Neuroanatomical Risk Factors for Post Traumatic Stress Disorder (PTSD)

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Introduction/Motivation: Low hippocampal volume could serve as an early risk factor for Post-traumatic Stress Disorder (PTSD) in interaction with other brain anomalies of developmental origin1. One such anomaly may well be a presence of large Cavum Septum Pellucidum (CSP), which has been loosely associated with PTSD2,3. Here, we tested the relationship between CSP volume and hippocampus volume in a large cohort of recent trauma survivors, using structural MRI and a within-subject repeated-measures approach. We hypothesized that at one-month after trauma, the relation between hippocampal volume and PTSD symptom severity will be moderated by CSP volume, and that this early interaction will account for persistent PTSD symptoms at subsequent time points.

Methods: 171 adults (average age=34.22, range=18-65, 87 females and 84 males) admitted to a general hospital’s emergency department following a traumatic event, underwent clinical assessment and structural MRI within one-month after trauma. Follow-up clinical evaluations were conducted at six (n=97) and fourteen (n=78) months after trauma. Hippocampus and CSP volumes were measured automatically by FreeSurfer software and further verified manually by a neuroradiologist (see Figure 1).

Results and Discussion: At one-month following trauma, CSP volume significantly moderated the relation between hippocampal volume and PTSD severity (p = 0.026), and this interaction predicted symptom severity at fourteen months post-trauma (p = 0.018). Specifically, individuals with smaller hippocampus and larger CSP at one-month after trauma, showed more severe symptoms at one- and fourteen-months following trauma exposure (see Figures 2 and 3). Our study provides evidence for an early neuroanatomical risk factors of PTSD, which could also predict the progression of the disorder in the year following trauma exposure. Such a simple-to-acquire neuroanatomical signature for PTSD could guide early management as well as long-term monitoring.
Figure 1: Cavum Septum Pellucidum (CSP). Coronal view of the T1-weighted (MPRAGE) image of an example subject. A red line marks the CSP as identified by Freesurfer automatic volumetric segmentation.

Figure 2: Interaction between hippocampus and CSP volumes at TP1 in predicting TP1 PTSD symptoms. Conditional effects of TP1 CSP volume on TP1 CAPS-4 total scores at different TP1 hippocampal volumes of 133 individuals (Q1=Low Hippocampal Volume in red, Q2=Median Hippocampal Volume in green, Q3=High Hippocampal Volume in blue). Both hippocampal and CSP volumes are centered. Hippocampal volume is presented as a categorical variable with three-levels for illustration purposes, even though it was used as continuous variable in the analyses. *significant at p<0.05

Figure 3: Interaction between hippocampus and CSP volumes at TP1 in predicting TP PTSD symptoms. Conditional effects of TP1 CSP volume on TP3 CAPS-4 total scores at different TP1 hippocampal volumes of 78 individuals (Q1=Low Hippocampal Volume in red, Q2=Median Hippocampal Volume in green, Q3=High Hippocampal Volume in blue). Both hippocampal and CSP volumes are centered. Hippocampal volume is presented as a categorical variable with three-levels for illustration purposes, even though it was used as continuous variable in the analyses. *significant at p<0.10

References:
Investigation of the Relationship Between the Brain and Visual Impairment
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Introduction/Motivation:
Visual impairment occurs across a wide range of ages and the aim of this study is to investigate the relationship between brain diseases and such optical impairment. Diseases that have impacts on a person’s vision include albinism, age-related macular degeneration, glaucoma, and ischemic optic neuropathy. The approach to this project has been guided by the following questions to better understand how the damage to the eyes could be linked to the neurological injuries to the human brain. What has been discovered from published studies on the matter? Does the use of computers influence the human brain and ultimately, vision? How could we use this brain-computer interfaces (BCIs) to improve any treatments for vision impairment? The damaged areas of the cerebrum are the drivers that eventually lead to these types of eye diseases and, by studying the activity within this region using sensors and recorded interactions with computers, the human brain can be studied extensively to understand what can be done to advance therapies.

Methods:
The study looks at a comparison of patients’ neuroimaging scans from various ages, genders, and ethnicities with the eye diseases of interest. The structural neuroimaging could be performed using MRI, DTI, VBM, or others depending on the specific type of disease studied using the procedures. Through the MRI examination, the differences/changes in the patient’s brain on eye diseases that have been discovered underlines the relationship between the brain and the disease. BCI system is used to investigate glaucoma disease under standard automated perimetry. Dry electroencephalogram, electrooculogram, and a head-mounted display are utilized to distinguish between glaucomatous eyes and healthy ones. Two devices of BCIs are invented to help the patient “see” the world. The procedure is done in two different ways, one through a mouthpiece by which the patient senses the shape of the object transferred on the mouthpiece to the tongue by electrodes, and the other is by transmitting the image information into electrodes and transfer them directly to the brain.

Results:
Optical impairment is caused by the abnormality of parts of the cerebrum related to optical activity. Different kinds of visual impairment show various types and degrees of abnormalities in the brain. Computers are able to detect stimulatory signals from the human brain to determine which general thought processes are being used by the person. It is hard to confirm if the disease occurred first or the change in brain. The portable device, nGoggle, can identify whether the patient has glaucoma disease. However, this BCI needs to be studied further in order to identify other eye related disorders. Patients can use BrainPort to visualize their surroundings through the sensation of their tongue, which helps the patient to travel around without the cane. Argus II helps the blind people to actually visualize the world, however, without any color and not as clear as what healthy eyes see.

Conclusions:
There is definite relationship between brain and diseases, and BCIs are possible but not mature enough to accurately perform the task we want. There is still room for improvement in order to invent a better BCI device that can help not only the people with visual disabilities, but those with mobility difficulties.
References:


Pentecostal healing services. The shock induction hypnosis, REM and the neuro-linguistic programming: the (Holy) Spirit behind the scenes

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Introduction:
The purpose of this research was to tackle the problem of implementing particular hypnosis techniques by Pentecostal leaders during the so called – healing services – organized for the mass audience on regular basis. The study concentrated on the meetings led by Benny Hinn who claims himself the Neo-Pentecostal preacher. The above-mentioned pastor tends to approach the participants, especially those in spiritual needs, in order to prove the presence of the Holy Spirit. In reality, the moment of coming closer has nothing in common with the supernatural intervention. Conversely, the phenomenon of a sudden, deep relaxation is believed to be triggered by the fact of implementing the widely-known – shock induction technique (Jones, 2008). Such practices lead to the process of entering into the REM state and also – experiencing catalepsy (Nolen, 1974). Moreover, the above-mentioned preacher focuses to a great extent on the so called anchoring which is ascribed to NLP (neuro-linguistic programming). The anchoring technique consists in creating a unique stimulus response pattern affecting one’s behaviour and well-being (Jones, 2010).

Methods:
The case study method, whose principal objective was to concentrate on a particular religious leader and his practices, was applied in this research. Two videos presenting the course of the healing services led by Benny Hinn were analyzed in details. He’s Here Right Now was the first video. It shows a medium-sized group gathered in Benny Hinn’s own church in California while the second video, namely the Heavy Anointing of the Holy Spirit, presents a large group of believers taking part in a meeting organized in Orlando, Florida. The analysis centred on the process understood as healing. More specifically, it focused on the implementation of the shock induction hypnosis combined with the anchoring technique ascribed to NLP by the above-mentioned leader (Jones, 2010). Furthermore, his verbal messages as well as his body language were emphasized.

Results and Discussion:
The results showed that there was a considerable similarity between the practices employed by Benny Hinn and those used by the trained therapists during the hypnosis sessions and the NLP sessions. The methods applied by Benny Hinn have nothing in common with the presence of the Holy Spirit. Conversely, they can be labelled as psychological manipulation with the emphasis put on the stimulus-response pattern.
References:


The region of the perilocus coeruleus α organizes the gradual transition between slow wave sleep and REM sleep

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[Introduction/Motivation:] There is little information but much controversy regarding the transition between slow-wave sleep (SWS) and rapid eye movement (REM) sleep, as well as about its neurobiological bases. Some authors have proposed a “flip-flop” model for switching between the two states, which is based on mutual inhibitions between hypothalamic and pontine neuronal groups with opposite actions [1]. However, other authors support the existence of a gradual transition state with own entity and different characteristics to those of SWS and REM sleep. In fact this transition state, known as the intermediate state (IS), is well defined in rats [2], but poorly characterized in cats and humans. Most IS characteristics, including the presence of ponto-geniculo-occipital waves (PGO) and EEG synchronization with δ wave reduction, are observed during a dissociated state of sleep (SPGO state) triggered by cholinergic stimulation of the perilocus coeruleus α region (PLCα) in the pontine tegmentum of cats. Therefore, the aims of our study were (1) to characterize the IS in the cat, and (2) to study the analogy between the SPGO state and the IS to clarify the mechanisms underlying the SWS-REM sleep transition.

[Methods:] Polygraphic recordings of 10 cats chronically implanted with electrodes for chronic sleep recording were used. In 7 of them, carbachol microinjections (20-30nL, 0.01M), a long lasting cholinergic muscarinic agonist, were performed in the PLCα. In the different states, PGO waves were analyzed and power spectra obtained for the δ, Θ, α and β bands from the cortical EEG (frontal and occipital leads), and for the Θ band from the hippocampal EEG. Statistical comparisons were carried out among the values obtained from the different states.

[Results and Discussion:] Our results [3] indicate that in the cat, as in the rat, the IS constitutes an independent sleep stage with features that differ from both the preceding SWS and the following REM sleep (Figure 1), highlighting a noteworthy increase in the α band power (8-14Hz) of the EEG from both frontal and occipital cortices. These results imply that “flip-flop” models proposing sharp transitions between SWS and REM sleep should be revised. The striking rise of the α band voltage during IS correlates with the entrance into REM sleep in humans through the N2 phase, that displays predominant spindle α activity [4]. These facts suggest that for REM sleep to occur, hyperpolarization levels in thalamo-cortical cells, responsible of the SWS or NREM sleep biolectric manifestations [5], must vary beforehand. Furthermore, the IS presents a high analogy with the SPGO state, so this state induced by cholinergic stimulation of the PLCα nucleus seems to be an expression of the physiological IS of the cat. Therefore, we propose the PLCα region as the organizing structure steering the transition from SWS to REM sleep, which does not constitute an abrupt phenomenon, quite the contrary it requires changes at multiple levels of the central nervous system, that are anatomically connected with the PLCα (Figure 2).
References:


A spatial graph-theoretical model to describe neuronal connectivity

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Introduction:
In this work we address a fundamental issue in brain science: how to mathematically describe the connectivity properties of a network of neurons, in such a way to be consistent with quantitative and qualitative experimental findings. Solving this problem could have an enormous influence on our understanding of how the brain works, and any large initiative on brain research worldwide dedicates quite significant efforts to this problem. The current approaches, in building large-scale neuronal networks, are either to explicitly impose a rule-based probabilistic connectivity or to implement quite complex and computational demanding touch-detection algorithms. In both cases, connections are tailored on sparse experimental observations that may bias the overall result. Here we propose a theoretical convolutive model that is able to reproduce and explain the full range of connection degrees observed in brain networks and their spatial organization.

Methods:
We started from a Price model including spatial information [1]. The Price model is a well-known power law model ([2]) in which the network is built based on preferential attachment, i.e. every newly added node has a probability to be connected to another node proportional to its degree. This implies that a node with a high degree has a higher probability to be connected to a new node, with respect to a node with a low degree. This rule creates a relatively large number of hubs and the consequent characteristic power law tail of the degree distributions. To add spatial information (i.e. the soma locations) to the network building process, we minimize the cost function $C_{ij}=(\delta d_{ij}+h_j)$ in j, which is the connection cost from the new node i to the existent node j, where $d_{ij}$ is the Euclidean distance between the spatial positions of the nodes i and j, $h_j$ is the network-based distance of the node j from the centre of the network (which is usually the first added node). The model can be considered as a standard simple BA model [1], where we added a random variable $\Gamma$ (like in [2]) regulating the number of new connections in creating a new node. The space is further separated in a number of blocks, corresponding for example to the different layers observed experimentally, and for each block we calculate the connectivity. Using a convolutive model, the blocks are then connected with each other with a random connectivity [3].

Results and Discussion:
We tested our model with the 5000-neuron inhibitory network of a data-driven large-scale neocortical model [4]. Since the cortex is structured in 6 layers, with interneurons in each on them, we subdivided the model space in 6 regions, following their anatomical extension [5] (Fig.1). Assuming a uniform neurons distribution in the (500x500x2000) $\mu m^3$ space, as in the original model, the aim was to find a representation of the observed connectivity as a function of the distance between neurons. For this purpose, we subdivided the model column in 6 layers with realistic thickness (Fig.1) and each layer in 9 equal portions, obtaining 54 blocks. By using a manual trial-and-error procedure we then found the model parameters best fitting the indegrees distribution. The model results for all distributions
(indegree, outdegree, and connection length) are compared with the data calculated from the original cortical model in Fig.2. As can be seen, the model was able to reproduce not only the entire range of indegree but also the outdegree and the connection length distributions. A typical 5000-neuron network took approximately 50sec to be built. A use case with the algorithm will be implemented on the Brain Simulation Platform of the HBP.

Figure 1: (Left) Spatial distribution of the neurons, divided in 6 independent layers corresponding to the experimentally observed cortical layers (from [5]).

Figure 2: Model and data distributions for the indegree (left), outdegree (middle) and connection length (right). Data was taken from inhibitory network of [4] (about 5000 neurons).

References:

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Episodic Future Thinking Deficit in Cannabis Users: an fMRI Study of Neurofunctional Alterations

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Background and Aims:
In recent years, researchers in the field of addiction have become increasingly interested in Cannabis. The leading cause of this is due to evidence from epidemiology studies which have reported Cannabis to be the most commonly abused illicit substance worldwide (National Academies of Sciences, Engineering, and Medicine, 2017). Although the effects of Cannabis have been studied on several cognitive and physical functions, Episodic future thinking (EFT) is understudied in this population. Episodic future thinking is defined as the mental simulation of future events and the ability to mentally visualize oneself in possible situations in the future that plays an essential role in the daily plans of individuals (Schacter et al., 2017). Episodic future thinking role is significant in the context of addiction, due to its association with impulsive decision-making and goal-directed behaviors (O'Donnell et al., 2017). The present study attempted to compare this cognitive function using behavioral and brain imaging methods (fMRI) in two groups of healthy and Cannabis users to determine whether this substance is associated with functional alterations in brain regions associated with episodic future thinking.

Method:
The present study consists of 40 participants in two groups of healthy non-user and Cannabis users that underwent functional and structural MRI and a neuropsychological assessment for evaluating their episodic memory (Rey’s Auditory Verbal Learning Test).

20 cannabis users (CU) and 20 healthy non-user (NU) individuals between 18 and 40 years of age (M= 26.70, SD=3.38) were included. The groups were matched by age, gender and educational level. Baseline assessments for the study, including the Edinburgh Handedness Test, the Beck Anxiety Inventory, the Beck Depression Inventory, the Montreal Cognitive Assessment, and a 6-panel Oral fluid test, were carried out prior to the imaging session. 20 episodic auditory cues were recorded and provided by an MRI-compatible headphone during imaging with a randomized order. During the imaging session, participants constructed and recalled the presented episodic events, in as much detail as possible, and scored the vividness of their mental imagery quality on a Likert scale. The fMRI experimental design is illustrated in figure 1. Functional magnetic resonance imaging of their brain took place using a Siemens MAGNETOM Prisma 3Tesla scanner and analyzed using FEAT analysis tool, part of FSL software.(Z-threshold= >2.3)

Results and Discussion:
The results indicated a significant difference between healthy subjects and cannabis users in depression (P-value=0.024), baseline cognitive functions (P-value= 0.003), and the vividness of their recalled episodic memories (P-value= 0.002). Also, the fMRI results showed a significant decrease in the brain activity of cannabis users in the Cerebellum, the medial and superior temporal gyrus, the lateral occipital cortex, and the occipital fusiform gyrus, while engaging in the episodic future thinking task (CU<NU) (Figure 2 and 3). The CU group did not show any higher brain activations in any of the three experimental conditions, compared to the NU group (CU>NU). The cannabis-user group also showed a worse performance in the RAVLT neuropsychological assessment (P-value= 0.02).

In general, the present study results are consistent with former studies results showing deficits in Episodic future thinking cognitive function in Cannabis users (Mercuri et al., 2018), adding neuroimaging evidence to prior behavioral results.
Figure 1. The experimental design of the fMRI task

References:


Abnormal MEG Resting-State Functional Connectivity as Neurophysiological Biomarker of Future Alcohol Binge Drinkers.

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Introduction
In recent years, adolescent alcohol Binge Drinking (BD) has become an increasing health and social concern (1). Adolescence is a critical neurodevelopmental period, entailing important neurobiological changes, which makes the brain particularly vulnerable against alcohol neurotoxicity (2, 3). However, evidences for neurophysiological and neuropsychological binge drinking predisposition profiles remains unveiled. For this purpose, in this research, we evaluated a cohort of initially alcohol-naïve adolescents (n = 67) in a two-year longitudinal study with Magnetoencephalography (MEG).

Methods
Participants’ neurophysiological cortical activity was recorded in an eye-closed resting-state session, in order to characterize the brain functional networks of teenagers who will transit into intensive alcohol consumers two years later. Complementarily, they fulfilled a battery of tests to assess impulsivity and dysexecutive traits. Two years later, we subdivided the sample in two groups according to their alcohol consumption habits (22 Binge-drinkers and 17 Light/no drinkers). Subjects with intermediate alcohol intake rate were ruled out. Functional connectivity (FC) analysis was performed over initial MEG recordings in order to explore prior neurophysiological differences. FC is defined as the existence of statistical dependencies between the time series of two or more sites, engaging in a functional network (4). It was estimated under the hypothesis of phase synchronization and using Phase Locking Value (PLV) (5). Nodal-strength (NS) and seed-based (SB) approaches were used with the purpose of discover which regions suffers the highest global FC abnormalities (NS), and subsequently which brain sources were abnormaly connected with those regions and freq. bands (SB).

Results & Discussion
For the first time, we detected abnormal hyper-connectivity in MEG functional connectivity networks of those adolescents who, two years later, engaged in BD consumption. FC NS analysis displayed a significative clusters for alpha (p = 0.0148) and beta (p = 0.0146) bands, encompassing lIFG, lIns and lSTG brain sources (fig.1), importantly related to inhibitory control (6). Additionally, SB analysis over these clusters, showed a significant intra-band hyperconnection (alpha p = 0.0330; beta p = 0.0100) with clusters located in rIFG and rDlPFC (fig.1, fig.2). Moreover, higher scores in impulsive and dysexecutive behaviors were found, correlating positively with those FC measures (fig.2b). These results evidence abnormalities in brain functional networks prior to alcohol consumption onset, reflecting potential neurobiological vulnerabilities towards the engagement in risky behaviors. We hypothesize that these abnormalities are due to neurodevelopmental and neurobiological differences, involving neuro-receptors such GABRA2 and DRD2 (7, 8), which, in turn, would cause the functional networks dysfunctions.
References


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**Figure 1. Nodal-strength connectivity analysis**

Fig. 1 location of nodal-strength hyper-connected clusters for future binge-drinkers group.

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**Figure 2. Nodal-strength and seed-based analysis**

a) Alpha (8 – 12 Hz) NS Cluster

b) Beta (12 – 30 Hz) NS Cluster

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**Fig.2 Hyperconnected** alpha (red) and beta (orange) nodal-strength clusters in left inferior frontal gyrus, left insula and left temporal gyrus for future binge-drinkers group. Using these clusters as seeds, intra-band seed-based connectivity analysis revealed hyper-connected interhemispheric clusters (yellow) in right dorsolateral and inferior frontal gyrus for future binge-drinkers group.
Functional Connectivity patterns in cognitively healthy individuals at increased risk for AD. A MEG Study.

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Introduction: Early detection of Alzheimer’s disease (AD) is the basis for developing interventional strategies to slow the further cognitive decline associated with AD. Magnetoencephalography (MEG) has proven to be a useful tool for AD continuum characterization. In previous studies we have reported consistent MEG biomarkers of the early AD stages such as Mild Cognitive Impairment or Subjective Cognitive Decline [1], [2],[3],[4]. In this study, we examined the presence of neurophysiological changes in cognitively healthy individuals at increased risk for AD, namely, first-degree relatives of AD patients. Specifically, we examined the alpha band functional connectivity (FC) in known areas of early development of AD (anterior cingulate and precuneus).

Method: The sample of 127 individuals is divided into 92 first-degree relatives of AD patients (REL) and 35 individuals with no records of AD in their family (CN). All participants underwent a complete battery of neuropsychological tests, blood extraction, a MEG recording and a MRI scan. The FC was calculated in source space using LCMV beamforming [5] and Phase-Locking Value (PLV) [6]. The FC of each area with the rest of the cortical areas was compared between groups using an independent-sample t-test and a Cluster-Based Permutation Test [7].

<table>
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Results: We found a hyper-synchronization between the left anterior cingulate cortex and a posterior cluster comprising both left and right posterior cingulate cortex, the left inferior occipital area and a part of the left precuneus. We found as well a hyper-synchronization between the left precuneus and the left posterior and middle cingulate cortex, the posterior segment of the superior frontal gyrus, and the right precuneus. Finally, we found a hyper-synchronization between the right precuneus and both left and right middle cingulate cortex, the right posterior cingulate cortex and both left and right superior frontal gyrus.

Discussion: The group of first-degree relatives of AD patients did not show differences in neuropsychological performance with the control group of age and educational matched participants. These results suggest that even in a young population at risk, decades before the typical age for developing cognitive impairment, there was already a malfunction of their brain networks.
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Introduction:

The study of cultured neuronal network has recently achieved a major relevance as an alternative to in vivo models, being a simplified version of a more complex network of the central nervous system with a complex self-organization [1,2]. Structural and functional networks and their synchronization are studied in these cultured networks. Dynamical state has been always assumed as a result of the anatomic structure [3] but it has been less explored the fact that this structural-dynamical interaction also plays in the other way around: just as the dynamics of each node influences the ensemble, the ensemble imprints its structural marks into the dynamics of each individual node [4,5,6]. Our motivation is to infer the degree node and its position on the structural network using its role in the functional network in a simulated network and in an experimental cultured neuronal network.

Materials and Methods:

We grow cultured neuronal networks (Fig. 1) extracted from isolated neurons from frontal ganglion of Schistocerca gregaria on top of microelectrode arrays (MEA), allowing the recording of their electrophysiological signal. Neurons start to establish connections between them in day in vitro (DIV) 3 and the culture is monitorized for 14 days. Structural network is extracted with a segmentation algorithm (Fig. 3) and we explore the structure-dynamics relationship by statistically analyzing the experimental electrical time series and simulating a biophysically plausible dynamical model, the Morris-Lecar neuron [7], on top of each cultured structural networks’ nodes. Statistical complexity of each node of the simulated dynamical network is calculated using entropy and disequilibrium obtained from the ordinal patterns formalism of their spike timestamps.

Results and Discussion:

After DIV 3, the clustering coefficient in the formed structural network is increased and the shortest path is decreased (Fig. 2), revealing Small-World properties in the mature state of the network. Data from the simulated dynamical network shows the statistical complexity of each single node dynamics is found to be anti-correlated with their degree centrality, with nodes of higher degree, displaying lower complexity levels while the lower ones are associated with higher statistical complexity (Fig. 4). Our results imply that it is possible to infer the degree distribution of the network connectivity only from individual dynamical measurements. Future work aims to record the experimental functional network of a culture neuronal network knowing its topological network, expecting to see a similar behavior with the degree of the node.
Figures:


Analysis with MEG of functional connectivity in default mode network associated with neuropsychological rehabilitation in stroke

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INTRODUCTION. The term vascular cognitive impairment (VCI) refer to all forms of mild to severe cognitive impairment associated with and presumed to be caused by cerebrovascular disease [1]. Within this broad spectrum, it is necessary to highlight the relevance of stroke, due to its high incidence. It represents the second cause of death worldwide. Furthermore, a high percentage of survivors suffer from significant chronic cognitive and physical deficits, which significantly hamper their independency in their daily activities. In this sense, long-term cognitive and functional improvement, achieved with rehabilitation treatments, is a crucially important clinic, scientific and social goal. Thanks to the development of neuroimaging tools and the study of the functional brain networks getting physiological evidence of the cognitive improvement is possible. This information reinforces the evidence of long-term patients cognitive rehabilitation [2,3,4,5].

METHODS. Twenty subjects participated in the study, and they involved two groups: 10 stroke diagnosed patients (8M/2F, age X=44.9; SD=12.7), recruited from CEADAC and LESCER, and 10 age- and gender-matched healthy control (8M/2F, age X=43; SD=8.9). An extensive and complete neuropsychological battery, including all cognitive domains and daily life independence measures, was used to extract accurate cognitive profiles. Five minutes of resting-state with closed eyes were recorded with Magnetoencephalography (MEG) to obtain brain functional information. Both, neuropsychological and neurophysiological measures were collected before and after 7 months rehabilitation program [6] for patients and just once for healthy participants as control baseline condition. Therefore, this work focuses on: 1) checking the cognitive performance of stroke patients before and after the neurophysiological treatment compare with healthy participants; 2) studying disruption and reorganization of Default Mode Network (DMN) functional connectivity, registered with MEG, of stroke subjects along rehabilitation against controls; and 3) analyzing the correlation between the brain functioning and the neuropsychological profiles.

RESULTS AND DISCUSSION. After non-parametric comparison analysis corrected by false discovery rate (FDR), first results reveal significant improvements in different cognitive domains for the experimental group, after the treatment, even equating their performance to the control group in executive functions and working memory related test. According to the neurophysiological modification in stroke patients an important finding is the interhemispheric hypersynchronization in beta (12-30Hz) between bilateral posterior cingulate cortex in patients before rehabilitation compare to control groups (p<0.05) which disappear after treatment, see Figure 1. Furthermore, a negative correlation was found between physiological and cognitive results, where the higher beta hypersynchronization in DMN, the worse cognitive performance in “pre” condition; and the beta hypersynchronization extinction after treatment correlates with neuropsychological improvements.

In order to improve psychological approaches to VCI it is important to develop neuroscientific perspective studies that include neuroimaging tools and neural functioning analysis, to reinforce the results and add value to the cognitive rehabilitation, providing robust evidence of the treatment’s influence, not only at the cognitive level, but also at the neurophysiological base of the brain.
References:


Figure 1 Interhemispheric hypersynchronization in beta (12-30Hz) frequency band between bilateral posterior cingulate cortex
Cortical excitability transiently increases during attentional lapses

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Introduction/Motivation:
Cortical excitability is modulated both by conscious states, sleep homeostasis and circadian rhythm, following a nonlinear dynamic across the day.² It is low during wakefulness and REM sleep, where subjects experience phenomenological states, and high in conditions such as NREM sleep and Disorders of Consciousness (DoC), where there is inappropriate or absent processing of external stimuli.³ Cortical excitability increases across the day, peaking at night after habitual sleep time where behavioral impairments such as attentional lapses are more common. Previous researches demonstrated that, at night, lack of vigilance is connected with lower frontoparietal effective connectivity.⁵ However, no study has investigated whether there is a transient increase of cortical excitability during attentional lapses per se. This would be in line with the idea that the brain is less efficient to engage in the ongoing task, acting similarly to an “unconscious state”. To test this hypothesis, we compared cortical excitability during normal awakening and attentional lapses.

Methods:
Data included in this analysis were retrospectively selected among 3 different studies including repeated assessment of cortical excitability using Transcranial Magnetic Stimulation (TMS) of the superior frontal gyrus coupled to high-density Electroencephalography (hdEEG). This region was selected because it is sensitive to sleep pressure¹ and has been implicated both for motor and cognitive tasks.⁶ To increase the likelihood of attention lapses, data was selected among nighttime sessions. Attention lapses were detected based on the performance to a continuous Compensatory Tracking Task (CTT) completed simultaneously to TMS-EEG recording. Volunteers with at least 25 lapses were included to reach a total sample of 26 healthy individuals in 2 age groups (young, N= 13, 18-30 y; old, N = 13, 50-69 y). As previously published,³ cortical excitability was inferred from amplitude and slope of the first component of the TMS-evoked EEG potential (TEP; 0–30 ms post-TMS, Figure 1). Latencies of the negative and positive peaks of this evoked potential were also extracted. Statistics were run on SAS 9.4 with a Generalized Linear Mixed Model (GLMM) (for more details, description of Table 1).

Results and Discussion:
Cortical excitability showed a strong change from no-lapse to attention lapse. In particular, there was a significant increase of amplitude, with a smaller latency of the negative component and a bigger latency of the positive one, leading to an increase in slope (for more details, Table 1). These results suggest that there is a transient increase of cortical excitability during vigilance lapses pointing to an alteration of the brain function that could be similar to what is observed when sleep need is high compared to well-rested condition, or during states of altered consciousness (e.g. sleep). These results could constitute an epiphenomenon of the likelihood of transitions of conscious states or rather a sheer marker of errors. Alternatively, they could reflect a local sleep phenomenon over the target area. Future researches should validate the extent of this description and fathom its molecular mechanisms.
Figure 1: Visualization of excitability measures: A) Latency of the negative peak B) Latency of the positive peak C) Peak to Peak amplitude D) Slope of the curve. Here, represented the tangent at the inflection point.

Table 1: Excitability results

<table>
<thead>
<tr>
<th>Measure</th>
<th>F-Value</th>
<th>Adjusted $p$-value</th>
<th>R-squared beta star</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude</td>
<td>12.03</td>
<td>0.002</td>
<td>0.34</td>
</tr>
<tr>
<td>Slope</td>
<td>7.02</td>
<td>0.014</td>
<td>0.23</td>
</tr>
<tr>
<td>Negative Latency</td>
<td>12.66</td>
<td>0.002</td>
<td>0.36</td>
</tr>
<tr>
<td>Positive Latency</td>
<td>8.12</td>
<td>0.009</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Table 1: Results from GLMM model. GLMMs were adjusted according dependent variables distribution and included Study, Age, Sex, BMI and TMS parameters as covariate. Subject was set as random factor while lapse/no lapse condition was included as repeated measure with autoregressive covariance. Statistical significance was set at $p < 0.05$. Degrees of freedom in GLMMs were estimated using Kenward-Roger’s correction. Semi-partial $R^2$ ($R^2_{\beta*}$) values were computed to estimate effect size of significant fixed effects as in Jaeger et al. (2017).  

References:
Are mental disorders malfunctions of the brain?

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[Introduction/Motivation:] The problems faced by psychiatry have raised the need to look for a new conceptualisation of mental disorders. Some authors have suggested a neurocentric conceptualisation: to increase precision in psychiatry we should understand mental disorders as 'precisely brain disorders' [1]. Thus, ‘mental disorders’ would not be different to any other neurological condition: a malfunction of the brain would be causing the observed symptoms. However, some authors have already been arguing against this view (e.g. [2], [3], [4]). Hence, the aim of this abstract is to analyze the conceptualisation of mental disorders as brain disorders and present an alternative one.

[Methods:] In this abstract, we are presenting a conceptual analysis of the term ‘mental disorder’ – the methodology commonly employed in analytical philosophy. To this end, (1) we will critically analyze the neurocentric concept of mental disorder, questioning (i) whether there is always a brain alteration for every mental disorder (ii) whether brain alterations are malfunctions of the brain (iii) whether brain alterations are the cause of mental disorders. Afterwards, (2) we will offer an alternative conceptualisation of mental disorder that is in line with the suggestions made by different frameworks in Philosophy, Psychology and Psychiatry, such as Network Theory, Radical Behaviourism and 4E Cognition (Embodied, Embedded, Enactive and Extended Cognition).

[Results and Discussion:] We propose reconceptualising mental disorders as a network of ‘symptoms’ that are a consequence of a learning process. Organisms are constantly learning how to interact with the environment from experience. A mental disorder would arise when the long-term consequences of that learnt interaction are dysfunctional. The observed brain alterations in mental disorders would be a consequence –rather than a cause- of these learning processes due to brain plasticity [5]. Thus, learning processes arise as the differential element between neurological and mental disorders: while learning does not play a role in the development of neurological conditions, it is essential in mental disorders. Importantly, this conceptualisation does not imply that mental disorders are under voluntary control or that they are easily changed or modified: most of the learnings we experience are in fact beyond our voluntary control and are reluctant to change. Also, our claim is not that all mental disorders that have been traditionally considered as such belong in this new conceptualisation. Diagnoses in psychiatry have changed throughout the years, and it might be the case that some of the present-day considered ‘mental disorders’ are in fact reducible to neurological disorders. Our claim is that at least an important subset of them should be understood from this non-neurocentric conceptualisation.
References:
Synaptology of human temporal neocortex: 3D-ultrastructural analyses

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Introduction

Brain organization is extremely complex and our current knowledge it is far from being completed. The cerebral cortex attracts the researcher’s attention because is where cognitive process takes place. To understand how neuronal circuits contribute to the functional organization of the cerebral cortex, a detailed ultrastructural analysis of neuronal connectivity is required. In particular, Brodmann’s area 21 is involved in high level cognitive functions like language [1]. This region is a highly connected cortex that integrates and distributes the information in many circuits [2]. These circuits are mainly established by cortico-cortical layer III projecting neurons, which process the information through synapses [3]. We have performed a detailed three-dimensional ultrastructural analysis of the neuropil, the region where most of the synapses are located. The goals of this study were to provide data about synaptic characteristics.

Methods

Human brain tissue samples were obtained from 8 control individuals (4 women and 4 men, whose ages ranged between 24 to 53 years old). Ultrastructural images were obtained using FIB/SEM, which removes 20 nm-thick layers of material and images the exposed surface. This procedure is continuously repeated, leading to fully reconstruct of a given volume [4]. The volume obtained by the FIB/SEM was analyzed using EspINA software [5]. Each synapse was identified individually and classified as asymmetric (AS; excitatory) or symmetric (SS; inhibitory) based on its post-synaptic density [6]. Since EspINA reconstructs semi-automatically the synapses in 3D, morphologic categories (macular, perforated, horseshoe or fragmented) can be done attending to its shape [7]. EspINA also provides in each synapse the area of synaptic apposition surface (SAS) [8] and the position of its centroids [9], which allows to analyze the synaptic size and its spatial 3D distribution, respectively.

Results and discussion

Preliminary results based on 11158 μm³ examined tissue sample and 5356 synapses showed a mean synaptic density of 0.649 synapses/μm³ (Figure 1), most synapses were AS (93.51%) versus SS (6.49%; Figure 2), which concur with human related literature.

The macular morphologic category was the most frequent (87.10%) following by perforated (9.26%), horseshoe (2.88%) and fragmented (0.77%) categories, being the macular shape-synapses smaller than perforated, horseshoe and fragmented synapses (Figure 3), which concur with current hypothesis.

Furthermore, the spatial distribution study of synapses showed its 3D distribution correspond to random pattern, which could be an intrinsic characteristic of cortical circuit’s organization.
Bibliography

Figure 1: Synaptic density. Each point represent synaptic density in a single stack of images. The colors represents the stacks of images obtained from the same case.

Figure 2: Synaptic proportion. Mean proportion of AS (excitatory, green) and SS (inhibitory, red) synapses in stacks of images grouped by cases.

Figure 3: Shape and size of synapses. A. Morphologic categories of synaptic reconstructions: macular (blue), perforated (orange), horseshoe (pink) and fragmented (green). B. Frequency of each morphologic category in AS and SS synapses. The legend shows the mean synaptic apposition surface in each category.
Uncovering the neural circuits of learning motivation in intellectually gifted individuals
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[Introduction/Motivation] A century of research demonstrated that high general cognitive ability \((g)\) is related to a broad set of positive social correlates, including greater educational achievements, more efficient job performance, better mental and physical health, or longevity [1]. Because of their relevance for the entire society, intellectually gifted individuals can be seen as potential “outstanding creators of modern culture” [2]. Hence, children with high abilities are potential high achievers. However, they might fail to realize their potential because of various obstacles, including unchallenging curriculum, one of the major factors causing underachievement in gifted students and a great loss for our society. Why gifted children are so eager to learn and question the world? What drives their insatiable curiosity that can lead to outstanding achievement and innovation, well beyond average?

Despite the relevance of these questions, the neurological study of intellectual giftedness – i.e. understanding the neural architecture and processes that support such a level of performance – has received very limited attention. Most neuroimaging studies on high intelligence focused on specific cognitive abilities, such as mathematical or memory abilities, usually with small samples [3]. Furthermore, almost no research has studied the relationship between the neural bases of intellectual giftedness and the neural circuit of motivation. This review will also provide new knowledge to help answering an exciting question from Ericsson and Pool: “Is deliberate practice producing changes in the brain structures that regulate motivation and enjoyment?” (p.192) [4].

As highlighted by Haier [5] “the ultimate purpose of intelligence research is to enhance general cognitive ability”. In this perspective, understanding how very efficient brains work and how motivational brain circuits influence and shape learning can bring critical insights on how to foster learning motivation for every child, considering the new challenges and opportunities in modern education.

[Methods] In order to help uncovering the neural processes underlying high cognitive ability \((g)\) and its relation to motivation, the first step of this research project is writing a review about this surprisingly unexplored topic. The main eligibility criteria for the articles selection process are: papers written in English or in French, from any country, published between 2000 and 2019 in peer-reviewed journals. The review article follows the 27-item checklist and the four-phase flow diagram proposed by the PRISMA statement for reporting systematic reviews [6].

[Results and Discussion] The proposed abstract aims at presenting the results of this review (currently under examination) and proposing practical applications to support academic achievement by designing educational interventions that specifically target the motivational brain circuit. This theoretical work is the first step of an possible postdoctoral research project that has wide interdisciplinary applications (from neurology, psychology to education and brain sciences) in a modern world with new challenges. As mentioned by the Center for Research and Interdisciplinary about the Open Science of Learning: “The need for a revolution in learning is clear. Many of our greatest current opportunities and pressing social challenges were unheard of a few decades ago — but our education systems have changed little”.¹

¹ https://research.cri-paris.org/
References:
Mesoscopic spiking neuronal network model capturing the remote activation of "epilepsy" focus

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Introduction: Spontaneous focal synchronization of collective spiking followed by induced traveling waves can occur in the cortical sheet and in cultured planar neuronal networks. In the first case, it is focal epilepsy leading to a seizure and, in the second, it is synchronization that originates from one of a few steady nucleation sites resulting in a so-called population spike. Assuming functional similarity between the nucleation sites and non-lesional epileptic foci, the major unsolved issue in both cases is that whether activation of the focus occurs inside it (i.e., autonomously relative to the interaction with surrounding neuronal tissue) or from the outside. The "internal" scenario implies that the focus spatially contains some pacemakers. In turn, several experimental findings indicate a complex spatially non-local activation of epileptic focus [1-7]. In modeling studies, we address the issue in order to verify the validity of this conclusion.

Methods: We use generative mechanistic model of planar neuronal network exhibiting irregular spontaneous population spikes, which emerge from a few spontaneously-formed stationary nucleation sites. The model consists of leaky integrate-and-fire neurons connected by synapses with short-term plasticity, forming spatially-dependent "small-world" network topology, where synaptic connection probability decreases exponentially with the distance between neurons. Spiking activity in the network occurs due to some fraction of pacemaker neurons. Importantly, the spatial configuration of pacemaker neurons was artificially engineered in order to resolve the above-mentioned problem: all pacemakers were placed within a circular central spot so that their spatial density was equal to the average density of neurons. Leaving the global dynamic regime unaffected, this spatial configuration crucially helps to clarify the activation process, visualizing of which is hindered at spatially-uniform pacemaker distribution.

Results and Discussion: Extensive simulations [8] have shown that steady and spontaneous nucleation sites of population spikes (i) can emerge in spatial regions, which are far away from the spot with pacemakers (see Fig. 1) and (ii) can be activated even without direct links from pacemakers. The results demonstrate the principle possibility of external, or remote, activation of a focal source of epileptic activity in the brain and favor the interpretation in above-mentioned experimental findings. The suggested deterministic model provides the means to study this network phenomenon systemically and reproducibly.

References:
Figure 1: Simulation of spiking activity of the neuronal network consisting of 50 thousand LIF-neurons (80% excitatory, 20% inhibitory) statistically uniformly distributed over the square L×L. Synaptic connections have been formed with probability $p_{\text{conn}}$ that decreases exponentially with increasing distance $r$ between neurons, $p_{\text{conn}}(r, \lambda) = \exp(-r/\lambda)$. At $\lambda = 0.01L$ this gives 32 ± 6 (mean ± SD) outgoing connections per neuron. All pacemaker neurons (3.4% of the total number of neurons) are exclusively localized in the central circular region of radius $R = 0.1L$. The value of $R$ is chosen such that the average density of pacemakers inside the region is the same as the average density of neurons throughout the square. **TOP**: Network spiking activity, averaged over 2 ms and normalized to the total number of neurons, during 10 seconds of the simulation. **BOTTOM**: The network activity and exact raster of active neurons (left), and six frames of the corresponding spatial dynamics (right) for the population spike marked by the arrow in the top graph. On the frames, blue dots depict inactive neurons and red dots highlight active neurons. Each frame corresponds to the whole area $L\times L$. The round area containing pacemakers is highlighted by the grey circle. There are no pacemakers outside this circle. Finally, on the first three frames (A, B, C) the outgoing connections of active neurons are shown by green lines. It is seen that the nucleation site of the population spike occurs at sufficiently large distance from the circular spot with pacemakers.
Workflow for subcellular neuronal modeling

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Introduction/Motivation:

One of the main goals in systems biology is building mathematical models that describe various biological processes. In neuronal signaling, a variety of genetic, biochemical, structural and electrical models from molecular dynamics to large networks exist and are stored in various formats, many of which, however, are often not human readable. Moreover, the modeling process is frequently idiosyncratic complicating collaborations and shareability. This poses a need for standardization in model and data formatting and processing. Therefore, we have developed a workflow for building biochemical pathway models using pre-existing tools that could be utilized for the storage and refinement of models in all phases of development, ensuring interchangeability with other formats and toolkits at every step in the pipeline.

Methods:

We have chosen the SBtab format [1] which allows the storage of biochemical models and associated data in a single file and provides a human readable set of syntax rules and conventions to structure data in a tabulated form making it easy to share and convert to various other model formats, such as SBML. Next, we implement custom-made MATLAB® scripts that convert the model into Simbiology, a MATLAB® application, and the data into a MAT file, and can utilize various MATLAB® tools, such as optimization, sensitivity analysis and profile likelihood, that can be used for model refinement. Finally, the model can then be converted back into SBtab or SBML which can then be read by various software tools (Figure 1).

Results/Discussion:

As a test case, we have chosen a previously developed pathway model of the emergence of temporal constraints in the integration of Calcium and Dopamine signaling in striatal medium spiny neurons [2]. Following our workflow, we replaced the rate equation of CaMKII autophosphorylation with a set of reactions and performed an optimization
for the parameterization of the replaced module using simulated data from the original model. As such, the model will be used in simulators that only allow bimolecular reactions, such as STEPS, and after conversion into a MOD file will be implemented in single cell electrical models and neuronal microcircuits in NEURON.

Figure 1. Simplified scheme of the workflow. Black arrows indicate steps for which we have developed automated tools. Black text refers to existing software and data formats.

References:


Ultrastructural analysis of postsynaptic elements from thalamocortical axons to somatosensory cortex

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Introduction:
Thalamocortical synapses onto cortical cells are key cellular links in sensory information processing. In rodents, thalamocortical synapses from the ventral posteromedia thalamic nucleus (VPM) drive layer 4 cells of the vibrissal primary somatosensory cortex (S1) with high efficacy and temporal acuity [1]. These functional features correlate with structural traits such as large and complex active zones, large vesicle pools and large mitochondrial volumes near synapses [2]. Elevated efficacy may also result from high spatial or temporal convergence [3]. Here we set out to investigate whether other synapses on the postsynaptic dendrite region contacted by an identified VPM bouton have a similar morphology (and hence a possible thalamic origin) or the VPM synapses are unusual [2]. To this end, we measured and compared the morphology of all synapses in the elements postsynaptic to identified VPM axon synapses.

Methods:
C57/BL6 mice received iontophoretic biotinylated dextran amine (BDA) microinjections in VPM to selectively label thalamocortical axon arborizations in S1 layer 4. Following a 5 day survival, mice were perfused, and their brains sectioned (50µm) on a vibratome into two parallel series of coronal sections. BDA-labeled VPM axon arborizations were localized on a series of sections. Adjacent sections were stained for BDA without Triton, and included and stained for electron microscopy. Serial volumetric image samples of layer 4 of the barrel cortex were obtained with a FIB/SEM electron microscope [4]. We obtained 8 stacks of images, with a resolution of 5 nm in the xy plane, and 25 nm in z, the number of images per stack varied between 149 and 303 images. Using EspINA software identified labeled axons were and 3D reconstructed, and structures postsynaptic to them were fully reconstructed and measured [5].

Results and Discussion:
Our results are consistent with previous evidence that VPM axon synapses are mostly located (>90%) on spiny cell dendrites, and very few on smooth, spineless dendrites (putative interneurons) [6]. The results show that spiny dendrite segment regions targeted by VPM synapses receive numerous synaptic contacts but in any case as large and complex as those of VPM axons, both in dendritic spine head volume and PSD area terms. These results are also consistent with previous studies determining a larger size for thalamocortical synapses [6,7] and seems to indicate that connections in spiny dendrite segment regions targeted by VPM are not of thalamic origin which raises questions about connectivity patterns inside rodent primary somatosensory cortex.
Figure 1: 3D FIB/SEM reconstruction of labeled thalamocortical axons segments (blue) and the associated post-synaptic dendrites (yellow) on a 3-axis projection of the neuropil.

References:


Practical use cases exploiting the ACP framework for the SpiNNaker neuromorphic platform

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[Introduction/Motivation:] In this work we propose practical examples (use-cases) designed to highlight the enhanced features offered by our software component called Application Command Protocol (ACP) [1], designed to optimise data exchange and memory management of the SpiNNaker board. We designed the proposed examples to show the benefit in both the application domains for which SpiNNaker is used: simulations of biological neural networks and innovative brain-inspired computational paradigms.

[Methods:] The Application Command Protocol (ACP) provides a mechanism to remotely trigger the execution of high-level instructions by the cores and manage their application memory, while supporting a more flexible computational model and memory management. ACP is implemented in two libraries, Spynnaker-ACP (Python) and SpinACP (C).

In the first use-case, a Synfire Chain simulation [2], we embedded some of the ACP components in the implementation of the neuron model to allow reconfiguration of operating parameters of synapses during the simulation. We use the memory entities provided by ACP to manage a set of modifiers of the model parameters and modify the delay of synapses in real-time while the simulation is running (Fig. 1).

In the second application, we used ACP to manage the transfer of data from host to board in the execution of a matching algorithm for DNA sequences based on the Message Passing Interface (MPI) standard. The whole transfer can be performed in a simple and transparent way, without the requirement for the user to know the position and structure of the memory being written.

[Results:] We added ACP to a neuron model used during the SNN Simulation phase of the Synfire Chain. The implementation is lightweight and can be easily embedded into the neuron model applications, allowing the user to change operational parameters at run-time. This case study demonstrates that ACP framework can be used for effective host-controlled SNN parameters exploration.

In the second use case, ACP Memory Entities provide an efficient framework to enable data transfer and communication between host and board during the execution of a general-purpose algorithm on the SpiNNaker board, opening up more possibilities in the field of massively parallelised computing.

ACP enables users to better exploit many-core neuromorphic platforms, without requiring specific knowledge of hardware details. Moreover, it allows users to implement new features that are not yet supported by the standard software stack. ACP’s high-level abstraction of the processors’ memory allows users to access it easily and freely even at execution time, facilitating the implementation of complex applications such as multicompartmental neural models.
Fig. 1: ACP reconfiguration of neuronal parameters. Above: the test configuration and the benchmark network used. Below: the graph of the spikes emitted by the neurons (blue), mean network activity (red). The series of spikes changes slope after receiving the synaptic delays reconfiguration commands at 10 ms, 1 ms and 7 ms.

Fig. 2: DNA Matching Algorithm with MPI and ACP. Above: a visualization of the Boyer-Moore search procedure. Right: Flowchart of the implementation on a general purpose architecture and on SpiNNaker. Step A performs the configuration, step B executes the matching; step P is the ACP-powered preliminary phase transferring data to the SpiNNaker board.

References:
Role of Bilingualism on Executive Functioning and Grammatical Comprehension in Older Adults

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[Introduction/Motivation:]
Bilingualism has been frequently proposed as a factor contributing to the enhancement of Executive Functions (EEFF) and inhibitory control, as well as a protective factor against cognitive decline associated with aging, but research related to the topic shows apparently contradictory results[1,2]. Some critics of the bilingual advantage theory have proposed confounding variables as the truly cause of the observed differences; nevertheless, even when the effect of these variables is controlled, the results obtained remain unclear[3].

The present study evaluates the effect of sequentially acquired bilingualism on several tasks designed to assess EEFF, as well as Grammatical Comprehension (GC), statistically controlling the effect of possible confounding sociodemographic variables. In contrast to previous studies, which only address Inhibition but generalize the results to all EEFF, the current project aims to study the different components proposed by the EEFF model of Miyake et al (2012)[4].

[Methods:]
A sample composed by 95 healthy older Spanish adults (67 bilinguals, 28 monolinguals) completed several tasks designed to assess EEFF: “Trail Making Test” (TMT-A & TMT-B)[5] to measure Switching, “Digit Memory Test”[6] and “Letters Memory Task”[7] to measure Updating, and the “Stroop Test”[8] to measure Inhibition. Finally, the “Exploración Cognitiva de la Comprensión de Oraciones para mayores” (ECCO_Senior Test; English translation: Cognitive Assessment of Sentence Comprehension for seniors)[9] was used to measure GC.

[Results and Discussion:]
Significant differences in the time spans of the “TMT-B” and “TMT-B/TMT-A” ratio were found, as opposed to the “TMT-A”, which indicates a bilingual advantage in the Switching Ability. There were significant differences in both the “Digit Memory Test” and the “Letters Memory Task”, showing a bilingual advantage in the Updating Ability. However, no significant differences were found in the “Stroop Test”, measuring the Inhibition Ability. Regarding the “ECCO_Senior Test”, significant differences were found, specially in the interaction between simpler and more complex propositions.

These results seem to show a positive relationship between bilingualism and the EEFF specific components for Updating and Shifting, as well as with Grammatical Comprehension, but not for the Common EEFF component or the Inhibition Ability (Figure 1). These results could explain some of the apparently contradictory results found in the literature, where many of the studies only evaluate “pure” Inhibition tasks, without analyzing other EEFF.
Figure 1: Apparent differences found, following the Miyake et al. Model. No significant differences were found in Inhibition Ability, which only contributes to the Common EF; on the other hand, there were significant differences in Updating Ability and in Shifting Ability, contributing each of them to both, their specific component and the Common EF.

References:


Individual electromagnetic profiles for the prediction of cognitive decline in the early stages of dementia

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[Introduction:]
In recent studies, a conceptualisation of AD in three different stages (preclinical, prodromal and dementia) has emerged, suggesting that along the progressive neurological deterioration, cognition also deteriorates gradually\cite{1}. Some of these changes involve Executive Functions (EF), which have been observed to be affected in both, patients with MCI and AD\cite{3}. In an effort to identify and characterise biomarkers that allow for an early diagnosis and treatment or intervention, some authors suggest that the study of the early stages of the continuum, might aid in the early detection of a possible cognitive decline and subsequent dementia. In this sense, the study of functional connectivity through magnetoencephalography and diffusion weighted imaging have yielded interesting results\cite{2,4,5}.

[Objectives:]
The main purpose of this study is to determine which variables allow for the differentiation of those who will have a worse cognitive evolution.

[Methods:]
The sample consisted of 99 Spanish subjects (age 71.13 ± 4.59). Fourteen of them were diagnosed with MCI, the remaining 85 did not present any objective neuropsychological impairment and were further subdivided in two groups: 35 healthy controls and 50 with SCD. Participants were followed longitudinally and evaluated at two points in time, approximately 3 years apart.

All of them underwent a neuropsychological evaluation, a magnetoencephalography and a magnetic resonance. Functional connectivity, power spectrums of ROIs defined by a reduced version of the AAL and the alpha peak in the calcarine region, along with fractional anisotropy and mean diffusivity values, were used as predictors of the cognitive change experienced in a factor of EF, created through PCA. A predictive model was calculated using a stepwise general linear model.

[Results and discussion:]
The resulting model (Rsquared = 0.407, p < 0.01) included, as predictors of change in EF, variables such as the power of delta in frontal regions (\( \beta = -33.14 \)), the fractional anisotropy of the left uncinate fasciculus (\( \beta = 2.25 \)). While the betas are not interpretable, these regions and tract have been previously reported to play a role in executive functioning\cite{6,7,8}.
[References:]
Design Rule for Enabling Synaptic activity in Resistance Change Memories

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[Introduction:]

The increasing popularity of neuromorphic computing expedites the journey of new memory technology. Regardless of the recent advancement, a breakthrough of the present memory architecture is, however, highly required for designing an efficient neuromorphic computing system. To programme the currently available neuromorphic computing devices thousands of transistors and capacitors are used. This increases the overall power consumption and introduces an encumbrance for a large number of device integration. In this respect, resistive switching (RS) memories are showing great promise due to their simple two-terminal device architecture, self-programmed operations, and excellent device properties. Indeed, neuronal communications are facilitated via alteration of the synaptic strength, in particular, either by strengthening or by weakening the synaptic conductivity, called potentiation or depression. Such mechanism underlies the basis of learning, memory and forgetting of the brain. Emulating that behaviour (potentiation or depression) in self-programmed nanoscale RS memories and detailed understanding of their mechanistic transformations continues to exist as one of the central challenges of the present RS-based neuromorphic engineering.

[Methods:]

This work illustrated a connection between the two conventionally different class of RS memories, i.e., valence change memories and electrochemical metallization memories, and devised a new design rule for tuning the performance of the artificial synapse. Here, we showed that neuronal communications in the artificial synapse (RS memories) can be regulated by controlled incorporation of cationic dopant (Ni) in the host dielectric (anatase-TiO₂). For detail understanding of the conduction mechanism in the artificial synapse, high-angle annular dark-field (HAADF) imaging, X-ray absorption near-edge structure (XANES) measurements, X-ray photoelectron spectroscopy (XPS) and electrical characterizations were done and complemented by density functional theory (DFT)-based first-principles calculations.

[Results and Discussion:]

By precise engineering of cationic activity in the artificial synapse (AS), we achieved excellent device properties, ON/OFF ratio of 10³, data retention ability of up to 10⁴ cycles. In addition, a gradual change in synaptic strength is also realized. Such properties are proposing the suitability of the present AS for a high-quality storage device, as compared with the available literature. A detailed experimental and computational study was performed to understand the origin of such enhanced RS-characteristics. It revealed that two different Ni-active layers were present within the AS, named as Ni-rich and Ni-poor layers. Here, Ni-rich layer exhibited a strong electronic exchange with the host lattice and introduced trap states within the forbidden energy gap, whereas, Ni-poor layer served as the oxygen-reservoir. These collectively regulated the transport mechanism, especially the device conductance similar to GABAergic synaptic activity in the hippocampus.

Figure 1:(a) I-V characteristics (b) potentiation and depression curve of the artificial synapse (c) HAADF image (d) plot of electron localisation function (ELF).
References:


Characteristics of corticothalamic relays in mouse models of autism

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²University of Warsaw, College of Inter-Faculty Individual Studies in Mathematics and Natural Sciences, Krakowskie Przedmieście 26/28, 00-927 Warsaw, Poland
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Motivation:
Autism spectrum disorders (ASD) are characterised by handicapped ability to initiate and engage in social interaction, impairments in communication skills, pervasive repetitive behaviours and, last but not least, by disturbed sensory processing [1,2]. According to Markram and Markram [3], the core neuropathology is hyper-activity and hyper-plasticity across multiple regions of the brain leading to over-sensitivity. The Intense World theory of autism, similarly to much ASD research, is centred on the neocortex and the amygdala circuits. Little is known about the effect of ASD on the central station of sensory pathways – the thalamus – and their corresponding corticothalamic connections. In this pilot study, electrophysiological properties of neurons in the higher order somatosensory thalamus (posterior medial nucleus – PoM) were investigated in mouse models of ASD.

Methods:
Two mouse models of autism were used: BTBR T¹Ipr3⁰J (BTBR, 6 cells) and Fmr1 knockout (5 cells). C57BL/6J (C57, 13 cells) and Fmr1 heterozygous (7 cells) mice served as respective control groups. Using current-clamp whole-cell recordings in thalamocortical slices, we obtained electrophysiological characteristics of individual PoM neurons. Then, using another electrode located in the capsula interna, series of electrical impulses (5 impulses, 200 μs each, 100 μA – 600 μA, 20 Hz) were applied to stimulate descending cortical fibres. Excitatory postsynaptic currents (EPSCs) were recorded in voltage-clamp mode to characterize properties of corticothalamic synapses in the studied cells. Each cell was stimulated with the train of impulses from 5 to 8 times and the recordings were averaged to obtain a mean response of the cell.

Results and Discussion:
No significant differences were found in intrinsic excitability of the cells from different experimental groups. When postsynaptic responses were analysed, the corticothalamic EPSCs in BTBR strain were larger and displayed stronger frequency dependent facilitation than currents in the control C57 mice. The differences were statistically significant (two-way ANOVA mouse strain x current amplitude: F(4, 64) = 13.01, p < 0.0001; mouse strain x facilitation: F(4, 56) = 3.626, p < 0.05) and are presented in Figures 1 and 2. Similar but weak trend was observed between Fmr1 groups’ amplitudes. The experiment showed that excitability of corticothalamic pathways may be enhanced in autism, presumably contributing to overwhelming tactile sensations affecting individuals with ASD.
References:


Acknowledgment:

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Learning and Memory Phenotype, Monoamine Neurotransmission and Hippocampal Morphology of Subtype-Specific Rap1A GTPase Knockout Mice

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Introduction

Ras-related Rap GTPases are ubiquitously expressed [1]. Rap1 is encoded by two separate genes (Rap1A and Rap1B) that share 95% amino acid sequence identity, but are found to play differing cellular functions, indicative of their functional divergence [2, 3]. Rap1 signaling has been shown to participate in neuronal cell polarity [4, 5], differentiation [6, 7] and synaptic plasticity [8]. However, elucidation of Rap1A subtype-specific functioning, in terms of neurophysiological aspect remains largely elusive. This study aimed to decipher Rap1A’s role in cognitive functioning, monoaminergic neurotransmission in prefrontal cortex (PFC) and hippocampus (HC), and HC morphology.

Methods

The genetically engineered C57BL/6 mice were genotyped for Rap1A knockout (Rap1A\textsuperscript{KO}), heterozygous (Rap1A\textsuperscript{HET}) and wild-type (Rap1A\textsuperscript{WT}) identification, using PCR and gel electrophoresis [2]. Cognitive functioning was evaluated by administering novel object recognition test (NORT), and Morris water maze (MWM) test. The isolated PFC and HC were subjected to reversed-phase HPLC with an electrochemical detection method for quantification of basal monoamine neurotransmitter concentrations. Sagittal sections of the brain were H&E, and cresyl violet stained for hippocampal morphology analyses.

Results

Loss of Rap1A did not contribute to object recognition memory (short-term) alterations (discrimination index: $p > 0.05$) in Rap1A\textsuperscript{KO} mice versus other genotypes. However, genetic inactivation of Rap1A contributed to a spatial memory deficit as determined by reduced time spent in target quadrant by Rap1A\textsuperscript{KO} mice ($p < 0.01$) versus other genotypes, whereas Rap1A\textsuperscript{HET} group presented trend for elevated crossings in target quadrant ($p < 0.2$) compared to other genotypes in probe trial (MWM test). The 5-hydroxyindoleacetic acid concentration was elevated in PFC of Rap1A\textsuperscript{HET} mice compared to Rap1A\textsuperscript{WT} mice. Analyses of HC exhibited increased hippocampal area ($p < 0.001$) for Rap1A\textsuperscript{HET} mice versus other genotypes, with other changes in organization of HC between genotypes. Moreover, dispersed pyramidal cell layer was observed in hippocampal CA3 sub-region, for Rap1A\textsuperscript{KO} mice versus other groups.

Discussion

This study suggests a potential role for endogenous Rap1A signaling in the regulation of spatial memory, serotonergic neurotransmission in PFC, and architecture of HC. Future studies directed at exploring molecular events downstream of Rap1A may help identify therapeutic targets against associated neurological disorders.
References:


Spatial Navigation in the Neurorobotics Platform by using a Sensor-equipped Mobile Robot

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[Introduction:]
The Neuorobotics Platform (NRP) is a simulation infrastructure that aims to bridge the gap between neuroscience and robotics by providing biologically realistic brain models to virtually embodied agents (e.g., mobile robots). Nevertheless, it can also be useful to run experiments by employing machine learning algorithms, taking advantage of the capabilities of the NRP and using realistic sensors [1] [2]. To perform a navigation task, we designed an experiment via a deep reinforcement learning algorithm -- i.e., Deep Q Learning (DQN) with experience replay [3]. The robot used for the simulation is the Husky mobile robot (illustrated in figure 1 left) -- i.e., an unmanned ground vehicle (UGV) with four wheels. The Husky robot starts at the center of the world, which is a simple grid of 16x16 meters (depicted in figure 1 right). The actions are composed of three motion primitives: move forward, turn left and move, turn right and move.

[Methods:]
In this work, we performed an extended simulation with respect to our recent work [4], with the same network architecture proposed with the addition of experience replay mechanism. The network is comprised of three hidden layers with 128 units with a Rectified Linear Unit (ReLU) as an activation function and used the RMSprop algorithm to minimize the Root Mean Square Error (RMS). The input of the network is the robot position and orientation, combined with the laser and camera data. The reward positions are located at the corners of the map: the robot receives a reward of 10 if it reaches one of these locations, a reward of −2 if it bounces against an obstacle, or 0 otherwise. The Husky robot is trained for 800 episodes, each one consisting of 36 steps. In order to implement experience replay, at each step the network is fed with a sample batch of size 12.

[Results:]
We analyzed the performances of the model with three metrics: the first one depicts the number of episodes in which the robot reached one of the reward locations, the second one represents the cumulative reward obtained by the robot, while the third one is the total number of steps needed by the mobile robot to reach the goal -- that is, the episodes which the robot found one of the rewards. To observe the trends in score curves, we computed a running average with a window size of 160. It can be seen, from figure 2, that as the score values increase, the number of steps required to reach a reward location decreases. Overall, the results obtained from this experiment indicate that the mobile robot learns to navigate the environment by using the DQN method in the NRP.
Figure 1: Husky-mobile robot (left) and experiment environment (right).

Figure 2: Metric scores. From top to bottom: number of successful episodes, cumulative reward, number of steps.

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This research has received funding from the European Union’s Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 785907 (Human Brain Project SGA2).

References:
Decoding Saccadic Eye Movement Directions from ECoG data

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[Introduction/Motivation:]
Saccades are fast ballistic movements of the eyes that are performed in order to bring relevant objects onto the fovea. Although they are ubiquitous in natural viewing conditions, the caused rapid changes of visual inputs are hardly consciously perceived. This stability in visual perception is assumed to be achieved by a mechanism that suppresses the visual input during saccade execution, the so called saccadic suppression. There is experimental evidence that saccadic suppression takes place in early visual areas, manifested as a suppression of high-gamma activity around saccades onset [1]. However, it remains unclear if different directions of these saccadic eye movements cause varied brain responses that can be succesfully decoded from intracranial recordings in early visual areas.

Thus, in the current study we have used both classic machine learning methods and deep learning approach to shed light on this question. Since saccadic suppression effects begin to take place already before the start of a saccade [2], we were especially interested if the different saccade directions can be succesfully decoded even before saccade onset. Insights in this direction could be crucial for future applications where an imminent saccade is to be predicted, e.g., modern retina implants with artificially controlled eye balls.

[Methods:]
We used dataset consisting of spontaneously performed saccades that occurred in non-experimental viewing conditions during the hospital stay of four epilepsy patients that had intracranially implanted electrodes in early visual areas. Individual electrode contacts were assigned to cytoarchitectonically defined brain areas using the open-source toolbox ELAS [3]. The number of electrode contacts, electrode placement and the number of saccade events varies between patients. A total of 7785 saccade events were analysed in the 4 patients investigated. Saccade events were labelled manually by using simultaneously recorded digital video and the corresponding EOG signal. Eight different classes of saccade events were analysed, corresponding to eight direction of saccades (right, left, up, down, left-up, left-down, right-up, right-down).

For the decoding a time window from 250 ms before to 50 ms after onset was used, which corresponds to approx. 300ms to 0ms before onset when taking processing latency of striate cortex into account.

We have used both, feature based decoding, e.g., wavelet powers in relevant frequency bands and an end-to-end approach, in which the raw data was only downsampled and low-pass filtered. We evaluated both classical machine learning methods (rLDA, logistic regression, support vector machines, random forests) as well as deep learning approaches. For the deep learning approaches, we examined two convolutional neural networks architectures previously succesfully applied to EEG decoding and publicly available in braindecode toolbox: Convolutional Deep4Net and ShallowFBCSPNet [4].
For model evaluation we have performed a 5-fold cross-validation on the training set, which is 80% of the whole data. Decoding accuracies are calculated as average over CV folds for each patient, respectively. The final evaluation will be done on the 20% held back evaluation set.

**Results and Discussion:**

All decoding algorithms showed decoding accuracies significantly above chance level.

Further analyses will be performed, e.g., Riemann-geometry-based decoding, LSTMs, as well as automatic hyperparameter optimization for existing deep network architecture. Statistical testing with the aim to compare the performance of different models will be carried out.

Future directions will also include the prediction of the EOG signal based on the ECoG recordings using deep regression based on Deep4Net architecture.

**References:**


Executive functions in Fibromyalgia patients
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[Introduction/Motivation:]
Fibromyalgia (FM) is a rheumatologic syndrome characterized by chronic pain along with the presence of cognitive deficits, which significantly affect the daily life of patients (Wolfe et al., 2010). In this way, some authors have found alterations in working memory, inhibition and flexibility (de Guevara et al., 2018), while others didn’t find them (Cherry et al., 2012; Kim et al., 2012). Moreover, the increasing interest in these executive deficits is due to the fact that they can be the ones that are underlying to the alterations in other cognitive domains (Bell et al., 2018).

[Methods:]
For this purpose, 40 women with FM and a healthy women group matched by aged (CG = 48.8 (8.06); FM = 51.1 (10.1); t = -.128; p=.20) were included. Both groups were evaluated using the Digits and Cubes in regression (NEUROPSI Ostrosky et al., 2003), the Stroop test (Stroop, 1934), The Trail Making Test (TMT A and B; Reitan & Wolfson, 1985) and the Map Zoo test (Wilson et al., 1996). The statistical analyses were conducted using SPSS version 23.0 software. For the aim of the study, equal variance analyses were conducted using the Student t-test after analyzing the data normality.

[Results and Discussion:]
The differences in the Executive Processes between FM and the CG are presented in Table 1. The results of the present study indicate that, when the verbal information load is increased, FM patients had greater difficulties in the process of updating and maintenance, maybe due to a more interference and less ability to manipulate information in comparison with the control group. These difficulties can also be found in the inhibitory control task, where FM patients showed alterations in their capacity to suppress information and greater levels of interference. FM patients also showed a higher execution time in the flexibility task, but, these may be associated with processing speed problems. Moreover, this is one of the few studies that have measured the planification process, showing the results that FM patients had more difficulties to plan when they had to monitoring their actions and execute the correct path without an external guide. Finally, executive function impaired could be associated and potentiate alterations in other cognitive domains, so, future studies should address it and, apart from that, specific interventions should be designed for these patients to improve these executive alterations.

References:


Table 1. Differences in the Executive Processes between FM and Control Group

<table>
<thead>
<tr>
<th></th>
<th>GC n=36 M (SD)</th>
<th>FM n=40 M (SD)</th>
<th>t</th>
<th>p</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digits in regression</td>
<td>4.80 (1.16)</td>
<td>3.95 (0.91)</td>
<td>3.46</td>
<td>.00**</td>
<td>0.82</td>
</tr>
<tr>
<td>Cubes in regression</td>
<td>5.11 (1.16)</td>
<td>4.98 (1.04)</td>
<td>0.54</td>
<td>.59</td>
<td></td>
</tr>
<tr>
<td><strong>Inhibitory Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop word</td>
<td>115.11 (17.87)</td>
<td>100.03 (21.98)</td>
<td>3.26</td>
<td>.00**</td>
<td>0.75</td>
</tr>
<tr>
<td>Stroop colour</td>
<td>80.63 (13.68)</td>
<td>66.75 (15.33)</td>
<td>4.15</td>
<td>.00**</td>
<td>0.96</td>
</tr>
<tr>
<td>Stroop Effect</td>
<td>51.06 (11.15)</td>
<td>39.50 (9.20)</td>
<td>4.95</td>
<td>.00**</td>
<td>1.13</td>
</tr>
<tr>
<td>Interference index</td>
<td>3.78 (7.13)</td>
<td>-0.32 (7.75)</td>
<td>2.30</td>
<td>.02*</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Flexibility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TMT-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Execution time</td>
<td>41.67 (13.06)</td>
<td>61.77 (21.42)</td>
<td>-4.95</td>
<td>.00**</td>
<td>1.14</td>
</tr>
<tr>
<td>Correct responses</td>
<td>24.97 (0.16)</td>
<td>24.60 (1.66)</td>
<td>1.41</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>TMT-B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Execution time</td>
<td>58.06 (21.93)</td>
<td>92.38 (44.93)</td>
<td>-4.15</td>
<td>.00**</td>
<td>0.97</td>
</tr>
<tr>
<td>Correct responses</td>
<td>24.40 (1.72)</td>
<td>23.38 (3.40)</td>
<td>1.62</td>
<td>.11</td>
<td></td>
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<tr>
<td><strong>Planification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Zoo MAP</td>
<td></td>
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<tr>
<td>Part 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct score</td>
<td>3.50 (3.52)</td>
<td>0.83 (3.35)</td>
<td>3.38</td>
<td>.00**</td>
<td>0.78</td>
</tr>
<tr>
<td>Total errors</td>
<td>1.39 (1.95)</td>
<td>2.50 (2.39)</td>
<td>-2.21</td>
<td>.03*</td>
<td>0.51</td>
</tr>
<tr>
<td>Planification time</td>
<td>70.33 (54.75)</td>
<td>71.25 (81.58)</td>
<td>-0.06</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Execution time</td>
<td>87.19 (58.45)</td>
<td>138.43 (89.77)</td>
<td>-2.91</td>
<td>.01*</td>
<td>0.68</td>
</tr>
<tr>
<td>Part 2</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>Direct score</td>
<td>7.31 (1.43)</td>
<td>6.40 (2.78)</td>
<td>1.75</td>
<td>.08</td>
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<tr>
<td>Total errors</td>
<td>0.25 (0.55)</td>
<td>0.50 (1.09)</td>
<td>-1.24</td>
<td>.22</td>
<td></td>
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<tr>
<td>Planification time</td>
<td>11.00 (18.34)</td>
<td>15.58 (28.93)</td>
<td>-0.81</td>
<td>.42</td>
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<tr>
<td>Execution time</td>
<td>66.47 (33.29)</td>
<td>76.93 (33.19)</td>
<td>-1.36</td>
<td>.18</td>
<td></td>
</tr>
</tbody>
</table>

CG= Healthy Group; FM = Fibromyaliga Group; **p<.01; *p<.05; d= Effect size.

d≥ .80 = big effect; d≥ .50 = medium effect; d≥ .20 = small effect.
Mechanisms for Cannabinoid Receptor I and Myosin II in regulation of growth cone filopodia and optic axonal pathfinding in the optic tract

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[Introduction/Motivation:]
Recent studies show that the main cannabinoid receptor in the brain - CB1R- functions to modulate axon pathfinding and targeting in diverse neuronal circuits. However, questions remain about the cell biological mechanisms of CB1R in formation of axonal connections, especially in neurons developing in their native environment. Here, we studied how CB1R and the actin regulator non-muscle Myosin II, influence growth cone filopodia and optic axon pathfinding in the optic tract in whole brains from Xenopus tadpoles.

[Methods:]
Embryos and tadpoles containing small numbers of GFP optic axons were bathed in pharmacological inhibitors specific for CB1R (AM251) or Myosin II (Blebbistatin) during developmental stages when optic axons normally navigate through the optic tract. The tadpoles were then fixed and their brains were dissected, and the individual GFP optic axons were imaged in the optic tract of the whole brains.

[Results and Discussion:]
Analysis of these images showed that optic axons exposed to AM251 and Blebbistatin both formed growth cones that contained increased numbers of filopodial protrusions. However, in addition, application of CB1R inhibitor AM251 resulted in extremely aberrant navigation of optic axons in the tract, whereas the Myosin II inhibitor Blebbistatin inhibited the extension of optic axons through the optic tract in situ. These results suggest that CB1R and Myosin II similarly modulate growth cone filopodia but exert different effects on optic axonal pathfinding in the optic tract. More broadly, our findings imply that optic axonal growth cones may contain subtypes of filopodia that are differentially associated with distinct axon pathfinding events such as navigation and outgrowth.

References:
Reacting to emotional sounds entering peripersonal space

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[Introduction/Motivation:]

Precision in locating a moving sound source depends strongly on sound direction: we overestimate the position when sounds are reaching us [1] while the opposite happens when sounds are leaving us [2]. This bias in distance perception in the near-space suggests the presence of a higher state of alert for stimuli close to the body [3] which mediates interactions between the body and the environment [4]. Several neurophysiological and neuroimaging studies indicated the presence of audio-visual and tactile spatial maps in the brain, suggesting a bold relationship between near stimuli and actions [3]. It is shown that stimuli (visual or auditory) reaching the body boosts the sensory information processing, enhances the activity of the motor representation and modulates neural activity within the motor system [3, 5]. It is worth to notice that natural stimuli usually convey meanings by inducing emotions that evolved to prepare individuals to emotional sounds that reach their Peripersonal Space (PPS). We compared Normal Hearing (NH) individuals with Cochlear Implanted (CI) individuals since the cochlear implant presents reduced availability to acquire relevant physical properties of the sound [8] affecting the localization and the appreciation of the emotional content [9] of the sounds.

[Methods:]

A total number of 20 NH and 10 CI individuals were asked to react to sounds carrying different emotional contents (Applause: Positive, P; CarWreck: Negative, Ne; PinkNoise: Neutral, Nu) virtually ending at five different distances from their body. Pre-motor Reaction Times (PRTs), Motor Reaction Times (MRTs), and Reaction Times (RTs) were detected via EMG from postural muscles and acceleration recorded by accelerometers attached to the wrists of individuals while they react with fast arms flexion to the sound offset. Then, while listening again to the same sounds, participants were asked to locate where the sounds stopped and to rate the sounds’ level of valence and arousal by means of the Self Assesment Manikins (SAM).

[Results and Discussion:]

NH modulated their PRTs based on the sounds distance: the closer the sound the faster the reaction; which is in line with previous studies showing higher activity of the motor system for near stimuli [3, 5](Fig.1). MRTs in NH were not changing as a function of distance, showing that the adapted strategy was mainly based on anticipatory mechanisms. CI individuals did not modulate PRT and MRT across the different distances. Both groups presented shorter PRT to Nu as compared to P and N sounds (Fig.1) probably due to the less decoding required for Nu sounds. Sounds’ valences were correctly categorized by both groups: P more positive than N and Nu in between P and N. Both NH and CI individuals showed the ability to locate the different sound sources distances. CI individuals were probably relying on the temporal sounds components due to the high temporal resolution provided by the implants [10]. Critically, results revealed that while NH individuals changed their arousal level as a function of the sound distance, CI individuals did not (Fig.1). Acting with sounds, require the capacity to perceive different aspects of sounds emphasizing the necessity of specific auditory information.
Fig. 1 Data of PRT (left column), Bnorm (Middle column), which is the estimated distance normalized to the max and min range defined by each individual, and Arousal rating (right column) for both NH (top) and CI (bottom) individuals. Asterix shows a significant difference by p < 0.05

[References:]
3D stem cell models to study the effect of TREM2 on the hallmarks of AD

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[Introduction/Motivation:]
Alzheimer’s disease (AD), the most frequent cause of dementia is characterized by amyloid plaques, neurofibrillary tangles, and neuroinflammation, causing death of neurons. AD is a heritable disease due to mutations in APP and PS1, but the cause in >90% of patients is unknown. A number of gene abnormalities are known to increase the risk, such as TREM2, a receptor found on microglia and monocytes. Microglia are brain resident immune cells and control brain homeostasis and inflammation. The TREM2-R47H substitution increases the risk for AD 4-fold. Patients with complete loss of TREM2 develop plaques, tangles and dementia by the age of 30.

[Methods:]
Via the integration of three different kind of brain cells (Neurons, microglia, and astrocytes), differentiated from PSCs, into a 3D semi-synthetic engineered gel, a model can made to mimic the brain in vitro. By integrating mutant cells into the system, AD pathology can be studied.

[Results and Discussion:]
A differentiation towards microglia-like cells has been optimized and is equally efficient for WT, TREM2-R47H and TREM2-KO stem cell lines. Microglia-like cells have been characterized in vitro. RNAseq showed similarity between the differentiated microglia-like cells and human cultured fetal and adult microglia. A defect of phagocytosis in TREM2 deficient microglia-like cells was observed.
A differentiation towards cortical neurons is well established and can be done for WT PSCs or iPSCs derived from a patient with familial AD. Markers of different cortical layers are expressed over time. Spontaneous electrical activity can be measured from DIV50 onwards.
Astrocytes can be differentiated via the overexpression of SOX9 which has been integrated under an inducible promotor in the aavs1 locus. Expression on both gene and protein level of astrocytic markers can be detected. Stopping the expression of the SOX9-cassette does not result in loss of the astrocyte signature.
A 3D culture system is developed via the integration of brain-specific peptides and biodegradable crosslinkers in a PEG-gel to mimic the brain environment. Eventually, neurons (derived from WT or a familial AD iPSC line), microglia-like cells (either WT or mutant), and astrocytes can be seeded in the 3D environment to assess the formation of plaques, tangles and neuroinflammation.
Short-term hypoxia differentially affects excitatory and inhibitory retinocollicular synaptic transmission

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[Introduction/Motivation:]
Hypoxia is one of the main causes of the optic nerve disorders that lead to gradual and irreversible disruption of the visual signal transmission from the retina to the visual centers of the brain. Retinocollicular projections represent the first part of the secondary visual pathway from retina to the visual cortex. The lesions of this pathway lead to navigation, orientation, and visual attention deficits and could also be involved in several neurological and psychiatric disorders such as dyslexia and autism. Structural and functional responses to hypoxic injury in retinocollicular projections were demonstrated using functional magnetic resonance imaging [1], [2]. Whereas, hypoxia-induced effects on this synaptic transmission were not previously investigated.

[Methods:]
Using the paired patch-clamp technique, we studied the effects of short-term hypoxia on retinocollicular synaptic transmission. Originally designed coculture of dissociated retinal cells and superficial superior colliculus (SSC) neurons was used as in vitro model of the visual retinocollicular pathway (Fig. 1. C). In coculture individual synaptic couples of retinal ganglion cell (RGC) – SSC neuron were easily identified due to their spatial location, morphological and electrophysiological characteristics. Each synaptic couple reflected a single fiber of the retinocollicular pathway. Pharmacologically isolated NMDA−, AMPA− and GABA− mediated postsynaptic currents (PSCs) were evoked in SSC neurons by generation action potentials in presynaptic retinal ganglion cells. Spontaneous and miniature PSCs were recorded in SSC neurons in the absence of presynaptic stimulation. Method of fast local superfusion was used for application (up to 5 min) of hypoxic solutions on synaptically connected neurons.

[Results and Discussion:]
Short-term hypoxia induces long-term potentiation of NMDA transmission (Fig. 1. A), long-term depression of GABAergic neurotransmission (Fig. 1. B) and temporary suppression of AMPA transmission. Also, we observed a hypoxia-induced reduction of voltage-dependent magnesium blockade of evoked NMDA response. All postsynaptic currents were analyzed in terms of a binomial model. This analysis revealed that hypoxia acts mainly presynaptically on excitatory neurotransmission and both pre– and postsynaptically on inhibitory retinocollicular transmission. The physiological role of GABAergic retinocollicular projections is thought to be in regulation of activation and plasticity of excitatory NMDAR-mediated transmission [3]. Hypoxia-induced LTD of GABAergic transmission enhances the pathological effect of LTP of NMDAR-mediated transmission in retinocollicular synapses and possibly is an additional hypoxia-induced injury of neurotransmission from the retina to subcortical visual center. Thus, we showed for the first time hypoxia-induced bidirectional long-term plasticity of the retinocollicular synaptic transmission. The results obtained reflect the electrophysiological basis and may serve to reveal new approaches for pharmacological and therapeutic interventions for hypoxia-involved pathological lesion of the retinocollicular pathway.
Figure 1: Hypoxia-induced long-term potentiation of NMDA and long-term depression of GABA_A retinocollicular synaptic transmission. (A, B) The dynamics of NMDA and GABA_A evoked postsynaptic currents (PSCs) amplitudes (normalized) recorded during control, hypoxia (red) and reoxygenation, respectively. Representative recordings of evoked PSCs are plotted against corresponding period (control, hypoxia and reoxygenation). (C) Reconstructed microphotography of synaptic couple of presynaptic retinal ganglion cell (RGC) and postsynaptic SSC neuron in coculture during paired patch-clamp recording at 29-th day in vitro; the scale marker corresponds to 100 μm.

Acknowledgments:
We thank Oleg Rikhalsky (Bogomoletz Institute of Physiology, National Academy of Sciences of Ukraine, Department of Neuronal Networks Physiology, 4 Bogomoletz street Kyiv 01024, Ukraine) for technical support and Dr. Vitaly Maslov (Bogomoletz Institute of Physiology, National Academy of Sciences of Ukraine, Department of Neuronal Networks Physiology, 4 Bogomoletz street Kyiv 01024, Ukraine) for helpful comments on our manuscript.

References:
Effect of APOE4 genotype and Alzheimer’s-related cerebrospinal fluid markers on cognitive decline in non-demented elderly

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Background:
Alzheimer’s disease (AD) affects millions worldwide, primarily in the elderly population. To date, virtually all drug therapies have failed to effectively treat AD (1). Subjects carrying the APOE4 gene are known to be at up to 12-times increased risk for AD (2). The underlying pathological changes in the form of β-amyloid plaques (Ab) and tau tangles are detectable two decades before symptoms of memory decline arise and can be measured in cerebrospinal fluid (CSF) (3–7). Early detection of AD in cognitively normal elderly would open a window of opportunity for treatment and preventative measures. This study aims to determine whether APOE4 genotype and AD-related pathological load in the form of CSF-derived Ab and tau can be used for prediction of mnemonic discrimination performance in non-demented elderly.

Methods:
A total of 37 non-demented, healthy elderly were tested for APOE4 genotype. A subset of 16 female subjects underwent lumbar punctures to acquire CSF measures for Ab38, Ab40 and Ab42. Eight subjects were additionally tested for total tau levels, and 11 subjects underwent hyperphosphorylated tau measures. Cognition was measured through a behavioural mnemonic discrimination task for object, spatial and temporal domains.

Results:
Age had no effect on CSF Ab and tau measures. APOE4 genotype, CSF Ab42 and p-tau status did not affect all three mnemonic discrimination domains. In a subset of females, performance on the object discrimination task decreased with age and increased with continuous CSF Ab38 levels.

Conclusion:
Neither APOE4 genotype nor CSF Ab and tau levels could explain differences in mnemonic discrimination ability, likely due to complex underlying interactions among several factors other than genetic risk or pathological load present in preclinical AD. Effects on object discrimination are likely caused by selective disruption of the perirhinal cortex (PrC) - lateral entorhinal cortex (LEC) object processing pathway in earlier stages of pathological spread. In future, multivariate studies are needed to investigate changes of CSF longitudinally, which could potentially lead to the discovery of AD biomarkers.
Acknowledgements:
We thank Dr Soyun Kim and Dr Michael Yassa from the Yassa Translational Neurobiology Lab, University of California, Irvine for the great mentorship and assistance throughout the course of the project.

References:
Neurophysiological features of the brain functioning of veterans of the armed forces of Ukraine with traumatic brain injuries and post-traumatic stress disorders during testing of simple sensorimotor reaction

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Introduction:
Traumatic brain injures (TBI) in combatants in eastern Ukraine occupy the second place after bullet and fragment wounds of the body and extremities [1]. Most patients with TBI have no trauma-dependent abnormalities on computed tomography [2]. At the same time, manifestations of TBI, such as cognitive deficits, headaches, anxiety, depression, and more, overlap with symptoms that are characteristics of post-traumatic stress disorders (PTSD). PTSD occurs as a result of a traumatic event with a risk of serious physical injury or personal injury and at the same time a response to that event involves intense fear, horror, or helplessness [3].

Methods and materials:
The study involved a control group of 18 male volunteers, aged 18 to 21 with no health complaints, right-handed, 18 male volunteers, servicemembers with TBI, aged 20 to 51, right-handed and 10 male volunteers, servicemembers with PTSD, aged 20 to 51, right-handed. All subjects had electroencephalogram (EEG) recorded during a computer testing of simple sensorimotor reaction. The Neuro-Spectrum-4/EPM (NeuroSoft) complex was used for EEG registration and analysis. Analysis of the distant brain synchronization was performed using coherent analysis. In addition, the LORETA neuroimaging program [4] identified three-dimensional coordinates of the activity dipoles when performing a test task for all frequency ranges. Statistical analysis of the data was performed using STATISTICA 6.0 (StatSoft, USA).

Results:
Statistical analysis showed a significantly longer latency period in the group with TBI compared to the control group, but no difference was found between control group and the group with PTSD. In the control group during simple sensorimotor testing the reactions was involved brain processes of detection of targeted stimuli, mental representation, planning of motor response and its implementation. These processes were consistent with the basic processing of visual information based on the integration of dorsal and ventral visual streams and with the merging of the elements into the aggregate image. At the same time fronto-parietal-occipital neural networks, verbal decision making processes, executive control and coordination of behavior based on processing of current sensory information were involved. In the PTSD group we found a shift in brain activity to the zones in the occipital area that are responsible for the primary and secondary visual information processing, and a decrease in the number of interregional brain connections in the low-frequency bands that indicate more local information processing. In the TBI group we found decreased activity in the frontal cortex and increased activity in the parietal zone, especially in the left hemisphere and only local neural networks in the high-frequency range in the fronto-parietal areas were formed.

References:


An innovative Neurofeedback for children with ADHD using Virtual Reality

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Introduction
Attention deficit hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disease in childhood, it affects between 5 and 7 % of children and is characterized by hyperactivity and/or attention deficit. ADHD diagnosis and assessment can be based on questionnaires, neurophysiological tests or neurophysiological signals[1]. Three main treatments exist today: medication (Methylphenidate intake), behavioural treatments and neurofeedback. In the context of this work, the attention will focus on the third method: neurofeedback (NF). NF consists of a real-time representation of the brain activity (in an understandable form) to teach how to self-regulate specific functions. For instance, in the case of children suffering from ADHD neurofeedback aims to help the patient to detect the inattentive phases and to teach her how to inhibit them in the future (Figure 1).

Methods
The goal is to design a serious game embedded in a virtual reality (VR) environment to provide NF training. It has been proven that VR has a higher ecological validity for neurophysiological assessment [2]. Moreover, VR brings more freedom for the environment creation and control with greater safety. The signals considered for neurofeedback will be electroencephalogram signals (EEG) and gaze direction. Recent works addressing NF on these two signals (García-Baos [3] et al. with Recogneyes, for the eye-tracking and Bioulac et al.[4] with Mensia-koala, for EEG) have shown encouraging results on hyperactive children. In that sense, It could be interesting to consider EEG and eye-tracking in VR to identify possible improvements (comp. to a 2D environment). In brief, the goal is to detect the attention state from these signals and to use it to influence the VR environment parameters (e.g. lighting).

Another important aspect considered in this thesis is the use of Machine learning (ML), and especially deep learning, models for the signal classification between attentive vs. inattentive patterns. During the last decade, a lot of ML classifiers have been designed for the classification of EEG rhythms and/or temporal patterns as presented in Lotte et al. 2018 [5]. Tan et al. [6] performed a ML classification of EEG signals from children with ADHD through VR brain-computer interface but without feedback (i.e. dynamic environment modification).

Results and Discussion
The goal of this thesis is to design a novel neurofeedback method for ADHD children using ML models for signal classification and a VR environment for NF training. The next steps will be: 1) The first deliverable for June 2020: a prototype aiming to create the dataset through a serious game evolving in a VR environment promoting concentration and attention, but also allowing the measurements of several features (physiological signals and cognitive abilities). 2) Dataset creation and ML model development for June 2021: the creation of the dataset employing the first deliverable and development of a ML-based model for attention state classification. 3) The second deliverable for January 2022: a prototype including a feedback loop that will allow the patient to correct his symptoms by herself, by associating game reactivity with real-time physiological signals. Thanks to the multiple...
collaborations with different faculties (in particular neuroscience department), a validation of the NF will be made in parallel with the third step by specialists.

![Diagram of neurofeedback process]

Figure 1: Overview of neurofeedback for children with ADHD.
1. Signal (EEG) acquisition from the patient.
2. Signal processing and analysis to deduce the attention state.
3. Game reaction in real-time in the VR environment.

References:
Deep Learning-based Neurofeedback Targeting Semantic Memory in Alzheimer’s Disease

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Introduction
During childhood, humans acquire many concepts organized into semantic knowledge. This semantic network becomes denser and denser as the child grows to store concepts and their meanings. In the opposite, as Alzheimer's Disease (AD) spreads semantic memory will decline.

Based on the retrogenesis hypothesis, the memory deterioration process should follow the inverse mechanism than memory development during childhood [1]. Therefore, understanding the development of semantic memory in children would help investigate the deterioration mechanisms.

Nowadays, there is good evidence that semantic memory is part of an integrated memory system grounded in the sensorimotor system (fig. 1) [2]. In this view, children sensorimotor cortex supports low-level concepts encoding. This knowledge is then stored in semantic memory.

Training AD patients to activate the neuronal circuits responsible for the interaction between sensorimotor and semantic systems could therefore slow down the memory loss. In that way, a neurofeedback treatment is an interesting lead that has already shown encouraging preliminary results [3]. This project aims to develop a neurofeedback prototype for AD patients targeting the sensorimotor-semantic circuits from electroencephalogram (EEG) signals.

Methods
The first step is to transform EEG data into the corresponding brain activation through inverse modeling. Then, the connectivity analysis will allow us to identify the interaction between the targeted brain regions, while microstates analysis and Hidden Markov Models (HMM) [4] will be used to extract the sequence of states leading to the targeted activation (i.e. the dynamics of the system) [5].

From this new knowledge, a convolutional neural network (CNN) will be trained from EEG recordings of 210 patients (including children, adults and elderly people with or without AD \(\rightarrow\) \(~\)300 minutes recordings) to recognize the targeted activation in a robust way that is generalizable across patients [6]. Analyzing the latent space will help us to interpret the classification [7].

Finally, a neurofeedback prototype will be designed in a custom way through a transfer learning approach to fit EEG signals of each patient (fig. 2). The psychologists with whom we collaborate will perform an additional study at the end of this thesis to validate the efficiency of our neurofeedback treatment.

Conclusion:
This thesis aims to: 1) identify the interaction between sensorimotor cortex and semantic memory over the lifespan, 2) create a CNN-based model to classify this interaction in the EEG domain. Given the medical context, an additional study will be led to interpret the result of this classification, 3) develop an EEG-based neurofeedback prototype that targets the identified co-activation between sensorimotor and semantic systems.
References:
Changes Observed in Simon Effect due to Consecutive Repetition of the Simon Task

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[Introduction/Motivation:]
Response selection is a stage of decision making for a suitable response given against a stimulus. The Simon Effect gives us insight into "response selection" and is calculated from the results obtained from the Simon Task. The Simon Task fundamentally demonstrates that the response time shortens when there is a match between the features of the stimulus and the response. The Simon Effect, has became a widely researched concept throughout the years. The reason for this is that previous researches have shown that the irrelevant information cannot be excluded from processing, although subjects are instructed to respond only to the relevant stimulus dimension. The answer to the question why this process happens will likely tell us much about how stimulus properties enter into the selection of action. The purpose of this study is to review if this tendency could be eliminated or neutralized when the task is consecutively repeated and to enlighten how stimulus properties enter into processes of selection.

[Methods:]
In this experiment, data were recorded from 10 different trials of the Simon Task performed consecutively by 16 volunteer subjects (with a mean age ± SD 16,78 ± 0,801). Participants were selected upon who had never encountered this test before in order to eliminate any previous learning processes. In the task, taken from Psychokit, the words left and right appear on either side of the screen and the subjects are instructed to press keys according to the word itself. For example when the word right appears on the right side of the screen (compatible) or the left side of the screen (incompatible) the pressed key should be the same. There were approximately 30 stimuli in each trial, which consisted of both compatible and incompatible stimuli generated randomly. In the calculation of the average response time for compatible and incompatible stimuli, the wrong answers and the answers with a response time that exceeded 800 milliseconds were excluded and the Simon Effect was calculated by subtracting the average response time of incompatible stimuli from compatible stimuli.

[Results and Discussion:]
As demonstrated in Fig. 1, the average reaction time for compatible stimuli was mostly constant and no significant changes were observed. However, the average reaction time for incompatible stimuli varied greatly and showed a decreasing trend throughout the trials which indicates an increase in performance(p=0.015)(Fig.2). In the first trial participants were adjusting to the concept, therefore it was not included to the calculations in order to eliminate a negative value of Simon Effect. The impact is demonstrated in Figure 3-4. As was hypothesized, an increase in the number of trials caused the Simon Effect to decrease aligning with the previous findings. Due to the consecutive repetition of this task, the inhibitory processes of the direct spatial pathway would be reinforced, which would result in a lower response time for the incompatible stimuli. Although the decreasing trend was observed by a previously made experiment as well, the results obtained from this experiment suggested that the value of Simon Effect will eventually become negative after several consecutive trials. In the experiments cited there was a decrease in Simon Effect; however, the value remained positive. Therefore, the results obtained from this experiment is the first of its kind. This difference may be due to the young age of the participants, which may make them more flexible in decision making.
Figure 1: Average Reaction Time for Compatible Stimuli

Figure 2: Average Reaction Time for Incompatible Stimuli

Figure 3: Values of the Simon Effect with the First Trial

Figure 4: Values of Simon Effect without the First Trial

References:
The problem of ethics of Artificial Intelligence from the perspective of the European 'normative power'.

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[Introduction/Motivation:] The aim of the study is to propose a way of approaching the problem of ethics of Artificial General Intelligence (AGI) via the concept of European 'normative power' (NP) and 'ethical power' (EP) on the level of international institutions. AGI may potentially impact the outside world and society as far as it is supposed to make critical decisions. The nature of AGI implies transnationality that increases the chances for AGI to violate human rights and state sovereignty. In this regard, it becomes necessary to create universal ethical norms for AGI, basic heuristics embodied in 'ethical algorithms' (EA). European Union has developed a range of discursive identity practices, which is NP, that creates a framework for global ethics establishment for the sake of what political philosophy traditionally defines as common good.

[Methods:] The problem of Ethics is addressed in terms of constructivist theoretical approach. Main method is the discourse analysis of the EU's official rhetoric on AI ethics from the point of European and Russian academic discussions. Much attention is paid to works on machine consciousness and moral agency. Scenario method is used to define the driving forces and the consequences to be derived from them for AGI ethics issues. The process tracing method is used to define institutions European NP proceeds through.

[Results and Discussion:] AGI cannot become a moral agent itself, as far as moral agency is common solely to conscious social beings, and consciousness is viewed as a biological phenomenon. At the same time, trends in machine learning suggest that architectures are most likely to develop into AGI, if they simulate the evolutionary development. If so, potential EA must include mechanisms for adaptation to provide it's flexibility. NP is a political technology that is considered successful if the norms are reassessed providing that the recipient of norms is eventually willingly incorporated in them. Western countries share the norms, so the main recipients for European NP and EP are those countries that have resources to develop AGI, and share different from European norms. United Nations Organization is an institution that embodies European norms, so the scenario suggests the following: existing EU High-Level Expert Group AI is transformed into UN level international Committee on AI ethics; committee is subdivided into three working groups – developers and machine learning engineers, neuroscientists and psychologists, experts in human rights, ethics and philosophy of science; EA are developed by the Committee and ratified by an international treaty of UN member states providing EA implementation in AI laboratories worldwide; national programs for AGI development both in commercial and non-commercial purposes are revised and approved by the Committee.
References:


The surface geometry of cerebral cortex induces topological changes of cortical traveling waves

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[Introduction/Motivation:]
Recent neural activity on the surface of the human brain has been measured by various methods, and it has been found that the neural activity appears as traveling waves\cite{1}. These waves not only propagate but also collide, fuse, and split (topological change). From the viewpoint of mathematical modeling, it is known that the traveling direction of the wave depends on the surface geometry, but it is not known that the traveling wave causes a series of topological changes such as collision, fusion, and division as a result of the traveling direction.

[Methods:]
To confirm that this series of topological changes are caused by the surface geometry of the cerebral cortex, we performed numerical simulations of traveling waves on the curved surface using the Finite Volume Method\cite{2}. To simplify the analysis, a two-dimensional Gaussian function that appears repeatedly on the cerebral cortex\cite{3} was used as a curved surface, and a FitzHugh-Nagumo type reaction-diffusion equation\cite{4} was used as a traveling wave.

[Results and Discussion:]
In this study, we first demonstrated that the curved surface geometry induces bending, collision, and splitting of a planar stable wavefront by numerically solving an excitable reaction-diffusion equation on a bell-shaped surface\cite{5} (Fig.1). We determined two necessary conditions for inducing the topological change: the characteristic length of the curved surface (i.e., the height of the bell-shaped structure) should be greater than the width of the wave, and the ratio of the height to the width of the bell shape should be greater than a threshold. As for the geometrical mechanism of the latter, we found that a bifurcation of the geodesics on the curved surface provides the alternative minimal paths of the wavefront, which circumvent the surface region with high local curvature, thereby resulting in the topological change. This surface geometry-controlled wave topology may be functioned in the cerebral cortex of human embryo and fetus, where the spontaneous activity of subplate neurons emerges with diffusive neuronal interaction but immature nerve fibers. Recent studies have reported that neuronal activity in the fetal subplate induces the migration of the cells\cite{6}. To confirm this result, we applied our mathematical model to the early developmental human cerebral cortex\cite{7} (Fig. 2). During development, we expect to appear some surface strictures that can occur the topological change of traveling wave, this change affects drastically the early development of the human brain.

References:


Fig.1 A time series of topological change of traveling wave
The colors indicate the wave phase determined by an amplitude of voltage of neural activities.

Fig.2 Traveling wave on human brain at 32 weeks
During the fetal, cortical traveling waves occur at random locations. Here, a simulation of a traveling wave propagating forward was performed with the back of the brain as an initial value. The colors indicate the same in Fig.1.
Counting temporal classes in a resting-state fMRI exam

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[Introduction/Motivation:]
This work aims to compute the number of temporal classes within a resting state fMRI examination. Researchers are interested in investigating the bio-markers underlying the fMRI resting functional state, that are co-related spatial networks [1], focusing on the physiological regularities in healthy subjects and pathological alterations in patients. Clustering is an unsupervised learning method used to study the network connectivity in the resting state experiment [2]. The classical way to apply clustering algorithms is in finding homogeneous classes of signal signatures, i.e., the so-called spatial clustering or clustering of spatial patterns. Moreover, the crossed clustering [3] is the adoption of both spatial clustering and temporal clustering, where the temporal clustering is the detection of homogeneous classes of temporal patterns, that are represented by brain volumes sharing a common brain status. In this work the perspective of temporal clustering is adopted to investigate how many temporal classes are in a resting state fMRI experiment.

[Methods:]
The data used is from the fMRI NITRC repository [4] and regard one subject (Female, 31 years-old, healthy). The processing pipeline adopted encompassed temporal and spatial filtering, motion correction, standard registration and ICA-based noise removal [5]. The clustering algorithm used is the fuzzy c-means (FCM) [6]. The validation of the clustering outcomes has been made by the fuzzy partition coefficient (FPC) [7]. The experimental procedure regards the computation of the fuzzy partition matrix varying the exponent M from 1.1 to 2 and the number of clusters with the range 2, 5, 10, 20, 50, 100. The result is a clustering evaluation matrix.

[Results and Discussion:]
Figure 1 shows the complete clustering outcomes of the computational experiments. Since the best clustering has the FPC value close to 1, the clusters that are associated with the highest FPC values are the optimal number of temporal classes, given a specific configuration of the FCM algorithm. The lower values of the fuzzy exponent M (1.1-1.3) are associated with the highest FPC values (>0.6) in combination with all the range of clusters (2,5,10,20,50,100). Instead, values of M greater than 1.3 combined with a low number of clusters (2,5) are associated with medium FPC values (0.4-0.6) or with low FPC values (<0.4) if there are high number of clusters (10,20,50). Considering that the lowest values of the exponent M are extreme experimental cases, the other values of M associated with good FPC are the ones related with the lowest number of clusters. Therefore, the number of clusters that represents the candidate number of temporal classes of a resting state are 2 and 5. The limitations of this study are the usage of one subject and the adoption of a specific clustering algorithm with a
related validation measure. In the extension of this work, there will be a comparison of results obtained with multiple subjects and the adoption of other validation measures for fuzzy clusters (given the results in [8]), taking also into account different steps for number of clusters and the fuzzy exponent M. Other future works could regard a comparison of spatial clustering with the temporal clustering of resting state fMRI data (see [3] for an example) and active fMRI studies.

![Figure 1](image)

*Figure 1 shows the relation of the fuzzy partition coefficient FCM with the fuzzy exponent M and number of clusters values decrease close to the minimum values (blue colour).*

[References]


Prediction of a cell-type specific mouse mesoconnectome using gene expression data

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Reconstructing brain connectivity at sufficient resolution for computational models designed to study the biophysical mechanisms underlying cognitive processes is extremely challenging [1]. For such a purpose, a mesoconnectome that includes laminar and cell-type specificity would be a major step forward. We analysed the ability of gene expression patterns to predict cell-type and laminar specific projection patterns and analyzed the biological context of the most predictive groups of genes.

To achieve our goal, we used publicly available volumetric gene expression and connectivity data and pre-processed it for prediction by averaging across brain regions, imputing missing values and rescaling [2,3,4]. Afterwards, we predicted the strength of axonal projections and their binary form using expression patterns of individual genes and co-expression patterns of spatial gene modules.

For predicting projection strength, we found that ridge (L2-regularized) regression [7] had the highest cross-validated accuracy [6] with a median $r^2$ score of 0.54 which corresponded for binarized predictions to a median area under the ROC value of 0.89 (fig. 1). Next, we identified 200 spatial gene modules using the dictionary learning and sparse coding approach [5]. We found that these modules yielded predictions of comparable accuracy, with a median $r^2$ score of 0.51 (fig. 1). Finally, a gene ontology enrichment analysis [8] of the most predictive gene groups resulted in significant annotations related to postsynaptic function (fig. 2).

Taken together, we have demonstrated a prediction pipeline that can be used to perform multimodal data integration to improve the accuracy of the predicted mesoconnectome and support other neuroscience use cases.
References:
Towards a computational model of cortical and subcortical network underlying implicit motivation in voluntary motor control

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Experimental results on basal ganglia (BG) output activity, in a dopamine-depleted state, have revealed an influence of BG on the control of movement kinematics [1]. Behavioural studies on arm reaching movements, in patients with Parkinson's disease (PD) [2-3], have recently suggested that reaching speed must be determined not only on the basis of a trade-off between speed and accuracy, but also by an implicit “motor motivation”, independent of the behavioural context and influenced by the energetic cost of the movement [4]. At present, a comprehensive computational model of BG and motor cortex able to replicate the influence of an implicit motor motivation on the kinematics of human reaching movements, is still missing. The objective of this research is to define a computational model of the interplay between the BG and the motor cortex for voluntary limb movements, describing the specific influence of motor motivation in the circuit of motor control.

Methods:
A preliminary model of the motor cortex, inspired by a state-of-art optimal control scheme [5], was developed. The motor cortex was simulated as an artificial feed-forward neural network that sends motor commands to a bidimensional biomechanical model of the arm [6] to reach predefined targets on a bidimensional workspace (Fig.1). This model was static, i.e. it optimized the initial hand velocity, without any feedback from the periphery. The cortical activity was found by minimizing a cost function that penalized a kinematic error between the actual and the desired velocity, but also high values of neural and muscle activities, so that the energetic cost of the movement was minimized as well (see [5]). Optimizations were run in MATLAB, using conjugate gradient descent. Custom code of the backpropagation algorithm was built to compute partial derivatives necessary for the optimization function.

Results and Discussion:
The static model is optimal to initiate the reaching movement with a desired velocity and minimum energetic effort [5]. In order to simulate the entire reaching task, a dynamic model of the motor cortex, receiving on-line state-feedback from the periphery, is under development. Future directions will consist in modelling the interactions between BG and motor cortex in a dynamic simulation of the control of voluntary limb movements. For this purpose, the BG network will receive as input an efferent copy of the motor command and will modulate an output signal of movement vigour, according to an implicit motor motivation signalled by a dopamine input [4]. Lesions of BG circuit should disrupt the influence of motivation on the production of adequate movement commands, thus leading to altered motor behaviours. The power of prediction of the model will be then tested with an experimental setting planned to involve parkinsonian patients in reaching tasks not comprising any explicit reward.
Figure 1: Static neural network of the motor cortex controlling a 6 muscles limb model (2-link planar arm, taken from [6]). The muscle activity $u$ was obtained from the neural activity $z$ through sigmoidal activation functions. Subsequent transformations from muscle activity to muscle tension forces, and from tension to joints’ torques, led to the determination of the kinematics of the joints, from which the velocity in the task space $\dot{y}$ was computed. \( m_1 - m_4 = \text{monoarticular arm muscles, } m_5, m_6 = \text{biarticular arm muscles.} \)

Acknowledgements:  
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References:
Analytical solution of linearized equations of the Morris-Lecar neuron model at large constant stimulation

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Introduction: The Morris-Lecar model [1, 2], along with the more complex Hodgkin-Huxley model [3], is a classical biophysical model of spike generation by the neuron, which takes into account the dynamics of voltage-dependent ion channels and realistically describes the spike waveform. Both models predict that upon stimulation of the neuron with a sufficiently large constant depolarizing current $I_{\text{stim}}$, there exists a finite interval of $I_{\text{stim}}$ values where periodic spike generation occurs [4-6]. Numerical simulations show that in the Morris-Lecar model the cessation of periodic generation of spikes above the upper boundary of this interval (i.e. at $I_{\text{stim}} > I_{\text{max}}$, see Fig. 1, left graph) occurs through a damping of the spike amplitude, arising with a delay inversely proportional to the value of $I_{\text{stim}}$ [7]. In particular, the damped dynamics can be divided into four successive stages: 1) minor primary damping, which reflects a typical transient to stationary state, 2) plateau of nearly undamped periodic oscillations, which determines the aforementioned delay, 3) strong damping, and 4) reaching a constant stationary asymptotic value $V_{\text{st}}$ of the neuron potential. As the last two stages resemble the well-known exponentially-damped harmonic oscillations, we tackled to find an analytical description for these.

Methods: First, we have linearized the Morris-Lecar model equations at the vicinity of the asymptote $V_{\text{st}}$. The resulting equations have been then reduced to an inhomogeneous Volterra integral equation of the second kind. In turn, the latter has been transformed into an ordinary differential equation of the second order with a time-dependent coefficient at the first-order derivative. As this time dependence is just an exponential decay with the small pre-exponential factor, we considered its asymptotic value and analytically solved the final equation. In order to verify the analytical solution found, we have compared it with the numerical solution obtained using the standard MATLAB tools for systems of ordinary differential equations.

Results and Discussion: We have accurately shown that the linearized system of equations of the Morris-Lecar model can be reduced to a standard equation of exponentially damped harmonic oscillations for the neuron potential. Since all coefficients of this equation are explicitly expressed through the parameters of the original Morris-Lecar model, one can directly (i.e. without any fitting) compare the numerical and analytical solutions for dynamics of the neuron potential at last two stages of the spike amplitude damping (Fig. 1, right graph). The results allow a quantitative study of the applicability boundary of linear stability analysis that implies exponential damping.
References:

Figure 1: Left graph: Dependence of spike generation frequency on constant stimulating current $I_{stim}$ and, on the gray inset, typical examples of dynamics of the neuron potential in the corresponding ranges of $I_{stim}$ values for the Morris-Lecar model with the first excitability type [2]. Spikes are characteristic pulses of the neuron potential (see gray inset in the range from $I_{min}$ to $I_{max}$). Right graph: The gray curve is a numerical solution for dynamics of neuron potential $V(t)$ in the Morris-Lecar model with the first excitability type at $I_{stim} = 116.3$ µA/cm² > $I_{max} = 116$ µA/cm², the red curve is an analytical solution of linearized system of equations of the Morris-Lecar model with initial conditions taken at the point of a local maximum of the potential ($t_0 = 693.3$ ms, $V(t_0) = 16.35$ mV).
Decoding of motor intention in the premotor cortex: information content of fast spiking and excitatory neurons.
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Introduction

The premotor and motor cortex are important in the planning and execution of movements, neurons in these areas encode for movement related features [1].

In the mouse cortex, two types of neuronal classes have been identified: putative inhibitory, fast spiking neurons (FS), and putative excitatory (PE) neurons [2]. However, how those two types of neurons influence the movement planning is not well understood.

Brief and localized optogenetic silencing experiments found an Area which shows preparatory activity for the licking behavior, this area is the Anterior Lateral Motor (ALM) cortex [3] in which most of the neurons show ramping activity preceding the behavior. Recording during a whisker-based object localization task with a delay, show neurons with activity both before and after the movement [3].

We used a decoding approach to investigate the change of information content, approximated by the decoding performance, about the upcoming licking movement of FS and PE neurons.

Methods

We isolated the single neurons with a spike sorting software (OfflineSorter$^\text{™}$v3.3.5, Plexon); then we split the neurons in 2 classes using a k-means clustering, in the same 2D features space described in [2], as showed in Figure 1.

We associated a trial to each isolated starting licking event, each trial lasted 1.2s, starting 0.8s before the event and ending 0.4s after.

To evaluate the change in decoding performance over time, every trial has been split in overlapping windows of 0.15s, spaced 0.05s one to each other. For each window we trained a 2-layer deep feed forward neural network to distinguish if the trial, the window belongs to, contains an event or not. The performance of each window is calculated as the mean across 10 non-overlapping subsets of trials of the area under the receiver operating characteristic curve (AUC). We used all the neurons for the classification task then, to isolate the contribution of the two subpopulations of neurons, we used only the FS or the PE.

Results and Discussion

As showed in Figure 2, the AUC with the FS reaches a peak at approximately 0.2s before the start of the licking event while using only the PE neurons the max performance is obtained 0.2s after.

This result suggests that the activity of the FS neurons precedes the one of the PE, and may help shaping their responses.
Figure 1. Clustering of Fast spiking and pyramidal neuron. a). Normalized mean waveform of each neuron in the feature space; each square represents a neuron; red neurons belong to the putative excitatory (PE), black neurons belong to the fast spiking cluster (FS). On the x-axis there is the peak-through ratio, on the y-axis there is the difference in time from the through and the peak. b). Representation of all the waveforms belonging to the FSNs cluster, in black, and to the pyramidal cluster, in red. The waveforms are normalized. On the x-axis the time in ms is presented. c). Mean waveform of the two clusters, in red the mean waveform of the pyramidal cluster, in black the one of the FSNs cluster; the mean waveforms are normalized.

Figure 2. AUC over time. Overlapping of the AUC over time obtained with the FS neurons, black line, pyramidal neurons, red lines, and All the neurons, green line. The respective light-colored areas spawned from 25 percentile to 75 percentile. On the x and y axis there are, respectively, the time in seconds and the AUC.

References:
A new Smart Region Growing algorithm for segmenting single neurons from confocal datasets

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Introduction and algorithm outline:
Accurately digitizing the brain at the micro-scale is crucial for investigating brain structure-function relationships and documenting morphological alterations due to neuropathies [1,2]. Here we present a new Smart Region Growing algorithm (SmRG) for the segmentation of single neurons in their intricate 3D arrangement within the brain. The workflow of the SmRG is sketched in Figure 1. Its Region Growing procedure is based on a homogeneity predicate determined by describing the pixel intensity statistics of confocal acquisitions [3] with a mixture model [4], enabling an accurate reconstruction of complex 3D cellular structures from high-resolution images of neural tissue. The algorithm’s outcome is a 3D matrix of logical values identifying the voxels belonging to the segmented structure, thus providing additional volumetric information on neurons (Figure 2).

To highlight the algorithm’s full potential, we compared its performance in terms of accuracy, reproducibility, and precision of 3D neuron reconstructions against both manual and state-of-the-art reconstruction tools.

Methods: Evaluation of SmRG performance
The confocal datasets representing dense-packed PCs from 1 mm-thick slices from clarified L7GFP murine cerebellum were those already manually segmented in Magliaro et al., 2016 [5]. Specifically, n = 3 Purkinje cells were segmented automatically with SmRG and manually by 6 experts with the ManSegTool, a tool purposely developed for facilitating the manual segmentation of 3D stacks [6].

The segmentation accuracy was evaluated by comparing i) the surface area, ii) the volume and iii) the area under the curve (AUC) of the profiles obtained through Sholl analysis of the segmented structures. Statistical differences between manually segmented structures and those resulting from the SmRG were evaluated by means of the Friedman’s test. Reproducibility was performed by segmenting the same PCs starting from 10 different seeds and quantified as the coefficient of variation of each measure.

Moreover, in order to highlight the SmRG’s ability to segment single-neurons from confocal datasets represented densely-packed cells, we also processed a 3D image stack with the App2, MST, SIGEN and MOST tools. Reconstructions provided by these tools and by SmRG were visually compared.

Results and Discussion:
The Friedman’s test showed no significant differences between the SmRG and the ManSegTool outcomes in terms of surface area, volume and Sholl profiles (p = 0.8233), demonstrating that their are comparable in terms of accuracy. As regard the reproducibility, the coefficients of variation of volume, surface area and AUC of Sholl profiles for each segmented neuron are reported in Table 1. The maximum coefficient of variation is equal to 0.0258, demonstrating SmRG robustness to changes in the position of a seed belonging to the structure.

Figure 5 shows an example of the outputs obtained segmenting the same 3D stack with the SoA tools (i.e. App2, MST, SIGEN and MOST) and with the SmRG. We were only able to assess the comparisons visually, since none of them was able to handle such dense datasets.

In conclusion, the SmRG could provide a valid alternative to SoA tools for the segmentation of such datasets. Further validation of the method is ongoing to confirm its robustness when dealing with different neuronal types.
Figure 1: **SmRG workflow.** A) Seed selection. B) Dip test to test for unimodality against multimodality on a MxNx3 crop centred on the seed. The threshold is determined with Otsu’s method or through the Mixture Model according to whether the distribution is multimodal or not. C) 3D segmentation of a MxNx3 crop. D) The regional maxima of the distance transform of the segmented MxNx3 crop are chosen as new seeds. E) The procedure iterates until there are no more new seeds.

![SmRG Workflow Diagram](image)

Figure 2: **An example of SmRG outcome.** A) a Purkinje cell from clarified murine cerebellum acquired using a Nikon A1 confocal microscope; B) the same Purkinje cells identified within its confocal dataset.

![Example of SmRG Outcome](image)

Table 1: Results of SmRG’s reproducibility. Coefficients of variation for neuron volume, area and AUC for n different seeds.

<table>
<thead>
<tr>
<th>Neuron</th>
<th>Volume</th>
<th>Area</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>0.0015</td>
<td>0.0025</td>
<td>7.8e-04</td>
</tr>
<tr>
<td>#2</td>
<td>0.0176</td>
<td>0.0258</td>
<td>0.0138</td>
</tr>
<tr>
<td>#3</td>
<td>0.0017</td>
<td>6.1e-04</td>
<td>0.0028</td>
</tr>
</tbody>
</table>

The coefficient of variation corresponds to the standard deviation divided by the mean (σ/μ).

![Table 1](image)

Figure 3: **A confocal dataset representing PCs segmented with SoA tools and SmRG.** None of the SoA tools is able to deal with dense datasets, while the SmRG is able to isolate the PCs. Different colours refer to different neurons recognized.

![Confocal Dataset](image)

**References:**
Learning and sleep in a thalamo-cortical multi-area model

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[Introduction/Motivation:] Wakefulness and sleep are brain-states that are essential for cognitive performances. During wakefulness, our perceptual system is continuously subjected to sensory inputs from different sources and modalities. The involved brain areas process the input in a framework set by previous knowledge (acquired through individual and evolutionary experience) with a crucial role played by the exchange of signals with other brain areas. The ability of the brain to integrate and segregate this information by building a coherent and complete representation of the environment is impressive. Despite there is plenty of empirical evidence suggesting that the nervous system uses a statistically optimal approach in combining external information, little is known about how the brain implements these strategies. Moreover, recent studies have shown that sleep plays a central role in storing and reorganizing information gained while awake and in the optimization of the energetic post-sleeping rates.

[Methods:] Starting from these results and a recent\textsuperscript{1} simplified single area thalamo-cortical model, our work focuses on two main issues. First, we aim to simulate the ability of the awake brain to combine different kinds of information, throughout multisensory perception, with contextual information\textsuperscript{2} starting from the case of the integration of the two visual hemicampi that in the brain are processed by areas placed in two different hemispheres. Second, we study the beneficial effects of a deep-sleep-like biologically plausible\textsuperscript{3,4} slow oscillation activity on the classification accuracy.

In summary, in this work, we create a simplified thalamo-cortical multi-area simulation model trained to learn, sleep and perform a classification task on handwritten digits.

[Results and Discussion:] Starting from results presented by Larkum et al.\textsuperscript{2}, we have studied the interaction between contextual and sensory information demonstrating the advantages of setting the network in a regime that we named Under-threshold to stress the necessity of simultaneous action of contextual and bottom-up sensory flow. Moreover, we compared the network behaviour and performances in a single area versus a multi-area model within a noisy environment showing a higher resilience to noise in the multi-area model. Also, we explored the formation of groups of neurons with a precise temporal order whenever dynamic examples are presented to the network during both the training and the testing phases demonstrating easier learning over moving inputs rather than static ones. We demonstrated better performances when learning moving inputs (either vibrating or sliding) rather than static inputs. Finally, we observed that the novel two-hemicampi model exhibits superior improvement in the classification accuracy induced by deep-sleep-like slow oscillation activity compared with that observed in the single-area model. Through the talk, we will focus in more detail on the behaviour of the 2-hemicampi model within a noisy environment and compare its performances when trained over static and moving inputs. Future work might include a refinement of the multi-area structure including more layers, encoding for various levels of complexities.
**Figure 1**: Structure of the network. The input image needs to be pre-processed in order to be encoded into the thalamus. Proceeding bottom-up: the first layer is made of thalamic excitatory (blue) and inhibitory (pink) populations, the second layer is made of cortical excitatory (green) and inhibitory (pink) populations. A contextual signal coming from outside the network is provided in order to implement the learning process.

**References:**


Towards a Workflow of Rodent Microelectrode Array Data Analysis: *In vitro* and *In silico* Characterization of Cortical Network Activity Dynamics

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**Introduction:**

As the number of data sources for building detailed computational models of neuronal networks increases it is necessary to keep a record of the origin of the experimental *in vitro* and computational *in silico* processes in a research project [1, 2]. We here present our *in vitro* [3] and *in silico* [4] studies and the related workflow developed to explain the dependence of network dynamics on synaptic transmission in rodent cortical networks. These cells show spontaneous synchronized activity that is crucial for the formation of networks *in vitro*. In this activity, oscillating network bursts (NBs), mediated by the excitatory and inhibitory transmission via AMPA, NMDA and GABA<sub>A</sub> receptors (Rs), spread rapidly across the entire network. The effects of these receptors and their complex interplay on NB dynamics are not well understood. The aims of this study are twofold: 1) to examine the complex interplay between the excitatory and inhibitory receptors in networks *in vitro* and *in silico* and 2) to promote the reproducibility of studies by presenting a workflow of microelectrode array (MEA) data analysis for characterizing in detail the role of receptors in initiating, propagating and terminating NBs.

**Methods:**

To examine the dependence of NBs on synaptic receptors, the here presented workflow is created with multiple steps as shown in Figure 1. First the rodent forebrain was prepared as cortical network on a MEA plate. Second the network activity was recorded with MEA technique under different pharmacological conditions of receptor antagonists in *in vitro*. Third the multivariate data analysis was done in a format that supports both the biological question layout and the validation of computational models to qualitatively produce the experimental results. Fourth the computational models are simulated with different parameters to test putative mechanisms responsible for network activity.

**Results and Discussion:**

In short, multivariate analysis shows that AMPARs rapidly initiate and recruit NBs and NMDARs maintain the elevated NBs. GABA<sub>A</sub>Rs strongly inhibit the AMPAR-mediated spiking and further dampen the NMDAR-mediated termination phase. The results indicate an interaction between the GABA<sub>A</sub> and AMPAR-mediated activities. The obtained results reveal a unique contribution of each receptor type to the overall network activity, both in *in vitro* and *in silico*. These entries, together with additional *in vitro* data, data analysis workflows, computational models as well as *in silico* data, will be integrated as part of the EU FET Flagship HBP infrastructure, the Collaboratory/EBRAINS. A well-defined workflow for storing recording protocols, data analysis methods, computational models, and results, as suggested in [2], can reduce the amount of biological experiments, promote the use of MEA and improve reproducibility of computational research in the field of human neuroscience.
Figure 1: Workflow of rodent microelectrode array data analysis for in vitro and in silico characterization of network burst dynamics. Figure is reproduced and modified from [3, 4].

References:

Acknowledgements:
This work was supported by the Academy of Finland through grants (297893, 318879) and the European Union’s Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 785907 (Human Brain Project SGA2).
Whole-brain network modelling of psilocybin treatment for depression

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Introduction

Recent developments in psychedelic medicine have revealed novel avenues for a treatment of treatment-resistant depression (Carhart-Harris et al. 2016). In order to move towards understanding of how psychedelic drugs such as psilocybin (a psychoactive component of ‘magic’ mushrooms) and LSD modulate the brain’s dynamical repertoire, it is essential to look at the underlying mechanisms (Lord et al. 2019) (Deco et al. 2018). Here, we focus on patients with treatment-resistant depression pre- and post- treatment with psilocybin by studying the brain dynamics using fMRI. Moreover, we deploy a computational whole-brain model to simulate the underlying brain dynamics during the experiments and through perturbation identify the possible outcome treatment activity.

Method

In this study, we investigated a cohort of treatment-resistant patients undergoing psilocybin intervention. 15 subjects underwent T1w and fMRI scans pre- and one-day post- the psilocybin intervention (Carhart-Harris et al. 2016). The patients were divided into responders and non-responders according to their depressive scores 5 weeks post-treatment. To obtain brain state representations across time for all the subjects and for pre- and post- treatment conditions, we performed leading eigenvector dynamics analysis (LEiDA) (Figure 1A and 1B) (Cabral et al. 2017). Furthermore, we implemented a Hopf-bifurcation model for each brain region connected through structural connectome and simulated the arising brain activity (Deco et al. 2017). First, to describe the ‘depressive’ brain pre- psilocybin treatment, the model was fitted to the pre-treatment recordings. In the later stage, the model was systematically stimulated to map the important regions responsible for the treatment effects.

Results

We found the probabilistic metastable substates (PMS) of state three to be significantly different between the two conditions for treatment-respondent patients between the conditions (permutation paired t-test (5000 permutations), p-value = 0.026, fdr-corrected) (Figure 1B). We constructed and validated the Hopf network model to the PMS to obtain the most accurate spatio-temporal representation of the states from brain activity (Figure 1C). Through a nodal stimulation of the whole-brain model, we determined the regions that causally affect relevant network changes resulting from the psilocybin treatment in the patients with positive outcome.
References


Figure 1: Experimental Design Summary: Modelling of Dynamic Functional Connectivity – Hopf-bifurcation model is fitted to the fMRI timeseries. Brain Stimulation – A: The whole-brain model is fitted to the ‘depressive’ brain, B: – Validated whole-brain model is systematically stimulated to obtain treatment-successful brain representation.
Maximum Likelihood Methods for Biologically Plausible Learning of Temporal Sequences in Recurrent Spiking Networks

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Introduction

Recurrent Networks are powerful architectures for highly complex temporal information processing. In recent years, a wealth of significant contributions to this topic has expanded the reach of capabilities and valuable applications of such systems, from Reservoir Computing to FORCE, full-FORCE [2][3] and e-prop training algorithms to cite a few. However, both theoretical underlying principles and important considerations concerning biological plausibility are still partially addressed issues. In this work we propose a principled-based novel maximum-likelihood method for learning temporal sequences in recurrent spiking systems and provide extensive analysis on how the derived learning rule can be implemented in a biological neural network. Quantitative comparisons with other models, including e-prop 1 systems, on a pattern generation task are discussed, highlighting the superior performances and improved realism of the model of our proposal.

Methods

Given the stochastic nature of the elementary unit in a recurrent network, it is possible to define the likelihood of the system expressing a particular trajectory. We formalize learning as the likelihood maximization of a defined target sequence. In the pattern generation task [1] the system is asked to reproduce a three-dimensional wave signal composed of four frequencies. In the initial phase, this signal is provided via random projections to the system, together with an external clock, and the resulting activity is defined as the encoded target temporal activity. We then train both an external linear readout layer to decode this pattern and the recurrent network by maximizing the likelihood of expressing this very same trajectory when only the external clock is provided.

Results and Discussion

In this work we have introduced a novel maximum-likelihood method for training recurrent spiking networks. The theoretical-based approach allowed for the explicit analytical derivation of the synaptic update rule, which in turn fostered relevant biological interpretations of the obtained expression. We test our model on a pattern generation task in which it outperformed e-prop 1 based systems. This novel theoretical framework is flexible and can be applied to different models of neurons, providing analytically a target-based - rather than backpropagation-based - learning rule in a recurrent neural spiking network.
Figure 1: In this Figure we report the successful completion of the Pattern Generation task by our model. It achieved a MSE (Mean Square Error) of 0.003, which is a remarkable improvement with respect to the best MSE = 0.01 of e-prop 1 algorithm on the very same benchmark.

References:


EEG channel-selection method based on NSGA-II for source localization
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Introduction:
The source reconstruction based on EEG signals has been used to identify the sources in the brain that lead a certain potential activity recorded by electrodes on the scalp, as a rule, the source localization is performed using high-density EEG montages, however, several EEG devices in the market provide low-density recording systems and thus are considered out of the scope to perform source localization. In this work, we analyze if we can use a lower number of channels while keeping the same localization error. To evaluate this concept, a set of EEG signals were simulated and the channels were selected using a genetic algorithm to find the best channel combination to localize the source with the lower localization error as possible.

Methods:
The genetic algorithms (GAs), which mimic Darwinian evolution, are normally used to solve complex optimization problems, the population for GAs is comprised of a set of candidate solutions, each with chromosomes that can be mutated and altered. In a multi-objective optimization problem, there is a set of solutions that is superior to the others in the search space when all the objectives are considered, but inferior to the other solutions for one or more objectives. Such solutions are known as Pareto-optimal solutions or non-dominated solutions and the rest as dominated solutions. The non-dominated sorting ranking selection method is used to emphasize good candidates and a niche method is used to maintain stable sub-populations of good points, the non-dominated sorting genetic algorithm (NSGA) was designed based on this concept [1]. NSGA-II solved some problems related to the computational complexity, non-elitism approach, and need to specify a sharing parameter to ensure diversity in a population presented in the first version. Additionally, the elitism approach was introduced by comparing the current population with the previously found best non-dominated solutions. NSGA-II was used for channel selection, we defined a two-objective optimization problem as [No_c, Error], where the objective No_c represents the number of channels used to perform the source reconstruction, and the objective Error is the localization error obtained with a combination of channels represented in a chromosome as shown in Fig. 1. Each channel is a gene of the chromosome and can take a binary value, 1 if the channel will be used for the source localization process and 0 if not. A set of chromosomes was randomly created for the initial population and it is evolving in the time searching for the combination of fewer channels that lead to a minimal localization error. The source reconstruction was performed using the standardized low-resolution tomography (sLORETA) [2] algorithm over a synthetic EEG with
60 channels and 0dB signal-to-noise ratio. The activity of one source was simulated on the occipital region based on a sinusoidal windowed activity as made in [3]. Using the reconstructed activity, we measured the error localization between the true source location and the estimated source location using the L2 norm, where the estimated position was selected choosing the source with the maximum activity from the reconstruction.

**Results and discussion:**
Using all the EEG channels or the best combination with six electrodes found by NSGA-II, we obtained zero error localization, which represents that a certain source can be accurately located using a reduced set of electrodes. Regarding the evolution of the localization error, the NSGA-II effectively searched for the best combinations of channels keeping the localization error as low as possible, it can be seen in Fig. 1 at right, that even with a certain combination of two electrodes the localization error is below 10mm. This could represent that the source analysis of a certain region of interest can be performed with a sparse number of electrodes with high accuracy.

![Fig. 1](image)

Fig. 1. (Left) Search space for NSGA-II, (Center) estimated source localization using the following six found channels Fpz, O1, Oz, PO7, POz, and Iz. The source location is marked with a blue circle and the localization error was zero mm. (Right) Pareto front, error localization versus number channels.

**References:**
Towards a BCI based on Color Exposure Recognition

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Introduction
The most common visual paradigms of BCI control are based on an external flickering stimulator (SSVEP and P300). Looking for avoiding this drawback, our project assesses the feasibility of using only the EEG responses to primary color exposure, keeping in mind that color-based cues are already a part of our daily life such as traffic lights, allowed/forbidden access doors, etc. Also, with this neuro paradigm and all the environment required for home automation, our project will be useful for elderly and handicapped people, allowing them a level of independence in their activities by means of the control of music players, lights, and computer along with the possibility to respond phone calls and ask for help in case of an emergency.

There exists some evidence about differences between colors following an event-related potentials (ERP) approach [1], which is based on the averaging of the EEG signals for each color and all subjects. However, its automatic discrimination for controlling devices has been only approached in [2]. Even though they recorded the EEG signals from 7 subjects using a 4-channel EEG cap (P1, P2, O1, and O2) whose frequency sampling is 256Hz, their outcomes were overestimated due to the use of the same information during the training and testing. Besides, looking for a wearable design, it is unclear what performance could be achieved without this overestimation and using dry electrodes.

Methods
We have scheduled two scenarios of analysis (offline and online) for our project. In the offline analysis, we will assess the feasibility of a color-based BCI using pre-recorded signals, whereas in the online we will work on how to recognize the target activity from the idle states and to control an automatized door using online EEG signals. Both analyses imply the application of algorithms for artifact removal, signal processing, machine learning, and their parameters' optimization. Specifically, we assessed in feature extraction stage two techniques, discrete wavelet transform (DWT) and empirical mode decomposition (EMD). Whereas in the classification stage, we analyzed 4 classifiers Naive Bayes, K-nearest neighbors, support vector machine (SVM) and Random Forest (RF), getting the best preliminary results with SVM and RF, which are described below.

Results and Discussion:
For the offline scenario, the first advances are described here. Looking for solving the drawbacks in [2] and assuring an independence of our results from a specific dataset, we designed a protocol to record the responses to the color exposure, resulting in an additional dataset composed of the EEG signals belonging to 18 subjects.
(more than in [2]) and 30 trials per class for each subject (52 trials in [2]). The EEG signals were recorded using a gTec Sahara device and the analyzed channel locations were FP1, FP2, AF3, AF4, P03, P04, O1 and O2. These locations were selected based on the related works [1,2]. Our dataset was recorded in a dark room and following the next protocol timeline per each trial: a 2-seconds gray screen with a fixation cross for indicating the subjects to pay attention, a 3-seconds screen with the target color’s exposure, and a short and randomized pause screen (1-2 seconds). The average performances for RGB classification were 37.64% (RF and DWT-based features) using the previous dataset [2] and 37.5% (EMD-based features and SVM) in our dataset. We observed that the performances were subject-dependent in both datasets regardless of their sizes. In some subjects, their performances overcame 40%, which is higher than the chance level for 3 classes. These outcomes make necessary more research looking for providing more evidence on RGB classification, especially, it is necessary to collect more instances for each color aiming to enhance the machine learning performances.

Whereas looking for providing a first attempt towards an online scenario, we have analyzed if a machine learning algorithm can distinguish between the target colors (seen as a single class) and idle state using the dataset recorded in [2] and ours. This was done since the method should be able to discriminate between these activities in an online scenario. In this case, the best average accuracies were 98.76% (SVM and EMD-based features) for the previous dataset, and 92.5% (RF and EMD-based features) and 94.6% (SVM and EMD-based features) using two different types of idles states (break-related and attention-related epochs) in our dataset. This suggests that a machine learning algorithm can accurately recognize between both classes, regardless of the dataset analyzed. A second step is to design a method based on short windows for a fast detection of the target colors and idle states looking for the implementation of an online BCI based on color exposure. As a third step, this project considers evaluating a real scenario for controlling an automatized door for which the interface to control the door’s actions and to convert the algorithm outputs will be developed.

Finally, a wireless device called Flex-EEG™ is being developed with the financial support of our university as a main part of our research. This device is based on dry electrodes on a headset design, which means it would be wearable and it could cover a specific region, like a head-band does. This design will allow us the analysis of primary visual cortex in our study, but keeping its flexibility to cover other interesting brain regions (even in both hemispheres) in BCI from prefrontal to occipital region (including the motor cortex). Then, FlexEEG’s performance will also be assessed in the most common neuro-paradigms VEPs, P300 and motor imagery.

![FlexEEG Design](image)

Figure 2: Flex-EEG Design

References


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Data sharing through the online EBRAINS platform: a new service for brain research

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Enhancing the reproducibility and transparency of research is an emerging theme across scientific disciplines, driven by new technological advances, and captured by the Open Science concept. The heterogeneity of research data, which often hinders direct comparisons of findings, adds a layer of complexity to this effort. To address these challenges in neuroscience, the Human Brain Project has developed a new research infrastructure, EBRAINS, providing tools and services to the neuroscientific community. The EBRAINS data curation service offers comprehensive stewardship for sharing experimental and computational data. New workflows and standards for neuroscience data and metadata management have been developed to make the research results discoverable, comparable across modalities, and possible to reanalyse and reuse in new combinations. Here we present our workflows and curation services tailored for sharing heterogeneous neuroscience data. We demonstrate the integration of such data in the infrastructure, and highlight some practicalities for researchers who want to share their neuroscience data through EBRAINS.
David versus Goliath: Low-density EEG unravels its power through adaptive signal analysis -- FlexEEG

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Introduction:
A new EEG concept is envisioned to realize a low-cost, real-time and flexible EEG solution for everyone. This new EEG concept will be based on an optimized design with a reduced number of channels and the use of wireless dry non-invasive active electrodes to support portability and ease of use. While a laboratory setting and research-grade EEG equipment ensure a controlled environment and high-quality multiple-channel EEG recording, there are applications, situations, and populations for which this is not suitable. Conventional EEG is challenged by high computational cost, high-density, immobility of equipment and the use of inconvenient conductive gels/saline solutions. One consequence of high-density EEG is that interpretation in real-time is not available today. Technological advancements in dry sensor systems have opened avenues of possibilities to develop wireless and portable EEG systems with dry electrodes to reduce many of these barriers. While being portable and relying on dry-sensor technology, it will be expected to produce recordings of comparable quality to a research-grade EEG system but with wider scope and capabilities than conventional lab-based EEG equipment. In short, a single more intelligent active EEG electrode could defeat high-density EEG. Through this new concept, the range of applications of EEG signals will be expanded from clinical diagnosis and research to health-care, to a better understanding of cognitive processes, to learning and education, flexible neurofeedback and to today hidden/unknown properties behind ordinary human activity and ailments (e.g., acute chronic pain, resting-state, walking, complex cognitive activity, etc.). The effect of both, electrode localization and the number of electrodes, will be explored by gradually removing electrode information, taking into account very important characteristics; sex, age, hemisphere lateralization, intelligence quotient, and the paradigm used. It will make possible to materialize a low-cost EEG device within the reach of everyone. A low-density EEG device with dry electrodes will take less time to install, will be more user-friendly, will consume less power and possible to use for a prolonged time. All these achieved at a lower cost.

Methods:
Wet electrodes are not suitable for prolonged time monitoring due to their dry out procedure which might lead to losing the signal. While dry electrodes don't need any saline or gel in order to improve their contacts, they are a promising solution. As dry electrodes impedance is much higher than wet electrodes, we are trying to decrease the impedance and design a compatible amplifier to a high impedance electrode. Main stages to design: decrease the input-referred noise of electrode and amplifier, high input impedance, and high CMRR amplifier. Using EEG signal analysis methods and extracting the information from specific brain areas related to the task/paradigm/Subject/sex, the use in real-time will be possible. The main stages to analyze are feature extraction, channel reduction/selection, machine- and deep- learning architectures. In addition, using brain mapping methods to provide an estimation of the activity inside the brain, the neural activity map in terms of localization and intensity can be used as a source of new features for classifying the evoked activity in specific tasks, moreover, to unravel the specific characteristics and behavior of brain in a given neuro paradigm. The inverse problem of estimate the activity is ill-posed due the reduced number of electrodes and the high number of possible sources of neural activity, however, applying signal analysis techniques and using partial zone brain models, the activity will be estimated using a reduced number of electrodes, providing feasible solutions to the inverse problem in reduced times for real-time applications.

Results:
In order to minimise the input-referred noise, an inverter-based differential amplifier is utilised. Meanwhile, a DC servo loop is designed to reject the DC offset of the electrode. Since all of the stages required a common-mode feedback, for each of the amplifiers a suitable circuit was used. The designed circuit is simulated in a standard 180 nm CMOS technology. The designed chopper amplifier consumes just 1.1 µW at a 1.2 V supply. The midband gain
is 40 dB while the bandwidth is from 0.5 to 200 Hz. The total input-referred noise is 1 µVrms in its bandwidth. CMRR is 124 dB with 6.9 dB standard deviation. Some applications following the ideas of this project, are briefly described. **Subject identification from low-density EEG-recordings of resting-state [1].** EEG recordings of resting-states were analyzed with SVM, k-NN, and naive Bayes classifiers using the Empirical Mode Decomposition (EMD) and Discrete Wavelet Transform (DWT) as the basis for feature extraction. To explore the feasibility of using fewer channels with minimum loss of accuracy, the methods were applied to a dataset of 27 Subjects (From 5 sessions of 30 instances per Subject) recorded using the EMOTIV EPOC device with 1 set of 14 channels and 4 subsets (8, 4, 2 and 1 channel) that were selected using a greedy algorithm known as backward-elimination algorithm. The experiments were reproduced using fewer instances each time to observe the evolution of the accuracy using both; fewer channels and fewer instances. The results of this experiments suggest that EMD compared with DWT is a more robust technique for feature extraction from brain signals to identify Subjects during resting-states, particularly when the amount of information is reduced: e.g., using Linear SVM and 30 instances per Subject, the accuracies obtained using 14 channels were 0.91 and 0.95, with 8 channels were 0.87 and 0.89 with EMD and DWT respectively but were reversed in favor of EMD when the number of channels was reduced to 4 channels (0.76 and 0.74), 2 (0.64 and 0.56) and 1 channel (0.46 and 0.31). The general observed trend is that, Linear SVM exhibits higher accuracy rates using high-density EEG (0.91 with 14 channels) while Gaussian naive Bayes exhibits better accuracies when using low-density EEG in comparison with the other classifiers (With EMD 0.88, 0.81, 0.76 and 0.61 respectively for 8, 4, 2 and 1 channel). **Channel selection based on non-dominated sorting genetic algorithm for epileptic seizure classification.** We present a multi-objective optimization method for EEG channel selection based on the non-dominated sorting genetic algorithm (NSGA) [2] for epileptic-seizure classification. The features were selected based on EMD or DWT. We tested the complete method on data of 11 patients from the CHB-MIT public dataset. NSGA-II and NSGA-III were tested, showing accuracies of up to 0.98 and 1.00 with only one EEG channel for both methods, using EMD or DWT, respectively, for feature extraction using different classifiers.

![Figure 1](image)

**Figure 1**: EEG Channel selection for epileptic-seizure classification of patient 19. Comparison using NSGA-III and the backward-elimination algorithm.

**References:**


Analysis of transcriptomics and metabolomics data from different stages during in vitro development of the human cerebral cortex using schizophrenia patient derived induced pluripotent stem cells

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[Introduction/Motivation:]
Schizophrenia (SCZ) is a complex mental disorder that is characterised by deficits in thought, mood and behavior [1]. The world–wide risk for SCZ is about 1%, with an estimated heritability of 80%. Genetic studies of SCZ have shown that genes associated with SCZ are highly polygenic, heterogeneous between individuals, and overlap with the risk for other mental disorders such as bipolar disorder and autism [2-5]. Currently, SCZ is seen as one of various possible clinical outcomes from disruption in brain development caused by genetic and/or environmental factors [6]. The developmental hypothesis is supported by studies that revealed many of the genes associated with SCZ and other mental disorders to be involved in early neurodevelopmental processes such as neuronal proliferation, differentiation, maturation, migration, or synapse formation [7-8]. However, both the etiological factors and pathogenesis of SCZ have not been clearly identified yet [9].

[Methods:]
A potential way of breaking down the contributions of genetic and environmental risk factors and untangle the discrepancies between genotype and phenotype might be the use of induced pluripotent stem cells (iPSCs) to build accurate models of neuronal development in vitro. Patient derived iPSCs retain all genetic predisposition of the donor, while the epigenetic state of the cell is set back into an embryonic–like state [10], making it possible to link genetic mutations with a cellular phenotype.

[Results and Discussion:]
To elucidate the pathology of SCZ on a cellular level, we characterized the transcriptomic and metabolic phenotypes of SCZ patient derived iPSCs at six time points using a model of in vitro development of the human cerebral cortex [11]. The data was tested for differences in metabolite abundance and gene expression for each of the individual time points in the context of SCZ. For a systems–wide analysis the transcriptomics and metabolomics data was integrated with biochemical networks and databases. Finally, a subnetwork of differentially regulated genes and metabolites was
visualized and analysed for biological functions to get a better understanding of the onset and progression of SCZ on a cellular level.

References: