64±9	65±8
2 (β)	67±4	65±6	68±6	67±9
3 (μ and β)	66±7	59±10	58±20	55±18

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ELECTROPHYSIOLOGICAL CHARACTERIZATION OF THE MESOLIMBIC CIRCUIT IN WILD MICE

L. Andreoli[1], J. W. R. de Freitas[1], E. Morya[1], R. C. Moioli[1], M. F. de Araújo[1]

[1]Neuroengineering Postgraduate Program, Edmond and Lily Safra International Neuroscience Institute, Macaiba, Natal, RN, Brazil.

Introduction: Currently about 450 million people are affected by mental disorders. The underlying neurophysiology of these disorders is not fully understood, but many studies suggest that dopaminergic pathways are related to the pathophysiology of these diseases. Mesolimbic pathway dysfunction changes anxiety and hyperactivity levels, which are symptoms of many psychiatric disorders. This study aimed at characterizing the electrophysiological activity of the mesolimbic circuit of wild mice in an experimental paradigm designed to assess exploratory activity and anxiety levels. **Materials and Methods:** All procedures were performed according to approved protocols by AASDAP Ethics Committee under no. 02/2013. A 32-channel microelectrode array (tungsten 30μm coated wire) recorded local field potentials (LFP) of eight wild mice freely behaving in an elevated plus-maze task testing anxiety. The microelectrode array recorded simultaneously four areas of the mesolimbic pathway in both hemispheres with four electrodes in each area: ventral tegmental area (VTA), nucleus accumbens (Nac), basolateral amygdala (BLA) and prelimbic cortex (PrL). LFPs were acquired with the MAP system (2 kHz, Plexon Inc, USA), videos were recorded with the Cineplex software (80 Hz, Plexon Inc, USA) and data were analyzed with the Chronux Toolbox [1] for Matlab (MathWorks, Natick, MA). **Results:** We found differences in time ($F = 23.62$, $p<.05$), distance ($F = 20.77$, $p<.05$) and speed ($F = 25.7$, $p<.05$) of mice on the closed arms of the maze in comparison to the open arms.For the electrophysiological results, power spectra and coherence at the open and closed arms of the elevated plus-maze were compared to that when the mice were in the nesting box. At the open arms of the maze, there was an increase ($p<.05$) in the power spectrum between 10 and 16 Hz in the right Nac and between 8 and 12 Hz in the left Nac; at the closed arms, we found a significant increase between 10 and 16 Hz in both Nac and between 70 and 100 Hz in the right Nac. Coherence of oscillations increased in the 8 – 12 Hz band between left VTA and PrL and in the 35 – 40 Hz band between left Nac and VTA when animals were at the open arm; at the closed arms, coherence increased in the 8 – 12 Hz band between VTA e PrL. **Discussion:** Our results with the elevated plus-maze were similar to those found in the zero-maze [2]. We observed synchrony in the 35 - 40 Hz band between Nac and VTA, which might relate to anxiety behavior at the open arms of the plus-maze. This supports the hypothesis that changes in Nac-VTA synchrony reflect neurophysiological circuit changes underlying the expression of anxiety-related behaviors. In addition to previous work [2], we also observed a change in synchrony between VTA and PrL in the 8 - 12 Hz band when animals were in the nesting box or in the maze. Since both areas connect with Nac, an area with an important role in anxiety-related behaviors, this could explain the synchrony modulations found in the experiment. **Conclusion:** Our findings corroborate with the hypothesis that changes in Nac-VTA synchrony reflect neurophysiological circuit changes underpinning anxiety-related behavior and reinforces the role of mesolimbic pathway structures in anxiety and other mental disorders symptoms.

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RELATIONSHIP BETWEEN GRIP STRENGTH AND DEXTERITY IN INDIVIDUALS WITH PARKINSON'S DISEASE

C.C.G. Alonso[1], P. B. de Freitas[2], R. S. Pires[1], D. Lustosa[1], S.M.S.F. de Freitas[1]

[1]Universidade Cidade de São Paulo, Pós-Graduação em Fisioterapia, Laboratório de Análise do Movimento (LAM-I), [2]Universidade Cruzeiro do Sul, Pós-Graduação em Interdisciplinar em Ciências da Saúde, Laboratório de Análise do Movimento (LAM).

Introduction: Parkinson's disease (PD) is characterized by the presence of movement disorders, with classic signs and symptoms that may affect upper limb (UL) such as bradykinesia, rest tremor and rigidity[1]. Movement slowness, reduced movement amplitude, and difficulty in performing sequential tasks are observed in individuals with PD while performing UL movements[2]. PD individuals also presented reduced maximal hand power grip strength (GS_{Max}) and dexterity[1,4]. Altogether these movement characteristics may affect the performance of daily, leisure, and self-care activities in individuals with PD. The Jebsen-Taylor Hand Function Test (JTHFT), a standardized test used to assess the hand function of individuals with stroke, has been recently applied to evaluate the global hand dexterity of PD individuals. Overall, the individuals needed more time to complete the JTHFT compared to healthy adults[3]. However, whether the reduction in JTHFT score is associated with the decrease in GS_{Max} is still unknown. Therefore, the aim of the present study was to examine if there is a relationship between the performance of individuals with Parkinson's disease in the JTHFT and GS_{Max}. **Materials and Methods:** Twenty-eight, right-handed individuals (14 with PD and 14 healthy controls) performed the JTHFT and the hand power and pinch Grip Strength tests. Individuals with PD were determined by the Hoehn and Yahr Scale as in stage 1-3. Participants performed a single trial of each subtest of the JTHFT (except the writing sentences task that was not assessed in the current study). Half of the participants started each subtest with their right hand (dominant) while the other half started with the left hand. Next, the participants performed three trials of the hand power and three of the pinch grip strength test. The time spent to complete each JTHFT subtest and the sum of the times of these subtests were compared between groups and hands. The maximum hand power ($PwGS_{Max}$) and pinch ($PnGS_{Max}$) grip strength were also compared between groups and hands. Analyses of variance (ANOVA) and Pearson's correlations were carried. The significance value was set at 0.05. **Results:** ANOVA revealed that individuals with PD were slower than controls in the time to perform the following JTHFT subtests: lifting small objects; lifting large light objects; and simulated page turning. Individuals with PD were not different than controls when performing the subtests stacking checkers and lifting large and heavy objects. Group by hand interaction was observed only for the subtest simulated feeding. ANOVA also revealed a lower $PnGS_{Max}$, but not $PwGS_{Max}$, in individuals with PD than in controls. All Pearson's correlation coefficients between strength tests and each subtest of the JTHFT were non-significant. **Discussion and Conclusion:** As in the study by Mak and colleagues[3], we observed that individuals with PD are slower than controls during the performance of the most of JHTFT subtests, confirming the decline of the hand function of individuals with PD. However, these deficits could not be explained by the lower Grip Force, as we found no correlation between the grip strength tests and the performance in any of JTHFT subtests.

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NEUROPROTECTIVE EFFECT OF *LEPIDIUM MEYENII* WALP. IN RATS WITH CEREBRAL ISCHEMIA

K. Taboada-Rosell[1], L.R. Oliveira[1,2], E.P.N. Sales[1,2], V.S. Sales[1,3], L. Malavolta [2], A. Pino-Figueroa[4], T.J. Maher [4], R.M. Arida[3], K.J. Vera-Lopez [5], F.R. Cabral[1,2]

[1]Neuropsychopharmacology Group - Hospital Israelita Albert Einstein; [2]Faculdade de Ciências Médicas da Santa Casa de São Paulo; [3]Physiology Dept. – UNIFESP; [4]MCPHS University, 179, Longwood Avenue, Boston, MA, 02115, USA; [5]Universidad Católica de Santa Maria, Arequipa, Peru.

Introduction: Stroke is the main cause of death in Brazil with age-adjusted morbity and mortality rates higher than in other South American countries.[1,2]*Lepidium meyenii* (Maca) is a plant used as a dietary supplement by peruvian native population due to its medicinal properties. This present study had as objective determine of neuroprotective effect of extract of *Lepidium meyenii* Walp (yellow Maca) at the dose of 5mg.kg-1 immediately after reperfusion, followed by daily doses of 1 mg.kg-1 orally for 10 days in rats submitted to focal cerebral ischemia. **Methods:** The animals were submitted to a model of middle cerebral artery occlusion (MCAO) with reperfusion (2h). The animals were divided into four experimental groups, such as, healthy group (n=11), stroke group (n=11), vehicle group (n=11) and maca group (n=11). Then, a behavioral analysis was performed by applying a neurological scale, the open field test and passive avoidance. Finally, the infarcted area was evaluated by the software ImageJ. **Results:** The treatment with Maca reduces the infarct volume in 77,37% (2,50 ± 0,286, p≤0,01) when compared to stroke group (11,05 ± 0,961) and reduce in 79,07% (2,50 ± 0,286, p≤0,01) when compared to vehicle group (11,95 ± 1,114). The analysis of neurological scale showing a significant improvement in Maca group sensory-motor evaluation 23,01% (11,24 ± 0.673, p≤0.01) when compared to the stroke group (8.45 ± 0.439) and 32.39% (11,24 ± 0.673, p≤0.01) when compared to the vehicle group (8,49 ± 0,487). The analysis of the open field showed that the maca group decreased significantly the number of quadrants traversed in 52,92% (17,22 ± 1,865, p≤0,05) when compared to the stroke group (39,35 ± 5,859) and in 64,74% (17,22 ± 1,865, p≤0,01) when compared to the vehicle group (41,36 ± 4,517). Rearings in 59.66% (1,66 ± 0,251, p≤0,05) when compared to the stroke group (3,85 ± 0,813) and vehicle group (0,86 ± 0,180); and increased significantly the time of immobility in the group maca (117,2 ± 16,800, p≤0,001) when compared to the stroke group (42,27 ± 7,849) and vehicle group (36,88 ± 6,212, p≤0,05). The maca group (131,50 ± 35,970, p≤0,05) presented a significant increase of aversive memory when compared to the stroke group (22,48 ± 4,998) and Vehicle group (21,59 ± 2,075). **Discussion:** The post-treatment with pentanic extract of Lepidium meyenii (Maca) was able to prevent the increase in infarct area in 77,37%, indicating neuroprotective effect. The locomotor activity was evaluated in the animals that suffered ischemic motor deficits. In a preliminary study, locomotor activity was observed in the open field test, where there was a non significant trend of reduction in the number of crossings and increased immobility time compared to the control group.[3] Others studies also identified a dysfunction in the behavior and was evaluated the sensoriomotor capacity before and after inducing this animal model for 90 days, using the Garcia scale (1995) as a method to assess the neurological capacity in long term.[4,5] In our study, demonstrating that the treatment with Lepidium meyenii (Maca) is able to significantly improve the neurological capacity. **Conclusion:** The Lepidium meyenii extract (Maca) prevented memory deficits, sensorimotor, neuronal damage, and increased survival of neurons in rats submitted to experimental MCAO.

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UNCERTAINTY IN TARGET LOCATION AFFECTS THE ARM REACHING MOVEMENTS DURING STANDING IN STROKE INDIVIDUALS

R.B.S.C. Garbus[1], S.R. Alouche[2], A.G. Nardini[1], S.M.S.F. Freitas[2]

[1]Phd Student of Universidade Cidade de São Paulo (UNICID); [2]Master and Doctoral Program in Physical Therapy, UNICID, Laboratory of Movement Analysis (LAM).

Introduction: Individuals with mild post-stroke hemiparesis present several motor impairments that can negatively affect the performance of arm reaching during upright standing. Uncertainty in target location has been described to affect these arm movements in healthy individuals[1,2]. These effects were observed in stroke individuals only when arm movements were performed in sitting position[3]. Therefore, the aim of this study was to examine the effects of the target uncertainty on the arm reaching during standing in stroke individuals. **Materials and Methods:** Nineteen individuals with mild post-stroke hemiparesis divided in two groups (nine on the right and ten on the left side) stood in upright position and performed reaching movements with their arm ipsilateral to the brain lesion. Eighteen healthy individuals for control group also performed the reaches with either right (n=8) or left (n=10) arm. Reaches were performed towards a target shown in a monitor placed at a distance of 105% of the upper limb's length and the targets were presented in one of three heights (a center target placed at the eye level or 10 cm upper or 10 cm lower to the center target). There were two experimental conditions, certain (i.e. the participant know where the target was) and uncertain (i.e. the target moved

for the upper or lower position or remained in the center). Each participant performed 60 trials (20 trials for each target height and its order was randomized across them). Participants were instructed to reach and touch the center of the target displayed on the monitor as fast as possible after the target changes its color. Time elapsed from this color stimulus until participants' movement initiation (time of movement onset), time spent to complete the task (movement time) and the accuracy (constant error) were compared among target heights, experimental conditions and groups using Analysis of Variance (ANOVA). Bonferroni adjustments were used when necessary. The significance level was assumed in $p<0.05$. **Results:** For the time of movement onset, ANOVA revealed a condition effect ($p<0.001$), which individuals spent more time (about 120 ms) to reach under the uncertainty compared to the certain condition. In addition, the time of movement onset was 130 ms greater for the stroke compared to control group ($p<0.001$). For the movement time, ANOVA revealed main effects of target height ($p=0.002$) and group ($p=0.016$). There was also an interaction between target height and group ($p=0.018$), indicating that the effect of height was observed only for stroke group as they spent more time to reach the upper target. For the accuracy, there was an interaction between condition and height ($p=0.002$) and a triple interaction between condition, height and group ($p=0.004$). The accuracy was greater in higher targets for the stroke group and in lower target for control group. **Discussion**: The uncertainty in target location affected mainly the time of movement onset for both groups, indicating that the prior knowledge of the target location is important to plan the reach[1]. Uncertainty also reduced the accuracy. Although these effects were observed for both groups, post-stroke individuals spent more time to initiate their movements and were less accurate for higher targets. They also needed more time to reach the target as observed in a previous study[3], particularly for higher targets, probably due to several deficits after the brain lesion in the movement execution. **Conclusion:** The uncertainty in target location affects the arm reaching movements during standing in stroke individuals.

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A SSVEP-BCI MODEL TO MAKE CORRECT DECISIONS ON TRAFFIC SIGNS

R. Hübner[1], P. V. O. Miguel[2], L. B. R. Aylon[3], G. Barreto[4]

[1]Computer Department (DACOM), Federal University of Technology, Paraná (UTFPR); [2] Informatics Department (DIN), State university of Maringá (UEM); [3]Technical College of Campinas (COTUCA); [4]Faculty of Electrical and Computing Engineering (FEEC), University of Campinas, UNICAMP, São Paulo, SP, Brazil.

Introduction: Brain-Computer Interfaces (BCI) has been used to perform an interaction with electrical and electronic devices. Applications in BCI paradigms are used as patterns to map the brain interface and what it will be externally controlled. A widely paradigm used for that purpose isSteady State Visual Evoked Potential (SSVEP), where frequencies evoked by the user can be discriminated through the acquisition of a signal obtained by an electroencephalogram (EEG) positioned in the user's visual cortex. In this study, we used a BCI to assist in potentially risky traffic situations, in this case, traffic signs to make a correct decision. Such decisions may be to stop a vehicle or not, which can bring some danger to the individual making a decision. **Materials and Methods:** In order to perform the data acquisition, it was used a low cost EEG equipment. The equipment used is the OpenBCI board, in the version with 32 bits of processing. The scenario used to create the decision situations was implemented through a computational simulation, thus preserving the integrity of the users. The software used are: OpenBCI GUI (EEG signal pipeline), OpenVibe (simulation, signal processing and feedback). Eight electrodes were scattered throughout the region in the visual cortex, respecting the 10-20 system and the duration of each experiment was six minutes, with a single user, and it was performed three times. The simulation presents a view of a driver inside a car, who is observing traffic lights that may be red or green. The main filters used are Common Spatial Pattern (CSP) and bandpass filters (Butterworth). The extraction of characteristics was applied in this sequence: squaring, signal average and logarithm. The classifier used was the Linear Discriminant Analysis (LDA). **Results:** Some results were obtained in this preliminary experiment. The experiment was performed with a simulation with only green and red traffic lights and sound signals (cop whistle), and the user would have to make only one decision: to stop the car or not. This decision is known in the literature as "go" and "no-go", and it was obtained an accuracy rate of 73% in the best case. Using the SSVEP-BCI paradigm we are able to increase this accuracy significantly. **Discussion:** The first results demonstrate this methodology can be used to make the correct decision in a situation of risk, which are applied in the simulation of driving a vehicle. Some issues must still be better studied such as standardizing the duration of events, improving signal filtering and compare other classifiers to select the correct stimuli. On the other hand, "plastering" the model to get best results implies that the simulation will be far from reality. **Conclusion:** Preliminary results and current related works confirm that with the use of an BCI model using Event Related Potential (ERP) paradigm, it is possible to characterize external events with a neural interface. With the current study we want to increase the accuracy of the obtained results using an initially SSVEP-BCI model as well as at the same time to approximate the simulation of real situations.

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COMPARISON OF TWO TRACTOGRAPHY APPROACHES IN HEALTHY ADULTS

Y. F. Ribeiro, R. Frayne, A. Tsang

[1]Instituto de Sistemas Elétricos e Energia, Universidade Federal de Itajubá, Itajubá, MG, Brasil; [2]Departments of Radiology and Clinical Neuroscience, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada;[3]Seaman Family MR Research Centre, Foothills Medical Centre, Calgary, Alberta, Canada.

Introduction: Tractography is a 3D-modelling technique that uses diffusion tensor imaging (DTI) data to visually represent white matter (WM) fiber tracts in the brain. A common approach uses the tensor model to estimate fiber orientation on a voxel-by-voxel basis to delineate WM tracts[1]. This approach has been widely used in studies to investigate WM changes in disease and normal aging. However, it has been shown that the tensor model fails to correctly delineate WM tracts in voxels with multiple fiber orientations that accounts for 90% of WM voxels[2]. Constrained spherical deconvolution (CSD) is an approach proposed to mitigate the limitation of the tensor model using fiber orientation distribution in each voxel for WM tract delineation[2,3]. The objective of this study is to compare metrics that infer WM microstructure derived from both tensor and CSD methods in healthy subjects over the adult lifespan. **Materials and Methods:** DTI data from 216 healthy participants (18 to 87 years) were collected as part of the Calgary Normative Study on a 3-T scanner (Discovery 750, General Electric). Raw diffusion images were corrected for subject motion and eddy-current-induced distortions. Four commonly used DTI data metrics: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were obtained. Tractograms also were generated to visualize WM tracts from tensor model and CSD methods (MRTrix, http://www.mrtrix.org)[3] using seed regions defined by seven template-defined resting state networks (RSNs)4. Statistical analysis (SPSS Statistics, IBM) were conducted using paired *t*-test and Pearson correlation as appropriate. **Results:** The CSD method allowed visualization of more WM tracts compared to the tensor model and better delineated WM in voxels with crossing fibers, as expected (Figure 1). Mean MD, AD and RD of WM tracts associated in each RSN were significantly (*i.e.*, $p<0.05$) higher, while mean FA was significantly lower, for CSD over the tensor model. Mean MD, AD and RD were positively correlated while mean FA was negatively correlated with age in all RSNs for both methods (Table 1). **Discussion:** Our results agree with a recent study that compared metrics derived from tensor model and CSD methods in chronic stroke patients[5]. In addition, we demonstrated significant correlation between MD, AD, RD, and FA with age in most RSNs for both methods. At present, the tensor model is the most widely used tractography method, however, it has been shown to misrepresent the actual WM anatomy in certain brain regions compared to the CSD method[2] Previous normal aging studies may have underestimated WM changes if they based their findings on the tensor model. **Conclusion:** CSD method yields significantly different results than the tensor model and appears to provide more reliable result that better reflect anatomy and inferences about WM in normal aging.

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THYROID HORMONE SIGNALING IN MOUSE BRAIN FOLLOWING PILOCARPINE-INDUCED STATUS EPILEPTICUS

B. P. P. Nascimento[1,2], B. M. L. C. Bocco[1,3], T. L. Fonseca[3], A. C. Bianco[3], M. O. Ribeiro[2]

[1]Department of Translational Medicine, Federal University of São Paulo, São Paulo, SP, Brazil; [2]Department of Health and Biological Sciences - CCBS, Mackenzie Presbyterian University, Sao Paulo, SP, Brazil; [3]Department of Internal Medicine, Division of Endocrinology and Metabolism, Rush University Medical Center, Chicago, IL, United States.

Introduction: Thyroid hormones (TH) play an important role in the maintenance of central nervous system (CNS) through the control of gene expression[1,2]. Thyroid gland synthesize about 93% of T4 and 7% of T3, the active form of TH[3]. The activation of T4 to T3 in the brain is catalyzed by type 2 iodothyronine deiodinase (D2). Although serum concentration of THs is remarkably stable, D2 regulate T3 signaling in the neurons in a precise spatio- and temporal-manner by controlling the activation of TH[4,5]. D2 expression and activity can change in critically ill patients and consequently the T3 signaling in the tissues[6]. Status epilepticus (SE) is a well-known insult to the CNS that can be defined as a state of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures and may leads to the development of Temporal Lobe Epilepsy (TLE)[7]. Here we hypothesize that seizures could induce changes in D2 expression and activity in the brain with consequent variations in T3 signaling. The shift in T3 signaling could be involved in the altered behavior observed in patients with TLE. Thus, we studied prefrontal cortex, amygdala and hippocampus of mice after induction of SE to evaluate expression and activity of D2 and mRNA levels of T3 regulated genes. **Methods:** 2 months old C57Bl/J6 male mice were treated with lithium-pilocarpine as a model of epilepsy[8,9]. The seizures were interrupted by Diazepam 3 hours after the beginning of SE and the mice were killed 30 minutes after that. mRNA levels of D2 and T3-regulated genes were analyzed by real-time PCR, and we also analyzed the enzymatic activity of D2. **Results:** Notably, SE caused an increase in D2 mRNA levels and its activity in the hippocampus, amygdala and prefrontal cortex. mRNA levels for 4 negative regulated genes (Hapln1, Dgkg, Fxyd6, Syce2) decreased and 1 (Slc1a3) increased, and 1 positive regulated gene (Itga7) decreased in hippocampus; 3 negative regulated genes (Hapln1, Dgkg, Slc1a3) decreased and 2 positive regulated genes (Rc3, Aldh1a1) decreased in prefrontal cortex; 1 negative regulated gene (Fxyd6) decreasedand 1 positive regulated gene (Aldh1a1) decreased in amygdala. **Discussion:** Our data showed changes in TH signaling in mice brain after SE. These changes are possibly due to the increase in D2 expression and activity, although we cannot conclude that this resulted in a hyperthyroid brain since there is a significant variation in the expression of T3 regulated genes.**Conclusion:** Our results showed that SE causes subtle changes in some T3-regulated genes suggesting changes in T3 signaling in the brain.

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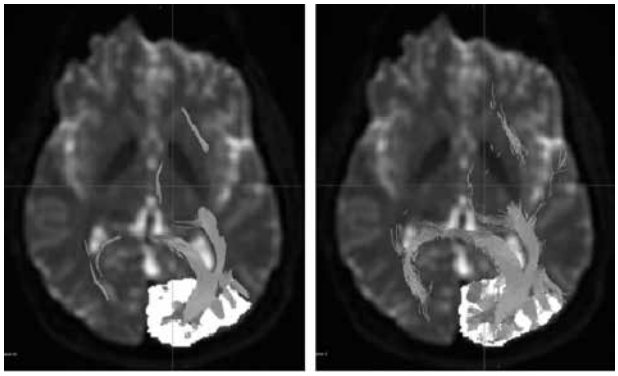

Figure 1. WM tracts depicted from DTI (left) and CSD (right) methods using a seed region in a representative subject.

Table 1. Pearson correlation versus age in WM tracts associated with the default mode resting state network

DTI metric	tensor	CSD
FA	-0.47 (p<0.001)	-0.39 (p=0.001)
RD, mm^2 s^{-1}	0.59 (p<0.001)	0.73 (p<0.001)
AD, mm^2 s^{-1}	0.44 (p<0.001)	0.69 (p<0.001)
MD, mm^2 s^{-1}	0.56 (p<0.001)	0.73 (p<0.001)

THE FUNCTION OF B2 ADRENERGIC RECEPTOR IN MEMORY

T. T. Ravache[1], P. S. Braga[1], T. G. B. Gomez[1], F. B. Lorena[2], M. O. Ribeiro[1]

[1]Department of Health and Biological Sciences-CCBS, Mackenzie Presbyterian University, São Paulo, SP, Brazil; [2]Department of Translational Medicine, Federal University of São Paulo, SP, Brazil

Introduction: Memory formation is divided in three moments: learning, consolidation and evocation and can be classified by its duration: short-term and long-term memory and its nature: explicit or implicit. The hippocampus and the amygdala are fundamental for memory formation participating in the process of memory consolidation and learning. Noradrenaline is a neurotransmitter with important role in the memory formation that exert its effect through adrenergic receptors, α and β. There are three isoforms of β-adrenergic receptors, β1, β2 and β3, all expressed in the amygdala and hippocampus. Previous studies performed in mammal demonstrated important participation of β1 and β2 adrenergic receptors in memory consolidation through pharmacological approaches, method that presents limitation due to poor agonists and antagonists specificity. The aim of this study is to evaluate the function of β2 adrenergic receptor in memory using knockout mice for β2 adrenergic receptor gene (Adrβ2KO), a more clean approach. **Materials and Methods:** The short and long-term explicit memory was evaluated by object recognition test while social memory was evaluated by three-chamber social novelty test. Anxiety was evaluated by elevated plus-maze and neuromotor dysfunction through open field test. Two weeks after the behavior assessment, the animals were killed and amygdala and hippocampus were removed and frozen at -80°C for gene expression analysis by Real-Time PCR. For behavioral tests we used 10 wild type (FVB) mice as control group and 7 Adrβ2KO mice as experimental group, and for RT-PCR were used 5 FVB mice and 7 Adrβ2KO mice. The Student's *t*-test was used only when two groups were part of the experiment. One-way ANOVA was used to compare more than two groups, followed by the Student–Newman–Keuls test to detect differences between groups. $p<0.05$ was used to reject the null hypothesis. **Results:** In the Open field test the Adrβ2KO mice showed no motor impairment and a higher frequency of crosses suggesting an increase in motor activity when compared to wild type. Elevated Plus-Maze test showed the Adrβ2KO remain more time in the open arms when compared to wild type. The Object Recognition test showed that Adrβ2KO mice are able to form short term memory but not long term memory. The Social Novelty test showed that Adrβ2KO mice did not present any impairment in social memory, responding equally to wild types. There was no difference in expression of genes related to memory formation in the amygdala and hippocampus between the groups. **Discussion:** Our results suggests that the lack of β2 adrenergic receptor do not interfere in locomotion and in fact leads to an increase in motor activity indicating a possible hyperactivity. The literature has already shown that propranolol, an Adrβ blocker promotes anxiolytic effects, that was confirmed in the elevated plus-maze test indicating a role for Adrβ2 in the anxious behavior. The short-term memory does not depend on Adrβ2 but for long-term memory can be a key. **Conclusion:** The present study confirmed that the β2 adrenergic receptor is important for the explicit long-term memory, but not for explicit short term-memory or social memory. These results show that the different isoforms of the β adrenergic receptors have different roles in memory formation process. Furthermore, this study also demonstrates that the absence of the β2 adrenergic is important to mediate the anxious behavior.

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CORRELATION BETWEEN THE PRESENCE OF THE POLYMORPHISM ALA D2 OF THE ENZYME DESIODASE TYPE 2 (DIO2) AND THE FUNCTIONALITY OF INDIVIDUALS WITH AUTISM SPECTRUM DISORDER

T. G. B. Gomez[1], T. T. Ravache[1], S. Mansour[1], Q. Cordeiro[2], R. Lowenthal[2], C. S. de Paula[1], M. O. Ribeiro[1].

[1]Department of Health and Biological Sciences-CCBS, Mackenzie Presbyterian University, São Paulo, SP, Brazil; [2]Center for Integrated Attention to Mental Health, Holy House of Mercy of São Paulo, São Paulo, SP, Brazil.

Introduction: The presence of Thr92Ala-D2 polymorphism in homozygous individuals seems to be related to an increase in oxidative stress in the cells, although it does not cause any phenotypic alterations. The hypothesis of our study considered the possibility that in an individual with ASD the presence of the polymorphism can lead to worsen in the behavior of these patients. **Methods:** We evaluated 97 patients diagnosed with ASD and accompanied at the Center for Integrated Mental Health Care (CAISM) using the Vineland Adaptive Behavior Scales, second edition. The genotyping of the patients was performed through buccal epithelium that was collected using a swab smear. The DNA isolation and extraction kit (Norgen Biotek Corporation, Canada) was used for DNA extraction according to the manufacturer's own protocol. For the genotyping procedure, the manufacturer's own protocol (Thermo Fisher) using the Applied Biosystems StepOne ™ equipment (Thermo Fisher, USA) and identifying the homozygous genotype for Thr92AlaD2 (AA), non-polymorphic homozygous (TT) and heterozygous (TA). We used the Autism Behavior Checklist (ABC), Communicative Difficulty Questionnaire (QDC), and the Vineland Adaptive Behavior Scale, 2nd edition applied by professionals during consultations at CAISM - Vila Mariana. For all statistical analyzes of the vineland scale, the one-way ANOVA test with Tukey post-test was used. **Results:** Our results show that the presence of Thr92Ala-D2 polymorphism in homozygotes improves the functionality of autistic individuals in the subdomains of Communication, Language, Daily Activities and the Adaptive Level, the presence of the 92Ala-D2 allele appears to exert a dose-dependent effect, because when present in heterozygosis the score presents intermediate values between the individuals' scores in polymorphic (AA) and non-polymorphic (TT) homozygotes. **Discussion:** The results obtained were exactly opposite to our initial hypothesis, which is very interesting since the presence of the polymorphism stresses the cell and we expected that the ASD along with the cellular stress would act synergistically worsening the functionality of the patients. Thus, we hypothesized to try to explain the possible mechanisms involved in the apparent improvement in the functionality of individuals with ASD. The changes in ubiquitin and neuregulin 1 pathway present in the polymorphism could be the reason why individuals with ASD and polymorphism could explain the improvement in the functionality of those individuals. **Conclusion:** The present study showed that the presence of the Thr92Ala-D2 polymorphism when improves functionality in communication, daily activities, social aspects, general adaptive level in individuals with ASD.

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POSSIBLE CORRELATIONS BETWEEN THYROID HORMONE AND DEPRESSIVE AND ANXIOUS BEHAVIOR IN OBESE RATS

F.B. Lorena[12], J.N. Panizza[1], B.P.P. Nascimento[12], E.L.R.A. Camargo[1], M.E.S. Brandão[12], A.C. Bianco[23], M.O. Ribeiro[12]

[1]Department of Health and Biological Sciences - CCBS, Mackenzie Presbyterian University, Sao Paulo, SP, Brazil; [2] Department of Translational Medicine, Federal University of Sao Paulo, Sao Paulo, SP, Brazil; [3]Department of Internal Medicine, Division of Endocrinology and Metabolism, Rush University and Medical Center, Chicago, IL, United States.

Introduction: The thyroid hormone (TH) modulates the development and functioning of the central nervous system by regulating the expression of genes related to brain plasticity. There is a well described relationship between the thyroid hormone and mood changes such as depression and anxiety that may generally be reversed by treatment with T3. Obesity is related to depressive and anxious behavior and the very same genes regulated by T3 are changed in obesity. Thus, our working hypothesis is based on the possibility that obesity leads to changes in T3 signaling in the brain of rats that may be involved in the depression and anxiety observed in these animals. **Methods:** To test our hypothesis we treated male Wistar rats with high fat diet (40%) for 32 weeks. At the end of this time the animals were subjected to behavioral testing to assess their memory acquisition, anxious and depressive behavior. We also evaluated changes in the expression of genes involved in depression, genes regulated by T3 and genes related to inflammation in pre-frontal cortex and hippocampus of the obese rats.**Results:** Through behavioral tests we found that obesity induces a depressive and anxious behavior, but does not lead to memory impairment. The gene expression analysis showed that obesity leads to increase in mRNa for TH transporters (OATP1), for TH receptors (TRα, TRβ, PPARG and PPARbeta) and a decrease in two genes positively regulated by T3 (Aldh1a1 and RBM3) and an increase in Halpln1, a gene negatively regulated. We also found an increase in expression of genes related to inflammation (NFKB and MMP9).**Discussion:** It is possible that obese individuals show a lower availability of T3 in the brain, which induces a local moderate hypothyroidism with a decrease in the T3 signaling pathway.The mild hypothyroidism could be underlying the depression observed in obese rats. The increase in transporters and receptors for T3 could be a compensatory mechanism to counteract this hypothyroidism. Furthermore, we observed a significant increase in the expression of genes related to inflammation, which may also be associated with the phenotype found in these animals. **Conclusion:** Our results suggest that there is a change in TH signaling in the rat brains that may be involved in the development of a depressed and anxious phenotype induced by obesity.

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CORRELATION BETWEEN THE POLYMORPHISM THR92ALA OF THE DEIODINASE TYPE 2 ENZYME AND ADAPTIVE BEHAVIOR IN DOWN SYNDROME

A. Batistuzzo[1], B.P.P.Nascimento[2], R.A.C.B. Novaes[3], M.M.M. Silva[4], L.Segretti[5], R. Lowenthal[6], C.F. Pinto[7], M.M. Rocha[8], M.O. Ribeiro[9]

[1]Department of Health and Biological Sciences, CCBS, Mackenzie Presbyterian University; [2]Department of Translational Medicine, UNIFESP; [3]College of Psychology, CCBS, Mackenzie Presbyterian University; [4]College of Psychology, CCBS, Mackenzie Presbyterian University; [5]College of Psychology, CCBS Mackenzie Presbyterian University; [6]CAISM, Santa Casa de Misericórdia; [7]AMOR-SD, Santa Casa de Misericórdia, Department of Health and Biological Sciences, CCBS, Mackenzie, [9]Department of Health and Biological Sciences, CCBS, Mackenzie Presbyterian University.

Introduction: The present study aimed to identify a possible correlation between the presence of the Thr92Ala mutation of the enzyme deiodinase type 2 and adaptive behavior in children with Down syndrome (DS). Approximately 12 to 36% of the population presents homozygous for this polymorphism and positive correlations have already been found between mutations in D2 with intellectual deficiency, bipolarity and psychosis. It has recently been shown that this mutation leads to modifications in the cellular transcriptome in human brains that appear to relate to changes in pathways involved in the modulation of cognitive development and in Parkinson's disease, Alzheimer's and schizophrenia. DS is the most common autosomal aneuploidy, affecting on average 1/660 newborns and represents about 18% of the total number of mentally handicapped in specialized institutions. In addition to cognitive deficits, neuropathology, such as Alzheimer's, is common in individuals with DS[1]. Based on the data described, we asked whether the Thr92Ala-D2 mutation could contribute to changes in the adaptive behavior of individuals with DS. **Methods:** To answer this question, we screened the presence of the Thr92Ala-D2 polymorphism in 29 children with DS, aged between 2 months and 18 years, and their adaptive behavior through the Vineland Adaptive Behavior Questionnaire. The genotype was determined by real-time PCR technique from the DNA obtained through collection of buccal epithelial cells by Swab. **Results:** We found that the frequency in our population was 20.69% wild (TT), 55.17% heterozygous (AT) and 24.14% polymorphic (AA), a similar result to those found in other studies. The presence of the mutated allele in AA homozygosis when compared to the wild TT results in a significant worsening in low adaptive level frequency in the subdomains Domestic(83.33% AA and 14.28% TT), Community (100% AA and 42 , 85% TT), Interpersonal Relations (83.33% AA and 28.57% TT) and Social Rules (66.66% AA and 28.57% TT). **Discussion:** The worsening in the adaptive behavior in the polymorphic DS children may be due to the altered expression of genes involved in the processing of beta-amyloid, in neuronal apoptosis, EGFR pathway, oxidative phosphorylation, and mitochondrial dysfunction. These pathways were altered in in the brain of

typical patients with the polymorphism (AA)[2]. Together, these changes may interfere with cognitive functions explaining the differences observed between the DS with the polymorphism and DS without the polymorphism. **Conclusion:** The present work confirmed that the frequency of the Thr92-Ala polymorphism in individuals with DS is similar to the population. More importantly, we found that the presence of the polymorphism impairs the functionality of these individuals.

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ORIGINS AND PROPERTIES OF THE HUMAN BRAIN AT REST: A COMPARATIVE NIRS AND FMRI STUDY

S. L. Novi[1,2], W. A. A. Rocha[1,2,3], A. C. Carvalho[1,2], G. H. Scavariello[1,2], R. M. Forti[1,2], A. Quiroga[1,2], M. M. Cordeiro[2,4], C. L. Yasuda[2,4], R. C. Mesquita[1,2]

[1]Neurophysics Group, IFGW, UNICAMP; [2]Brazilian Institute of Neuroscience and Neurotechnology; [3]Institute of Mathematics, Statistics and Computing Science, IMECC, UNICAMP; [4]Neuroimaging Group, FCM, UNICAMP.

Introduction: Recent studies from near-infrared spectroscopy (NIRS) and functional magnetic resonance imaging (fMRI) have agreed that, at rest, spontaneous brain activity (SBA) across different brain regions is connected through some sort of network structure, presenting several complex features. In fact, graph theory has been a successful methodology to characterize the human brain at rest. In this work, we present our most recent advances on combining NIRS and fMRI to investigate low-frequency SBA over the whole head with graph theory. **Materials and Methods:** We simultaneously performed NIRS (continuous-wave NIRScout, NIRx Medical Systems) and fMRI (3T Philips) in 28 healthy subjects during resting-state. For each subject, 300-s baseline runs were performed from 2 to 6 times. The NIRS geometry was designed to cover the whole head, employing 16 sources (760 and 850 nm each) and 32 detectors. The fMRI protocol included acquisition of structural and functional (TR 2s) images (TR 2s) sequences. For pre-processing, we employed standard procedures from NIRS[1] and fMRI[2] to extract hemoglobin concentration changes and BOLD time courses, respectively. We employed our graph analysis methods[3] to estimate global network parameters and network topological organization. In parallel, we simulated the Ising Model in two dimensions with periodic boundary conditions at the critical, super-critical and sub-critical temperatures, with the aim to understand the origins of the interactions that yield the network parameters measured by fMRI and NIRS. **Results and Discussion:** Our results suggest that during the resting state brain networks present a high density of local connections with few long-range links. Brain regions that are symmetrically located or that share the same functionality are highly connected. We also observed that although networks built from graphs are variable over short periods of time, global network properties remain stable. This stability suggests that the human brain at rest is capable to organize itself in such a way that preserves its global topological properties. We identified that the distribution of hubs from oxy-hemoglobin-, deoxy-hemoglobin-, total-hemoglobin- and BOLD-time courses are very similar. The network hubs were located mostly in the frontal and parietal lobes, with slight predominance in the left hemisphere. Regarding differences in the NIRS contrasts, networks derived from BOLD and deoxy-hemoglobin exhibit a similar behavior as function of the correlation coefficient, while they differ from oxy- and total-hemoglobin networks. Last, we could successfully simulate the main network features from deoxy-hemoglobin and BOLD networks by analyzing spontaneous fluctuations of the Ising model. Near the phase transition of the system, the model strikes several properties of the brain networks during the resting state. **Conclusion:** Overall, our methodology opens new directions to the investigation of the human brain connectivity at rest as a complex system. We developed an efficient approach to generate networks based on the most robust connections that is capable to elucidate fundamental questions regarding brain network topology, such as the presence of hubs and brain asymmetry. In addition, our results suggest that deoxy-hemoglobin and BOLD networks have similar properties but oxy- and total hemoglobin may provide different information that can be valuable to comprehend the human brain. Last, by simulating and analyzing spontaneous fluctuations of the Ising Model at several temperatures, we provided evidences to support the conjecture that, at rest, the human brain behaves like a dynamical system near the critical point. This work enhances the importance of multimodal experiments to better understand brain function and organization.

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LEPIDIUM MEYENII WALP (MACA) INCREASES THE ANTI-INFLAMMATORY CYTOKINES LEVELS AND IMPROVE MEMORY IN ELDERLY RATS

B. S. Sousa[1,2], E. P.N. Sales[1,2], L.R. Oliveira[1,2], V.S. Sales[1,3], L. Malavolta[2], R.M. Arida[3], K.J. Vera-Lopez[4], S.G. Silva[5], F.R. Cabral[1,2]

[1] Neuropsychopharmacology Group, Hospital Israelita Albert Einstein; [2]Faculdade de CiênciasMédicas da Santa Casa de São Paulo, SP; [3]Physiology Dept. UNIFESP; [4]Universidad Católica de Santa Maria. Arequipa, Peru; [5]Universidade de Mogi das Cruzes.

Introduction: Aging is often accompanied by cognitive decline, memory impairment and an increased susceptibility to neurodegenerative disorders. Most of these age-related alterations have been associated with deleterious processes such as changes in cytokine expression. In the aged brain, the pro-inflammatory cytokines have been found chronically increased, while reduced levels of anti-inflammatory cytokines have been detected[1,2]. Studies suggest that *Lepidium meyenii* (Maca) may reduce the inflammatory cytokines levels, improve memory and health status in individuals living at high altitudes. The aim of this study was to analyse the hippocampal levels of pro and anti-inflammatory cytokines and cognitive performance of rats treated with Maca extract during 21 days. **Materials and Methods:** Wistar, male rats (N=68), divided in four groups: Control (CTL-Y) young (4 months of life. N=17); Control (CTL-E) Elderly (18 months of life. N=17); Vehicle (VLE) Elderly (18 months of life. N=17) and Elderly + Maca (18 months of life. N=17). Then, the rats were treated for 21 days with Maca extract (0.5 mg/kg given by gavage). After 21 days, were subjected to behavioral studies (N=10) by testing the Step-down avoidance, which assesses learning and information retention (memory) and Morris water maze, which assesses learning and spatial memory. After this, the brain was immediately removed and the hippocampus dissected and frozen at -80 Celsius degree. The pro-inflammatory and anti-inflammatory cytokines were analyzed by Luminex® technology (N=7). All experimental procedures were approved by the Animal Care and Use Committees of the Albert Einstein Hospital. Intra-groups comparisions were made with Kruskal Wallis test followed by Dunns test (cytokines), ANOVA followed by Bonferroni test (Water maze), two-way ANOVA followed by Tukey test (Step-down avoidance) and p value ≤0,05 was considered as significant. **Results:** In the behavioral tests, the elderly rats of the control and vehicle groups presented low cognitive performance when compared to young rats. However, this cognitive deficiency did not occur in the elderly Maca rats. It was observed that elderly rats treated with Maca presented improvement of memory and learning in relation to the control and vehicle groups. Cytokine analysis, statistical difference was found in the levels of IL-4, IL-5, IL-10, IL-13, and IL-17A in elderly rats treated with Maca in relation to the elderly control rats. The analysis of pro-inflammatory cytokines did not present significant results ($p > 0.05$). **Discussion:**In our studies we found that animals treated with Maca showed increased levels of anti-inflammatory cytokines accompanied by improved memory performance. Between the anti-inflammatory cytokines interleukins 4 and 10 showed important roles in synaptic function hippocampal region, such as reduction of inhibition of glutamate release induced by IL-β1, on long-term potentiation and control over the pro-inflammatory cytokines that induce performance deficits in cognitive processes mediated by the hippocampus[2,3,4].**Conclusion:** These findings suggest a favorable effect of Maca treatment during aging, mainly to reduce the risk for age-like cognitive decline. Moreover, the results suggest that the use of Maca extract improves the hippocampal levels of anti-inflammatory cytokines.

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LEPIDIUM MEYENII WALP INDUCE NEUROPROTECTION IN ANIMAL MODEL OF CEREBRAL ISCHEMIA WITH REPERFUSION

F.R. Cabral[1,2], V.S. Sales[1,3], L.R. Oliveira[1,2], E.P.N. Sales[1,2], L. Malavolta[2], A. Pino-Figueroa[4], T.J. Maher [4], R.M. Arida[3], K.J. Vera-Lopez[5]

[1] Neuropsychopharmacology Group, Hospital Israelita Albert Einstein; [2] Faculdade de Ciências Médicas da Santa Casa de São Paulo, SP; [3]Physiology Dept. – UNIFESP; [4]MCPHS University, 179, Longwood Avenue, Boston MA 02115, USA; [5]Universidad Católica de Santa Maria, Arequipa, Peru.

Introduction: *Lepidium meyenii* is an herbaceous plant belonging to the

Brassicaceae family, known as Maca, from central Peruvian Andes (4000 – 4500m), particularly in Junin plateau[1]. Different biological effects were described when Yellow, Red and Black Maca were assessed[2,3]. In this study, the herbaceous plant, known as Maca, was tested in two models of focal cerebral ischemia in rats in order to study neuroprotection. **Materials and Methods:** All experimental procedures were approved by the Animal Care and Use Committees of the Albert Einstein Hospital. The animals were housed on a 12h light/dark cycle in groups of 4-5 with food and water ad libitum. We used two different animal models to induce AVCI. The Middle Cerebral Artery Occlusion (MCAO) was conducted with permanent occlusion or occlusion (2h) following reperfusion. 119 Wistar male rats (280 – 320g) were used, divided in thre groups (AVCi Control, AVCi Vehicle (Treated with aqueous PVP solution) and AVCi Maca (Six Groups, treated with doses of 0,5; 1; 2,5; 5; 3 and 8 mg/kg). 24h after the treatment, the animals were deeply anesthetized with i.p. ketamine – xylasine, and decapitated. The brains were separated and cut to 2 mm thick and stained with triphenyltetrazolium chloride 2% (TTC, Sigma-Aldrich) solution for 30 min at 37°C. The infarct volumes were measured using the Image J program and expressed as percentages relative to the total tissue in the brain hemisphere. Intra-groups comparisions were made with one-way ANOVA followed by Bonferroni test and p value ≤0,05 was considered as significant. **Results:** In the permanent focal cerebral ischemia, the effect of *Lipidium meyenii* (Maca) on infarctsize was evaluated by TTC staining, not observed that Maca treatment decreased the lesions in striatum and overlying brain cortex in groups treated with pentane extract or compared to control group. However a transient focal cerebral ischemia 2,5 and 5 mg/kg of the pentane extract showed a reduction from 26.6 ± 0.9% control group to 14 ± 2.5% (p=0.003) and 12.1 ± 1.9% (p=0.0002) respectively in the percentage of infarcted tissue resulting from MCAO. **Discussion:** The discovery of new substances for the treatment of ischemic stroke is something extremely promising as we are in a time where there has been little investment by the pharmaceutical industry. We believe that the neuroprotective effect of Maca could be attributed to inhibition the endocannabinoids degradation in penumbra area, because the endocannabinoid system has a strong neuroprotective effect in cerebral ischemia. **Conclusion:** This work provides scientific evidence that Maca may afford neuroprotection for stroke, optimizing treatment.

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SYMBOLIC ENTROPY FOR CONNECTIVITY ANALYSIS OF *IN VITRO* HIPPOCAMPUS EPILEPTIFORM ACTIVITIES

N. S. Araújo[1], S. Z. Reyes-Garcia[1], E. M. Yacubian[1], Centeno, R. S.[1], E. A. Cavalheiro[1], C. A. Scorza[1], J. Faber[1,2]

[1]Laboratoryof Neurofisiology, EPM, UNIFESP; [2] Nucleus of Neuroengineering and Computation, ICT, UNIFESP.

Introduction: The characterization of epileptiform activity in TLE (temporal lobe epilepsy) allows for understanding this disease and its drug resistance mechanisms[1], providing new clinical treatments[2]. This work proposes a statistical evaluation of interictal-like events activity, along signals recorded from human tissue, by using symbolic entropy analysis in order to describe its main features. **Material and Methods:** The signals were recorded through electrophysiology *in vitro* technique from human hippocampal slices from patients with pharmacoresitant epilepsy (approved by the UNIFESP Research Ethics Committee number CAAE 47551015.1.0000.5505). The signals were obtained from a single patient with interictal-like events. We developed a set of algorithms, in MATLAB®, in order to identify the epileptiform events, for each recording. By measuring the interval peaks of the epileptiform activity we were able to construct a tachogram signal[3]. Each tachogram was transformed into symbolic series following the method described in[4]. Accordingly, each three points sequence of the epileptiform activity signal recorded was assigned to one of the six symbols, and their occurrence were counted. Finally, probability distributions of the symbols, for each hippocampal region, were compared by Kullback–Leibler metric[5]. **Results:** The symbolic entropy analysis indicates the differences in complexity in each hippocampal region. This approach was validated using the trisynaptic circuit (dentate gyrus - DG, CA - *cornu Ammonis* 1 and 3), in order to evaluate the functional correlation among regions given by Kullback–Leibler metric (Figure 1D. **Discussion:** The symbolic analysis

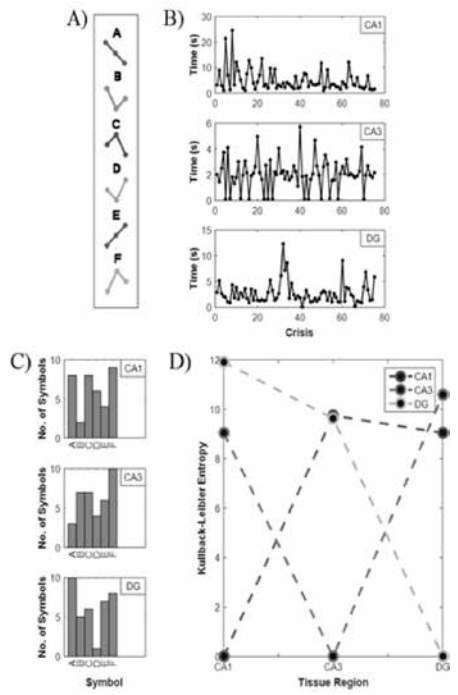

Figure 1. Symbolic analysis of interictal-like events. A) Symbols (three points length) used in symbolic analysis [4]. B) Tachogram of epileptiform activity recorded from each hippocamapal region. C) Distribution of six symbols in each region. D) Correlation of each hippocampal region by Kullback–Leibler metric.

characterization of epileptiform activity is still underway. For better validation of this approach, further tests need consider additional parameters such as types of epileptiform activity, and other brain regions. Moreover, the symbolic analysis could be consider as a new approach to characterize recurrent patterns in epileptiform activities. **Conclusion:** Here, we propose the symbolic entropy approach in order to characterize epileptiform activity. Through this approach we are able to identify features of functional and structural hippocampal connectivity, that the main approaches cannot evaluate[1,2].

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PERFORMANCE OF THE ELDERLY ON THE EXECUTION OF VIRTUAL REALITY ACTIVITIES AND COGNITIVE EVALUATION AFTER A PREVENTION PROGRAM OF MULTI-COMPONENTS FALLS

R. B. Lanzotti[1], F. G. Casemiro[1], A. J. Vianna[2], J. P. Silvano[2], G. C. Pomponio[2], M. Petrella[3], M. Silva[2], L. N. C. Pelegrini[1], A. Brandão[4], K. Gramani-Say[2]

[1]Department of Nursing, DENF, UFSCar; [2]Departament of Gerontology DGero, UFSCar; [3]Departament of Physiotherapy UFSCar; [4]Neurophysics Group, IFGW, UNICAMP.

Introduction: In addition to the new demands arisen with the aging process, many physical and cognitive declines are also related to this process, which considerably increases the risk of falls and overloads for Brazilian Health System (SUS - of Portuguese, Sistema Único de Saúde) in all its levels[1]. Thus, aiming at maintaining and improving quality of life, as well as physical and cognitive aspects, it is recommended to create a multi-component fall prevention program for the elderly. Cognitive stimulation, physical activity, dual task training and health education are thought to be relevant features to be part of such program. **Materials and Methods:** This is a cross-sectional and descriptive study. Seven older adults (5 females, 2 males), mean age 70.5 years old (± 8.35), education 10.2 years (± 5.07), mean weight of 70.85 kg (± 9.76) and height 1.64 m (± 0.09). The instruments used were: Mini Mental State Exam (MMSE); Addenbroke's-revised (ACE-R); Brief Cognitive Battery (BCB), simple Time Up and Go (TUG) test, cognitive TUG and the time in seconds to complete the assembly of a puzzle controlled by the participant's upper limbs. For this evaluation was used the GesturePuzzle

gesture recognition application, developed in the Immersive, Interactive and Collaborative Visualization Laboratory (LaVIIC) of the Department of Computer Science at UFSCar. The paired t-test was performed for the parametric variables and Wilcoxon for the non-parametric (SPSS) ($p \leq 0.05$). Pre and post evaluations were made, respectively, before and after the intervention of a multicomponent fall prevention program, which happened in 16 sessions. **Results:** A statistical difference was found between the pre (45,14s) and post-tests (32,43s) ($p = 0.042$). There was no statistical difference on the other tests. **Discussion:** As an alternative to falls risk assessments, the use of Virtual Reality (VR) may be a prominent factor in screening capacity. The interest in the use of this resource has increased as evaluation and not intervention; also it has been used with individuals with different characteristics[2]. VR equipment can contribute with instruments that evaluates body posture, which can make such evaluations easier and also aid to adapt the accuracy of the postural equilibrium[3]. Moreover, this differentiated approach can serve as an attractive factor for the elderly to participate in these tests.It also allows to verify whether physical and cognitive training was beneficial or not for each participant[4], as shown by the results of this study, which proved that after the use of a differentiated program, the assembly time of the puzzle decreased significantly. **Conclusion:** This experiment was done with older adults participants of a multi-component fall prevention program and suggest their performance was improved in VR tests that measure attention. This indicates VR as being an interesting tool to evaluate the elderly.

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THE RELATIONSHIP BETWEEN BLOOD SERUM BDNF AND SEIZURE FREQUENCY IN TLE-HS PATIENTS

M. K.M. Alvim[1], C. L. Yasuda[1], M. E. Morita[1], A. C. Coan[1], R. Barbosa[1], I. Lopes-Cendes[2], A.L. Teixeira[3], F. Cendes[1]

[1]Neurology Dept, FCM, University of Campinas, UNICAMP; [2]Genetics Dept., FCM, UNICAMP; [3]Neuroscience Division, Federal University of Minas Gerais, UFMG.

Introduction: Brain-derived neurotrophic factor (BDNF) is a neurotrophin widely distributed in the central nervous system[1]. BDNF is mainly concentrated in the hippocampus and entorhinal cortex[2], areas involved in the origin of seizures in patients with temporal lobe epilepsy associated with hippocampal sclerosis (TLE-HS), which is often refractory to pharmacotherapy. BDNF appears to be involved in the modulation of synaptic efficacy in the hippocampus[2]. The aim of this study was to evaluate the association between serum BDNF levels with seizure frequency in patients with TLE-HS. **Materials and Methods:** We included 157 TLE-HS patients (defined by ILAE criteria and MRI visual analysis) aged 18-70 years who were under antiepileptic-drug treatment. All patients performed an MRI and had their blood samples collected right after the image acquisition. We reviewed clinical data from all patients. Levels of BDNF were blinded measured by enzyme-linked immunosorbent assay (ELISA). Patients were divided into two groups: 1). Frequent seizures (n=96): patients with at least one seizure with loss of consciousness every two months or at least one generalized convulsion every 6 months and 2). Infrequent seizures (n=61): patients with less than one seizure with loss of consciousness every two months and less than one generalized convulsion every 6 months or with seizure control. Groups were similar regarding sex distribution, age and seizures onset. **Results:** The comparison between the two groups demonstrated that patients with frequent seizures presented higher BDNF levels than the group with infrequent seizures ($p = 0.009$) (Figure1). **Discussion:** Our results show that blood serum levels of BDNF are associated with frequent seizures in TLE-HS patients. The exact role of this neurotrophin in the pathophysiology of TLE-HS remains unknown; however, previous studies already indicated that BDNF may be involved in TLE-HS[3]. In vitro analysis suggest that seizures cause BDNF expression up regulation and that the BDNF up regulation occurs in the dentate gyrus and CA1–CA3 pyramidal cell layers of the hippocampus[2]. Furthermore, this neurotrophin has been considered a pro-epileptogenic factor, as it seems to be involved in the enhancement of neuroexcitatory synaptic transmission, thus, increasing neuronal activity[2,4]. **Conclusion:** Our finding agrees with previous studies and suggests that BDNF may not only play a role in the pathogenesis of TLE-HS, but may also be associated with seizure frequency.

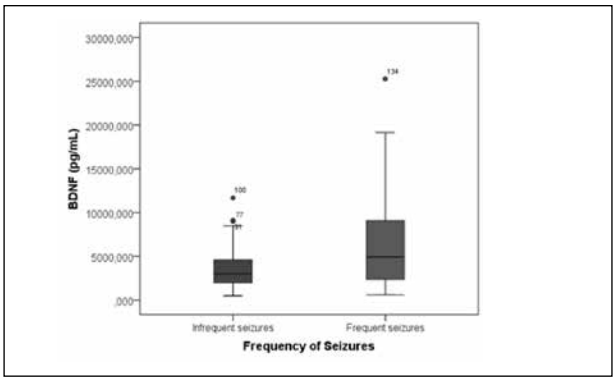

Figure 1. Box plot showing the distribution of BDNF levels in patients with frequent and infrequent seizures.

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IMPROVING ATTENTION THROUGH NETWORK-BASED NEUROFEEDBACK TRAINING

G. S. P. Pamplona[1], F. Scharnowski[2], Y. Koush[3], C. E. G. Salmon[1]

[1]USP, Ribeirão Preto, Brazil; [2]University of Zürich, Lausanne, Switzerland; [3]Yale University, New Haven, EUA.

Introduction: Real-time fMRI neurofeedback allows participants to see and learn to voluntarily control their own brain activity (1). Most real-time fMRI neurofeedback studies so far have trained participants control over single regions, although most mental functions are associated with functional networks. For example, neuroimaging research has identified the sustained attention network (SAN), which becomes active during attention-related tasks (2). Conversely, mind-wandering is associated with reduced activity in the SAN, and increased activity in the default mode network (DMN) (3,4), so this anticorrelation reflects competition between sustaining attention and interference from task-irrelevant thoughts. Here we propose to modulate this competition using a novel network based neurofeedback approach to simultaneously increase SAN and decrease DMN activity. If successful, this approach might provide a promising tool to enhance sustaining attention.

Materials and Methods: 11 healthy young adult volunteers participated in this experiment. Data was acquired on a 3T Philips Achieva MR scanner, using a T2*-weighted EPI sequence with 240 repetitions per run (TR=2s, 37 slices, matrix size 80x80, voxel size 3x3x3mm^3, TE=22ms). Real-time fMRI processing was done using a customized Matlab-based toolbox on a high-performance computer, and included real-time spatial realignment, spatial smoothing, coregistering of the ROI masks, head movement correction, suppression of spikes and high frequency noise using a modified Kalman filter, and signal normalization (5). Before and after the neurofeedback training, 150 volumes of resting fMRI data with the same parameters were acquired to search for differences in connectivity. The 3 SAN ROIs were defined as 6-mm spheres at clusters derived from a meta-analysis (2). The 3 DMN ROIs were individually defined by an ICA analysis from the resting-data acquired before training. These 6 ROIs plus the entire SAN and the entire DMN were considered for the connectivity analysis. Neurofeedback training took part on three days and consisted of 2-4 runs per day. Every run consisted of a 60s baseline block to compute the baseline for both networks, followed by five 60s up-regulation blocks interleaved with four 30s down-regulation blocks. The feedback signal corresponded to the differential activation between SAN-DMN and was provided in the form of a thermometer display projected in the scanner. To facilitate learning, we suggested the use of maintaining attention and refocusing strategies to up-regulate SAN and down-regulate DMN, and mind-wandering to achieve the opposite. Before and after training, participants performed self-regulation in the absence of feedback (transfer runs) as well as standardized attention tests

(i.e. Continuous Performance (CPT), Psychomotor Vigilance (PVT), Switcher, and Stroop tasks).

Results and Discussion: With the help of neurofeedback, participants learned to voluntarily control both the SAN and DMN (positive betas training runs, $p<0.0008$). Once learned, the ability to self-regulate these networks remained even without neurofeedback (last transfer run, $p<0.003$). Successful self-regulation was positively correlated with self-report scores of how they felt they were in control of the feedback signal, and how much they focused during training (all ps<0.02). Also, the improvement in the Stroop reaction time test for congruent stimuli after compared to before neurofeedback training was positively correlated with training success ($r=0.70/p=0.02$), but not for neutral ($r=0.59/p=0.06$) and incongruent stimuli ($r=0.51/p=0.11$). Supplementary motor area was less positively connected ($p=0.0002$) to right middle frontal gyrus and less negatively connected ($p=0.04$) to precuneus after training, what is contrary to the initial hypothesis of more anticorrelated networks after training, but this could mean instead more fatigue after training compared to the first resting-data acquisition. **Conclusion:** Using differential neurofeedback, it is possible to modulate the relative dominance of two competing brain networks through training, namely the SAN and the DMN. Shifting this dominance requires effort and concentration, and might lead to improved attention.

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DEVELOPMENT OF A P300-BASED BCI: PRELIMINARY RESULTS

T. B. S. Costa[1,2], C. A. Stefano Filho[2,3], M. B. Kersanach[1,2,4], L. F. S. Uribe[1,2], S. N. Carvalho[2, 5], D. C. Soriano[2,6], G. Castellano[2,3], R. Attux[1,2]

[1]FEEC, UNICAMP, [2]Brazilian Institute of Neuroscience and Neurotechnology, BRAINN; [3]IFGW, UNICAMP; [4]CTI Renato Archer; [5]UFOP, [6]CECS, UFABC.

Introduction: This study presents preliminary results of a P300-based Brain-Computer Interface (BCI) under development by our group. BCI is a communication system connecting brain activities and machines [1]. P300, registered from Electroencephalography (EEG), is an enhanced positive-going component of Event-Related Potentials (ERPs), with a latency longer than 275 ms, a maximum positivity at parietal and central lobes, evoked by task relevant stimuli, and influenced by the subject's ability in identifying and selecting events into appropriate categories [2]. Farweel and Donchin were the first researchers to show the feasibility of using P300 as a paradigm for BCI [3] and, since then, several studies have been carried out to develop signal processing techniques that reliably detect this component. This work is inserted in the same context. **Materials and Methods:** Three healthy volunteers, 1 female and 2 males, 20-32 years old, participated of the experimental protocol – approved by the Ethics Committee of UNICAMP. The EEG data were recorded with the g®.USBamp biosignal amplifier and the g®.SAHARAsys dry electrodes, whose array was positioned according to the international 10-10 system in the following locations: PZ, POZ, P1, CPZ, P2, CP1, CP2, CZ, C1, FCZ, C2, FC1, FZ, FC2, F1, F2; with reference to linked mastoids. During capture, signals were sampled at 256 Hz and band-pass filtered at 0.1-30 Hz; electrode impedances did not exceed 5 kΩ. The P300-based BCI approach was inspired by the Oddball paradigm, obeying a sequence generating rule (visual in our case) [2]. Indeed, subjects were presented to a 6-by-6 matrix, whose cells exhibited alphanumeric characters, displayed on a 14-inch monitor with refresh rate of 60 Hz. In every trial, all rows and columns of the matrix were intensified for 125 ms, one at a time. The Inter-Stimulus Interval (ISI), i.e. the interval between the start of two subsequent intensifications, was 500 ms; and the rows/columns blinked in a random order. Subjects were instructed to pay attention to a given character and to run a mental count every time they realized it had flashed [3]. Ten such sessions were performed, 8 for training and 2 for validating. Offline extraction and identification of the P300 component were fulfilled through the following steps: band-pass filtering at 1-10 Hz, selecting the first 20 principal components – based on Principal Component Analysis (PCA) –, sorting attributes using the Pearson correlation coefficient, classifying them using Linear Discriminant Analysis (LDA) and deciding by minimum Hamming distance. **Results:** Table 1 exhibits the accuracy to detect subject's intent (or effectiveness to identify the characters) and the ranked electrodes whose attributes were considered the best. **Discussion/Conclusion:** The overall results show an average hit rate of 66% among all subjects, still below the rates reported by the specialized literature (usually above 80%) [3]. Despite this, as a first attempt to establish a computational process to, in the future, create an online P300-based BCI, these results look promising. Detecting ERPs components among noisy EEG deflections is not a trivial task. Albeit challenging, our final goal is to develop a system whose operation has similar performance to the currently available P300-based BCIs.

Table 1. Decision maker's performance and ranked electrodes.

Volunteers	Accuracy	Selected electrodes
Subject 1	100%	CPZ, C1, CP2 e C2
Subject 2	50%	P1, P2, CP1, CPZ, FC2, FZ, C1, CZ, CP2, FCZ
Subject 3	50%	POZ, C1, F1, FZ

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STRATEGIES OF REAL-TIME RIPPLE DETECTION FOR CLOSED-LOOP MANIPULATION OF MEMORY-RELEVANT NEURAL SYSTEMS

E. F. de Oliveira1[3], C. Lopes-Aguiar[2], K. Maboudi[5], L. R. Zacharias[6], L. B. Peres6, K. Diba5, J. P. Leite[6], D. C. Soriano[3,4]

[1]CMCC, UFABC; [2]Núcleo de Neurociências, Departamento de Fisiologia e Biofísica, ICB-UFMG; [3]CECS, UFABC; [4]Brazilian Institute of Neuroscience and Neurotechnology,BRAINN; [5]Department of Psychology, UWMilwaukee,[6]FMRP, USP.

Introduction: How do memories persist? Network activity during sleep is thought to support memory through a process known as systems consolidation. Sharp-wave ripples (SWR) seem to provide effective means for information transfer out of the hippocampus, being hypothesized that this activity would provide a mechanism for systems consolidation[1]. However, only a few recent studies have been provided causal evidence to confirm it, which usually require the use of a closed-loop control system to detect ripples in real-time and simultaneously actuate in downstream circuits [2,3]. Here, we compared three different feature extraction usually employed in real-time strategies for ripple detection by means of the Receiver Operating Characteristic (ROC) curve. **Materials and Methods:** We employed 33 min recording from CA1 stratum radiatum in awake behaving rat containing 311 ripples detected in offline methods. The signal was cut in buffers of 34.1 ms. We tested three different amplitude based features for event detection: (1) a 50 points signal Root Mean Square (RMS); (2) a demodulation strategy based on the modulus signal cross product with a sine and cosine in 140 Hz, a typical ripple component; (3) the instantaneous amplitude of the Hilbert transform (HT). For all methods, we build a threshold based on the first 2 s of the signal for ripple detection. **Results:** The obtained ROC curves (Figure 1) shows similar (better) performances of RMS and HT, which is not attained for Demodulation. The false discovery rate of the best approach was 0.92, providing a sensitivity of 0.78 and a specificity of 0.20. Figure 1: Left up side, coronal brain section showing location of recordings; Left down side, example of sharp-wave (down black trace) and ripple (up black trace). Right side, ROC curves. **Discussion:** Here, we successfully implemented three different approaches for real-time ripple detection that achieve the performance described in the literature and can be used for further experiments in neurobiology of sleep and memory. However, the false discovery rate revealed that even under the best approach, the number of false positive is considerably

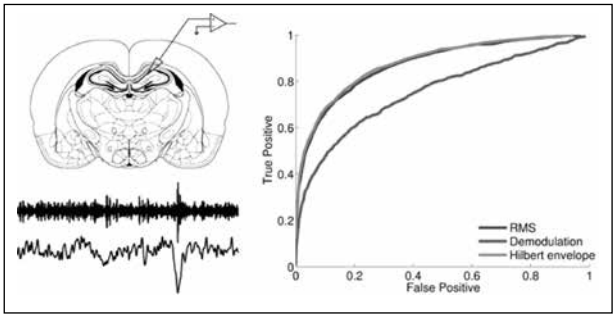

Figure 1.

high. **Conclusion:** Amplitude based detectors are satisfactory for ripple detection, even with the significant number of false events. These results justify the investigation of new features that could be integrated into a better classifier to minimize the false detection.

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

M. Martin[1], S. H. Avansini[1], A.S. Vieira[1], R. Secolin[1], M.L. Santos[1], F. R. Torres[1], F. Rogério[3], A. C. Coan[2], M.K.M. Alvim[2], M. E. Morita[2], C. L. Yasuda[2], R. Barbosa[2], F. Cendes[2], I. Lopes-Cendes[1]

[1]Department of Medical Genetics; [2]Neurology and; [3]natomical Pathology School of Medical Sciences, University of Campinas, UNICAMP, Campinas, SP, Brazil and the Brazilian Institute of Neuroscience and Neurotechnology, BRAINN, Campinas, SP, Brazil.

Introduction: The diagnosis of epilepsy is a challenging procedure leading to a priority in the development of innovative biomarkers, since it is estimated that misdiagnosis of epilepsy occurs in around 25% of cases [1] and one third of patients with epilepsy do not have seizure remission despite appropriate therapy with anti-epileptic-drugs. Major causes of drug resistant epilepsy (DRE) are mesial temporal epilepsy and focal cortical dysplasia. The identification of biomarkers for response to treatment could potentially speed-up the diagnosis of medically refractory seizures, which in turn would lead to an earlier indication of an effective alternative treatment [2,3]. One potential candidate for biomarkers is circulating microRNAs; these are small noncoding RNAs present in extracellular human body fluids including plasma or serum. It is well known that induced changes of microRNAs levels are stable in plasma, can be strongly associated with specific disease states and it is noninvasively and easily quantifiable [4]. In this context, the aim of this project is to investigate whether circulating microRNAs could be used to improve diagnosis and/or management of patients with severe forms of epilepsy, including mesial temporal lobe epilepsy (MTLE) and focal cortical dysplasia (FCD).**Materials and Methods:** The study is currently being performed in two phases: an initial discovery phase and a subsequent validation phase. Initial screening of 40 patients, including 10 drug-responsive MTLE patients, 10 drug-resistant MTLE patients, 10 patients with FCD, 10 patients with genetic generalized epilepsies, and 10 control individuals was done using plasma samples obtained. Subsequently, in a validation phase, we will enroll an additional independent cohort of at least 100 patients with MTLE using the same diagnostic criteria as previously described. We will also recruit an additional 200 healthy individuals without epilepsy as a control group. Next-generation sequencing technology (RNA-seq) will be used to identify candidate biomarkers in an initial cohort, and RT-qPCR will be done in additional patients in a validation phase. **Results and Discussion and Conclusion:** This project is still in its initial phase and to date, we have tested modifications in the RNA isolation protocol in order to identify the best recovery of high quality and high yields fraction of enriched small RNA molecules use in the RNA-seq experiments.

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TBSS LONGITUDINAL ANALYSIS IN PARKINSON'S DISEASE

R. Guimarães[1], T. Rezende[2], L. Campos[3], L Piovesana[3], P. Azevedo[3], A. D'Abreu[1,3], F. Cendes[1,3].

[1]Laboratory of Neuroimaging, UNICAMP; [2]Neurology Dept., FCM, UNICAMP.

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. It is a chronic and progressive disease. Its prevalence was estimated in 16.1 million in 2011, and this might double over the next twenty years[1]. Understanding the disease pathophysiology and how it progresses is important for a better patient management and to follow improvements achieved by medication or rehabilitation. **Materials and Methods:** We included 28 patients (24 men, mean age 60.89, SD 7.051; mean disease duration 8.92, SD 7.57). Patients underwent MRI acquisition at two time points (t1 and t2) with a mean interval of 3 years. Differences of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) were analyzed using tract based spatial statistics (TBSS). **Results:** We observed increased MD, RD and AD values in the corticospinal tract (CST), internal capsule, inferior and superior longitudinal fasciculus and splenium, body and genu of corpus callosum; the same areas had lower FA, however, alterations were less intense. All alterations regard t2 in relation to t1. **Discussion:** The longitudinal TBSS analysis of PD patients showed a significant evolution of white matter alterations, particularly in the CST and internal capsule. There was substantial overlap of increased AD and RD values, in similar brain regions. Previous studies suggest that AD alteration relates to axonal degeneration and RD might be associated with demyelination[2]. However, the biological behavior of tensor changes is not entirely understood. The microstructural changes that occur with PD may be associated with alterations in the cortical plasticity of the primary motor cortex[3]. **Conclusion:** DTI has proved its effectiveness in monitoring the progression of the disease by detecting evolving microstructural damages in WM regions.

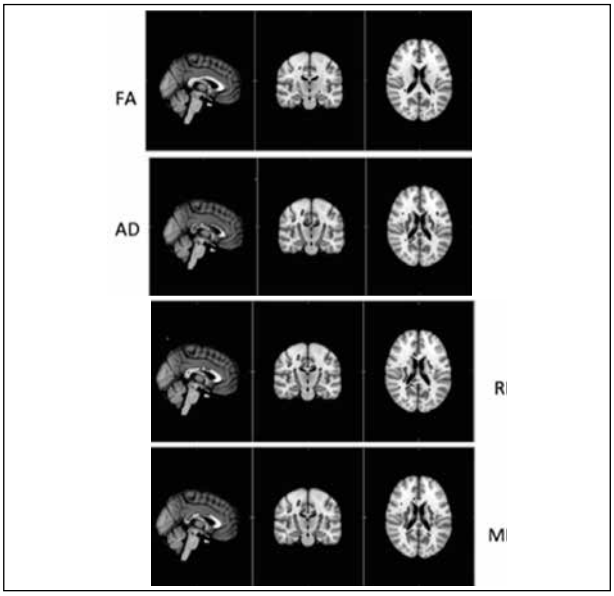

Figure 1. Results of the TBSS analysis between t1 vs. t2 MRI acquisition. Areas of decreased FA are shown in red-yellow scale and areas of increased AD, RD and MD are shown in blue--lightblue ($p<0.05$, TFCE). FA-fractional anisotropy, AD-axial diffusivity, RD-radial diffusivity and MD-mean diffusivity.

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BOTULINUM TOXIN FOR HEREDITARY SPASTIC PARAPLEGIA: EFFECTS ON MOTOR AND NON-MOTOR MANIFESTATIONS

K.R. Servelhere[1], P.T. I. Faber[1], A. Martinez[1], R. Nickel[2] , A. Moro[2], F. M. B. Germiniani[2], M. Moscovich[2], C. C. Mello[2], T. R. Blume[2], N. Becker[2], R. P. Munhoz[2], H. A. G. Teive[2], M. C. França Jr[1]

[1]Department of Neurology, Hospital de Clínicas, University of Campinas, UNICAMP, Campinas, SP, Brazil; [2]Movement Disorders Unit, Neurology Service, Internal Medicine Department, Hospital de Clínicas, Federal University of Paraná, Curitiba, PR, Brazil.

Introduction: Motor and non-motor manifestations are common, disabling and bothersome features of Hereditary spastic paraplegia (HSP), a heterogeneous group of neurodegenerative disorders characterized by progressive spasticity and weakness of the lower limbs. Botulinum toxin type A (Btx-A) is considered an effective and first-line treatment for spasticity. Therefore we intent to assess the efficacy of Btx-A in patients with HSP. **Materials and Methods:** Thirty-three Brazilian patients with pure and complicated HSP were evaluated before and after the administration of Btx-A by the Spastic Paraplegia Rating Scale, Modified Fatigue Impact Scale, Epworth Sleepiness Scale, Brief Pain Inventory, Beck Depression Inventory, Modified Ashworth Scale, Medical Research Council scale and walking speed for 10 meters. **Results:** Mean age of patients was 41.7 ±13.6 years and there were 18 women. Most patients had

a pure phenotype and *SPG4* was the most frequent genotype (45.4%). Btx-A applications resulted in decrease of spasticity at the adductor muscles, but no other significant motor change. In contrast, patients noticed improved fatigue after the treatment. This study occurred between February/2013 and December/2014. **Discussion:** In terms of motor manifestations, our study identified hip adductor spasticity improvement as the main result but no significant functional gain, since gait velocity remained stable between applications. This is in contrast to Rousseaux and De Niet who found positive results with Btx-A in comfortable gait velocity, but not in maximum gait speed. We believe that such differences might be due to the different application protocols and also the distinct profile of the patients in each study. The major contribution of this study was the assessment of Btx-A on HSP-related non-motor manifestations. We found a significant improvement of fatigue after treatment, especially its physical domain. So, we hypothesize that Btx-A relieves spasticity, improves the biomechanics of gait and therefore, improves fatigue in these subjects. Pain is another important and frequent non-motor feature of HSP, affecting 73.3% of patients and surprisingly, we were not able to demonstrate significant pain improvement after Btx-A injections. One possible explanation is that this cohort was largely pain-free (mean BPI intensity score <2), so that identification of further improvement was difficult (floor effect). Additionally, injection protocols were different for each patient in terms of doses and application sites. So, we believe that some patients might have improved, whereas others did not. Then, lumping all patients together, we might have lost statistical significance on these effects. **Conclusion:** In this uncontrolled study, Btx-A resulted in no significant functional motor improvement for HSP, but fatigue improved after treatment. Further controlled studies are needed to determine whether Btx-A is useful for subjects with HSP.

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LINEAR DISCRIMINANT ANALYSIS AS A POTENTIAL TOOL TO IDENTIFY VARIANTS OF SIGNIFICANCE FOR COMPLEX DISORDERS

M. G. Borges[1,2], R. Secolin[1,2], B. S. Carvalho[1,2,3], I. Lopes-Cendes[1,2]

[1]Deptament of Medical Genetics, FCM, UNICAMP; [2]Brazilian Institute of Neuroscience and Neurotechnology; [3]Institute of Mathematics, Statistics and Scientific Computing, IMECC, UNICAMP.

Introduction: With the introduction of next-generation-sequencing it comes feasible to identify millions of variants in a single experiment. In this context, an important computational challenge is to correctly annotate these variants for downstream analysis in order to prioritize and filter variants with biological and clinical significance. Currently, filtering parameters used are variant allele frequencies, genomic location or previous disease associations. Cut-off points have been well established for these parameters in the context of Mendelian disorders, with a major gene effect. However, these may not be applicable to disorders with complex inheritance, since importunate candidate variants may filtered-out by the current modelsHere we propose a methodology that could be applied to disorders with a complex mode of inheritance using linear discriminant analysis (LDA). **Materials and Methods**: LDA is useful in statistics for pattern recognition and machine learning in order to find a linear combination of features, which characterizes or separates two or more classes of objects or events[1]. Here we applied LDA to a training set, of 5,718 arbitrarily selected variants from 2,504 individuals from the 1000 Genomes Project[2], comprising variants within the interval chr20:60,343-250,214 (hg19). In order to construct our model, we excluded variants with a correlation ratio higher than 0.9 within the five super population group comprising: AFR (African), AMR (Ad Mixed American) EAS (East Asian), EUR (European) and SAS (South Asian). **Results**: As a result, we were able to create a model that unequivocally reclassified all the super-populations from our dataset using 3,277 variants. Given the model, we selected variants which contributed at least with 1% to the classification, resulting in 972 variants that could discriminate the super populations with 92.65% of assertiveness. **Discussion**: The methodology presented here proved effective to reclassify individuals from the four super populations even given an arbitrary set of variants from a single chromosome. Using the complete set of variants from the genome, or those in exons, we could have added more robustness with a more functional spectrum to our predictions with the cost of a large processing time. This methodology has also the potential of application in complex traits with a large number of individuals, helping to reveal the summative effect of a group of variants within the phenotypes. **Conclusion**: Given our results, we identified that less than 17% of the original arbitrary variants classify individuals from the 1000 Genomes Project with a high confidence level, showing that this LDA-based method could be applied to variants within exons or the entire genome in assist in the identification of the genetic basis of complex disorders.

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DETERMINISTIC AND STOCHASTIC WRAPPERS FOR MOTOR IMAGERY BCIS

L. F. S. Uribe[1,2], M. B. Kersanach[1,2,3], T. B. S. Costa[1,2], S. N. Carvalho[2,4], D. C. Soriano[2,5], R. Attux[1,2]

[1]FEEC/UNICAMP; [2]Brazilian Institute of Neuroscience and Neurotechnology, BRAINN; [3]CTI Renato Archer; [4]DEELT/UFOP, [5]CECS, UFABC.

Introduction: Electrode selection using two different wrappers approach, stochastic and deterministic, is investigated for motor imagery brain-computer interfaces (BCIs) with sets of paired combinations of four possible commands. The stochastic wrapper is proposed based on a version of a progressive wrapper that selects an electrode with a probability directly proportional to its associated success rate over a validation set (evoking the concepts of stochastic hill climbing and roulette wheel selection in genetic algorithms)[1]. The motivation is to verify if the BCI could benefit from the possibility of scape from local optima on the focused stage with relative simplicity. **Materials and Methods:** Electroencephalography (EEG) data of three healthy volunteers were recorded under 4 motor imagery tasks: left and right hands, feet and tongue. The acquisition procedure was approved by the Ethics Committee of UNICAMP (n. 791/2010). Sixteen electrodes were distributed on the subject scalp, mostly near to the sensorimotor regions. The interface setup included: (1) common average reference (CAR) filtering; (2) feature extraction using Welch method for the following bands: 7,5-14 Hz and 18-26 Hz; (3) channel selection via progressive, regressive and a stochastic progressive wrapper, and (4) classification based on linear discriminant analysis (LDA). **Results:** Table 1 presents the mean accuracy (20 trials per class) for all subjects and all pairwise movement combinations. **Discussion:** For all pairs of analyzed classes, it was found that the best discrimination is obtained for either left hand versus tongue or right hand versus tongue. The stochastic wrapper had a consistent performance in comparison with the standard wrappers, outperforming them in a number of instances. **Conclusion:** The work provided an overview of performances for three kinds of wrappers under different pairs of motor imagery tasks. The use of hand and tongue imagination was favored and the stochastic wrapper proved itself to be a relevant option. Perhaps the addition of a greedy search mechanism thereto can lead to a performance improvement.

Table 1. Best results (mean accuracy) for the different tested cases – with P (progressive), R (regressive) and S (stochastic), LH (left hand), RH (right hand), T (tongue) and F (feet).

		Class											
Subject	Wrapper	LH	RH	LH	T	LH	F	RH	T	RH	F	T	F
1	P	0.54	0.49	0.85	0.60	0.75	0.61	0.87	0.75	0.79	0.76	0.57	0.56
	R	0.55	0.69	0.65	0.62	0.75	0.62	0.94	0.70	0.78	0.63	0.53	0.62
	S	0.58	0.62	0.90	0.70	0.80	0.66	0.80	0.80	0.81	0.66	0.50	0.62
2	P	0.50	0.48	0.99	0.95	0.95	0.83	0.99	0.94	0.85	0.74	0.69	0.70
	R	0.56	0.55	0.98	0.86	0.97	0.84	0.85	0.85	0.75	0.66	0.69	0.67
	S	0.56	0.51	1.00	1.00	0.90	0.92	1.00	0.90	0.92	0.83	0.67	0.66
3	P	0.46	0.64	0.69	0.73	0.73	0.85	0.78	0.82	0.83	0.21	0.73	0.51
	R	0.45	0.64	0.74	0.91	0.45	0.50	0.72	0.75	0.66	0.69	0.64	0.53
	S	0.49	0.72	0.80	0.90	0.80	0.83	0.73	0.80	0.74	0.72	0.60	0.59

References: [1] Castro LN, Foundations of Natural Computing. CRC Press, 2006.

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MULTI-OBJECTIVE TRANSFER LEARNING FOR EPILEPTIC SEIZURE DETECTION

F. S. Beserra, M.M. Raimundo, F. J. Von Zuben
LBiC, DCA, FEEC, UNICAMP, Campinas, SP, Brazil.

Introduction: Due to the scarcity of well labeled epileptic seizure data and the usual rarity of seizure events of an average patient, it becomes relevant to develop methods capable of using data from multiple patients aiming at improving classification performance on a specific patient. With this purpose in mind, we propose a method that uses a multi-objective optimization method to share data and learning parameters from a source patient to a target patient. **Materials and Methods:** The data consisted of EEG recordings of 14 selected patients with labeled seizures, available at[1,2]. Features were extracted from properties of a graph formed by the correlations between electrodes, as in[3]. In this work, the methodology consists of generating multiple models using NISE[4] (a versatile multi-objective optimizer), considering two objective functions, and selecting a classifier, among the generated efficient candidate solutions, using a harmonic mean between sensitivity and specificity. Each classifier adopts a two-phases synthesis approach: the first phase involves training the source task model, and the second phase is devoted to transferring parameters and data from a source to a target model. The generated model is denoted TLNISE (transfer learning NISE). **Results:** The comparison benchmarks presented in Table 1 were: a regularized Logistic Regression (LogReg) as well as a single-task NISE (STNISE) formulation, which considers only target patients' data. Additionally, to illustrate the best achievable performance of TLNISE, it is also considered a best *a posteriori* model (PTLNISE), supported by the classifier's performance in the real test case (which violates any fair design principle, thus serving just as a reference). TLNISE and the benchmarks were evaluated using sensitivity (SEN), specificity (SPE) and the area under the curve (AUC) of the ROC curve. The first three columns of Table 1 present the average Friedman rank among all patients for each metric, while the last three columns present the average values across all patients. **Discussion:** Table 1 shows that TLNISE has the best ranking for AUC, a middle performance on SPE, while PTLNISE, exhibits a better ranking for SEN. This suggests that TLNISE struggles particularly in its last stage of model selection. The first position in AUC ranking suggests that this transfer learning scheme has a potential to simultaneously benefit the performance on both SEN and SPE metrics, while the single-task methods STNISE and LogReg tend to favor single metrics. **Conclusion:** This work reveals a good performance of transfer learning for seizure detection, based on a multi-objective approach (TLNISE). The results indicate that further improvements in model selection are welcome, and the next research step will be the usage of ensemble approaches, since TLNISE generates multiple diverse models.

Table 1. Friedman rank (the lower the better) and average values (the higher the better) for SEN, SPE and AUC metrics.

	Rank			Average		
	SEN	SPE	AUC	SEN	SPE	AUC
STNISE	2.643	3.286	2.571	0.863	0.968	0.982
TLNISE	3.143	1.786	2.214	0.849	0.974	0.982
LogReg	3	1.429	2.939	0.825	0.978	0.977
PTLNISE	1.214	3.5	2.286	0.955	0.961	0.982

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EPIGENETIC CHANGES IN THE *HIPPOCAMPUS* OF AN EPILEPSY MODEL

D. B. Dogini[1]; A. S. Vieira[1], W. Souza[1], I. Lopes-Cendes[1]
[1]Departments of Medical Genetics and The Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), School of Medical Sciences, University of Campinas, UNICAMP, Campinas, SP, Brazil.

Introduction: Epigenetic summarizes alterations to the chromatin template that collectively establish and propagate different patterns of gene expression without changes in DNA sequence. To better understanding the role of epigenetic changes in epilepsy, we determined the methylation profile of an animal model of temporal lobe epilepsy in comparison with control animals. **Material and Methods**: We used laser capture microdissection to obtain tissue from the *hippocampus* of rats treated with pilocarpine (n=2) as well as control animals (n=2) and we performed two technical replicates. DNA was extracted using proteinase K protocol with modifications and it was converted by bisulfite with EZ DNA Methylation-Lightning™ Kit (Zymo Research). After conversion libraries were generated using TruSeq DNA Methylation and sequencing was performed in an Illumina HiSeq 2500. **Results**: We found 51 differently methylated regions (DMR) along the 20 rat chromosomes. 21 DMR were found within known genes (in exons and/or introns). In these regions we identified several genes, including Scrib (scribbled planar cell polarity protein) involved in astrocyte cell migration; Cacna1d (calcium voltage-gated channel subunit alpha1 D) a divalent metal ion transport; Gabbr2 (gamma-aminobutyric acid type B receptor subunit 2) which inhibits high voltage activated calcium ion channels; Csnk1e (casein kinase 1, epsilon) which is involved in cellular response to nerve growth factor stimulus and others. **Conclusion**: Although preliminary, our results show that the epileptogenic insult induced by pilocarpine injections in rats resulted in significant methylation changes when compared to control animals. These changes involve genes, which have been already recognized as implicated in epileptogenesis; however, as our data is further analyzed and validated we may find new molecular pathways contributing to the epileptogenic process.

A 2D CNN APPROACH FOR SKULL-STRIPPING IN MR IMAGING

O. A. S. Lucena[1], R. M. Souza[1], R. A. Lotufo[1]
[1]MICLab – Medical Image Computing Laboratory, School of Electrical and Computer Engineering (FEEC), UNICAMP

Introduction: Skull-stripping (SS) from magnetic resonance imaging (MR) images consists of segmenting brain from the non-brain tissue. Such method is the first step in many applications, for instance in tissue segmentation. Deep neural networks (DNNs) have been used for SS[1]. Nonetheless, a large amount of data is needed for such approach and manual segmentations for medical images, which labels data to feed in the DNNs, are time-consuming and impracticable sometimes. In this context, the Simultaneous Truth and Performance Level the Estimation (STAPLE) algorithm considers a collection of segmentations generated by different segmentation techniques and computes a probabilistic estimate of the true segmentation[2]. The results generated by STAPLE are often used as a silver standard to be used in the development of automatic methods. This work presents a 2D convolutional neural network (CNN) approach for SS in MR Imaging using STAPLE outputs as inputs for the CNN. **Materials and Methods:** All images used in this work are from the Calgary-Campinas-359 (CC-359) dataset (http://miclab.fee.unicamp.br/calgary-campinas-359). We used 349 subjects, which were split into two groups, 250 for train and 99 for testing. Next, as a preprocessing step, we crop the mid-sagittal slice for each subject. Sequentially, we randomly sampled 100 patches for each training subject slice at patch size 64x80 (CNN input size), and we sampled with stride size 1x1 all the testing subject slices with the same patch size of training. The next step consisted of training the CNN architecture of U-NET[3] and test it. Lastly, we evaluated the algorithm performance using DICE, Sensitivity, and Specificity. **Results:** Examples of the CNN segmentations are presented in Figure 1. A box-plot of the results is shown in Figure 2. **Discussion:** The final results

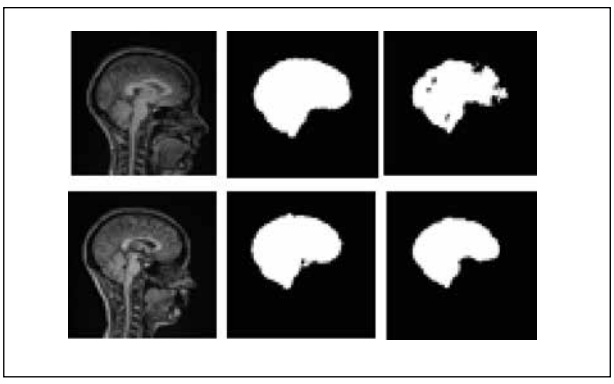

Figure 1. MR Images (1), STAPLE Masks (2), and CNN segmentations (3).

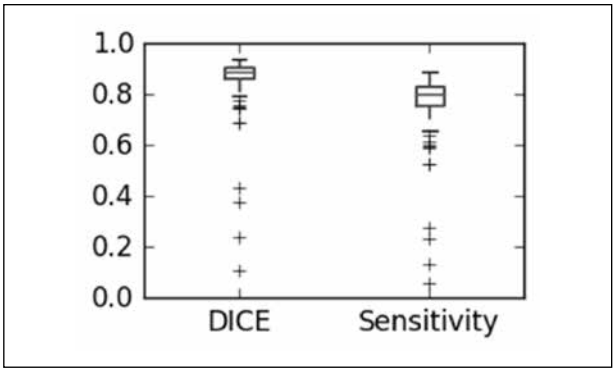

Figure 2. DICE and Sensitivity box-plots.

for the DICE, Sensitivity, and Specificity, respectively were 0.850.13, 0.760.14, and 1.000.00. Removing outliers greater than two standard deviations, the results for Sensitivity and Specificity respectively were: 0.880.05 and 0.780.07. **Conclusion:** The preliminary results are lower than the 3D approach in[1], but performing a 2D algorithm. Also, our segmentation presented many outliers, and we used few samples for training. Therefore, It is expected that training the CNN with more data can achieve better results.

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RANDOM FOREST AS A GENE SELECTION METHOD FOR A MOLECULAR SIGNATURE OF EPILEPSY

B. Henning[1], A. M. do Canto[1], A. S. Vieira[2], I. Lopes-Cendes[1], B. S. Carvalho[3]

[1]Genetics Dept., FCM, UNICAMP; [2]Fun. Str. Biol. Dept., IB, UNICAMP, [3]Statistics Dept., IME, UNICAMP.

Introduction: Classifying individuals as normal or affected by a condition based on molecular information can be used for diagnostic purposes in clinical practice, particularly in the context of precision medicine[1]. The classification process involves the identification of molecular profiles, which can discriminate individuals between conditions, focusing on the detections of the smallest possible set of informative molecular predictors that can still provide adequate predictive performance[2,3]. Identifying signatures based on molecular data is a combinatorial search problem that can be suitably handled with optimization methods[2]. Random forest (RF) is an ensemble method that uses multiple weak learners to improve predictive power that could be obtained from any of them alone4. This learning method constructs multiple decision trees that are later used on a voting system to create predictions5. The algorithm combines boosting and bagging[5] to provide unbiased and accurate predictions. We applied this approach to proteomics and transcriptomics data on model organism samples for epilepsy and their control counterparts to identify a predictive molecular signature that would classify subjects into cases and control groups. **Materials and Methods:** We obtained transcriptomic and proteomics data from previously published work[6]. Data included 14 subjects, 6 induced epilepsy model individuals and 8 healthy ones used as control. We had 22,686 ENSEMBL identifiers in the original data. After appropriate data preprocessing, we built random forest models using the *H2O* R package[7]. We performed a grid search on the parametric space, combined with 3-fold cross-validation, to identify the setting that would maximize the predictive power of the model, defined by the Area Under the Curve (AUC) statistic. **Results:** We found that the best model resulted from a random forest built with 100 decision trees and 16 variables as the maximum depth. On both training and out-of-bag samples, we obtained AUC=1, 100% accuracy and low mean square error. **Discussion:** High accuracy and small mean square errors as we obtained are likely to be associated to the small sample size. However, this strategy provides us with a strong candidate of molecular signature that can be later used, and further improved, to classify subjects into phenotypic groups.Our preference for using RF is due to the good statistical properties of the strategy, namely unbiasedness and prediction power, added to the ability of assessing the relative importance (based on Gini index) of every input variable, which is essential for the clinical assessment of the model and further development into a tool that can be effectively used in clinical practice. **Conclusion:** Molecular signatures are key for the development of Precision Medicine. The present work suggests that a combination of solid statistical procedures to minimize technical variability with the latest machine learning strategies creates a strong framework for the identification of such signatures and provides us with strong candidates for the improvement of the tools used in Precision Medicine.

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MONITORING NEUROCRITICAL PATIENTS WITH DIFFUSE OPTICAL TECHNIQUES

R. M. Forti[1,2], A. Quiroga[1,2], M. Katsurayama[2,4], L. Valler[4], J. Rubianes[2,3], S.T. Wu[2,3], R. C. Mesquita[1,2]

[1]Neurophysics Group, IFGW, UNICAMP; [2]Brazilian Institute of Neuroscience and Neurotechnology, BRAINN, Campinas, SP, Brazil; [3] Faculty of Electrical and Computer Engineering, UNICAMP, [4]Clinical Hospital, UNICAMP, Brazil.

Introduction: The immediate intervention and continuous monitoring of neurocritical injuries are essential to avoid more damage. In the neuro intensive care unit (NICU) clinicians usually rely on systemic physiological data readily available to decide on therapeutic strategies. There is an urgent need for the development of tools for assessing cerebral physiology non-invasively and at the bedside. Diffuse optical techniques have been shown to register brain physiology continuously and non-invasively[1], during hospitalization and also during surgery[2]. By shining light onto the scalp, it is possible to recover in real time the cerebral oxygen saturation (), cerebral blood flow () and the cerebral metabolic rate of oxygen (). Recently, we translated a novel homemade metabolic monitor () into the NICU3. In this work, we present a clinical application for this monitor as a bedside marker of brain injuries. **Materials and Methods:** All measurements were performed with our metabolic monitor, which combines two diffuse optical techniques: diffuse optical spectroscopy (DOS)[4] and diffuse correlation spectroscopy (DCS)[5]. The system is also integrated with a neuronavigator system (VMTK) for real-time assessment of the injury location with greater accuracy. We present a case study of a subarachnoid hemorrhage (SAH) patient who was monitored with our optical system during the whole hospitalization period. The patient was admitted to the hospital with a SAH in the right hemisphere (confirmed by computed tomography, CT) and Hunt-Hess scale of 5. We monitored the patient with the metabolic monitor for approximately 1 hour per day on each hemisphere during the whole hospitalization period. All the systemic parameters, such as the mean arterial pressure (MAP), arterial oxygen saturation (SaO_2), heart rate variability (HR) and respiratory frequency (FR) were monitored. No treatment decisions were made on the basis of the measured values, and all procedures were supervised by a neurologist. **Results and Discussion:** On the second day after admission, when the hemorrhage was expanding, CBF in the ipsilesional hemisphere was an average of 20% higher than the CBF on the contra-lesional hemisphere, which is consistent with the CT hemorrhage diagnosis. The patient's right hemisphere evolved to ischemia between the fourth and fifth days of hospitalization, as confirmed by an updated CT scan. On the sixth day of hospitalization, the metabolic monitor revealed significantly lower CBF (-56%) and $CMRO_2$ (-54%) in the ipsilesional hemisphere, which is again consistent with the patient diagnosis. In the following days a slower decrease of flow and metabolism was observed, in comparison with the patient's state at the beginning of the experiment. This is consistent with the worsening of the patient. The patient eventually died on the ninth day of hospitalization, with CBF and $CMRO_2$ indexes on the ipsilesional hemisphere 65% and 60% below the initial values, respectively. **Conclusion:**By comparing the hemodynamic physiology in the cortical region with the CT images for the case studied, our results suggest that diffuse optical techniques can reliably monitor the evolution of neurovascular injuries in real time, non-invasively and at the bedside. Our system is sensitive to brain injury and thus could be a helpful tool for the individualized monitoring of neurocritical patients.

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NOVEL INTERACTION TECHNIQUES FOR NEUROSURGICAL PLANNING

D. Oliveira[3], W. S. Loos[1], S.-T. Wu[1], E. Ghizoni[2,3]

[1]Computer Engineering and Automation Dept., FEEC, UNICAMP; [2]Neuroimages Laboratory, FCM, UNICAMP; [3]Dept. of Neurology, FCM, UNICAMP.

Introduction: Small and under surface lesions, infiltrating lesions and near eloquent areas lesions of the brain are quite challenging to the neurosurgeon perform a safe resection. Mastery of neuroanatomy and meticulous neurosurgical planning are the fundamental keys for surgical success. Sulci and giri surface anatomy is not always evident on the craniotomy field and even with a neuronavigating system one can become insecure about the correct localization of the lesions and eloquent brain areas. Superficial veins of the brain can, however, be visualized pre- and intra-operatively. Therefore, the relations between veins and brain anatomy are helpful in neuroanatomy recognition during pre-operative planning. On top of the well-established curvilinear reformatting tool for locating lesions in the prototype VMTK [1], we build an interactive interface. This interface not only provides a view of the brain and veins that a neurosurgeon has in the operating field, but also improves the exploration of the underlying anatomical structure as well. Based on the information gathered from the visual exploration, the neurosurgeon can identify the anatomy and perform a safe surgery. **Materials and Methods:** We assess prospectively the usefulness of the developed tool in brain surgery planning. After loading contrast enhanced T1-weighted magnetic resonance imaging volume of a patient, the display of the blood vessels and the relevant anatomical fiducial marks must be improved by adjusting color and opacity of tissues. Then, scalp is cropped off for revealing the underlying region of interest into which the neurosurgeon can navigate with cursors, explore its surrounding eloquent structures and assess its position relative to the anatomical fiducial marks. This tool was initially used in four patients with supratentorial lesions who underwent surgery in the University of Campinas General Hospital from January to February 2017. **Results:** The patients have small and under surface lesions. Surgical planning was performed using VMTK and intra-operative images were acquired to compare veins and brain surface with that produced by the software. Relations between veins and brain surface obtained by VMTK showed to be very reliable with that visualized on surgery, as illustrate the images on the right side. **Discussion:** Neuronavigation systems are very useful to locate brain lesions, but are still expensive and is subject to errors like brain shifting. Moreover, they do not provide a real 3D reconstruction of the brain surface and the surgeon must perform a 3D reconstruction in his mind from axial, coronal and sagittal slices. VMTK showed to be an important tool to neurosurgical planning, since its curvilinear reformatting tool performed in the patient native space is fundamental for the correct interpretation of brain surface anatomy. **Conclusion:** VMTK can be an important tool for neurosurgical planning, bringing benefits to patients. It can help to define a craniotomy basis and to identify the brain surface anatomy. This software can be used in conjunction with a neuronavigation system or alone, and, once it is a free software, can be very useful in low income countries.

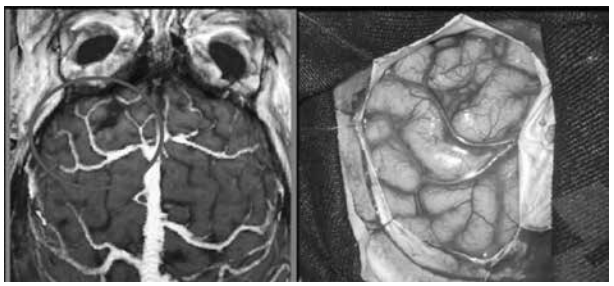

Figure 1. Comparison of the image created by the VMTK and the brain surface found in the surgery.

References: [1] Wu, et al. VMTK.http://www.dca.fee.unicamp.br/projects/mtk/wu_loos_voltoline_rubianes/index.html

METHOD FOR MOTOR CORTEX MAPPING USING NAVIGATED TRANSCRANIAL MAGNETIC STIMULATION

R. H. Matsuda[1], V.H. Souza[1], V.V. Cuziol[1], O. Baffa[1]

[1]Laboratório de Biomagnetismo, DF, FFCLRP, USP-RP.

Introduction: Neuronavigation systems are important for instantaneous localization of brain structures with high accuracy during transcranial magnetic stimulation procedures, named navigated TMS (nTMS). One of the main applications of nTMS is identify the cortex area responsible to control a certain muscle mapping the motor cortex representation[2]. However, there is still no consensus in literature about the best methods to define the mapping area and errors associated to nTMS[3]. The aim of this study was to develop a method to create a map of cortical motor representation of hand and forearm muscles and analyze the stimulus variability during motor mapping procedures. **Materials and Methods:** Thirteen healthy and right-handed subjects underwent nTMS motor mapping for the right flexor pollicis brevis (FPB), abductor digiti minimi (ADM) and flexor carpi radialis (FCR) on the left hemisphere. All subjects' images were acquired in a 3T MRI scanner (Philips Achieva, Netherlands). The motor evoked potential (MEP) were recorded with electrodes in monopolar configuration digitized and amplified by EMG410C (EMGSystem, Brazil). Stimulation was performed using a figure-of-eight coil connected to the Neuro-MS (Neurosoft, Russia) stimulator. Finally, InVesalius Navigator [https://github.com/biomaglab/invesalius[3] with MicronTracker (ClaroNav, Canada) was used for real time neuronavigation. Motor mapping session consisted in applying TMS pulse at 20 coordinates around each muscle hotspot (Figure 1). Three pulses were applied to each coordinate, and MEPs of all three muscles were recorded simultaneously. This procedure was conducted for the three hotspots muscles and for each subject, repeated in two different days. For each site, the Euclidean distance between all three stimuli coordinates were calculated to estimate the variability of mapping procedure.**Results:** Peak-to-peak amplitude of each MEP was normalized, interpolated and projected over the polygonal mesh of a segmented cortical surface (Figure 2). Resulting map provides visual feedback of cortical region associated to targeted muscle. Estimated variability for each site was 3.5 ± 2.1 mm. **Discussion**: Estimated variability of consecutive coordinates were greater than the total InVesalius Navigator accuracy, i.e. 2.6 ± 0.4 mm. Thus, it is most likely that this increase in variation is associated to low frequency movements of coil during manual mapping procedure. Small coil movements may affect an accurate definition of the mapping area and probably contribute to a greater variability in MEP responses. This highlight the necessity of a nTMS system to take the coordinate variability while generating the motor mapping. Our study is still under development and next step will target a definition of mapping features over realistic cortical surface. **Conclusion**: The present method allows the integration of motor mapping procedures to the InVesalius Navigator software and highlight the importance of neuronavigation to understand the TMS variability.

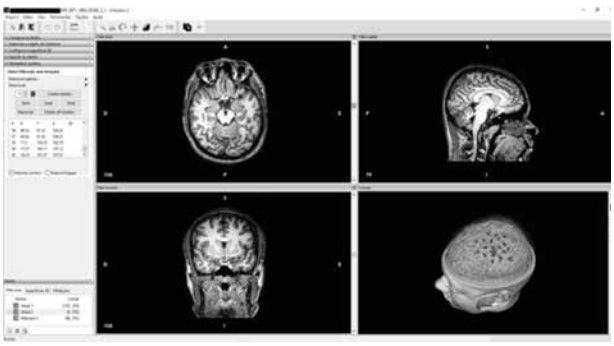

Figure 1. InVesalius Navigator.

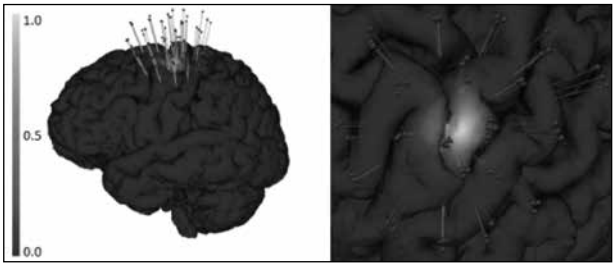

Figure 2. Cortical map of representative subject. Red dots represent the stimulus coordinates.

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HYBRID HUMAN-MACHINE INTERFACE FOR PROSTHETIC HANDS BASED ON ELECTROMYOGRAPHY AND MOTION

D. T. G. Andrade[1], A. N. Junior[1], E. Rohmer[1]
[1]School of Electrical and Computer Engineering, FEEC, UNICAMP.

Introduction: In Brazil, approximately 15% of amputees have issues interacting with devices that require manipulation skills. High-end prosthetic hands can improve their quality of life, but at a high price. An algorithm classifies a combination of several Electromyography (EMG) signals from a complicated contraction scheme of groups of muscles. It requires an intensive and tiring training from the user without a guaranteed success. The result triggers a desired predefined grasp. We propose here the use of a hybrid Human-Machine Interface (HMI) based on a combination of a reduced number of EMG signals and an Inertial Measurement Unit (IMU), to smartly select and trigger one of the fifteen predefined grasps available on a high-end prosthesis. **Materials and Methods:** Figure 1 presents the architecture of the system where EMG signals and IMU pose are classified in strong contractions and directions to let the controller define the grasp to be achieved by the simulated prosthesis[1]. It also has feedback information, so the user knows whether or not they send a valid request. Two prototypes were developed for evaluation purposes. Although they share the system architecture, they differ regarding hardware and communication protocols used. One of them is composed of an EMG channel (e-Health platform) and an accelerometer to get direction; Serial Peripheral Interface (SPI) access EMG data while Inter-Integrated Circuit (I2C) access the direction. The other one uses an armband composed of 8 EMG channels, a 9-axis IMU and Bluetooth protocol to access data. **Results:** Two prototypes of hybrid HMI for prosthetic hands were developed based on EMG and motion. This solution reduced the time spent in planning actions to perform a task. The activation commands are combinations of the number of contractions performed by the user and the direction of the prosthesis during the movement. For example, the system will understand that one contraction to the right is a command for precision closed grip. Moreover, human operability, a key factor for the success of artificial manipulation systems[2], is achieved because the interaction with the machine becomes easier for the user when using a combination of input sensors. **Discussion:** The electrodes may lose sensibility over time, resulting in more effort required from the user to send a command and in a noneffective system. The electrodes on the e-Health Platform lost sensitivity and needed replacement every hour of training. This problem did not happen while using the armband since its electrodes have a different setup and do not need replacement. **Conclusion:** Hybrid HMI can be used in the development of high-end prosthetic hands since it reduces implementation complexity and training time because the user does not have to train a particular group of muscles to send the correct command to the prosthesis. Consequently, it increases the chances users will wear the prosthesis and not give up using them.

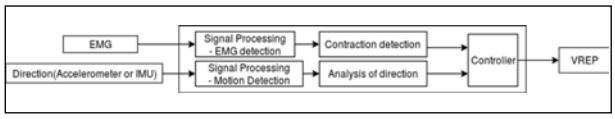

Figure 1. Overview of the proposed platform.

References: [1] Rohmer E, Singh SPN, Freese M. V-REP: A versatile and scalable robot simulation framework. In 2013 IEEE/RSJ Int. Conf. on Intel. Robots and Sys. 2013;1321-6; [2] Bicchi A. Hands for dexterous manipulation and robust grasping: A difficult road toward simplicity. IEEE Transactions on Robotics and Automation. 2000;16(6):652-62.

DEVELOPMENT OF GAME-LIKE INTERFACES FOR NEUROFEEDBACK TRAINING

F. C. Vivaldi[1,2], G. H. Scavariello[2,3], L. T. Menezes[2,3], G. Castellano[2,3]
[1]FACAMP, Campinas, SP; [2]Neurophysics Group, IFGW, UNICAMP, Campinas, SP; [3]Brazilian Institute of Neuroscience and Neurotechnology,BRAINN, Campinas, SP.

Introduction: Neurofeedback training (NFB) is a technique where brain signals are measured from a subject and presented in real-time back to him/her, and the subject is then asked to modify these signals (for example, to increase or decrease their amplitude)[1]. NFB has been used to treat several neuropsychological conditions, such as attention deficit hyperactivity disorder (ADHD), autism and depression. However, results are still controversial. This work is part of a larger investigation that aims to evaluate the NFB technique. Since subjects need to undergo many training sessions that last between 20 minutes to 1 hour, watching their own signals can be tedious and this may work against the technique. Therefore, many works use game-like interfaces, which are controlled by the brain signals, therefore making the training procedure more fun. The aim of this work was to develop game-like interfaces for NFB. **Materials and Methods:** In our group, NFB signals have been acquired with either electroncephalography (EEG) or near-infrared spectroscopy (NIRS). In both cases, the acquisition software has been designed such as writing files with the measured digital signals. The games were programmed in Java, using Netbeans as the platform. The interface works like this: there is an infinite loop where every half second the program reads a new NFB signal (measured from either EEG or NIRS) and updates the game. **Results:** We created two game-like interfaces. One of them shows a car race (Fig. 1a). There are two cars: one that represents the subject and another that represents the ideal NFB signal. So, the subject needs to concentrate to reach or overcome the other ("ideal NFB") car. The second is simpler and represents a face (Figure 1b). The objective is to make the face smile. If the amplitude of the NFB signal is very low, the face will be sad. As the signal amplitude increases, so increases the smile on the face. **Discussion/Conclusion:** All the game-like interfaces worked correctly, but up to now they have only been tested with simulated data files. Our next step is to test the interfaces in a real situation, i.e., during an NFB training session, with real NFB signals. We also plan to develop a third interface, whose aim is to increase or decrease the brightness of the computer screen, according to the amplitude of the measured NFB signal.

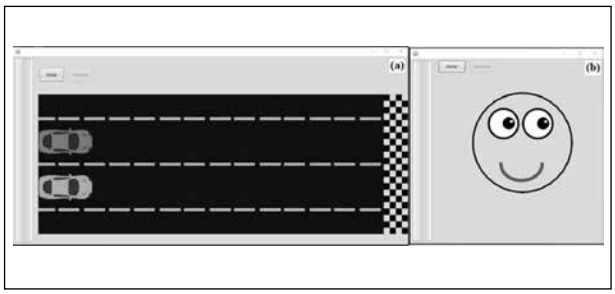

Figure 1. Developed interfaces for DFB signals.

References: [1] Gruzelier JH, Neurosci Biobehav Rev. 2014;44:124-41.

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- ***Keppra®** tem **bom perfil de tolerabilidade**, **baixa incidência de eventos adversos significativos**, **sem interação medicamentosa** clinicamente significativa[2]*
- ***Keppra®** é um fármaco **antiepiléptico** de **amplo espectro de ação**[2]*

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CONTRAINDICAÇÃO: Hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **INTERAÇÃO MEDICAMENTOSA:** Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam.

Referência Bibliográfica: 1. Wilmshurst JM, Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. - Epilepsia. 56(8):1185-97. Aug. 2015. **2.** Panayiotopoulos CP, A Clinical Guide to Epileptic Syndromes and their Treatment - Revised Second Edition - Chapter 18, Symptomatic and Cryptogenic (Probably Symptomatic) Focal Epilepsies, -ed. London UK - Springer-Verlag; page 485, 2007.

Keppra® (levetiracetam). **Apresentação**: comprimidos revestidos de 250 mg em embalagens com 30 ou 60 comprimidos ou comprimidos de 750 mg também em embalagens com 30 ou 60 comprimidos. **Indicações**: é indicado como monoterapia para o tratamento de crises parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia. Keppra® também é indicado como terapia adjuvante no tratamento de: - crises convulsivas parciais com ou sem generalização secundária em adultos, adolescentes e crianças com idade superior a 6 anos, com epilepsia; - crises convulsivas mioclônicas em adultos, adolescentes e crianças com idade superior a 12 anos, com epilepsia mioclônica juvenil; - crises convulsivas tônico-clônicas primárias generalizadas em adultos, adolescentes e crianças com mais de 6 anos de idade, com epilepsia idiopática generalizada. **Contraindicações**: Hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **Cuidados e Advertências**: para informações completas de advertências, vide bula do produto. A administração de Keppra® em pacientes com comprometimento renal poderá necessitar de um ajuste da dose. Foram notificados suicídio, tentativa de suicídio e ideias e comportamento suicida em pacientes tratados com levetiracetam. *Gravidez*: categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. Levetiracetam é excretado no leite humano materno. **Keppra®** é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas. *Interações medicamentosas* (*vide bula completa do produto*): Dados indicam que levetiracetam não influencia as concentrações séricas de medicamentos antiepilépticos existentes (fenitoína, carbamazepina, ácido valproico, fenobarbital, lamotrigina, gabapentina e primidona) e que estes medicamentos antiepilépticos não influenciam a farmacocinética de levetiracetam. A probenecida (500 mg quatro vezes ao dia), um agente bloqueador da secreção tubular renal, mostrou inibir a depuração renal do metabólito primário, mas não a do levetiracetam. Contudo, a concentração deste metabólito permanece baixa. Levetiracetam 1000 mg por dia não influenciou a farmacocinética dos contraceptivos orais (etinilestradiol e levonorgestrel). Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam. A extensão de absorção do levetiracetam não sofreu qualquer alteração com a ingestão de alimentos, mas a taxa de absorção diminuiu ligeiramente. Não estão disponíveis dados sobre a interação do levetiracetam com o álcool. *Reações Adversas*: para informações completas de reações adversas, vide bula do produto. Os eventos adversos mais comumente reportados nos estudos clínicos foram astenia, fadiga, dor de cabeça e sonolência. Adicionalmente às reações adversas relatadas durante os estudos clínicos, as seguintes reações adversas foram reportadas na experiência pós-comercialização, além de outras mencionadas na bula completa do produto: comportamento anormal, raiva, ataque de pânico, ansiedade, estado de confusão, alucinação, distúrbios psicóticos, suicídio, tentativa de suicídio e ideação suicida, parestesia, coreoatetose, discinesia, letargia. **Posologia**: A dose inicial recomendada para monoterapia no tratamento de crises parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia, é de 250 mg duas vezes ao dia, a qual poderá ser aumentada para uma dose terapêutica inicial de 500 mg duas vezes ao dia, após duas semanas. A dose máxima é de 1500 mg duas vezes ao dia. Nos casos de terapia adjuvante, para adultos e crianças acima de 12 anos e com mais de 50 kg, a dose terapêutica inicial é de 500 mg/duas vezes ao dia. Esta dose poderá ser iniciada no primeiro dia de tratamento, a dose diária poderá ser aumentada até o máximo de 1500 mg/duas vezes ao dia. Ainda nos casos de terapia adjuvante, para crianças (dos 6 aos 11 anos) e adolescentes com peso inferior a 50 kg a dose terapêutica inicial é de 10 mg/kg duas vezes ao dia, a dose pode ser aumentada até 30 mg/kg duas vezes ao dia. A alteração das doses não deve exceder aumentos ou reduções de 10 mg/kg duas vezes ao dia, a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A posologia em crianças com peso igual ou superior a 50 kg é igual à dos adultos. A forma farmacêutica comprimido revestido não é adaptada para bebês e crianças com menos de 6 anos. Keppra® solução oral é a forma farmacêutica ideal para uso nesta população. **USO ADULTO E PEDIÁTRICO ACIMA DE 06 ANOS DE IDADE. USO ORAL. VENDA SOB PRESCRIÇÃO MÉDICA – SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.** Para maiores informações, consulte a bula completa do produto. (0302040013 R9 Rev. Agosto 2015). www.ucb-biopharma.com.br **Reg. MS – 1.2361.0083**

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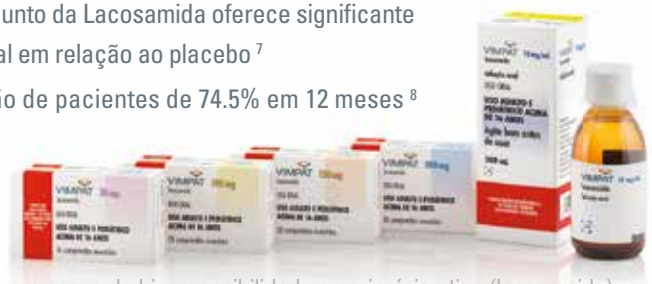

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CONTRAINDICAÇÃO: em casos de hipersensibilidade ao princípio ativo (lacosamida) ou a qualquer um dos excipientes.
INTERAÇÃO MEDICAMENTOSA: medicamentos conhecidos por prolongar o intervalo PR e antiarrítmicos classe I.

Referências Bibliográficas: 1. Alemanha, Argentina, Austrália, Áustria, Bélgica, Bulgária, Canadá, Chile, Chipre, Colômbia, Coréia do Sul, Dinamarca, Equador, Eslováquia, Eslovênia, Espanha, Estados Unidos, Filipinas, Finlândia, França, Grécia, Holanda, Hong Kong, Hungria, Índia, Irlanda, Israel, Itália, Luxemburgo, Malásia, México, Moldávia, Noruega, Nova Zelândia, Polônia, Portugal, Reino Unido, República Tcheca, Rússia, Suécia, Suíça, Tailândia, Turquia e Ucrânia. **2.** Rosenfeld W, et al. Evaluation of long-term treatment with lacosamide for partial-onset seizures: a pooled analysis of open-label extension trials. Presented at the 65th Annual Meeting of the American Epilepsy Society (AES); 2011. Dec 2-6; Baltimore, USA. www.aesnet.org. **3.** Chung S, et al. Examining the clinical utility of lacosamide: pooled analyses of three phase II/III clinical trials. CNS Drugs. 2010;24(12):1041-54. **4.** Cross SA, et al. Lacosamide: in partial-onset seizures. Drugs 2009; 69 (4):449-459. **5.** Fountain NB et al. Safety and tolerability of adjunctive Lacosamide intravenous loading dose in lacosamide-naive patients with partial-onset seizures. Epilepsia 2013; 54(1):58-65. **6.** Kellinghaus C, et al. Intravenous lacosamide for treatment of status epilepticus. Acta Neurol Scand. 2011; 123(2): 137-41. **7.** Sake J-K, et al. A pooled analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs. CNS Drugs. 2010;24(12):1055-68. **8.** Rosenow F[1], Kelemen A[2], Ben-Menachem E[3], McShea C[4], Isojarvi J[4], Doty P[4]; SP774 study investigators. Long-term adjunctive lacosamide treatment in patients with partial-onset seizures. Acta Neurol Scand. 2015 Jul 2. doi: 10.1111/ane.12451. [Epub ahead of print]. **9.**Vimpat comprimidos revestidos 50, 100, 150 e 200 mg. Informação para prescrição. Reg. MS - 1.2361.0081. **10.** Vimpat solução oral 10 mg/mL. Informação para prescrição. Reg. MS - 1.2361.0081.

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