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Abstract Booklet

Poster Sessions:

Poster Session A: Thursday, September 18th 1:00-3:00PM, 5:45-6:30PM

Poster Session B: Thursday, September 18th 6:30-7:30PM, Friday, September 19th 1:15-3:15PM

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Poster Session A: Thursday, September 18th 1:00-3:00PM, 5:45-6:30PM

A1

A Multi-patterned Mechanotransduction Sensor to Investigate the Relationship between Receptor Colocalization and Traction Force

Abhishek Sinha*, Sébastien G. Ricoult, Liangcheng Xu, David Juncker, and Timothy E. Kennedy

Cells navigate through complex environments, full of diverse cues that are often surface-bound. Cells can apply a traction force on these proteins in a process called mechanotransduction, which is necessary for cell navigation and proliferation. Despite the importance of this process, no work has been done to investigate cellular mechanotransduction in the presence of multiple surface-bound cues. Previous techniques have been limited by the inability to study cellular response to multiple cues, which would provide a more realistic representation of the extracellular matrix. Our sensor is based on a micropillar array detector (mPAD) which resembles a bed of needles, whereupon deflections caused by cell forces can be measured to derive traction forces. The pillar tips are decorated via humidified microcontact printing, a novel surface patterning technique that manipulates the surface chemistry of the sensor and enables the creation of multi-protein patterns. Here, we developed a novel nanoforce sensor that allows the precise quantification of cell traction on multi-protein patterns. The force sensing capabilities of the sensor were first demonstrated by measuring C2C12 myoblast traction forces on surfaces of different affinities, and comparing the findings with focal adhesion density. The mPADs were then patterned with juxtaposed stripes of the proteins netrin-1 and fibronectin to investigate the force distribution when cells are exposed to multiple protein cues. In parallel, on flat surfaces, TIRF microscopy was conducted to assess the spatial and temporal distributions of receptors on the multi-protein patterns. By combining both sets of data, we established the localization of integrin $\alpha 5$ relative to fibronectin stripes and DCC to netrin-1 stripes and determined the forces engaged by cells responding to these two proteins. This data brings to light a potential mechanism through which cells control traction force on various proteins, via differential receptor recruitment. To investigate the relationship between receptor colocalization and traction force on a single ligand, function blocking experiments can be performed on both surfaces. The presented sensor, for the first time, enables the investigation of mechanotransduction in the presence of multiple cues and opens the door for more complex traction force studies that will expand our understanding of the process of mechanotransduction.

A2

Retinotopic Mapping of a Hemispherectomy Subject with Blindsight

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Previous studies have investigated the neural correlates of blindsight, and have successfully identified certain anatomical structures mediating the residual visual function following destruction of the occipital cortex. However, it is unknown whether hemispherectomy induces a functional reorganization of visual input in the visual areas of the remaining hemisphere. In this study, ultra high field magnetic resonance imaging (7T) was used to non-invasively investigate the neural substrates mediating the unconscious residual vision in the blind hemi-field of a hemispherectomized subject (DR) exhibiting blindsight. As a preliminary step, retinotopic mapping using a checkerboard rotating polar angle wedge (8 clockwise cycles), and a checkerboard eccentricity circle were used to delineate visual areas V1, V2, and V3 in subject DR and 3 healthy controls. The time courses of each area were examined to define their response properties. The results showed that not only does information from both visual hemifields enter the remaining visual cortex of the blindsight subject, but this information also reaches both healthy hemispheres in control subjects. To rule out light scatter as a cause of this bilateral visual input, we rescanned a healthy control using a retinotopy stimulus that was limited to the periphery (4° from fixation). The results confirmed our finding of bilateral input to both hemispheres. We hypothesize that while visual information from both visual hemifields enters both hemispheres in healthy controls, ipsilateral representation undergoes inter-hemispheric transcallosal suppression. Conversely, following destruction of the visual cortex in hemispherectomized subjects, lack of transcallosal suppression combined with functional and anatomical plasticity, allows this information to be accessed and further processed. A cortical thickness analysis was performed on the delineated visual areas of both DR and three healthy controls, and the results indeed suggest anatomical reorganization. While the mean gray matter thickness over visual areas for the healthy controls was 1.2mm, the mean thickness over the same areas was 1.7mm for patient DR.

A3

The Role of Constitutively Active Kinases in Learning and Memory

Larissa Ferguson*, Margaret Hastings, Wayne Sossin

Learning induces memory formation through distinct physical and biochemical neuronal changes, what we call the molecular memory trace. Protein kinase M zeta (PKMzeta) has been shown to play a role in memory maintenance by preventing AMPA receptor endocytosis at the synapse, and we investigate possible mechanisms through which this kinase could function to achieve this goal. In *Aplysia californica* cell cultures, we found that phosphorylation of the protein Numb increased in the presence of PKMzeta overexpression, suggesting that Numb is a likely substrate of PKMzeta. Utilizing a pH-sensitive GFP-AMPA receptor construct--the efficacy of which has been confirmed here--we hope to further investigate the role of the PKMzeta-Numb pathway in AMPA receptor endocytosis during memory maintenance.

A4

Christianson Syndrome-Linked Mutation in the Na⁺/H⁺ Exchanger SLC9A6 Disrupts Recycling Endosomes and Synaptic Structures

Jonathan Reid*, Alina Ilie, Hervé Barriere, Emily Deane, Gergely Lukacs, R. Anne McKinney and John Orłowski

The Na⁺/H⁺ exchanger SLC9A6/NHE6 is a recycling endosomal pH-regulating transporter that is abundant in the CNS. Within hippocampal CA1 pyramidal neurons, NHE6-containing vesicles are distributed throughout the soma and dendrites, with noticeable accumulation at dendritic spines and presynaptic terminals. A number of mutations in NHE6 have been identified in different families with neurodevelopmental disorders, including a 6 base-pair deletion that results in the loss of amino acids E287 and S288 (Δ ES) located near predicted membrane-spanning segment 7. To better understand the nature of this defect, Δ ES as well as single (E287Q, E287A and S288A) and double (E287Q-S288A) mutations were engineered in wild-type (WT) NHE6, and the effects on its biosynthesis, post-translational oligosaccharide processing, membrane trafficking and function were assessed in transfected AP-1 cells as well as cultured hippocampal neurons. We found that only constructs containing mutations of E287 displayed impaired glycosylation and decreased half-life compared to WT. The mutants were still able to traffic to the plasma membrane, though their cell surface levels and rates of endocytosis were significantly diminished. Further examination of the Δ ES mutant revealed a pronounced impairment of recycling endosomal pH and cargo trafficking. Transient expression of the WT and Δ ES mutant in cultured hippocampal neurons also revealed aberrant trafficking of NHE6 Δ ES-containing vesicles that accumulated within the soma, were poorly sorted along the dendritic processes and lead to a reduction in synapses.

A5

The effect of contexts in the interpretation of the feelings of others.

Priscille-Nice Sanon*, Lena Gu, Daina Crafa, Mathieu Brodeur

The interpretation of the emotions of others depends largely on the context in which these emotions appear. A laugh can be happy or sarcastic depending on the circumstances. The importance of context is particularly important when emotions are difficult to decode, when they are ambiguous. In this project, we seek to understand how the information of a scene is used to interpret the emotions of others, especially the ambiguous ones. To do so, we asked 40 participants (20 controls (10 Anglo, 10 French) and 20 patients (10 Anglo, 10 French) to identify emotions of individuals photographed within scenes where ambiguous and non-ambiguous emotions are displayed. During the task, we recorded the brain activity of each participant (EEG) and two types of scene were presented to each one of them. In one, the whole scene helped to interpret the emotions and in another, it didn't. The comparison of these types helped us first identify the type of emotion who are easily identified when in context. These stimuli are then used to investigate a possible abnormal use contextual information among people with schizophrenia . The stimuli were normalized and six pilot subjects were tested. We noticed that the effect of the social context had an impact on ambiguous emotions but not on unambiguous. This effect recalls very much the 300-1000 ms modulation that was observed for the recognition of objects except for the fact that the social context effect is frontally distributed. Accordingly, our preliminary results suggest that brain processing of unambiguous emotions is unaffected by the consistency of the context in contrast to ambiguous emotions which have their activities strongly modulated. This modulation, which reflects the influence of social context, is expected to be of an amplitude significantly smaller than in schizophrenia subjects and its magnitude should predict the severity of delusions.

A6

Neuroanatomical correlates of pitch and time processing in musicians versus nonmusicians

Anastasia Sares*, Nicholas E.V. Foster, Kachina Allen, Krista L. Hyde

Prosody consists of changes in pitch, timing and amplitude of speech that add meaning beyond words, and is useful for analyzing the intersection of speech and music. Here, we sought to investigate the effect of musicianship on prosody processing and brain structure. Adult musicians versus non-musicians were tested on a battery of prosodic tests in which they had to detect changes in pitch in short sentences or their tonal analogues. As expected, participants performed better with larger pitch and time changes in both speech and music, but musicians outperformed nonmusicians overall. Structural MRI data were also obtained, and preliminary structural analyses revealed that better performance on the pitch task was positively correlated with the thickness of the cortex in the posterior STG/STS.

A7

Neural Correlations in the Electrosensory Lateral Line Lobe of the Weakly Electric fish, *Apteronotus leptorhynchus*: Analysis of Multi-Channel Recordings

Teerawat Monnor*, Michael G. Metzen and Maurice J. Chacron

It is recognized that perception and behavior result from the activities of large neural ensembles. As such, it is key to understand the mechanisms that give rise to correlated activity in the brain. However, correlated activity is highly plastic as it is regulated during specific behavioral contexts. In this work, we aim to understand how activation of neural circuits can shape correlated activity by using the weakly electric fish, *Apteronotus leptorhynchus*. We performed multi-channel recordings in the electrosensory lateral line lobe, which benefits from well-characterized neural architecture. First, a spike-sorting algorithm was applied on the recorded signals to extract neural units. Then, correlated activity can be examined from pairwise population-averaged cross-correlograms calculated from all pairs of the extracted units. We found that the activities are positively correlated for neurons of the same type (ON-ON, OFF-OFF), but negatively correlated for neurons of opposite type (i.e. ON-OFF). Also, the effect of different stimulus characteristics on the correlation is observed. While the correlation is decreased by conspecific-like stimuli, it is increased by prey-like stimuli. Furthermore, some neurons tend to fire synchronously at particular portions of stimulus, e.g. at specific phases of sinusoidal stimuli. Thus, this work will give important insights in how correlated activity contributes to the processing of natural stimuli.

A8

Quantification of Protein Levels in Single Cells In Vivo

Chiu-An Lo*, Ibrahim Kays*, Farida Emran, Tsung-Jung Lin, Vedrana Cvetkovska, Brian E. Chen

Accurate measurement of the amount of specific protein a cell produces is important for investigating basic molecular processes of the cell. The current methods for determining protein amounts have poor cellular resolution and are inherently destructive to cells, limiting the accuracy and relevance of the measurements. We have developed a technique that allows for quantitation of protein levels in single living cells. This Protein Quantitation Ratioing (PQR) technique uses a genetic tag that produces a stoichiometric ratio of a fluorescent protein reporter and the protein of interest during protein translation. The fluorescence intensity (i.e., brightness of the cell) is directly proportional to the number of molecules produced of the protein of interest, and thus is used to determine the relative protein amount within the cell. Using quantitative imaging and electrophysiology, we demonstrate that PQR can produce stoichiometric separations and linear relationships between different genes. We use genome editing techniques to insert Protein Quantitation Reporters into endogenous genomic loci in three different genomes for quantitation of endogenous protein levels. Fluorescence quantification of endogenous RPL13A protein levels in a neuron can be used to normalize across experimental and optical conditions, such as spherical aberrations, optical distortions, calcium imaging, and imaging depths during in vivo imaging. The Protein Quantitation Ratioing technique allows for measurements of endogenous or exogenous protein amounts in single living cells in vivo, to relate cellular phenotypes as a function of protein concentrations.

A9

Monocular luminance reduction decreases dichoptic processing in primary visual cortex.

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The mechanisms of suppression in binocular vision might involve a delay in signal processing. Mean luminosity change can cause such a delay in monocular and binocular condition. However, we do not know how reducing the luminance in one eye will modulate the processing of the two eyes. Here, we assessed this dichoptic processing at different luminance conditions with MEG.

We presented two different flickering noise stimuli at 4 and 6Hz in each eye respectively, to elicit a frequency-tagged steady state visual evoked response that was readily detectable in MEG traces. Then, we manipulated the luminance of the eye receiving the 6Hz stimuli with a 1.5ND neutral density filter. We then analyzed the power and dynamics of the response in V1. The ROI was defined from the fMRI retinotopic maps, all the analysis was performed in Brainstorm TM.

In a monocular condition, we observed a delay in the scout time series and a decrease in the power of the response in V1 when the ND filter was applied to the eye. In the dichoptic masking condition, application of the filter to one eye dramatically decreased the contribution of this eye to the dichoptic response: it delayed and decreased the power of the response from the same eye more abruptly than in the monocular condition. In turn, it also greatly increased the power of response in the other eye compared to its dichoptic performance in no-filter condition, therefore making it more dominant.

Luminance is an essential factor in dichoptic vision that can be efficiently assessed with MEG. Our results correlate with previous behavioral findings describing the decrease in binocular function induced by luminance reduction.

A10

Methylene Blue inhibits Caspases by oxidation of the catalytic cysteine

Prateep Pakavathkumar*, Gyanesh Sharma, Vikas Kaushal, and Andrea C. LeBlanc

Caspase-6 activity is found abundantly in the neuropil threads, neuritic plaques and neurofibrillary tangles of familial and sporadic forms of Alzheimer disease. Methylene blue (MB) is a phenothiazine that is currently in phase 3 clinical trials as a Tau aggregation inhibitor for Alzheimer disease. MB prevents aggregation of Tau through oxidation of cysteine residues. Since caspases are dependent on their catalytic cysteine for activity, inhibition of the enzymatic activity of caspase-6 and other caspases by MB was tested.

Recombinant active caspase-6, caspase-3 and caspase-1 were incubated with MB or its metabolites, azure A and azure B. Caspase-6 was inhibited by MB (IC₅₀ = 650 nM), azure A (IC₅₀ = 1320 nM) and azure B (IC₅₀ = 700 nM). Kinetic studies determined that caspase-6 inhibition by MB followed a competitive-mechanism with a K_i of 361 ± 85 nM. MB inhibited caspase-3 (IC₅₀ = 1400 nM) and caspase-1 (IC₅₀ = 3300 nM) but with lower potency than for caspase-6. Non-toxic concentrations of MB, azure A, and azure B were assayed on caspase-6-transfected human colon carcinoma cells. MB and azure B significantly inhibited caspase-6 activity measured by in vitro fluorogenic assay and by detection of caspase-6-cleaved α-tubulin. In addition, MB, azure A, and azure B significantly inhibited Casp6 activity and α-tubulin cleavage in serum-deprived human primary neurons. To determine if the catalytic cysteine of caspase-6 (C163) was oxidized upon addition of phenothiazines, recombinant active caspase-6 was incubated in the presence or absence of MB or azure B and was analyzed by LC/MS/MS. The catalytic C163 was oxidized into the sulfenic form (R-SOH) in 15% and 7.7% of peptides only in the presence of MB or azure B, respectively.

Thus, this study reveals sulfenation of caspase-6 by phenothiazines as a novel inhibitory post-translational modification regulating caspase activity. However, the mechanism of inhibition of other caspases by MB requires further investigation. In addition, the inhibition of Tau aggregation (IC₅₀ = 2000 nM) occurs at a concentration at which caspase-3 (IC₅₀ = 1400 nM) was found to be inhibited by MB. Therefore, careful monitoring of patients receiving MB is warranted since chronic inhibition of caspase-3 could lead to tumor initiation. Finally, caspase-6 was identified as a novel target of MB. This result suggests that the therapeutic benefits of MB in Alzheimer disease patients might be attributed to inhibition of axonal degeneration and memory impairment mediated by caspase-6.

A11

Energy deficient neurons drive vessel growth in a mouse model of proliferative retinopathy

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Vessels deliver oxygen and nutrients to match the energy demands of neurons. Although hypoxia is a well-characterized driver of angiogenesis, little is known about the neuronal energy signals that may stimulate vascular growth. Here we show that energy deficient neurons drive angiogenesis to restore energy homeostasis in a mouse model of retinopathy of prematurity (ROP), the leading cause of blindness in children. Sirtuin-3 (Sirt3), a key mitochondrial deacetylase that regulates energy metabolism, is highly expressed in retinal ganglion neurons and photoreceptors. Inhibition of Sirt3 in retinal neurons promotes the acetylation of isocitrate dehydrogenase, thereby decreasing production of α -ketoglutarate (KG), an important metabolite of the Krebs cycle. Since α -KG is a cofactor required for the degradation of HIF1 α , accumulation of this transcription factor in neurons triggers the secretion of vascular endothelial growth factor (Vegfa). In oxygen-induced retinopathy, a common murine model of ROP, Sirt3 deficient mice (Sirt3^{-/-}) showed increased rates of retinal revascularization compared to wild-type animals, consistent with greater production of vascular growth factors despite identical initial vaso-oblivation. Moreover, faster revascularization in Sirt3^{-/-} mice was protective against pathological neovascularization typically associated with severe ROP. Neuronal energy metabolism may therefore drive retinal angiogenesis in addition to hypoxia, uncovering a novel potential therapeutic target.

A12

The E3 ubiquitin ligase TRAF6 stimulates mutant SOD1 aggregation and interacts with mitochondrial surface-associated misfolded species.

Sabrina Semmler*, Sarah Pickles, Laurie Destroismaisons, Heidi McBride, Christine Vande Velde

Amyotrophic lateral sclerosis (ALS) is a progressive and ultimately fatal neurodegenerative disease, characterized by the loss of motor neurons in the spinal cord and consequent paralysis of skeletal muscles. Mutations in superoxide dismutase 1 (SOD1) account for 20% of familial and about 3% of sporadic ALS cases and mitochondria have long been proposed as targets for toxicity. Mutant SOD1, adopting an aberrant protein folding pattern, preferentially binds to the outer face of mitochondria in patient-derived cell lines and in an age-dependant manner in rodent models of ALS. The presence of misfolded SOD1 on mitochondria correlates with abnormal mitochondrial morphology, dysfunctional mitochondrial protein import and excessive production of superoxide. However, the exact mechanism of misfolded SOD1-mediated mitochondrial dysfunction and motor neuron toxicity remains unexplained.

In a screen for interacting partners of mitochondrial-associated misfolded SOD1 in the SOD1G93A rat model, we identified the E3 ubiquitin ligase TNF-receptor associated factor 6 (TRAF6). TRAF6 is already reported to play a role in various neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's disease, where it frequently ubiquitinates disease-associated mutant proteins and engages in their accumulation into potentially toxic aggregates. We hypothesize that TRAF6 is also involved in the ubiquitination and aggregation of mutant SOD1 on mitochondria and thereby contributes to mitochondrial malfunction and the degeneration of motor neurons in ALS.

Here, we show that misfolded SOD1 interacts in a conformation-dependant manner with TRAF6 on spinal cord mitochondria of symptomatic SOD1G93A rats. TRAF6 is not transcriptionally upregulated, but rather recruited to the mitochondrial surface with disease progression. Interestingly, the immunoprecipitate of the TRAF6-interacting misfolded SOD1 conformer on mitochondria is polyubiquitinated and in an aggregated state. In culture, we demonstrate that the knockdown of TRAF6 alleviates mutant SOD1 aggregate formation. To establish relevance for TRAF6 in the cell type primarily lost in ALS, we find TRAF6 predominantly expressed in lumbar spinal motor neurons.

A13

The Link between Dysregulation of Neurofilament Metabolism and Mitochondrial Form and Function in Autosomal Recessive Cerebellar Ataxia of Charlevoix-Saguenay (ARSACS)

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Introduction: Autosomal Recessive Cerebellar Ataxia of Charlevoix-Saguenay (ARSACS) is a complex inherited neurodegenerative disorder typically presenting in early childhood with progressive cerebellar ataxia, spastic paraplegia and motor-sensory neuropathy, leading to a significant decrease in mobility and death in the fifth decade. ARSACS, first described in Quebec, is caused by mutations in the SACS gene, encoding the giant protein of 4579 amino acids, Sacsin. Sacsin has been localized to mitochondria and the cytoplasm, but its function is unknown. In cellular models (Sacs^{-/-} mice and derived spinal cord-dorsal root ganglion (DRG) cultures; skin fibroblasts cultured from patients) the ARSACS team has identified disruption of intermediate filament (IF) organization as well as changes in mitochondrial morphology.

Purpose of the study: IF play important roles in organizing the cytoplasm, including placement of the nucleus and organelles including mitochondria, and regulating mitochondrial dynamics. We are investigating the hypothesis that ARSACS is a disorder of intermediate filament organization leading to changes cellular organization and in mitochondrial morphology and function. My thesis project is to measure several aspects of mitochondrial function in relation to changes in expression and organization of IF proteins.

Methods: Dissociated spinal cord-DRG cultures were prepared from E13 Sacs^{-/-} embryos and the following parameters measured at intervals up to 7 weeks. Nuclear placement and integrity of the nucleo-cytoskeleton was examined by phase microscopy and by immunolabeling of emerin, a nuclear lamina-associated protein mediating anchorage of the nuclear membrane to the cytoskeleton. IF organization was investigated using antibodies to NFL and NFH. Mitochondrial length was measured after labeling of TOM20 or Cytochrome C. Production of mtRNA and/or formation of RNA granules is being monitored using incorporation of BrU and antibodies to BrU and FASTKD2. Production of mtDNA and/or formation of mitochondrial nucleoids is being monitored by incorporation of BrdU and antibodies to BrdU and TFAM. Cultured fibroblasts from control and ARSACS individuals are being used to evaluate integrity of mitochondrial respiratory chain complexes and energy metabolism using Blue Native gel electrophoresis and Oxygraph respirometry, respectively.

Results and Discussion: Bundling of neurofilaments (NF) and increase in levels of NFH preceded changes in mitochondrial morphology and displacement of organelles. Bundles and juxtannuclear aggregates of NF were detected in motor and sensory neurons of Sacs^{-/-} spinal cord-DRG cultures by 3 weeks in vitro. Subsequently, nuclei were displaced toward the periphery, but otherwise emerin labeling appeared normal. By 5 weeks, mitochondria were elongated in motor neurons, but fragmented in sensory neurons. Studies of mitochondrial function are ongoing. Preliminary data support altered IF metabolism being a primary result of ARSACS mutations.

A14

Plasticity of the Dopaminergic System in Fear Conditioning and Extinction

Jennifer I. Lissemore*, Atsuko Nagano-Saito, Paul Gravel, Marco Leyton & Chawki Benkelfat

Background: A conditioned dopamine (DA) response has been found to occur during associative learning with reward in humans. In animal studies, DA has also been shown to play a role in associative learning with aversive cues, also known as fear conditioning. Brain regions implicated in fear conditioning studies with animals include the amygdala, hippocampus, nucleus accumbens, ventral tegmental area-substantia nigra, and the medial prefrontal cortex (mPFC); in addition, the extinction of fear learning has been shown to involve the ventromedial prefrontal cortex. Although activity in these areas has been reported in humans during fear conditioning, little is known about the dopaminergic correlates/activity. The current study uses PET and 18F-Fallypride to investigate DA release in nodes of the fear circuit, in healthy adults, during fear conditioning and extinction.

Methods: Five healthy volunteers have completed the study to date. All showed an adequate acute physiological response to the aversive stimulus, a mild electric shock to the wrist (heart rate increase of $>1SD$, or skin conductance response increase of $>10\%$). PET imaging was carried out using a high-resolution research tomograph (HRRT) and 18F-Fallypride to measure DA release in brain regions of interest (ROI). After an initial PET scan without shock exposure, participants learned to associate the electric shock with a neutral cue through a trace conditioning procedure with a 30% contingency rate. Participants were then presented with the shock-paired stimulus during a second PET scan. Lastly, the association between the conditioned stimulus and aversive shock was extinguished by repeatedly presenting the cue in the absence of the electric shock, and participants then had a third and final PET scan while being repeatedly exposed to the extinguished cue. ROI analyses were performed on binding potential (BP) data. The skin conductance response (SCR), heart rate (HR) and plasma cortisol levels were measured as physiological measures of fear throughout all sessions. Subjective ratings were also recorded to assess whether the correct association was learned, and to measure the level of anxiety experienced by participants in response to the neutral cues.

Results: Following the fear conditioning regimen, the shock-paired cue significantly increased SCR ($p < 0.05$) as compared to baseline. Following extinction, the SCR fear response was significantly reduced ($p < 0.05$) and BP was lower than baseline in the posterior cingulate gyrus (PCG; 18% displacement; $p < 0.01$), suggesting increased DA release as compared to baseline. No significant differences in BP between scans were observed in nodes of the fear circuit ($p > 0.05$).

Discussion: These very preliminary findings suggest that the PCG, a region believed to be involved in the default mode network, plays a role in the dopaminergic control of extinction. Advancing our understanding of the specific neurochemical mechanisms underlying fear learning and extinction may have implications for the pathophysiology and treatment of stress and anxiety related disorders.

A15

Dietary effect on the expression of the cholesteryl ester transfer protein and cellular stress in the brain

Felix Oestereich*, Paoula Gueorguieva, Lisa Munter

Background: The cholesteryl ester transfer protein (CETP) is a soluble glycoprotein that shuttles cholesteryl esters and neutral lipids between lipoproteins. Lipoproteins play an important role in atherosclerosis, considering that a decreased ratio of high to low density lipoproteins is a major risk factor. Reduced CETP function results in the increase of the anti-atherogenic HDL and a reduced risk for atherosclerosis. Additionally, the diet has a substantial impact on lipoprotein homeostasis and diets enriched in fat and cholesterol can induce cellular stress and apoptosis. So far the role of CETP in the brain, especially in conjunction with dietary fat and cholesterol intake, is poorly understood.

Hypothesis: I hypothesize that CETP expression in the brain induces stress responses, especially in conjunction with an atherogenic diet.

Method: Using CETP transgenic mice and different diets, I analyze the effects of CETP expression and diet on the brain lipid and cholesterol metabolism and cellular stress.

Results: CETP transgenic mice show high CETP expression in the brain and dietary cholesterol further increases CETP activity and mass.

A16

Prenatal Maternal Stress from a natural disaster predicts hippocampus volumes in males at age 11: Project Ice Storm

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Introduction: The hippocampus develops primarily during the fetal period and plays a pivotal role in learning and memory. Non-human primate studies have demonstrated that early and late in utero exposure to maternal stress results in reduced hippocampal volumes. However, no human prospective studies of the effects of prenatal maternal stress (PNMS) on the hippocampal development have been conducted.

Objective: To determine whether in utero exposure to disaster-related PNMS is associated with altered hippocampal volumes in 11½ year-old children. We hypothesized that higher maternal objective and/or subjective PNMS levels would be related to smaller hippocampal volumes.

Methods: Measures of maternal objective (i.e., events the women experienced) and subjective (i.e., the women's psychological response to the crisis) PNMS were obtained after the 1998 Quebec Ice Storm. We obtained T1-weighted images of 33 males and 32 female 11½ year olds. Hippocampal segmentations from native MRI scans were performed using the automatic SACHA method. The number of obstetric complications was recorded using hospital records.

Results: Overall, more obstetric complications were related to smaller right hippocampal volumes (RHCV). Higher levels of maternal objective PNMS were related to smaller RHCV in males only. Inspection of the objective hardship x obstetric complication interaction revealed that males exposed to high levels of objective hardship or obstetric complications or both had smaller RHCV compared to males exposed to low levels of objective hardship and obstetric complications.

Conclusions: Our results suggest that higher levels of disaster-related objective PNMS, but not subjective PNMS are related to smaller RHCV in male but not female adolescents. It remains to be determined whether this alteration in RHCV in 11½ years old males is related to observable phenotypes.

Acknowledgements: This research was funded by grants from the March of Dimes foundation and the Canadian Institutes of Health Research.

A17

Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides

Susana G. Torres-Platas*, Cristiana Cruceanu, Gary Gang Chen, Julia Devorak, Gustavo Turecki, Naguib Mechawar

Background: Despite all the evidence supporting the neuroinflammatory theory of depression, there is currently limited information regarding the state cerebral macrophages in individuals suffering from major depression. The aim of the present study was to examine the morphology and distribution of microglial cells and other cerebral macrophages in the dorsal anterior cingulate cortex (dACC) white matter of depressed suicides and matched nonpsychiatric controls. This region is of particular interest since we previously described the presence of hypertrophic astrocytes in depressed suicides and imaging studies have confirmed its implication in mood disorders.

Methods: Using immunostained sections with the macrophage-specific marker ionized calcium binding adaptor molecule 1 (IBA1), distributions of microglial phenotypes were assessed using stereology and cell morphometry. Blood vessels were characterized as being associated with either a high or a low density of macrophages in IBA1 and CD45-IR sections. The mRNA expression levels were quantified using real time-PCR.

Results: Total densities of IBA1-immunoreactive (IR) microglia were statistically similar between groups. However, the relative proportions of primed microglia were significantly increased in depressed suicides. The proportion of blood vessels surrounded by a high density of IBA1-IR macrophages was significantly higher in depressed suicides than in controls (87% vs 42%, respectively). Consistent with these findings, the mRNA expression levels of both IBA1, MCP-1, a chemokine involved in the recruitment of circulating monocytes, and Zona Occludens-1 were significantly upregulated in depressed suicides. Furthermore, the mRNA expression levels of CD45, a marker enriched in perivascular macrophages, showed a significant increase in samples from depressed suicides but the proportion of blood vessels surrounded by a high density of CD45-IR cells was similar between groups.

Conclusion: Our results show evidence of microglial priming and a possible recruitment of macrophages in the dACC white matter of depressed suicides. However, we cannot exclude the possibility of other types of macrophages (including microglia) accounting for the observed increase in macrophages associated with blood vessels. Altogether, these findings suggest that the previously reported depression- and suicide-related increases in circulating pro-inflammatory cytokines may be associated with low-grade cerebral neuroinflammation involving the recruitment of circulating monocytes.

A18

RHBDL4 mediated cleavage of Amyloid precursor protein

Sandra Paschkowsky*, Felix Oestereich, Mehdi Hamze and Lisa Munter

Undeniably one of the most devastating modern diseases, with 500000 patients only in Canada, is Alzheimers disease. It's still not fully understood how the generation of so called A β peptides ultimately leads to the manifestation of neurodegeneration and memory loss. A β oligomers are considered the toxic species and one of the main reasons for AD pathology. The generation of A β occurs upon a very specific processing of the transmembrane amyloid precursor protein (APP), which involves two subsequent cleavages by β -secretase and γ -secretase. So far no pharmacological treatment was able to halt or reverse the progression of Alzheimers, which is why new potential targets need to be evaluated.

Here we investigated the human rhomboid-related protein4 (RHBDL4) for its involvement in Alzheimers disease. Rhomboid proteases belong to the class of intramembrane proteases, consisting of 5 active human isoforms, while so far only the mitochondria associated PARL is well characterized and associated with Parkinsons disease. RHBDL4 was shown to be important for ERAD mediated degradation of different transmembrane proteins and ER stress has also been described in Alzheimers disease. Interestingly, we showed now that APP is a substrate for RHBDL4. Upon overexpression of APP and RHBDL4 in HEK 293 T cells we observe a strong reduction of full length APP and the appearance of a 75kDa APP ectodomain fragment. This effect wasn't observed with a catalytically inactive RHBDL4 mutant. Further we observed a change in the pattern of C-terminal fragments (CTF) of APP. In addition we detected a clear reduction in soluble APP levels in the supernatant as well as in A β levels as determined by western blotting. In a cell surface biotinylation approach we found these CTFs localized at the plasma membrane. Preliminary data also indicated an upregulation of RHBDL4 on mRNA level from AD patients compared to aged matched controls in the hippocampus as well as the frontal cortex. Combined with data from the Allan brain atlas, which suggests the expression of RHBDL4 in various brain regions, we therefore propose RHBDL4 as a possible new target for the regulation of APP processing.

A19

The specificity of dance versus music training on gray matter structure

Falisha Karpati*, Chiara Giacosa, Nicholas E.V. Foster, Virginia Penhune, Krista L. Hyde

Introduction:

Individuals with specialized training, such as musicians and dancers, provide a unique way to study human brain plasticity. Here we compared gray matter structure in professional dancers and musicians relative to untrained controls in order to examine what brain areas might be the same or different across these two auditory-motor art forms.

Methods:

We used magnetic resonance imaging to measure cortical thickness (CT) in 20 dancers, 19 musicians and 20 controls. Participants were also tested on a battery of music- and dance-related tasks. Statistical analyses were performed across the whole brain to test for group differences in CT and regions where CT is correlated with task performance.

Results:

Dancers showed thicker cortex than controls in several regions including bilateral superior temporal gyrus (STG). Musicians showed thicker cortex than controls in several occipital and temporal regions, including right STG. Musicians showed thicker cortex than dancers in small regions of the left parahippocampal gyrus and right postcentral gyrus. Cortical thickness in temporal and occipital regions were correlated with task performance.

Conclusions:

These results suggest that dance and music training similarly affect brain regions associated with auditory processing, specifically the STG. This work advances our understanding of the specificity of the neural correlates of dance and music training, and may have potential applications in therapies for motor disorders.

A20

TrkA as a pharmacological target to modulate memory formation

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Our research focuses on the Nerve Growth Factor (NGF) receptor tropomyosin-receptor-kinase A (TrkA). NGF and TrkA are expressed in the cholinergic neurons of the CNS and are key molecules for the maintenance of neuronal homeostasis, proliferation, circuitry formation, and memory. Accordingly, decreased TrkA density and function correlate linearly with disease progression in Alzheimer's disease (AD), Down's syndrome, and cognitive impairment linked to ageing. Also, NGF transport has been shown to be impaired in AD.

By synthesizing agonists of TrkA, our lab aims to stop (and possibly reverse) the memory deficits observed in these pathologies, through neuronal rescue. Our lab reported a small molecule TrkA partial agonist termed D3, which activates TrkA and potentiates the effect of NGF. D3 improved long-term memory (LTM) in aged, memory-impaired rats; as well as learning and short-term memory (STM) in an APP-overexpressing mouse model of memory-impairment. Paradoxically, however, two-week administration of D3 impaired LTM in healthy, young, wild type mice without effects on learning or STM, and without signs of toxicity. Here we report putative underlying pathways leading to this impairment.

Young wild type mice were treated with intraventricular D3 for 2 weeks and their brains were studied biochemically and by immunofluorescence. The mice had altered signaling pathways in the hippocampus, a memory relay organ, but not in the cortex. We detected significantly increased pAkt, CREB and Erk5; these are signals downstream of TrkA, that are reported to be relevant to memory formation. Conversely, we detected decreased BrdU+ neurons in the CA1 region of the hippocampus, likely due to abnormal neuronal migration and/or exhaustion. We also noted a significant decrease in CaMKII α in synaptosome preparations collected two months after treatment. We hypothesize that this disruption of the normal (wild type) TrkA/NGF homeostasis may cause defects in hippocampal synapses and therefore the LTM impairment quantified in wild type mice. This work will shed light on the mechanisms elicited by D3 and its possible use (or that of similar molecules) as a treatment for memory-related pathologies.

A21

Early signs of activation in the chick embryo cholinergic system

Aimee Chan*, Maria Pompeiano

The cholinergic neurons of the dorsal pontine tegmentum (DPT) are most active during waking and rapid eye movement (REM) sleep in adult mammals, in which they regulate cortical activation. However, their involvement in the emergence of waking-like states or development of REM sleep in developing embryos is less known. To examine this issue we use chick embryos to examine this as birds (chickens) exhibit similar sleep and wake characteristics as mammals but are developmentally isolated and thus free of external influences (Rattenbourg and Martinez-Gonzalez 2012). As well, a waking-like state can be induced in late-stages of embryonic development (Balaban et al. 2012), and REM-sleep-like EEG patterns can also be seen around this time (Martinez-Gonzalez et al. 2012), making the chick embryo an ideal animal model for our experiments.

Fertilized eggs were incubated under standard conditions (37.5°C and 50-60% relative humidity). At varying ages, embryos and hatchlings were sacrificed and intracardially perfused with fixative. Brains were frozen and sections cut at a cryostat. Immunofluorescent double-labelling was done using antibodies against choline acetyltransferase (Millipore) and cFos (Santa Cruz Biotechnology), a marker of neuronal activation.

Activation, as determined from cFos expression, was first detected at E16 although it was minimal. However, as development proceeds there is an increase in cholinergic activation which reaches its' peak in pipped (air-breathing) embryos. Activation levels declined to basal levels in awake hatchlings, although levels were increased in adult (P21) chicks. cFos expression was also seen in non-cholinergic cells, but within the immediate vicinity of the DPT.

These results suggest that the cholinergic DPT neurons may be involved in the emergence of sleep-like states in the final few days before hatching, but less so in waking compared to mammals. Ongoing experiments are increasing the sample size in both embryonic and post-hatched, asleep animals. Further work is also necessary to better characterize the neurotransmitter phenotypes of the active non-cholinergic neurons in these areas, which may also contribute to the development of sleep and waking regulation.

Determining the oligomeric state of the beta-site APP-cleaving enzyme 1 (BACE1) in natural membranes

Filip Liebsch*, Mark Aourousseau, Lisa M. Munter, Holger Sieg, Tobias Bethge, Derek Bowie, and Gerd Multhaup

Background:

The beta-site APP-cleaving enzyme 1 (BACE1) has a transmembrane sequence (TMS), which is necessary for effective BACE1 cleavage of the amyloid precursor protein (APP). An uncommon sulfur-rich motif, MxxxCxxxMxxxCxMxC, spans the entire TMS of BACE1. The sequence is highly conserved among homologues and is reminiscent of a high-affinity binding site for Cu(I) found in other copper-transporting proteins.

Methods:

We designed model peptides of the BACE1-TMS to investigate metal-ion binding and oligomerization uncoupled from the cytoplasmic and the ectodomain. A set of biophysical and colorimetric methods was used to investigate peptide-metal ion complex formation. The role of the metal-ion binding motif in potentially pre-existing oligomers of full-length BACE1 was assessed by Foerster resonance energy transfer, automated single-molecule fluorescence counting in living cells, as well as by blue-native and SDS-gel electrophoresis.

Results

We found that the sulfur-rich core motif MxxxCxxxM is involved in metal-ion coordination and oligomerization of BACE1. Addition of Cu(II) facilitated the formation of dimers and trimers of the BACE1 TMS. Importantly, the peptide undergoes a redox reaction with copper ions, resulting in a disulfide bridge involving Cys466 in the center of the conserved MxxxCxxxM motif as the key amino acid. Further, we find peptide trimerization to depend on (i) the presence of monovalent copper ions and (ii) the sulfhydryl group of Cys466.

For the full-length protein, FLIM-FRET experiments revealed that BACE1 oligomers are naturally present in living cells, as the oligomeric state of BACE1 remained unchanged in the absence or presence of metal-ions. We determined a stable trimeric assembly of BACE1 in the plasma membrane by accurate single-molecule fluorescence counting. Although the oligomeric state of full-length BACE1 was not altered by the addition of copper in living cells, the addition of monovalent metal-ions was required to visualize di- and oligomers by Western blot analysis.

Conclusion:

We propose that BACE1 acts as a bona fide metalloprotein in an oligomeric form in vivo. Additionally, our results demonstrate a novel metal-ion controlled stabilization mediated by the TMS of the BACE1.

Optogenetic investigation of septal GABAergic modulation of hippocampal theta rhythm.

Richard Boyce*, Stephen Glasgow, Sylvain Williams and Antoine Adamantidis

Hippocampal neurons oscillate in synchrony at theta (4-10 Hz) frequencies during periods of wakefulness and rapid-eye-movement (REM) sleep, and evidence suggests that these theta rhythms are required for cognitive processing. The hippocampus receives cholinergic, glutamatergic and inhibitory GABAergic inputs from the medial septum (MS), a brain region required for normal theta rhythm generation in vivo. Previous work using lesional, pharmacological or electrical modulation of MS cell activity suggested that septal GABAergic neurons may be important for theta rhythm generation. However, due to the difficulty in achieving both temporal precision in combination with cell-type specificity using these methods, the causality of this neural pathway on hippocampal theta rhythms remains to be clarified. Here, we genetically targeted archaerhodopsin (ArchT), a silencing opsin to GABAergic neurons of the MS. We found that yellow light pulses reliably hyperpolarized ArchT-expressing cells by ~ 40 mV, preventing spiking in transfected neurons completely, in the MS in brain slices in vitro. Using a combination of optogenetic and electrophysiological (MS unit recording and dorsal hippocampal CA1 field potential and unit recording) techniques in freely-moving mice, we further found that spiking of canonically GABAergic neurons in the MS was completely blocked and hippocampal theta power was significantly (> 60%) and reversibly attenuated when septal GABAergic neurons were optically inhibited during periods of active wakefulness or REM sleep. These results demonstrate that septal GABAergic neurons are critical for normal hippocampal theta rhythm in vivo. Additionally, this data may implicate this neuronal population as an important component of cognitive processing mechanisms during wakefulness as well as REM sleep, a concept that is presently being tested experimentally.

Investigating the role of Fragile-X related protein 1 in Brain Plasticity

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Fragile X Related Protein 1 (FXR1P) is one of two autosomal homologues of the Fragile X Mental Retardation Protein (FMRP), a protein whose expression is significantly reduced in Fragile-X Syndrome. Like FMRP, FXR1P is an mRNA binding protein that is implicated in regulating the synthesis of specific target proteins. However, in comparison to FMRP, little is known about the function of FXR1P in brain function. Our lab has recently discovered that FXR1P co-localizes with translational machinery near synapses suggesting that it could play a role in locally controlling the levels of proteins involved in synaptic plasticity and learning and memory. In order to test this, we have generated an FXR1 conditional knockout mouse model where the FXR1 gene is conditionally ablated from neurons in the forebrain, including the hippocampus. Interestingly, we have found that FXR1P is critical for regulating the expression of the AMPA-type glutamate receptor subunit GluA2; a protein known to have a profound role in synaptic plasticity and learning and memory. Moreover, we have also found that FXR1P conditional knock-out mice have significant changes in synaptic plasticity, synaptic morphology, and cognitive function. We are currently investigating the mechanism through which FXR1P regulates GluA2 expression, and in turn understand the implications of this mechanism in learning and memory and autism-like behaviors.

A25

IgLON proteins shed from the cell surface of cortical neurons to promote neuronal growth

Ricardo Sanz*, Gino B. Ferraro, Alyson E. Fournier

Matrix metalloproteinases (MMPs) and A disintegrin and metalloproteinases (ADAMs) are members of the zinc endopeptidases, which cleave components of the extracellular matrix as well as cell surface proteins resulting in degradation or release of biologically active fragments. Surface ectodomain shedding affects numerous biological processes including survival, axon outgrowth, axon guidance and synaptogenesis. In the present study, we evaluated the role of metalloproteinases in regulating cortical neurite growth. We find that treatment of mature cortical neurons with pan-metalloproteinase inhibitors or with tissue inhibitor of metalloproteinases 3 (TIMP3), reduces neurite outgrowth. Through mass spectrometry we characterized the metalloproteinase-sensitive cell surface proteome of mature cortical neurons. Members of the IgLON family of glycosyl-phosphatidyl inositol (GPI)-anchored neural cell adhesion molecules were identified and validated as proteins that are shed from the surface of mature cortical neurons in a metalloproteinase-dependent manner. Introduction of IgLON proteins in early embryonic neurons is sufficient to confer sensitivity to metalloproteinase inhibitors in neurite outgrowth assays. Outgrowth experiments on immobilized IgLON proteins revealed a role for the IgLON family members Neurotrimin and NEGR1 in promoting neurite extension from cortical neurons. Together our findings support a role for metalloproteinase-dependent shedding of IgLON family members in regulating neurite outgrowth from mature cortical neurons

A26

Real time source imaging neurofeedback with MEG

Soheila Samiee*, Sylvain Baillet

There is a considerable and renewed interest in brain-computer interface and a range of new therapeutic applications using biofeedback techniques, whereby subjects are informed in real-time of their performance in meeting a specified target based on physiological metrics. A major impediment to biofeedback so far, has been the limited specificity of measured signals. For instance, heart rate is only an indirect measure of stress levels; the smeared brain signals captured with electroencephalography (EEG) electrodes are nonspecific of targeted brain regions.

In the Neurospeed lab, we developed an approach to biofeedback, based on a real-time brain imaging with magnetoencephalography (MEG) system, having a unique combination of spatial specificity (to monitor activity emerging from predetermined brain regions) and temporal resolution (to monitor rapid processes in ongoing neural activities). In this real-time technique, all the processing steps from noise removal, to source imaging, and biometric extraction, are being performed online within only 22.5 ± 1.1 ms. In the present study, we introduce: a low-delay neurofeedback loop for realtime MEG source imaging, a novel dynamic visual feedback display, and evaluation of the specificity of the training effects. Overall, the technique enables modulation of targeted neural dynamics in specific, predefined brain regions.

A27

An optogenetic kindling model of epilepsy

Elvis Cela*, Andrew J Chung, Taiji Wang, Jesper Sjöström

Epilepsy is a common neurological disorder characterized by aberrant firing of neurons. To study local circuit changes associated with epileptogenesis, we developed a novel optogenetic animal model of epilepsy. We drove expression of Channelrhodopsin-2 (ChR2) in primary motor cortex (M1) using AAV-CaMKIIa-hChR2-E123T/T159C-p2A-EYFP and used repeated high-frequency stimulation (kindling) with 445-nm laser pulses to elicit seizures while recording EEG in awake behaving animals. We could not elicit seizures in early sessions but seizures were consistently evoked after ~15 sessions. We quantified seizure duration by EEG, and their severity using a modified Racine scale and found that the duration and severity of seizures increased with sessions. This progressive development of seizures was similar across animals. To our knowledge, our results are the first demonstration that repeated optogenetic stimulation alone can elicit epilepsy in otherwise healthy animals. Additionally, our optogenetic model allows the identification of directly activated cells, which may allow for elucidation of the role of specific cell populations in epileptogenesis.

A28

Kainate receptor heteromers and auxiliary proteins relieve channel block by facilitating polyamine permeation

Patricia MGE Brown*, Mark RP Arousseau, Maria Musgaard, Philip Biggin, Derek Bowie

Channel block and permeation by cytoplasmic polyamines is a common feature of many cation-selective ion-channels. Although the physiological basis of the channel block mechanism has been studied extensively, the significance of polyamine permeation is less clear. Here, we show that kainate receptor (KAR) heteromers and their auxiliary proteins, Neto1 and Neto2, attenuate polyamine channel block by facilitating blocker permeation. The relative permeability of the polyamine, spermine, to Na⁺ is significant in GluK2 KARs in complex with auxiliary proteins or as GluK2/K5 heteromers but undetectable when expressed alone. Relief of block in heteromers is due to a single proline residue that is predicted to alter the permeation pathway by kinking a re-entrant alpha-helical loop in the channel pore. Ongoing experiments are testing whether the effect of auxiliary proteins is also reliant on a similar structural mechanism. Since native receptors assemble as heteromers in complex with auxiliary proteins, our data identifies an unappreciated role of polyamine transport in shaping the signaling properties of neuronal KARs.

Spontaneous and stimulus-entrained cross-frequency coupling: spiking-neuron modelling and experimental results from human visual gamma oscillations

Peter Donhauser*, Esther Florin, Sylvain Baillet

Cross-frequency phase-amplitude coupling (PAC) between neural oscillations in different frequency bands has been observed in field recordings of the hippocampus and neocortex [1,2]. Whereas PAC in the hippocampus is confined to nested theta-gamma oscillations, cortical PAC has been reported between gamma and a wide range of delta/theta oscillations. These have been proposed to support attentional selection of rhythmic sensory stimuli [3]. Here, we discuss interactions between intrinsic oscillatory processes and external stimuli on a mechanistic level using spiking neuron simulations. The models differ in their flexibility to changes in the frequency content of stimuli and the strength of gamma modulation. Further, we aim to test these interactions using MEG recordings from the human brain. In the context of visual gamma oscillations, we demonstrate reliable modulation of slow oscillations and gamma amplitude by periodic stimuli and a maintenance of this pattern through periods without stimulation, arguing for intrinsic oscillatory mechanisms rather than pure stimulus induced patterns.

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A30

Dimensionality reduction in exploratory large-scale functional connectivity analysis

Guiomar Niso*, Sebastien Dery *, Francois Tadel, Sylvain Baillet

To identify the dynamical interactions between multiple regions of the human brain has attracted major interest in recent years. A wide variety of functional and effective connectivity models and metrics have been proposed to reveal regional neural interactions from MEG and EEG source time series. However, this is leading to a computational conundrum, because of the necessity of sampling the convoluted geometry of the brain with thousands of elementary current sources, hence yielding exponential pairwise combinations for extracting region-to-region interactions.

The restriction of connectomic analyses to a small set of predefined anatomical regions of interest is an option to keep “the curse of dimensionality” under control. However, this approach is not adequate for exploratory data analysis. Here we propose a new data-driven selection scheme based on multi-resolution clustering indexed on the similarity of minimum-norm imaging kernel across the source support, and compare this new approach with other, more common procedures. Performance was tested on 100 scenarios based on synthetic data: we generated 6 signals using AR models in 6 random and spatially-extended locations of the brain, assigning a known pattern of connectivity including unidirectional connections (trees, chains, loops), bidirectional relationships and isolated regions. We simulated the sensor data generated by these random scouts following MEG forward modelling, with additional physiological noise. Finally, source maps were retrieved from the weighted minimum-norm estimator of Brainstorm and connectivity analysis was performed using the proposed new approach. We obtained ROC curves of sensibility and specificity for the performance of the different approaches tested, as well as a comparative estimate of the computing times required.

Our results indicate improved performances in terms of sensitivity, specificity and computational time required, and offer promising perspectives for the effective exploration of brain connectomics at the global brain scale, from time-resolved data.

A31

Luman contributes to ER stress-induced PRNP gene expression by interacting with the ERSE26 element

Marc-Andre Dery* and Andrea C. LeBlanc

The prion protein (PrP) is a widely expressed sialoglycoprotein notorious for its role in the aetiology of familial and sporadic prion diseases. However, despite that (1) PrP is necessary for prion disease, (2) PrP levels influence disease progression, and that (3) prion protein protects human primary neurons and the breast carcinoma cell line MCF-7 against cell death, the regulation of the prion protein gene (PRNP) expression is still not fully understood. ER stress was recently identified as a regulator of PRNP gene expression and this regulation was shown to be partly mediated by cleaved Activating Transcription Factor 6 (ATF6a) and spliced X-Box protein 1 (sXBP1). Luman is an ubiquitously expressed, non-canonical mediator of the unfolded protein response. The objective of this study was to investigate the contribution of Luman to the up-regulation of the PRNP gene expression by ER stress.

Human MCF-7 cells, neurons and astrocytes were treated with the pharmacological ER stressor brefeldin A (BFA). Following ER stress treatment, Luman mRNA levels were assessed by RT-PCR and Luman proteolytic activation was confirmed by western blot. The impact of cleaved Luman (N-Luman) on PRNP gene expression was investigated by assessing PrP mRNA and protein levels in N-Luman-overexpressing MCF-7 cells. The contribution of Luman to ER stress-induced PRNP gene expression was addressed by determining the effect of silencing Luman on BFA-induced increase in PrP levels. The influence of N-Luman on the PRNP gene promoter activity was investigated by co-transfecting N-Luman with a PRNP promoter luciferase reporter plasmid. Site-directed mutagenesis of the PRNP promoter was used to identify which ERSE element is necessary to the regulation of PRNP promoter activity by N-Luman. Interaction between N-Luman and the PRNP promoter was assessed by chromatin immunoprecipitation.

BFA treatment increased Luman mRNA in MCF-7, neurons and astrocytes. BFA treatment also lead to Luman proteolytic activation. N-Luman overexpression increased both PrP mRNA and protein levels. Silencing of Luman reduced BFA-induced increase in PrP protein levels. N-Luman overexpression increased PRNP gene promoter activity and mutation of the PRNP ERSE26 element reduced N-Luman-induced increase in PRNP promoter activity. N-Luman binding to the ERSE26 region was confirmed by chromatin immunoprecipitation. We conclude that N-Luman contributes to ER stress-induced PRNP gene expression by interacting with the ERSE26 element. This suggests that PrP plays a role in the unfolded protein response. However, by raising PrP levels, this regulation could collaterally contribute to prion disease progression.

Regional variability of the brain hemodynamic response to spontaneous and step-induced CO₂ changes

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Abstract: The cerebral vasculature is exquisitely sensitive to arterial CO₂ variations, especially respiratory-related areas in the brainstem and the thalamus, as shown by standard voxelwise analysis of BOLD fMRI data [4],[3]. Here, we examine in detail the characteristics of the hemodynamic response function (HRF) between CO₂ changes and the BOLD fMRI signal in small voxel neighbourhoods using linear input-output models and functional expansion techniques. The results reveal regional variability of the HRF and its features, such as peak value, time-to-peak and area.

Methods: We acquired 16 coronal oblique slices of the brainstem of 12 healthy volunteers (voxel size 2.5x2.5x3mm). During spontaneous breathing conditions, conducted first, the subjects were not asked to perform a particular task. Following this, CO₂ challenges were delivered via a computer controlled dynamic end-tidal forcing system, which raised end-tidal CO₂ (PETCO₂) by either 2 or 4mm Hg and maintained end-tidal O₂ at 200mmHg [3]. Initially, PETCO₂ time-series along with averaged BOLD time series within larger anatomically or functionally defined regions of interest (ROIs) were employed in order to define a range of possible values for the time extent of the HRFs in different areas, using the Laguerre expansion technique [2]. Based on these, we defined an extended set of gamma pdfs and we applied singular value decomposition (SVD) to obtain a reduced basis set and achieve more robust estimation in smaller voxel neighbourhoods, whereby the signal to noise ratio (SNR) is much lower. Thereafter, we constructed group spatial maps in the MNI space for the HRF peak value, time to peak, and area, for both resting and forcing conditions. Nonparametric statistical comparisons were performed [1] to identify their significant differences.

Conclusions: The results reveal considerable variability in the HRF features during both experimental conditions (resting and forcing). They also reveal that the HRF during resting conditions exhibited a late undershoot that was absent during forcing conditions. The results of the spatial maps for the HRF peak suggest that during resting conditions, reactivity to CO₂ is overall stronger in cortical areas compared to subcortical areas. However, during forcing conditions, reactivity in cortical areas such as the thalamus and brainstem becomes more pronounced, which generally agrees with the voxel-wise results presented in [3].

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A33

AMIGO-1 regulates the targeting of olfactory sensory neuron axons

*Reesha Raja, Emilie Dumontier, and Jean-François Cloutier

Proper sensory system functioning relies on the development of precise connections between sensory and second order neurons in a topographic manner. Sensory axons are guided toward their correct synaptic partners by various axon guidance and cell adhesion molecules (CAMs). In the olfactory system, olfactory sensory neurons (OSNs) expressing the same olfactory receptor (OR) innervate specific stereotypically located glomeruli in the olfactory bulb (OB). While several guidance molecules help segregate OSN axons into broad zones of the OB, less is known about molecules regulating their coalescence into individual glomeruli. The few families of CAMs implicated in local axon sorting are unlikely to be sufficient to coordinate the sorting of axons expressing over 1000 different OR types into their appropriate glomeruli. Aiming to identify other CAMs in this process, we have found one member of the ‘amphoterin-induced gene and ORF’ (AMIGO) family of transmembrane proteins as a regulator of axonal coalescence in the OB. AMIGO-1 expression is confined to the ventrolateral regions of the olfactory epithelium, and AMIGO-1-expressing OSN axons project to the ventral region of the OB. AMIGO-1 null mutant mice show improper targeting of MOR28-positive OSN axons within this ventral region but do not display defects in MOR174-9-positive axon targeting to the dorsal region of the OB. Furthermore, MOR28 glomeruli, formed in the ventral region of the OB, are significantly smaller in size in these mice. These findings identify Amigo-1 as a key regulator of OSN axonal targeting in the mouse OB.

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A34

Changes in Inhibition and Excitation with Monocular Deprivation

*Sébastien Proulx, MSc, Jiawei Zhou, PhD, Simon Clavagnier, PhD, Reza Farivar, PhD, Robert Hess, PhD

The inhibitory neurotransmitter GABA has been implicated in the mechanisms underlying ocular dominance and inter-ocular suppression. A few hours of monocular deprivation in humans is capable of shifting the ocular dominance balance toward the deprived eye, which we hypothesized as being related to a reduction of GABA in primary visual cortex. In this ongoing study, we are using single-voxel Magnetic Resonance Spectroscopy (MRS) to non-invasively measure GABA concentration in the occipital lobe of healthy human subjects before and after ~160 min of monocular deprivation. The behavioural effect on ocular dominance is assessed through binocular combination and binocular rivalry tasks. Location of the MRS voxel within-subjects before and after deprivation agreed to ~95% all five subjects acquired so far but one, which was excluded from the analysis. Although monocular deprivation induced the expected shift in ocular dominance toward the deprived eye in all subjects, no systematic changes in GABA were found. Subjects showed both increase (up to 17%) and decrease (up to 11%) in GABA levels relative to baseline. This between-subject variability of the GABA change does not seem to relate to the variability of the behavioral effect. Relatively low within-session coefficients of variation, ranging from 4 to 6%, suggest that monocular deprivation induces non-systematic changes in GABA. A sham condition is however needed to exclude between-session measurement error. More subjects will also be needed to exclude a relation between behavioral ocular dominance dynamics and our putative MRS-measured GABA modulations.

Deep brain stimulation in Parkinson's patients: How does the outcome relate to the characteristics of microelectrode-recorded signals in the subthalamic nucleus?

*Kostoglou K., Michmizos K.P., Stathis P., Sakas D., Nikita K.S., Mitsis G.D.

Aim: Subthalamic nucleus (STN) deep brain stimulation (DBS) is considered as the most effective surgical treatment for Parkinson's disease symptoms. Good clinical results mainly depend on the exact implantation of the stimulation electrode inside the sensorimotor area of the STN. To this end, we analyzed the information obtained from resting-state microelectrode-recorded signals (MERs) and extracted the most significant features related with the clinical outcome of STN DBS. Such features can be used in the future as a control signal for closed-loop DBS.

Methods: MERs during DBS comprise both fast events called Action Potentials (spikes) and slow events known as Local Field Potentials (LFPs) that reflect the synaptic activity of a population of neurons. The spiking activity of large or nearby neurons, called Multiunit Activity (MUA) is transformed into spike trains. The Background Unit Activity (BUA) represents smaller sub-noise level spikes. Feature extraction both in time and frequency domain was applied to all the aforementioned type of signals. Other features like the distance of each MER from the stimulation contact, the hemisphere from which the MER was obtained and the clinical preponderance of each subject were also taken into account. Each MER that came from a good (bad) response patient was labeled as 1 (0). Classification and feature selection was performed using Random Forests (RF). Significant features related with improvement in the Unified Parkinson Disease Rating Scale (UPDRS) before and after the surgery during "off" medication state were also extracted using a regression RF scheme.

Results: A clear distinction was evident between good and bad DBS response patients (100% subject-wise classification accuracy). One of the most significant features was the position of the stimulation contact and the distance from each MER. Specifically, for the group that exhibited the highest UPDRS improvement the stimulation contact was located closer to the ventral-lateral-posterior subthalamic area. In the "off" Parkinsonian motor state beta band activity is prominent. However, the bad response group was characterized by elevated BUA power in the theta band (tremor sites) and exhibited significant high gamma LFP oscillations (especially patients with right preponderance) that were negatively correlated with the power of the LFP in the beta/gamma band. The LFP cross-frequency coupling between delta & beta (higher in bad response patients with left preponderance) and delta & high gamma bands (higher in good response patients) played also a key role in the discrimination of the two groups indicating that the phase of delta activity modulates the communication between cortical structures, thereby enabling or preventing the transfer of information.

The effect of musical expertise on intonational phrase processing

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Background: Intonational phrase boundary processing, a mechanism crucial for language comprehension, is reflected neurophysiologically in a specific event-related potential (ERP) component – the Closure Positive Shift (CPS). An analogous component has been found in the studies of musical phrase processing, being more right-lateralized in non-musicians compared to musicians. Nevertheless, it is still unclear whether the two components - the “language” and the “music” versions of CPS - have the exact same nature, since the latency and the morphology of the signals seem to differ significantly. A widely used way to investigate the shared nature of a specific neurocognitive mechanism involved in both language and music is to study transfer effects from music to the linguistic domain. The present research aimed at investigating such transfer effects from music to language in phrase processing by looking at the corresponding ERP components in non-musicians and professional musicians.

Method: Fifteen musicians and 15 non-musicians (German native speakers) listened to phrased sentences and melodies while their electroencephalogram was recorded. The design of the speech part of the experiment corresponded to the original study of CPS. The phrased and unphrased music stimuli were composed following basic conventions of Western musical form. The musical phrased conditions included a manipulation of purely auditory cues (fading amplitude of the pre-boundary note and presence of the pause) and of musical syntax information (full-cadence vs. half-cadence endings of a phrase).

Hypotheses and predictions: On the basis of previous research in phrase processing, we hypothesized that CPS reflects a shared neurocognitive chunking mechanism for phrase processing in language and music. Therefore, we predicted to see a general transfer effect from music to language reflected in the amplitude difference of language CPS in musicians compared to non-musicians, and in the direct relation of this difference to the music CPS differences in our two groups of participants.

Interest: The study is relevant for both, neurocognitive theories of syntactic parsing and intonation, and the clinical field of neurological musical therapy in language disorders.

A37

Effects of HPRT deficiency in human induced pluripotent stem cells and neural progenitor cells

Liam Crapper*, Carolina Giguek, Alpha Diallo, Gilles Maussion, Gustavo Turecki, Carl Ernst

In humans HPRT deficiency causes Lesch-Nyhan disease (LND), a rare developmental disorder with a variety of metabolic and neurological symptoms including chronic self injury, gout, dystonia, and intellectual disability. While the metabolic symptoms of LND can be easily treated this has no impact on the neurological symptoms, which remain poorly understood. This is in part due to the difficulty of studying LND in animal models, which do not show any behavioural phenotypes resulting from HPRT deficiency. We have created novel models of LND by deriving induced pluripotent stem cell lines (iPSCs) and iPSC derived neural progenitors from patients with LND, and by knocking down HPRT1 expression in human ventral midbrain derived neural precursor cells. Using transcriptome sequencing and western blotting, we have identified substantial alterations in the expression of genes related to metabolism and protein translation

Investigating inflammatory markers in the choroid plexus of depressed suicides

J. Devorak*, S.G. Torres-Platas, M.A. Davoli, N. Mechawar

Several lines of evidence, from animal models to clinical studies, indicate that increased levels of circulating pro-inflammatory cytokines can trigger or accompany depressed mood. While this likely involves cerebral inflammation, there exists little supporting evidence in the literature. The choroid plexus (ChP), a highly vascularized tissue that produces cerebrospinal fluid and lacks a blood-brain-barrier, is at the interface of peripheral and central immune responses. This postmortem study aims to investigate and compare cell populations as well as molecules known to be implicated in central and peripheral inflammatory responses between depressed suicides and psychiatrically healthy controls. Preliminary analyses of ChP macrophages immunostained for ionized calcium-binding adaptor molecule 1 (Iba-1) in samples from both subject groups indicate that, in general, the morphology and distribution of ChP Iba1-immunoreactive (IR) cells are distinct from those previously described in cerebral cortex (Torres-Platas et al., 2014, *J Neuroinflammation*, 11:12). Iba1-IR cells in the ChP overwhelmingly display an amoeboid morphology. Furthermore, the morphological features of Iba1-IR cells in the ChP vary as a function of their location within the tissue. While amoeboid-like cells are observed throughout the ChP, including the stroma, villi, and extensive vascular network, variations in this amoeboid-like morphology are observed between ChP compartments. Iba1-IR cells in the stroma often display one or two unramified processes, whereas cells localized within the villi or in close proximity to blood vessels are more frequently devoid of processes. Microglia-like Iba1-IR cells displaying multiple processes appear confined to the stroma. Further investigation of macrophage subtypes and their comparison between depressed suicides and controls will also be presented.

Platelet-derived growth factor (PDGF) signaling in a new model of glioblastoma (GBM)

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Glioblastoma (GBM) is a fatal brain cancer, characteristically 'driven' by mutations in multiple tyrosine kinase signaling pathways accompanied by loss of function of the p53 and RB tumour suppressor genes. Further understanding of the molecular underpinnings of GBM will be crucial to improving, targeting and personalizing treatments. We have developed a new model of GBM in which the sequence of molecular events that underlie human GBM might be explored. In our model, cells from the subventricular zone (SVZ) of p53^{-/-} mice are cultured in serum-free media supplemented with platelet-derived growth factor-A (PDGF-A) and grow as neurospheres. These cells have an attenuated proliferative capacity initially, but after 3-4 months in culture, abruptly proliferate rapidly to form large loosely adherent spheres, and quickly become exogenous growth factor (i.e., PDGF-A) independent. When transplanted into the brains of immune-competent, p53^{+/+} mice, they form high-grade, GBM-like tumours. In contrast, p53^{-/-} SVZ cells grown in EGF/FGF remain exogenous growth factor dependent and never transform. We examined growth factor signaling in vitro in order to elucidate the mechanism of sustained cell proliferation in SVZ cells that become PDGF-A independent. In growth factor independent cultures, we observed that the PDGF receptor- α (PDGFR- α) remains phosphorylated and highly active in the absence of exogenous PDGF. Future experiments will examine the nature of receptor activation to determine whether PDGFR- α signaling is occurring through an autocrine loop or is indicative of a constitutively active PDGFR- α . We will also examine the gene expression profile of GBM xenografts to assess whether these GBM-like tumours resemble a particular molecular subtype of human GBM. Our model might be used to study gliomagenesis and identify GBM inhibitors.

Mapping neural function in individuals with DCC haplotype

D Vosberg, A Chalupa, D Allard, H Theoret, A Dagher, C Benkelfat, M Srour, R Joobar, F Lepore, M Lassonde, G Rouleau, C Flores, M Leyton

In laboratory animals, axon guidance molecules direct axonal pathfinding and synapse formation, leading to changes in neuronal connectivity, neuronal function, transmitter release and behavior. The present project has the rare opportunity to characterize effects of an axon guidance molecule in humans. Neural wiring and function is being mapped in a large four-generational Quebec family, half of whom possess an autosomal dominant mutation in the axon guidance molecule receptor gene, DCC (deleted in colorectal cancer). 75% of those carrying the DCC mutation exhibit a congenital phenomenon known as “mirror movements,” in which voluntary movements on one side of the body elicit concurrent, involuntary movements on the contralateral side. The precise mechanism underlying mirror movements remains elusive, but animal studies suggest that the DCC mutation gives rise to disturbances during development in (i) the midline crossing of M1 motor neurons, and (ii) ascending dopamine pathways. These alterations might affect susceptibility to multiple neuropsychiatric conditions, including putative hyper-dopamine related disorders such as substance abuse and psychoses.

Three groups are being tested. 1) DCC mutation carriers. 2) Family members without the DCC mutation. 3) Demographically matched unrelated controls. Functional connectivity is assessed using functional magnetic resonance imaging (fMRI) and motor responses to transcranial magnetic stimulation (TMS). Anatomical connectivity is assessed using diffusion tensor imaging (DTI), a technique that indirectly measures the orientation and morphology of axons. Dopamine release is estimated using positron emission tomography (PET) and striatal [11C]raclopride binding potential values following administration of placebo vs. d-amphetamine (0.3 mg/kg, p.o.).

Based on the animal models and behavioral features of the DCC mutation carriers, it is hypothesized that, relative to controls, they will exhibit increased unilateral M1 neuronal output to both sides of the spinal cord, increased contralateral M1 cortical crosstalk (possibly due to decreased inhibitory input), and decreased amphetamine-induced striatal dopamine release. A wide range of personality traits and other behavioral features will be assessed also, and it is hypothesized that the DCC mutation carriers, relative to controls, will differ in risk taking, novelty seeking, reward sensitivity, impulsivity, and histories of substance use.

Synaptopodin, an actin-associated protein, regulates dendritic spine stability and LTP through RhoGTPases

F. Guido*, P.KY. Chang, R. Gill and McKinney R.A.

Synaptic plasticity is the ability of synapses to adapt to incoming neuronal activity and has been hypothesized to be the cellular basis of learning and memory. Interestingly, synapses can respond differently to the same stimulus, but the underlying mechanisms of this heterogeneity are unknown. The majority of postsynaptic excitatory synapses are dendritic spines, morphologically and biochemically distinct protrusions found on the dendrites of principal neurons. Spines are highly dynamic and can respond to changes in neuronal activity, in an actin-dependent manner regulated by Rho-GTPase signaling pathways. Dynamic morphology of dendritic spines correlates to their relative strength, i.e. the larger the spine, the stronger the synapse. It has been proposed that the heterogeneous response of synapses is due to the distinctive protein composition of a spine. In order to investigate the differences of heterogeneous synapses, we chose to investigate the role of synaptopodin, a protein only present in a subset of mature spines and kidney podocytes. Synaptopodin has been shown to be involved in synaptic plasticity and synaptopodin null mice display functional deficits in spatial learning and memory. Recently, in kidney podocytes it has been shown that synaptopodin can regulate the actin cytoskeleton through the actions of RhoGTPases, such as Rac1, RhoA and Cdc42. Therefore, we hypothesize that synaptopodin regulates synaptic plasticity through an interaction with actin through RhoGTPases.

Using organotypic hippocampal slice cultures, we induced LTP with a chemical protocol (chem-LTP) to examine structural plasticity dendritic spines globally. Under control conditions, 55% of all dendritic spines experience a volume increase following chem-LTP, while only 29% of all dendritic spines increased in volume in the synaptopodin null group ($p < 0.05$). More specifically, we observed mature mushroom spine destabilization that was accompanied by volume decreases compared to control ($p < 0.05$), whereas, the thin spines are relatively unaffected. Our findings support that lack of functional plasticity experienced by the synaptopodin-knockout mice is mirrored at the structural level and may explain the learning deficits observed in these animals. In addition, we investigated the expression of members of the RhoGTPase family, RhoA, Rac1, and Cdc42 in the hippocampi of adult wild type and synaptopodin null mice by western blot analysis. We have detected a significant increase in RhoA and Cdc42, with no significant change in Rac-1 in the synaptopodin null mice compared to wild type.

In conclusion, our findings support the conclusion that synaptopodin may regulate synaptic plasticity through RhoGTPases in mature dendritic spines.

Insulin Regulated Aminopeptidase (IRAP) as a Potential Cerebrovascular and Neuroprotective Mechanism in a Mouse Model of Alzheimer's disease

Royea J*, Zhang L, Ozcelik S, Martinot P, Tong X-K, & Hamel E

Introduction: We recently found that the angiotensin II (AngII) type 1 receptor (AT1R) antagonist losartan restored cerebrovascular and cognitive deficits in an Alzheimer's disease (AD) mouse model¹. The mechanism underlying these beneficial effects is unknown. Yet, blockade of the AT1R may favor conversion of AngII to angiotensin IV (AngIV)². AngIV interacts with insulin regulated aminopeptidase (IRAP), which has been linked with improved cognitive performance of rats whereas IRAP gene knockout mice ensue spatial and short term memory deficits^{3,4}. Hence, we investigated whether IRAP mediates the benefits of chronic losartan treatment in transgenic mice overexpressing the Swedish and Indiana mutations of the human amyloid precursor protein (APP mice, line 20).

Methods: APP mice and wild-type controls (2-3 months old) received losartan (10 mg/kg/day, in the drinking water, 4 months) in combination with intracerebroventricular administration of artificial CSF (control) or divalinal (~1 nmol/day), an IRAP blocker, during the last month of losartan treatment using osmotic minipumps.

Results: Divalinal countered losartan's capacity to rescue cerebral vasodilatory function, neurovascular coupling to sensory stimulation, and spatial learning and memory measured in the Morris Water Maze. Neither losartan nor divalinal altered the A β pathology or arterial blood pressure.

Conclusions: We conclude that the AngIV/IRAP cascade likely mediates the beneficial effects of the AT1R blockade in APP mice. This mechanism could possibly explain the reported decreased incidence of AD in hypertensive patients treated by AT1R blockers⁵. It may also represent a new therapeutic target in AD.

References:

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Poster Session B: Thursday, September 18th 6:30-7:30PM, Friday, September 19th 1:15-3:15PM

B1

Teneurin-m regulates precise synaptic targeting in Drosophila mechanosensory neurons

Vedrana Cvetkovska* and Brian E. Chen

Teneurins are a highly conserved family of cell surface receptors that have important roles during nervous system development for axon guidance, cell adhesion, and synaptic specificity. Drosophila Teneurins have been shown to regulate synaptic partner matching between classes of olfactory neurons and at the larval neuromuscular junction. However, it is not clear how Teneurins regulate axonal targeting decisions at the level of single neurons and its effect on circuit function. To address this issue, we use the Drosophila hard-wired mechanosensory circuit for identification and quantitative analysis of axonal targeting errors, with a functional assessment of synaptic connectivity through behaviour. We found that RNAi knockdown of Ten-m solely within specific mechanosensory neurons produced stereotyped axonal targeting errors, including mis-routing of axonal branches, inappropriate midline crossing, and premature branch termination or extensions. We assessed mechanosensory circuit function by stimulating mechanosensory bristles to elicit a cleaning reflex in Ten-m RNAi mosaic animals. We found that loss of Ten-m within neurons reduced the ability of the animal to perceive a mechanical stimulus. Our results demonstrate that Ten-m is required for precise synaptic targeting in single sensory neurons and for proper circuit function. In humans, the TEN-M1 gene is located in a region associated with X-linked mental retardation; thus, further examination of the roles of Teneurins in the developing brain may provide insight into the mechanisms of miswiring in disease.

B2

Canadian media discourse about Fetal Alcohol Spectrum Disorder

John Aspler*, Natalie Zizzo, Emily Bell, Nina Di Pietro, Courtney Green, and Eric Racine

Background: Fetal Alcohol Spectrum Disorder (FASD), a range of neurodevelopmental disabilities resulting from prenatal alcohol exposure (PAE), is the leading developmental delay in North America. FASD affects roughly 9 in 1000 Canadians; however, due to diagnostic confounds, its actual prevalence may prove much higher. One such confound is our limited ability to measure PAE, which relies largely on maternal self-reports and retrospective questionnaires. Unfortunately, our understanding of the associations between 1) the amount, timing, and frequency of alcohol consumption during pregnancy; 2) the resulting levels of PAE; and 3) the development of an FASD remains controversial. As such, most medical guidelines recommend abstention from alcohol when pregnant. Given both continued uncertainty in the literature and the importance of informed public discourse about science, health, and policy issues, we explored Canadian media discourse about FASD.

Objective: To identify and address gaps or contradictions in the information presented by the Canadian print media about FASD.

Methods: We conducted a content analysis of 193 Canadian news articles published between 2002 and 2011. These articles were retrieved from the 12 most widely distributed Canadian print news sources using the Factiva database. We retained these 193 articles from an original 284 after manually screening for relevant non-duplicates. To ensure the reliability of the data, we conducted coding reliability pretests and assessed inter-coder reliability.

Results: Major themes that emerged throughout the analysis included 1) descriptions of FASD (e.g., disabilities, severity); 2) systemic concerns (e.g., inadequate social services, inadequate criminal justice accommodation); 3) medical concerns (e.g., access to – and efficacy of – diagnoses, preventions, treatments); and 4) social concerns (e.g., criminality, stigma, race and class myths).

A number of gaps and contradictions about levels of PAE exist in the Canadian print media. Questions about the impact of different levels of alcohol consumption when pregnant remain largely undiscussed (28 of 193 articles) despite their centrality to understanding FASD. Additionally, media messaging about PAE is confusing given the contradictory health research findings reported (i.e., that small amounts of alcohol harm, do not harm, or can even benefit the developing fetus).

Conclusion: Tension exists between both the need to inform the public about recent scientific developments and accepted medical guidelines/public health communication strategies. We encourage 1) clearer media discourse about FASD; 2) a greater involvement of experts in media discourse so as to better contextualize the state of research related to PAE; and 3) increased public discussion about FASD in general.

B3

The Geriatric Depression Scale (GDS-15): Is cognitive ability associated with how geriatric patients respond to self-reported depressive symptoms?

Mei Huang*, Lisa Koski

Background: Since the GDS-15 is a self-report screening tool targeted for geriatric populations, its validity may be compromised by cognitive impairment or dementia. Some studies report that the GDS-15 validity is influenced by severity of dementia, however more recent studies argue otherwise. No studies have yet to illustrate whether patients with low cognitive ability respond differently to the GDS-15 compared to patients with high cognitive ability.

Purpose: To determine whether response patterns to the GDS-15 differ between geriatric patients with low, medium or high cognitive ability.

Methods: Data (n=225, M=81 years, SD=6.3 years) were collected from retrospective chart reviews from two university based geriatric outpatient clinics in Montréal. Severity of depressive symptoms was assessed by the GDS-15 and cognitive ability by the Mini-Mental State Examination (MMSE). Patients were stratified into three groups based on previously reported probable dementia cut-off scores (≥ 26 normal, 21-25 mild dementia, ≤ 20 moderate & severe dementia). Differential item functioning (DIF) analysis using Rasch software (RUMM2030) on GDS-15 items allowed for group comparison.

Results: Response patterns for all GDS-15 items, except item 6 “Are you afraid that something bad is going to happen to you?” ($p < .001$, Bonferroni corrected), did not differ significantly between the three cognitive ability groups. Patients with lower MMSE scores were less likely to endorse item 6 compared to patients with higher MMSE scores.

Conclusion: Response patterns to the GDS-15 do not differ based on cognitive ability among geriatric outpatients except for item 6. Fear about the future contributes less to severity of depressive symptoms in patients with lower cognitive ability. Further consideration of removing unstable item 6 might potentially improve GDS-15 validity among older adults with dementia.

B4

Fetal brain-gut communication is disrupted during sepsis and associated with a higher degree of intestinal inflammation: implications for non-invasive monitoring

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Disruption of inter-organ communication has been proposed as the pivotal event during septic shock resulting in multi-organ dysfunction syndrome. Higher levels of vagal activity are associated with lower systemic levels of pro-inflammatory responses and activation of macrophages, mediated by the cholinergic anti-inflammatory pathway (CAP). The gut represents the biggest vagus-innervated organ. Fetal heart rate variability (fHRV) serves as a proxy marker of CAP activity. Consequently, changes of fHRV may reflect changes of inflammatory status in gut presenting an avenue to monitor the brain-gut communication in health and sepsis, a condition associated with high morbidity and mortality in neonates.

We hypothesized that fHRV can identify fetuses with gut inflammation.

Near-term fetal sheep were surgically prepared with vascular catheters and ECG electrodes. 27 animals served as controls. In 14 fetuses, inflammation was induced with lipopolysaccharide (LPS) I.V. Fetal arterial blood samples were drawn at baseline and seven selected time points to profile inflammation. At 54 h post LPS, necropsy was performed. Blood samples were analyzed for IL-6 and TNF- α . FHRV was quantified by Continuous Individualized Multivariate Variability Analysis (CIMVA) for Skewness, Asymmetry Index (AsymI), Sample Entropy (SampEn) and Complexity. The time-matched fHRV measures were correlated to the levels of IL-6 and TNF- α and to the Iba1+ cell density in terminal ileum, locus minoris resistentiae for necrotizing enterocolitis (NEC) of the premature neonate, to quantify the degree of macrophage activation in relation to CAP activity. Results are reported for $P < 0.05$.

LPS resulted in a pronounced gender-independent ileum inflammation. In the LPS, but not in the control group, at 3 hours post LPS, IL-6, but not TNF- α , was elevated. AsymI and Skewness of fHRV correlated to Iba1+ cell density ($R = -0.53$ and $R = 0.60$, respectively).

Confirming our hypothesis multiple fHRV measures correlated to the degree of intestinal macrophage activation. This supports the notion of a common neuroregulatory mechanism via CAP. Non-invasively obtained fetal CAP response signatures may help identify babies at risk of developing life-threatening gut inflammation such as NEC.

B5

The amblyopic deficit for 2nd order processing: Generality and Laterality

Yi Gao*, Alexandre Reynaud and Robert F. Hess

A number of previous reports have suggested that the processing of second-order stimuli by the amblyopic eye (AE) is defective and also that the fellow non-amblyopic eye (NAE) also exhibits an anomaly. Second-order stimuli involve extra-striate as well as striate processing and provide a means of exploring the extent of the cortical anomaly in amblyopia using psychophysics. We use a range of different second-order stimuli to investigate how general the deficit is for detecting second order stimuli in adult amblyopes. We compare these results to our previously published adult normative database using the same stimuli and approach to determine the extent to which the detection of these stimuli is also defective for both amblyopic and non-amblyopic eye stimulation. The results suggest that the second order deficit affects a wide range of second order stimuli, and by implication a large area of extra-striate cortex, both dorsally and ventrally. The NAE is affected only in motion-defined form judgments, suggesting a difference in the degree to which ocular dominance is disrupted in dorsal and ventral extra-striate regions.

B6

Dynamic role of 'top-down' influences during learning of a novel auditory discrimination task

Jonathan Côté*, Étienne de Villers-Sidani

“Top-down” influences are known to powerfully modulate information processing in primary and secondary sensory cortical fields. In humans and rodents, this top-down control increases the contrast of behaviorally relevant sensory stimuli in a contextual manner. Such dynamic filtering is crucial, among other things, to block irrelevant or distracting stimuli such as background noise during conversations. This system fails in a number of common clinical syndromes including, attention deficit disorder, schizophrenia, and age-related cognitive decline. In humans, the dorsolateral prefrontal cortex (DLPFCx) is activated during sensory discrimination, especially in the context of unfamiliar tasks.

Its role during familiar tasks where we are relative experts and for which reaction times have to be very short, such as listening to speech in noise for example, is not as clear. One possibility is that more efficient specialized local auditory circuits play a more important role.

To further investigate this possibility, we examined how brain activation patterns evolve during intensive training on a novel auditory discrimination task aimed at improving the discrimination of the spectral features of complex sounds. Task-related activity in core auditory areas, DLPFCx and connectivity between the two areas were monitored with high temporal resolution using magneto-encephalography before, during and after a plateau in performance on the training.

We found that connectivity between DLPFC and core auditory areas was maximal in the early phases of training and gradually weakened with greater proficiency on the task. Furthermore, as further mastery was gained on the task, non-target stimuli activated a smaller area in core auditory areas indicating a more efficient filtering of distractors. Target-related activation remained unchanged. Lastly, training resulted in an improved ability to understand speech in noise (transfer of trained abilities). The magnitude of the benefit was proportional to the progress made on the training.

Those results demonstrate that top-down influences on sensory cortical fields could be more important in the learning phase of a novel unfamiliar task whereas tasks on which we are “experts” might rely on more local and probably more efficient processing.

B7

CdGAP, a Rac1/Cdc42 GTPase regulator is involved in vasculogenesis and VEGF-induced neuritogenesis

Lou Beaulieu-Laroche*, Jonathan DeGeer, Vilayphone Luangrath and Nathalie Lamarche-Vane

CdGAP is a GTPase activating protein (GAP) specific to Rac1 and Cdc42, two well-characterized small GTPases. CdGAP is known to be expressed in the adult brain, but its role there remains completely unknown. The goal of the project was to investigate the function of CdGAP in the developing brain. We first assessed the protein expression levels in E17.5 rat brains and observed that CdGAP was widely expressed but enriched in the hippocampus. Analysis of protein lysates from dissociated cortical and hippocampal neurons revealed that CdGAP expression increases for the first week in culture and then stabilizes. We then assessed CdGAP knockout (KO) mice to gain further insight into the function of our protein of interest. We found that CdGAP KO embryos have a striking hypovascularized phenotype. At the cellular level, CdGAP KO dissociated cortical neurons differ from wild type dissociated cortical neurons in their cytoskeletal architecture. These structural differences evoke the possibility that CdGAP regulates actin dynamics in neurons through its GAP activity. Finally, we found that CdGAP KO dissociated cortical neurons did not respond to VEGF-induced neuritogenesis while wild type neurons did, suggesting that CdGAP is required for VEGF's action on cortical neurons.

B8

Complete reversal of neuropathic and inflammatory mechanical allodynia in pregnant mice.

Sarah F. Rosen*, Jean-Sebastian Austin, Ann Chen, Loren Martin, Jeffrey Mogil

We have recently observed that administration of intrathecal glial inhibitors only reverse neuropathic and inflammatory mechanical allodynia in male mice, and have no effect in female mice. We have collected evidence suggesting that whereas male mice employ a microglia-dependent mechanism to mediate allodynia, and female mice instead employ T cells to the same ends. A possible explanation for this sex difference is that males and females have different T cell immune environments: males have a Th2-dominant and females a Th1-dominant immune environment. However, during pregnancy, due to changes in sex hormone levels, females shift to a Th2-dominant immune environment. We wished to investigate the implications of this for microglia-dependence of mechanical allodynia. We show here that pregnant female mice do indeed switch to a microglia-dependent mechanism to mediate allodynia. In addition, we observe that in late pregnancy female mice that once suffered from a neuropathic injury have little to no evidence of pain. Female mice with spared nerve injury (SNI) or injected with complete Freund's adjuvant (CFA) progressively lose mechanical allodynia during pregnancy; shortly after delivery the mechanical allodynia returns to pre-pregnancy levels. This phenomenon has been reported clinically, but has never been studied in animal models. Current experiments are examining the role of gonadal hormones, T-helper cells, and opioid receptors in these phenomena. Here we show that T-cell deficient, nude pregnant mice do not exhibit a blockade of mechanical allodynia during late pregnancy after SNI, suggesting that T-cells are playing a significant role in the phenomenon.

B9

Brain imaging to understand HIV-associated neurocognitive disorder and predict response to cognitive training

Fernandez Cruz AL*, Fellows LK

The development of effective antiretroviral therapy has enabled patients with Human Immunodeficiency Virus (HIV) to enjoy longer lives, converting HIV into a chronic disease with disabling effects on cognition and mental health. Even with excellent viral control, 30 to 50% of patients with HIV suffer from mild cognitive impairment, exacerbated in patients over 50. Importantly, impaired cognition affects occupational and social functioning, quality of life and medication adherence. Progress in predicting, treating and mitigating the impact of poor brain health requires a better understanding of the most important factors contributing to cognitive impairment in people living with HIV, and also of the factors that predict resilience and positive response to interventions. The cognitive domains most affected in HIV are those that rely on extended brain networks (e.g., attention, working memory, and other executive functions relying on fronto-parietal and -striatal circuits). The present project hypothesizes that the typical patterns of cognitive deficits in HIV reflect degraded brain network functioning, likely due to a combination of insults: some generic (aging), and some HIV-related (deficient initial infection control predisposing to neurodegeneration, chronic inflammation, or accelerated atherosclerosis). We propose that the reliance on extended networks that puts these cognitive functions most at risk also offers therapeutic hope: these functions may be particularly remediable with intervention. The specific aim of this project is to study the EEG and MRI markers that 1) discriminate patients with higher or lower cognitive ability at baseline, 2) predict those who will have a positive response to cognitive training, and 3) are sensitive to the effects of cognitive training. This study will be the first to use neuroimaging methods to understand the brain substrates of cognitive training response in HIV. It will also test, for the first time, the hypothesis that the cognitive difficulties of HIV patients reflect network degradation, rather than domain-specific injury. In addition to these fundamental insights, it will provide evidence to select optimal neuroimaging markers for risk of cognitive decline, and response to intervention, informing future large-scale clinical trials in HIV, and perhaps eventually contributing to the routine clinical treatment of this common and disabling feature of chronic HIV infection.

B10

Axon branch addition is instructed by synaptic activity of neighbouring inputs in the *Xenopus laevis* visual system

Tasnia Rahman*, Martin Munz, Delphine Gobert, Anne Schohl, Edward Ruthazer

The selective strengthening and pruning of synapses by temporally correlated activation of the presynaptic and postsynaptic cell contributes to the developmental refinement of neural connections. Although retinal ganglion cell (RGC) axons in *Xenopus laevis* tadpoles project to the contralateral optic tectum, in a fraction of tadpoles a few axons are misguided to the ipsilateral tectum. When such an ipsilateral RGC axon is asynchronously activated relative to neighbouring contralateral inputs in the tectum by stimulating the two eyes out of phase, the rate of axon branch additions increases. In the case of synchronous stimulation, there are fewer new branches but they exhibit increased stability. To explore how synaptic transmission is involved in axon remodelling and stability we transfected ipsilateral RGCs to express tetanus toxin light chain (TeNT-LC) to prevent synaptic vesicle release. Two-photon imaging of TeNT-LC-expressing ipsilateral RGC axons revealed that when both eyes are stimulated simultaneously there is an increase in the number of branch additions. A similar increase is seen when only the contralateral eye is stimulated. However, if the TeNT-LC-expressing ipsilateral eye is stimulated alone, only a baseline level of branch addition is retained. Thus, presynaptic axonal firing is neither necessary nor sufficient in promoting axon remodelling beyond baseline when synaptic transmission is prevented. However, synaptic activity of surrounding contralateral axons is sufficient to promote the growth of new axon branches, suggesting a heterosynaptic mechanism.

B11

Montreal MEG Repository (R2M)

Guiomar Niso *, Christine Rogers, Li-Yuan Chen *, Jeremy Moreau *, Cecile Madjar, Samir Das, Alan Evans, Pierre Jolicoeur, Sylvain Baillet

Multimodal neuroimaging research has shown promising results for early diagnosis of brain disease. One of the primary challenges in this field is integrating heterogeneous data acquisition processes into a joint patient and normative database combining demographic information, clinical data, and Magnetic Resonance Imaging (MRI) images enriched with Magnetoencephalography (MEG) time-resolved datasets. To provide such infrastructure, we have collaborated with the McGill Centre for Integrative Neuroscience (MCIN) to develop the Montreal MEG Repository (R2M, <https://r2m.loris.ca>; login: demo; password: demo@r2m) that is built on MCIN's LORIS neuroimaging data management platform. R2M is a multi-site and multimodal MEG database that will include data from patient volunteers and healthy controls and be open to the scientific community for data sharing and contributions. R2M was designed to store and link multimodal data collected across multiple sites with MEG, structural MRI, as well as clinical and behavioural datasets (including questionnaires and scored assessments). This Open-Neuroscience initiative will enable future research in the field of high-powered detection of contrast effects between 1) an individual or a small group of patients when compared with a large group of age-matched healthy controls and 2) distinct groups of subjects categorized by age, gender, education level, behavioral test scores, and other factors. Overall, the objective of R2M is to establish the standard levels of brain activity in a population of healthy participants with relation to standard factors (e.g., age, gender, and standardized behavioral tests scores) in order to reveal new markers of abnormal brain activity in patients affected by neurological and mental health conditions.

B12

Overweight is not associated with cortical thickness alterations in children

Rachel J Sharkey*, Sherif Karama, Alain Dagher

There is a well-established relationship between excess weight and reduced cortical thickness in adults. Obese adults routinely display reduced cortical thickness in areas which are behaviourally associated with self-regulation, especially the prefrontal cortex. The same association is less well established in adolescents where it has been found in some cohorts but not in others. This study used multilevel modelling of data from the NIH Pediatric MRI Data Repository, a mixed longitudinal and cross-sectional database, to examine the relationship between cortical thickness and body weight in children. No significant association between the two was found.

B13

The effects of DCC on the development of prefrontal cortex dopamine connectivity determine behavioral responses to drugs of abuse

Matthew Pokinko*, Luc Moquin, Alain Gratton, Cecilia Flores

The netrin-1 receptor, *dcc*, determines a) the extent of dopamine (DA) innervation to the medial prefrontal cortex (mPFC), b) the organization of local circuitry, and c) individual vulnerability to effects of drugs of abuse. Adult *dcc* haploinsufficient mice have a selective increase in mPFC DA fiber innervation and DA release in comparison to wild-type littermates. Furthermore, adult *dcc* haploinsufficient mice show blunted DA release in the nucleus accumbens (NAcc) and reduced locomotor activity when challenged with drugs of abuse such as amphetamine (AMPH). Because mPFC DA transmission in the mPFC can negatively regulate DA release in the NAcc in response to drugs of abuse or stressors, we hypothesized that the blunted effects of AMPH in *dcc* haploinsufficient mice result from increased mPFC DA innervation. We therefore examined the effects of selective mPFC DA depletion on AMPH-induced locomotion in *dcc* haploinsufficient and wild-type mice. Adult mice received bilateral mPFC injections of 6-hydroxydopamine (lesion) or vehicle (sham) 1 week before an i.p. AMPH challenge. In wild type mice, AMPH-induced locomotion was similar between lesion and sham groups. Remarkably, mPFC DA lesions in *dcc* haploinsufficient mice reversed their blunted response to AMPH. These findings demonstrate that the protective phenotype of adult *dcc* haploinsufficient mice results from the effects of DCC on the organization of mPFC DA connectivity.

B14

Distinctive changes in cortical surface-based morphometry of subjects with Parkinson's disease with L-Dopa induced dyskinesia

Rhea Coriaty*, Alexander Thiel and Caroline Paquette

Parkinson's disease (PD) is a neurodegenerative disorder for which dopamine replacement therapy (Levodopa) is the most effective drug to alleviate PD-induced symptoms. Despite all benefits, this drug induces dyskinesia (ie, involuntary movements) in over 75% of patients treated with Levodopa in the first five years of treatment (Brotchie. *Ann Neurol.* 2000;47:S105-12). Treatment for dyskinesia is limited due to a lack of understanding of the underlying mechanism. There is evidence that the pathologically altered output from the basal ganglia toward the premotor and motor cortices may be a significant factor in the pathogenesis of these symptoms (Brotchie 2000; Obeso et al. *Ann Neurol.* 2000;47:S22-32). It has been suggested that this altered output generates long-lasting changes in the cortex which will increase the patient's susceptibility to fluctuations in dopaminergic tone (Brotchie 2000; Obeso et al. 2000). The purpose of the study was to determine if structural alterations in cortical architecture of the brain, namely cortical thickness and surface area are found in patients with dyskinesia.

Fourteen subjects with PD (mean age= 60; range [49-68]) and 20 healthy control subjects (mean age- 60; range [42-79]) were recruited. Eight out of 14 of subjects with PD were diagnosed with dyskinesia by a blinded assessment conducted by two neurologists. Cortical thickness and surface area were measured using the CIVET pipeline (Lerch & Evans. *Neuroimage.* 2005;24:163-73) on 1mm isotropic T1 MR images (Siemens Tim Trio 3T scanner). Three bilateral regions-of-interest (ROI; primary motor cortex, premotor cortex and supplementary motor area from the Juelich Atlas thresholded at 50%) were used to extract mean cortical thickness and surface area. A 2-way repeated measures ANOVA (Group: Dyskinetic, Non-dyskinetic vs. Control X Side: Most vs. Least affected) was conducted with significance level at $p < 0.05$.

Surface area was increased in the primary motor cortex (PMC) of subjects with dyskinesia compared with control subjects (Dyskinetic: 2.52 mm [SE 0.06] vs Controls: 2.25 mm [SE 0.04], $p < 0.05$), with no significant effect of side. Non-dyskinetic subjects had similar surface area on both sides as control subjects (Non-dyskinetic: 2.42 mm [SE 0.07], $p > 0.05$). There was no significant difference in cortical thickness between groups.

Our findings support that there are distinctive changes in brain surface area PD subjects with dyskinesia, particularly in the PMC. Our study therefore provides evidence that levodopa alters the anatomy, namely the surface area of this region, which can be linked to changes in neuroplasticity specific to subjects with dyskinesia.

B15

Anatomical Changes in Thickness, Volume and Surface Area of the Cortex in Regions of the Locomotor Steering Network

*Rehka Raveendrakumar, *Kelly Perlman, Jean-Paul Soucy and Caroline Paquette

Introduction: We recently reported a brain network specific to steering of locomotion recruiting most importantly parietal and sensorimotor regions (Paquette and Soucy, ISPGR World Congress. 2014; P2-O-83). In addition, we saw that patterns of activation in this network became asymmetrical in subjects who had a mild stroke in regions remote to the steering network. Subjects with stroke have reduced cortical thickness in ipsilesional M1 (Zhang et al. Stroke. 2014;45:788-93) and increased cortical thickness in the ventral postcentral gyrus (Schaechter et al. Brain. 2006;129:2722-33). Our aim was thus to determine whether gray matter changes are observed in terms of increased thickness and changed surface area and volume in specific regions of the locomotor steering network in subjects with stroke who exhibit asymmetrical changes in this functional network activation.

Method: Three stroke patients (mean age of 62 [range: 58-69] 1 female) with mild motor impairment (mean NIH stroke scale score: 3.33 [range: 1-6]) and four healthy age- and gender-matched controls (mean age 60 [range: 55-63]) were scanned with a 3T MRI. The T1-weighted images were run through the CIVET pipeline (Lerch & Evans. Neuroimage. 2005;24:163-73) to extract surface, volume and cortical thickness information. Seven bilateral regions of interest (somatosensory cortex, parietal operculum, primary motor cortex (PMC), premotor, secondary motor cortex, superior parietal lobule, and anterior intraparietal sulcus; Juelich atlas maximum probability map in MNI space) were used to calculate the average cortical thickness, volume and surface area. Finally, a two-way ANOVA (group X side) with repeated measures on side was used to quantify differences between subjects with stroke and controls.

Results: A significant increase was observed in mean thickness in the PMC and premotor and decrease in mean surface area in an area of the parietal operculum (ie., Juelich atlas SII OP3) between the least activated (LA) and most activated (MA) sides of stroke patients (PMC LA:2.37±0.33mm [range: 1.99-2.67mm] vs. PMC MA:2.67±0.35mm [2.30-2.92mm] ; Premotor LA: 2.33±0.23mm [2.309-2.55mm] vs. MA:2.59±0.28mm [2.33-2.89mm] ; OP3 LA:2.18±0.32mm [1.81-2.38mm] vs. MA:1.84±0.37mm [1.42-2.12mm] , p<0.05). No significant differences were observed in cortical thickness, volume and surface area in the sensorimotor or parietal regions between stroke patients and controls.

Conclusion: We showed that thickness and surface area changes in gray matter are observed in subcortical stroke patients between the MA and LA side, mainly in the PMC, premotor and parietal operculum. It is difficult to link changes in function to the changes in gray matter due to the small sample of our study.

Maladaptive Neuroplasticity in Parkinson's Disease

Jennifer Beer*, Alexander Thiel, Caroline Paquette

Adaptive neuroplasticity is necessary for sensory reorganization and to optimize neuronal activity during motor learning. However, changes synaptic connections can be maladaptive – interfering with motor performance and/or leading to a characteristic movement disorder. Levodopa-induced dyskinesia (LID), a common complication of treatment for Parkinson's disease (PD), is a movement disorder involving involuntary muscle contractions. It is hypothesized that maladaptive neuroplasticity may be a cause of the movement disorder (Brotchie *Ann Neurol.* 2000;47:S105-12; Obeso et al. *Ann Neurol.* 2000;47:S22-32). Corticospinal neurons originating from the premotor cortex can be stimulated directly using TMS (Teitti et al. *Neuroimage.* 2008;40:1243-50). In contrast to the primary motor cortex, this “secondary” motor area is less somatotopically organized and simultaneous activation of proximal and distal muscles have been shown to produce movement patterns resembling dyskinesia. Increased excitability in the premotor cortex of subjects with LID may indicate an increase in synaptic plasticity which could be related to dyskinesia. Our research investigates a possible relationship between LID and increased cortical excitability in the premotor cortex.

We recruited 15 subjects with PD (aged 60 ± 5 yrs) of which eight had LID. The premotor cortex was mapped bilaterally with single pulse transcranial magnetic stimulation (Neuronavigated Nexstim System) at 110% of the resting motor threshold (first dorsal interosseous (FDI) muscle) using a 1cm^2 grid centered at the dorsal premotor cortex. Motor evoked potentials of the FDI, extensor carpi radialis, and biceps brachii muscles were recorded. Excitability of the pre-motor cortex was quantified with muscle responses.

Responsiveness of each subject was characterized by total responses per total stimuli. No significant differences in responsiveness were found between the dyskinetic and non-dyskinetic groups (LID Left Hemisphere $12 \pm 3\%$, LID Right Hemisphere $27 \pm 13\%$, non-LID Left Hemisphere $25 \pm 11\%$, non-LID Right Hemisphere $28 \pm 12\%$). Our analysis was unable to determine a difference in the excitability of the premotor cortex between PD patients with LID and those without LID. This suggests that there may be no relation between premotor excitability and LID which may suggest that maladaptive neuroplasticity of the premotor cortex may not be a cause of LID. Further research is needed to explore this finding.

B17

The effect of selective entorhinal cortex lesions on spatial memory and executive control

Karim Bouayad-Gervais*, Yogita Chudasama

It has long been known that the entorhinal cortex is a cortical gateway to the hippocampus providing highly processed visuospatial information from perirhinal and postrhinal areas in the temporal lobe. In Long-Evans rats, projections originating laterally in the entorhinal cortex terminate in septal (dorsal) levels of the hippocampus, whereas projections originating medially in the entorhinal cortex terminate in temporal (ventral) levels in the hippocampus. This topographical organisation of entorhinal projections along the dorsoventral axis of the hippocampus has led to the suggestion that spatial information coming into the hippocampus is processed relatively independently by different portions of the entorhinal cortex (Dolorfo and Amaral, *J. Comp Neurol*, 1998; 398-48; see also Van Cauter, 2013; *Cerebral Cortex*, 23:451). The entorhinal cortex also receives information from the limbic and prefrontal cortex. We recently demonstrated that the ventral hippocampus receives disynaptic input from the ventral prefrontal cortex via a potential relay in the rostral ventromedial portion of the entorhinal cortex. In contrast, the dorsolateral entorhinal cortex serves as a potential relay between the dorsal prefrontal and retrosplenial cortex, and dorsal hippocampus (Prasad and Chudasama 2013, *J. Neurosci.* 33:8494). Lesions of the dorsal hippocampus and retrosplenial cortex affect spatial memory, whereas ventral hippocampal and ventral prefrontal cortex lesions affect behavioural control. This suggests that the entorhinal cortex, and its divisions thereof, may relay information that is not only relevant to spatial navigation, but also nonspatial executive control. In this study, we explore this possibility by examining the effects of selective entorhinal lesions in spatial tasks that are hippocampal-dependent (i.e., mazes which require the integration of allocentric cues), and nonspatial tasks which are prefrontal-dependent (i.e., operant paradigms which require attention, inhibition and decision making). Our preliminary data reveal that lesions of the dorsolateral entorhinal cortex do not affect executive control functions such as attention and inhibitory control. Surprisingly however, rats with dorsolateral entorhinal lesions showed normal acquisition of a spatial memory task. One possibility is that these animals are sensitive to changes in the spatial environment following previously well-learned spatial cues, rather than acquiring spatial associations, a topic of current research. These data will be compared with the effects of ventromedial entorhinal cortex lesions on the same tasks.

B18

Insight and Schizophrenia: Psychological and Biological Determinants

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Schizophrenia is a chronic psychiatric illness characterized by delusions, hallucinations, thought disorder, emotional dysfunctions, social withdrawal and cognitive dysfunctions. With a typical age of onset in the late teens or early 20s, schizophrenia can lead to profound academic, occupational and social impairment.

Schizophrenia is distinguished from other psychiatric conditions by a characteristic unawareness of major aspects of the illness – present in as high as 40-60% of this population, according to several large field studies. This lack of insight into the illness has profound prognostic and therapeutic consequences for these patients: poor insight has been related to low medication adherence, negative attitudes towards medication, greater frequency of hospitalizations and relapses, and diminished social and vocational functioning. Some evidence indicates that poor insight may even affect the severity of positive and negative symptoms. Although it is now well established that poor insight negatively affects clinical and functional outcomes, very little has been developed in terms of pharmacological or psychological interventions for insight.

Although insight has been explored in previous studies, our study seeks to remediate the limitations of previous work by conducting a large cross-sectional study of multiple dimensions of insight in which several biological and psychological variables will be systematically examined. We aim to identify potentially malleable psychological factors that are related to level of insight, and we will examine the structural and functional brain changes that lead to impaired insight. This research project has the potential to inform the development of new pharmacological and psychosocial interventions to improve insight in psychosis.

B19

Beat processing ability in congenitally blind adults

Laureline Arnaud*, Lucie Ménard, Vincent Gracco

Introduction: The brain has a remarkable ability to adapt when problems occur early in development. In congenitally blind adults (CB), brain reorganization occurs and brain areas devoted to vision are taken over for other senses. Apparently as a result, CB adults often exhibit better performance for auditory processing tasks including pitch processing [1-3]. The present study is part of a comprehensive project designed to extend our understanding of auditory processing in CB and to identify the neuroplastic changes that accompany enhanced auditory performance.

Methods: An adaption of the Beat Alignment Test [4] was used in which participants were asked to determine whether a beep track presented simultaneously along with musical excerpts was on or off the beat. In the second part of the experiment we assessed synchronization with a musical beat. A combination of MRI functional and structural imaging techniques will be used to obtain a comprehensive description of the neural mechanisms underlying enhanced auditory perception in CB adults. In total, fifteen CB adults and fifteen sighted controls will participate in the study.

Results: The results to date are for sighted participants.

Perception: The discrimination thresholds for the sighted group ranged from 44ms to 83ms ($m=58$, $SD=14$). We predict that CB participants will display smaller discrimination and a better ability to synchronize with the beat.

Synchronization: Sighted participants tapped along with 14 musical excerpts. Results show that subjects were able to find the beat in most of the excerpts. Matching of tapping tempo to the music tempo was evaluated with correlation coefficients quite high ranging 0.832 and 0.911 ($m=0.869$, $SD=0.025$). The variability of tapping was evaluated using the coefficient of variation of the intertap interval (ITI CV). The ITI CV varied over a range from 8.0 % to 23.2 % ($m= 15.8$, $SD =5.3$). We predict that CB participants will show an enhanced ability to synchronize with the beat with smaller variability.

In addition to this and other behavioral tests evaluating speech perception ability, we will evaluate neuroimaging differences in the two groups. A better understanding of the neural mechanisms and behavioral consequences associated with sensory deprivation from birth has important implications for understanding neurodevelopmental processes and the mechanisms associated with neuroplasticity.

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B20

Variations in Early Life Maternal Care Program Molecular Determinants of Hippocampal Plasticity and Intrinsic Excitability

Huy-Binh Nguyen*, Michael J. Meaney, Tak Pan Wong

Naturally occurring variations in early life maternal care modulate hippocampal development and function to program distinct cognitive phenotypes which persist into adulthood. Adult rat offspring which received low maternal licking and grooming (low LG offspring) show reduced long term potentiation (LTP), and impairment in hippocampal-dependent spatial memory tasks. However, previous studies focused uniquely on the dorsal hippocampus (DH). Emerging evidence suggests a distinct role of the ventral hippocampus (VH) in mediating fearfulness and fear memory formation, behaviours in which low LG offspring are increased. We have presently found that the early life environment differentially programs hippocampal function along the dorsal-ventral axis. Low LG offspring were suppressed in DH-LTP, but enhanced in VH-LTP. CA1 pyramidal neurons in the VH of low LG offspring fired action potentials at lower threshold voltages, which were larger in amplitude and faster in rise rate than those recorded in high LG offspring. Furthermore, we found a specific enhancement of synaptic potential-to-spike coupling (E-S coupling) in VH of low LG offspring. Expression of the voltage-gated sodium channel NaV1.2-coding mRNA SCN2A is specifically enhanced in the VH of low LG offspring, providing a candidate molecular mechanism. Taken together, these findings suggest that low maternal care in early life programs intrinsic excitability specifically in VH, which in turn associates with enhanced synaptic plasticity and the capacity for fear-associated hippocampal cognition in these offspring.

B21

Changes in nerve growth factor levels in a model of chronic inflammatory arthritis

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A reported 16.5% of Canadians suffer from arthritis, and chronic pain is the most common symptom. Pain relief is an important treatment goal but as relatively little is known about the mechanisms that drive this pain, the results pain treatments are suboptimal. To tackle this problem, we are investigating the modulation of nerve growth factor (NGF) levels as a potential therapeutic target for the management of inflammatory arthritis. NGF is known to be a key mediator of inflammation and pain. It has been shown that NGF is released extra-cellularly as a precursor, proNGF, together with the enzymatic cascade responsible for its cleavage into mature NGF (mNGF) and degradation. Previous work from our lab using Complete Freund's Adjuvant (CFA) induced arthritis in rats has shown de novo sympathetic fibres sprouting in, and around the inflamed joint. These have been confirmed to have a role in nociception and are correlated with increases in the NGF cascade. In naïve rats, inhibition of mNGF degradation leads to sympathetic sprouting and hyperalgesia. Inversely, blocking the cleavage of proNGF to mNGF reduces mNGF protein levels and alleviates hyperalgesia in the CFA model.

To more closely replicate the gradual onset and disease progression of inflammatory arthritis as seen in the clinical setting, and to enable the study of mNGF inhibition at later time points, a model has been developed using a low dose intra-articular injection of CFA into the ankle joint of rats. Nociceptive mechanical and thermal sensitivities were tested at different time points, up to 6 weeks, following CFA injection. Von Frey filaments, a cold plate assay and the Hargreave's test were used. At specific time points, paw skin was processed for immunohistochemistry and Western blotting. To identify peptidergic nociceptive fibres and myelinated afferents, anti-Calcitonin Gene-Related Peptide (CGRP) and anti-vesicular monoamine transporter-2 (VMAT-2) antibodies were used respectively. Separate antibodies were used to detect pro and mature forms of NGF by Western blot.

Nociceptive mechanical and thermal behaviours had developed by 2 weeks post CFA. We expect that there will be an increase in mNGF and sympathetic fibre sprouting in the skin. In the joint capsule it is expected that peptidergic and sympathetic fibres will be present.

Paranode Maintenance Requires Netrin-1 Expression by Oligodendrocytes

Jenea M. Bin* and Timothy E. Kennedy

Myelinated axons are divided into several specialized domains: the node of Ranvier, the paranode, the juxtaparanode, and the internode. The secreted protein netrin-1 is sequestered at paranodes and is required for their maintenance. Both neurons and oligodendrocytes express netrin-1, but it has not been determined whether paranode maintenance requires netrin-1 made by the oligodendrocytes, the axon, or both. To address whether cell-autonomous expression of netrin-1 by oligodendrocytes is required for myelin maintenance, we transplanted oligodendrocyte precursor cells (OPCs) from netrin-1 knockout pups into organotypic cerebellar slices from shiverer mice. In slices transplanted with netrin-1^{-/-} OPCs there was a delay in the sequestering of sodium channels compared to slices transplanted with OPCs from control littermates. In addition, in long term, but not short term, netrin-1^{-/-} OPC transplanted cultures the paranodal caspr immunoreactive domain was extended and the juxtaparanodal kv1.2 channel domains were closer together resulting in a loss of the juxtaparanode-paranode boundary. This leakage of proteins into neighbouring domains could be explained by the loss of contact between the oligodendroglial loops and the axon, as observed by electron microscopy. Together these results indicate a role for netrin-1 expressed by oligodendrocytes in paranode maintenance. Uncovering the fundamental mechanisms that regulate myelin maintenance is an important step in identifying novel therapeutic targets to protect and repair myelin in patients with demyelinating diseases.

Characterization of a 'hotspot' in the AMPA receptor activation pathway.

Dawe, G. Brent*; Aourousseau, Mark; Musgaard, Maria; Biggin, Philip; Bowie, Derek

Ionotropic glutamate receptors (iGluRs) are ion channel proteins expressed ubiquitously throughout the mammalian brain, and consequently they facilitate the majority of excitation at neuronal synapses. iGluRs are divided into three major subclasses: NMDA (NMDAR), AMPA (AMPA), and kainate (KAR) type receptors. Recently, the full-length iGluR structure has been elucidated, although the molecular-level chain of events between glutamate binding and channel opening remains unclear. We have previously described how the occupancy -by sodium- of an electronegative pocket in the extracellular ligand-binding domain (LBD) is necessary for KAR activation (1). Presently, we wanted to examine whether this pocket, conserved amongst iGluRs, has an important role in AMPAR activation. We employed a combination of outside-out patch-clamp electrophysiology (recording from recombinant receptors expressed in HEK 293 cells) and molecular dynamics (MD) simulations to study the site.

Since the separation of subunits (arranged as dimers) at the LBD is thought to underlie iGluR desensitization, our first strategy involved engineering a mutant GluA2-type AMPAR to form a cross-subunit electrostatic tether (a charged lysine residue) into the negative pocket. Through three mutations we were able to create a receptor for which desensitization was greatly attenuated and channel-open probability became much higher than the wildtype GluA2 receptor. In agreement, MD analysis suggested that the lysine could reach into the pocket, albeit unstably. We therefore suspected the GluA2 pocket might be smaller than in GluK2, and ion replacement experiments showed extracellular lithium to have a dramatic effect toward eliminating receptor desensitization, especially upon removing an endogenous lysine residue near the pocket. MD simulations also showed lithium, and not larger ion species, was attracted to the pocket, indicating that cation occupancy of the AMPAR pocket (as in KARs) prevents the onset of desensitization. Finally we asked whether cross-subunit electrostatic interactions adjacent to the AMPAR pocket were responsible for the effects of lithium. The replacement of three charged amino acids with alanine residues produced a receptor which could not activate unless the allosteric modulator cyclothiazide was also applied with glutamate. Interestingly, the co-expression of this mutant GluA2 receptor with the transmembrane AMPA receptor regulatory protein (TARP) subunit γ -2 restored functionality, suggesting that TARPs might stabilize inter-subunit contacts at the apex of the LBD to modify AMPAR gating behaviour.

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Relationship between intracortical inhibition and anxiety/depression experienced by healthy individuals and people with multiple sclerosis

Julia C Nantes* & Lisa Koski

Abnormalities in the brain's main inhibitory neurotransmitter, γ -aminobutyric acid (GABA), have been linked to chronic psychiatric and neurological diseases. In particular, intracortical inhibition (a noninvasive biomarker of GABAergic activity measured using transcranial magnetic stimulation (TMS)) has been reported to be abnormally low among people with a variety of mental health disorders, as well as among people with multiple sclerosis (MS). As the prevalence of anxiety and depression is exceptionally high among people with MS, the present study sought to estimate the extent to which intracortical inhibition is associated with symptoms of anxiety and depression in this population. Fifty people with MS and 28 age- and sex-matched healthy controls were recruited to participate in the present study. Exclusion criteria included diagnosis of a mental health disorder prior to MS onset. Participants underwent the short-interval intracortical inhibition (SICI) TMS paradigm, and filled out the Hospital Anxiety and Depression Scale (HADS). HADS scores of people with MS were significantly higher than healthy individuals ($t(76) = 5.27, p < 0.001$), indicating more severe depression and anxiety among MS participants. Group differences in SICI did not reach significance ($p < .05$). Among the healthy control group, lower SICI predicted higher HADS score ($r(27) = -0.45, p > .01$) while no relationship was observed among the MS group ($r(49) = 0.03, p > .05$). This is the first study to report that intracortical inhibition fluctuates with normal levels of anxiety and depression experienced by otherwise healthy individuals, rather than exclusively among people with diagnosable mental health disorders. However, depression and anxiety among people with MS is not directly related to intracortical inhibition, potentially due to disease-related factors (e.g. structural brain damage) that may weaken this relationship.

B25

Female suprachiasmatic nucleus (SCN)-specific BMAL1 knockout mice show luteinizing hormone surge and is thought to be correlated with ablation efficacy.

Caroline Lin* Adrienne Chu Ian Blum Lei Zhu Florian Storch

The circadian clock machinery has been known to play a vital function in reproduction. Ovariectomized (OVX) rodents supplemented with surge-permissive estradiol exhibit a daily luteinizing hormone (LH) surge albeit in constant darkness, providing evidence that the surge is circadian regulated. While we've shown that mice lacking clock function in all tissues (Bmal1KO mice) completely lacked a LH surge, the contribution of individual clocks in specific hypothalamic-pituitary-gonadal (HPG-) axis elements to the surge is still largely unclear. We generated mice carrying a gonadotrope-specific disruption of the essential clock component Bmal1 (GBmal1KO) by means of Cre-LoxP technology and found that it has no major role in the generation of the preovulatory LH. This suggests that circadian clocks elsewhere are required for surge production. In situ hybridization staining revealed that global Bmal1KO mice lack AVP expression in the SCN as compared to wild-type (WT) animals. Therefore, we postulate that AVP-expressing cells in the SCN may be responsible for the lack of LH surge observed in Bmal1KO mice. To test this hypothesis, we generated a mouse line with SCN-specific Bmal1 ablation by mating mice with the Cre recombinase gene inserted into the Synaptotagmin10 (Syt10) locus, a gene that is mostly enriched in the SCN region, with mice bearing a floxed allele of Bmal1. We found that SCN-specific Bmal1KO females transit through all estrous stages and were able to mount a LH surge. However, they produce peaks that are significantly lower than the LH peaks exhibited by the WT animals, and we speculate that the peak may be due to incomplete ablation. By performing immunohistochemistry (IHC) staining on brain sections of SCN-Bmal1 KO mice for Bmal1, we will be able to assess Bmal1 ablation efficacy and possibly correlate this with peak levels of luteinizing hormone surge.

Functional neuroplasticity in compromised long distance cortical coupling

Sebastien Dery*, John Lewis, Sylvain Baillet

The human brain is a remarkably dynamic system conditioned in such a way as to adapt facing ever changing conditions and experiences. Local reorganization in the neurons integrative functions and connections has been postulated to permit this dynamic adaptation for various evolutionary and physiological purposes. The mechanisms driving both the individual neurons while maintaining long-term functional stability nevertheless remains an important conundrum. Thanks to recent advances in computational method, the use of high-temporal electrophysiological recordings now allows for the exploration of the resulting changes through their spectral signature across the whole brain. Studies over the last decade has provided strong support to the notion that integration of information may be facilitated, if not gated, by slow synchrony between neuronal populations. When faced with compromised linking between two distant assembly, adaptation must take place in order to keep functions intact. Here we used electroencephalography to measure task-related change in functional connectivity, as manifested by a phase-locking of low-gamma oscillations, between visual cortices of typically developing healthy individuals and a structurally compromised corpus callosum population of elderly subjects as they passively viewed various drifting grating patterns. We interrogate the synchronicity profile of interhemispheric connections across primary visual cortex and extra striate areas and investigate their relation with structural measures recorded from diffusion imaging (DTI). Interestingly, we observe a pronounced decrease in synchrony between visual cortices, suggesting independent computation from both hemispheres. This observation is further supported by a local increase within each hemispheres at distinct frequencies, potentially extending to higher order visual areas as a mean to aggregate further cortical resources in compensation for the cut-off components. These results suggest that facing compromised coupling, the visual network appears split into two independent oscillators increasing their local connections to compensate for the loss in cortical resources.

B27

Investigating the impact of a family history of Alzheimer's disease on fMRI activity during a contextual memory paradigm.

Lindsay Wallace*, Diana Kwon, David Maillet, Elizabeth Ankudowich, Stamatoula Pasvanis, Alexander Swierkot, M. Natasha Rajah.

Episodic memory impairment is one of the most consistent and pronounced deficits reported in pre-clinical stages of late-onset sporadic Alzheimer's Disease (AD). Recent studies indicate that AD-related brain pathologies arise decades before AD memory symptoms are apparent, and may be present in middle aged adults at risk of developing AD. We have shown that episodic memory tasks for encoding and retrieving spatial and temporal contextual details (context memory tasks) are sensitive to episodic memory decline in healthy middle aged adults. Therefore, context memory tasks are a means to explore the brain changes associated with early signs of episodic failure in middle aged adults at risk of AD. However, little is known about the neural correlates of context memory in middle aged adults with risk factors for AD (i.e. positive family history). In light of this, the objective of the present study was to investigate whether there are differences in brain activation, as measured by fMRI, between middle-aged adults with vs. without a family history of AD (+FH, n=23; -FH, n=29) during the performance spatial and temporal context memory tasks for faces. Each experimental task also differed on difficulty level (easy vs. hard) to facilitate differentiation between group-related and performance-related effects. Subjects were scanned during both encoding and retrieval. The behavioural results indicated that there were group differences in retrieval accuracy. Specifically, there were differences in retrieval accuracy between young and middle aged -FH adults, but not between young and +FH adults. fMRI analysis indicated that there was a group by memory-phase (encoding vs. retrieval) interaction. The -FH group showed over-activation of the parahippocampal region at encoding compared to retrieval, while the +FH group demonstrated opposite results: over-activation of the parahippocampal region at retrieval compared to encoding. Group related differences were also apparent in areas of the prefrontal and parietal cortices during context memory performance. This suggests that brain changes related to AD risk factors may emerge at middle age, despite lack of marked memory performance decrements.

Gray matter structure and auditory-motor synchronization in children with autism

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction and communication, as well as atypical sensory perception. Individuals with ASD often have diminished processing of speech but can have enhanced processing of basic, non-verbal material like music. Auditory-motor synchronization is critical to both speech and music, but no study has examined how basic auditory-motor skills map onto brain structure in ASD. Here we sought to investigate: 1) basic auditory-motor synchronization in children with ASD versus typically developing (TD) children, and 2) how performance maps onto brain structure. Subjects were ASD and control children who participated in the 'NeuroDevNet ASD project'. Groups were matched on age and all subjects had IQ above 70. Subjects were tested on an auditory-motor synchronization task in which they tapped in synchrony with auditory rhythms of varying metrical complexity. Brain structural MRI data were acquired and analyzed in terms of cortical thickness. Both ASD and TD children performed worse on more complex rhythms, but ASD performed better than TD on the most complex rhythms. Preliminary brain structural analyses showed that cortical thickness in motor-related cortex was correlated with performance differences on the auditory-motor synchronization task. These results are consistent with current models of enhanced processing of basic stimuli in ASD, and may signal potential alterations in an auditory-motor action-observation system in ASD.

B29

ERP functional brain network entropy and aging

Xiaoling Fang*, Alan Evans

Based on Shannon Entropy, Network Entropy was defined to measure the ability of brain to obtain information. Using event-related potentials (ERPs) elicited by unattended stimuli in young (M=25.5 yrs) and old (M=71.3 yrs) subjects both healthy, the effects of brain aging had been explored by graph theoretical analysis and Network Entropy analysis. The results show both the global efficiency and average local efficiency of Young people's brain networks are distinctly larger than that of old people's brain networks ($p < 0.01$). More importantly, younger brain could create more network entropy than the old ones. It indicates that aging may correlate with the inability of the brain to get enough information. Network entropy may be a useful approach to study the mechanism of aging and neurodegenerative disease.

B30

RhoA proteolysis: A novel mechanism for RhoA regulation in cell stress and apoptosis

M.-P. Girouard*, M. Pool, A. E. Fournier

RhoA, a member of the Ras-related family of GTPases, is ubiquitously expressed in eukaryotic cells and is involved in many cellular functions, including regulation of the cytoskeleton. As such, it promotes the assembly of actin-myosin filaments known as stress fibers, limits actin depolymerization and stabilizes microtubules. RhoA regulates numerous cellular processes such as cytokinesis, adhesion and migration. RhoA is tightly regulated by a variety of mechanisms such as GTP-binding, phosphorylation and prenylation. Our laboratory has found that RhoA is processed through proteolytic cleavage to generate a 10kDa stable amino terminal fragment (NTF-RhoA), suggesting a novel regulatory mechanism for this protein. Our studies revealed that RhoA proteolysis is activity-dependent, and is regulated by both phosphorylation and prenylation. Furthermore, it is promoted following oxidative stress induced by hydrogen peroxide treatment and following initiation of apoptosis with Staurosporine. Investigation of the proteases involved in RhoA processing using specific protease inhibitors revealed that Calpain and Caspase activity result in degradation of NTF-RhoA. Introduction of NTF-RhoA into serum-starved Swiss 3T3 fibroblasts leads to mild stress fiber formation while introduction of the C-terminal fragment promotes the formation of nuclear actin rods, a hallmark of cell stress observed in some neurodegenerative diseases. Thus, our findings describe a novel mechanism of RhoA proteolysis occurring in conditions of cell stress and apoptosis. Future work will investigate RhoA proteolysis in neurons and its effects on growth cone collapse and neurite retraction. We are seeking to determine how this mechanism may impact neuronal regeneration following central nervous system injury.

B31

Visual remapping is more impaired in patients with unilateral parietal lesion than in hemidecorticate patients as revealed by novel version of the double step task

Kate Rath-Wilson*, Daniel Guitton

Studies of remapping abilities in human patients with distinct cortical lesions are inconclusive. Patients with parietal lobe lesions, primarily of the right side, tested on the classical double-step task have a particular deficit in generating an ipsilesional saccade if it follows a contralesional saccade (Duhamel et al, 1992 & Heide et al, 1995). This deficit has been explained as an inability to generate/ interpret corollary discharge for saccades elicited by the lesioned hemisphere. Recent studies, however, have called this finding into question. A review has re-interpreted the data from these earlier publications, suggesting that these results are actually evidence of right-hemisphere dominance in human visual remapping (Pisella et al, 2011). Several studies of patients with right parietal lesions have determined that ipsilesional but not contralesional eye movements can result in a deficiency in remembering spatial information from previous fixations (Vuilleumier et al, 2007 & Russel et al, 2010). We tested hemidecorticate subjects on a novel version of the double-step task, adapted because our patients are hemianopic. We found that they do not have any impairment in remapping in either direction. We have tested a right parietal patient with this novel double-step task and found that he is unable to generate a contralesional saccade when it follows an ipsilesional saccade, in opposition to the findings of Duhamel et al, 1992. We are in the process of testing more patients with our novel paradigm to provide further insight into the saccadic remapping system in humans.

B32

Developmental abnormalities in the cerebellum of spinocerebellar ataxia type 6 mice

Sriram Jayabal*, Lovisa Ljungberg, Thomas Erwes, Alexander Cormier, and Alanna J. Watt

Spinocerebellar ataxia type 6 (SCA6) is a late-onset neurodegenerative disorder caused by a polyglutamine expansion in P/Q-type calcium channels (P/Q channel) that are richly expressed in Purkinje cells. However, the pathophysiology of SCA6 is not yet fully understood. Since P/Q channels play a role in synapse elimination of climbing fibers onto Purkinje cells during development, we wondered whether it is affected in a mouse model of SCA6. Using a knock-in mouse model with a hyperexpanded polyglutamine tract (SCA684Q KI mice), we made whole-cell patch clamp recordings from Purkinje cells in acute sagittal slices (250 μ m) from lobule III of cerebellar vermis at 31-32°C from homozygous SCA684Q KI (SCA684Q/84Q) and litter-matched wildtype (WT) control mice. We evoked excitatory post-synaptic currents (EPSCs) in Purkinje cell by stimulating climbing fibers with an extracellular stimulation electrode positioned in the granule cell layer. At a developmental stage when the majority of WT Purkinje cells in lobule III are innervated by one or two climbing fibers (P10-13; 85% of WT Purkinje cells innervated by ≤ 2 climbing fibers, N = 19 cells), significantly fewer Purkinje cells from SCA684Q/84Q mice were innervated by 1 or 2 climbing fibers (53% innervated by ≤ 2 climbing fibers, N = 17 cells; P < 0.005), suggesting that the polyglutamine expansion in the P/Q channel affect synapse development in the SCA6 mouse cerebellum. Synaptic properties such as EPSC amplitude, 10-90% rise time, decay time constant, disparity index, and disparity ratio between multiple inputs were not affected at this developmental age (P>0.05). However, a week later, when the majority of WT Purkinje cells are innervated by one climbing fiber (P18-24; 73% of WT Purkinje cells are monoinnervated, N= 22 cells), there are no differences in the number or synaptic properties of climbing fibers innervating SCA684Q/84Q Purkinje cells (70% of SCA684Q/84Q Purkinje cells are monoinnervated, not significantly different from WT, P>0.05, N=23 cells). These results suggest that the polyglutamine expansion in the P/Q channel that gives rise to SCA6 also delays the functional maturation of climbing fibers early in development, but that the circuit is able to overcome this delay later in young adults to form mature climbing fiber – Purkinje cell synapses that are indistinguishable from those in WT mice.

Functional Neural Correlates of Social Approval in Schizophrenia - Preliminary Findings

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Individuals seek to establish a good reputation among their peers by engaging in prosocial behaviours and acting appropriately in social situations. Social approval is a type of reward that uses specific abstract social reinforcers. While reward processing is clearly altered in schizophrenia, few studies have specifically explored social reward processing and its related neural substrates in this population. The presented analysis reports preliminary findings of a functional magnetic resonance imaging study that explores social approval in schizophrenia. 13 patients with schizophrenia and 12 healthy controls participated in a two-part study, consisting of a self-introduction phase conducted in the laboratory and a social approval task administered in the scanner. Participants were led to believe they were participating in a personality study, where their results from various questionnaires and a short interview would be assessed by a panel of clinicians. Participants were then presented with the results of their supposed evaluation in the scanner. In reality, the presented personality traits were chosen from a predefined list. The social approval task involved obtaining subjective reports of pleasure associated with receiving positive or slightly negative feedback about the self, compared to viewing the evaluation of a stranger. Results within the control group revealed significant activation of basal ganglia structures (e.g. caudate and putamen) and limbic structures such as the parahippocampal gyrus and amygdala; by contrast, patients did not show activation of such regions when receiving both positive and slightly negative feedback directed towards the self. Overlapping brain activation was found, where patients recruited medial prefrontal cortical regions, but in a differential manner compared to controls. Both groups rated traits from the high social reward condition as significantly more pleasurable than the low social reward condition, confirming the established reward valence of the presented personality traits. However, patients' subjective ratings of slightly negative/neutral feedback was significantly higher than controls, suggesting that patients did not perceive feedback from the low social reward condition as negatively as controls. These findings reveal that patients exhibit differential patterns of brain activation when interpreting the reward value of presented traits in the scanner, targeting the construct of social approval. Patients failed to elicit the same amount of activation in brain structures believed to underlie reward and affect-related processing as controls. Evidence suggests a potential deficit in cognitive processing underlying the representation of social reputation in schizophrenia.

B34

Saccadic eye movements and face recognition

Hassan Akhavein*, Dr.Reza Farivar Mohseni

Investigating where human fixate on a face can give us insight into the mechanism through which the brain gather information for cognitive processes in face recognition. Research on face recognition demonstrated the existence of preferred landing positions after a saccade mostly around the eyes, nose and mouth. These fixation patterns could be varied by the nature of the task, the difficulty and also presence of 3D depth cues like stereo. Previous studies reported areas of interest in saccadic landing positions while viewing faces defined by combined 3D information. However the eye movement strategy in recognition of faces defined purely by isolated 3D depth cues is an open question. Here we examined the effect of difficulty of the task and different 3D information on eye movements recorded during face recognition. We used three different types of depth cues (Stereo, Shading and Texture) to define the face surface and systemically altered the identity information of the face to parametrically vary the difficulty. The position, duration and temporal sequence of fixations were analysed. As expected, the recognition performance varied with different depth cues and difficulty. Interestingly, the duration of fixations was unaffected by the type of depth cue. The position of fixation was consistent between texture and shading, but stereo showed a more distributed pattern. These results suggest that the human visual system uses predefined strategy in obtaining information in order to optimizing face recognition, and difficulty of the task and the type of 3D information defining faces have limited effects on eye movements.

B35

Neurocognition of Language Lab at McGill

Karsten Steinhauer*, Kristina Kasparian, Stefanie Nickels, Anastasia Glushko, Fayden Bokhari, Jessica Cooper

This poster will introduce current research conducted by the members of the 'Neurocognition of Language Lab' at McGill's School of Communication Sciences and Disorders (Lab Director: Dr Karsten Steinhauer). Most of our research uses event-related brain potentials (ERPs) to investigate the neurocognitive real-time mechanisms underlying language in native speakers, language learners, and special populations.

Research questions concern topics such as (1) the neural reorganization of language processing while language learners become more proficient (and while immigrants lose their mother tongue), (2) the online integration of syntactic, semantic and prosodic information, and (3) similarities and differences between speech and music processing.

Spike Time Prediction from Local Field Potential in Monkey Visual Cortex

*Kostoglou K., Hadjipapas A., Lowet E., Roberts M.J., De Weerd P., Mitsis G.D.

Aims: The temporal structure of a spike train is a significant element in neural coding since information is carried in terms of the precise timing of spikes. In the visual cortex it is known that temporal coding is important for distinguishing contrast differences of a visual stimulus. Even though the predictive relationship between collective population activity (LFP) and spiking activity underpins functional network computation, it remains poorly understood. In this study, we utilized a data-driven approach to model the causal and dynamic relationship between local field potentials (LFP) and multi-unit spike trains in monkey early visual cortex during passive viewing of grating stimuli and predict individual spike times.

Methods: The monkey visual cortex dataset contained one contrast condition (the contrast giving the strongest gamma oscillation power). The relationship between LFPs and multi-unit spike was analyzed using a system identification approach based on the Laguerre-Volterra network (LVN) methodology. The LVN is a Volterra-equivalent network model that employs filter banks of discrete-time Laguerre functions to preprocess the input signal and a single hidden layer with polynomial activation functions. A sigmoidal activation function transforms the continuous model output into probabilities of firing and a threshold is applied for spike generation. The network parameters were trained based on a hybrid Genetic Algorithm – Interior Point optimization method and model selection was achieved via cross-validation between trials. The Matthews Correlation Coefficient ($-1 < \text{MCC} < 1$) served as a measure of correlation between predicted and observed spike trains with a ± 1 ms accuracy.

Results: The improved performance of the 2nd order nonlinear models indicated a nonlinear relationship between LFPs and spikes. Single trial MCCs ranged from 0.45 to 0.66 (median=0.60). Consistent with other studies, we identified two basic nonlinear mechanisms that are related with spiking activity; Nonlinear phase-amplitude cross-frequency coupling between low (theta, alpha, beta) and gamma LFP frequencies and nonlinear interactions mainly in the gamma/high gamma frequency bands. The latency of the first spike known to carry information about the stimulus could also be accurately predicted.

Conclusions: We were able to predict multi-unit spike times from LFPs with reasonable accuracy. Given the importance of spike precision and spike timing, our approach can be useful in the study of the neural code. The results obtained are also important in terms of validating spike time dependent computation schemes.

B37

Training induced dynamic filtering of auditory distractors in the rat primary auditory cortex

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We communicate better when we effectively sort out sounds based on their relevance: we ignore distracting sounds while we emphasize those that carry important information. This ability is increasingly impaired with aging even without significant hearing loss, supporting an underlying mechanism of disrupted auditory cortical processing in the aged brain. However, little is known about the mechanism by which sounds are dynamically filtered according to their contextual meaning in adulthood and aging. Currently, researchers know that learning to discriminate between sounds according to their contextual meaning relies on finely orchestrated changes in the excitatory-inhibitory balance at synapses in auditory cortices. Therefore, here we hypothesized that training to anticipate a sound associated with a rewarded - hence meaningful - behavior would make contextual filtering more robust and specific and help us to understand its dynamics in the aged brain.

We trained adult (16 mo) and aged (28 mo) Brown-Norway rats using an auditory training strategy based on detecting fine spectral features of complex sounds after the occurrence of an auditory cue. We then densely mapped their primary auditory cortical (A1) responses to simple and complex trained and untrained sounds in the presence of background distractors. Similar recordings were performed in naïve untrained rats.

In trained animals the occurrence of the auditory cue significantly altered the contrast between trained target and non-target sounds in A1. Training also resulted in a better discrimination between these complex sounds in the presence of background distractors.

Our findings suggest that predictive cues can lead to a dynamic modulation of A1 sensitivity to complex sounds that could serve to improve the detection of familiar sounds in distracting or noisy conditions.

Affordance and the Anterior N400

Karim Ghorayeb*, Mathieu Brodeur

Introduction: It has long been demonstrated that concrete stimuli (e.g., pen) automatically initiate plans of actions (e.g., writing), a phenomenon known as motor affordance. However, because these actions are inappropriate or useless in most contexts, plans are rarely executed. The present project used the event-related potentials (ERPs) to probe the brain processes involved in the inhibition of motor affordances. It was hypothesized that these processes would be reflected by changes of voltage amplitude of the N400, one component of the ERPs known for indexing inhibitory processes in other experimental conditions.

Method: The protocol involves a single task with two experimental conditions each composed of 60 trials. In the first condition, four images of objects will appear on the screen. The 4 objects will be of different types (e.g., a chair, a pencil, an apple, and a cell phone). The four images will appear after which another screen will appear presenting an image of an action one can do on or with one of the four objects (e.g., a hand writing with a pencil). Afterwards, a prompt will appear asking the subject to name the action presented in the previous screen. The prompt will appear indefinitely until the subject is ready to start the next trial at which point the subject will press enter.

In the second condition, four images of objects will also appear on the screen. However, unlike the first condition, two duos of images will appear where the first two images will represent the same type of object and the other two images will display another type of object (e.g., 2 different staplers and 2 different hammers). The four images will be followed by the presentation of the action image. The action will be consistent with one of the duos (e.g., someone "who staples documents"). The images will be presented following the same parameters as in the first condition and again subjects will be asked to say aloud the action depicted in the image of the action.

Results and conclusions: I don't have any data collection up to now but I will have results before the IPN retreat. In the meantime, the expected results are that the inhibition will be studied by comparing the two conditions. More inhibition is expected in the first condition because subjects will have to ignore the affordances associated to three of the four different objects. In the second condition, subjects will only have to ignore the affordances triggered by one duo of objects. Also, amplitudes of the N400s are expected to be larger in the first condition due to a higher inhibition of affordances.

B39

Direct current stimulation disrupts consolidation of auditory pitch discrimination learning

Reiko Matsushita*, Jamila Andoh, Robert J. Zatorre

Background: Transcranial direct current stimulation (tDCS) is known to modulate cortical activity in a polarity-specific manner; anodal tDCS increases cortical excitability and cathodal tDCS decreases it. Several studies suggest tDCS induces an LTP-like effect and in fact, involvement of tDCS in motor learning has been demonstrated at a behavioral level. However, the role of tDCS on auditory learning is largely unknown. Here we address the effect of tDCS on a melody discrimination task. We targeted right auditory cortex because of its known role in tonal processing. We hypothesized that tDCS over this region would modulate learning over time.

Methods: Forty-two participants were trained with a melody discrimination task over three consecutive days. We used micromelodies, which contain pitch intervals that are smaller than one semitone. Learning to discriminate small pitch intervals with this task has been shown to correlate with hemodynamic changes in the right auditory cortex in fMRI studies. We implemented a psychophysical staircase procedure to establish a pitch discrimination threshold for performance. Baseline threshold was measured on Day1. On Day2, participants received either anodal tDCS or cathodal tDCS targeting right auditory cortex, or sham tDCS for 20 minutes. On Day3, participants did the same training task without tDCS. For the analysis, pitch discrimination thresholds were compared across groups.

Results: Performance of the anodal tDCS group didn't significantly change over three days whereas the cathodal and sham stimulation group showed significant learning by the end of the training, as expected. In addition, no significant effect of anodal tDCS was observed during performance on Day2, suggesting that anodal tDCS doesn't interfere with perception, but probably interferes with consolidation.

Conclusion: We observed that anodal tDCS blocked learning consolidation overnight. This result is consistent with several studies showing that tDCS affects task performance offline, rather than online. Our result supports this tDCS effect on between-session learning, and provides causal evidence for the importance of right auditory cortex to melody processing.

B40

DNA methylation in the striatum of individuals with cocaine dependence

Kathryn Vaillancourt, Gang G. Chen, Alpha Diallo, Raphael Poujol, Carl Ernst, Deborah C. Mash, Gustavo Turecki

Multiple interacting genes and environmental factors determine the risk and trajectory of drug addiction. Expression of genes involved in the risk and consequences of addiction is influenced by environmental factors that, in many cases, are likely to leave persistent epigenetic marks on an individual's DNA and chromatin. Recently, several studies have identified epigenetic mechanisms that are associated with the acquisition of compulsive drug seeking in animal models, but little is known about the role of epigenetics in human cocaine dependence. Of particular interest is DNA methylation as it represents a mitotically stable mark that has been shown to be altered by environmental experience. We have profiled epigenetic marks in cocaine abusers in two dopamine dependent brain regions, the dorsal and ventral striatum. We used Reduced Representation Bisulfite Sequencing (RRBS) on nucleus accumbens and caudate tissue from 25 dependent cocaine users and 25 drug-free and age-matched controls to detect genome-wide methylation. RRBS is a high throughput sequencing based approach, which enriches for CpG dinucleotides and generates methylation data at base-pair resolution. This technique identified differentially methylated CpGs between groups and brain areas. All RRBS libraries contained more than 4 million reads at 10X coverage and over 65% of reads in each library were aligned to the human genome. In addition, all libraries were bisulfite converted with over 98% efficiency. High throughput discovery of cocaine-associated networks and pathways allow us to investigate the epigenetic changes in brain that accompany the transition from cocaine abuse to chronic cocaine dependence. Funded by a grant NIDA (DA033684).

B41

New formulation of lithium improves cognitive performance in early stages of Alzheimer-like amyloid pathology in transgenic rats

Edward N. Wilson, Jr.* , M. Florencia Iulita, Simon Allard, Sonia Do Carmo, Adriana Ducantenzeiler, Adam Marks & A. Claudio Cuello

Background:

Lithium, a drug widely used for treatment of bipolar disorder, has disease-modifying properties both in patients at risk for developing Alzheimer disease and in AD transgenic animal models. However, an understanding of the exact active mechanisms underlying lithium-mediated neuroprotection remains elusive. Moreover, conventional lithium has a narrow therapeutic window and many significant adverse neurotoxic side effects, making it inappropriate for long-term treatment.

We have developed a transgenic rat model of Alzheimer-like A β pathology (coded McGill-R-Thy1-APP) that incorporates Swedish and Indiana human APP gene mutations. These rats develop A β plaques as early as 6-9 months of age, and display intraneuronal A β accumulation of the toxic oligomeric soluble form before plaque formation – as has been shown to occur in human AD and Down's syndrome. It is significant that McGill-R-Thy1-APP rats present progressive behaviour impairments starting at 3 months of age, while no amyloid plaques are yet present, when subjected to Morris water maze, auditory fear conditioning, and Novel Object Recognition and Location tasks. In this study, we have evaluated the therapeutic efficacy of a recently developed transmucosal formulation of lithium whose lower dose achieves therapeutic effects in the absence of associated side effects.

Methods

Prior to the onset of A β plaque deposition in the transgenic animals, Mcgill-R-Thy1-APP transgenic rats and non-transgenic littermate controls were treated and cognitively assessed. Both groups received a novel formulation of lithium or vehicle control for six weeks and were assessed using the cognitive tests described above. Modifications of the APP cascade, markers of synaptic plasticity and neuroinflammatory processes were examined by ELISA, Western blotting and immunohistochemistry.

Results

Lithium-treated transgenic rats displayed notable improvements on Novel Object Recognition, Morris water maze and fear-conditioning paradigms compared to vehicle-treated transgenic animals. Improvements in cognition were accompanied by modulation of synaptic and inflammatory markers, hippocampal neurogenesis, APP processing through BACE1, and occurred in the absence of the regular negative side effects previously observed following treatment with standard lithium.

Conclusion

We conclude that this novel formulation of lithium has a therapeutic effect in APP transgenic rats at the earliest stages of Alzheimer-like amyloid pathology.

Instructions for Presenters

You must stand by your poster during your assigned poster session.

Putting up your posters

Session A posters must be put up between 8:30AM and 10AM on Thursday September 18th

Session B posters must be put up before 3:00PM on Thursday September 18th

Taking down posters

All posters must be removed between 3:00PM and 3:15PM on Friday September 19th. Posters that remain will be discarded.

N.B. If you submitted an abstract, but fail to present a poster, you will be fined for the cost of the poster board.