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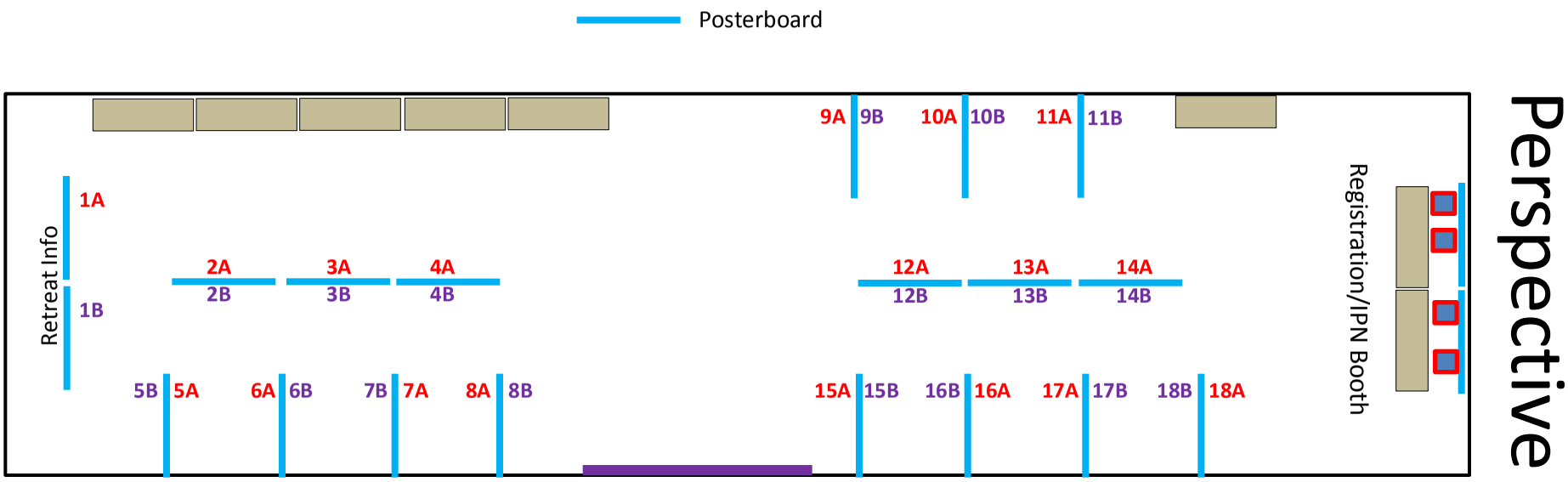

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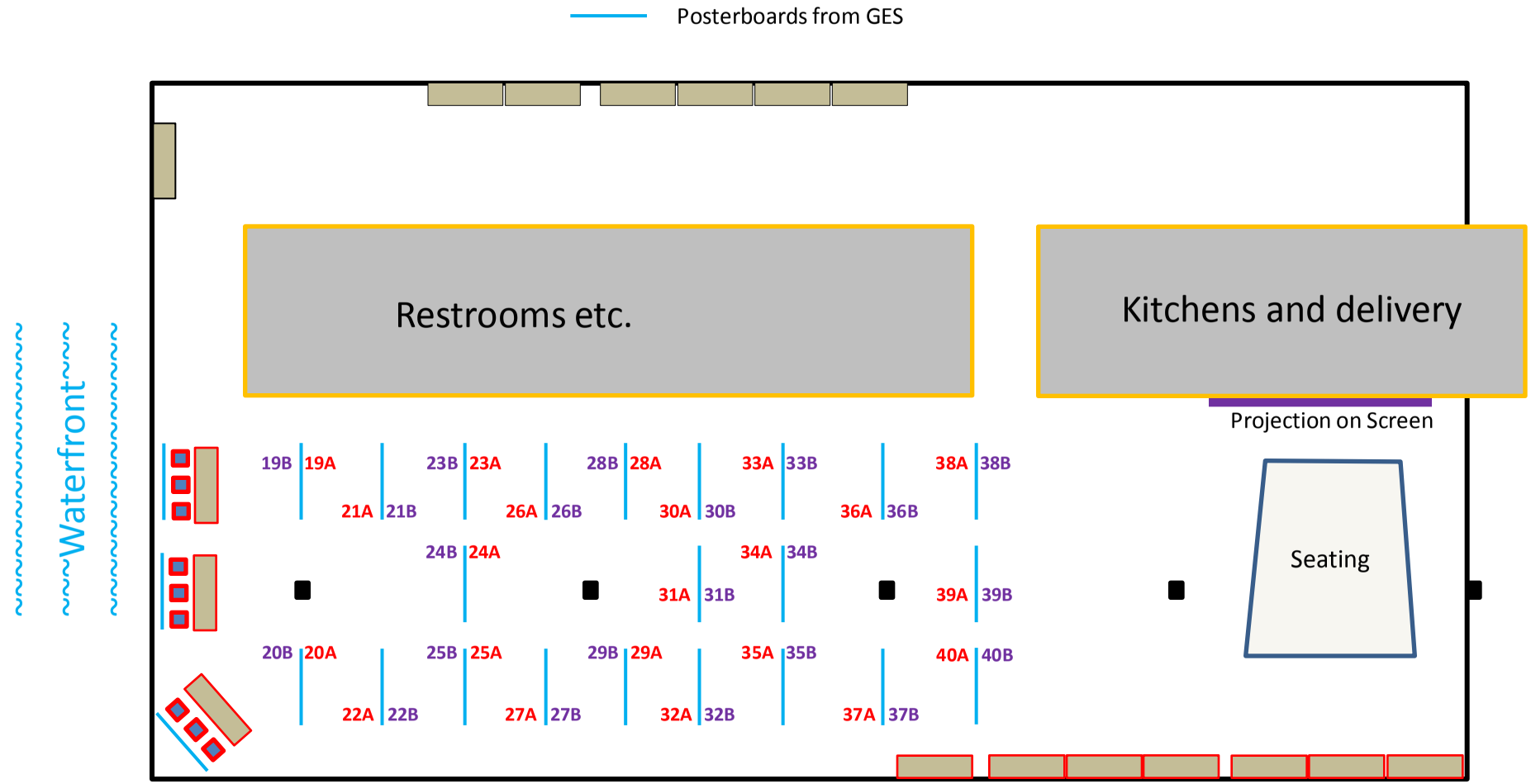

PASS-1-A

Abnormal TrkB Signaling Contributes to Striatal Neuron Vulnerability in Huntington Disease

Khanh Nguyen*,
Abbas Sadikot

Huntington disease (HD) is caused by an expanded CAG triplet repeat in the huntingtin gene. This gene produces an elongated mutant huntingtin protein. Degeneration of striatal projection neurons is the earliest and most significant neuropathological finding, and correlates with the cardinal motor symptom of Huntington's Chorea. The mechanism by which mutant huntingtin causes selective striatal degeneration is not known.
Striatal neurons receive a large glutamatergic innervation from cortico- and thalamo-striatal afferents and dopaminergic innervation from nigro-striatal afferents. These afferents also release brain derived neurotrophic factor (BDNF), which mediates trophic support via the receptor TrkB that is expressed by striatal neurons. Previous studies have inconsistently reported decreased levels of BDNF and TrkB expression in striatal tissue samples from human HD cases or transgenic mouse models expressing mutant huntingtin protein.
We assessed striatal BDNF, TrkB and downstream signaling proteins in the R6/2 transgenic mouse model of HD. First we found that in vivo striatal expression of BDNF and TrkB in presymptomatic 5 week old R6/2 mice were normal, but the downstream proteins phospho-TrkB phopho-Erk1/2 and DARPP32, a phenotypic marker of striatal neurons, were reduced in R6/2 compared to wildtype mice. Subsequently we hypothesize that if mutant huntingtin disrupts BDNF-TrkB signaling, then striatal neurons cultured from R6/2 mice would exhibit a reduced trophic response to BDNF treatments. Immuofluorescent cell counts show that BDNF treatments yield a greater trophic effect on wildtype than on R6/2 striatal cultures. Western blot analysis of the TrkB signaling pathway shows that BDNF treatments increase the levels of activated phospo-TrkB and phospho-Erk1/2 in wildtype cultures but to a significantly smaller degree in R6/2 cultures.
These results suggest that abnormal BDNF-TrkB signal transduction results in a reduced trophic support of R6/2 striatal neurons.

PASS-1-B

Blood-Brain Barrier (BBB) and Meningeal Endothelial-Cell (EC) Soluble Products Differentially Impact MS-Relevant B-Cell Responses

Antonia Kobert,* Jorge Ivan Alvarez, Cornelia Podjaski, Alexandre Prat, and Amit Bar-Or

Multiple sclerosis (MS) has traditionally been conceptualized as a primarily T-cell mediated disease; however, B cells have recently emerged as important contributors to MS pathophysiology in the periphery. Moreover, B cells are able to persist within the CNS of MS patients, where they may drive the global, percolating inflammatory processes characteristic of the progressive stages of disease. The factors that contribute to a permissive environment within the inflamed MS CNS, however, have remained poorly understood.

We considered soluble factors from human blood-brain barrier (BBB) and meningeal ECs (MECs) as potential contributors to a B-cell fostering environment within the inflamed MS CNS. Normal human B cells were cultured with culture supernatants from BBB ECs and MECs that had either been stimulated with 100U/ml IFN-gamma and TNF-alpha or were cultured in medium only. B-cell survival and co-stimulatory molecule expression were assessed by flow cytometry following 24h and 72h in culture. IgM and IgG concentrations in the B-cell culture supernatants were assessed following 14 days in culture.

Supernatants from stimulated BBB ECs significantly increased B-cell survival and CD86 expression following 24h and 72h in culture. Stimulated MEC supernatants did not significantly increase B-cell survival, but survival was reduced in B cells cultured with unstimulated MEC supernatants following 24h and 72h in culture. Nonetheless, supernatants from stimulated MECs significantly increased CD86 expression following 24h, and there was a trend towards significantly increased CD86 expression following 72h in culture. Furthermore, supernatants from stimulated BBB ECs and MECs increased B-cell production of IgG, but not IgM, following 14 days in culture.

Our observations suggest that ECs in the inflamed MS CNS may be able to either support or regulate B-cell survival and pro-inflammatory B-cell responses, depending on their activation state and the compartment in which B-cell:EC interactions occur.

PASS-2-A

The Epigenetics of Suicide

Adel Farah*, Benoit Labonte, Gustavo Turecki

Background: Suicide is a worldwide public health problem accounting for more deaths than war and homicides combined. Among various risk factors, childhood sexual abuse (CSA) and childhood physical abuse (CPA) have been linked with higher risk for suicide. A growing body of evidence suggests that the hypothalamus-pituitary-adrenal axis (HPA) is susceptible to the effects of early life adversity. Dysfunction in the HPA axis activity has been associated with suicidal behaviours. More recently, it has been suggested that epigenetic mechanisms underlie these alterations. For example, early life adversity has been shown to be linked to hyper-methylation of the glucocorticoid receptor which is associated with decreased expression of this HPA locus of control. However, it remains unknown whether other regulators of the HPA axis may be affected by similar mechanisms.
Results: In this study, abused suicide completers were compared to non-abused suicide completers and accidental death controls. The results suggest site specific differential methylation in the promoter of key HPA associated genes such as corticotropin releasing hormone and its receptors in the hippocampus of abused suicide completers. In this same group, higher expression levels of those genes were also measured in the hippocampus and interestingly in other brain regions such as anterior cingulate cortex.
Conclusion: Taken together, these results suggest a putative locus of control whereby the environment might be affecting the activity of systems in the brain such as the HPA. These changes may place affected individuals on a maladaptive developmental trajectory and lead to an increase in risk of suicidal behaviour.

PASS-2-B

Endocannabinoids improves low light vision through modulation of retinal ganglion cell chloride homeostasis.

Miraucourt LS*, Tsui J, Desjardins JF, Castonguay A, Wiseman PW, DeKoninck Y, Ruthazer ES

Type I cannabinoid receptor (CB1R) expression has been found throughout the retina of all vertebrates, from human to fish, whereas no clear functional role has yet been shown for the endocannabinoid system (ECS) on vision. We studied the influence of ECS signaling on visual circuit function using the retinotectal system of Xenopus laevis tadpoles. Using a behavioral assay based on their innate ability to escape dark moving dots, we found that tadpoles treated with CB1R agonist WIN 55,212-2 performs better at low light intensity than control animals. In vivo patch clamp recordings from tectal neurons shown, that WIN application enhanced the excitatory postsynaptic currents evoked by direct electrical stimulation of retinal ganglion cells (RGCs) in the eye. This effect was blocked by bath application of the CB1R antagonist AM-251, the glycine receptor antagonist strychnine or the NKCC1 chloride transporter blocker bumetanide. Responses evoked by direct stimulation of RGC fibers in the optic tract in an isolated brain preparation were unaffected by bath application of WIN, implicating the retina as the site of relevant CB1R activation. Extracellular recordings of ganglion cells in the inner retina show that WIN increases the spike frequency of light-evoked responses, an effect that was also prevented by pretreatment with AM-251, strychnine or bumetanide. However, electroretinograms (ERGs) show no effect of WIN on light-evoked response, implicating the inner part of the retina rather than the outer part. Consistently, in vivo time-lapse 2-photon imaging of retinal neurons transfected to express the fluorescent ratiometric chloride indicator clomeleon, revealed that the application of WIN rapidly decreases intracellular chloride concentration of RGCs, but induces no change in bipolar, amacrine or muller glia cell types. Taken together, these results present a model where endocannabinoids improves vision at low light condition by modulation chloride homeostasis in RGCs and favor their excitability.

PASS-3-A

Identification of Rare Susceptibility Variants for Bipolar Disorder by Exome Sequencing

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Background: Bipolar disorder (BD) is a complex psychiatric condition characterized by manic and depressive episodes. In spite of the strong support for the role of genetics in BD, molecular studies have by-and-large had minimal success in identifying disease-causing genes. This is likely because of high levels of heterogeneity in the sample sets used, but the problem may be minimized by focusing on a well-defined sub-phenotype of BD. Our group has led efforts to characterize BD patients that respond positively to Lithium (Li) therapy, and shown that Li-response clusters in families. Research in BD genetics to date has consisted of linkage and genome-wide association studies, which presume that common variants in a small subset of genes are the cause for BD. However, the minimal success of this approach suggests that BD is caused by highly penetrant rare variants in a large number of different genes across the population. Methods: Our approach focused on a well-defined clinical subtype of BD (Li-responsive) to minimize clinical heterogeneity, and we used massively-parallel next-generation sequencing to re-sequence the exomes of all affected individuals from multi-generational family units with Li-responsive BD. To identify relevant BD susceptibility genes we prioritized rare variants that segregate with affected status within each family. To validate candidate variants we used Sanger sequencing in all family members. Results: We found that each family shared a limited number of potentially highly penetrant (e.g. protein-truncating or missense) or functionally relevant (e.g. 3'UTR, 5'UTR, splicing) variants. After Sanger sequencing validation we were able to narrow in on strong candidates for BD causality or susceptibility within each family, and to further explore the mechanisms by which these variants could lead to pathology. Conclusion: By focusing on rare variants, rather than common variants, we hope to have narrowed in on the key genes and biochemical pathways that play an important role in bipolar disorder and can lead directly to clinically relevant diagnostic and therapeutic applications.

PASS-3-B

Mechanisms of Radial Glia Motility in Response to Neural Activity

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Neurons and glia cells are by now understood to engage in constant two-way communication. A subtype of glial cells called radial glia have been demonstrated to participate in a number of different functions like neuron migration, axon guidance and synapse formation. However, the mechanisms of radial glia involvement in synapse formation and neural circuit refinement have remained largely unexplored. Our published data has revealed that radial glia respond to neural activity by modifying both the rate of their intracellular calcium transients and filopodial probing of the environment. We have focused on elucidating the details of this neuron-glia interaction by visualizing glial process motility in response to genetic and pharmacological manipulations in the living intact Xenopus laevis brain by two-photon microscopy. We have developed a novel algorithm and an associated user interface to objectively quantify the cell membrane dynamics. We propose that signaling from neurons to glia involves synaptic activity-dependent nitric oxide release from the neurons leading to guanylate cyclase and cGMP-dependent protein kinase G (PKG1) activation in the glia that in turn regulates downstream cytoskeleton modifying proteins. We have demonstrated, that manipulating PKG1 activity affects glia process motility. Furthermore, our data show that compromising PKG1 function perturbs the interpretation of neural activity-derived signals by glia. We can conclude, that PKG1 is an important regulator of neural activity-dependent behaviour in radial glia having a role in translating synaptic activity levels to changes in glia process motility.

PASS-4-A

The effect of lithium treatment on SSAT expression in Bipolar Disorder

Jeffrey Gross*, Cristiana Cruceanu, and Gustavo Turecki

In recent years, the link between depression and polyamine metabolism has gained significant support. Most notably, genome-wide brain expression studies have consistently identified spermidine/spermine N1-acetyl transferase (SAT1), the rate-limiting enzyme of polyamine catabolism, as a key player in the neurobiological alterations associated with depression. In light of these finding, we hypothesize that SAT1 is also dysregulated in other mood disorders. In this study, we focused on bipolar disorder (BD), which is characterized by elevated mood, known as mania, as well as depressive episodes. BD is most effectively treated by lithium as it is known for its mood-stabilizing properties and is also a common treatment for other mood disorders. To model the genetic background of lithium-responder BD patients, long-term lithium treatment assays were performed in B-lymphocytes from BD patients classified as lithium responders or non-responders, as well as healthy, non-psychiatric controls. In addition, a neuroblastoma cell line was used to model brain expression and to determine whether the differences in doses of lithium treatment affect SAT1 expression. Quantification of gene expression was performed using real-time PCR with SYBR green primers for SAT1 and endogenous controls. Our results suggest that SAT1 expression is altered by lithium treatment, and that SAT1 may be involved in the pathway of lithium metabolism.

PASS-4-B

Temporal modulation of visual activity regulates axon branch dynamics in the developing visual system

Mr. Martin Munz , Ms. Jessie Poquérusse , Dr. Edward Ruthazer

In Xenopus laevis the optic tectum is innervated by retinal ganglion cell (RGC) axons from the contralateral eye. However, in some cases a few RGC axons (<1%) are mistargeted to the ipsilateral tectum. These axons innervate tectal neurons mainly driven by the contralateral eye;
consequently they fire out of synchrony with their synaptic partners. To determine how correlation in patterned vision regulates the developmental remodelling of RGC axons, GFP-expressing RGC axons were imaged in vivo by 2-photon microscopy every 10 min for >5h while presenting visual stimuli. Optical fibers delivered light directly to the eyes to control their firing independently.
After imaging axon dynamics for 90 min in darkness, visual stimuli designed to either decrease or increase correlation between the two eyes were applied. We show rapid changes in the rates of
branch motility in response to these stimuli. To determine the effects of correlated activity on RGC axon morphology over longer periods, behaving tadpoles were reared under visual
stimulation designed to alter correlation of firing between the two eyes. We imaged individual RGC axon terminals daily for up to ten days. Tadpoles reared with moving dots to asynchronously activate the two eyes developed larger, more complex and dynamic ipsilateral
RGC axon arbors than animals strobe-reared to correlate firing across both eyes. We show that specific patterns of sensory input differentially modulate the rapid dynamics and morphology of developing axonal arbors resulting over many days in dramatic changes in arbor size and structure.

PASS-5-A

Increased proNGF levels in Down's Syndrome

Iulita MF*, Ower A, Busciglio J and Cuello AC

Objectives: Atrophy of nerve growth factor (NGF)-dependent nucleus basalis cholinergic neurons is a central feature of Alzheimer's disease (AD)-related cognitive decline. Our group recently reported marked alterations in NGF metabolism in AD and Mild Cognitive Impairment (MCI) brains, specifically, a failure in NGF maturation and its increased degradation. Given the trisomy of chromosome 21, Down syndrome (DS) individuals overexpress the amyloid precursor protein (APP) and progressively accumulate amyloid--beta (A-beta) peptides since early life. Thus, DS provides a compelling model to study NGF-metabolic changes in relation to the progression of AD pathological hallmarks.
Methods: We investigated signs of NGF dysmetabolism in temporal cortex homogenates from DS cases and age-matched controls (mean age 50-55 years), from the Brain Tissue Repository at the University of California, Irvine, USA.
Results: DS brains exhibited increased APP ($p<0.05$) and proNGF levels ($p<0.05$). We investigated the expression of APP metabolic products and observed an increase in the 12kDa A-beta-immunoreactive (IR) material ($p=0.058$) and increased insoluble A-beta-42 levels ($p<0.001$) in DS brains. ProNGF expression positively correlated with APP levels (Spearman r 0.6396, $p=0.014$), suggesting a link between this increase and APP overexpression. The levels of the 12kDa A-beta-IR band positively correlated with neuroserpin (Spearman r 0.6703, $p=0.012$) and APP levels (Spearman r 0.7582, $p=0.003$).
Conclusions: We observed increased proNGF and preliminary signs of NGF dysmetabolism in temporal cortex tissue from DS subjects. It remains to be established whether other members of the NGF pathway are also altered in an AD-like manner. We are currently extending our studies to frontal and parietal cortex, to follow amyloid pathology progression and possibly ascertain the onset of the postulated NGF metabolic dysregulation.

PASS-5-B

Local and global visual processing strategies for social and non-social information in autism

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Individuals with Autism Spectrum Disorder (ASD) present both an atypical and distinctive visuo-perceptual profile. Despite marked social and behavioural impairments, individuals with ASD often excel at tasks requiring the local analysis of detailed information and preferentially attend to the constituent parts of a stimulus rather than its whole form. It remains unknown, however, whether a bias for such local analysis is at the origin of other aspects of the social cognitive phenotype in ASD, such as facial information processing. To address this question, we assessed local and global visual processing strategies used during social (Experiment 1) and non-social (Experiment 2) visuo-perceptual tasks in the same group of 57 children and adolescents (6-15 years) with and without ASD. In experiment 1, participants completed a socially-laden, facial identity discrimination task across same-view (biasing local analysis) and view-change (biasing global analysis) conditions (Morin et al. 2012). In experiment 2, local and global visual processing of non-social information was assessed using the Navon task (Navon 1977): a well-known hierarchical figures task. We found comparable between-group performance for the social, facial identity discrimination task in local and global conditions. For the non-social, Navon task, the autism group performed significantly worse in the global condition, reflected by an increase in reaction time. Performance was positively correlated for both the autism and control groups across social and non-social tasks. While no superior performance in local processing was found for the autism group, our results suggest that a similar strategy may be used by both groups for information processed optimally using a global strategy, whether social or non-social in nature. The findings further suggest that reported strengths in local processing in ASD may be more apparent beyond the ages assessed in the present study, indicating that development and/or experience may play a role in strategy-specific perceptual strengths in autism.

PASS-6-A

Using Atomic Force Microscopy as a tool for micromanipulation and construction of neuronal networks

Monserratt Lopez

PASS-6-B

Modeling MRI-based g-ratio Measurements in Demyelinating Diseases

Nikola Stikov*, Bragi Sveinsson, Christine L Tardif, Robert F Dougherty, G Bruce Pike

Introduction:

The myelin g-ratio is defined as the ratio between the axon caliber (diameter) and the total caliber of the axon plus its myelin sheath. While the optimal g-ratio in healthy white matter is around 0.6 (Rushton, 1951), the g-ratio increases dramatically in demyelinating diseases such as multiple sclerosis. Measuring the g-ratio noninvasively could provide insight into the process of demyelination and possible remyelination. Recently, we proposed a technique for measuring the g-ratio in-vivo, based on a quantitative tissue model and magnetic resonance imaging (MRI) measurements of water diffusion and magnetization transfer (Stikov et al, 2011). This work proposed a simple formula relating the g-ratio to axon size and myelin content but it did not examine the effect of the myelin thickness on the diffusion parameters. In this work we simulate the process of demyelination by varying the g-ratio, while maintaining constant axon diameters in several fiber arrangements. We look at the effect of demyelination on the diffusion parameters in a uniform rectangular grid of fibers, as well as in a more realistic fiber distribution found in the body and splenium of the human corpus callosum.

Methods:

The tissue model consists of a set of pairs of concentric cylinders, representing white matter fibers, packed into a small (60 μm^3) voxel. The inner cylinder of each pair models an axon and the outer cylinder models the myelin sheath. Diffusion simulations were performed using a numerical diffusion simulation method (Sveinsson and Dougherty, 2011; Balls and Frank 2009; Sen and Basser, 2005) for a range of axon caliber distributions (Aboitiz, 1992) and for g-ratios reported in multiple sclerosis histopathology studies (Schmierer, 2004). For each
fiber distribution, we computed the diffusion parameters and the fiber volume fraction (FVF), defined as the proportion of the voxel occupied by a fiber (axon plus myelin sheath).

Results:

As expected, thinner fibers (higher g-ratio) are characterized by lower FA and higher mean and radial diffusivity. While there is not a simple one-to-one correspondence between the diffusion parameters and
the g-ratio, there is an almost linear relationship between the diffusion parameters and the fiber volume fraction. We found that in two areas with a similar fiber volume fraction but different fiber size distributions (such as the splenium and the mid-body of the corpus callosum) the effect of the fiber size on the diffusion parameters is small, making the g-ratio the main contributor
to the drop in FA and the increase in MD and RD.

Conclusions:

The diffusion model is robust to changes in the myelin thickness, making it possible to infer a one-to-one correspondence between the FVF and the diffusion parameters regardless of the fiber size and
the myelin sheath thickness. Simulations with uniform size distribution can be misleading regarding the relationship between the fiber volume fraction and FA - with realistic size distributions, there is almost no effect of axon size on the FA. Hence, the formula for g holds for a wide range of fiber sizes and myelin content, making it a plausible tool for evaluating demyelination and remyelination in multiple sclerosis and other demyelinating diseases.

References:

Aboitiz, F. (1992), 'Fiber Composition of the Human Corpus Callosum', Brain Research, vol. 598, no.1-2, pp. 143- 153.

Alexander, D.C. (2008), 'A General Framework for Experiment Design in Diffusion MRI and its Application in Measuring Direct Tissue-Microstructure Features', Magnetic Resonance in Medicine, vol. 52, no.4, pp. 1374-1389.

Balls, G.T. (2009), 'A Simulation Environment for Diffusion Weighted MR Experiments in Complex Media', Magnetic Resonance in Medicine, vol. 62, no.3, pp. 771-778.

Rushton, W.A.H. (1951), 'A Theory of the Effects of Fibre Size in Medullated Nerve', Journal of Physiology, vol. 115, no.1, pp.101-122

Schmierer, K. (2004), 'Magnetization Transfer Ratio and Myelin in Postmortem Multiple Sclerosis Brain', Annals of Neurology, vol. 56, pp. 407-415

Sen, P.N. (2005), 'A Model for Diffusion in White Matter in the Brain', Biophysical Journal, vol. 89, pp.2927-2938

Stikov (2011), 'Bound Pool Fractions Complement Diffusion Measures to Describe White Matter Micro and Macrostructure', Neuroimage, vol. 54, pp.1112-1121

Sveinsson and Dougherty (2011), 'dSim: Simulating Diffusion in Biologically Realistic Tissue Models.' Stanford Center for Cognitive and Neurobiological Imaging, Technical Report CNITR-001.

PASS-7-A

The role of cations in kainate receptor activation: lessons from single channel recordings.

G. Brent Dawe*, Elizabeth Andrews, Bryan Daniels, Maria Musgaard, Philip Biggin, Derek Bowie

Glutamate is the major excitatory neurotransmitter in the brain, activating NMDA-, AMPA-, and kainate- (KAR) selective families of ionotropic receptors. Like AMPARs, KARs rapidly desensitize in the continued presence of glutamate, a process thought to protect against neuronal excitotoxicity. However, unlike AMPARs, the KAR subunit GluK2 requires external ions, in addition to glutamate, to produce a detectable current. Although KAR ion binding sites have been associated with desensitization, there is no direct functional evidence linking ion occupancy with channel openings or closures. With this in mind, we studied two GluK2 mutants thought to block desensitization. One (Y521C/L783C) has been shown to function in the absence of external ions, while the other (D776K) possesses a mutant lysine residue believed to act as a surrogate cation. Through electrophysiological experiments performed on outside-out patches excised from transfected tsA201 cells, we found that only D776K was nondesensitizing. Its glutamate potency curve matched that of wild-type GluK2 (WT) receptors following brief agonist applications (prior to desensitization). Furthermore, single D776K channels remained open, except for brief closures, as long as glutamate was applied. In contrast, Y521C/L783C channels opened briefly and spent long periods in closed states. In order to explain this discrepancy in behaviour, we turned to molecular dynamics (MD) simulations of the cation binding site. These simulations support the prediction that residue 776K stably occupies the same binding pocket as sodium would in WT GluK2. Not surprisingly, D776K was able to gate in the virtual absence of external ions. MD also predicted that sodium quickly evacuates this pocket in Y521C/L783C, while remaining fixed over the same time scale in the WT counterpart. Accordingly, occupancy of the cation binding site appears to keep KARs in an activated state with high open channel probability, which is unable to undergo desensitization.

PASS-7-B

Photoswitchable Polyelectrolyte Multilayers: Towards Directed Cell Growth

A. Goulet-Hanssens*, K. Wai Ling Sun, T.E. Kennedy, C.J. Barrett

Polyelectrolyte Multilayers (PEMs) have gained prominence in recent years as a biocompatible surface coating that is easy to tailor for specific hardness, moisture content and surface charge. Other work in biocompatible surface research has focused on designing switchable surfaces that can drive cytophilicity on or off. These triggers need to operate in the presence of cells, these triggers can only be driven by electrical potential or light. Peptide containing azobenzene has been shown to induce a cell response based on the chromophore being in a cis or trans state. Work in our groups is geared towards PEM assembly conditions to create cytophilic films. Along with this approach, we present the synthesis and application of a new class of polyelectrolytes containing azobenzene monomers linked to RGD and c(RGDfK) peptides which can be isomerized "on" and "off". Physical measurements of surface properties will be compared to NIH 3T3 cell cytophilicity assays to try to rationalize biological behaviour in measurable parameters.

PASS-8-A

Heteromeric kainate receptors are ion-independent

Patricia Brown*, Mark Aurousseau, Hugo McGuire, Rikard Blunck, Derek Bowie

Kainate-type ionotropic glutamate receptors (KARs) assemble primarily as heteromeric complexes at glutamatergic synapses. In most cases, KAR-mediated synaptic events exhibit slow and variable deactivation kinetics in contrast to the fast gating properties typically observed with recombinant KARs. To date, emerging evidence suggests that heteromerization of different subunits and their association with auxiliary proteins underlie some of these differences. Despite this, it remains to be understood how brief synaptic exposures to the low affinity neurotransmitter, L-Glu, triggers prolonged KAR activations. Here, we investigated the functional and stoichiometric properties of recombinant heteromeric KARs assembled from the two most widely expressed subunits, GluK2 and GluK5. To do this, we used a combination of outside-out patch electrophysiology to examine functionality and a fluorescent subunit counting technique to assess stoichiometry. As expected, the degree of heteromerization with GluK2/GluK5 subunits in individual patch recordings showed a positive correlation with slow deactivation kinetics and responsiveness to the agonist, AMPA. Data from subunit counting experiments reveal that the stoichiometry of heteromeric KARs is fixed. As a consequence of this structural constraint, GluK2/GluK5 heteromers display functional properties that are distinct from their homomeric GluK2 counterparts. First, the gating of heteromeric KARs is independent of external ions. Since the ion-binding sites line the interface between KAR subunits, this suggests that heteromer assembly affects functionality by disrupting this region. Second, preliminary evidence suggests that this “dimers of heterodimers” assembly governs the process of recovery from desensitization.

PASS-8-B

What eyes tell us about bilingual language production: Increased second language (L2) proficiency and inhibitory capacity help bilinguals resolve competition during bilingual speech planning.

Irina Pivneva*, Abigail Free*, Debra Titone

Successful bilingual language production requires that speakers optimally balance knowledge of multiple language systems when they produce speech, a cognitive process that requires inhibitory control. Indeed, bilinguals are thought to enjoy global advantages in non-linguistic cognitive control because of their greater need, vs. monolinguals, to reduce cross-language interference. We recently provided evidence that spontaneous monologue and dialogue speech is more effortful for bilinguals who have reduced inhibitory capacity, controlling for second language (L2) ability. We now extend this work to the more tightly controlled domain of semi-spontaneous multiple picture naming, which uses eye movement measures of production effort. In this task, 24 French-English and 24 English-French bilinguals produced sentences in response to picture arrays (e.g., "The hose and the stove are above the bridge"), where the second picture varied in the number of possible labels (e.g., sofa/couch vs. bowl). There were three experimental blocks, consisting of an L1-, L2-only, and L1-L2 mixed block. Gaze-contingent methods blocked any parafoveal preview prior to picture fixation, and filler trials contained other arrangements of pictures to naturally vary the syntactic form of what was produced. To assess speech-planning effort, we measured gaze-speech latency, which is how long people fixate a picture before they begin to name it (Spieler & Griffin, 2006). As expected, gaze-speech latencies were longer for L2 vs. L1 production, and for pictures with many vs. fewer possible labels, and these effects were generally mirrored in terms of production accuracy. More interestingly, both increased L2 proficiency and inhibitory capacity significantly predicted L2 vs. L1 costs in gaze-speech latency and accuracy for pictures across language-pure and language-mixed blocks. These findings suggest a tight coupling between success at bilingual language production and increased inhibitory control capacity, which is the presumed mechanism of bilingual advantages in non-linguistic cognitive control.

PASS-9-A

Optogenetic probing of Melanin-Concentrating Hormone modulation of the sleep states

Sonia Jego(*), Stephen Glasgow, Carolina Gutierrez, Richard Boyce, Denis Burdakov and Antoine Adamantidis

The hypothalamus consists of intermingled inhibitory and excitatory neural circuits modulating homoeostatic physiological processes, goal-oriented behaviour and sleep-wake cycle. The activity of some hypothalamic neuronal population correlates with vigilant states, including wake, non-Rapid Eye Movement (REM) sleep or REM sleep. In recent correlative studies, neurons expressing Melanin-Concentrating Hormone (MCH) have been identified as possible sleep-promoting neurons, however, the precise physiological function and mechanisms of action of the MCH system on the sleep-wake cycle remain unclear. Here, we targeted the expression of channelrhodopsin-2 (ChR2) and halorhodopsin (eNpHR3.0) selectively to MCH neurons. We showed that optical stimulations reliably activate and inhibit ChR2- and eNpHR3.0-expressing MCH neurons, respectively. We further found that bilateral semi-chronic optical activation of the MCH neurons increased both overall NREM and REM sleep quantities. These results indicate that MCH neurons act as a sleep-promoting system and may play a role in the maintenance of NREM or REM sleep.

PASS-9-B

The structure of parkin RING domains reveals auto-inhibitory and catalytic mechanisms

Jean-François Trempe*, Véronique Sauvé, Marie Ménade, Edward Fon, Kalle Gehring

Parkin, a RING1-In-Between-RING-RING2 (RBR) E3 ubiquitin ligase responsible for an autosomal recessive form of Parkinson's disease, exhibits low basal ubiquitin conjugation activity compared to other E3s. Here we describe the mechanism of this auto-inhibition based on the crystal structure of the entire set of parkin zinc fingers. We find that three of the four zinc fingers adopt novel zinc-binding topologies not typical of RING domains. In this inactive conformation, the “RINGs” mediate intramolecular interactions that interfere with E2 binding to RING1 and that occlude the active site Cys431 in RING2. We also identify a catalytic triad involved in ubiquitin-isopeptide bond formation by enhancing the transesterification of the ubiquitin-thioester on Cys431. Mutations in this catalytic triad suppress parkin activity whereas mutations that disrupt the intramolecular interactions activate parkin. The work provides insight into the mechanism of ubiquitination by RBR E3 ligases with important implications for Parkinson's disease.

PASS-10-A

The role of spontaneous activity in Eph/ephrin signaling.

Daniel Morales*, Chris Law, and Artur Kania

Nervous system assembly requires the precise formation of neuronal circuits, which depend on the action of guidance cue molecules on the growth cones of axons. Neurons fire spontaneous bursts of rhythmic activity throughout this process, but whether this activity is necessary for proper axon guidance is still unresolved. Previous studies have shown that abolishing or even manipulating the pattern of spontaneous firing alters the growth cone's response to cues, but other experiments suggest that axon pathfinding is independent of activity. Ephrin ligands and Eph receptors are a conserved guidance cue family ideal to address this issue due to their well-established roles in circuit formation. By using activity-blocking mechanisms in combination with fluorescent calcium imaging, we will test whether activity is necessary for growth cone response to ephrins in chick spinal motor neurons.

PASS-10-B

Neuronal microRNA dysregulation in multiple sclerosis

Camille A. Juzwik*, Omar de Faria Junior, Amit Bar-Or, Alyson E. Fournier

Multiple sclerosis (MS) is an autoimmune disease characterized by the infiltration of peripherally activated immune cells into the central nervous system. Current MS therapies are immunomodulatory rather than neuroregenerative, making neural repair or injury prevention an ideal direction for future work. Previously we have identified neurite outgrowth inhibition by immune cell subtypes and their conditioned media. Our lab is thus interested in how immune cells and their products affect neuronal viability, repair and phenotypes at a molecular level.

MicroRNAs (miRNA) are short single-stranded RNA sequences ~22 nt in length. A single miRNA is able to target several different mRNA, providing significant information about pathological processes. Altered miRNA expression has been identified in blood cells of MS patients, as well as active and inactive MS lesions. MS-related miRNA dysregulation has not been investigated yet in neurons, though there exist several examples of miRNA gene expression control in neuronal development and differentiation. An investigation of neuronal miRNA expression can provide further insight into immune-neural interactions in MS.

We developed a list of candidate miRNA to investigate during neurite outgrowth inhibition in mouse cortical neurons following treatment with peripheral blood mononuclear cell (PBMC) conditioned media. Specifically, levels of mmu-miR-383-5p increase in response to stimulation with PBMC conditioned media raising the possibility that it may be involved in neurite outgrowth inhibition. This is emphasized by previous screens in the literature which show a decrease in miR-383 during a sciatic nerve lesion, a growth-promoting state. Future work involving miR-383 knockdown and over-expression can provide more information concerning its role in neurite outgrowth, along with other neuronal phenotypes in MS.

PASS-11-A

Deciding whether a social role fit us or not: An electrophysiological pilot study of the timing of role processing.

A.L. Fernandez Cruz*, I. Walpola, R. Rahgoshai & J. B. Debruille

Social roles are understood as the parts we could represent in our social environment. Being a teacher, a basketball player or a parent constitute very different roles and yet we are capable of considering ourselves representing all these roles. This means that we have memorized representations of all these roles and of our will to play them. Neural indexes of such complex representations about our social status are so far unknown. To start exploring them, Event-related potentials (ERPs) were recorded while 14 participants observed names of social roles and decided whether or not they could consider themselves representing those roles at any moment in their lives. We used two categories of social roles, those usually perceived as favorable (e.g., coach) and those perceived as unfavorable (e.g., beggar). Unfavorable roles evoked greater anterior N400s when compared with favorable ones. Previous studies have shown that stimuli with negative valence evoke less negative deflections in the N400 time window than positive stimuli. Hence, the difference between the favorable and unfavorable roles doesn't seem to be related to the valence of the roles. In keeping with the hypothesis that the N400 indexes inhibition processes triggered by processing at the highest associative level, we suggest that these anterior N400 effects could reflect the inhibition of a representation of ourselves playing the unfavorable roles. The 'earliness' of the beginning of the effect is surprising for such a higher order process but in line with the theoretical framework in which the N400 inhibition hypothesis is included.

PASS-11-B

Characterization of emotional behavior and serotonin neurotransmission in California mice after paternal separation

Rebecca Howell(*), Sergio Dominguez-Lopez and Gabriella Gobbi

Parental care during the postnatal period has a major role in emotional development of the offspring. In the biparental species, the California mouse (Peromyscus californicus), both the father and the mother have a highly participative role in the postnatal care of pups. Previous studies have shown that if the father is removed, the mother does not compensate for his absence, thus the pups are deficient in care. Here we present results obtained after evaluating the emotional behavior and serotonin (5-HT) neurotransmission of adult California mice after father separation.

Pairs of California mice were used for breeding and on postnatal day (PND) 3, litters were randomly designated to either be left with only the mother (paternally separated, PS) or with both parents (control, CTRL). Mice were weaned at PND 30 and after PND 70, behavioral tests were conducted including the open field, elevated plus maze, novelty suppressed feeding and forced swim tests. In vivo single unit extracellular recordings were performed in the dorsal raphe nucleus to assess 5-HT neuronal firing activity.

According to our results, the absence of the father during the postnatal period does not affect the behavioral response of adult California mice in the open field and the forced swim test, although interestingly in both tests these animals display high levels of activity. PS animals display less time in the open arms of the elevated plus maze ($F(1,62)=3.93$, $p=0.052$) and have a higher latency to eat in a novel environment after food deprivation ($F(1,57)=3.999$, $p=0.05$). While these two last results could be interpreted as an increase of anxiety-like behaviors, PS animals also had decreased food consumption in their home cage ($F(1,57)=5.404$, $p=0.024$), which raises questions of whether their latency to eat was due to anxiety, or that they were not as hungry. PS seems to have an impact in the 5-HT firing activity of the dorsal raphe nucleus. Compared with CTRL, in PS animals the mean 5-HT firing rate was decreased ($F(1,120) = 5.017$, $p = 0.027$), and the number of neurons per track was also decreased ($F(1,39)=6.087$, $p=0.018$.

Our results suggest the absence of the father in a bi-parental species, such as California mice, could induce a slight increase in anxiety-like behaviors in response to stressful situations and decreased 5-HT neurotransmission in adulthood.

PASS-12-A

miRNA Expression in the Prefrontal Cortex of Suicide Completers

Juan Pablo Lopez*, Raymond Lim, Cristiana Cruceanu, Liam Crapper, Benoit Labonte, Jennie Ping Yang, Volodymir Yerko, Carl Ernst, Naguib Mechawar, Paul Pavlidis, Gustavo Turecki.

Suicide is a major public health problem. It was estimated in 2007 that suicide accounts for 1.5% of the total deaths in Canada. Over the last decades, a large body of evidence has shown that individuals who commit suicide have a predisposition that is mediated by neurobiological factors. MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by means of RNA degradation or translational repression. A growing body of evidence supports the role of miRNAs in neuropsychiatric disorders such as schizophrenia, bipolar disorder and major depression. Based on this evidence we believe that miRNAs have an important role in the neurobiology of suicidal behaviours. As such, we sought to identify miRNA differences in the brain of suicide completers as compared to controls. We profiled genome wide expression of miRNAs in the prefrontal cortex of suicide completers and controls using miRNA microarrays. We validated our findings using quantitative real-time PCR and identified target genes of the differentially expressed miRNAs using bioinformatics analysis. Later, we performed functional experiments using miRNA mimics and target protectors on HEK-293 cell lines to confirm the interaction between miRNAs and their targets. Finally, we investigated the effects that two commonly prescribed antidepressants have on miRNAs, using human neural progenitor cells (NPCs). Our results revealed an interaction between miR-1202 and the Metabotropic Glutamate Receptor 4 (GRM4) gene in the prefrontal cortex of suicide completers. We found that miR-1202 is specific to primates and enriched in humans. Furthermore, we found that across human tissues, this miRNA shows the highest expression in the brain and responds to antidepressant treatment. These results suggest that the relationship between miR-1202 and GRM4 in postmortem brain tissue is associated with the pathophysiology of suicidal behaviors. Ultimately, our results highlight new evidence of the role of miRNAs neuropsychiatric disorders, and provide important steps in the development of early diagnostic tools, preventive strategies, and effective pharmacological treatment for mood disorders.

PASS-12-B

Differential Tissue Sensitivity to Induction of Heat Shock Proteins: Preferential Induction of Hsp70 in Cardiac and Skeletal Muscle

Kyle J.H. St. Louis*, Jieun R.C. Cha, Ruihong Chen, Sandra Minotti and Heather D. Durham

The heat shock response (HSR) is an evolutionarily conserved cellular mechanism essential for cell survival under stressful environmental conditions. The “master regulator” of this response is heat shock factor 1 (Hsf-1), one of several transcription factors that associate with heat shock elements (HSE) in the promoter regions of target genes following their stress-induced nuclear translocation. Many of these target genes encode chaperone-type proteins that guard against aberrant protein interactions and conformational changes. The HSR is thus an attractive therapeutic target in the context of neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), where the aberrant formation of protein aggregates is a common pathological phenotype. NXD30001 (NXD) is a novel Hsp90 inhibitor (Hsp90I)-class compound developed by NexGenix Pharmaceuticals. NXD has demonstrated blood-brain barrier permeability and high-affinity Hsp90 binding in the absence of Hsp90I-associated hepatotoxicity. NXD also demonstrated Hsf-1 dependent induction of the heat shock proteins (HSP) stress-inducible 70 (iHsp70) and Hsp40 expression in a primary motor neuron cell culture. The next objective was to conduct in vivo studies to evaluate NXD's HSR-inducing capacity in mammalian tissues and to determine the time course of HSP induction, allowing for the establishment of long-term dosing regimens with disease-related end points. The study at hand assessed NXD's ability to induce expression of HSPs (specifically, iHsp70 and its cochaperone Hsp40), in murine skeletal muscle, cardiac muscle, liver, kidney, brain, lumbar spinal cord and sciatic nerve tissues following acute, intraperitoneal injections of NXD in wild-type mice and a model of ALS, SOD1G93A transgenic mice.

PASS-13-A

Generation and Characterization of an Induced Pluripotent Stem Cell Model of Lesch-Nyhan Syndrome

Liam Crapper*, Gustavo Turecki, Carl Ernst

Lesch-Nyhan syndrome (LNS) is a rare x-linked disorder caused by the disruption of the gene encoding hypoxanthine-guanine phosphoribosyltransferase (HRPT1), an enzyme involved in purine metabolism. Classic LNS symptoms include gouty arthritis, mental retardation, dystonia, and chronic self-injury. While the causes of these neurological phenotypes remain unknown, several findings have suggested the involvement of the dopaminergic system, presenting a link between LNS, and a variety of complex human behaviours and disorders. We will develop a novel patient derived model of LNS by generating neuronal cell lines via induced pluripotent stem cells (iPSCs). These cell lines will be differentiated to a mid-brain like dopaminergic cell type and their development, function, and molecular characteristics will be assessed. Comparisons will be made between LNS patients who do and do not self-injure, and noremal controls, helping to illuminate the mechanisms of the dopaminergic system's involvement in the complex behaviours seen in LNS.

PASS-13-B

Maintaining calcium homeostasis in a primary culture model of amyotrophic lateral sclerosis

Luan T. Tran*, Katie E. Sullivan, Heather D. Durham

Ca2+ dyshomeostasis has been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS). Limiting Ca2+ entry into motor neurons, the ultimate cell-type that is lost in ALS, has been shown to protect these cells from ALS-causing mutant Cu2+/Zn2+ superoxide dismutase (SOD1) toxicity. Lomerizine, a dual L- and T-type voltage-gated Ca2+ channel antagonist, is well tolerated in humans, making it a favorable candidate for therapeutic development in ALS. Lomerizine protected cultured motor neurons from acute glutamate excitotoxicity by reducing the accumulation of cytoplasmic Ca2+. In a primary culture model of ALS due to mutations in SOD1 (fALS1), lomerizine protected motor neurons against multiple measures of mutant SOD1 toxicity, including, Ca2+ overload, reduced mitochondrial trafficking, mitochondrial fragmentation, partial depolarization of mitochondrial membrane potential, formation of mutant SOD1 inclusions, and loss of viability. To assess whether lomerizine would be useful in other forms of ALS, calcium homeostasis was evaluated in culture models of ALS due to mutations in the genes encoding fused in Sarcoma (FUS) and TAR DNA-binding Protein 43 (TDP43). However, Ca2+ dyshomeostasis was not shown to play the same role in the toxicity of these mutant proteins as it does with mutant SOD1 and lomerizine failed to prevent abnormal subcellular localization of mutant TDP-43. These experiments affirm that mechanisms of pathogenesis differ among different types of ALS and show the utility of primary culture models in comparing those mechanisms and effectiveness of therapeutic strategies.

PASS-14-A

Exploring T1 Structural Neuroimaging for Potential Markers of Suicide Risk : A Multi-Site Neuroimaging Study

Yang Ding*, Gustavo Turecki, Fabrice Jollant

Patients with a past history of suicidal behavior have shown a range of neurobiological alterations including structural neuroimaging differences in comparison to patients with no such history. It is hypothesized that these alterations may underlie vulnerability to suicidal acts in stressful situations. T1-Magnetic Resonance Imaging is a relatively simple method that may help to develop brain markers of risk. Previous studies have reported several observed gray matter structural changes in different brain regions. Yet, the whole brain neuroimaging findings within current literature show strong heterogeneities. This may be accountable due to the differences in analysis approach used, small sample size as well as within population heterogeneity.

Our current study aims to thoroughly examine T1 structural changes in gray matter in suicide attempters with clear control for confounds, and to specifically explore changes in gray matter volume, cortical thickness and cortical surface area. To increase sample sizes, we contacted 16 neuroimaging groups who has conducted neuroimaging studies in suicide attempters and obtained agreement from six groups so far. All imaging groups have acquired neuroimaging data from three separate population bases: healthy controls without history of mental disorder or suicidal behaviour, affective controls with past history of depression but not suicidal acts and suicide attempters with a past history of both depression and suicidal acts. Participants are of both genders from varying age groups ranging from teenagers to elderly. Various types of scanners and sequences were used to acquire the T1 weighted MRI structural scans while subjects were in varying clinical states from current depression to normothymia. However, within each study site, the selection condition is highly consistent and comparable across all three population bases, allowing us to focus exclusively on the contrasts between population bases to highlight suicidal behaviour related changes. Scanner sequence type, population age, gender will be included as covariates in the final analyses.

Here we present early partial findings from voxel-based morphometry and cortical thickness and cortical surface area analyses based on data acquired from five populations from 3 different research sites. Despite whole-brain VBM result analyses from one particular group suggesting reduction in volume in suicide attempters, we were not able to show significant structural alterations associated with suicidal behavior in any population. In addition, combined analyses using all currently available data failed to pinpoint any specific regions that are uniquely altered in suicide attempters. Our data so far suggest that simple T1-acquisition may not yield strong and universal structural markers of suicide risk. Additional analyses on more patients will be conducted to detect sub-groups.

PASS-14-B

Factors Controlling Subcellular Localization and Inclusion Formation of ALS-linked FUS/TLS

Michael Tibshirani*, Benoit J.C. Gentil, Tanya Gupta, Xenia Cravetchi, Daniel Wilkenfeld, Heather Durham

Mutations in the gene encoding the DNA/RNA binding protein FUS/TLS have recently been implicated in the neurodegenerative disease Amyotrophic Lateral Sclerosis (ALS). Although FUS is mainly found in the nucleus its many roles in RNA processing and transport require its shuttling between the nucleus and the cytoplasm. Post-mortem analysis of human spinal cord reveals strong cytoplasmic accumulation of FUS in the form of inclusions in motor neurons of sporadic and some familial cases of ALS. The common behaviour of both wild type and mutant FUS in ALS suggests an important role for FUS mislocalization in ALS pathogenesis. The goal of this study is to determine the mechanisms underlying cytoplasmic accumulation and aggregation of FUS in motor neurons. Our data suggests a role for arginine methylation, PKC activation and the presence of neurofilaments in promoting accumulationof FUS in the cytoplasm, where it is prone to aggregate.

PASS-15-A

Spatial Localiztion abilities of a single hemisphere: a study of saccadic motor efference in a hemidecorticate patient

K. Rath-Wilson*, D. Guitton

The study of hemidecorticate patients has allowed us to discover that a single hemisphere is capable of generating accurate saccades to the left and right, a task thought before to be governed only by the hemisphere contralateral to the saccade. Research has since attempted to further characterize the abilities of a single hemisphere to elicit and control bilateral eye movements. It has been shown that hemidecorticate patients are able to monitor eye position during smooth pursuit movements in either direction using a corollary discharge (CD) signal to determine where the eyes have moved in space. With this study, we sought to determine whether the hemidecorticate brain is capable of generating a similarly effective CD signal for bilateral saccadic eye movements as well. The literature suggests that lesions of the frontoparietal areas cause marked deficiencies in saccadic eye movement monitoring contralesionally. Given this, we were unsure how our patient would perform. By using a novel version of the classical double-step paradigm (adapted because our patient is blind contralesionally) and analysing our patient's eye movements, we have shown that a single hemisphere does in fact monitor previous eye movements, and integrate this information into subsequent movements in the dark. While his performance is markedly worse than controls, he is surprisingly more capable than patients with isolated unilateral frontoparietal lesions performing similar tasks.

PASS-15-B

Endoplasmic reticulum stress-induced prion protein gene expression

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Prion protein (PrP) inhibits Bax-mediated cell death in human primary neurons and breast carcinoma MCF-7 cells. While the role of PrP in neuroprotection has been widely investigated, few studies have evaluated the role of PrP in cancer. PrP is associated with resistance to anthracycline-based chemotherapy in breast cancer and plays a role in resistance to tumor necrosis factor-alpha and TRAIL-induced apoptosis in MCF-7.

The objective of this study was to determine how ER stress increases PrP levels in breast cancer cells and assess the clinical relevance of this regulation.

We first observed that three pharmacological ER stressors, Thapsigargin, Tunicamycin and Brefeldin A, increased PrP mRNA and protein levels. This increase was blocked by Actinomycin D indicating a transcriptional response. Four ER stress response elements (ERSE) were identified in the human PRNP promoter and luciferase reporter assays confirmed their involvement in both basal and ER stress-induced PrP expression. Overexpression of ATF6a, sXBP-1, but not ATF4, increased PrP levels while silencing of ATF6a decreased the ER stress-induced PrP levels in cells. Chromatin immunoprecipitation (ChIP) assays confirmed the binding of ATF6a and sXBP-1 to the PRNP promoter region during ER stress. From a functional standpoint, siRNA-mediated silencing of PrP highlighted a protective role of PrP by delaying ER stress-induced apoptosis in MCF-7 cells.

To evaluate the clinical relevance of ER stress-dependent regulation of PrP expression, we studied PrP levels by immunohistochemistry in human breast cancer tissue microarrays and correlated them with ER stress marker, BiP, levels. Average PrP intensity score was significantly higher in high BiP-expressing cores. PrP levels were also associated with higher tumor grade. Analysis of PrP mRNA levels from published studies further strengthened these findings by showing that PrP is associated with estrogen receptor-negative tumors, poorer prognostic and that its expression is significantly higher in the more aggressive basal cell lines than in luminal cell lines.

Overall, this work characterizes ER stress-induced PrP expression in breast cancer MCF-7 cells and reports a protective role for PrP against ER stress-induced cell death. Correlating PrP with the ER stress marker BiP in human breast tumour tissue as well as analysis of published mRNA levels suggests this regulation could be clinically relevant.

PASS-16-A

Role of Neogenin in olfactory epithelium development

Joseph Kam*, Emilie Dumontier, Jean Francois Cloutier

The birth and differentiation of Olfactory Sensory Neurons (OSNs) is critical for our ability to detect and decode odorant information from the environment. To better define the molecular mechanisms that control neurogenesis in the Olfactory Epithelium (OE), we have examined the role of the transmembrane protein Neogenin in olfactory neurogenesis. Neogenin has been implicated in the regulation of diverse processes during development of the nervous system. Furthermore, multiple families of proteins can bind to the extracellular region of Neogenin including Netrins, Repulsive Guidance Molecules (RGM), and Bone Morphogenetic Proteins (BMP). Using various approaches, we have examined the pattern of expression of Neogenin and of its ligands in the OE. Our analyses have revealed that Neogenin is expressed at high levels in the basal progenitor cell region of the OE and in mature OSNs. In contrast, the expression of RGM-b, is restricted to immature OSNs. These patterns of expression suggest that RGM-b-Neogenin interactions may regulate the differentiation of progenitor cells into OSNs. To test this hypothesis, we have examined the development of OSNs in Neogenin mutant mice. Ablation of Neogenin expression leads to an increase in the number of proliferating cells, and to a decrease in the number of mature OSNs, indicating that Neogenin regulates the differentiation of progenitor cells into OSNs. We are currently assessing the role of RGM-b in this process by using both in vitro and in vivo approaches. Our findings therefore define a new role for Neogenin in olfactory neurogenesis.

PASS-16-B

Evaluation of a novel Caspase-6 inhibitor as a potential treatment for Alzheimer Disease.

Prateep Pakavathkumar*, Jan-Eric Ahlfors, Andrea C. LeBlanc

Background: Caspase-6 activity is found abundantly in the neuropil threads, neuritic plaques and neurofibrillary tangles of familial and sporadic forms of Alzheimer disease. Caspase-6 induces axonal degeneration and memory impairment in mice (manuscript in progress). Therefore, inhibiting Caspase-6 represents a potential treatment for Alzheimer disease. Unfortunately, there are no known natural inhibitors of Caspase-6. In this study, we investigated a newly developed irreversible Caspase-6 inhibitor called NWL-117 developed by New World Laboratories.

Objective: Determine if the NWL-117 compound can be used as a potent, specific, and non-toxic inhibitor of active Caspase-6.

Methods: The toxicity of the Caspase-6 (Casp6) inhibitor, NWL-117, was verified on the HCT116 cell line and human primary neurons by MTT. Dose-dependent inhibition of Casp6 was assessed by in vitro fluorogenic assays with purified recombinant active Casp6 and on HCT116 cells transfected with a self-activated form of Casp6. Inhibition of active Casp6 was also assessed in primary human neurons in culture. Casp6 activity in cellulo was assessed with FLICATM-Casp6 assays. The ability of NWL-117 to inhibit Caspase-3 in cellulo was investigated on staurosporine treated HCT116 cells by fluorogenic assays.

Results: The NWL-117 was not toxic to the HCT116 cells or the neurons at 20 to 100 µM concentrations. In vitro, a dose dependent inhibition of recombinant active Casp6 was observed between 50 nM (50%) and 5 µM (100%). NWL-117 was more potent than the peptide inhibitor, Ac-VEID-fmk. A 1 µM concentration of NWL-117 inhibited almost 50% of active Casp6 in HCT116 cells and showed a dose-dependent inhibition between 5 µM and 100 µM concentrations. Western blot analyses showed that the Casp6 was processed into its active form in the absence or presence of the inhibitor. NWL-117 also inhibited Caspase-3 activity in staurosporine treated HCT116 cell extracts measured by fluorogenic assays.

Conclusions: These results show that NWL-117 is cell permeable and non-toxic at high concentrations. NWL-117 is a potent inhibitor of the processed active form of Casp6. Therefore, NWL-117 can be used to assess if Casp6-mediated axonal degeneration can be inhibited and possibly reversed in primary human neurons and mouse brains. If so, this compound is an interesting “lead” compound to develop as an inhibitor of Casp6 in Alzheimer disease patients.

PASS-17-A

Auditory-motor synchronization in children with autism spectrum disorder

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Auditory-motor integration is critical to processing speech and music. Neuroimaging studies in typically-developing (TD) individuals have implicated a fronto-temporal brain network on auditory-motor tasks in what has been termed an auditory action observation (or 'mirror neuron') system. However, little is known about auditory-motor synchronization in autism spectrum disorder (ASD). Based on the hypothesis of an impaired mirror neuron system in ASD, one would predict impaired auditory-motor synchronization in ASD on complex speech perception and production tasks. Alternatively, based on the hypothesis of enhanced perceptual functioning on low-level tasks in ASD, one would predict superior performance in ASD on basic tasks (e.g., tapping in time to a beat). Here we sought to investigate basic auditory-motor synchronization in a large group of ASD versus TD children. We present preliminary data from 21 high-functioning ASD and 38 TD children that participated in a multi-site study on brain and behavioral development. In a rhythm synchronization task, subjects were asked to tap in synchrony with rhythms of varying complexity. Performance was calculated as the ability to reproduce time intervals between each event in a sequence. Both groups performed worse on more complex rhythms, but children with ASD performed better than TD on the more complex rhythms. These preliminary findings are consistent and extend the theory of enhanced perceptual functioning of ASD by showing that basic auditory-motor synchronization is enhanced in ASD. We are currently examining how auditory-motor synchronization maps on to brain structure and function in ASD versus TD.

PASS-17-B

BACE1 DIMERS/TETRAMERS ARE STABILIZED THROUGH THE TRANSMEMBRANE SEQUENCE

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Background:
The beta-secretase (beta-site amyloid precursor protein cleaving enzyme 1, BACE1) catalyzes the first step in producing amyloid beta, the core component found in plaques of Alzheimer's disease patients. We described previously that BACE1 dimers can be isolated from human brain (Schmechel et al., 2004). The overall stability of the BACE1 homodimer is based on intermolecular interactions that were not affected by high salt, nonionic detergents or reducing conditions.
Results:
The conserved amino acid motif (M462xxxC466xxxM470) in the BACE1 transmembrane sequence (TMS), is reminiscent of a high affinity binding site for Cu(I) of copper-transporting proteins. We discovered that copper stabilizes BACE1 dimers and tetramers, and that the central cysteine within the M462xxxC466xxxM470 motif is crucial in this mechanism. Importantly, Cu-stabilized dimers/tetramers exhibited an increased beta-cleavage of the amyloid precursor protein (APP).
Conclusion:
Since copper stabilizes BACE1 dimers/tetramers via the TMS and these oligomers possess an enhanced APP processing capacity, we suggest that the BACE1 TMS might be a pharmacological target. Additionally, we are envisioning that BACE1 operates in cellular copper homeostasis.

PASS-18-A

Generation and Regeneration of ALS-relevant Spinal Motor Neurons

Adele Salin-Cantegrel* and Stefano Stifani

ALS is a neurodegenerative disorder caused by motor neuron (MN) loss leading to death because of muscle atrophy, in particular muscles controlling respiration. There is no cure to reverse the course of the disease. This is why increasing success of stem/progenitor cell-based protocols of in vitro MN generation holds promise for the goal of regenerating MNs lost in ALS. However, our ability to regenerate specific types of MNs, such as respiratory MNs and promote functional recovery is currently hindered by our limited understanding of the events regulating the generation of specialized MNs and the formation of specific motor circuits.
Previous studies have identified transcriptional corepressors (TLEs) as important regulators of early stages of MN development. These factors are also expressed in post-mitotic MNs, but little is currently known about their functions during post-mitotic MN development. The aim of this study was to characterize the involvement of TLEs in the development of spinal MNs controling respiratory functions.

PASS-18-B

Devastating effects of homodimeric precursor proteins of Alzheimer's disease

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Background:
Alzheimer's disease (AD) is most likely caused by amyloid-beta peptides (A-beta), which are proteolytically derived from the amyloid precursor protein (APP). Dimerization of APP via the GxxxG-interaction motif within the APP transmembrane sequence (TMS) is a major driving force for amyloid generation. Scanning mutagenesis determined that the key residue is glycine 33 in A-beta40 or A-beta42 generation.

Results:
The APP TMS dimerization strength is gradually affected by mutations of the key residue glycine 33. The dimer stability coincides with the polarity of the substituted amino acid. The less polar the amino acid used for substitution is, the less it is promoting dimerization. We have systematically investigated the influence of amino acid substitutions and significant levels of A-beta40 and A-beta42 were only found produced when a threshold level of 60% - 70% is exceeded in dimerization strength compared to the wild type.

Conclusion:
Dimerization of precursor molecules determines the amount of amyloid A-beta produced. Consequently, compounds diminishing APP dimerization by ~ 30% will be sufficient to drastically decrease amyloid levels and might represent preventive and even therapeutic tools.

BELV-19-A

Synaptopodin stabilizes dendritic spine head protrusions in the hippocampus

David Verbich*, Denise Becker, Andreas Vlachos, Thomas Deller and R. Anne McKinney

In the hippocampus, the heterogeneity in intracellular components of dendritic spines may determine their propensity for morphological remodeling. Recently, we found that when synaptic activity is reduced in the mature hippocampus, a subset of large dendritic spines can extend thin protrusions from their spine heads that persist for hours and form new synapses. However, spine head protrusions only form on some spines; why this is the case is unknown. Interestingly, in a subset of spines, the presence of the actin-binding protein synaptopodin impacts calcium dynamics and sustains spine head enlargement during long-term potentiation. Here we hypothesize that synaptopodin is found in spines forming spine head protrusions and that it regulates their formation in a calcium-dependent manner. We first localized synaptopodin in dendrites of CA1 neurons by immunostaining for synaptopodin in hippocampal slice cultures. We found that ~ 70% of protruding spines contained synaptopodin. Next, we used synaptopodin-knockout mice to determine if protrusions still occurred. Surprisingly, we found that although spines from synaptopodin-knockout mice formed protrusions, most were transient and retracted within 10 min. Moreover, blocking calcium-induced calcium-release also caused most spine head protrusions to become transient, mimicking synaptopodin loss. Taken together, our findings show that synaptopodin is found in spines forming protrusions and that synaptopodin stabilizes spine head protrusions. By regulating both functional and structural synaptic plasticity, synaptopodin modulates the fine-tuning of synapses.

BELV-19-B

Investigating the Role of the mRNA Binding Protein FXR1P in Brain Plasticity

Erin Nuro*, Denise Cook, Joseph Rochford, Keith K. Murai

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. 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 (Cook et al., 2011), suggesting that it could play a role in locally controlling the levels of proteins involved in synaptic plasticity. In order to test this, we have generated an FXR1P conditional knockout mouse model where FXR1P is conditionally ablated from neurons in the forebrain, including the hippocampus (a brain region important for learning and memory). Interestingly, we have found that FXR1P conditional knock-out mice have profound changes in synaptic plasticity, synaptic morphology, and cognitive function. We are currently investigating the role of FXR1P in learning and memory and autism-like behaviors.

BELV-20-A

Characterization of Sodium Proton Exchangers 6 and 9 in Mouse Hippocampus

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Sodium proton exchangers (NHEs) are a family of transmembrane-spanning proteins which allow electroneutral transport of alkali cations and protons across biological membranes. These ion transporters are important for many homeostatic mechanisms, such as maintaining pH levels and cell volume. Two recently discovered isoforms, NHE6 and NHE9, have been linked to neuropsychological disorders: mutations in NHE6 have been discovered in human populations with Autism Spectrum Disorders and X-linked mental retardation while NHE9 mutations have been found in subgroups with Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorders. Previous studies have shown that both of these exchangers are expressed in the brain however, despite their association with learning deficits, their precise localization and function remain uncharacterized. Here we aim to study NHE6 and 9 localization in the mouse hippocampus during postnatal development, and to determine their involvement in synaptic maturation and function. Cryostat-cut brain sections, organotypic hippocampal slices and primary neuronal cultures were prepared from transgenic mice expressing membrane-targeted eGFP in a subset of principle neurons. Sequential confocal imaging of eGFP-positive neurons enabled analysis of fine neuronal structures and precise protein localization using immunocytochemistry. We show that NHE6 and 9 are expressed in the developing and mature hippocampus in neurons and particularly at dendritic spines, the postsynaptic compartment of most excitatory synapses in the brain. Furthermore, colocalization of NHE6 with specific endosomal markers reveals that NHE6 is expressed in a subgroup of recycling endosomes. We hope that this study will help reveal how these exchangers are involved in neuronal connectivity and development.

BELV-20-B

GABAA Transmission Regulates Dendritic Spine Formation in the Developing Organotypic Hippocampal Slice

Christopher K. Salmon*, Emma V. Jones, Keith K. Murai

The neurotransmitter -gamma-aminobutyric acid (GABA) plays an integral role in the mature CNS, where it is the main inhibitory neurotransmitter. Remarkably though, GABA is excitatory in the immature brain. During this immature phase, glutamatergic synapses are actively forming and maturing on dendritic spines. To determine if early GABAergic neurotransmission influences the formation of excitatory synapses, we modulated GABAergic transmission while monitoring the formation of dendritic spines on CA1 neurons in mouse organotypic hippocampal slices. In line with previous findings, inhibiting GABAA transmission with gabazine (Gbz) or bicuculline in slices grown for 5 days in vitro (DIV) caused robust spine loss. Surprisingly, the same manipulation in younger slices (3 DIV) increased spine density by 33% while driving GABAA transmission at 3 DIV caused an opposite 25% decrease in spine density. To follow up on the effects of GABAA antagonists on spines we monitored the developmental expression of potassium-chloride cotransporter-2 (KCC2), a transporter that shifts GABA from excitatory to inhibitory by gradually moving chloride out of neurons. As expected, KCC2 levels increased between 3 and 5 DIV, suggesting the switch in the action of GABA may account for the differential effects of GABAA antagonists on spines. As KCC2 itself plays a structural role in spine stabilization, we asked if Gbz treatment increases KCC2 levels. This was not the case. Together, our findings suggest that early, excitatory GABAA transmission regulates excitatory synapse formation in the developing hippocampus.

BELV-21-A

Age related changes in resting-state connectivity: A connectome-wide association study

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Resting-state functional magnetic resonance imaging is a promising tool that can be utilized to characterize changes in connectivity with age in healthy subjects. Existing studies have examined relatively few brain regions or were limited by averaging results over large distributed networks. Conversely, we performed a connectome-wide association study to systematically characterize changes in resting-state connectivity with age. We also tested the impact the size (scale) of the resting-state networks had on the results. Using this method we identified more extensive changes in connectivity due to normal aging than what has previously been reported.

BELV-21-B

Cross-frequency coupling mechanisms of neural oscillations in the resting-state of the brain

Esther Florin*, Sylvain Baillet

Introduction:
During the past decade, reproducible connectivity patterns of brain activity during rest have been identified and thoroughly investigated using PET and fMRI (Gusnard & Raichle, 2001; Raichle et al., 2001; Greicius et al., 2003). However, little is still known about the electrophysiological correlates of structured BOLD fluctuations and correlations detected during the resting-state. In the present study, we propose and demonstrate with MEG source imaging a possible electrophysiological mechanism underlying resting-state BOLD fluctuations. Our approach is based on the hypothesis of cross-frequency coupling as a vehicle of communication and integration between and within brain regions (Steriade, 2006). As such, this mechanism would represent an ideal candidate to support the resting-state networks that have been shown to match some of the major anatomical connectivity pathways across the whole brain.

Methods:
6 healthy subjects were measured with MEG in a seated position during rest with their eyes open, for durations ranging from 10 to 30 minutes. After preprocessing, image reconstruction of the sources of the ongoing MEG data was obtained from a cortically-constrained minimum-norm model using Brainstorm (Tadel et al., 2011).
For each cortical location (15,000 sources in total), the phase-amplitude coupling (PAC) indices (Özkurt & Schnitzler, 2011) between oscillations in the low-frequency range (2-48 Hz) and the high-gamma range (80-150 Hz) were computed and the optimal nesting lowfrequency for the gamma amplitude was determined.
Based on this cross-frequency coupling we propose a model to predict the main resting state networks from the ongoing neural oscillations. Therefore, for each cortical source time-series, phase troughs and peaks of the nesting low-frequency were determined. A new time-series was generated from the interpolated gamma amplitude at the peaks and troughs of the nesting low-frequency. The resting state networks were extracted with singular value decomposition from the correlation matrices.

Results:
The results revealed that delta (2-4 Hz) and theta (4-8 Hz) are the main nesting oscillatory frequencies of the phase coupling with the gamma amplitude. A few regions showed coupling in the alpha frequency range and no coupling was found with the beta and low-gamma frequency on average. Since the phase-amplitude coupling was found over the whole cortex, it is very likely that it is a central means for communication between different brain areas.
The extracted resting-state networks from our model based on phase-amplitude coupling revealed the expected resting-state networks in each tested individual. After standardizing the individual correlation maps on the Colin27 MNI anatomical brain template, the expected resting-state networks were also found at the group level.

Conclusions:
This study demonstrates that phase-amplitude coupling during rest can be detected using MEG source imaging. We showed that such coupling exists across the cortex and is essentially driven by ongoing oscillatory components in the delta and theta ranges, with few exceptions in the alpha range. Overall, such mechanism may enable long-range communication in the brain during rest. We proposed a generative model that revealed from MEG data the same resting-state networks that are commonly identified with fMRI. Overall, our results suggest that the mechanisms that reveal the brain's resting-state networks with fMRI are based on the cross-frequency coupling between the phase of a nesting low-frequency and the amplitude of high-gamma oscillatory fluctuations.

References:
Greicius, M.; Krasnow, B.; Reiss, A. & Menon, V. (2003) 'Functional connectivity in the resting brain: a network analysis of the default mode hypothesis', Proceedings of the National Academy of Sciences, vol. 100, pp. 253 -258.
Gusnard, D. & Raichle, M. (2001) 'Searching for a baseline: functional imaging and the resting human brain', Nature Reviews Neuroscience, vol. 2, pp. 685-694.
Özkurt, T.E. & Schnitzler, A. (2011) 'A critical note on the definition of phase-amplitude cross-frequency coupling', J Neurosci Methods, vol. 201, pp. 438-443.
Raichle, M.; MacLeod, A.; Snyder, A.; Powers, W.; Gusnard, D. & Shulman, G. (2001) 'A default mode of brain function', Proceedings of the National Academy of Sciences, vol. 98, pp. 676 -682.
Steriade, M. (2006) 'Grouping of brain rhythms in corticothalamic systems', Neuroscience, vol. 137, pp. 1087–1106.
Tadel, F.; Baillet, S.; Mosher, J. C.; Pantazis, D. & Leahy, R. M. (2011) 'Brainstorm: A User-Friendly Application for MEG/EEG Analysis', Computational Intelligence and Neuroscience, vol. 2011, pp. 13.

BELV-22-A

The effects of sexual orientation on stress reactive cortisol

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BACKGROUND: Lesbian (L), gay (G), and bisexual (B) individuals frequently report heightened distress due to discrimination, yet investigations into their physiological stress responsivity are missing from the literature. Our group recently showed that disclosing one's sexual orientation corresponds with comparatively lower psychiatric symptoms and morning cortisol levels than those who remain 'in the closet'. Extending from our earlier studies, the current study investigated whether sexual minorities might manifest differential cortisol levels than heterosexuals (Hs) in response to social-evaluative threat.

METHODS: Participants included 87 healthy adults (mean age 25, 54% men) identifying as L/G/B (n = 46) or as Hs (n = 41). Stress was induced using the Trier Social Stress Test (TSST) and 10 salivary cortisol samples were collected throughout a two-hour afternoon visit. Repeated measures ANCOVA split by sex with sexual orientation as the between-subject factor and cortisol as the with-subject factor while controlling for age, self-esteem, and disclosure status.

RESULTS: Results reveal that L/B women had higher cortisol levels than Hs women 40 minutes after stress exposure. As a group, G/B men had significantly lower cortisol levels in contrast to Hs men. The covarying effects of age, self-esteem, and disclosure status intermittingly contributed to time and group effects for both sexes.

CONCLUSIONS: Our findings demonstrate that relative to Hs controls: (1) L/B women displayed higher cortisol levels late after TSST exposure while (2) G/B men displayed lower overall cortisol levels throughout testing. We previously reported that G/B men in our sample manifested lower allostatic load based on 20 biomarkers compared to Hs men. It is possible that G/B men who are able to successfully overcome stigma may be resistant to chronic stress and stress reactivity. Yet, the opposite might be true for L/B women who displayed heightened distress during recovery that may indicate ruminative processes. These results suggest that it is important to include intra-sex variations like sexual orientation as well as unique developmental challenges like disclosure processes in future psychoneuroendocrine studies.

BELV-22-B

Real-Time Functional Brain Imaging with Feedback to Subject using MEG

Soheila Samiee*
Esther Florin
Elizabeth Bock
Sylvain Baillet

Magnetoencephalography (MEG) is a neuroimaging method which captures the small magnetic fields generated by neural currents, with millisecond time resolution. Combined with models of the geometry and electromagnetic properties of head tissues, image reconstruction techniques can be applied to the MEG raw data, thereby yielding dynamical images of brain activity. Image reconstruction is typically performed offline, after the MEG data is acquired and pre-processed for noise reduction.Our MEG Program has developed the technology for accessing the dynamics of cortical currents in real-time, thereby creating a fast, online image reconstruction techniques. Multimodal feedback (visual, haptic, auditory) can be provided to the subject, also in real-time, thereby closing the loop of a genuine brain-computer interface imaging system. We present our current real-time setup and demonstrate that the neurofeedback technique can modulate specific features in the dynamics of brain activity, at targeted brain locations. The perspectives for clinical applications are wide open: from new approaches to epileptic seizure control, to personalized and optimized programs for language and motor rehabilitation after stroke.

BELV-23-A

Effect of neonatal immune-activation in mice carrying a mutation in schizophrenia-susceptibility gene, Dysbindin-1

Sara Jamali(*), Sanjeev K Bhardwaj, Lalit K Srivastava

Genetic factors and early adverse environmental events interact to contribute to the pathogenesis of schizophrenia. Here, we investigated if immune-activation during development interacts with a susceptibility gene to produce schizophrenia-related phenotypes. We injected mice with a loss of function mutation in dysbindin-1, a schizophrenia-risk gene and controls with either Poly I:C, a viral mimic or saline, at postnatal days (PD)5,6 and 7. At PD60, possible gene-environment (GxE) interaction was studied using tests of behaviours relevant to schizophrenia as well as examination of postnatal neurogenesis. Our data showed a significant effect of genotype on spontaneous locomotion as dysbindin-1 homozygous mice displayed increased locomotor activity. Further, we observed a significant effect of genotype as a decrease in the number of newborn cells in the glomerular layer of OB. Analyses of the data did not reveal an interactive effect between dysbindin-1 and Poly I:C exposure as far as spontaneous locomotion, pre-pulse inhibition of the acoustic startle, novel object recognition memory, elevated plus maze, fear memory, the number of newborn cells in the dentate gyrus and granular cell layer of the olfactory bulb are concerned. These preliminary results demonstrate lack of an interactive effect between this schizophrenia candidate gene and this viral mimic at neonatal periods on selected behavioral and neurobiological measures. Further investigation using different doses of the immune activator and/or different timing of treatment are needed to fully test GxE hypothesis.

BELV-23-B

THE NICOTINIC ALPHA 6 SUBUNIT GENE AFFECTS CHRONIC PAIN SENSITIVITY VIA AN INTERACTION WITH P2X2/3 RECEPTORS

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Aim of Investigation: It is widely acknowledged that significant interindividual variability exists in an individual's propensity to experience chronic pain following similar insults. Since much of this variability is genetic, the identification of genes predisposing to severity of symptoms of chronic pain could be of great value in terms of early intervention and drug development. Applying expression genomics, we have identified the alpha 6 subunit of nicotinic acetylcholine receptors and demonstrated its involvement in chronic pain conditions using null mutant (knockout) and gain-of-function (L9'S) mutant mice. Here, we investigate the mechanism of Chrna6's role in allodynia in inflammatory and neuropathic models of chronic pain.

Methods: Using Chrna6 knockout, gain-of-function, wild-type, and outbred CD-1 mice, mechanical allodynia thresholds were recorded following spared nerve injury (SNI) and intraplantar complete Freund's adjuvant (CFA) injection. Varying doses of nicotine (0.15 mg/kg - 3.6 mg/kg) were subsequently administered systemically. To study the interaction between Chrna6 and purinergic receptors, A-317491, a selective P2X2/3 and P2X3 antagonist, was administered, followed by nicotine injections 15 min later.

Results: Both SNI and CFA injections caused reproducible allodynia in all groups tested. Systemic nicotine injections produced dose-dependent anti-allodynia following SNI or CFA, in wild-type, CD-1, and gain-of-function mutant mice, but had no effect inChrna6 knockout mice. A-317491 injections also produced anti-allodynia in all strains tested. When nicotine and A 317491 were co-administered in the gain-of-function mutant mice, less anti-allodynia was observed, despite the high levels of anti-allodynia when each drug was administered on its own.

Conclusions: The findings presented here demonstrate the necessity of Chrna6 in nicotine induced anti-allodynia. Further, using nicotine and A-317491, we demonstrate a pharmacological interaction between Chrna6 and P2X2/3 and/or P2X3 receptors, suggesting a mechanism by which Chrna6 could exert a protective role in chronic pain. Ultimately, with a clearer understanding of Chrna6's mechanism of action, novel therapeutic approaches and drugs could be developed that target the symptoms of various debilitating pain conditions.

BELV-24-A

Effects of running exercise on disc degeneration and low back pain in mice

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Aim of Investigation: Chronic low back pain (LBP) affects over 10% of Canadians and seriously decreases quality of life. The aging intervertebral disc (IVD) is prone to degeneration, frequently contributing to low back pain. Physical activity influences IVD physiology, and animal studies show that cyclic loading increases proteoglycan synthesis in the disc, suggesting a role for running exercise in disc repair. Our laboratory has validated a rodent model of LBP, the aging SPARC-null mouse, which displays axial and radiating pain that parallels LBP in humans and is pharmacologically reversible. We therefore aim to demonstrate that running exercise will delay disc degeneration and decrease pain behavior in the aging SPARC-null mouse.

Methods: 3-4 month old male SPARC-null and C57B wild type mice were used in this study. After recording baseline behavioural measurements, animals had free access to either a circular treadmill (exercise group) or a fixed non-rotating treadmill (control group) in their home cages. Axial LBP was assessed using the tail suspension test, and radiating LBP with the acetone test in the hindpaw, at two weeks and monthly thereafter. The experimental procedure was then repeated in 8-9 month old animals. After sacrifice, disc height was calculated from X-ray images of the animals' lumbar spines.

Results: After two months with access to running wheels, SPARC-null mice show significantly reduced cold sensitivity in the hindpaw compared to baseline ($p<.05$) and control group ($p<.01$) with no accompanying change in mechanical sensitivity, indicating a reduction of radiating pain. Axial pain was unaffected as shown by the tail suspension test, suggesting an effect specific to radiating pain. In the older cohort of animals, cold sensitivity was significantly reduced compared to control group after four months ($p<.01$), suggesting exercise is still beneficial in animals with more advanced disc degeneration. X-ray analysis showed that older SPARC-null animals display significant improvement in lumbar disc height after exercise exposure ($p<.01$).

Conclusions: Voluntary running exercise could partially block or reverse the development of radiating LBP in SPARC-null mice. Reversal of axial pain may require longer exposure.
Disc degeneration will be further assessed using histological methods. Future directions include immunohistochemical investigation of markers of nerve root compression and neuronal damage in the spinal cord and lumbar dorsal root ganglia, and an exercise-and-removal study in these animals.

BELV-24-B

Defining How the Brain Processes Speech Sounds in Children who are Deaf and Use Cochlear Implants to Hear

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Introduction: Children who are deaf can learn to hear through cochlear implant (CI) use, yet their novel aural sense differs from normal hearing because: 1) their auditory system was deprived of input prior to implantation, 2) CIs convert acoustic sound into electrical pulses, and 3) many children receive a CI in only one ear. These differences could affect auditory development and auditory pathway responses to specific sounds.
Purpose: In our study, we examined speech processing in the auditory cortex of children using CIs. We specifically asked: 1) Does the auditory cortex respond differently to speech and non-speech sounds? 2) How can we distinguish brain activity from CI activity?
Methods: We acoustically presented 700ms click trains and spoken words to normal hearing participants and recorded evoked cortical responses at 64 scalp locations. Using the same setup, we measured electrically evoked responses to 36ms biphasic pulses in children who had used a CI for over 10 years before receiving an implant in the opposite ear. We performed independent component analysis and systematically removed artifacts reflecting CI activity. We analyzed the latency and morphology of the evoked responses in both conditions.
Results: Cortical responses to speech in normal hearing children have longer latencies in response to speech sounds when compared to non-speech sounds. The response amplitudes remained constant. Furthermore, removing all artifacts reflecting CI activity leaves the clearest cortical responses.
Conclusion: Increased knowledge of cortical speech processing in normal hearing children and effective separation of cortical and CI activity define a platform to further investigate how children who use CIs learn to process speech.

BELV-25-A

Decreased Spinal Morphine Efficacy in the Absence of the delta Opioid Receptor.

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Aim of investigation:
Morphine is widely used in pain management. It is generally accepted that the μ opioid receptor (MOR) subtype mediates its antinociceptive effects. While it is ineffective in MOR-knock out (KO) mice, its antinociceptive efficacy is unchanged in -delta opioid receptor (DOR)-KO mice. However, morphine-related interactions between MOR and DOR have been reported at the spinal level. The role of DOR in spinal morphine antinociception needs further evaluation. Therefore, we sought to investigate the role of DOR in the antinociceptive effect of morphine and other opioids at the spinal level.

Methods:
3-6 month old male C57Bl6 mice (WT) and mice with a deletion in the Oprd1 gene (DOR-KO) were used. The effect of systemic (i.p.) morphine antinociception was evaluated in the hot water tail flick assay. The effect of spinal (i.t.) morphine, deltorphin II (Delt II) and DAMGO was evaluated in the hot water tail flick assay and the substance P (SP) behavioral assay.

Results:
When administered systemically, there were no differences in morphine potency, efficacy and time course of action in the tail flick assay. In contrast, spinally administered morphine produced a delayed effect in DOR-KO mice and efficacy was compromised. This strain difference was not observed with spinal morphine in the SP assay.
The effects of spinally-administered subtype-selective agonists were also evaluated. DAMGO, a MOR selective agonist, was equally potent and efficacious in both WT and DOR-KO mice in the tail flick assay and the SP assay. The loss of DOR resulted in the complete loss of Delt II efficacy in the SP assay as expected.
Finally, we confirmed that while DOR mRNA is absent in the spinal cords of DOR-KO mice, MOR expression was unaltered compared to WT mice.

Conclusions:
We conclude that DOR is necessary to obtain full spinal morphine efficacy in the tail flick assay. While the absence of MOR completely ablates morphine antinociception, the absence of DOR impairs it significantly. Thus, morphine should be considered as a mixed MOR-DOR agonist.

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BELV-25-B

Diurnal rhythms of activity in dopamine and serotonin neurotransmission

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Objectives: In this work we characterized the firing activity of dopamine (DA) and serotonin (5-HT) neuronal populations in the ventral tegmental area (VTA) and the dorsal raphe (DR) nuclei, respectively, across the light-dark cycle.

Methods: Rats kept under a constant 12/12h light-dark cycle (lights on at 0700h) were used to perform in vivo single-unit extracellular recordings under chloral hydrate anaesthesia at 6 different time intervals of 4 hours (0700-1100h, 1100-1500h, 1500-1900h, 1900-2300h, 2300-0300h and 0300-0700h).

Results: In the VTA, DA firing rate oscillates between intervals with a peak of activity at 1900-2300h and lower levels detected at 1100-1500h and at 2300-0300h (0700-1100h: 3.5±0.4 Hz; 1100-1500h: 2.4±0.2 Hz; 1500-1900h: 2.8±0.4 Hz; 1900-2300h: 4.1±0.7 Hz; 2300-0300h: 2.6±0.2 Hz; 0300-0700h: 2.7±0.4 Hz; $F(5,279)=2.327$, $p=0.043$). A no significant decrease in the number of spontaneously active DA neurons was observed at 1500-1900h and at 1900-2300h (0700-1100h: 2.4±0.2 neurons/track; 1100-1500h: 2.1±0.2 neurons/track; 1500-1900h: 1.9±0.2 neurons/track; 1900-2300h: 1.7±0.2 neurons/track; 2300-0300h: 2.5±0.2 neurons/track; 0300-0700h: 2.5±0.3 neurons/track; $F(5,122)=1.79$, $p=0.12$).

In the DR, the 5-HT neuronal activity decreases during intervals corresponding to the dark phase. In particular, 5-HT firing rate significantly decreases at 3-7h (0700-1100h: 0.9±0.1 Hz; 1100-1500h: 0.85±0.1 Hz; 1500-1900h: 0.98±0.09 Hz; 1900-2300h: 0.75±0.1 Hz; 2300-0300h: 0.65±0.06 Hz; 0300-0700h: 0.53±0.09 Hz; $F(5,253)=2.841$, $p=0.016$) and the number of spontaneously active 5-HT neurons decreases at 1900-2300h and at 2300-0300h (0700-1100h: 3.0±0.6 neurons/track; 1100-1500h: 3.7±0.2 neurons/track; 1500-1900h: 3.8±0.3 neurons/track; 1900-2300h: 2.6±0.3 neurons/track; 2300-0300h: 2.4±0.2 neurons/track; 0300-0700h: 2.6±0.3 neurons/track; $F(5,79)=3.331$, $p=0.009$), compared with the peak of activity detected at 1500-1900h in both parameters ($p<0.05$, in all cases).

Conclusion: These data suggest that DA and 5-HT neuronal populations have distinct diurnal rhythms of firing activity. Implications of these findings in the physiopathology of psychiatric disorders remain to be explored.

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BELV-26-A

Neural network synchronization and temporal lobe epilepsy

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Temporal lobe epilepsy is one of the most common forms of partial epilepsy whereby recurrent seizures appear in early adulthood. There is often a history of an initial brain insult (such as febrile convulsions, encephalitis, or status epilepticus) years prior to the onset of seizures. Symptoms consist of recurrent partial or secondarily generalized seizures which mostly originate from the hippocampus, the amygdala or entorhinal cortex and are often refractory to medication. In our laboratory, we aim to better understand the cellular mechanisms that lead to epileptogenesis as well as those involved in generation and termination of seizures (also term ictogenesis). These tasks are achieved by using in vivo and in vitro electrophysiological tools to analyze the role of GABA type A receptor-mediated mechanisms in neuronal synchronization, the influence of neurosteroids on epileptogenesis, as well as the involvement of high-frequency oscillations (80-500 Hz) in ictogenesis.

BELV-26-B

The role of the deubiquitinating enzyme USP2 in circadian rhythms and behaviour

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It is well established that ubiquitin ligases are involved in the regulation of circadian rhythms but it remains unknown whether deubiquitinases, which perform the reverse reaction, are also involved. The ubiquitin specific protease 2 (USP2) is a deubiquitinase that presents circadian rhythms in most tissues, a property shared mainly by clock genes. This prompted us to study the role of USP2 in the circadian clock of the suprachiasmatic nucleus and in other brain functions.

To determine whether USP2 is involved in the molecular clockwork, we conducted immunoprecipitation experiments which revealed a direct interaction between USP2 and the core clock component PER1. Furthermore, coexpression of the two proteins revealed that USP2 can deubiquitinate PER1. The locomotor activity of Usp2 knockout (KO) mice was monitored in running wheels and we found that these mice have a significantly elongated free-running period as well as altered light responses. Next, we tested Usp2 KO mice on a battery of neurophenotyping tests in order to assess other USP2 functions in the brain. While Usp2 KO mice show no difference in locomotor activity, motor coordination, spatial memory and depression-like behaviour compared to WT littermates, they present a decreased anxiety-like phenotype in two anxiety tests. We also studied Usp2 expression in the brain by in situ hybridization and found expression in the hippocampus, cerebellum, cortex, olfactory bulb and other regions.

In conclusion, our studies indicate that USP2 plays an important role in the circadian clock and its response to light cues, as well as in other brain functions.

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BELV-27-A

Localization of two potential negative regulators of cell cycle in the sensory epithelium of mouse inner ear

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Negative regulator genes are key elements for cell-cycle exit during the development of the mammalian inner ear. After exiting from the cell cycle, progenitor cells in the sensory epithelium differentiate into hair cells and supporting cells. The expression of negative regulators begins at early developmental ages and remains active in both hair and supporting cells even after birth. It is believed that persistent expression of negative regulators prevents adult supporting cells from proliferating and regenerating new hair cells after damage caused by mechanical or chemical traumas. Therefore we hypothesize that genes limiting cell proliferation will have early and persistent expression through adulthood.

Recent studies showed that knocking out negative regulators in mice such as the retinoblastoma (Rb) gene, which regulates cell-cycle transition from G1 to S, and P27kip, a cyclin-dependent kinase inhibitor, led to significant cell cycle re-entry and the production of new hair cells. However, in neither case was gene deletion sufficient for recovering functional hearing.

In the current study we are focusing on other potential negative regulators in mouse inner ear as candidates for hair cell regeneration. We have selected 20 candidate genes with ongoing expression in mouse inner ear supporting cells from embryonic to postnatal ages. We have done this by analyzing gene chip data from populations of hair cells or supporting cells at different developmental time points (gene chip data courtesy of Dr. Zheng-Yi Chen, Harvard Medical School).

Thus far we have confirmed the expression of 12 of these candidate genes in mouse inner ear using RT-PCR. In this poster we will show the data for Cav2 and Frk. These candidates play a role in cell cycle progression in other epithelial cells. For instance, isolated lung endothelial cells from Cav2 knockout mice showed more cell proliferation than did their wild type counterparts (Razani B et al 2001). Over-expression of FRK in breast cancer cell lines also leads to cell cycle arrest (Brauer et al 2009).

We are using in situ hybridization to examine their expression in different cell types at a variety of embryonic ages.

BELV-27-B

CIRCADIAN VARIATION IN THE RESPONSE OF T CELL TO ANTIGEN

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Circadian clocks regulate many important aspects of physiology, and their disturbance leads to various medical conditions. Cytokine levels, white blood cell subsets and inflammatory responses have been shown to present circadian variations in humans and in rodents. Most of what is known about circadian rhythmicity in the immune system focuses on the innate immune response, and very little is known about the circadian control of the adaptive, i.e. antigen (Ag)-specific immune response. We hypothesised that the response of T cells to Ag presentation occurs with a circadian variation.
First, we collected mouse lymph nodes (LNs) every 4 h over 24 h, and stimulated T cells in vitro via the T cell receptor (TCR). T cells collected in the late day and in the night proliferated faster than T cells collected in the early day. This rhythm was lost in LNs from Clock mutant mice. Western blot analysis of LN extracts collected every 6h revealed that a key tyrosine kinase, ZAP70, which is just downstream of the TCR in the T cell activation pathway and crucial for T cell function,exhibits rhythmic protein expression, which might underlie the rhythm in T cell proliferation. Finally, circadian regulation of T cells also occurs in vivo: mice immunized in the day with dendritic cells loaded with ovalbumin peptide Ag generate a 2-3 fold stronger T cell response than mice immunized in the night.
These data show that the response of T cells to a mitogenic signal and the Ag-specific immune response in vivo are under circadian control. This implies that long-term protection against infection may be improved by administering vaccines at optimal times of day.

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BELV-28-A

FMRI Activity in the Hippocampus of Older Adults Correlates with Spatial Strategy Use During Virtual Navigation Task

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Navigation in a virtual maze relies on spatial or response strategies. Spatial strategies involve using environmental landmarks while response strategies involve forming a pattern or series of movements from certain stimuli. Using functional Magnetic Resonance Imaging (fMRI), we have previously shown that younger adults who use spatial memory strategies have increased activity in the hippocampus, whereas response strategies are associated with activity in the caudate nucleus. This study was undertaken to examine the effects of aging on navigational strategies and brain function. Healthy participants (N=53) were tested on a virtual maze task in a 1.5 T fMRI scanner; 23 young adults (mean age: 24.2) and 30 older adults (mean age: 64.7). Young adults who were previously shown to favor the spontaneous use of spatial strategies, had fMRI activity in the hippocampus. On the other hand, older adults who were previously shown to predominantly use response strategies, had caudate nucleus activity. Interestingly, the older participants who used a spatial strategy to learn the task, similar to young adults, also had activity in the hippocampus. These findings suggest that the aging process involves a shift from hippocampal-dependent spatial strategies towards caudate nucleus-dependent response strategies. This reduced use of hippocampal-dependent spatial strategies may lead to hippocampal atrophy, which is a risk factor for cognitive deficits in normal aging and Alzheimer's disease. Conversely, increased use of spatial strategies may be associated with a healthy hippocampus and successful aging.

BELV-28-B

The adrenal circadian clock is entrained by SCN-independent retinal light input

Silke Kiessling*

The suprachiasmatic nucleus (SCN) is situated in the hypothalamus and is seen as the master pacemaker of the circadian system, orchestrating subordinated peripheral clocks. Light entrains the SCN clock to the day/night cycle via the retinohypothalamic tract. It is believed that the SCN directly links hypothalamic retinal input with the descending autonomic pathway to the adrenal, because SCN lesion abolishes the adrenal response to light. However, SCN lesions also destroy retinohypothalamic afferents that project around and/or through the SCN. Genetic experiments have shown that a functional adrenal clock transplanted in an arrhythmic host is sufficient to restore rhythmicity when kept under light dark cycle. Thus, the possibility is raised that the SCN is not an obligatory regulator of the retina-adrenal-connection. To test this hypothesis, we compared light-evoked responses in the SCN and in the adrenal. We observed clear differences in the pattern of light-dependent clock gene induction between the SCN and the adrenal suggesting that light-induced Per gene expression in the adrenal is not regulated by the SCN clock. To underline the physiological importance of these findings, we found, in parallel to clock gene induction, a stimulation of corticosterone secretion. To discover this SCN-clock-independent light input pathway to hypothalamic pre-autonomic neurons, we performed transneuronal pseudorabies virus (PRV) tracing from the adrenal combined with cholera toxin labelling of retinal fibers and presynaptic (VGlut2) and postsynaptic (PSD-95) markers. We found retinal afferents to PRV-labelled neurons in the subPVZ which is next to, but distinct from the SCN. Taken together, these results suggest a light input pathway to the hypothalamus that circumvents the SCN, with synapses on pre-autonomic neurons that regulate the adrenal clock. The impact of this SCN-independent retinal pathway might be important for autonomic nervous system entrainment of peripheral clocks and overall physiology and metabolism.

BELV-29-A

Wayfinding in a virtual town: the effects of large displays, 3D perception and correlation with human virtual navigation analogues of rodent radial maze tasks

Louisa Dahmani*, Andrée-Anne Ledoux, Patrice Boyer, Nicole Etchamendy, & Veronique D. Bohbot

Aim: Large displays and three-dimensional (3D) perception were shown to improve performance in several virtual navigational tasks. The current study sought to determine whether wayfinding in a virtual town, a task which requires the use of hippocampus-dependent spatial memory, could benefit from these factors. In addition, we investigated the correspondence between wayfinding, our 4 on 8 virtual maze (4/8VM), and our Concurrent Spatial Discrimination Learning Task (CSDLT).

Methods: Healthy young participants (N=30, mean age: 21.2) explored a virtual town and had to remember the locations of several landmarks. There were three viewing conditions: a desktop monitor, a large screen, and a large screen on which the town was viewed with 3D glasses. Spatial memory was tested by asking participants to navigate from one landmark to another, taking the shortest route possible. A second group of 30 participants (mean age: 26.5) was additionally tested on the 4/8VM and the CSDLT which were previously shown to be sensitive to hippocampal grey matter and function. The 4/8VM consists of a radial maze with eight arms: four accessible and four blocked. Participants had to retrieve objects located at the end of the accessible arms. Then, all eight arms became accessible and participants had to retrieve the objects, now located in the four pathways that were previously blocked. To find the rewarded arms, spatial learners spontaneously used environmental landmarks in contrast to response learners who used a pattern of open and closed arms from a given starting position. The CSDLT is a virtual 12-arm radial maze in which six invariant pairs of arms are repeatedly presented one at a time. Within each pair, one arm always contains an object and one is empty. Participants had to learn the reward contingency of each arm pair (stage 1). After this learning phase, the pairs of arms are recombined but the reward contingency among the arms remains the same (stage 2). To find the objects in stage 2, people have to use knowledge of the object locations relative to landmarks (a spatial strategy).

Results: No differences were found between the three groups in terms of the distance traveled to target locations in the wayfinding task. From this we can conclude that large displays and 3D perception do not significantly contribute to wayfinding. Moreover, wayfinding performance correlated positively with the use of spatial strategies in the 4/8VM and CSDLT.

Conclusion: We have shown that the 4/8VM and the CSDLT show significant internal consistency with the wayfinding task. Furthermore, the wayfinding task is just as valuable when administered on a standard desktop as it is on more sophisticated and costly equipment.

BELV-29-B

The effects of a cortisol analog on human circadian oscillators

Marc Cuesta, Nicolas Cermakian, Diane B. Boivin

In mammals, the circadian system is composed of a central clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus and peripheral oscillators found in various cell types such as peripheral blood mononuclear cells (PBMCs). In humans, we previously showed that the central clock is quickly reset during a simulated shift work with bright light exposure at night, while resetting of clock genes expression in PBMCs is slower, leading to temporary misalignment between various oscillators. Glucocorticoids (GCs) follow a circadian rhythm controlled by the SCN. In contrast to most of the brain and periphery, the SCN do not contain GCs receptors. We aimed to test in humans the resetting effects of GCs on central and peripheral circadian oscillators. We enrolled 16 young male subjects (mean age ± SD: 24 ± 3 years old) to a double-blind placebo-controlled study on the effects of Cortef, an exogenous GC. A 1st visit to the laboratory was done to obtain baseline rhythm of peripheral (clock genes expression in PBMCs) and central circadian markers (core body temperature, plasma cortisol) over 48 h. During this visit, we also tested the acute effect of Cortef 20 mg, given orally 10 h after wake time on the 2nd laboratory day. The treatment was continued at home for 5 additional days, followed by a 2nd laboratory visit. During both visits, blood samples were collected during an 8-h sleep period followed by a 40-h constant routine. In all subjects, central markers expressed significant circadian rhythms at baseline with no change of their phase and amplitude after 6 days of Cortef or placebo administration. In the subjects analyzed so far (placebo: n=2; Cortef: n=2), a rapid induction of PER1 expression was observed in PBMCs 2 and 4 h after Cortef administration during the 1st visit. Moreover, expression of PER1, PER2, PER3 and BMAL1 in PBMCs at baseline followed a circadian rhythm that was shifted by several hours for PER2, PER3 and/or BMAL1 on the 2nd visit after 6 days of Cortef administration. These preliminary results suggest that GCs can reset peripheral oscillators without shifting the central master clock.

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BELV-30-A

Association between amyloidosis, synaptic dysfunction, and confrontation naming in early MCI, late MCI and AD: an [18F]AV45/[18F]FDG PET Study

Antoine Leuzy, * Liyong Wu, Jared Rowley, Sara Mohades, Marina Tedeschi Dauar, Vladimir Fonov, Jianping Jia, Serge Gauthier, Pedro Rosa-Neto and the Alzheimer's Disease Neuroimaging Initiative.

Introduction: A neurodegenerative condition characterized by amyloid accumulation and synaptic dysfunction, Alzheimer's disease (AD) is characterized clinically by progressive cognitive impairments, including naming deficits, which can be assessed using the 30-item Boston Naming Test (BNT). Though naming in AD and Mild Cognitive Impairment (MCI) has been investigated using markers of amyloidosis and glucose metabolism our understanding of the interaction between these elements remains limited. Using BNT total score we aim to determine the relationship between confrontation naming, amyloidosis and glucose metabolism.

Methods: We analyzed a subsample of participants (ADNIGO+ADNI2) who had clinical, neuropsychological, and [18F]AV45/[18F]FDG data collected in the course of a single visit. Diagnosis of cognitively normal (CN), early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI) and Alzheimer's dementia (AD) was adjusted using ADNI2 guidelines. T1 MRIs underwent non-uniformity correction, were skull-stripped and nonlinearly registered to MNI152 space. After registration to MRI, PET uptake ratios (UR) were calculated by dividing [18F]AV45 and [18F]FDG scans by the median counts of cerebellar GM and pons, respectively. PET images were subsequently registered to MNI152 space using non-linear transformations. Global [18F]AV45 and [18F]FDG estimates were conducted in native space grey matter regions. Voxel-based age-corrected regression analysis was calculated from images resampled in MNI152 after 6mm Gaussian convolution (figure 1 provides a schematic overview of this section).

Results: When all groups were collapsed, an association was found between amyloidosis and BNT (bilaterally/symmetrically) in the base of the temporal lobe (TL). For FDG UR, associations were found in the left IPC, left hippocampus, left anterior temporal neocortex and the base of the TL (see figure 2B). At a subgroup level, associations were confined to AD (left Tneo).

Summary: Naming deficits are associated with amyloidosis and synaptic dysfunction in language areas. These effects are less evident at the subgroup level where (1) amyloidosis was not found to be associated with performance on the BNT and (2) the association between BNT performance and synaptic dysfunction was found present in only AD.

BELV-30-B

Discrete Wavelet Transform (DWT) Of The ERG More Accurately Predicts The End Stage Of Retinal Degenerative Disorders

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Purpose: DWT (time-frequency domain) and, less accurately, amplitude [time-amplitude domain: TAD)] analysis of normal ERGs reveal that the progressive decay in b-wave amplitude obtained with the Photopic Hill (PH) is achieved in two asymptotical steps of 14.44±2.18µV/0.2 log-unit of flash attenuation (step1) and -1.38±0.48µV (step 2). The asymptotes intersection is normally observed in ERGs evoked to a -1.21 log cd.s.m2 stimulus. We examined if knowledge of the above could help in the design of follow-up strategies for patients affected with severe outer retinal degeneration such as retinitis pigmentosa (RP). Methods: DWT and TAD descriptors obtained from follow-up (4 to 10 visits; monitoring period: 5 to 25 years) photopic ERGs (flash intensity: 0.64 log cd.sec.m-2; background: 30 cd.m-2) of patients (n=60) were plotted against the first up to the second to last follow-up ERG. In order to predict the last (known) measure (i.e. 4th or 10th values), longitudinal regressions were used to build pathological degeneration models, where ERGs were normalized according to the normal ERG amplitude evoked to the same flash luminance, yielding a percent-of-normal (PON) value. Prediction errors (% of error) were computed for each predicted ERG values. Results: DWT prediction errors [mean error: 5.94±7.12%; max: 55.84%; min: 0.29%] were significantly smaller ($p<0.05$) than TAD errors [mean error 23.35±31.28%; max: 88.12%; min: 5.21%]; an advantage that was found to be critical when analyzing highly corrupted signals (signal-to-noise ratio<1) such as those that often characterize the end-stage of severe degenerative retinopathies. Two distinct asymptotical rates of degeneration were observed, namely: -6.22±2.11% / year (rate1: 42% of patients) and -1.31±0.51% / year (rate2: 57% of patients). The two asymptotes intersected at a PON value of approximately 40%. Conclusions: Once again our results confirm the superiority of time-frequency analysis of the ERG. Similar to what was previously reported for the normal photopic ERG, with advancing retinopathy, the pathological photopic ERG also degraded following two distinct asymptotes, the difference between the two asymptotes being slightly larger in normals. Of interest outer-inner retina correlations (a-b waves correlations) also suggest that both models (Photopic Hill and progressive retinal degeneration) are nearly identical [PH: b-wave = 3.5(a-wave)+0.22µV, $R2=0.94$; Patho: b-wave = 2.9(a-wave)+0.22µV, $R2=0.84$; $p>0.05$]. Our finding of a biphasic degenerative process that is ERG determined should permit a more accurate staging and prognosis for these patients. Funded by FFB (USA) and Réseau-Vision.

BELV-31-A

Decreased pain sensitivity in obesity may be related to local, not systemic factors

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Aim of Investigation

With increasing rates of obesity worldwide, the rate of surgical procedures in obese patients has substantially risen. Due to concomitant respiratory complications, morbidly obese patients are highly susceptible to the respiratory depressive effects of postoperatively administered opioids. Although, previous studies suggest decreased pain sensitivity in obese humans and animal models, results have been inconclusive. We therefore performed a detailed psychophysical investigation of pain perception in obese human volunteers. If pain perception is indeed decreased in obesity, lower doses of opioids during and after surgery may be used safely to reduce the risk of postoperative respiratory complications in the morbidly obese patients.

Methods

Fifteen obese (7F/8M) and 16 non-obese, age- and gender-matched control subjects (8F/8M) were included. Exclusion criteria included medical treatment for hypertension and diabetes which may directly or indirectly influence pain perception. Demographic data including age, gender, height, weight, and waist-to-hip ratio were recorded. Since blood pressure (particularly systolic blood pressure) is associated with decreased pain sensitivity and obesity is associated with hypertension, resting systolic blood pressure was measured non-invasively from an upper extremity as a potential confound. Sensory detection thresholds, pain thresholds, and pain tolerance were assessed using a 16x16mm thermode (Medoc, TSAII, Israel) on standardized sites on the forehead and abdomen. Using the same thermode, heat and cold pain stimuli of one minute duration were applied to the forehead and abdomen, which were rated by the participants every 15 seconds using visual analogue scales for pain intensity. Pressure pain thresholds were assessed on thenar eminence and thumbnail of the non-dominant hand.

Results

Obese and control groups did not differ in age ($p>0.1$, mean (STD), obese 24.1(5.2) and control 24.7(5.6)). Obese subjects had greater BMI and WHR than controls (BMI: $p<0.001$, mean (STD), obese 41.1(10.3) and control 23.6(2.8); WHR, $p=0.006$, obese mean (STD) 0.9(.08) and control 0.8(.6)). On the abdomen, obese participants had higher thresholds (i.e. were less sensitive) for cold detection ($p=0.05$), warm detection ($p=0.001$), heat pain ($p=0.004$), and heat pain tolerance ($p=0.079$) compared to controls. Similarly, obese subjects had significantly lower intensity ratings for the one minute long cold stimulus on the abdomen compared to controls ($p=0.03$). In contrast, compared to controls, obese participants did not differ in their response to thermal stimulation (heat or cold) applied to the forehead or to pressure pain applied to the hand (p's>0.1). Although obese subjects had higher mean systolic blood pressure compared to controls ($p=0.035$), systolic blood pressure was not correlated to pain sensitivity in either group (p's>0.1). Finally, heat pain threshold was significantly correlated with waist-to-hip ratio in obese subjects ($r=0.54$, $p=0.046$) but not in controls ($p>0.1$).

Conclusions

Compared to normal-weight controls, obese subjects demonstrated decreased pain sensitivity on the abdomen but not the forehead or hand. Furthermore, in the obese, a measure of decreased pain sensitivity correlated with waist-to-hip ratio. We speculate that the site-specific decreases in pain sensitivity may be related to the underlying regional excess adiposity. Moreover, such a site-specific effect argues against a systemically-mediated difference in sensitivity to pain.

BELV-31-B

Retinopathies of the newborn with elderly consequences: Comparing Oxygen and Light-Induced Retinopathies

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Purpose: In albino rats, postnatal exposure to different sources of environmental stress such as intense bright light (Light-induced retinopathy; LIR) or high levels of oxygen (Oxygen-induced retinopathy; OIR) triggers severe and irreversible impairments of retinal structure and function early in life, changes that are reported to be non-progressive. The aim of this study was verify this claim (until ~12 months of age) with the two models.
Methods: Young albino Sprague Dawley (SD) rats were exposed to either 80% O2 for 22.5 hours from P0-14 (n=12) or to a bright cyclic light (12D: 12L; 10 000lux) from P14-28 (n=12). Scotopic (-6.3 to 0.6 log cd.sec.m-2) and photopic (0.9 log cd.sec.m-2; background: 30 cd.m-2) fERGs and retinal histology were performed at different pre-determined days until one year post-exposure.
Results: Scotopic fERG a- and b-waves were gradually reduced from 6% and 23% (P30) to 8% and 17% (P365) of control in LIR and from 80% and 37% (P30) to 5% and 7% (P365) of control in the OIR model ($p<.05$). Similar effects were also observed with the photopic ERGs. Retinal histology revealed that initially (P30), oxidative stress affected differently both models. In LIR, the damage was circumscribed within a specific region of the superior retina [extend of loss: 810.7±137.2µm to 1484.1±40.2µm from the optic nerve head (ONH)], affecting mainly the outer retina [OS, IS and ONL]. In OIR, the damage was post-receptoral [OPL and INL] and was more uniformly spread across the entire retina. However, with time, the damage in the OIR extended to the outer retina and by P365, a similar zone devoid of the outer retina (superior retina) was found in both models [extend of loss from optic nerve head: OIR (ONL and INL: 2000um) and (OPL: 3200um); LIR (ONL and OPL: 2040um)]. In contrast, retinal periphery was relatively speared in both models.
Conclusions: In the acute phase (i.e. early postnatal days) of both retinopathies, a distinctive pattern of structural and functional deficits characterizes the two conditions, suggesting that each retinopathy is triggered by unique pathophysiological process. Interestingly however, with the chronic phase, irrespective of the initial insult, a similar vulnerability of the photoreceptors is observed in the superior retina (zone devoid of outer retina), resulting in a similar asymmetry along the superior-inferior axis. Our findings thus suggest that irrespective of the oxidative stress used, a direct (affecting the phototransduction cascade; LIR) or an indirect (probably the loss of connections and inner cells that leads to photoreceptor inactivity and consequently their death; OIR) photoreceptor deficit will occur, resulting in similar phenotypes. Although each model is believe to reflect/represent a specific human retinal disease such as Retinitis Pigmentosa and Age-related Macular Degeneration (LIR) and Retinopathy of Prematurity (OIR), one wonders if the mechanisms behind both models might be more closely linked than previously thought. Supported by NSERC.

BELV-32-A

Long-term effects of neonatal hypoxia-ischemia on the retina in Long-Evans rats.

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Objective: Birth asphyxia, i.e. insufficient delivery of oxygen and blood to the organs around the time of birth, leads to significant neurological complications including cerebral palsy, mental retardation and blindness. Although birth asphyxia has been extensively studied, relatively few studies explored the impact of neonatal HIE on the retinal tissue. Furthermore, eye examination is currently not part of the standard monitoring protocol of asphyxiated newborns. The objective of the current study was to investigate the impact of neonatal hypoxia-ischemia (HI) on retinal function and cytoarchitecture.
Methods: Neonatal HI was induced in Long-Evans rat pups by left common carotid ligation followed by 2-hour hypoxia (8% oxygen) on postnatal day 10 (P10). At P60, electroretinograms (ERGs) were recorded in HI animals, as well as in control shams, in order to assess function of the retina. Animals were then sacrificed; their eyes were removed and fixed by immersion in 4% paraformaldehyde and subsequently embedded in resin. Sections of the retina were stained with toluidine blue, in order to investigate the cytoarchitecture of retinal cell layers.
Results: Compared to the control shams, ERGs of the HI animals demonstrated 30% reduction in the scotopic a-wave amplitude and 84% reduction in the scotopic and photopic b-wave amplitudes, suggesting that the function of the photoreceptors (where the a-wave is generated) was relatively preserved, whereas that of inner retinal neurons (where the b-wave is generated) was severely impaired. Supportive of the latter, retinal histology of the HI animals showed reduction in the thickness of the inner retina, including outer plexiform layer (none vs. 11.88±1.09 µm in controls), inner nuclear layer (17.44±4.29 µm vs. 26.66±3.40 µm), inner plexiform layer (18.46±26.10 µm vs. 50.69±0.16 µm) and ganglion cell layer (7.20±10.18 µm vs. 13.90±0.36 µm). In contrast, the photoreceptor outer nuclear layer remained intact in all HI animals (50.07±7.42 vs. 46.94±3.06 µm).
Conclusions: Our findings suggest that neonatal HI induces permanent damages to the structure and function of the inner retina (i.e. the layers of cells connecting the photoreceptors to the brain), but less so to the photoreceptors, which appear to be protected from HI insult. These findings may be explained by the fact that photoreceptors and inner retina have different blood supplies (choroid and retinal vasculature, respectively) and that these blood supplies may have different sensitivity to HI.

BELV-32-B

Evaluating The Protective Effect Of A Yellow Filter In The Rodent Model Of Light-induced Retinopathy (LIR)

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Purpose: There are indications that compared to clear intraocular lenses (IOL), yellow IOL may protect the retina from the deleterious effects of light by blocking the “blue” light. We assessed this with our rodent model of LIR.
Methods: Adult (n=20) and newborn (n=12) mice were exposed (adults: 6 consecutive days; neonates: between postnatal days 14-28) to a bright luminous environment of 2500 lux within clear Plexiglas cages covered (YL) or not (BL) with a Roscolux #98 yellow filter (i.e. the same spectral characteristics as commercially available “yellow” IOL's). The efficacy of the yellow filter was evaluated with the electroretinogram (ERG) at 1 and 7 days post exposure.
Results: (Adult mice): On day 1, both groups yielded amplitude measurements that were significantly reduced ($p<.05$) compared to normal values. Of interest, the photopic ERGs of the YL group was the largest (70± 21µvolts vs 85± 24µvolts); a difference that was, however, no longer measurable by day 7. (Neonate mice): Photopic (normal: 72± 10µvolts, BL: 43± 14µvolts, YL: 60± 10µvolts) and scotopic (normal: 676± 113µvolts; BL: 289± 43µvolts, YL: 330± 28µvolt) ERGs were significantly ($p<.05$) reduced in amplitude following bright light exposure. However, while there were no significant differences in scotopic amplitudes between the BL and YL groups ($p>.05$), photopic ERGs were significantly larger in the YL group ($p<.05$).
Conclusions: We have previously shown that in our model of LIR, the scotopic ERG is affected earlier and significantly more compared to the cone ERG. Blocking the blue light contribution to the bright luminous environment did not prevent damage to the rod-driven ERG but appeared to have successfully protected the cone mediated ERG; the latter effect being most pronounced in our neonate LIR model. It remains to be determined however if this protective effect is permanent or transient as suggested from our adult mice model. Supported by NSERC and Réseau Vision.

BELV-33-A

A Balance of Neuroprotective versus Neurotoxic Mechanisms in Glaucoma: the dual role of neurotrophin receptors

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Purpose: Glaucoma is a major disease that causes blindness, due to the death of retinal ganglion cells (RGCs), the neurons that transmit visual signals from retina to brain.
We aimed to understand mechanisms of death of RGCs in glaucoma, and to design neuroprotective strategies.
In experimental glaucoma there is up-regulation of neurotrophins such as NGF, which are not able or sufficient to provide long-lasting neuroprotection. Thus, we asked whether endogenous agents may negatively modulate neurotrophin signals. We also asked whether there are conflicting actions by each neurotrophin receptor: p75 are expressed primarily in glia, whereas neuroprotective Trk receptors are expressed in RGCs.
Methods and Results:
Aqueous humor samples from human glaucoma or cataract patients were collected. Also aqueous humor and retinas were collected from experimental rat models of glaucoma. Samples were studied quantitatively for expression of -alpha2-macroglobulin and TNF--alpha, two neurotoxic factors. In human glaucoma and rat experimental glaucoma we detected up-regulation of a soluble protein, -alpha2-macroglobulin, which negatively modulates NGF-TrkA action, and is directly neurotoxic to RGCs. TNF--alpha is also up-regulated and kills RGCs which express TNF--alpha-receptors. Both neurotoxic factors are released by activated glia, and this requires the activity of the p75-NGF receptor.
Then we tested, in experimental therapeutic models, agents that regulate TrkA, p75, and -alpha2-macroglobulin activity. In a rat model of glaucoma we applied intravitreal injections of test agents or controls at day 14 of glaucoma. Measurements of the nerve fiber layer using FD-OCT were done longitudinally over 42 days of glaucoma, and at the day 42 endpoint retinas were excised and the surviving RGCs were quantified.
Pharmacological reduction of -alpha2-macroglobulin reduces neurotoxicity and results in RGC survival. A mutant form of NGF that is not neutralized by -alpha2-macroglobulin but activates TrkA receptors promotes RGC survival, but wild type NGF does not. Direct activation of the NGF receptor TrkA with drug-like small molecules provides neuroprotection. Antagonists of p75 afford RGC survival by reducing the neurotoxic stress of -alpha2-macroglobulin and TNF--alpha.
Conclusions: In glaucomatous processes there is a balance of p75 actions in glia and TrkA actions in RGCs. Antagonists of p75 or -alpha2-macroglobulin reduce neurotoxicity. Selective agonists of TrkA provide direct neuroprotection. This work may help to design better strategies for glaucoma and other neurodegenerative disorders.

BELV-33-B

An Investigation of the expression of oligodendrocytes and oligodendrocyte progenitor cell markers in the corpus callosum of major depressed suicides

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Introduction: Major depressive disorder (MDD) is a major cause of long term disability and mortality, with a high proportion of more than 800,000 global annual suicides having suffered from MDD. The etiology of MDD and suicide remain poorly understood. Given that abnormalities in white matter tracts are increasingly associated with MDD, the objective of our study is to characterize the expression of proteins specific to oligodendrocytes (OL) and their progenitors in postmortem white matter samples from individuals having suffered from MDD and matched controls. We report the results of pilot experiments conducted with samples of corpus callosum dissected from a region adjacent to Brodmann area 24. Design: Brain samples from 23 individuals having suffered from MDD and 14 matched sudden death controls were obtained from the Douglas-Bell Canada Brain Bank (Douglas Institute). Proteins extracted from corpus callosum were subjected to SDS-PAGE and immunoblotting with antibodies directed against OLIG2, a master regulator of OL development and CNS myelination, NG2 – an oligodendrocyte progenitor marker which can give rise to mature oligodendrocytes, Myelin Basic Protein (MBP), a major myelination protein and ErbB3, a neuregulin 1 receptor implicated in the proliferation and maturation of OL. Results: A highly significant increase was observed in the expression of MBP in samples from MDD versus control individuals ($p=0.01$), whereas expression of OLIG 2 ($p=0.788$), NG2 ($p=0.18$) and of ErbB3 ($p=0.708$) were similar between groups. Conclusion: These pilot data suggest an alteration in myelination features involving MBP in MDD, at least in this region of the corpus callosum. We are currently investigating other white matter tracts to determine the specificity of these findings.
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BELV-34-A

AMNIOTIC FLUID IN THE MIDDLE EAR:EFFECTS ON OTOACOUSTIC EMISSION IN A CHINCHILLA ANIMAL MODEL

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Introduction: The middle ear functional status is important in interpreting OAE results. This is of interest in Universal Newborn Hearing Screening where high levels of test failure have been associated with presence of middle ear liquid (amniotic fluid).
The aim of this study was to investigate the impact of human amniotic fluid and normal saline on distortion product otoacoustic emissions amplitudes in the chinchilla animal model.
Methods: Healthy female chinchillas with normal pinna reflex were used for this study. These animals had initial auditory brainstem, evoked response assessment, OAE and Tympanometry to ascertain normal auditory functioning. The initial measurements served as baseline, when normal. There were 8 groups of animals based on the type and amount of liquid introduced into the middle ear; either saline or amniotic fluid in volumes of 0.5ml, 1 ml, 1.5ml and 2ml. Each animal had one ear randomly assigned to receive the liquid, the other served as control. Repeat hearing assessments were thereafter performed.
Results: There was marked reduction of the distortion product otoacoustic emissions amplitudes with liquid in the middle ear. The volume rather than the type of fluid affected the passage of OAEs signal. The absorbance function of the middle ear correlated with the passage of OAE signals in the presence of middle ear liquid.
Conclusion: In normal hearing chinchillas, presence of amniotic fluid in the middle ear produced markedly reduced OAE signals and signal to noise ratio. There was no statistically significant difference in the measurements obtained with saline and amniotic fluid.

BELV-34-B

Improvements on the Semi-Automated analysis of Xenopus Laevis behavioral response to visual stimuli

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As information at the molecular and cellular level are archived, behavioral analysis of a subject response to a stimuli is becoming indispensable to understand the fully behaving animal subjects. In this work, we present a novel behavioural analysis based on the
single particle tracking technique to measure systematically the response probability of a single tadpole to a visual stimuli. While visual stimuli are moving through the tadpole swimming area, each tadpoles are individually tracked in space and time. By knowing the position of each tadpole and stimulus, we show that it is possible to systematically extract the response probability for a specific behaviour. This new assay is promising in order to study specific behavioural response type.

BELV-35-A

Physiological evidence for feedback in the hippocampus from the subiculum and CA1 to CA3.

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The hippocampus is synaptically organized in a unidirectional arrangement of excitatory synapses. Part of this circuit, known as the tri-synaptic pathway, connects regions CA3, CA1, and the subiculum. Region CA3 sends excitatory projections to CA1 and CA1 can relay this information to the subiculum also via excitatory synaptic mechanisms. Therefore, it is currently understood that CA3 is not influenced by neural activity in the CA1 or subicular regions. This basic organizational principle is the cornerstone of all current theories of memory formation and retrieval in the brain. We demonstrate here that neural activity in CA3 is influenced by the ongoing rhythmic activity in the subiculum and CA1. We were able to unmask these influences using the isolated hippocampal formation in vitro where rhythmic activity is spontaneously and simultaneously generated in both CA1/subiculum and in CA3 but at different frequencies. All cortical inputs to the hippocampus are therefore removed and so any common cortical input to CA1 and CA3 and subiculum are removed. Therefore we were able to dissociate (both statistically and physiologically) CA3 outputs with activity arising from regions CA1 and subiculum. The local field potentials and spike timing in CA3 were significantly influenced by theta rhythms in CA1 and subiculum as demonstrated by correlational analysis, Granger causality methods, and inactivation experiments. Therefore, rather then a rigid unidirectional flow of information in the hippocampus, feedback from the subiculum and CA1 to CA3 also exists. These results suggest an alternative view regarding the role of rhythmic activity in relaying information within hippocampal circuits.

BELV-35-B

Generation of microisland cultures using microcontact printing to pattern protein substrates

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The capacity to isolate small numbers of neurons in vitro is an essential tool to study the cell biology of synapses and the development of neuronal networks by specific cell types. Microisland culture assays allow for single neurons, or simple neural networks, to be isolated on islands of glial cells; however, the techniques commonly used to produce microisland substrates are expensive, challenging to control, and typically result in many discarded substrates. Here, we used microcontact printing to pattern a glass surface with islands of extracellular matrix proteins known to support neural cell growth and differentiation. To promote segregation of the cells to the islands, the substrate surrounding the islands was backfilled with polyethylene glycol (PEG), forming a relatively non-permissive surface on which cell attachment is limited. Astrocytes, and subsequently hippocampal neurons, were then seeded onto the islands of patterned protein. Using this method, readily reproducible patterns of protein islands were produced that permit cell attachment, differentiation, and growth. The technique is a rapid, inexpensive, and reliable means to generate patterned substrates appropriate for microisland cultures.

BELV-36-A

Abstract 1: INACTIVATION OF THE VENTRAL HIPPOCAMPUS IMPAIRS BEHAVIORAL FLEXIBILITY IN THE CROSS-SHAPED MAZE

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Abstract: The complex cognitive function that allows the rapid adaptation to the changes in the environmental conditions is known as behavioral flexibility. This ability is modulated by the proper function of the prefrontal cortex, the orbitofrontal cortex and the nucleus accumbens, which receive important projections from the ventral hippocampus (vHPC). However, the particular role of vHPC in behavioral flexibility remains to be defined. Here, we inactivated the vHPC by infusing tetrodotoxin (TTX) bilaterally in normal rats and, then, tested animals' performance in the allocentric- egocentric switching task using the cross-shaped maze. Bilateral inactivation of the vHPC impaired strategy switching from allocentric to egocentric (Experiment 1), and from egocentric to allocentric (Experiment 2) learning strategies. Furthermore, TTX infusion did not impair allocentric or egocentric learning themselves, thus, inactivation only affected strategy switching. Collectively, these results suggest that vHPC may regulate behavioral flexibility.

BELV-36-B

Sensory and Motor Integration: Speech motor control and learning in clinical and non-clinical individuals.

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Sensorimotor integration is a process by which incoming sensory feedback, and outgoing motor signals, and combined to control motor output processes and calibrate sensory to motor correspondences. In studying sensorimotor integration, we have recently focused on adaptation to altered auditory feedback. We have used several modalities and populations in this effort. Some of our lab members have examined how the deficits in basal ganglia function in Parkinson's patients affect their ability to integrate sensory and motor cues during speech motor learning, compared to age-matched controls. In another study, we have compared the roles of right and left supramarginal gyrus and middle frontal gyrus in controlling speech motor learning using repetitive transcranial magnetic stimulation, creating virtual lesions to examine the functional role of those brain regions during the task. For the sensory side of integration, we have recorded auditory brainstem responses to specific stimuli to examine the signal correspondence in specific brainstem regions with brief and periodic characteristics of the stimuli.

Some of our planned research deals with the impact of early infancy brain injury on multisensory integration in speech perception. We plan to investigate the ability of children with cerebral palsy to perceive congruent and incongruent multisensory speech stimuli, using the McGurk effect, and EEG or magnetoencephalography. These techniques will allow us to consider timing-dependent effects of the speech stimuli and distinguish the preferred perceptual strategies of the children. Other research will consider the relationship between compensation for unpredictable perturbation of auditory feedback, a sensorimotor control process, and adaptation for predictable perturbations, a sensorimotor learning process. Using behavioural and neuroimaging techniques, as well as rTMS, we can evaluate the behavioural and neural independence of the two processes.

In our continuing research programme, we want to better understand how sensory and motor cues are integrated in speech and instantiated in the brain. This research draws both on clinical populations, with known functional and neural deficits, as a naturally-impaired group, as well as non-clinical populations in which we can induce temporary virtual lesions. These behavioural and lesion methods, combined with our neuroimaging work, builds a complete picture of the relationship between behaviourally-defined processes and how those processes interact with the brain. Through this, we plan to improve both basic models of speech production and perception, as well as influence clinically-oriented work with populations who experience speech difficulties in their daily lives.

BELV-37-A

Working memory in eating disorders: Relationship to impulsivity?

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In the previous literature on eating disorders (EDs), impulsivity has often been found to distinguish "bingers" (ED subtypes that binge) from "restricters" (ED subtypes that do not binge). Although working memory capacity (WMC) has yet to be tested in relation to impulsivity in EDs, theory and evidence from the cognitive literature suggest that WMC plays an important role in impulse control and inhibition by providing the individual with the resources needed to override automatic response tendencies in favour of ones that are deliberated and controlled. In this study, we tested the hypotheses that (1) bingers would display more deficits in WMC compared to restrictors and that (2) differences in self-report impulsivity would account for these differences. To evaluate these hypotheses, 16 eating disordered women completed a self-report assessment of impulsivity and engaged in a complex working memory task (an “n-back” task). Compared to restrictors, bingers committed more working memory-related errors and also displayed slower reaction time (RT) on error trials. However, group differences in error rate did not remain after covarying for impulsivity, suggesting that binger-restrictor differences in working memory capacity were directly related to group differences in impulsivity. These findings suggest that poor working memory capacity may at least partially account for the higher rates of impulsivity observed in binger groups.

BELV-37-B

Dissociable contributions of the ventral hippocampus and orbitofrontal cortex to decision-making with a delayed or uncertain outcome

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In this study, we examined how risk and delay influence rats' decision-making, and the role of the ventral hippocampus and orbitofrontal cortex in the valuation of these two factors. Rats with hippocampal lesions tend to prefer to choose an option that delivers a small reward immediately to one that delivers a large reward after a delay (McHugh et al., 2008, Beh Neurosci, 122:1; Cheung & Cardinal, 2005, BMC Neurosci, 6:36). In contrast, the effects of OFC lesions in rats have been mixed, resulting in delay sensitivity similar to rats with hippocampal lesions as well as normal performance (e.g., Rudebeck et al., 2006, Nat Neur, 9:1161; Mariano et al., 2009, EJN, 30:472). Furthermore, in probability discounting, rats with OFC lesions prefer a small, certain reward to a large reward associated with a cost of uncertainty or risk (Mobini et al., 2002, Psychopharm, 160:290). In rats, the ventral hippocampus (vHC) projects directly to the OFC (Jay & Witter, 1991, J Comp Neurol, 313:574). We have previously shown that rats with vHC lesions are averse to the cost of waiting for a large, delayed reward (Abela et al., 2011, SfN Abstr. 511.10), but perform normally under conditions of uncertainty. Here, we report the effects of OFC lesions on probability and delay discounting using the same novel touchscreen version of these tasks for direct comparison with the effects of vHC lesions. Unlike rats with vHC lesions, rats with OFC lesions were highly sensitive to the cost of uncertainty, preferring the small, certain reward to the large, uncertain reward. Intriguingly, rats with lesions of the OFC did not differ from sham controls when the larger, more advantageous choice was delayed. This double dissociation suggests contrasting roles for the vHC and OFC in learning to make advantageous choices involving different kinds of costs.

BELV-38-A

The MEG Functional Brain Imaging Program at The Neuro

Elizabeth Bock*, Sylvain Baillet

MEG (Magnetoencephalography) is a neuroimaging technology for cognitive and clinical brain research. In a nutshell, MEG measures non-invasively the tiny magnetic fields generated by neuronal currents. A unique asset of MEG imaging is its unrivaled temporal resolution, reaching the millisecond time scale across the entire brain volume. On the clinical side, MEG has been typically indicated for the pre-surgical work-up of severe, drug-resistant epilepsy and the functional pre-surgical mapping of brain tumors. There is however great potential to use MEG as an instrument of choice to investigate other neurological syndromes and neuropsychiatric disorders (e.g., stroke, dementia, movement disorders, depression, etc.). Overall, MEG has strong value in revealing the dynamics of brain activity involved in subject's perception, cognition and responses: it has provided unique insight on the time-resolved processes ruling brain functions (resting-state dynamics, language, motor control, visual and auditory perception, etc.) and dysfunctions (movement disorders, tinnitus, chronic pain, dementia, etc.). There are about 200 MEG centers worldwide. The MEG community is constantly contributing new methods and improving software tools to make the technique more accessible to a wider range of investigators.

Our Mission: The MEG Program @ McGill was created on September 2011 as part of the Montreal Neurological Institute's McConnell Brain Imaging Centre. Our mission is to provide state-of-the-art support and expertise to investigators interested in using MEG as a tool for their cognitive and clinical neuroscience studies.

BELV-38-B

Brainstorm: A User-Friendly Application forMEG/EEG Analysis

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Brainstorm is a collaborative open-source application dedicated to magnetoencephalography (MEG) and electroencephalography
(EEG) data visualization and processing, with an emphasis on cortical source estimation techniques and their integration
with anatomical magnetic resonance imaging (MRI) data. The software is developed by the MEG Program at McGill's and The Neuro's McConnell Brain Imaging Centre, in collaboration with multiple international partners and is currently funded in part by the NIH.

The primary objective of the software is to connect MEG/EEG neuroscience investigators with both the best-established and cutting-edge methods for data analysis, through a simple and intuitive graphical user interface (GUI). The software, source-code, extensive documentation, tutorial data, user forum, and reference publications are available for free download at http://neuroimage.usc.edu/brainstorm.

BELV-39-A

Spatiotemporal neural dynamics of mismatch responses to speech and non-speech sounds in aging

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Although aging-related alterations in the maintenance of auditory-sensory memory have been widely studied, it remains unclear whether the mismatch negativity (MMN) or its magnetic counterpart (MMNm) in response to short stimulus onset asynchrony (SOA) is modulated by physiological aging. We used magnetoencephalography (MEG) source imaging to characterize the spatiotemporal dynamics of MMNm in healthy young and aged male adults. The automatic cortical discrimination of speech (/ba/ versus /da/) and non-speech (1000 Hz versus 1100 Hz) sounds was detected by a 306-channel whole-head MEG system. Distributed source modeling identified the fronto-temporo-parietal neural regions underlying MMNm to frequency and phonetic deviants. Compared to younger participants, elderly volunteers exhibited a widely-distributed reduction of cortical responses to both frequency-MMNm and phonetic-MMNm. Furthermore, hemispheric asymmetries were also less lateralized in the aging group, particularly in the orbitofrontal and inferior parietal cortices. In conclusion, our results suggest a prominent decline in auditory sensory memory at short SOA associated with aging.

BELV-39-B

Effects of long-term musical training on neuronal correlates of auditory imagery

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Long-term musical training influences both auditory perception and cognition, but little is known about how it affects auditory imagery. Previous studies have shown that mental imagery of music recruits secondary auditory and premotor areas, and association areas in frontal and parietal lobes. The aim of the present study was to investigate the long-term effect of musical training on auditory imagery by comparing musicians and nonmusicians using functional magnetic resonance imaging. Participants listened to the beginning and imagined the continuation of familiar melodies in the scanner. To test accuracy of mental imagery, we asked participants to judge whether a subsequent probe tone correctly fit into the imagined melody. In the perception conditions, participants merely judged if the last tone of the presented melody was correct or not. In two control conditions, participants listened to random tone sequences or rested in silence. Functional data were acquired in a sparse sampling design that was optimized with respect to the expected imagery-related brain activity. Preliminary results show that both musicians and nonmusicians were able to correctly imagine the melodies as evident from their above-chance performance on the imagery task, but musicians showed better performance than nonmusicians. During imagery, a cortical network encompassing auditory, motor and association areas was activated in both groups. However, groups differed regarding their activation in the supplementary motor area. This indicates an effect of long-term music training on the motor preparation network, which is involved not only in motor, but also in auditory imagery.

BELV-40-A

Microfluidics, Silicon Devices & Nanotools for All

Dr Margaret Magdesian*

McGill ANANDA (Advanced Nano Design Applications). Would you like to improve your results by using microfluidics and silicon-based devices? Microfluidic devices for cell culture based assays and protein micro-patterning are new methods for miniaturizing, controlling and quantifying cellular responses. Miniaturized versions of bioassays offer many advantages, including: design versatility, low cost, minimal reagent and sample requirements, plus integration with other miniaturized devices. McGill ANANDA Services can provide your lab with a wide range of microdevices to extend axons, to culture axons and dendrites in different compartments, to co-culture different cell types, and to print your favorite protein in all sort of shapes and patterns to facilitate functional characterization. We offer low cost solutions for the design and manufacture of microdevices. Here we describe some of the solutions created to date, but we look forward to address unique lab and project specific challenges in the future.