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A1

Matrix Metalloproteinase activity modulates neurite outgrowth

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

Matrix Metalloproteinases (MMPs) are specific peptidases ubiquitously expressed in mammals that can remodel the extracellular matrix as well as the cell's surface through an active shedding mechanism. MMPs have been observed to play a role in multiple biological processes including embryonic development, angiogenesis, memory formation, plasticity, as well as remodeling many tissues and organs.

Previous findings have suggested a role for MMP activity in modulating neurite outgrowth. Our objective is to elucidate the developmental mechanisms underlying this phenotype. We demonstrate that MMP inhibitors can reduce neurite outgrowth from mature cortical and embryonic dorsal root ganglion (DRG) neurons. Interestingly, immature cortical and postnatal DRG neurons are not modulated by MMP activity suggesting that this process is developmentally regulated. We performed a proteomic analysis of cell surface proteins modulated by MMP activity and identified several adhesion molecules as potential candidates in modulated neurite outgrowth.

We are presently determining which of these proteins mediate the outgrowth phenotype we observed in the presence of MMP inhibitors. Our observations suggest that MMP activity can modulate neurite outgrowth in a substrate-independent manner.

A2

14-3-3 proteins regulate axonal growth cone cytoskeletal dynamics through the control of myosin II.

Dr. Tadayuki Shimada, Christopher Kent*, Dominique Guillet, Prof. Paul W. Wiseman, Dr. Alyson Fournier

The growth cone is a critical structure regulating the speed and direction of neuronal outgrowth during development. How the growth cone spatially and temporally regulates signals from guidance cues to alter the underlying cytoskeletal dynamics is not fully known. We have previously identified several isoforms of the 14-3-3 family of adaptor proteins as major constituents of the growth cone. 14-3-3 proteins bind and regulate the activity of multiple proteins through interactions with phospho-serine and phospho-threonine containing motifs. Functional analysis of 14-3-3 proteins through the use of a peptide inhibitor and live-imaging studies revealed an important role for 14-3-3 proteins in regulating the cytoskeleton. We observe that inhibition of 14-3-3 leads to a decrease in the rate of retrograde flow of F-actin in the peripheral domain and increases in filopodial length. These 14-3-3 loss of function phenotypes phenocopy the effects of myosin II inhibition. Furthermore, consistent with a role in myosin regulation, 14-3-3 inhibition alters myosin II distribution in the growth cone, and the phosphorylation status of the regulatory myosin light chain. Given the role of 14-3-3s in regulating cytoskeletal dynamics in growth cones we examined if these proteins were required for classical axon guidance events in the developing spinal cord. We observe that 14-3-3 inhibition abolishes netrin-1 induced growth cone expansion and that the attractive turning responses of commissural interneurons to netrin-1 are also lost. Together our data suggests 14-3-3 proteins play a critical role in axon guidance by regulating cytoskeletal dynamics in growth cones.

A3

CRMP4 regulates the neuronal cytoskeleton and neuronal responses to myelin inhibitors

Mohammad R. Khazaei*, Stephan Ong Tone, Alyson Fournier.

The CRMP family of proteins are phosphoproteins that are highly expressed in the nervous system during development. The first family member discovered (CRMP2) was identified for its role in mediating growth cone turning in response to the repulsive guidance cue Semaphorin 3A. CRMPs are expressed in neuronal growth cones and are known to have microtubule polymerization and F-actin bundling activity in vitro but how they function to regulate growth cone dynamics is not known. We have developed a particular interest in the CRMP4 isoform because this isoform uniquely binds to RhoA, a master regulator of the actin cytoskeleton, and plays a critical role in mediating neuronal responses to myelin-associated inhibitors that limit nerve cell extension. In this project we will explore the idea that CRMP4 regulates growth cone dynamics and nerve cell extension by directly regulating the neuronal cytoskeleton.

To gain insight into how CRMP4 influences the growth cone cytoskeleton and neurite outgrowth, we have used gain of function and loss of function approaches in hippocampal neurons to evaluate effects on the cytoskeleton. Depletion of CRMP4 using RNAi or introduction of a CRMP4 fragment that blocks CRMP4 binding to RhoA results in the formation of growth cones with multiple long tubulin positive branches with no clear lamellipodia. CRMP4 overexpression results in blunt ended growth cones with an increase in the number of short actin-rich protrusions along the axon shaft. These phenotypes could be attributed to CRMP4b effects on the actin or microtubule cytoskeleton. Our preliminary data indicate that CRMP4 does not affect microtubule polymerization in an in vitro turbidity assay raising the possibility that CRMP4 may mediate its effects through the actin cytoskeleton. Consistent with this idea, we have used mass spectrometry to identify multiple actin binding proteins as proteins that complex with CRMP4. Proteins that co-immunoprecipitate with CRMP4 include neurabin, frabin, drebrin, and cortactin. We will further pursue the nature and physiological relevance of these interactions with respect to CRMP4 effects on growth cone dynamics and neurite outgrowth. These studies will be facilitated by analyzing CRMP4 knockout mice, which we have recently generated in the lab.

A4

Membrane type matrix metalloproteinase-3 regulates neuronal responsiveness to myelin through Nogo Receptor 1 cleavage

Gino B. Ferraro, Elizabeth Gowing, Charlotte J. Morrison, Christopher M. Overall, Stephen M. Strittmatter and Alyson E Fournier

Nogo-66 receptor 1 (NgR1) is a glycosylphosphatidylinositol-anchored receptor for myelin-associated inhibitors (MAIs) that restricts plasticity and axonal regrowth in the CNS. NgR1 is cleaved from the cell surface of SH-SY5Y neuroblastoma cells in a metalloproteinase-dependent manner; however, the mechanism and physiological consequence of NgR1 shedding has not been explored. We now demonstrate that NgR1 is shed from multiple populations of primary neurons. Through a loss of function approach we find that membrane type matrix metalloproteinase-3 (MT-MMP3) regulates NgR1 shedding in primary cortical neurons. . Recombinant MT-MMPs 1, 2, 3 and 5 promote NgR1 shedding from the surface of primary neurons and this treatment renders neurons resistant to MAIs. Introduction of a cleavage resistant form of NgR1 reconstitutes the neuronal response to these inhibitors demonstrating that specific metalloproteinases attenuate neuronal responses to myelin in a NgR1-dependent fashion. Our expression analysis revealed the presence of several MT-MMPs in the hippocampus consistent with the proposed role of NgR1 in mediating hippocampal synaptic plasticity. We are now exploring the potential role of NgR1 shedding at the synapse. We demonstrate that synaptic NgR1 can be shed and we are addressing whether synaptic activity can modulate this process.

A5

Mechanisms of RhoA proteolytic processing

Marie-Pier Girouard*, Madeline Pool, Alyson Fournier

In the central nervous system, neurons fail to spontaneously regenerate following injury and this has devastating consequences in cases of neurological trauma. Inhibitory environmental cues including myelin-associated inhibitors (MAIs) and chondroitin sulfate proteoglycans (CSPGs) contribute to the regenerative failure. Many classes of inhibitory molecules inhibit neuronal regeneration by activating the small GTPase RhoA and clinical trials are currently in progress to assess the effectiveness of a RhoA antagonist in spinal cord injury. However, RhoA mediates multiple cellular processes in neuronal and non-neuronal cells and novel strategies to target RhoA may lead to the conception of a more specific therapeutic strategy. In our laboratory, we recently found that RhoA is cleaved to produce a novel cleavage fragment, suggesting a novel mechanism of RhoA regulation. We hypothesize that we can promote axonal regeneration by regulating the cleavage of RhoA.

Through both biochemical approaches and mass spectrometry, we are identifying the proteolytic site in RhoA that is responsible for the generation of a novel cleavage fragment and the protease that regulates this cleavage. Transfection of Flag-tagged RhoA constructs into COS7 cells has revealed the presence of a 10kDa RhoA cleavage fragment. Intriguingly, active GTP-bound RhoA is cleaved more robustly than wild type-RhoA and cleavage of inactive GDP-bound RhoA is nearly undetectable. This cleavage pattern is apparent when assessing cleavage of mutant RhoA constructs (Q63L or T19N) or when RhoA is inactivated or activated by co-transfecting GTPase activating proteins or guanine nucleotide exchange factors respectively. To determine which protease is responsible for RhoA cleavage, we have assessed RhoA cleavage in the presence of a panel of protease inhibitors. We observed an increase in the production of the cleavage fragment with calpain inhibitors (ALLN and calpeptin), with a pan-caspase inhibitor (z-VAD-fmk) and with a more specific caspase-1 inhibitor (z-YVAD-fmk). This suggests the presence of calpain and caspase-1 cleavage sites within the novel proteolytic fragment. Further, the serine-protease inhibitor AEBSF attenuates production of the RhoA cleavage fragment indicating that the protease responsible for generating the 10kDa cleavage fragment is a serine protease. Together, our data demonstrates that RhoA cleavage is dependent on the activity state of RhoA and that a serine protease is responsible for producing the novel RhoA cleavage fragment. Future experiments will focus on the identification of the protease responsible for this cleavage and on assessing the physiological relevance of this processing in neurite outgrowth and other RhoA-dependent processes.

A6

Attention Training in Children with ADHD

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Objective: We sought to determine the effects of an attention training (AT) program, adapted from the “Teach-The-Brain” program, in children diagnosed with Attention Deficit and Hyperactivity Disorder (ADHD). We compared training outcomes between preschool-aged children who participated in AT, placebo training, and waitlist controls.

Participants and Methods: 20 ADHD-diagnosed preschool children (4-6 years of age); 9 experimental; 6 placebo-control; 5 waitlist-control. The AT program comprised a series of 12 games played over the course of 10 sessions lasting half an hour each, for a period of 3-4 weeks. Placebo controls watched with videos showing the AT games within the same timeframe and environment as the experimental group. Pre- and post-assessment: verbal and non-verbal subtests of the Reynold’s Intellectual Screening Test (RIST); Parent and teacher reports using the Children's Behavior Questionnaire (CBQ). Post-assessments were conducted two weeks after finishing the training program. The performance evaluator was not the same as the trainer of an individual child. Waitlist controls received only pre- and post- assessments encompassing this same time frame.

Results: Analysis of Variance (ANOVA) showed significant group and session (pre/post) effects involving RIST measures ($F = 3.173$, $p < 0.016$). Non-verbal RIST scores significantly improved in the experimental ($p < 0.009$) group; Verbal RIST scores significantly improved in the experimental ($p < 0.002$) and placebo-control ($p < 0.003$) group. Parent and teacher reports did not reveal significant reduction in symptoms related to impulsivity, attention focusing, or inhibitory control.

Conclusions: Following our AT program, preschool children with ADHD improved their performance on both verbal and non-verbal measures of intelligence. Measures of verbal intelligence also improved following placebo training. Interestingly, these improvements in intelligence occurred despite no intelligence-training component in our AT program. Parent and teacher reports, however, do not appear to indicate behavioural improvements. The observed improvements in intelligence and behaviour show potential for administration of AT in children with ADHD, possibly as a school-based intervention. Further study remains to determine intellectual and behavioural effects using a larger sample size, in addition to elucidating the time sustainability of observed effects.

A7

The Effect of the Consent Form: Using Wisdom Tooth Extraction as a Lens

*Abbey, Erica and Raz, Amir

Informed consent is ubiquitous in modern medicine; however, the therapeutic effects it generates have been scarcely studied. The disclosure of details during the informed consent procedure may inadvertently increase potential harm to the individual due to the power of suggestion. The main objective of this study is to investigate the influence of the consent form in the postoperative experience of patients undergoing wisdom teeth extraction (WTE). Using two separate consent forms, both clinically accurate but voicing orthogonal tenors, we provide a carefully formulated message about the role of expectations and placebo effects in one compared to a standard consent form in the other. We hypothesize that the more optimistic consent form will decrease the expression, duration, and intensity of negative postoperative WTE symptoms. (e.g., swelling, pain, complications). Preliminary results from a randomized controlled pilot study we are currently running at the Jewish General Hospital indicate that the consent form can decrease overall symptom severity scores on the Postoperative Symptom Severity Scale for experimental subjects compared to controls. Our early findings suggest that altering expectations may eliminate or at least minimize manifested symptoms. These preliminary findings suggest that the information and tenor of the consent form influences outcome. We would like to further explore these effects in a larger study.

A8

Effects of Expectation on Hypnotizability

Michael Lifshitz*, Catherine Howells, & Amir Raz

Disparate theoretical viewpoints construe hypnotizability either as a stable trait, largely determined by underlying cognitive aptitude, or as a flexible skill amenable to attitudinal factors including beliefs and expectations. Circumscribed findings support both views. The present study attempted to consolidate these orthogonal perspectives through the lens of expectancy modification. We surreptitiously controlled light and sound to convince participants that they were responding strongly to hypnotic suggestions for visual and auditory hallucinations. Extending our previous findings, we indexed hypnotizability by de-automatizing an involuntary audiovisual phenomenon—the McGurk effect. Here we show that, in concert with other aspects of the procedure, expectancy modification led to heightened expectations concerning future hypnotic response. We found little effect of expectation, however, on actual response to suggestion. Our findings intimate that, at least in the present experimental context, expectation hardly correlates with—and is unlikely to be a primary determinant of—high hypnotizability.

A9

Suggestion Unmasked: A New Perspective on Automaticity

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Suggestion seems capable of shifting certain automatic processes back into the purview of control. However, it is still unclear whether suggestion can shift cognitive processes in the opposite direction – i.e., from controlled to automatic – without extensive practice. Adapting the Masked Diamond Paradigm – a well-documented visual task in which the absence of critical information suffices to transform the otherwise easy task into a difficult, even intractable, one – we designed a short online assessment to measure accuracy and reaction time on several variations of this paradigm (see http://razlab.mcgill.ca/demomotrak.html). More specifically, we explore whether suggesting the presence of critical information can simplifies, even trivializes, this challenging perceptual task. Findings from our preliminary analyses show that HSIs (Highly Suggestible Individuals) performed faster and more accurately under suggestion, while the accuracy of LSIs (Low Suggestible Individuals) was comparable regardless of suggestion. These findings propose that HSIs, unlike LSIs, may have successfully envisaged the missing critical information, and supports the notion that suggestion is capable of automatising a complex and effortful perceptual task.

A10

Relevance of endoplasmic reticulum stress-induced prion protein gene expression in breast cancer

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Besides its role in the initiation and propagation of both familial and sporadic prionopathies, some evidence supports a physiological role for the normal form of the prion protein (PrP). Our laboratory previously demonstrated that cytosolic PrP was able to counter Bax-mediated apoptosis in both human neurons and breast cancer cells, while cellular prion has been reported as a marker of resistance to anthracyclin-based chemotherapy in oestrogen-negative breast cancer tumours. Given that endoplasmic reticulum (ER) stress is known to occur in cancer and prionopathies, we decided to investigate the generation of PrP during ER stress. In this study we report that ER stress transcriptionally up-regulates PrP expression in human neurons and in the breast carcinoma cell line MCF-7 and further explored the implications of this finding using human breast cancer tissue microarrays (TMA).

We initially demonstrated that ER stress increased PrP transcription and protein levels. Four ER stress response elements (ERSE) were then identified in the PRNP promoter and luciferase reporter assays confirmed their involvement in both basal and ER-stress induced PrP expression. Interestingly, a discrepancy was observed in the regulation of PrP expression induced by the various pharmacological ER stressors (Thapsigargin, Tunicamycin and Brefeldin A). Chromatin immunoprecipitation (ChIP) assays were performed and determined that PrP induction was mediated by the ATF6? and sXBP-1 transcription factors. Furthermore, PrP provided resistance against early ER stress-induced apoptosis, thus delaying cell death in the MCF-7 cell line. These findings are of crucial relevance for cancer research, by promoting cell survival against ER stress-induced apoptosis. Considering the latter, we recently studied PrP levels and distribution in human breast cancer TMA by immunohistochemistry with the intention of correlating them with the ER stress marker BiP/GRP78. Other features, including the type of cancer, malignancy and survival time, will also be assessed in relation to PrP expression in human tumours. Preliminary results show varying PrP levels, in both cytosolic and nuclear compartments of distinct cell populations, but PrP was rarely present on cell membranes or myoepithelia.

Collectively, this work characterizes ER stress-induced PrP expression both in human neuronal and cancerous cells and should provide supporting evidence for ER stress-induced PrP expression in a clinically relevant setting.

A11

The investigation of Tau cleaved by Caspase-6 in the cerebrospinal fluid as an early biomarker for Alzheimer disease

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Alzheimer disease is a neurodegenerative disorder resulting in the decline of cognitive domains, most notably memory impairment. Diagnosing Alzheimer disease at an early stage pre-mortem is difficult because no specific test has been established. Early diagnosis of cognitive impairment is vital because it allows for prompt treatment with available therapies which can delay disease onset and progression. Due to this compelling need for early predictors, scientists are searching for potential early biomarkers. Evidence suggests that activation of the cysteinyl protease Caspase-6 is an early and important event in Alzheimer disease. Caspase-6 activation is observed in layer II of the entorhinal cortex, the area first affected in Alzheimer disease, in some non-cognitively impaired aged brains. In fact, Caspase-6 activity in the entorhinal cortex of non-cognitively impaired brains correlates negatively with global cognitive scores. Furthermore, Caspase-6 activation leads to axonal degeneration and since the neurons of the entorhinal cortex project to the hippocampus, the presence of Caspase-6 activity in the layer II of the entorhinal cortex predicts eventual memory deficits due to hippocampal neuron degeneration. Our objective is to determine if Caspase-6 activity can be detected in non-cognitively impaired individuals by assessing the amount of Tau cleaved by Caspase-6 in post mortem cerebrospinal fluid and brain tissue sections. Immunohistochemical analysis of paraffin-embedded adult human brain sections was used to detect Caspase-6 and Tau cleaved by Caspase-6 in 22 non-cognitively impaired brains. Semi-quantitative analysis was performed using a density scale of 0-3. An enzyme-linked immunosorbent assay is being set up in order to measure the levels of Tau cleaved by Caspase-6 in the post-mortem cerebrospinal fluid of these same cases. Purified Tau cleaved by Caspase-6 and Tau full length recombinant proteins will be used as positive and negative controls, respectively. It was previously shown that young non-cognitively impaired brains do not show any Caspase-6 or Tau cleaved by Caspase-6 staining. Semi-quantitative analysis revealed that more than 70% of the aged non-cognitively impaired brains had some active Caspase-6 and Tau cleaved by Caspase-6 in the CA1 region of the hippocampus (71% and 87%, respectively) and layer II of the entorhinal cortex (73% and 75%, respectively). Tau cleaved by Caspase-6 was more abundant than active Caspase-6 in most brain regions. Active Caspase-6 and Tau cleaved by Caspase-6 accumulated in neurofibrillary tangles, neuropil threads and neuritic plaques as well as immature and ghost tangles. Moreover, in several non-cognitively impaired cases active Caspase-6 showed a diffuse staining pattern which appeared to be synaptic. Thus far, the ELISA is effective at detecting Tau?Casp6 recombinant protein with a sensitivity of 0.78pg/µL. Most commercial assays can detect target proteins at about 10x this sensitivity (0.06pg/µL). Presently, the sensitivity of the assay is being increased by changing antibody dilutions and incubation times. The accumulation of active Caspase-6 in the hippocampus and entorhinal cortex of most non-cognitively impaired individuals suggests that Caspase-6 1) is involved in early tangle pathology, 2) likely plays a role in early disease progression and 3) contributes to or underlies the cognitive impairment associated with Alzheimer disease. Considering that synaptic loss is the best correlate of cognitive impairment, accumulation of Caspase-6 in what appears to be neuronal synapses suggests a direct role for Caspase-6 in synaptic degeneration and cognitive decline.

A12

The emerging role of Caspase-6 in Alzheimer Disease pathogenesis

Prateep Pakavathkumar*, Saskia Sivananthan, Steffen Albrecht & Andrea LeBlanc

Alzheimer disease (AD) is the most common cause of dementia in the elderly. Current strategies for treatment are ineffective and proposed disease modifying drugs focusing on depleting AD brains of the amyloid-? (A?) protein have failed in clinical trials. Consequently, renewed efforts focus on targeting molecular events occurring earlier during disease progression.

This poster summarizes a decade of research from our lab exposing the instigating role of Caspase-6 (Casp6) in neurodegeneration and AD neuropathology. ProCasp6 processing occurs via Casp1 in serum deprived primary human neurons (PHNs) (Guo et al. 2006) and requires intramolecular self-cleavage (Klaiman et al. 2009; Wang et al. 2010). The role of active Casp6 in neurodegeneration has been demonstrated by microinjection (Zhang et al. 2000), overexpression of amyloid precursor protein mutants (Sivananthan et al. 2010) in PHNs, and by identification of neuronal Casp6 substrates (Klaiman et al. 2008). Further, immunohistochemical studies of post-mortem brains of familial (Albrecht et al. 2009) and sporadic AD (Guo et al. 2004; Albrecht et al. 2007) patients using active Casp6 and Tau cleaved by Casp6 (Tau?Casp6) antibodies reveal all of the neuropathological hallmarks of AD. Lastly, Tau?Casp6 staining correlates inversely with cognitive scores of non-cognitively impaired individuals (Albrecht et al. 2007). These results implicate Casp6 early in the pathogenesis of AD.

Therefore, inhibiting Casp6 activity is of interest for preventing AD pathology. Inhibitors of apoptosis proteins (IAPs) are a family of proteins known to regulate caspase activity in cells. However, none of the known mammalian IAPs have the ability to inhibit active Casp6 (Roy et al. 1997, Deveraux et al. 1997). Our lab has identified caspase inhibitory factor (CIF) in PHNs through 17?-estradiol treatment (Zhang et al. 2001). CIF inhibits the processed and active form of Casp6 (Tounekti et al. 2004). In contrast, the alternative splice product of the CASP6 gene, proCaspb, inhibits the self-processing of proCasp6a through asymmetrical dimerization (Lee et al. 2010).

In conclusion, development of small molecule inhibitors against Casp6 may provide a novel therapeutic intervention to stop AD progression.

A13

Characterization of Na+/H+ exchanger NHE6 in the Mouse Hippocampus: Implications for Autism and Mental Retardation

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Background: The Na+/H+ exchanger (NHE) protein family mediates trans-membrane transport of protons and alkali cations, a process that underlies many homeostatic activities. Members of this family are conserved across mammalian species and expressed either ubiquitously or in a tissue specific manner. Interestingly, genetic disruption of one isoform, NHE6, has been implicated in X-linked mental retardation and Autism spectrum disorders. One mutation in SLC9A6 encoding NHE6 removes two highly conserved amino acids in the NHE6 ion exchanger domain, E287 and S288 (NHE6?ES), and produces a phenotype similar to Angelman syndrome. Despite these findings, the precise localization and function of NHE6 in the brain remains uncharacterized. This study aims to characterize the localization of NHE6 in the mouse hippocampus during post-natal development and to determine its involvement in synaptic maturation and function.

Experimental Methods: 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 (ICC). Activity-dependent modulation of NHE6 was assessed using a glycine-induced chemical long-term potentiation (chemLTP) protocol in primary neurons, which were then processed for NHE6 ICC. Finally, plasmid constructs containing fluorescently-tagged forms of mutant (NHE6?ES) and wildtype (NHE6v-1) NHE6 were introduced into mature primary neurons by lipid-mediated transfection to assess any aberrations in cell morphology or protein localization due to disruption of NHE6.

Results: In both cryostat and organotypic slices, NHE6 undergoes a significant increase in area CA1 during hippocampal maturation. NHE6 exhibits a punctate distribution throughout the somatodendritic compartment of CA1 pyramidal neurons. Notably, is found at 80% of dendritic spines, most frequently at the spine base and/or head and to a lesser extent at the spine neck. Furthermore, NHE6 localizes to 60% of putative presynaptic boutons. NHE6 partially colocalizes with internalized transferrin and syntaxin-13, previously established markers for recycling endosomes, at 60% and 40% of dendritic spines, respectively. NHE6 is most frequently found with these markers at the spine base, as has been previously reported for recycling endosomes in hippocampal neurons. With activity, there is an increase in total number of spines positive for NHE6, a decrease in NHE6 at spine necks of long and mushroom spines, and an increase in NHE6 at the spine heads of stubby and mushroom spines. Similar to endogenous NHE6, exogenous NHE6v-1 localizes throughout the somatodendritic compartment of primary neurons in small punctate clusters, extending into distal dendrites and into some putative dendritic spines. Exogenous mutant NHE6 (NHE6?ES), however, shows restricted distribution in primary neurons.

Conclusions: Association of NHE6 with endosomal compartments in both dendritic spines and axon terminals suggests that it may play a role in both pre- and post-synaptic function. Indeed its localization at dendritic spines and its activity-dependent modulation puts NHE6 in an appropriate context for involvement in receptor-mediated endocytosis and plasma membrane recycling, phenomena that have important roles in synaptic activity and dendritic spine morphology. Further understanding of the role of NHE6 in the brain may provide basis for improvement of therapeutic agents for individuals with neurodevelopmental disorders.

A14

Face perception in autism: assessing the effect of viewpoint change on identity discrimination

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Background: Face perception is the most commonly used visual metric of social perception in autism. However, when found to be atypical, the nature of its origin is often contentious. One hypothesis proposes that autistics' characteristic locally-oriented visual analysis ultimately affects performance on most face tasks where global analysis is optimal. Objective: We will evaluate this hypothesis by assessing face identity discrimination with synthetic faces presented with and without changes in viewpoint (access to local face attributes is minimized in the viewpoint change condition). Methods: 60 participants (autistics and non-autistics) matched for global IQ, age and gender performed a face identity discrimination task (Habak et al, 2008). This task included synthetic face stimuli (Wilson et al, 2002) extracted from traditional face photographs in both frontal and 20° side viewpoints. The face photographs were digitized from 37 points to provide a continuous measure of facial geometry. We obtained face identity discrimination thresholds using a two-alternative, temporal forced choice match-to-sample paradigm consisting of a target face, followed by a mask, then by two choice faces presented side-by-side. Participants were asked to identify which choice face matched the target. Results: Analyses revealed a significant interaction effect between groups and conditions, with a significant group difference found only for the viewpoint change condition. This result illustrated that autistic participants' performance was less efficient than that of non-autistic participants in this condition alone. Conclusions: The selective decrease in autistic performance for the viewpoint change condition suggests that face identity discrimination in autism is more difficult when (i) access to local cues are minimized, and/or (ii) an increased dependence on integrative analysis is introduced to the face task used. These results suggest a perceptual, rather than social origin of atypical face perception in autism.

A15

Chronic neuropathic pain in rats causes long-term increases in anxiety-like behaviours and deficits in attentional abilities

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Introduction/Aim: In order to make animal models of chronic pain more relevant to the human condition, many researchers now recognize the need to investigate complex cognitive processing in chronic pain models, since pain patients often manifest psychological co-morbidities such as anxiety, depression and cognitive deficits. However, the effects of chronic neuropathic pain upon anxiety-like behaviours in animals are usually only studied in the short term, i.e., within the first month after injury, whereas in humans anxiety and depression often do not emerge until months or years after the onset of a chronic pain condition. Consistent with the human condition, a pilot study in our lab found that after a nerve injury, rats only began showing anxiety-like behaviours 24 weeks after surgery. The current study was designed to examine the long-term effects of a nerve injury in rats on both anxiety and cognitive function, in order to produce a more complete behavioural phenotype of the impact of chronic pain in the rat.

Methods: Male rats received either a spared nerve injury (SNI, n=13) or sham surgery (n=13) and were monitored for up to 30 weeks post-surgery. Sensory testing measured mechanical and cold hypersensitivity using von Frey hairs and 50µl of acetone applied to the plantar surface of the hindpaw, and was performed at 5 different time points: 1 week pre-surgery, and 2, 8, 16, and 24 weeks post-surgery. Locomotion and exploration were measured using the open field test, and anxiety-like behaviours monitored by the elevated plus maze, both of which were performed at the same time points as sensory testing. Attentional capabilities were probed at the end of the experiment, between 25 and 30 weeks post-surgery, using a non-sustained, non-selective attention task.

Results: SNI (n=13) animals showed hypersensitivity to both mechanical punctate stimuli and acetone application in the ipsilateral paw only at all timepoints after surgery, compared to both the contralateral paw ($p<0.05$), and sham surgery controls (n=13, $p<0.05$). Testing in an open field arena showed no differences in locomotion, time spent around the perimeter, nor rearing behaviour between surgical groups at any time point ($p>0.05$). However, nerve injured animals showed marked anxiety-like behaviours in the elevated plus maze from the earliest time point to the latest – SNI animals spent more time in the closed arms (2 weeks: $p=0.0004$, 24 weeks: $p=0.0036$), entered the open arms less frequently (2 weeks: $p<0.001$, 24 weeks: $p<0.0001$), and reared less in the centre of the maze (24 weeks: $p<0.05$) compared to sham controls. In addition, SNI animals show attentional deficits in the attention test performed at the end of the experiment ($p=0.04$).

Discussion: These results suggest that long-term chronic neuropathy in animals does not affect an animal's general mobility or its willingness to explore, but causes increases in anxiety-like behaviours that begin shortly after injury and stay elevated over a period of more than 7 months. In addition, neuropathy appears to cause cognitive dysfunction, as seen by deficits in an attention task. This is similar to effects reported by human chronic pain patients that struggle with memory, attention and forward planning after long periods of suffering.

Conclusions: We present data from a number of sensory and cognitive modalities in the rat showing that spared nerve injury causes robust hypersensitivity persisting over a period of 24 weeks post-surgery. In addition, anxiety-like behaviours are increased in tandem with this hypersensitivity. After a period of 30 weeks, rats show attentional deficits, concomitant with human studies showing cognitive dysfunction after long periods of chronic pain. It will be important for future research to use chronic pain paradigms over long time courses such as this, to elucidate the cellular and systems mechanisms causing these deficits, potentially informing future treatments for human pain patients.

A16

SALT-LOADING REVERSES CHLORIDE GRADIENT VIA DOWNREGULATION OF KCC2 IN RAT SUPRAOPTIC NEURONS

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The K-Cl cotransporter 2 (KCC2) maintains the reversal potential (Erev) of GABAA receptors below action potential threshold so that synaptic activation of these receptors promotes inhibition. Chronic systemic hyperosmolality induces numerous changes in the supraoptic nucleus (SON) to facilitate excitation, vasopressin secretion and osmoregulation. We tested the hypothesis that 7-day salt-loading (SL) might attenuate GABAA mediated inhibition of SON neurons using intracellular recordings from rat hypothalamic explants in the presence of the APMA receptor antagonist CNQX (20microM). In control explants, electrical stimulation of the diagonal band of Broca (DBB) evoked bicuculline-sensitive postsynaptic potentials (PSPs) with an Erev of -59.4±1.6mV and peri-stimulus histogram (PSH) analysis showed that these resulted in a transient inhibition of action potential firing (+100.0±0%; n=6; P<0.05). In contrast, DBB stimulation in explants from SL rats evoked PSPs reversing at -31.7±5.2mV (n=13; P<0.001 vs. control) and PSH analysis revealed that these functionally increased the probability of firing (+1043.4±567.9%; n=6). The Erev of spontaneous PSPs were also more depolarized in SL rats (-36.4±1.9mV; n=10) than controls (-57.2±1.5mV; n=14; P<0.001). Moreover, application of the GABAA receptor antagonist bicuculline (10microM) increased the basal firing rate of SON neurons in control explants (dHz=0.62±0.18Hz; n=9) but inhibited those in SL preparations (dHz=-1.02±0.69Hz; n=14). Immunohistochemistry and Western blotting analyses showed that KCC2 protein levels are significantly reduced in the SON of SL rats compared to controls. These results suggest that chronic SL can abolish synaptic inhibition via downregulation of KCC2 in the SON.

A17

Brain alterations in nerve growth factor metabolism in a novel rat transgenic model of Alzheimer’s disease

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Alzheimer's disease (AD) is a neurodegenerative disorder that progressively impairs cognition. AD affects cholinergic neurons of the basal forebrain which are essential for learning and memory and depend on the supply of nerve growth factor (NGF) for phenotype maintenance. Our lab has demonstrated that AD interferes with the post-translational maturation and degradation of NGF. These brain alterations are also present at the AD prodromal stage (Mild Cognitive Impairment) and are likely to occur at earlier, clinically silent, stages. We have also demonstrated an involvement of inflammation in relation to this trophic disconnection. Transgenic (tg) animal models are most suitable to follow the progression of the pathology longitudinally and to study disease biomarkers. For this purpose, we have generated a rat tg model that carries a mutated version of the human APP gene and accumulates intracellular and extracellular Abeta. Cognitive impairments occur as early as 3 months before plaque deposition in the presence of intracellular Abeta oligomers. Using Western blotting we have shown that our tg rats display a pattern of cortex alterations in NGF metabolism similar to that observed in AD. We have observed increased proNGF and plasminogen levels, reduced tPA and increased MMP9 enzymatic activity, as determined by gelatin zymography. We have also observed increased proNGF, IL1beta and COX-2 levels before plaque depostion, hinting that these molecules may have potential as disease biomarkers. We are currently analyzing the levels and activity of plasminogen, tPA, plasmin, MMP9 and neuroserpin at these early time points. Our goal is to look at these molecules in body fluids of our tg rats to evaluate their potential as biomarkers of disease progression. This is a most urgent need for diagnostic purposes and for rational drug design with disease-modifying approaches.

A18

Neuromuscular demonstration of a subcortical visual-motor reflex in a hemidecorticate patient

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Lesions to the visual cortex results in an absence of visual awareness in the contralateral visual field, but in both humans and non-human primates the presentation of an unperceived stimulus in the blind field can still influence behaviour (“blindsight”). In subjects where an entire cortical hemisphere has been removed (hemispherectomy), this blindsight phenomenon has been observed via saccadic eye movements with the presentation of stimuli in the blind field, and is most likely associated with descending signals from the ipsilesional superior colliculus (SC). A recent study has shown patients are able to generate correct antisaccades and prosaccades in both an ipsi and contralesional direction in response to auditory stimuli. During prosaccades, express saccades and a gap effect were observed with contralesional but not ipsilesional saccades. These results indicate a possible disinhibition of the intermediate layers of the ipsilesional SC following hemispherectomy. Furthermore, a visual stimulus in the blind hemifield can influence the accuracy and latency of antisaccades towards that field.

Another line of research has shown that presentation of a visual stimulus elicits a time locked visual response on neck muscles. The characteristics of this recruitment profile mirror what is seen in the intermediate layers of the SC in response to visual stimuli. Given this, we hypothesized that presentation of a visual stimulus in the blind hemifield of a hemidecorticate patient would evoke a similarly timed visual response on neck muscles. We obtained bilateral intramuscular EMG (iEMG) recordings of splenius capitis (SPL; an ipsilateral head-turning muscle) while the patient performed antisaccades into her blind field in response to a visual cue flashed in the periphery of the ipsilesional (seeing) side. On some trials a visual probe was briefly presented at the location of the saccade goal in the contralesional (blind) side.

We analysed neck muscle recruitment on probe trials and found that on a subset of trials in which the antisaccade reaction time followed probe onset by 100-200ms, there was a burst of iEMG activity on the SPL muscle ipsilateral to the gaze shift. This burst had a 75-100ms latency relative to probe onset. Our findings support the proposition that, in hemispherectomy patients, visual signals conveyed via the retino-tectal pathway to the superficial layers of the SC descend to the intermediate layers where they summate with the developing antisaccade motor command.

A19

Inhibitory control and L2 proficiency modulate bilingual spontaneous language production in monologues and in dialogues

Irina Pivneva*, Caroline Palmer & Debra Titone

The production of fluent speech in one's first language (L1) is subjectively effortless, yet speech production involves a complex set of linguistic operations that require cognitive control. Production of fluent speech may be even more demanding for bilinguals, who must simultaneously manage knowledge and usage of one or more fundamentally distinct linguistic systems. Although individual differences in inhibitory control and second language (L2) proficiency have been shown to modulate performance at the level of single words during bilingual language production, it is an open question whether such effects are found in extended spontaneous speech. We investigate whether individual differences among bilinguals in inhibitory control, working memory, and L2 proficiency modulate L1 and L2 production in the context of spontaneous monologues and dialogues. Twenty-six English-French and twenty-four French-English bilinguals completed the Map task, during which they produced spontaneous speech in L1 and in L2 with and without a conversational partner. Participants also completed a test battery that assessed their inhibitory control, working memory, and L2 proficiency. We found that language planning and production were more difficult in the L2 than in the L1 at low levels of L2 proficiency. In addition, L1 language planning and production decreased as L2 proficiency increased. Finally, these effects interacted with communicative task demands and individual differences in inhibitory control. In sum, these findings suggest that individual differences in inhibitory control and L2 proficiency are related to language planning and production during extended spontaneous speech production in monologues and dialogues.

A20

Reading Abnormalities in Schizophrenia: Evidence from the Moving Window Paradigm

Veronica Whitford*, Gillian ODriscoll, Christopher Pack, Ridha Joober, Kirsty Coulter, & Debra Titone

Language disturbances are a defining feature of schizophrenia, with the majority of work emphasizing how semantic or conceptual meaning is built from utterances. Far fewer studies examine the basic perceptual channels through which language is encountered, such as skilled reading. People with schizophrenia show impairments on standardized tests of reading (Revheim et al., 2006), however, it is unclear how their impairment manifests in moment-by-moment reading processes.

We investigate this issue using eye movement recordings of sentence reading in people with schizophrenia and controls. We assessed both global aspects of reading performance (number and duration of forward fixations, number and length of forward saccades) and perceptual span using the classic moving window paradigm (McConkie & Rayner, 1975; Rayner, 1975). Healthy English readers normally distribute their visual attention 13-15 characters to the right of fixation and 3-5 characters to the left, which is defined as the perceptual span. We hypothesized that people with schizophrenia would show reduced perceptual spans and global differences in eye movement patterns compared to controls.

In this preliminary sample, 7 people with schizophrenia and 22 controls read 90 short, syntactically simple sentences in their mother tongue on a computer screen while their eye movements were continuously recorded. Using a gaze-contingent moving window display, five conditions manipulated the amount of parafoveal information available at each fixation: one no-window condition, and four conditions consisting of progressively narrower windows to the right of fixation (window size to the left of fixation was fixed at 4 characters).

For both groups, average first fixation duration was longer for the narrowest window relative to no window. Compared to controls, patients made more forward fixations, had shorter forward saccades, and read fewer words per minute across all windows (although reading rate was comparable across groups for the most restrictive window size). People with schizophrenia also showed evidence of having reduced perceptual spans. Several of these effects co-varied with standardized reading tests (e.g., Nelson-Denny, CTOPP) and non-linguistic oculomotor and visual processing measures (e.g., anti-saccade performance).

Although preliminary, the results suggest that people with schizophrenia engage in a different moment-by-moment reading strategy than controls. This reading strategy may allow them to compensate for a reduced perceptual span, whereby less information is extracted at each fixation. Thus, people with schizophrenia appear to show differences in how linguistic information is perceptually extracted during reading, which may subsequently affect higher-order language operations of the kind normally investigated in this population (e.g., semantic processing).

A21

Bilingualism: characteristics of intensive language training in the adult brain

Jennika Soles*, Megan Callahan, Jen-Kai Chen and Denise Klein

It has been suggested that the functional and structural architecture of the human brain can be modified by the acquisition of a second language (L2) (Mechelli et al., 2004; Perani et al., 1998). This study investigates whether the organisation of language in the brain changes as a function of increasing language proficiency. Using functional and anatomical magnetic resonance imaging (MRI), whole-brain images were acquired from English monolingual participants at the beginning of and after 12 weeks of intensive training in French, their L2. On a behavioural level, the participants showed increasing levels of proficiency as measured on a number of variables, including proficiency ratings and the complexity of sentences the participants produced. In preliminary analyses, the participants also showed changes in BOLD fMRI activation from time 1 to time 2. Our preliminary results show that even with a task as complex as learning a second language, changes in both behaviour and brain organisation can be detected after as little as twelve weeks of intensive language training.

A22

Calcium-permeable AMPA receptors and Tumor Necrosis Factor alpha mediate retinal ganglion cell death in experimental glaucoma

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Purpose: The primary mechanism of retinal ganglion cell (RGC) damage in glaucoma is not well understood. Tumor Necrosis Factor alpa (TNF-alpha) has emerged as a key regulator of neuronal glutamate receptors in the central nervous system. Here we tested the hypothesis that TNF-alpha mediates RGC loss in experimental glaucoma by stimulating plasma membrane insertion of calcium-permeable AMPA receptors (CP-AMPARs) in these neurons.

Methods: RGC retrograde labeling was carried out by application of DiI onto the superior colliculus. Ocular hypertension (OHT) was induced a week later by injection of hypertonic saline into an episcleral vein in Brown Norway rats. The expression of TNF-alpha and its receptors, TNFR1 and TNFR2, was examined by RT-PCR blots and immunohistochemistry. Cell surface CP-AMPARs were visualized using a cobalt staining technique. The following agents were independently injected into the vitreous chamber: the TNF-alpha inhibitors Ethanercept or Xpro1595, and the CP-AMPAR blockers GYKI 52466 or Philanthotoxin. RGC neuroprotection was evaluated by quantification of RGC soma and axons.

Results: Gene and protein expression of retinal TNF-alpha, TNFR1 and TNFR2 were rapidly upregulated following OHT surgery and prior RGC death. Cobalt uptake occuring selctively through CP-AMPARs was markedly increased in RGCs of glaucomatous eyes compared to control eyes, and was selectively blocked by GYKI or Philanthotoxin. Intraocular injection of the TNF-alpha inhibitor or the CP-AMPAR blockers led to RGC neuroprotection in experimental glaucoma.

Conclusion: Our data support a key role for TNF-alpha and CP-AMPAR in RGC loss in experimental glaucoma.

A23

Revealing the nature of kainate receptor gating through the allosteric effects lithium ions

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Kainate receptors (KARs) represent a unique class of non-NMDA glutamate receptors, which require the presence of external ions for channel activation. Although recent years have seen advances in both structural and functional analysis, it is unclear how KAR stimulation leads to responses with both transient (peak) and sustained (equilibrium) components. Recently, we have argued that the transient activation of KARs is governed by a pre-gating step that determines agonist efficacy. However, as yet, it is unclear what factors contribute to the equilibrium activation of KARs. Here, we report a novel effect of lithium ions (Li+) that is uniquely observed on pyrrolidine-containing agonists, such as kainate (KA) and domoate (Dom), which may provide information on the role of dimer stability in KAR steady-state activation. Specifically, we show that Li+ slows KAR decay kinetics by about 2-3 fold whilst promoting steady-state activation by at least 10-fold when compared to responses in external Na+. Single-channel recordings reveal that these effects can be largely attributed to the appearance of a higher conductance state, which is only found in external Li+. When taken together, we suggest that peak KAR responses are mediated by a much larger unitary conductance whilst steady-state activation is characterized by a conductance state of much smaller amplitude. Ongoing experiments suggest that Li+ achieves these effects by stabilizing the dimer interface of KARs.

A24

Gating and Stoichiometry of Heteromeric Kainate Receptors

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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. It is still not clear which factors contribute to the slowing of KAR responses at synapses, and it remains to be understood the low affinity neurotransmitter, L-Glu, triggers prolonged activations of KARs. Here, we investigated the biophysical and stoichiometric properties of recombinant heteromeric KARs assembled from the GluK2 and GluK5 receptor subunits. To do this, we used a combination of outside-out patch electrophysiology to examine functionality and a fluorescent subunit counting technique to assess heteromerization. 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. Interestingly, preliminary data from subunit counting experiments suggest that the stoichiometry of heteromeric KARs is fixed. Furthermore, electrophysiological experiments reveal that GluK2/GluK5 heteromers are insensitive to external anions and cations. Since both anion and cation binding sites line the interface between KARs subunits, our data suggest that the process of heteromer assembly affects functionality by disrupting this region of the mature protein.

A25

Kainate receptors exhibit different gating modes.

G. Brent Dawe*, Elizabeth Andrews, Derek Bowie

Glutamate is the most prominent excitatory neurotransmitter in the central nervous system, and elicits responses via tetrameric, ionotropic receptors, such as kainate receptors (KARs). During sustained activation, KAR responses rapidly peak, and then decay over milliseconds (macroscopic desensitization) into an equilibrium state. The decay mechanism has always been assumed to result from receptor desensitization, defined by relaxation of the KAR into a non-conductive conformation. However, we have recently characterized two mutants of the KAR subunit GluK2, D776K and Y521C/L783C, which have pharmacological properties matching the peak and equilibrium responses. Because their single channel conductances also differ, we suspect that entry into low conductance states, rather than desensitization, accounts for current decay in wild-type receptors. Furthermore, both mutants promote the cohesion of subunit dimers at their ligand binding domains, indicating that this region may not be critical for the appearance of desensitization, as previously thought. We are currently attempting to build a more complete model of KAR gating behaviour by understanding how these mutants function.

A26

The methamphetamine-sensitive circadian oscillator is dysfunctional in a transgenic mouse model of Huntington’s disease

Marc Cuesta*, Juliet Aungier and A. Jennifer Morton

A progressive disintegration of the rest-activity rhythm has been observed in the R6/2 mouse model of Huntington’s disease (HD). Rest-activity rhythm is controlled by a circadian clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus, although SCN-independent oscillators such as the methamphetamine (MAP)-sensitive circadian oscillator (MASCO), can also control rhythmicity, even in SCN-lesioned animals. We aimed to test whether or not the administration of MAP could restore a normal rest-activity rhythm in R6/2 mice, via the activation of the MASCO. We administered chronic low doses of MAP to wild-type (WT) and presymptomatic (7-8 weeks) R6/2 mice, in constant darkness. As expected, ~40% of the WT mice expressed a rest-activity rhythm controlled by the MASCO, with a period of around 32h. By contrast, the MASCO was missing from almost 95% of the R6/2 mice, even at early stages of disease. Interestingly, although the MASCO was deficient, initially MAP was able to stabilize the day/night activity ratio in R6/2 mice and delay the onset of disintegration of the rest-activity rhythm driven by the SCN. Furthermore, in presymptomatic R6/2 mice treated with L-DOPA, a MASCO-like component began to emerge, although this never became established. Our data show a major dysfunction of the MASCO in presymptomatic R6/2 mice that is likely to be due to an early abnormality of the catecholaminergic system. We suggest that the dysfunction of the MASCO in humans could be partially responsible for circadian disturbances observed in HD patients, as well as patients with other neurological diseases in which both catecholaminergic and circadian abnormalities are present, such as Parkinson’s disease and schizophrenia.

A27

A Drosophila model to study function and dysfunction of glial glutamate transport in vivo.

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Glutamate is the principal excitatory neurotransmitter in the mammalian central nervous system (CNS). Subtypes of glial cells in the CNS tightly regulate extracellular glutamate levels to control neurotransmission and protect neurons from excitotoxic damage. They do so by expressing Excitatory Amino Acid Transporters (EAATs) with high affinity for glutamate. We used Drosophila as a powerful genetic model to study the function of the glutamate transporter Eaat1 in vivo. We have shown previously that Drosophila null mutants for Eaat1 exhibit defective crawling at the first instar larval stage: they seldom make full-body peristaltic contractions and have long periods of inactivity that are only occasionally interrupted by attempted contractions that are often slow, incomplete, and leave the animal contorted. This was due to an acute requirement for Eaat1 in larvae, and was not secondary to developmental defects occurring during embryogenesis. We took advantage of this EAAT loss-of-function phenotype to study the pathogenic nature of a human EAAT mutation that has been reported previously in a patient with episodic ataxia type 6 (EA6). This is a rare disease in which patients with mutations in the human glial EAAT transporter known as GLAST exhibit periods of incoordination and imbalance and in some cases the disease also involves migraine, seizure, cerebellar atrophy and hemiplegia. We first asked whether expression of GLAST in null Eaat1 mutants can rescue the larval locomotion defect. We found that it did, which shows that the function of EAAT proteins is evolutionarily conserved between flies and humans. Then, we studied whether a mutation found in an EA6 patient (GLAST P290R, or its equivalent in flies Eaat1P243R) could do likewise, and found that it could not. Additional overexpression and rescue studies suggest that this EA6-associated mutation confers a dominant-negative capacity to the mutant transporter in vivo. We provide evidence that this could occur by interfering with endogenous, normal Eaat1 and perhaps also through an additional Eaat1-independent mechanism. Our study demonstrates the consequences of pathogenic mutation of a human glutamate transporter in an in vivo model, and could provide an efficient system with which to identify factors that influence glutamatergic neurotransmission in vivo.

A28

Large, Non-Plateauing Relationship Between Total Cerebral-White-Matter-Lesion Volume and Clinical Disability in Patients with Multiple Sclerosis

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Background: Previous studies of patients with multiple sclerosis (MS) have found highly-variable and, on average, only-moderate correlations between: (i) total volume of cerebral white-matter lesions that are hyperintense on T2-weighted magnetic resonance imaging (MRI), and (ii) clinical disability as measured using Kurtzke's Expanded Disability Status Scale (EDSS). Furthermore, recent studies have been unequivocal as to whether there is a plateauing relationship between total T2-hyperintense lesion volumes and EDSS-measured clinical disability.

Objectives: We tried to better characterize this relationship by: (i) minimizing non-biological sources of variability; (ii) increasing pathological specificity by also studying T1-hypointense lesions; and (iii) covering the entire range of the EDSS, which is not usually done.

Methodology: In a cross-sectional, retrospective study performed in a hospital-based MS clinic setting, we studied 110 untreated patients with either relapsing-remitting or secondary-progressive MS. Both T2-hyperintense and T1-hypointense lesions in the cerebral white matter of each patient were segmented using a manually-corrected, automatic Bayesian-tissue-classification approach, which was shown to have high intra- and inter-rater reliability. Patients' EDSS scores had been assigned by the same highly-experienced neurologist who had been following them within the MS clinic.

Results: We found a large, non-plateauing relationship between cube-rooted white-matter-lesion volumes and concurrent EDSS scores - more so with T1- than with T2-lesion volumes: $r = 0.62$ vs. 0.55. Correlations between EDSS and white-matter-lesion volumes diminished when, as is done in most clinical trials, only those patients with EDSS scores of 0-6.0 were studied ($n = 92$; $r = 0.52$ for T1 lesions, $r = 0.46$ for T2 lesions); importantly, a series of boot-strapped correlation tests suggested that this decrease was not due simply to smaller sample size.

Conclusions: Our findings suggest that a large, non-plateauing relationship exists between total cerebral-white-matter-lesion volume and EDSS-measured clinical disability when patients with MS are studied in an optimal way.

A29

The impact of obstructive sleep apnea/hypopnea on neurodegeneration in multiple sclerosis

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Introduction:

Neurodegeneration is an important part of the pathology of multiple sclerosis (MS). Accumulating brain imaging evidence has shown that patients with obstructive sleep apnea/hypopnea (OSAH) also show various signs of neurodegeneration. We recently have reported the novel finding that OSAH occurs with high frequency in patients with MS. The effect of OSAH on neurodegeneration in patients with MS has not yet been studied. We hypothesize that OSAH in patients with MS leads to more severe neurodegeneration.

Methods

MS patients with and without OSAH were recruited from the local MS clinic. An age and sex-matched control group with and without OSAH, but without concurrent neurological disease was also studied. To quantify neurodegeneration in vivo, we performed MRI to measure differences in total and regional brain volumes, and spectroscopy (MRS) to measure differences in the concentration ratios of N-acetyl groups/creatine (NA/Cr) between groups Since data collection is still in progress and the sleep status is currently blinded, all comparisons for this abstract were made between subjects with (n=45) and without (n=29) MS. Data collection is expected to finish by the end of April.

Results

Compared with non-MS controls, patients with MS exhibited lower NA/Cr in central brain and posterior cingulate cortex, smaller brains, cerebella, left and right hippocampi, and thinner cortex.

Discussion

Reduced global and regional brain size and lower NA/Cr ratio in patients with MS compared to subjects without MS confirm that MS is associated with neurodegeneration. The additional impact of OSAH will be examined when these data are unblinded.

Introduction: Neurodegeneration is an important part of the pathology of multiple sclerosis (MS). Accumulating brain imaging evidence has shown that patients with obstructive sleep apnea/hypopnea (OSAH) also show various signs of neurodegeneration. We recently have reported the novel finding that OSAH occurs with high frequency in patients with MS. The effect of OSAH on neurodegeneration in patients with MS has not yet been studied. We hypothesize that OSAH in patients with MS leads to more severe neurodegeneration. Methods: MS patients with and without OSAH were recruited from the local MS clinic. An age and sex-matched control group with and without OSAH, but without concurrent neurological disease was also studied. To quantify neurodegeneration in vivo, we performed MRI to measure differences in total and regional brain volumes, and spectroscopy (MRS) to measure differences in the concentration ratios of N-acetyl groups/creatine (NA/Cr) between groups Since data collection is in progress and the OSAH status is currently blinded, all comparisons for this abstract were made between subjects with (n=45) and without (n=29) MS. Data collection is expected to finish by the end of April.
Results: Compared with non-MS controls, patients with MS exhibited lower NA/Cr in central brain and posterior cingulate cortex, smaller brains, cerebella, left and right hippocampi, and thinner cortex. Discussion: Reduced global and regional brain size and lower NA/Cr ratio in patients with MS compared to subjects without MS confirm that MS is associated with neurodegeneration. The additional impact of OSAH will be examined when these data are unblinded.

A30

Characterization of brain atrophy in patients with rapidly-progressing Multiple Sclerosis treated with immunoablation and immune reconstitution via autologous hematopoietic stem cell transplantation.

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Arnold, DL

Background:
The aim of this study was to measure and characterize the longitudinal progression of patterns of global atrophy in secondary-progressive (SP) and relapsing-remitting (RR) Multiple Sclerosis (MS) patients following treatment with 1) immune-ablation (IA) with high-dose chemotherapy and 2) immune-reconstitution with autologous hematopoietic stem cell transplantation (AHSCT).

Methodology:
For each subject, a trajectory of relative brain volume change (relative to the baseline reference point) was obtained by calculating the sequential series of percentage brain volume changes between consecutive pairs of images. Then, each trajectory was described using a model function (single-exponential linear combination); nonlinear regression analysis was used to estimate the parameters of the model. Multiple regression analysis was used to analyze the relationship between the sets of estimated parameters (dependent variables) and the Busulfan dosage and the baseline T1-weighted lesion volumes (independent variables).

Results:
From the reference point (the last MRI scan taken before the IA/AHSCT during the period of autologous hematopoietic stem cell mobilization and peripheral blood collection) to the first MRI follow-up after the AHSCT, there were transient, accelerated percentage brain volume changes (median: -2.2%, in median 2.4 months; annualized median: -10% / year) for which the annualized median was 6 times larger than that of the baseline interval (annualized median: -1.7% / year). Subsequently the atrophy stabilized, indicated by a significantly lower mean annualized rate during the interval from 2 years after the AHSCT to the last available (median 66 months after the AHSCT) follow-ups, compared to that of the pre-AHSCT interval.
The model-fitting indicated median -3.7% decrease in the brain volume over the entire follow-up periods (median follow-up period: 50 months). The significant predictors of the magnitudes of brain volume decrease were both the dose of Busulfan (an index of the potential treatment-related toxicity: [mg/kg]) and the volume of T1-weighted lesion (an index of the amount of tissues lethally injured by the MS prior to IA/AHSCT, [mm3]), but not the interaction of them. The estimated model parameters suggested that the mean amount of the effect of the busulfan dosages on the post-AHSCT volume change was significantly greater than that of the baseline T1-lesion volumes. The exponential decay factor was significantly associated with the interaction of the amount of Busulfan dose and the volume of T1-weighted lesion.

Conclusion:
1) The consequence of IA/AHSCT is the transient accelerated brain volume decrease that stabilizes with time. The stabilization is indicated by the significantly lower mean rate of atrophy [%/yr.] from 2 years after the AHSCT to the last available follow-ups, compared to that of the baseline interval.
2) The amount of post-AHSCT brain volume decrease is associated with the treatment-related chemotoxicity (dose of busulfan) and the damages from pre-AHSCT disease burden (T1-lesion volume, i.e. portions of the lesional and perilesional tissues that are committed to degeneration), but not with the interaction of them. The mean amount of the effect of the busulfan dosages on the post-AHSCT volume decrease is significantly greater than that of the T1-lesion volume.
3) The effect of the busulfan dosage on the rate of volumetric decay (i.e. how fast a curve reaches the half-point) depends on the amount of the T1-lesion volume.

A31

Celastrol-Encapsulated Hydroxy-Terminus Poly(amidoamine) Dendrimers Inhibit Lipopolysaccharide-Mediated Inflammatory Signaling in Microglia

Ghareb Soliman, Sebastien Boridy*, Dusica Maysinger

Purpose: Celastrol is a quinone methide triterpene extracted from the root bark of Trypterygium Wilfordii (Chinese “Thunder God Vine”) that has long been used in traditional Chinese medicine for the treatment of inflammatory diseases, autoimmune diseases, and cancer. However, celastrol’s limited aqueous solubility and toxicity impede its clinical application. The objective of the present study was to encapsulate celastrol into both G4 PAMAM-NH2 and G4 PAMAM-OH and test which of the two nano-delivery systems would be most effective at (1) solubilising celastrol; (2) reducing its cytotoxicity; and (3) increasing its anti-inflammatory potency.
Methods: Celastrol aqueous solubility was tested in the presence of different concentrations of G4-PAMAM-OH and G4-PAMAM-NH2 dendrimers in PBS (pH 7.4). Anti-inflammatory activity of celastrol/PAMAM complexes was assessed in N9 microglial cells activated by lipopolysaccharide (LPS). Nitric oxide release from the cells was estimated by the Griess Reagentmeasured using the Griess test. The In addition, the inhibitionextent of MAPK (p38) phosphorylation inhibition in LPS-stimulated microglia in the presence and absence of celastrol alone and when incorporated into PAMAM dendrimers was also estimatedassessed by western blot.
Results: Celastrol aqueous solubility increased linearly with the concentration of PAMAM-OH and PAMAM-NH2 due to electrostatic and hydrophobic interactions between the drug and dendrimer. Incorporation of celastrol into PAMAM-OH abolished the cytotoxicity observed with the drug alone or when incorporated into PAMAM-NH2. Moreover, PAMAM-OH dose-dependently inhibited nitric oxide release on its own and to a greater extent with celastrol encapsulated. Celastrol-encapsulated PAMAM dendrimers inhibited LPS-induced phosphorylation of p38, supporting the link between p38 activation and NO release.
Conclusion: G4.0 PAMAM dendrimers greatly enhanced the aqueous solubility of celastrol and maintained preserved its anti-inflammatory properties while completely abolishing the cytotoxicity caused by the drug alone.

A32

Motion-defined contour processing in early visual cortex

Amol Gharat* and Curtis L. Baker Jr.

From our daily experience it is very clear that relative motion cue can be used for correctly identifying object boundaries and for perceiving depth. Motion defined contours are not only generated by the motion of objects in a scene, but also by the movement of an observer’s head and body. However, the neural mechanism involved in detecting these contours is still unknown.
To explore this mechanism, we extracellularly recorded responses of neurons in A18 of anesthetized and paralyzed cats while they were presented with visual stimuli. The goal of this study was to determine if neurons in A18 that have been shown to detect luminance, texture- and contrast-defined contours cue-invariantly could also detect motion-defined contours. Motion contours in the visual stimuli were generated using the relative motion between high spatial frequency sinusoidal luminance gratings (carrier gratings). The gratings used were outside the luminance band of a neuron and the sole presence of it within the receptive field of a neuron alone did not elicit a response.
It was found that most of the neurons in A18 that responded to contrast modulation contours also respond to motion defined contours. The orientation and direction selectivity of these neurons for both types of motion-defined contours was very similar to that of luminance gratings. A particular neuron also exhibited similar selectivity for the spatial frequency of the carrier grating of contrast- and motion-defined contours. These results suggest that A18 is a common brain area where different second-order contours are detected form cue-invariantly, through a common neural mechanism.

A33

REAFFIRMATION OF THE DELIBERATIVE ROLE OF BIOETHICS: THE CASE OF COGNITIVE ENHANCEMENT

Cynthia Forlini* and Eric Racine

Objective: Discourse on the issues related to the cognitive enhancement of healthy individuals using prescription medication has been firmly grounded in academic discussion. The ethics discourse, in particular, has yielded highly polarized viewpoints for and against cognitive enhancement (CE). Results from an emerging body of research examining the perspectives of stakeholders (e.g., university students, healthcare professionals and other members of the general public) have contributed to adding experiential facets to the ethics debate around CE that, when synthesized, can yield important messages that further complement and diverge from academic discussions.

Methods and results: We examined five stakeholder studies (Banjo et al., 2010; Forlini & Racine, 2009; Forlini & Racine, In press; Hotze et al., 2011; Sabini & Monterosso, 2005) with survey and focus group methodology for results and conclusions that diverged from the academic debate. The three points of contention we found were: (1) the discussion of safety and efficacy as a rate-limiting step in the progression of CE both practically and ethically; (2) the perception of both high and low prevalence in university students and consequences of the perceived prevalence; and (3) the ambivalence and ambiguity on the acceptability CE and the progression of the ethics debate around it.

Conclusion : These three points suggest that the ethics debate around CE in according to academic and stakeholder perspectives may be running on parallel tracks by: (1) prioritizing different ethical issues; (2) basing individual and collective decisions as well as policy on different perceptions of prevalence and (3) failing to incorporate complex and evolving ethical thinking in stakeholder groups. We propose that the discipline of bioethics needs to reaffirm its role as a meeting place for the traditional academic ethics debate on CE and the more experientially-based approach of stakeholders. Future deliberation on the ethical and social issues of CE may indeed be more productive by considering the current messages of stakeholders in concert with academic discourse.

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A34

The error-related negativity reflects behavioral adjustment, not the evaluation of response outcome

Avinash R Vaidya*, Eldad Y Hochman & Lesley K Fellows

The error-related negativity (ERN) is an event-related potential that is associated with execution of errors in choice reaction time tasks. This waveform is considered the electrophysiological signature of performance evaluation in the posterior medial frontal cortex (pMFC), though its functional significance remains contested. In the current study, we tested the hypothesis that the magnitude of the ERN depends solely on the representation of the erroneous response. Participants performed a 4-choice flanker task, responding with either their left or right index fingers alone (small representation) or their left or right index and middle fingers together (large representation). For errors committed between hands, errors with a large representation were found to evoke a larger ERN than those with small representation, independent of the size of the correct response. Furthermore, large and small corrective responses were found to be less frequent following large errors compared to small errors. These results indicate that the ERN does not reflect the evaluation or prediction of errors, but may be related to a process in the pMFC that terminates an erroneous response in order to facilitate a correction.

A35

EPIFLUORECENCE/BIOLUMINESCENT IMAGING PLATFORM: Around the Clock Imaging of Gene Transcription within Specific Cell Populations

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Firefly luciferase, an enzyme capable of generating light, can be expressed within mammalian tissue by means of transgenesis, whereby the luc gene is driven by a specific mammalian promoter. This allows for the collection of light intensity information which is directly correlated with promoter activity. One advantage of this technique over fluorescent imaging is the ability to record light levels over long periods of time within ex-vivo tissue cultures, as phototoxicity is not an issue. There is however, one major disadvantage: the only light source is the enzymatic reaction itself. Therefore the ability to resolve bioluminescent emissions relies almost entirely on the ability to collect photons at ultra-high efficiency. Until recently this meant using photomultiplier tubes, imaging devices able to count single photons events while sacrificing all spatial resolution, limiting investigations to the tissue level.

Owing to advances in digital imaging technology, we now possess the ability to observe the these events with spatial resolution capable of distinguishing individual cells. This technique has been used several times in recent years and has already produced stunning results. However, it does not let us address the specific roles of sub-populations of cells within heterogeneous tissues composed of many different cells types.

Since the magnification and resolution of these next generation bioluminescence platforms is necessarily low (approximately 5-10x), cell identity cannot be assessed using morphological analysis. Rather, it is necessary to label cells of interest in some way. In order to associate single, fluorescently labelled cells with luciferase-mediated light emission, we have designed and developed a custom bioluminescent imaging platform capable of epi-fluorescent illumination and image capture.

Here we present the design and construction of such a platform; pointing out the benefits and constraints of our design which, for the first time, allows us to directly combine fluorescence and bioluminscence imaging at ultra-low light levels in live tissues. We also present a short outline of planned experiments and suggest other possible uses for such a platform.

A36

Body-wide Clock Disruption Results in LH surge and Estrus Cycle Dysregulation While Gonadotroph Specific Disruption has Minimal Effect

Adrienne Chu*, Ulrich Boehm and Kai-Florian. Storch

Circadian oscillations on the transcriptome and proteome level have been observed in many tissues including those forming the hypothalamic-pituitary-gonadal axis. In rodents, the luteinizing hormone (LH) surge is temporally regulated by the circadian system and is thought to be critical for normal reproductive cycles. Mice with body-wide mutations of Bmal1, an essential clock component, exhibit irregularities in estrous cycling but the characteristics of their LH surge are unknown. While the multi-oscillator circadian timing system can affect reproduction at several levels, the intrinsic circadian clock in pituitary gonadotrophs might be of specific relevance in this context as they are central mediators of the LH surge. We therefore hypothesize that the intrinsic clock in the pituitary gonadotrophs influences reproduction by gating the LH surge; thus disruption of the circadian clock globally or selectively in gonadotrophs will result in altered LH surge and consequently altered estrous cycling. Two mouse lines were used in this study, a body-wide Bmal1 knockout and mice with a selective disruption of Bmal1 within pituitary gonadotrophs (PitBmal1KO). While both lines had prolonged and irregular estrous cycles, the body-wide mutants were more severely affected than their gonadotroph-disrupted counterparts. Furthermore, whereas the Bmal1 knockout had a blunted and/or inopportune LH surge, the PitBmal1KO exhibited regular LH surges on the afternoon of proestrus. The considerable differences between the two lines suggest that clocks within the pituitary gonadotrophs may have limited physiological relevance and that the timing of the LH surge is controlled by either other intrinsic clocks along the reproduction axis or upstream of the pituitary, potentially within the hypothalamus.

A37

Double Gradients in Axon Guidance: A Microfluidic Gradient Generator for Studying Growth Cone Response to Multiple Guidance Cues

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Objective: During embryonic development, the nervous system achieves precise mapping of sensory and motor neurons to their respective target areas of the brain and spinal cord by forming maps of guidance cues, which can be secreted or bound to the cell surface and serve as attractants or repellants to the growth cones of extending axons. The trajectory an axon must complete is complex and involves integrating multiple combined gradients of chemical cues. Previously established axon turning assays are limited because they typically allow for only a single cue at a time to be analyzed. Our goal was to develop a microfluidic gradient device to study the combined effect of multiple cues on growth cone turning.

Methods and results: We have modified the geometry of a microfluidic gradient generator to maximize the surface area on which cells can be plated, in order to have a large number of neurons analyzed per experiment. We first showed that our device can generate stable molecular gradients. We also established the culture conditions to maximize survival of primary rat embryonic spinal commissural neurons in our device for more than 7 days. Finally, we demonstrated that gradients of the chemoattractants Sonic Hedgehog (Shh) and Netrin-1, and of the chemorepellant Bone Morphogenic Protein-7 (Bmp7) bias the direction of axonal growth.

Conclusions: We describe the characterization of a microfluidic gradient generator, and optimization for use in growth cone turning assays with primary rat embryonic spinal commissural neurons. At present, the device can support growth for neurons for more than 7 days, and bias growth cone turning to diffusible gradients of Shh, Netrin-1 and BMP7. This is the first axon guidance assay that allows the combination of multiple soluble cues. We are currently using the device to compare turning responses of axons to multiple guidance cues in combined and counter-gradients to see if an attractant/repellant counter-gradient can cause more axon turning than an attractant/attractant combined gradient. Future experiments will involve counter-gradients of known attractants and repellants in order to determine which signaling pathways dominate within the growth cone, and in doing so attempt to systematically elucidate the logic of axon guidance.

A38

miRNA Expression in the Prefrontal Cortex of Suicide Completers

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Background: 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 binding to complementary sequences usually located in the 3' untranslated region (UTR) of a target gene, generally leading to mRNA degradation or translational repression. A growing body of evidence supports the role of miRNAs in neuropsychiatric disorders such as schizophrenia and bipolar disorder.

Methods: We assessed the expression of 952 human miRNAs from prefrontal cortex (BA44) of suicide completers (N=14) and controls (N=11) using Human Agilent miRNA microarrays V2. Target genes for differentially expressed miRNAs were predicted using several target prediction databases and cross-referenced to our existing mRNA microarray data. Validation of miRNA microarray results and putative target genes was performed using qRT-PCR.

Results: We found miR-1202 to be down-regulated in suicide completers compared to the control group. Several target genes were explored and glutamate receptor 4 (GRM4) was found to be up-regulated significantly in the same subjects. Furthermore, we demonstrated a negative correlation between miR-1202 and GRM4 expression to be significant.

Conclusion: Overall, these results suggest that the decreased expression of miR-1202 in post-mortem brain tissue may be associated with the pathophysiology of suicidal behaviours. Ultimately, our results provide new evidence of the role of miRNAs in neuropsychiatric disorders and a better understanding of the etiology of suicide.

A39

Structural Alterations Associated with Suicidal Behaviour: A Neuroimaging study using Voxel-Based Morphometry and Cortical Thickness and Surface Area Analyses

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Volumetric structural changes observed using T1 weighted MRI scans in numerous brain regions has been previously reported to be associated with suicidal behavior. Existing findings show distinctive gray matter alterations in suicide attempters. Heterogeneities in findings are likely due to the differences in design conditions and analysis approach used.

Our study aim to 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. We recruited 18 healthy controls without history of mental disorder or suicidal behaviour, 14 affective controls with past history of depression but not suicidal acts and 13 suicide attempters with a past history of both depression and suicidal acts for our study. All participants are males between 18 and 60 years old that underwent a T1 weighted MRI scans while in non-depressed state.

We confirm structural alterations associated with suicidal behavior from voxel-based morphometry, cortical thickness and cortical surface area analyses. Particularly, our whole-brain VBM result analyses show reduction in volume, and region of interest Freesurfer analyses show reduction in surface area and thickness mainly in triangular part of inferior frontal gyrus region when comparing suicide attempters with healthy controls. Additional studies will be necessary to understand the relationship between structural reduction in this particular region and cognitive deficits and clinical signs and symptoms that may underlie the suicidal process.

A40

Synapsin genes in bipolar and unipolar depression: a brain expression and epigenetic study

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The synapsin family of neuronal phosphoproteins is composed of three genes (Synapsin I, Synapsin II, and Synapsin III) with alternative splicing giving rise to 10 variants. We have previously identified Synapsin II as a candidate gene for the etiology of bipolar disorder (BD) and/or response to lithium (Li), one of the most common lines of treatment for mood disorders. Additionally, the other synapsin genes have been postulated to play roles in the etiology of psychiatric disorders such as schizophrenia. Given their degree of homology and postulated functional overlap, it is of interest to characterize these genes' expression in the brains of mood disorder patients. In the present study we have investigated variants of the three synapsin genes in BD and major depressive disorder (MDD) focusing on mRNA-level expression and the mechanisms by which this is regulated. Using qRT-PCR, we analyzed expression of Synapsin I, Synapsin II, and Synapsin III in the prefrontal cortex (BA10) of postmortem brains from BD and MDD patients compared to non-psychiatric controls. Furthermore, we investigated the potential mechanisms that regulate synapsin gene expression. We showed differential expression between BD and/or MDD and controls in various synapsin variants in postmortem brains. Several regulatory mechanisms were then investigated in an attempt to understand the factors involved in the observed gene expression changes. We have identified the synapsin family of genes as new candidates for the etiology of BD and/or MDD and we have shown distinct profiles of the genes' regulation in the two related disorders.

A41

Genome-Wide Epigenetic Regulation by Early-Life Trauma

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Background. Our genome adapts to environmental influences in part through epigenetic mechanisms, including DNA methylation. Variations in the quality of the early environment associates with alterations in DNA methylation in rodents and recent data suggest similar processes in humans in response to early life adversity. Methods. Promoter DNA methylation levels in hippocampal tissue from abused suicide completers and controls were profiled using methylated DNA immunoprecipitation followed by microarray hybridization. Results were compared to corresponding genome-wide gene expression profiles. Methylation differences were validated using the Sequenom EpiTYPER platform on both neuronal and non-neuronal DNA fractions isolated by fluorescence-assisted cell sorting. Functional consequences of site-specific promoter methylation were assessed by luciferase assays. Results. We identified 362 differentially methylated promoters in individuals with a history of abuse compared to controls. Among these promoters, 248 showed hypermethylation and 114 hypomethylation. Validation and site–specific quantification of DNA methylation in the most differentially methylated gene promoters indicated that methylation differences occurred mainly in the neuronal cellular fraction. Genes involved in cellular/neuronal plasticity were among the most significantly differentially methylated and among these, Alsin (ALS2) was the most significant finding. Methylated ALS2 constructs mimicking the methylation state in samples from abused suicide completers showed decreased promoter transcriptional activity associated with decreased hippocampal expression of ALS2 variants.
Conclusion. Our results suggest that childhood adversity associates with epigenetic alterations in the promoters of several genes in hippocampal neurons.

A42

Involvement of chromatin modifications in the extreme low expression of astrocytic genes in a subphenotype of suicide completers

Corina Nagy*, Carl Ernst, Gustavo Turecki

Background: The characteristics of suicide completers, both phenotypically and genotypically, are highly heterogeneous. Recently, we have characterized a subset of suicide completers by extreme low expression in genes relating to astrocytic function. In the present study, we used this well characterized subset of suicide completers to examine epigenetic modifications that could explain low astrocytic gene expression. We focused on chromatin modifications which are stable postmortem.
Methods: A total of 184 subjects (122 suicides and 62 controls) were included in this study. Prefrontal brain samples from these individuals were screened using a combination of techniques to identify samples with extreme low expression of genes associated with astrocytic regulation. Of the 184, a total of 21 (11.4%) suicide completers and no controls met the criteria for low expression. These samples were then subjected to chromatin immunoprecipitations using antibodies against various modifications indicative of gene silencing. The enrichment was then measured using qRT-PCR.
Results: The histone modifications H3K27me3 as well as H3K9me3 were examined in 6 astrocytic genes (SOX9, GLUL, GJA1, GJB6, SLC1A3, FGFR3). One of the most interesting results was found in the SOX9 gene, which showed a significant difference in the levels of the H3K27me3 modification (p value= 0.02) when compared to controls.
Conclusion: Within a sub-phenotype of suicide completers, chromatin modifications are involved in the epigenetic regulation of genes implicated in suicide behavior.

A43

Maintaining Calcium Homeostasis in Amyotrophic Lateral Sclerosis

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Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressing neurodegenerative disease characterized by preferential loss of motor neurons, resulting ultimately in death by respiratory failure. An early and key abnormality in ALS is impaired calcium (Ca2+) homeostasis leading to elevated intracellular Ca2+, promotion of protein aggregation into inclusions, and neuronal death. Ameliorating Ca2+ dyshomeostasis might therefore forgo multiple endpoints of ALS toxicity and serve as a potential ALS therapy. My project aims to characterize the dual L/T-type voltage-gated Ca2+ channel antagonist lomerizine's neuroprotective mechanism and test its feasibility as an ALS therapy.

A44

Regulation of nuclear-cytoplasmic shuttling of FUS/TLS harboring ALS-linked mutations by arginine methylation

Michael Tibshirani*, Miranda L. Tradewell, Zhenbao Yu, Marie-Chloe Boulanger, Heather D. Durham, Stephane Richard

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease leading to preferential death of motor neurons. Recently, mutations in the gene encoding Fused in Sarcoma/ Translated in Liposarcoma (FUS/TLS) were discovered in patients with ALS type 6. FUS/TLS functions as a DNA/RNA binding protein which normally shuttles between the nucleus and the cytoplasm, demonstrating the importance of its localization for proper function. Post-mortem analysis as well as studies using cell lines have shown a retention of FUS/TLS harboring ALS-linked mutations in the cytoplasm accompanied by inclusion formation. Post-translational modifications such as methylation can influence the nucleo-cytoplasmic shuttling of various proteins. Protein Arginine Methyltransferase 1 (PRMT1) is a ubiquitously expressed arginine methyltransferase, which has been shown to regulate the nucleo-cytoplasmic shuttling of other RNA binding proteins. We have developed a murine primary culture model of ALS type6 by expressing wild-type or mutant FUS/TLS in motor neurons (the cell type most vulnerable to the disease). Our data demonstrate, that the cytoplasmic retention and inclusion formation of FUS/TLS mutants is associated with their toxicity. Furthermore, our data demonstrate an interaction between FUS/TLS and PRMT1 and that inhibition of arginine methylation of FUS/TLS by PRMT1 can influence the subcellular localization of mutant FUS and potentially reduce their toxicity.

B1

Early Growth Response 1 & Agrin: Implications for Synaptic Dysfunction in Alzheimer’s Disease

Ryen MacDonald*, Louis-Eric Trudeau, Lorraine E. Chalifour, and Hemant K.Paudel

Alzheimer’s disease (AD) is the most common form of dementia and is characterized by the deposition of senile plaques and neurofibrillary tangles (NFTs), loss and dysfunction of synapses, and neuronal death. Synaptic dysfunction occurs early in AD pathogenesis, and has been shown to strongly correlate with cognitive impairment. The 3xTg-AD mouse is a well characterized model of AD that displays age-dependant tau and amyloid pathology as well as cognitive decline. More importantly, these mice show significant synaptic dysfunction, exhibiting impaired synaptic transmission and LTP by 6 months of age, as well as a reduction in synaptic protein agrin. Agrin is a heparansulfate proteoglycan that is widely expressed in the brain, and is now understood to be involved in neurite growth and synaptogenesis. This suggests that loss of agrin may contribute to synaptic loss in 3xTg-AD mice and, possibly, in AD. The mechanisms, however, are unknown. Egr-1 is a transcription factor that is increased in AD, and is involved in the regulation of several genes implicated in the disease. In this study, we found that agrin levels are significantly increased in Egr-1-/- mice. Using the rVista program, we have located multiple putative Egr-1 binding sites on the agrin promoter. Here we show that lentiviral overexpression of Egr-1 causes a decrease in synaptic marker protein synaptophysin and in glutamate-mediated postsynaptic events in primary neurons in culture. Our data indicates that Egr-1 may regulate the protein level of agrin in the brain and suggests that increased Egr-1 levels in AD brain, by reduction of agrin, may cause synaptic loss.

B2

The role of Neogenin in Olfactory Epithelium Development

Joseph Wai Keung Kam(*), David Da Silva, Jean-Francois Cloutier

Neogenin, a structurally homolgous transmembrane protein of DCC, has now emerged as a multiple functional receptor for the development and homeostasis of both vertebrates and invertebrates. While it was first identified as a receptor for Netrin-1, it is now established that it also binds the Repulsive Guidance Molecules, and the Bone Morphogenic Protein. In the murine model, binding of Neogenin to its respective ligands is implicated to mediate muscle differentiation, bone formation, hemostasis, as well as neuronal migration and proliferation. Previous studies have reported that Neogenin is expressed in the olfactory system, but its role is yet to be characterized. We have generated the Neogenin Knock Out mice to study the role that Neogenin plays in the development of the Olfactory Epithelium. Using the Neogenin mice, we have identified its expression in the basal and apical layers of the olfactory epithelium in both embryonic and postnatal mice. Morever, findings from our studies suggest that Neogenin plays a role in the regulation of the proliferation and differentiation of olfactory epithelial progenitor cells. Thus, our finding shows that Neogenin mediates the development of the mice olfactory epithelium.

B3

GABAA Transmission Regulates Dendritic Spine Density in the Developing Hippocampus

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

The neurotransmitter ?-aminobutyric acid (GABA) plays an important role in CNS development and function. Remarkably, synaptic transmission through GABAA receptors is excitatory in immature neurons during early postnatal development. During this time, excitatory glutamatergic synapses are actively forming and maturing into dendritic spines. We investigated the effects of GABAergic transmission on the formation and stability of dendritic spines on CA1 neurons in mouse organotypic hippocampal slices. The detailed morphology of dendrites, including spines, was monitored by expressing membrane-targeted enhanced green fluorescent protein in CA1 neurons, followed by confocal microscopy and image analysis. We found that at 3 days in vitro (DIV), inhibiting GABAA receptors with bicuculline increased spine density by 33%. Driving GABAA transmission with muscimol, in contrast, decreased spine density. However, the effects of manipulating GABAA transmission on spine density were transient, and by 5 DIV inhibition of GABAA receptor transmission significantly reduced spine density. We then followed up on the differential effects of GABAA receptor inhibition on spines by monitoring the developmental time course of potassium-chloride cotransporter-2 (KCC2), which helps establish the mature Cl- gradient in neurons. KCC2 levels increased between 3 and 7 DIV, indicating that a switch in the action of GABA (excitatory to inhibitory) may coincide with the switch in the effect of bicuculline on spine density. Together, our findings indicate that early GABAA transmission regulates excitatory synapse formation in the developing hippocampus.

B4

Peripheral nerve injury is accompanied by region-specific changes in global methylation in the brain

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Background
Chronic neuropathy is accompanied by severe pain and physical disability. Chronic pain is associated with mood disorders, cognitive impairment, and alterations in cortical structure and function. Chronic pain results in long-term biological changes that are difficult to reverse, including pathological changes in gene expression. Epigenetic modifications such as DNA methylation are involved in long-term regulation of gene expression. The role of epigenetic modulation in the development and maintenance of chronic pain is currently unexplored.

Objective
Identify changes in global genome-wide DNA methylation in the brain that are induced by chronic neuropathy.

Methods
Neuropathic pain was induced in 3-month old male CD1 mice using the Spared Nerve Injury (SNI) model. Animals were tested for hypersensitivity to mechanical and cold stimuli and for motor impairment using the von Frey, acetone and rotarod tests, respectively. Animals were sacrificed and DNA was extracted from the thalamus, amygdala, prefrontal and visual cortices. The luminometric methylation assay was used to measure global genome-wide DNA methylation.

Results
Following SNI surgery, animals develop hypersensitivity to cold and mechanical allodynia and motor dysfunction. Chronic neuropathic pain is accompanied by a bilateral decrease in global methylation in the prefrontal cortex and amygdala but not in the thalamus.

Conclusions
Peripheral nerve injury induces region-specific changes in global methylation in the brain. Future studies will identify specific genes whose promoters are differentially methylated in chronic pain conditions. Changes in DNA methylation could be an important factor in the development and maintenance of chronic pain.

Acknowledgements
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B5

Infants' perception of infant vowels

Matthew Masapollo (*), Linda Polka and Lucie Menard

Speech communication requires the ability to perceive phonetic categories among discriminably different phones. To accomplish this, listeners must identify phonetic categories (vowels or consonants) among acoustic signals that vary in an array of paralinguistic, non-phonetic properties, e.g., related to speaker differences, phonetic context, speaking rate, emotion, etc. With respect to vowels, the largest source of acoustic variability is due to age and sex-related variation in vocal tract size and morphology. Prior research shows that young infants can recognize equivalence among vowels produced by and men, women, and children. It is not known whether this ability extends to infant vowel productions. The vocal tract size and related formant frequencies specifying an infant vocal tract are quite distance from both adult and child values. Moreover, most pre-vocal infants have limited exposure to infant vocalizations. The goal of the current study was to examine whether pre-vocal infants can recognize category equivalence among vowels produced by different talkers when infant vowel productions are among the variants in the set.

We implemented a category-based discrimination paradigm using the look-to-listen procedure to test 4.5 to -6.5-month-old infants. The stimuli were isolated vowels, /i/ (“ee’) and /a/ (“aw”), synthesized to simulate productions by adult men, women, children (8-, 10-, and 12-year-olds) and a 6-month-old infant. Vowels were matched in their intensity and duration; f0 was age-appropriate. On each trial repetitions of the same vowel were played when the infant fixated on a static checkerboard. Infants (n=20) were first habituated to diverse productions of /i/ produced by several adult male, female and child speakers; once the habituation criterion was met infants were presented with infant productions of /i/ (familiar vowel) and novel /a/ (novel vowel) in four test trials. Test trials followed a familiar-novel-novel-familiar order (FNNF) for half of the infants and a novel-familiar-familiar-novel (NFFN) for the other half. ALL test trials consisted of infant vowel productions. A novelty effect (looking longer to N than F) was expected if infants recognize the infant /a/ as a novel vowel despite the change to infant vocal tract parameters.

Infants displayed the expected novelty response. They looked significantly longer to the novel vowel in the first FN test trial pair ($P = 0.02$), but not in the second FN test trial pair (see Fig.1). However, infants also clearly noticed the infant vocal parameters introduced in the test trials. Infants looked significantly longer to the first test trial compared to the last habituation trial in both the FNNF ($P = 0.01$) and NFFN ($P = 0.00$) test order (see Fig 2). Looking time typically doubled when the infant vowel sounds were played.

Overall results provide preliminary evidence that infants recognize vowel categories across talker-related variation that includes infant vowel productions. Pre-vocal infants also display a high interest in vowels produced by an infant vocal tract. The findings are discussed in terms of the emergence of perceptual constancy in the development of vowel perception raising issues about how and when such knowledge is acquired in relation to the infant’s own productions.

B6

GABA synchronisation, high-frequency oscillations and epilepsy

Shabnam Hamidi, Rochelle Herrington(*), Maxime Lévesque, Gabriella Panuccio, Pariya Salami(*), Massimo Avoli

Temporal lobe epilepsy represents the most common form of partial epilepsy, in which seizures originate from the hippocampus, entorhinal cortex and amygdala. Symptoms consist of recurrent partial or secondarily generalized seizures that appear after a latent period of many months or years (which is believed to represent the epileptogenic process) from the initial brain insult (such as febrile convulsions, encephalitis, or status epilepticus). In our laboratory, we aim to better understand the cellular mechanisms of epilepsy. We perform in vitro studies on the role of GABAergic currents on the modulation of neural network synchronization during epileptogenesis and ictogenesis. Using in vivo recordings, we also study the role of high-frequency oscillations (80-500 Hz), as they are thought to reflect underlying pathological processes underlying epilepsy.

B7

Testing the role of cell cycle genes for their ability to produce hair cell regeneration in the mouse inner ear

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Hearing deficits are found in two in 1000 newborns and increase with age to affect
40% of persons over age 75. Unlike in lower vertebrates, mammalian hair cells do not regenerate when lost due to aging, noise or chemical insults. Mammalian inner ear hair cells lose their ability of proliferation shortly after birth. It is thought that this quiescent state is maintained by the ongoing expression of negative cell cycle genes.

Recent studies identified the retinoblastoma (Rb) gene as key for cell cycle exit of inner ear hair cells. Although knocking out Rb led to hair cell proliferation, the new hair cells died by apoptosis. This study highlights the importance of negative cell cycle genes as targets for hair cell regeneration and the need to identify other key cell cycle genes.

When hair cells die, the inner ear sensory epithelia remains populated by supporting cells. Therefore, supporting cells are the key targets for inducing hair cell regeneration. Our goal is to identify negative cell cycle genes with ongoing expression in mouse inner ear supporting cells and test the hypothesis that disrupting their expression will lead to cell proliferation. Toward this goal, we have identified 20 putative supporting cell cell-cycle genes by comparing gene chip data of gene expression in hair cells and inner ear supporting cells. We are in the process of verifying their expression using RT-PCR and in situ hybridization. The next step will be to use siRNA in cultured inner ear organs to test the role of these genes in hair cell proliferation.

B8

Differential effects of early life maternal care on synaptic plasticity in the dorsal and ventral hippocampus

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Naturally occurring variations in early life maternal care produce distinct cognitive phenotypes which persist into adulthood through the modulation of hippocampal development and function. Previous studies have shown that adult rat offspring which received low maternal care (Low LG) displayed a reduction in magnitude of long term potentiation (LTP) in the dorsal hippocampus, associated with impaired spatial cognition. However, these animals display enhanced performance in a hippocampal-dependent fear memory task, which is proposed to be more closely associated with ventral hippocampal function. Intriguingly, the ventral hippocampus is distinct in its regulation of synaptic plasticity, although whether maternal care alters ventral LTP is unknown. Here, we present evidence that the early life environment differentially programs hippocampal function along the dorsal-ventral axis by enhancing LTP formation in the ventral CA1 in low LG offspring relative to high LG offspring. That a single early life environmental signal can result in opposite phenotypes in the dorsal and ventral hippocampus reinforces the distinction of the ventral hippocampus as a functionally and developmentally segregate structure. Developmentally, low levels of early life maternal care arising from a hostile rearing environment may serve as a signal to bias the low LG offspring towards a qualitatively distinct form of hippocampal cognition, a signal which may be transduced through or overlap with developmental mechanisms responsible for the longitudinal segregation of the hippocampus.

B9

EXPRESSION AND REGULATION OF GDNF RECEPTOR GFR?1 IN THE BASOLATERAL AMYGDALA OF DEPRESSED SUICIDES

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Multiple lines of evidence suggest that structural and functional alterations of the amygdala, including changes in dopaminergic transmission, may contribute to the etiology of depression. Glial cell line-derived neurotrophic factor (GDNF), a potent pro-survival factor for dopaminergic neurons, has likewise been implicated in depression, with whole blood and serum levels varying significantly with mood states. Furthermore, recent evidence from animal models suggests that central GDNF expression is associated with individual differences in resilience following stress. However, little attention has been paid as to whether central GDNF expression, particularly in limbic brain regions, is altered in depression and suicide. In the present study, we employed Western blotting to assess protein expression, and real-time polymerase chain reaction (qPCR) to quantify mRNA, of GDNF and its principal receptor, GFR?1, in the basolateral amygdala (BLA) of well-characterized depressed suicides (DS) and matched sudden-death controls (SDC). While GDNF protein and mRNA did not differ between groups, the DS group displayed a significant reduction in GFR?1 protein expression compared to SDCs (fold change: -1.24; $p = 0.002$). Unexpectedly, no significant differences in GFR?1 gene expression were found between groups, suggesting post-transcriptional regulation. We then tested the hypothesis that microRNAs (miRNAs) may be affecting GFR?1 protein expression through translational repression without altering total GFR?1 mRNA levels. We first identified candidate miRNAs predicted to target the 3' UTR of GFR?1 by using five target prediction programs. We only chose miRNAs expressed in the brain and whose binding was predicted by at least 4 databases. Expression of these candidate miRNAs in BLA was then quantified using qPCR. Two miRNAs were found to be significantly up-regulated in the DS group: hsa-miR-511 (fold change: 1.6; $p = 0.049$) and hsa-miR-340 (fold change: 1.8; $p = 0.028$). Additionally, there was a trend toward increased hsa-miR-511 expression being associated with decreased GFR?1 protein levels ($r = -0.46$; $p = 0.054$). Taken together, these results suggest that the decreased GFR?1 expression observed in the BLA of DS individuals may be mediated by miRNA regulation of protein translation. We are currently investigating whether overexpression or knock-down of these miRNAs are sufficient to alter GFR?1 protein expression in a human neuronal cell line.

B10

Peripheral neuregulin-1 administration increases hippocampal neurogenesis and induces delayed antidepressant effects

Ian Mahar*, Stephanie Tan, Maria? Antonietta? Davoli, Sergio Dominguez-Lopez, Calvin Qiang, Adeline Rachalski, Gustavo Turecki, Naguib Mechawar

Introduction
The neurotrophic factor neuregulin-1 (NRG1) is involved in many aspects of brain development, from cell fate determination to neuronal maturation. However, little is known of NRG1's influence on neurodevelopmental processes in the adult hippocampus. Adult hippocampal neurogenesis has been implicated in the mechanism of antidepressant effects, and neurotrophic factors can mediate the neurogenic changes underlying these effects. We hypothesized that peripheral NRG1 administration would increase cell proliferation and neurogenesis in the dentate gyrus (DG) of the hippocampus, and that these changes would be accompanied by antidepressant effects.
Methods
Adult male C57BL/6 mice were implanted with subcutaneous mini-pumps mini-pumps administering either 0.9% saline (controls) or NRG1? (10 µg/day in 0.9% saline) for 24h (proliferation experiment) or 72h (neurogenesis experiment). Mice also underwent behavioral testing (forced swim test and locomotor testing), 28d after treatment or acutely after 24h of i.p. injections. Expression of NRG1 receptors ErbB3 and ErbB4 in newborn dentate gyrus cells was assessed at various time points between cell birth and maturity. Phenotype of ErbB3-expressing progenitor cells was characterized with cell type-specific markers using nestin-GFP transgenic mice.
Results
Subchronic peripheral NRG1? administration selectively increased cell proliferation (by 71%) and neurogenesis (by 50%) in the caudal dentate gyrus within the ventral hippocampus. This pro-proliferative effect did not alter neuronal differentiation and may have been mediated by ErbB3 receptors, which were expressed by newborn dentate gyrus cells from cell division to maturity and colocalized with SOX2 in the subgranular zone. Furthermore, four weeks after cessation of subchronic treatment, animals displayed robust antidepressant-like behavior in the absence of changes in locomotor activity, whereas acute treatment did not produce antidepressant effects.
Conclusions
These results show that NRG1? has pro-proliferative, neurogenic and antidepressant properties, further highlight the importance of peripheral neurotrophic factors in neurogenesis and mood, and support the role of hippocampal neurogenesis in mediating antidepressant effects.

B11

Cytokine expression in the gray and white matter anterior cingulate cortex of depressed suicides

Susana Torres-Platas*, Giamal Luheshi, Gustavo Turecki & Naguib Mechawar

Background: Recent work done by our group showed the presence of hypertrophic astrocytes in the ACC white matter of depressed suicides suggesting alterations in the immune system in this zone. This astrocytic remodelling occurs in the white matter independently of the adjacent gray matter suggesting that inflammatory responses may be autonomously regulated. In this study we sought the levels of some inflammatory mediators of the immune system by absolute quantification in real time PCR, and determine the differences between gray matter and white matter in ACC of the same depressed suicides compared to non-psychiatric controls.

Methods: Postmortem ACC samples (BA24) from 10 well-characterized depressed suicides and 10 matched sudden-death controls were obtained from the Quebec Suicide Brain Bank. White and gray matter were dissected independently and absolute quantification of mRNA levels were of some proinflamamtory (Il-1?, IL-6 & TNF-?), antiinflammatory (IL-1RA, IL-10) cytokines as well as some receptor (IL-1R1, TLr-2) and some markers of astrocytic (GFAP) and microglia (IBA1) activity were determined by qRT- PCR, using ?-actin as an endogenous control.

Results: We found that IL-1?, and its antagonist IL-1RN were both significantly increase in the gray matter and significantly decreased in the white matter of depressed suicides when compared to controls. GFAP expression in the gray matter presented significant downregulation in depressed suicides, with an average value 25-fold lower than in controls. GFAP expression in the white matter was higher in depressed suicides compared to control, but this increase did not reach significance. TNF-? presented a 3-fold significant decrease in it mRNA levels in the BA24 white matter of depressed suicides when compared to controls.

Conclusions: The alteration of proinflamamtory and anti-inflammatory cytokines in ACC BA24, showed that the immune system is centrally altered in depressed suicides. These alterations are differentially regulated between the gray and white matter.

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B12

Tyrosine-specific regulation of the RhoGEF Trio in Netrin-1/DCC-stimulated signalling pathways during axon outgrowth

Jonathan DeGeer*, Jérôme Boudeau, Susanne Schmidt, Fiona Bedford, Anne Debant, and Nathalie Lamarche-Vane

During development, neurons extend axons towards their appropriate targets in a process mediated by extracellular cues. Netrins are a family of secreted proteins that act as bifunctional guidance cues, promoting either the attraction or repulsion of the growth cone of extending axons. In the developing spinal cord and brain of vertebrates, netrin-1 exerts its attractive functions by the receptor Deleted in Colorectal Cancer (DCC). Upon netrin-1 stimulation, DCC becomes phosphorylated by the Src-kinase protein Fyn, leading to downstream activation of the small GTPase Rac1. Recently, we have identified the RhoGEF Trio as essential in mediating Rac1 activation downstream of netrin-1/DCC in axon outgrowth and guidance. In this study, we have investigated whether Fyn regulates Trio function by phosphorylation. By over-expressing Trio and Fyn in HEK293 and N1E-115 neuroblastoma cells, we confirmed that Trio is a substrate of Fyn-mediated phosphorylation. We demonstrated that Trio phosphorylation by Fyn is potentiated by co-expression of DCC, while C-terminal truncations of DCC intracellular domain diminish this phenomenon. Furthermore, we have identified Y2622 of Trio as a Fyn phosphorylation site in vitro, and show that the expression of the phospho-null Trio-Y2622F mutant is sufficient to significantly impair Fyn-mediated Trio phosphorylation in N1E-115 cells. Expression of the Trio-Y2622F mutant in N1E-115 cells results in reduced neurite outgrowth relative to the expression of wild-type Trio, and Trio-Y2622F also impairs DCC-mediated neurite outgrowth upon co-expression with DCC. However, the Y2622F mutation does not affect the ability of Trio to activate Rac1 in HEK293 cells. Studies in the developing rat cortex reveal that Trio isoforms are tyrosine-phosphorylated in vivo upon netrin-1 stimulation in a Src-kinase-dependent manner. Furthermore, we show that DCC, focal adhesion kinase (FAK), and p21-activated kinase (PAK) co-immunoprecipitate with Trio from extracts of rat embryonic cortices treated with netrin-1, following the same kinetics of Trio tyrosine phosphorylation. Work is in progress to examine the effect of Trio-Y2622F expression on netrin-1-mediated axon outgrowth in embryonic cortical neurons. Taken together, these data support a novel regulatory mechanism wherein Trio tyrosine 2622 phosphorylation by Src protein kinases is acting to recruit DCC signalling protein complexes upon netrin-1 stimulation to mediate its cellular effects on axon outgrowth.

B13

THE INFLUENCE OF FEVER AND INFLAMMATION ON PERIPHERAL CLOCK GENE EXPRESSION

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Objectives: The circadian clock is a 24-hour biological timer regulating most physiological systems through a series of interlinked transcriptional regulators termed core clock components. The master clock resides in the suprachiasmatic nucleus (SCN) and maintains synchrony among peripheral oscillators through a unique, yet unknown, set of humoral, behavioural and/or neurological cues. Recently, the proinflammatory factors interleukin-6 (IL-6) and prostaglandin E2 (PGE2) were proposed to influence peripheral clock dynamics, raising the possibility that fever and inflammation affect clock function.

Our aim is to elucidate the time-dependent effects of fever and inflammation on core clock components in peripheral tissues and understand the mechanism accounting for these effects.

Methods: Turpentine oil (TURP) injected into the hind leg of rats is a model of inflammation and fever. After the formation of a local abscess, one proinflammatory cytokine – IL-6 – is released systemically inducing PGE2 expression in the brain resulting in fever. To assess the impact of TURP on clock dynamics, the core clock components Per1, Per2, and Reverb? in peripheral tissues were examined using quantitative PCR.

Results: We found that the time of TURP treatment affects the magnitude of cytokine response and clock gene expression. We show that animals treated with TURP at different times over 24hrs have the greatest IL-6 induction in the early night corresponding to the greatest deviation in clock gene expression. Further, the magnitude and time of sensitivity of clock gene expression to TURP treatment varied between peripheral tissues examined. Further, suppressing IL-6 expression with exogenous hrIL-1ra rescued some of the alterations in Per1 and Per2 caused by TURP, defining a possible of IL-6 in the deviations of clock gene expression to inflammation.

We intend to investigate the specific effect of PGE2 on clock gene expression by suppressing PGE2 expression with the COX-2 inhibitor celecoxib. Finally, we will investigate whether IL-6 and/or PGE2 act directly on liver using primary hepatocyte cultures treated with exogenous IL-6 or PGE2.

Conclusions: The time of day of TURP injection affects the responsiveness of both the proinflammatory cytokine induction and peripheral clocks. Further, the changes in clock gene expression correlate with the maximal responsiveness of cytokines and are tissue-specific. Using pharmacological techniques, we have established a possible role of IL-6 in the changes in clock gene expression but whether this effect is due to direct action on the peripheral organs or through a systemic response remains to be determined.

B14

Circadian variation of T cell response

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Circadian variations in white blood cell counts and in infection-induced mortality have been shown in rodents and in humans. Cytokine secretion by innate immune cells in vitro has been shown to demonstrate a circadian variation, giving clues that there are functional aspects of the immune response under circadian control. The adaptive immune response begins in the lymph node, where antigen is presented to T cells, causing them to proliferate and gain the effector function that allows this specific immune response to control infection. However, little is known about the timing of T cell-mediated events.
We show that there is a circadian variation in T cell proliferation in response to stimulation of the T cell receptor (TCR) in vitro. We show that the core TCR signalling molecule ZAP-70 is expressed rhythmically, suggesting that it plays a role in this rhythmic response. Strikingly, T cells respond in a time-dependent in mice immunized with peptide at different times of day, which has important implications in the development of more efficient vaccination strategies.

B15

Alpha- and beta-adrenergic receptors differentially modulate the emission of spontaneous and amphetamine-induced 50-kHz ultrasonic vocalizations in adult rats

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Amphetamine (AMPH) increases adult rat 50-kHz ultrasonic vocalizations, preferentially promoting frequency-modulated calls that have been proposed to reflect positive affect. The main objective of the present study was to investigate a possible noradrenergic contribution to AMPH-induced calling. Adult male Long-Evans rats were tested with AMPH (1 mg/kg IP) or saline combined with various systemic pretreatments: clonidine (alpha2 adrenergic agonist), prazosin (alpha1 antagonist), atipamezole (alpha2 antagonist), propranolol, betaxolol and/or ICI 118,551 (beta1/beta2, beta1, and beta2 antagonists, respectively), nadolol (beta1/beta2 antagonist, peripheral only) or NAD-299 (5HT1A antagonist). In addition, effects of cirazoline (alpha1 adrenergic agonist) and cocaine (0.25-1.5 mg/kg IV) were studied alone. AMPH-induced calling was suppressed by low-dose clonidine and prazosin. Cirazoline and atipamezole did not significantly affect calling rate. Propranolol, without affecting the call rate, dose-dependently promoted “flat” calls under AMPH while suppressing “trills”, thus reversing the effects of AMPH on the call subtype profile. This effect of propranolol appeared to be mediated by simultaneous inhibition of CNS beta1 and beta2 rather than 5HT1A receptors. Finally, cocaine elicited fewer calls than AMPH but produced the same shift in the call subtype profile. Taken together, these results reveal differential drug effects on flat vs. trill vs. other frequency-modulated 50-kHz calls. These findings highlight the value of detailed call subtype analyses, and show that 50-kHz calls are associated with adrenergic alpha1 and beta receptor mechanisms. These preclinical findings suggest that noradrenergic contributions to psychostimulant subjective effects may warrant further investigation.

B16

Monetary Reward Affects Subjective but not Physiological Pain Responses

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Rewarding stimuli have shown analgesic effects in humans and animals. Most human studies have investigated the influence of rewarding stimuli on subjective pain ratings but not on other pain responses like physiological reactions. We conducted a psychophysical study to compare the effects of monetary reward on both subjective and physiological pain responses.

Eleven healthy volunteers (five males) participated in a study with a wheel of fortune decision making task. In 48 trials, after the wheel spin participants received feedback on whether they had won (winning condition), lost (losing condition) or had neither won nor lost money (neutral condition). In 27 of these trials, a short thermal stimulus (2s) was applied to the participant's leg whilst being presented with the outcome of the wheel. The stimulus was either warm (control), mildly or moderately painful. After each thermal stimulation, participants rated the intensity and unpleasantness of the sensation on a visual analogue scale, indexing subjective pain perception. As an indicator for physiological pain responses, skin conductance was recorded throughout the experiment.

Winning or losing money affected subjective pain intensity ratings with higher ratings in the losing than in the winning condition for both painful temperatures. For the mildly painful temperature, pain intensity ratings were higher in the neutral condition than in the winning condition and lower than in the losing condition. Subjective pain ratings did not differ between the conditions for the warm (control) temperature. Similarly to the intensity ratings, stimulation was rated less unpleasant in the winning than in the losing condition for the painful temperatures; and unpleasantness was not different between conditions for the warm temperature.

In accordance with the subjective pain ratings, mean skin conductance responses (averaged over all conditions) were largest with moderately painful stimulation and smallest with warm thermal stimulation. In contrast, mean skin conductance responses did not differ between the winning, losing, and neutral conditions for any of the temperatures.

The findings show that monetary reward and loss affected subjective pain perception, with reward causing hypoalgesic effects and loss causing hyperalgesic effects, while physiological pain responses were unaffected. If replicated in a larger sample, the results suggest dissociative effects of rewarding stimuli on different dimensions of pain processing.

B17

Trk-dependent ADAM17 activation facilitates neurotrophin survival signaling.

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Signaling by TrkA and TrkB receptor tyrosine kinase is required for peripheral neuron survival. TrkA and TrkB signaling is facilitated by the p75 neurotrophin receptor (p75NTR), a member of the tumor necrosis factor (TNF) receptor superfamily, through mechanisms that remain obscure. Here, we demonstrate that TrkA and TrkB induces MEK-dependent phosphorylation of the transmembrane cysteine protease ADAM17 (a disintegrin and metalloprotease 17) at the intracellular residue threonine 735. Phosphorylation at this site activates ADAM17 and causes cleavage of p75NTR and production of the receptors' intracellular domain (p75NTR(ICD)) in PC12 cells and in primary cerebellar granule neurons. We show that Trk-induced ADAM17 phosphorylation and generation of the p75NTR(ICD) is required for neurotrophin-induced Erk and Akt activation and for neurotrophin-dependent survival signaling. Survival of PC12 cells maintained in 10 ng/ml nerve growth factor drops by 47% in cells depleted of ADAM17; this survival deficit is resolved if the p75NTR(ICD) is overexpressed in the ADAM17 depleted cells. These studies identify a novel signaling circuit in which Trk activates ADAM17-dependent p75NTR(ICD) production to feedback to sustain Trk signaling and Trk-dependent survival.

B18

In Vivo Imaging of Neuroprotection in Stroke: In Search of the Penumbra

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Functional imaging is vital to the diagnosis and treatment of stroke; however, current imaging methods lack refinement, requiring a battery of tests in order to assess an individual's prognosis. While positron emission tomography remains the gold standard in stroke imaging, multiple parameters are needed in order to operationally define the penumbra. There is a need for a more definitive way of identifying this area so that precious resources are saved, thereby allocating more time to treating a patient rather than submitting him or her to an array of tests. The proposed study develops a procedure to label erythropoietin, an endogenous cytokine that is upregulated in hypoxic tissue, with the radionuclide [18F] to assess its effectiveness in revealing damaged, yet viable, brain tissue in an animal model of stroke. The imaging parameters for [18F]-Erythropoietin will be determined, specifically the optimal post-stroke administration time and the post-injection peak binding time. It is hypothesized that [18F]-Erythropoietin will cross the blood-brain barrier and bind to the erythropoietin-ßc-heteroceptor complex that is expressed in the ischemic penumbra, thus leading to a novel method to image this region. The peak binding will most likely occur several hours after [18F]-Erythropoietin is injected into the blood stream, as it will take some time for the molecule to penetrate the blood-brain barrier. If successful, this technique may be used to identify the progress of damage after acute ischemic stroke. Establishing a novel penumbra tracer will enable clinicians to determine whether living tissue still exists in patients, thereby expediting the decision of whether to proceed with approved therapies.

B19

Early alterations in cytokine expression highlight the potential for glial cell influence in the developing stages of Alzheimer`s disease

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Inflammation is well known to be a key feature in the late stages of Alzheimer's disease (AD). However, increasing evidence points to the involvement of specific cytokines, classically regarded as inflammatory mediators, in the prodromal stages of the disease. In addition, early stages of AD progression involve synaptic dysfunction, as illustrated in transgenic AD models such as the TgCRND8 mice. Indeed, these mice show an increase in hippocampal network excitability by 1.5-2 months of age (Del Vecchio et al., Neurosci. Lett. 2004). Considering the role of cytokine, TNF-?, in the control of network excitability through synaptic scaling, we hypothesized that TNF-? induction precedes the previously reported hippocampal network dysfunctions. To investigate the level of TNF-?, as well as its putative cellular source in the hippocampus of 1-month-old TgCRND8 mice (1-mo-Tg), TNF-? expression was measured by ELISA on hippocampal extracts. Subsequently, immunohistochemistry was performed on serial, 20 ?m-thick hippocampal sections from 1-mo-Tg for phenotyping of microglia (CD11b) or astrocytes (GFAP). All studied parameters were assessed in parallel with non-transgenic (NTG) controls from the same litter. An additional control consisted of using hippocampal tissue from 6-7 month TgCRND8 mice (6-7 mo-Tg) displaying overt neuroinflammation (Jimenez et al., J Neurosci. 2008). We found a significant ($p<0.05$) increase in TNF-? expression in 1-mo-Tg in comparison to 1-mo-NTG. Interestingly, the magnitude of this increase (about 3-fold) was the same as that observed between 6-7 mo-Tg and their NTG littermates. Initial immunohistochemical experiments in 6-7 mo-Tg revealed the presence of astrocytes and microglia, but were inconclusive for 1-mo-Tg. Altogether, this data points to a very early, AD-related deviation in TNF-? expression. Experiments are currently underway to determine the precise glial source of elevated TNF-? and to characterize the associated glial state both biochemically and morphologically across the different groups. Supported by CIHR to RQ.

B20

White-matter Organization after Early Auditory Deprivation revealed by Magnetization Transfer Imaging

Martha M. Shiell*, François Champoux, Bruce Pike, Robert J. Zatorre

Previous neuroanatomical research with deaf people has been driven by the hypothesis that auditory deprivation leads to changes in auditory cortical regions. This hypothesis has been explored through magnetic resonance imaging (MRI) techniques such as voxel-based morphometry (VBM) and volumetry. However, previous applications of these techniques have produced inconsistent results. For example, using VBM to compare deaf and hearing people, Penhune et al. (2003) found preserved white matter (WM) and grey matter (GM) density in auditory regions of deaf people, and increased GM density in the left motor hand area, whereas Shibata (2007) found decreased WM density in the left posterior superior temporal gyrus and no differences in motor areas. Volumetry of auditory regions in the deaf uncovered bilateral decreased WM in Heschl's gyrus (Emmorey et al., 2003).
In an effort to disambiguate previous research, we used magnetization transfer imaging (MT), an MRI technique that is sensitive to WM myelination (Schmierer et al., 2004). Because MT is quantitative and closely related to myelination, it allows for a more specific interpretation of differences in WM density that are uncovered by VBM. We hypothesized that changes in WM density, as revealed by VBM, may reflect changes in myelination; therefore, we expected to find some overlap in the regions identified by these two techniques. We also hypothesized that MT captures differences in WM microstructure that are not evident through VBM.
Seventeen early-deaf and 17 hearing control participants were tested. Early-deaf participants had either congenital or acquired deafness before the age of 10 months, and were profoundly deaf. Groups were matched for age and gender. Participants were scanned in a Siemens Magnetom 3T MRI scanner using a T1-weighted sequence and two gradient echo sequences: with and without an MT saturation pulse, respectively. T1 images were registered to MNI standard space with a 12-parameter linear transformation (Grabner et al., 2006) and corrected for RF inhomogeneity (Sled et al., 1998). GM, WM, and cerebrospinal fluid were classified to create three separate images (Tohka et al., 2004).
The percent signal change between MT saturated and non-saturated images was calculated in order to obtain MT ratio (MTR) images (Pike, 1996). The MTR images were then non-linearly registered to standard space (Mazziotta et al., 2001). Finally, MTR, as well as GM and WM images, were convolved with a 3-dimensional Gaussian blurring kernel with 8-mm full-width-half-maximum. Differences between deaf and hearing groups were calculated in a voxel-wise manner using Surfstat software (http://www.math.mcgill.ca/keith/surfstat/). All results are reported uncorrected, $p < 0.001$.
Increased MTR, independent of a difference in WM density, was found in the right hemisphere planum temporale of deaf people, as compared to hearing. Deaf and hearing people displayed a converse increase and decrease in WM and GM density in the right, posterior middle temporal gyrus. An increase in WM density and in MTR was found in deaf people compared to hearing in the superior division of the right lateral occipital cortex, an area that has not typically been identified in previous research as a site of reorganization. These three anatomical changes were unrelated to sign language and hearing aid use, or the etiology of deafness.
The current results demonstrate both the complementary and independent natures of MT and VBM techniques. These techniques converge to reveal a change in a visual cortical area that may reflect increased myelination in deaf people. This change in myelination may be related to compensatory changes in the visual system after auditory deprivation, the nature of which remains to be specified.

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B21

Pre-clinical burnout symptoms among healthy workers and students are consistently associated with increased allostatic load and decreased morning cortisol responses

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Background: Chronic stress causes cortisol to strain many biological systems in a measurable process called allostatic load (AL). Using a clinical AL algorithm, we investigated whether burnout could be distinguished from depression that shares similar symptoms but a different biological signature. Concordantly, higher AL was hypothesized to be associated with increased chronic stress, burnout symptoms, and hypoactive diurnal cortisol levels.

Methods: Study 1 included fifteen neuroendocrine, immune, metabolic, and cardiovascular biomarkers from 30 healthy workers. Study 2 included twenty biomarkers collected from 86 young adults working and/or studying. Biomarker values were transformed into an AL algorithm based on clinical norms and grouped. Diurnal cortisol was measured at five time points (awakening, 30 minutes after awakening, 2:00PM, 4:00PM, and before bedtime) over two days. We also administered questionnaires of chronic stress, burnout, and depression.

Results: Results from Study 1 and Study 2 collectively demonstrate that increased AL is associated with increased chronic stress and burnout symptoms. The High AL group demonstrated lower morning cortisol levels compared to the Low AL group (Study 1) and compared to a Medium AL group (Study 2).

Conclusions: These findings provide support for the utility of a clinical AL index that is sensitive to physiological recalibrations intermittently observed in burnout research. If burnout is indeed characterized by hypocortisolism, than commonly prescribed anti-depressant treatment could be deleterious, as they decrease cortisol. The incorporation of AL algorithms tailored for clinicians and the use of salivary cortisol sampling might prove beneficial in informing refined diagnosis, treatment, and preventative strategies.

B22

Functional Interaction and Antagonistic Roles of NF-kappaB and Hes6 in the Regulation of Cortical Neurogenesis

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The involvement of nuclear factor-kappaB (NF-?B) in a number of processes in the postnatal and adult brain, ranging from neuronal survival to synaptogenesis and plasticity has been documented. In contrast, little is known about the functions of this pleiotropic transcription factor during early phases of brain development. It is shown here that NF-?B signaling is activated in cortical neural progenitor cells in the developing pallium. Blockade of NF-?B activity during cortical neurogenesis leads to premature neuronal differentiation and depletion of the progenitor cell pool. Conversely, NF-?B activation causes an arrest/delay of cortical neuronal differentiation and expansion of the progenitor cell compartment. This effect is antagonized by the pro-neuronal transcription factor, Hes6, which is expressed in cortical progenitor cells in which NF-?B signaling is activated and physically and functionally interacts with RelA-containing NF-?B complexes. In turn, NF-?B exerts an inhibitory effect on the ability of Hes6 to promote neuronal differentiation. These results reveal previously uncharacterized functions, and modes of regulation, for NF-?B and Hes6 transcription factors during cortical neuronal development.

B23

The CA3 area contains distinct slow-theta oscillators at the dorsal and ventral regions in the complete hippocampus in vitro.

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The hippocampus is functionally heterogeneous along the longitudinal axis; memory function occurs predominantly dorsally whereas emotional-related processing takes place ventrally. Although, significant differences in connectivity and molecular heterogeneity are present along this axis, it remains unknown if two separate networks are present dorso-ventrally. We demonstrate that two independent slow theta oscillators are present at dorsal and ventral ends of the hippocampus since these areas display low coherence (0.39±0.03, n=78), have distinctive properties such as: power (dorsal 17.1±3.1 kμV2 vs ventral 47.8±7.6 kμV2; n=78, p<0.001), frequency (dorsal 2.13±0.07 Hz vs ventral 2.34 ± 0.08 Hz; n=78, p<0.05) and oscillation strength (dorsal 37.2±1.2 vs ventral 42.7±1.3; n=78, p<0.01). Both oscillators were generated through the activation of AMPA and GABA A receptors, but NMDA receptors played a more prominent role ventrally than dorsally as assessed by its greater sensitivity to the NMDA receptor antagonist AP-5 (50 μM) (paired t-test, n=17, p< 0.001) or the NR2B subunit antagonist RO 25-6981 (5 μM) (paired t-test, n=6, p<0.01). Interestingly, it was found that rapidly increasing [Ca 2+]o from 2 to 4mM for 3 minutes, a classic protocol to induce LTP in slices, induced a long-lasting and rapid NMDA receptor-dependent increase in dorso-ventral coherence (from 0.35±0.08 to 0.77±0.05 n=6, p<0.01) suggesting that coherence along this axis between these two oscillators can be modulated as a function of plasticity. Finally, we investigated if one oscillator was able to lead the other. In control conditions, the dorsal oscillator usually led the ventral section by 36.1±15 ms, n=6. However, after the NMDA-dependent increase in coherence, the ventral section usually led the dorsal oscillator by 24.8±26.2 ms, n=6. Taken together, these data provide the first physiological evidence in vitro to support for the existence of the sub-regional network heterogeneity along the dorsal-ventral CA3 axis and provide evidence of the dynamics underlying their interaction.

B24

Fast and slow gamma rhythms are intrinsically and independently generated in the subiculum

Jesse Jackson*, Romain Goutagny & Sylvain Williams

Gamma rhythms are essential for memory encoding and retrieval. Despite extensive study of these rhythms in the entorhinal cortex, dentate gyrus, CA3 and CA1, almost nothing is known regarding their generation and organization in the structure delivering the most prominent hippocampal output: the subiculum. We show using a complete rat hippocampal preparation in vitro, that the subiculum intrinsically and independently generates spontaneous slow (25-50Hz) and fast (100 -150Hz) gamma rhythms during the rising phase and peak of persistent subicular theta rhythms. These two gamma frequencies are phase modulated by theta without any form of afferent input from the entorhinal cortex or CA1. Subicular principal cells and interneurons both phase lock to fast and slow gamma and are independently phase modulated by each form of gamma rhythm, enabling selective participation in neural synchrony at both gamma frequencies at different times. Fast GABAergic inhibition is required for the generation of fast gamma whereas slow gamma is generated by excitatory and inhibitory mechanisms. In addition, the transverse subicular axis exhibits gamma rhythm topography with faster gamma coupling arising in the distal subiculum region. The subiculum therefore possesses a unique intrinsic circuit organization that can autonomously regulate the timing and topography of hippocampal output synchronization. These results suggest the subiculum is a third spontaneous gamma generator in the hippocampal formation (in addition to CA3 and the entorhinal cortex), and these gamma rhythms likely play an active role in mediating the flow of information between the hippocampus and multiple cortical and subcortical brain regions.

B25

Impact of time based cross-correlation variations on functional connectivity and network stability

*Dickinson P, Bellec P

There is a growing interest in using resting state data derived from functional magnetic resonance imaging as a fundamental aspect of neuroimaging research. The identification of stable networks during resting state procedures has reinforced and driven this line of inquiry. In most studies, however, the calculation of connectivity is based on a single value of correlation between any two regions. This implies there is an indirect assumption that there is a fixed level of connectivity between the measured regions over time. The objectives of this preliminary study are to examine the variability of correlation coefficients over time; to determine whether the connectivity within stable networks varies coherently; and to determine the impact of time-variant correlational coefficients on network formation and stability. Based on initial observations there is a significant variability in the correlation between any two regions over time. To develop greater precision and accuracy the algorithms that are incorporated to identify stable networks and connectivity patterns should take the correlational variability into account.

B26

Altered Synaptogenesis, Synapse Function, and Synaptic Plasticity in Mice Lacking Receptor Protein Tyrosine Phosphatase Sigma

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The LAR subfamily of receptor protein tyrosine phosphatases in vertebrates comprises LAR, RPTP?, and RPTP?. Of these three, RPTP? is particularly widely expressed by neurons in the developing and mature mammalian CNS. Previous studies indicate that LAR and RPTP? promote axon extension and synaptogenesis during development, and that RPTP? promotes synaptic plasticity in the mature brain. RPTP?? has also been implicated in synaptogenesis, yet in contrast to the growth-promoting functions described for LAR and RPTP?, RPTP? is a receptor for chondroitin sulfate proteoglycans that inhibits axon extension during development and axon regeneration in the injured mature CNS. Addressing RPTP? function in the intact brain, we demonstrate that RPTP? is enriched in synaptosomes isolated from developing and adult CNS. In addition to pre-synaptic RPTP? promoting synaptogenesis, we report RPTP? enrichment in dendritic post-synaptic densities. RPTP? knockout mice exhibit increased synapse density in vitro, increased dendritic spine density and length in vivo, and increased mossy fiber axon sprouting as a result of aging or induced by seizure. RPTP? null mice also exhibit an increased frequency of miniature AMPA excitatory post-synaptic currents, greater paired-pulse facilitation, and reduced long-term potentiation at hippocampal Schaffer collateral-CA1 synapses, while behavioral testing identified enhanced recognition memory. Our findings, and previous reports by others, indicate that RPTP? and the Nogo receptor NGR1, receptors for the two major classes of inhibitors of axonal regeneration, chondroitin sulfate proteoglycans and myelin-associated inhibitors respectively, are both associated with synapses in the central nervous system and function to regulate structural and functional synaptic plasticity.

B27

Digital Nanodot Gradient

Sebastien G. Ricoult*, Mateu Pla-Roca, Roozbeh Safavieh, Monserratt Lopez-Ayon, Peter Grütter, Timothy E. Kennedy and David Juncker

We introduce an easy, low cost, and massively parallel nanopatterning method based on lift-off nanocontact printing using disposable polymer masters. We demonstrate its potential by simultaneously patterning 64 digital nanodot gradients (DNGs) on a glass slide, each comprising of up to 419,790 200-nm-dots of proteins and with a dynamic range of up to 4,400. Chemotaxis studies of C2C12 cells on DNGs of the RGD peptide validate DNGs for use in biological studies.

B28

Auditory speech processing in the visual cortex of congenitally blind adults

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Visual cues play an important role in the development of speech perception. Deprived of the visual correlates of articulatory gestures, congenitally blind speakers rely only on the auditory and somatosensory modalities to perceive speech. In order to test whether visual brain areas might be recruited in a compensatory cross-modal manner during speech perception, we here focus on the neural substrates of vowel perception in both congenitally blind and sighed adults. To identify possible cross-modal auditory-visual loops involved in predictive coding during vowel perception, we used a repetition suppression (RS) paradigm while measuring neural activity with functional magnetic resonance imaging (fMRI). Two groups of congenitally blind and sighted adults (N1 = 10, N2=10) participated to the fMRI study. As compared to sighted adults, vowel perception involved specific activation of the visual system. Furthermore, suppressed responses during repeated listening were bserved in these regions suggesting a role of the visual system in predictive coding of repeated auditory stimuli. Altogether, these results provide clear evidence for cross-modal plasticity due to early visual deprivation of the neural networks involved in speech perception.

B29

Functional differentiation of the insular cortex: Evidence from speech, language and cognitive processing.

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The insular cortex is located within the lateral sulcus of the brain, completely covered by the frontal, temporal and parietal opercula. Neuroanatomically, the insula sends and receives projections (generally reciprocally) to and from multiple cortical and subcortical sites along its length. Studies of human and nonhuman primates implicate the insular cortex in a wide range of visceral, autonomic, sensorimotor and cognitive functions. Modern functional neuroimaging studies employing a range of speech and language tasks such as syllable and word repetition, sentence production, propositional and nonpropositional speech, verbal fluency, word stem completion, sentence or word generation and reading aloud often report insular activation. More recently insular function has been associated with mirror neuron system properties for emotional recognition and empathy as well as performing a transformational or coordinating function between language processing and speech motor output. Such diverse functions within and across behavioral domains in a single brain structure suggests that the insular cortex is part of either a single, domain general functional system, a set of domain specific functional systems or a system with distributed functions. In order to evaluate the function or functions of the insula related to speech and language, we examined data obtained from multiple functional neuroimaging studies conducted in our lab, representing a wide range speech, language and cognitive processes. The tasks reflect speech production, speech perception (audio, visual and audiovisual), word reading, picture naming, word generation, and cognitive tasks. Here we focused on whole brain analyses of the location of insular activation with a secondary focus on the manner in which additional brain areas implicated in various aspects of speech and language are co-activated with changes in insular activation. Overall, the location of insular activation varied in a systematic manner with the different speech, language and cognitive tasks. A rostrocaudal gradient of insular activation was observed with more cognitive, integrative processes activating the most anterior portions of the insula and more sensory (auditory) processing in the posterior portion of the insula, in a region contiguous with the dorsomedial portion of the planum temporale. Speech and oral motor production was intermediately localized centered on the central sulcus of the insula. In general, all insular activations were bilateral with different degrees of asymmetry depending on the task. Activation in a number of other cortical and subcortical areas displayed a similar systematic change in location with changes observed in insular activation. For example, most anterior portion of the insula, active for more cognitive-like tasks, was mostly associated with concomitant pre- SMA, Broca’s area and caudate activation while activation in the more sensorimotor portion of the insula was co-active with the motor cortex, SMA proper and the putamen, without concomitant activation of Broca’s area. The results are consistent with the insula as a multifunctional cortical region engaged in many aspects of speech and language behavior from sensory to cognitive processing. The apparent functional specialization along its length and its differential functional connectivity suggests further that the insula is an integral component in a distributed network engaged in sensorimotor integration for multiple behaviors.

B30

Sensorimotor adaptation of speech in Parkinson's disease

Fatemeh Mollaei, Douglas M. Shiller and Vincent L. Gracco

The basal ganglia-thalamo-cortical circuit is known to be involved in establishing motor plans for a wide range of behaviors. Parkinson's disease (PD), a manifestation of basal ganglia dysfunction, is associated with a deficit in sensorimotor integration. PD impairment is also associated with difficulty in acquiring new motor sequences negatively affecting motor learning. Previous studies of sensorimotor integration and sensorimotor adaptation (SA) in PD have focused on limb movements using visual and forced field alterations (Contreras-Vidal & Buch 2003; Paquet et al. 2008; Messier et al. 2007; Stern et al., 1988). For speech, no study has examined SA in PD patients.

Here we report the results from two studies of SA to determine whether participants with PD are able to make speech motor adjustments to an auditory feedback manipulation. Participants produced speech while their auditory feedback was altered in a manner consistent with a change in tongue position. We used two different SA procedures that varied in their onset and offset characteristics. The PD subjects were able to adapt to the induced error but to varying degrees depending on whether the feedback alteration was introduced gradually or immediately. When the feedback alteration was immediately applied, adaptation was reduced in the PD subjects compared to age-matched control subjects. When auditory feedback was subsequently returned to normal, PD subjects exhibited an inability to return to baseline over the same time interval as the control subjects. The results indicate that sensorimotor integration and learning abilities in PD patients may differ from non-impaired subjects in multiple ways. The results will be discussed relative to the potential role of the BG in sensorimotor adaptation and the effects of PD on speech motor learning.

B31

A Functional and Structural Investigation of Cerebral Organization in Monolinguals and Bilinguals

Jonathan A. Berken*, Jennika Soles, Jen-Kai Chen, Megan Callahan, Vincent Gracco, Shari Baum, and Denise Klein

The study of bilingualism provides the opportunity to explore neural plasticity, the capacity of the brain to modify its structural and functional organization in response to changes in environmental input. The brains of musicians, taxi-drivers, and jugglers, for instance, demonstrate adaptations to the musical, navigational, and motor skills that their respective tasks require.

In this study, we capitalize on the bilingual environment of Québec to investigate potential differences in the structure and function of the brain in three subject groups: English and French monolinguals, simultaneous bilinguals (both first languages (L1) acquired early in life) and late bilinguals (second language (L2) acquired after age 5). This population facilitates a study of brain morphology that controls strictly for age of acquisition.

Here we present an overview of a research approach that is part of a large-scale study of the brain and behavioral effects of bilingual language acquisition. We use anatomical and functional neuroimaging techniques including voxel based morphometry, diffusion tensor imaging and resting state and functional magnetic resonance imaging in order to elucidate the neuroanatomical and functional brain activation differences among the three subject groups. In addition, we evaluate subjects using behavioral methods, including the LEAP-Q (language experience and proficiency questionnaire), WASI (intelligence test), as well as spontaneous and non-spontaneous speech samples in both languages (recounting a story vs. reading a paragraph, respectively). In this way, we can identify the within and across group factors that explain brain morphology and functional differences associated with early versus late second language learning, and clarify the neural elements that correlate highly with the potential for bilingual language proficiency. Preliminary results will be presented.

B32

Frontal activity during speech perception differs by modality and available information.

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Introduction: Activation of frontal brain regions occurs during a wide range of speech perception tasks, levels, and modalities. Research of this activation has focused on the perception of action sentences/words [1] or on discriminating between speech segments [2], based on the hypothesis of a mirror neuron system for speech. However, there has been little study of the involvement of frontal regions in non-action sentences, and there is disagreement regarding the association of frontal activation with modality-specific speech [3]. Based on phoneme-level findings [4], we expected to find that frontal components of high-level speech perception networks (particularly the precentral gyrus) are more associated with the visual speech signal than purely auditory signals.

Methods: We conducted an fMRI experiment to investigate networks active during perception of suprasegmental speech, using multi-modal non-action sentences. 10 right-handed participants (5 male, mean age 26, native/primary speakers of North American English, normal hearing, normal or corrected-to-normal vision) were presented with 120 affective (angry/happy) and 120 linguistic (question/statement) unique, semantically neutral sentences. For audio trials (A) a still image of the speaker with a neutral expression was presented with the audio stream. For video-only trials (V) all auditory input was removed from the video stream. Audiovisual trials (AV) presented both the video and audio streams. During each of the 4 runs, 80 stimuli were presented in event-related pseudorandom order (60 test trials bracketed by 10 rest trials); no more than two stimuli of the same modality played in a row. Each 9.0s trial began with a 3.0s volume acquisition, followed by a 0.2-1.0s jitter, a 2.5-2.8s stimulus, and then a right-hand keypad response. Participants were asked to identify sentences as angry vs. happy or question vs. statement. For each participant, functional images were aligned to their anatomical image, followed by volume registration, blurring using a 6.0mm FWHM kernel, and warping to MNI space. The haemodynamic response function was deconvolved with a piecewise linear spline; each sentence was collapsed into affective or linguistic sentences by modality, and into modality-only (AV, A, V) sentences using a general linear model. Group analysis was conducted using mixed-effect meta-analyses. Whole-brain activation was considered significant using $p = 0.005$ corrected to $p = 0.05$ using FWE cluster-size correction (minimum cluster size 40 voxels). Thresholded conjunctions were also created between modalities to explore auditory and visual networks.

Results: A conjunction from whole-brain maps showed significant common activation across all three modalities extending bilaterally along through the fusiform and inferior temporal gyri, in middle occipital gyri, inferior cerebellum, posterior superior temporal gyri (STGp), left precentral gyrus, and right middle temporal gyrus. Auditory signal (AVA) was associated with activation along the bilateral superior temporal plane, as well as near-significance clusters in left medial superior frontal gyrus (SFGm) and right inferior frontal gyrus pars triangularis (IFGtr). Visual signals (AVV) were associated with activation in the right STGp. Of note was that AV shared common sub-threshold activation within the IFG pars opercularis, while AVA shared activation within the IFGtr.

Conclusions: Contrary to our expectations, the visual signal was not associated with more frontal activation. Rather, frontal activation seems to be linked to the modality as well as the information available to the perceiver. The auditory signal is associated with the left SFGm and IFGtr; but given that IFGop was not active for AV sentences, it may come online only when a full complement of both auditory and visual information is not available.

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B33

The role of the Turtle-family members in axonal tiling

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Axonal/dendritic tiling is an important mechanism that patterns neuronal circuitry in the developing nervous system. Tiling refers to the avoidance between neurites from certain adjacent same-type neurons for complete but non-overlapping coverage of receptive fields, which is essential for spatial discrimination of sensory information. We have previously identified Turtle, a member of the conserved Turtle/DASM1/IgSF9 subfamily of the immunoglobulin superfamily as a key mediator of the projection of the R7 photoreceptor axons. Turtle mediates R7 tiling in a homophilic manner. To further understand the mechanism of Turtle action in axonal tiling, we have taken a combination of molecular and genetic approaches to identify Turtle-interacting proteins. We found that Baby Turtle (bTutl), another member of Ig-superfamily proteins, interacts with Turtle physically. Immunohistochemical analysis showed that bTutl is present at R7 terminal layer in the medulla. Genetic analysis revealed an interaction between btutl and turtle in mediating R7 axon tiling in an eye-specific manner. Furthermore, overexpression of btutl in the eye is able to induce a R7 axon tiling defect. Our results are consistent with a model in which Turtle antagonizes the function of bTutl to mediate R7 tiling.

B34

HIPPOCAMPAL-PREFRONTAL PATHWAY AND BEHAVIORAL FLEXIBILITY IN THE CROSS-SHAPED MAZE: EFFECTS OF PRENATAL STRESS AND PATHWAY DISCONNECTION

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Epidemiological studies have revealed that stressful situations experienced during pregnancy affect the development of the fetal brain, and increase the risk of psychiatric disorders with cognitive deficits in offspring later in life. There is evidence that prenatal stress alters normal function of the hippocampus (HPC) and the prefrontal cortex (PFC), pivotal structures for declarative memory and executive functions, respectively. In general, the ventral portion of the HPC sends dense projections to the prelimbic and infralimbic areas of the PFC. Interestingly; dysregulation in this pathway induces schizophrenia-like behavioral abnormalities in rats. However, the effects of prenatal stress on such HPC-PFC interaction and its function have not been elucidated. In experiment 1, we exposed pregnant rats to restraint stress between gestational days 14 and 21 and evaluated its effects on allocentric and egocentric spatial memories and flexible use of these memories in adult offspring. We found that prenatal stress did not affect allocentric and egocentric memories themselves, but enhanced switching from allocentric to egocentric, but not from egocentric to allocentric learning strategies. In experiment 2, we disconnected the vHPC-PFC pathway by infusing tetrodotoxin (TTX) into the unilateral vHPC and the contralateral PFC in normal animals. We found that vHPC-PFC disconnection enhanced strategy switching from allocentric to egocentric learning strategies. Collectively, these results suggest that prenatal stress may affect vHPC-PFC information processing that could, however, result in enhancement of flexible use of different modality of memories

B35

Influence of the copper binding domain in E1 of APP on APP-processing mediated by BACE1

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The central event in the protein-folding disease Alzheimer is the initial proteolysis of APP by BACE1, with subsequent formation of Abeta. Changes in copper homeostasis in the brain of Alzheimer's disease patients can be observed. In the course of developing therapies against Alzheimer's disease, it has been found that APP-processing can be influenced by copper. Although it is known that both, BACE1 and APP bind copper, it is not understood, whether copper binding is crucial for APP-processing.
In this context, we analyzed the influence of the copper binding site as part of the E1 domain of APP on APP-processing and could show that the presence of this site is not an indispensable requirement for the recognition of APP as a substrate of BACE1. Even an APP-deletion mutant, which is shortened by the E1 and adjacent acidic domain, could still be processed by BACE1, which became evident by detection of APP-processing products sAPPbeta and Abeta.

B36

Neurotoxic A?42 peptides of Alzheimer’s Disease are found in the nucleus and influence gene regulation

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The amyloid precursor protein (APP) is central to the pathogenesis of Alzheimer’s disease (AD). APP is a type I transmembrane protein which is cleaved by the ?-site-APP-cleaving enzyme (BACE) and the ?-secretase complex to generate A? peptides and the APP intracellular domain (AICD). The pathogenic effects observed in AD are ascribed to soluble low-n oligomers of A?42. Recently, we could show that toxicity of A? is not a simple cause of A? oligomerization but a consequence of the adoption of a specific conformation determined by the G29xxxG33 interaction motif. This motif is contained within the hydrophobic C-terminus of the A? peptide and places two glycines on the same face of a ?-sheet. We have discovered a possible role for A? in gene regulation, which could either represent a normal or a gain-of-function of A?. Both, in vitro and in vivo, we detected A? peptides in the nucleus. In in vitro studies we investigated a time-dependent accumulation of A? peptides in the nucleus. The neurotoxic A?42 wt decreased or increased mRNA levels of specific genes whereas the substitution peptide A?42 G33A is non-toxic and does not affect mRNA levels. We have evidence that A?42 wt interacts with specific promoters. The toxic mechanism of A? could be mediated through the interaction of A? with genomic DNA and thereby A? could ultimately affect gene expression. Since intraneuronal A? has been recognized as relevant for the pathogenesis, A? internalization and its gene regulating activity could be important in AD.

B37

Amyloid ? in the Parallel Artificial Membrane Permeation Assay (PAMPA)

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Soluble lown oligomers of A?42 are presumed to be causative for the pathogenic effects in Alzheimer‘s disease (AD). The GxxxG motif within the amyloid ? sequence plays a crucial role not only for the aggregation into oligomers but also for the cellular toxicity. A? 42 substitution peptides possessing an isoleucine substitution at amino acid position 33 (G33I) were much less toxic than A? 42wt (Harmeier et al., 2009). Recently, we have discovered a novel role for A?42 in gene regulation, which was specific for A? 42wt peptide but was not observed for the substitution peptide (Barucker et al., manuscript in preparation). Since this proposed gain-of-function requires transport of A? across cellular membranes, we investigated the molecular mechanism by using the Parallel Artificial Membrane Permeation Assay (PAMPA). With this test system permeability of drugs across phospholipid-coated filters can be determined by measuring the diffusion after a defined period of time. The concentration of the test agent is measured on the donor and acceptor compartments. In our initial experiments the filter was covered with a brain lipid extract (ble). The selective permeability of the lipid layer was assessed by substances that can or cannot diffuse through the membrane, i.e., brilliant cresyl blue and calcein. We have analyzed A? species of different lengths which were placed on the donor plate, which then was gently reassembled on the acceptor plate. After incubation at 37°C the concentration of A? species in the acceptor plate was analysed by Western blot. The in vitro model of passive, transcellular permeability allows testing of A? diffusion depending on lipid compositions and oligomerization states over a wide pH range and in alternative buffer conditions.

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B38

Neural activity-dependent mechanisms regulating radial glia motility

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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 wide number of different functions like neuron migration, axon guidance and synapse formation. However, the mechanisms of these interactions remain poorly understood. Our published data has revealed that radial glia respond to neural activity by modifying both the rate of intracellular calcium transients and their filopodial probing of the environment. We have focused on elucidating the details of this neuron-glia interaction by imaging glial cell behaviour in the living intact Xenopus tadpole brain by two-photon microscopy. 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 motility. Furthemore, 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 glia having a role in translating synaptic activity levels to changes in glia process motility.

B39

NEUROTENSIN INHIBITS ORGANUM VASCULOSUM LAMINA TERMINALIS INDUCED CLUSTERED FIRING IN RAT MAGNOCELLULAR NEUROSECRETORY CELLS

Michael Walsh and Charles Bourque

Magnocellular neurosecretory cells (MNC) in the supraoptic nucleus (SON) of the hypothalamus secrete oxytocin and vasopressin directly into the bloodstream to achieve osmoregulation. Sustained hypertonicity demands maximal hormone secretion, thus MNCs display clustered firing in vivo to avoid secretion fatigue. While the basis of clustering is unknown, previous studies have shown an NMDA-induced clustering which was blocked by the neuromodulator Neurotensin (NT). The organum vasculosum laminae terminals (OVLT), the body's primary osmosensor, sends glutamatergic afferents to the SON. In vitro single-unit extracellular recordings on superfused hypothalamic explants of the rat were performed to investigate the OVLT's ability to induce clustering through endogenous glutamate release, and whether NT blocks this effect. Electrical stimulation of the OVLT induced clustering in MNCs, which was significantly reduced during bath application of the NT active fragment 8-13, but not during application of the inactive NT fragment, 1-7. This study suggests a role for the OVLT in SON clustering, and that NT may play a modulatory role in this effect.

B40

Small compounds interfering with APP transmembrans sequence dimerization as promising therapeutic agents against Alzheimer’s Disease

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Alzheimer’s disease (AD) is the most common age-related neurodegenerative disorder currently affecting more than 30 million people worldwide. The key pathological agent in AD is the amyloid-? (A?) peptide derived from a much larger protein, the amyloid precursor protein (APP). The length of A? peptides is critical as the 42-residue isoform (A?42) is causally associated with the pathogenesis of AD. Once A?42 aggregates into oligomers, it can be directly toxic to cells. Recently, we reported that the transmembrane sequence (TMS) of APP homodimerizes via the GxxxG interaction motif. Dimerization has a substantial impact on the specific A? isoforms that are produced. Engineered GxxxG mutants gradually attenuating the dimerization strength of the APP-TMS specifically decrease the production of the aggregation-prone A?42 in favor of shorter A? species, e.g. A?38. Interestingly, the same beneficial effect on A? production was found for small compounds including sulindac sulfide and other non-steroidal anti-inflammatory drugs (NSAIDs).
However, the underlying molecular mechanism of the A?42-lowering effect by these compounds is still under debate.
We examined molecular interactions of sulindac sulfide and related compounds with potential targets by SPR experiments and NMR spectroscopy. Sulindac sulfide and derived A?42-lowering compounds directly bind to the A? sequence and the alternating glycine residues of GxxxG motif within the APP-TMS form an ideal contact site for those compounds as revealed by molecular modelling. To analyze the compound’s effect on APP-TMS dimerization stability in living cells we used a bacterial reporter gene-based dimerization assay (ToxR assay). Remarkably, we found that the helix-helix interaction of the APP-TMS is attenuated in a concentration-dependent manner by sulindac sulfide and other sulindac-related compounds.
Our data strongly suggest that small compounds as specific binding partners of the APP-TMS lower the production of A?42 by directly interfering with its dimerization. Taken together, we have identified a molecular link between APP-TMS dimerization and A?42 generation that classifies the APP-TMS as a highly potential drug target.

B41

Differential effects of ?-secretase on APP ?-CTF wt and FAD mutant cleavage and lipid interaction of amyloid-? peptides

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Alzheimer disease (AD) is the most prevalent neurodegenerative disease in the elderly worldwide. The disease
is pathologically characterized by high levels of the amyloid-? peptide (A?) in the brain, which is a cleavage product
of the much larger membrane bound amyloid precursor protein (APP). Recently it became evident that the
?-carboxyl terminal fragment (?-CTF) of APP is cleaved consecutively by the ?-secretase complex, releasing
the toxic aggregation prone A?42 form. To prevent A? toxicity it is important to understand
1) how the exact cleavage mechanism of the ?-secretase works and
2) how the different A? peptides interact with membrane lipids and thus may exert toxicity.

B42

Neural Correlates of Heading and Steering in Humans

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Optic flow is defined as a radially expanding pattern of motion that is created on our retina during locomotion. It helps us identify which direction we are heading in and thus enables us to steer towards the target. In our study, we aim to elucidate the neural correlates of heading and steering by having healthy young subjects complete a series of tasks in a virtual environment while in a 3T fMRI scanner. These tasks involve participants discriminating heading direction and actively steering with a joystick. We hypothesize that in addition to motion sensitive areas, such as the medial superior temporal area, a more extended neural circuit will be recruited to accomplish both heading and steering tasks. This includes the dorsal parietal sulcal area, premotor area, and superior parietal cortex for heading tasks and the cerebellum, supplementary eye-field, and dorsal premotor cortex for the steering tasks. Results of this study will help us understand which brain regions may be impaired for those with neuropathies that affect locomotion.

B43

In Vivo Effects of Simvastatin on Memory and Cerebrovascular Deficits in APP/TGF Bitransgenic Mice

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Background: Cognitive and cerebrovascular deficits are two manifestations of Alzheimer's disease (AD) to consider when aiming for effective therapy. Animal models have been invaluable in dissecting the pathogenic mechanisms and identifying drug targets, primarily for memory deficits. However, very few of these drugs have ameliorated the human condition. Here, we use bitransgenic APP/TGF mice that recapitulate the cerebrovascular and cognitive AD landmarks (1) to evaluate the efficacy of simvastatin on these clinical markers.

Objectives: APP/TGF mice, which overexpress a mutated form of the human amyloid precursor protein (hAPPSwe,Ind) and a constitutively active form of transforming growth factor-b1 (TGF), display the salient cerebrovascular and cognitive impairments of AD as early as six months of age. Using these mice, we aim to test the therapeutic potential of simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor with proven efficacy against these two deficits in singly APP mice (2,3).

Methods: Three-month-old APP/TGF and wildtype (WT) mice were treated with simvastatin (40 mg/kg/day in water). At age 6 and 9 months, mice were tested for learning in the hippocampal-based spatial Morris Water Maze (MWM), as described by DeIpolyi and colleagues (4) with visible and hidden platform; and for memory in the probe trial test. Post-training, the evoked cerebral blood flow (CBF) response to whisker stimulation was measured as an index of functional hyperemia. Mice were then sacrificed and the posterior cerebral artery (PCA) was used for assessment of cerebrovascular reactivity.

Results: Simvastatin treatment failed to improve spatial learning and memory deficits of APP/TGF mice tested at 6 and 9 months in the MWM. The decreased CBF response evoked by whisker stimulation in APP/TGF mice (-59%, $p< 0.001$) was also not normalized by simvastatin. Similarly, the 46% and 58% respective loss of dilatory ability to acetylcholine and calcitonin gene-related peptide of isolated PCA were not restored, but rather reversed to weak constrictions in treated APP/TGF mice. In contrast, the decreased synthesis of nitric oxide (-45%) in the vessel wall was totally normalized by treatment. Simvastatin had no deleterious effects on any parameters in WT animals.

Conclusion: In contrast to the beneficial cerebrovascular and mnemonic effects exerted by simvastatin in singly APP mice (2,3), our data show that the underlying mechanisms that allowed these improvements have been altered by the TGF transgene, making the bitransgenic APP/TGF mice more resistant to simvastatin. Together, these results suggest that therapeutic benefits in APP/TGF mice, which display a more complete array of AD salient features, are not as readily obtained as in APP mice. Further, as these mice better reflect the complexity that one faces when attempting to rescue function in AD patients, they may represent an improved model to test new therapeutic strategies.

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B44

Regulation of global cell surface protein expression of astrocytes and oligodendrocytes by soluble neuronal factors

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Neuron-glia interactions play important roles in CNS development and maintenance. In particular, several astrocyte cell surface molecules contribute to regulation of neuronal survival, synaptogenesis, and myelination. While considerable research has focussed on glial influences on neurons, much less is known about neuronal modulation of glial cell activities. We therefore analysed astrocytic protein expression after exposure of astrocytes to soluble neuronal factors. Using initially an unbiased proteomics approach and subsequent confirmation of particular candidates molecules, we found that neuronal factors regulated the expression of astrocytic cell surface proteins belonging to diverse functional classes including signalling molecules and adhesion molecules. We observed that the same soluble neuronal factors also regulated the cell surface protein expression of oligodendrocyte precursor cells and, quite surprisingly, a number of specific molecules were regulated in an opposite direction as compared to astrocytes. These included adhesion molecules like N-Cadherin and signalling molecules like Egfr and Trk-B which were found to be significantly down-regulated in astrocytes while oligodendrocytes showed a significant up-regulation upon exposure to neuronal factors. The differential regulation of these novel adhesion and signalling molecules, in astrocytes and oligodendrocytes, identified here will be of great interest in the further study of neuron-glia interactions both in normal development and plasticity as well as in the context of diseases including multiple sclerosis and neuromyelitis optica.

B45

Regulation of microRNAs miR-219 and members of the miR-338 and miR-17-92 clusters in primary human and rodent oligodendrocytes

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Short non-coding RNAs (microRNAs; miRs) regulate diverse molecular and cellular processes including oligodendrocyte precursor cell (OPC) proliferation and differentiation. However, human oligodendrocytes (OLs) differentiated from embryonic stem cells were recently shown to lack miRs that promote OL differentiation in rodents (miR-219-5p and miR-338-5p/3p). Here, we show that acutely isolated human OPCs and human OLs do express miR clusters important in rodent OPC proliferation and differentiation (miRs-219, and miR-338 and miR-17-92 clusters). In addition, miR profiling of human grey matter and white matter reveals that these miRs are enriched in glia. We conclude that rodent-relevant miRs may also regulate human OPC proliferation and differentiation and should be recognized as potential therapeutic targets in demyelinating disorders.

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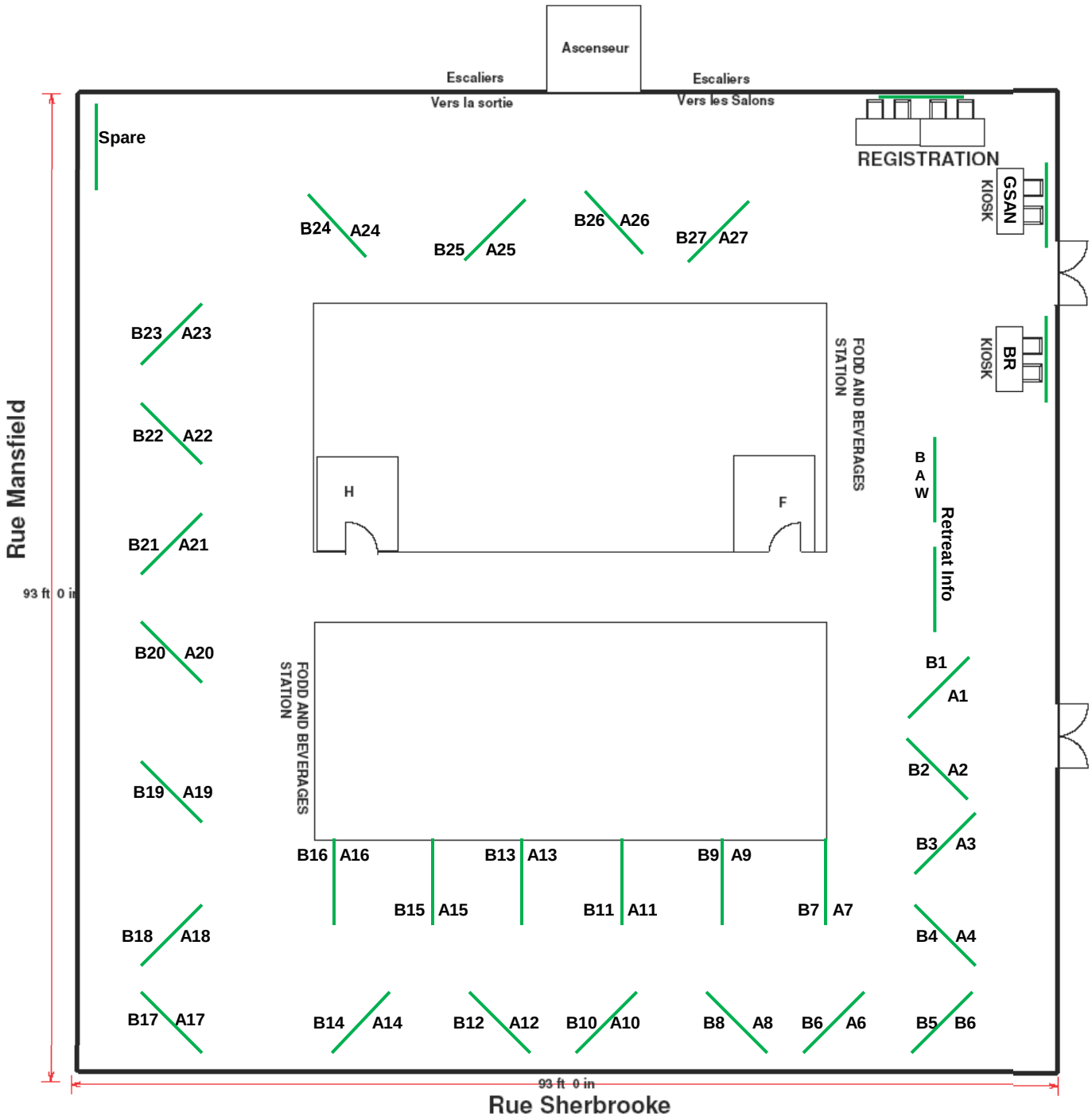

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