

31ST Annual Meeting of the
SOUTHERN ONTARIO NEUROSCIENCE ASSOCIATION
University of Guelph - May 9, 2011



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PROGRAM

7:00 Registration & poster set-up

8:00 Breakfast

8:50 Welcome

MINI-SYMPOSIUM I

9:00 RICHARD BENINGER, PhD (QUEEN'S UNIVERSITY)
Decreased dopamine and disincentive learning

9:45 PAUL FRANKLAND, PhD (UNIVERSITY OF TORONTO)
The network organization of long-term memory

10:30 Coffee Break

10:45 DAVID F. SHERRY, PhD (UNIVERSITY OF WESTERN ONTARIO)
Memory, neurogenesis and the brain of food-storing birds

KEY-NOTE LECTURE

11:30 HARRIET DE WIT, PhD (UNIVERSITY OF CHICAGO)
Determinants of drug preference in humans

12:30 Lunch (University Center) **POSTERS**

MINI-SYMPOSIUM II

15:00 ADAM ANDERSON, PhD (UNIVERSITY OF TORONTO)
Do vivid perceptions make for vivid emotional memories?

15:45 Coffee Break

16:00 CHERYL GRADY, PhD (ROTMAN RESEARCH INSTITUTE)
Mechanisms of cognitive aging: functional connectivity and brain "noise"

16:45 JESSICA GRAHN, PhD (UNIVERSITY OF WESTERN ONTARIO)
Investigating how movement areas in the brain support musical rhythm perception

17:30 Business meeting

POSTER ABSTRACTS

(in alphabetical order)

Research Theme: Neural Excitability, Synapses, and Glia: Cellular Mechanisms

Inhibition of glycogen synthase kinase-3 rescues Abeta-mediated inhibition of LTP in hippocampal slices.

Christine E. J. Acton,¹ Mariana Vargas-Caballero¹ and Ole Paulsen^{1,2}

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Amyloid β ($A\beta$) and tau protein are both implicated in memory impairment, mild cognitive impairment (MCI), and early Alzheimer's disease (AD), but whether and how they interact is unknown. Consequently, we asked whether tau protein is required for the robust phenomenon of $A\beta$ -induced impairment of hippocampal long-term potentiation (LTP), a widely accepted cellular model of memory. We used wild-type mice and mice with a genetic knock-out of tau protein and recorded field potentials in an acute slice preparation. We demonstrated that the absence of tau protein prevents $A\beta$ -induced impairment of LTP. A likely candidate for the $A\beta$ -tau link is glycogen synthase kinase (GSK-3 β), the primary kinase responsible for tau hyperphosphorylation. The aim of this study was to explore the effect of a specific inhibitor of the tau kinase glycogen synthase kinase 3 (GSK-3 β) on tau phosphorylation. A highly selective GSK-3 β inhibitor (AR-A014418 or AR-18) was used on LTP in hippocampal slices from young adult wild type mice. AR-18 (1 μ M) was shown to block the increased tau phosphorylation induced by $A\beta$ and prevent $A\beta$ -induced impairment of LTP in wild-type mice. Together, these findings show that tau protein is required for $A\beta$ to impair synaptic plasticity in the hippocampus and suggest that the $A\beta$ -induced impairment of LTP is mediated by tau phosphorylation. We conclude that preventing the interaction between $A\beta$ and tau could be a promising strategy for treating cognitive impairment in MCI and early AD.

Presenter: Christine Acton

Research Theme: Cognition and Behavior

Effect of chronic food deprivation on the development and expression of cocaine sensitization

C.P. Allen and F. Leri

Department of Psychology, University of Guelph, Guelph, ON, N1G 2W1 Canada.

Cocaine sensitization refers to a collection of physical and psychological changes which take place in the brain following chronic exposure to cocaine. Similar processes, including enhanced behavioural responses to acute cocaine, can also be observed in rodents following food deprivation. However, to date it remains unclear whether these two processes for producing sensitization are equivalent (utilizing the same mechanisms and enhancing the animal's response to cocaine towards a common asymptote), additive (utilizing mainly independent mechanisms to enhance cocaine's effect towards independent and combinable maximums), or interactive (sensitization mechanisms overlap and produce either sub or super-additive effects on performance).

To address this we conducted a study in which half of the animals were restricted to 85% of their free feed weight commencing 10 d prior to the start of testing and continuing throughout the experiment, while the remaining animals were free fed. Rats were administered a baseline test of locomotion of 1 hr following a saline injection and then 1 hr following a cocaine challenge (3, 9, or 15 mg/kg). The animals then received 5 injections (1/day x 5 days) of 30 mg/kg cocaine, in a novel environment, followed by 10 days off. A second locomotion test was then administered to determine the effects of cocaine exposure. This cocaine exposure paradigm has been previously shown to produce cocaine sensitization. Results from this study indicate that while food deprived animals show enhanced locomotor response at baseline, they are further enhanced following cocaine exposure.

Research Theme: Development

Developmental alterations in the limbic pathways of stress circuitry as a result of early immune activation

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¹Bachelor of Health Sciences (Honours) Program, McMaster University, Hamilton, ON

²Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, ON

The early-life environment is essential for the normal development of the neurocircuitry implicated in stress and the ability to adapt to new stressors. Disturbances in stress-coping mechanisms have been linked to the emergence of affective disorders at a later stage in life. Specifically, there is mounting evidence suggesting that the immune system plays an important role in CNS development and the “programming” of behaviour. Here we present evidence of the effect of early-life immune challenge with lipopolysaccharide (LPS) during the first week of life with respect to behaviour, stress neurocircuitry, and psychological stress reactivity during adulthood. Previous work in our lab has shown that LPS mice displayed sexually dimorphic disturbances in behaviour, specifically, alterations in emotionality. This phenotype was associated with differences in the trajectory of serotonergic gene expression during the 3rd week of life, a developmental window when anxiety emerges in mice. In the current study we investigated how the early-life immune challenge affects the development of stress circuitry, specifically gene expression of corticotropin releasing hormone and its receptors, as well as the major corticosteroid receptors. Mice were given LPS injections on postnatal days (P) 3 and P5 and gene expression was assessed using *in situ* hybridization on P14-P28. Target genes investigated were corticotropin releasing hormone (CRH), CRH receptor 1 (CRHR1), CRH receptor 2 (CRHR2), mineralocorticoid receptor (MR), and glucocorticoid receptor (GR). Stress reactivity was assessed in adulthood in response to repeated restraint stress. Our analysis identified alterations in the gene expression in stress circuitry during the 3rd week of life, specifically in limbic regions of the brain. These early changes in the trajectory of stress circuitry did not lead to altered stress reactivity at the level of corticosterone in adulthood. This finding was surprising as adult LPS mice showed increased stress-related behaviours. Our current work is investigating long-term changes in central stress circuitry to determine the neurobiological mechanisms underlying the persistent changes in behaviour.

Research Theme: Disorders of the Nervous System

Forebrain degeneration and ventricle enlargement caused by striatal stroke and beta-amyloid toxicity

Amtul, Z., Nikolova, S., Gao, L., Arany, E., Bartha, R., Hou, ST., Whitehead, SN., Wojtowicz, JM and Cechetto, DF

Stroke is one of the risk factors for vascular cognitive impairment (VCI) such as dementia and/or Alzheimer's disease. In this study we aim to provide molecular and histological proof-of-principle for treatment strategies by examining the molecular mechanisms leading to exacerbated degenerative changes into the brains of VCI animal models of vascular risk factors (such as stroke) in combination with high brain amyloid. Co-morbid occurrence of small striatal stroke and Ab resulted in striatal and hippocampal shrinkage, atrophy of hippocampal fimbria, corpus callosum and enlargement of the lateral ventricles. Caudate putamen, globus pallidus, corpus callosum, cerebral cortex, hippocampus, septohippocampal nucleus, lateral ventricles and revealed exacerbated cerebral and cerebrovascular pathology and a series of biochemical alterations, including microgliosis (OX-6), AD-like pathology (amyloid) and neuronal degeneration (FJB) in the co-morbid A β +stroke rats around the ischemic lesion and anterior horns of lateral ventricles. Piriform and temporal cortices were devoid of neuronal damage but revealed prominent activated microgliosis and large round or oval deposits of high density beta-amyloid immunoreactivity. The greater degree of widespread protracted degenerative changes in the co-morbid A β + stroke rats than either the stroke or Ab rats alone may explain the enhanced VCI in co-morbid patients observed clinically.

Research Theme: Cognition and Behavior

Music-dependent memory: an example of context-dependent memory or the consequence of distraction?

Author: Paul Armstrong, fourth year honors psychology student

Thesis Supervisor: Jessica Grahn, Ph.D., The University of Western Ontario

Music-dependent memory (MDM) is the concept that music can serve as an effective retrieval cue for previously learned information. Both mood and arousal levels have been shown to be important contextual components of MDM; however, the full range of underlying factors that contribute to MDM is still unknown. I manipulated mood, arousal levels, and type (genre) of music to determine the relative contributions of each of these factors to MDM. Participants learned face-name pairs while listening to background music varying in the mood and arousal levels. Participants then performed a recognition task on the previously learned face-name pairs during which the mood and arousal levels were the same as during the learning phase. The type of music, however, was varied. It was predicted that the contextual components of music are important causal factors of MDM and that memory performance would be enhanced when the contextual components during learning and testing were similar. Contrary to predictions, the results indicated that the type of music only had an effect on memory performance in the low arousal-negative mood condition: changing the specific musical piece within the same genre impaired memory performance relative to keeping the piece identical or changing the piece and the genre. The results suggest that low arousal-negative mood music affects recognition memory, but the nature of this effect depends on specific musical context.

Research Theme: Cognition and Behavior

VACHT knock-down mice show normal prepulse inhibition but disrupted long-term habituation of the acoustic startle reflex

Erin Azzopardi¹, Xavier De Jaeger², Vania F. Prado³, Marco A.M. Prado³, and Susanne Schmid³

¹ MSc candidate, ²PhD candidate, ³PhD, Anatomy & Cell Biology, Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON

The neurotransmitter acetylcholine (ACh) is involved in many cognitive processes including learning, arousal, and attention. Acetylcholine is hypothesized to be the main modulator of certain sensory filtering mechanisms. Two operational measures of sensory filtering are habituation and prepulse inhibition (PPI) of the acoustic startle response. To further investigate the role of ACh in sensory filtering, we tested vesicular acetylcholine transporter (VACHT) knock-down mice for short-term and long-term habituation as well as PPI. These mutants display a 65% reduction of VACHT, which is imperative for normal ACh transmission.

We tested adult knock-down mice and their wild-type littermates. After two days of acclimation to the startle boxes, mice were exposed to 30 startle pulse alone trials in order to measure habituation. Immediately thereafter, 70 pulses preceded by prepulses (at different ISIs) and pulse alone trials were presented in a pseudorandomized order for PPI measurement. The tests were performed on five times per animal on subsequent days. Baseline startle amplitudes, habituation scores, and prepulse inhibition percentages were calculated and analyzed.

Surprisingly, we observed that mutant mice had intact PPI. Furthermore, we observed normal short-term habituation in knock-down mice as compared to their wild-type littermates, but no long-term habituation of startle in mutants. The deficits in long-term habituation could be partially rescued by pre-testing injections of galantamine, an inhibitor of acetylcholine-esterase, but not by post testing injections.

A reduction in VACHT levels reduces the efficiency of ACh loading into neurosecretory vesicles. VACHT function in knock-down mutants may be still sufficient for transient pulsatile release of ACh but deficient for prolonged or tonic release. PPI might be dependent on a transient release of ACh and is therefore not affected in these mice. Our data further provides evidence that tonic ACh release is involved in long-term habituation of startle. Previously little evidence existed regarding ACh involvement in habituation of reflexes, and future studies will seek to understand the underlying mechanisms and circuitry.

Research Theme: Cognition and Behavior

Modulation of locomotor activity and cerebellar and frontal cortical redox profile in female wistar rats treated with anorexigenic amphetamine-like drug fenproporex

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In the past decade, there has been a marked increase in the use of appetite suppressant drugs use and a significant proportion of consumers are women who do not really need drugs to reduce weight. One of the most commonly used appetite suppressant is fenproporex (3-(1-phenylpropan-2-ylamino)propanenitrile hydrochloride), a noradrenergic drug that acts by releasing/blocking neuronal reuptake of noradrenaline and dopamine, and maintaining/increasing leptin transport into the brain. Although this drug has been suspended in many countries, fenproporex is sometimes combined with benzodiazepines, antidepressants and other compounds which are sold as "diet pills". Despite this, very little is known about the effects of this anorectic drug on behavioral and physiological parameters. In the present work, we have administrated (orally, gavage) different doses of fenproporex (0, 4, 8, and 16 mg/kg/day) in female Wistar rats (120 days-old, n=8 each group) for 7 days. Locomotor activity (open field test), and cerebellum and frontal cortex redox profile were assessed at the end of 7 days of treatment. Female rats treated with 8 and 16 mg/kg of fenproporex showed increased locomotor-exploratory activity ($P < 0.05$) suggestive of anxiety-like behavior. However, we found altered redox profile in female rats treated with fenproporex at all doses, with reduction in enzymatic (superoxide dismutase, glutathione peroxidase and S-transferase, and glyoxalase I) and non-enzymatic (total radical antioxidant potential) antioxidant activities. Similarly, an increased oxidation in thiol groups (-SH) was found in fenproporex-treated group at all doses ($P < 0.05$). This is the first study that investigated the effects of fenproporex administration on central nervous system (CNS) redox profile modulation in experimental animal model. Our data indicate that fenproporex administration modulates CNS redox profile, suggesting altered redox-dependent cell signaling. These data further suggest that its therapeutic use as an appetite suppressant should be prescribed with extreme caution. Support: Capes Scholarship - Proc. n° BEX 5383102 and CNPq-Brazil.

Research Theme: Cognition and Behavior

Allosteric modulation of the dopamine D2 receptor: potential for the treatment of schizophrenia

Michael Beyaert, M.Sc. Student, Department of Medical Sciences, McMaster University; Ritesh Daya, B.Sc. Student, Department of Life Sciences, McMaster University; Rodney Johnson, Ph.D., Department of Medicinal Chemistry, University of Minnesota; Ram K. Mishra, Ph.D., Department of Psychiatry and Behavioural Neurosciences, McMaster University

Objective: Allosteric modulators are emerging as a new class of therapeutics for the treatment of psychiatric disorders. Conventional antipsychotic drugs bind to the dopamine D2 receptor and compete with endogenous dopamine and cause adverse motor or metabolic side effects. Allosteric modulators are safer alternatives to conventional therapeutics as they interact with their receptor at a novel binding site and their activity is limited by levels of endogenous ligand. Our lab has synthesized and evaluated over 185 compounds for their activity at the dopamine D2 receptor. Of these compounds, PAOPA is the most potent allosteric modulator¹. Our lab has demonstrated that this compound is effective in treating the MK-801 induced preclinical animal model of schizophrenia without causing the adverse effects induced by currently prescribed antipsychotic drugs². The objective of this study was to further evaluate PAOPA's therapeutic potential for the treatment of behavioural and biochemical abnormalities in an amphetamine-sensitized model of schizophrenia. **Materials and Methods:** The sensitization regimen used in this study was adapted from Tenn *et al.*³. Four groups (n=10/group) of male Sprague Dawley rats received intraperitoneal injections three days per week on alternate days over three weeks. Group A received saline, group B received D-amphetamine (1mg/kg during week one, 2mg/kg during week two, 3mg/kg during week three), group C received PAOPA (1mg/kg), and group D received the same doses of amphetamine as group B with PAOPA (1mg/kg). Following a three-week withdrawal, each group was tested for prepulse inhibition, social interaction, and locomotor activity. Amphetamine-sensitized rats were subjected to the same tests following PAOPA administration (1mg/kg). Post-mortem striatal dopamine was measured in all groups using high performance liquid chromatography. Data were analyzed by one-way ANOVA or paired t test where appropriate. **Results:** Compared to saline, amphetamine sensitization decreased prepulse inhibition, social interaction, and post-mortem striatal dopamine, while increasing locomotor activity. Concurrent amphetamine and PAOPA treatment prevented all amphetamine-induced abnormalities. Furthermore, amphetamine-induced deficits in prepulse inhibition and social interaction were reversed one hour following PAOPA treatment. PAOPA treatment alone had no effect on behaviour or post-mortem striatal dopamine. **Conclusions:** These results demonstrate that PAOPA can prevent and reverse behavioural and dopaminergic abnormalities in amphetamine-sensitized rats. Allosteric modulation of the dopamine D2 receptor has potential for the treatment of schizophrenia. PAOPA could be developed into a safer alternative to conventional antipsychotic therapies for the prevention and treatment of schizophrenia.

Selected References

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Research Theme: Sensory and Motor Systems

A Bayesian ideal observer model for human vibrotactile perception

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Accurate perception requires efficient decoding of stimulus-evoked sensorineural activity. Here we present a Bayesian ideal observer model that optimally decodes neural population responses to low frequency (5-40 Hz) vibrotactile stimuli. Fed simulated firing rates calculated from response properties of primate rapidly adapting type-I (RAI) afferents (Johnson 1974), the ideal observer makes probabilistic inferences about stimulus amplitude and frequency.

We incorporated known densities of RAI afferents reported for human fingertip, and introduced variability into the stimulus-evoked firing rates to simulate responses in the periphery (low-variability RAI noise) or primary somatosensory cortex (high-variability Poisson noise). Implementing two-interval forced-choice procedures, we quantified the model's performance on vibrotactile threshold detection (TD), amplitude discrimination (AD), and frequency discrimination (FD) tasks.

On all tasks, the model perceived more accurately at the peripheral than cortical level, suggesting that cortical response variability impairs perception. Nevertheless, the model's performance at the cortical level far surpassed human perception, suggesting that humans fail to utilize all information carried in cortical firing rates.

While quantitatively the model outperforms humans, qualitatively the performance of the model is similar to that of humans. For example, the model's performance follows a psychometric function such that the probability of correct responses increases monotonically with stimulus amplitude (TD task), or with the difference in amplitudes (AD task) or frequencies (FD task) between two stimuli.

The model's performance sets a benchmark in vibrotactile perception against which to compare human performance in order to gain insights into the decoding efficiency of the human somatosensory system.

Research Theme: Neural Excitability, Synapses, and Glia: Cellular Mechanisms

No evidence for place cell disruption in rats acutely exposed to toluene vapour

Caleb Browne, B.Sc. student; Ali Gheidi, Ph.D. student; Mary Beth F. Dunn, B.A. student; Diano F. Marrone, Ph.D.; Bruce E. McKay, Ph.D., Department of Psychology, Wilfrid Laurier University.

Toluene is a psychoactive chemical found in organic solvents and is inhaled for its euphoric properties. Cognitive impairments accompany abusive toluene inhalation and include deficits in learning and memory; previous reports have suggested that toluene-induced memory impairments may be due to an effect of toluene on neurons in the brain's hippocampus. In the present experiments we specifically tested the hypothesis that toluene disrupts place cell activity in hippocampal regions CA1 and CA3. The number of cells transcribing the immediate early gene *Arc*, which is coupled to the activation of place cells by behavioural exploration and integral to plasticity of hippocampal neurons, was measured via fluorescence *in situ* hybridization and confocal microscopy. Naïve rats were exposed to either toluene vapour (n=8) or water vapour as a control (n=7) for a period of 25 minutes, which was immediately followed by an assisted behavioural exploration procedure to activate place cells. Rats receiving only maximal electroconvulsive shock (n=2) and rats sacrificed directly from their home cages (n=2) were used as additional controls to establish the upper and lower limits of CA1 and CA3 *Arc* transcription, respectively. Toluene vapour did not affect the number of CA1 or CA3 neurons transcribing *Arc*, suggesting that at least a single, acute exposure to toluene vapour does not impair subsequent place cell activation.

Theme Theme: Cognition and Behavior

Discrimination of ultrasonic signals in Long Evans rats

Matt Burton, B.Sc. Student, Centre of Neuroscience, Stefan Brudzynski, Ph.D., Department of Psychology and Centre for Neuroscience, Brock University.

Previous research suggests that rats use ultrasonic vocalizations for intraspecies communication. One specific type of ultrasonic vocalizations is the 50 kHz call, which is indicative of a positive, appetitive emotional state of the rats. The goal of the present study was to observe whether rats could distinguish small differences among 50 kHz tones closely resembling natural 50 kHz calls. Such differences are naturally occurring among different individuals among conspecifics. Twelve adult Long Evans rats were used in the following experiment. Two speakers were attached to each of the distal arms of a T-maze which emitted two slightly different artificially generated step-tones (45-55 kHz and 50-60 kHz). Five control sessions were given to the rats to explore the T-maze with only the two step-tones being presented. For the next 20 experimental sessions, the step-tones were randomly presented in one of the distal arms of the T-maze, and chocolate bait was placed in a petri dish and paired always with the 50-60 kHz step-tone. The latency it took for the rat to eat the chocolate, the total number of errors and the first choice errors were recorded for each session. Results indicated that upon successive sessions, the total number of errors significantly decreased. Both latency and the first choice errors also showed a significant negative relationship. These results show the rats can distinguish the 5 kHz difference between the acoustic stimuli. Thus, it can be suggested that rats may be able to distinguish among individual differences in the naturally-emitted 50-60 kHz.

The study was supported by N.S.E.R.C.

TRPM2 channel regulation by the Fyn Kinase

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Background: TRPM2 (transient receptor melastatin-like type 2) is Na⁺ and Ca⁺ permeable channel that has been associated with the neurodegeneration observed in Alzheimer's disease (AD). A key to this process is a disturbance in neuronal Ca²⁺ homeostasis, which has been correlated with increased levels of Amyloid- β (A β) peptide and neurofibrillary tangles -hallmarks of AD. A β induces neurotoxic factors, namely cytokines and reactive oxygen species (ROS). H₂O₂ has been shown to activate the TRPM2 channel via tyrosine phosphorylation and enable Ca²⁺ influx. However the mechanism by which this occurs has not been established. Given that the protein tyrosine phosphatase (PTPL1) and the tyrosine kinase inhibitors PP2 and genistein prevent the increase in Ca_{in} following H₂O₂ treatment, we propose that the tyrosine kinase Fyn regulates the TRPM2 channel via tyrosine phosphorylation.

Methods: In order to determine whether the Fyn kinase regulates the TRPM2 channel, we will use Ca²⁺ imaging to establish whether calcium influx is altered in induced TRPM2 expressing HEK cells (T-Rex cells) transiently transfected with Wildtype Fyn, dominant negative Fyn, or Constitutively Active Fyn. Moreover, in the same cell system, TRPM2 currents will be measured using the whole cell recording technique. Also, we will use immunoprecipitation to investigate whether there is increased TRPM2 phosphorylation in the presence of the Fyn mutants. With aims of investigating whether A β activates Fyn, the protein will be immunoprecipitated following A β treatment and probed for phosphorylation at specific activation sites.

Results: We have established that TRPM2 currents are potentiated in the presence of Wild Type Fyn.

Research Theme: Cognition and Behavior

Yohimbine stress increases oxycodone dose effect in reacquisition of conditioned place preference in rats

Amanda T. Campbell & Francesco Leri

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To investigate the effect of yohimbine-induced stress on reacquisition of oxycodone conditioned place preference, three studies were conducted in male Sprague-Dawley rats using a common procedure involving: place conditioning (0, 0.25, 2 or 5 mg/kg oxycodone; x 3 sessions), extinction (vehicle x 3 sessions), and reconditioning (0.25, 2 or 5 mg/kg oxycodone; x 1 session). Intraperitoneal yohimbine (2.5 mg/kg) or saline injections were administered 30 min prior to reconditioning. A dose dependant decrease in CPP was observed following conditioning, where the 0.25 mg/kg dose groups exhibited greater preference for the drug-paired environment than the 2 mg/kg dose group. No CPP was found for the 5 mg/kg dose group. Reacquisition of CPP was observed only in rats reconditioned with 2 and 5mg/kg oxycodone. A trend toward reacquisition of CPP was observed in the 0.25 mg/kg oxycodone group pre-treated with yohimbine, while yohimbine pre-treatment eliminated the place preference observed in the 5.0 mg/kg dose group. These data suggest that high doses of oxycodone produce aversive effects in rats, and indicate that yohimbine-induced stress may increase the effects of a given drug dose in reacquisition of conditioned place preference.

Research Theme: Cognition and Behavior

Examining the role of acetylcholine in destabilizing reactivated object memories

Justine Carlin, BSc. Student, Undergraduate Studies in Psychology: Brain & Cognition; Boyer Winters, PhD, Department of Psychology, University of Guelph

This research focuses on gaining a greater understanding of the role of acetylcholine in the dynamic nature of memory storage. When a memory is encoded, it is initially labile and requires protein synthesis in order to stabilize through the process of consolidation. Upon reactivation, stable memories are once again rendered labile and sensitive to disruption through destabilization of the memory trace. Novel protein synthesis is required in order to restabilize this memory through the mechanisms of reconsolidation. Recently, boundary conditions, including memory age and strength, have been shown to influence whether or not memories undergo destabilization. Additionally, the presence of novel information at the time of reactivation is sometimes required to destabilize an otherwise resistant memory trace. Importantly, encoding of novel information can be facilitated by acetylcholine. This study employed the spontaneous object recognition paradigm in rats to examine the possible involvement of cholinergic transmission in the novelty-induced destabilization of otherwise resistant object memories. Rats explored a pair of identical objects in the sample phase and, after a 48h delay, were given systemic injections of combinations of saline, MK-801 (NMDA receptor antagonist, previously shown to disrupt object memory reconsolidation), and the muscarinic receptor antagonist scopolamine prior to reactivation of the memory trace in the presence of a novel contextual cue (altered floor texture). Twenty-four hours later, rats were tested for discrimination between the familiar object and a novel object. Results replicated the finding that MK-801 can block object memory reconsolidation. However, when scopolamine was administered in combination with MK-801 upon reactivation of the memory, choice discrimination returned to control levels, indicating intact recognition memory. Thus, scopolamine appears to prevent destabilization of an object memory when reactivated in the presence of novel information. A second experiment involving oxotremorine, a direct agonist of muscarinic receptors, indicated that enhancing cholinergic transmission can encourage destabilization of an otherwise resistant object memory. These results highlight the role of acetylcholine in the memory reconsolidation process and extend our understanding of the neurobiological mechanisms of memory storage.

The role of taste and calories in access-induced excessive sweet solution intake by the rat

Adam Celejewski, Ph.D. Student, Graduate Studies in Psychology, Wilfrid Laurier University; Roelof Eikelboom, PhD, Wilfrid Laurier University

Access schedules to weak (4%) sucrose solutions can have a marked impact on consumption (Hewitt & Eikelboom, 2008). Rats provided with sucrose solutions on Discontinuous Access (DisA) schedules, 24 h once every three or four days, escalated their intake markedly relative to rats with ad lib or Continuous Access (ConA) to the same solution. In contrast to DisA rats, ConA rats maintained stable and lower sucrose intake levels. The intake differences between rats with DisA and ConA persisted after access schedules were changed to equivalent, alternate day sucrose exposures. The experiments reported here further examined factors contributing to these access-induced consumption changes by substituting saccharin for sucrose to eliminate or reduce postingestive properties (e.g. glycemic effects, insulin release, metabolizable energy) of sucrose. In Experiment 1, rats with DisA escalated their intake to consume much more saccharin solution than ConA rats over a range of concentrations (1, 0.5, 0.25, and 0.125%). Taste, even without the postingestive properties evident with sucrose, drove the access consumption effects and these effects were durable and long-lived. Once saccharin consumption differences were established between DisA and ConA rats in Experiment 2, they were maintained for over 50 equal access days even when saccharin was replaced with sucrose. Because single, longer periods of saccharin abstinence can lead to a transient intake increase known as the Deprivation Effect (DE) which may be related to DisA induced increases, DE expression was examined in rats with DisA or ConA to 0.25% saccharin (Experiment 2) and 4% sucrose (Experiment 3). In Experiment 2, a robust saccharin DE was observed in all rats but the intake differences induced by initial DisA/ConA were maintained. In Experiment 3, DisA/ConA differences emerged for sucrose but no DE was observed after either three or nine days of sucrose abstinence. Collectively these findings suggest that taste is sufficient for driving DisA/ConA induced differences and that the DisA/ConA difference and the DE may be under control of separate factors. Overall, these results highlight the importance of taste and not postingestive properties in access consumption effects and suggest that not all experiences with access interruptions are the same.

Research Theme: Disorders of the Nervous System

Inducibility of heat shock proteins by celastrol and temperature elevation varies with developmental age of primary cortical cultures

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Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), have been termed 'protein misfolding disorders' that are characterized by the neural accumulation of protein aggregates. Upregulation of heat shock proteins (Hsps) could alleviate neurodegeneration by modulating protein misfolding in affected neural cells. Hsps are 'protein repair agents' that provide a line of defense against misfolded, aggregation-prone proteins. Primary cortical cultures have been widely employed as a model system for studies that include the investigation of neuroprotective mechanisms. Here we investigate heat shock proteins along the time course of developmental age of rat primary cortical cultures. We noted that Hsp27 and Hsp32, but not Hsp70, demonstrated basal expression in the absence of inducing agents, with Hsp32 arising at an earlier culture age compared to Hsp27. Celastrol induced a robust induction of Hsp27 and Hsp32 but this was achieved only at culture ages that showed basal expression. Induction of Hsp70 by celastrol was observed solely in cultures of advanced age. Temperature elevation was a less effective inducer of Hsp27 and Hsp32 at all culture ages compared to celastrol and failed to induce Hsp70 at any stage. These results demonstrate that inducibility of potentially neuroprotective Hsps varies with the developmental age of primary cortical cultures and correlates with basal Hsp expression levels. In addition, temperature elevation, the classical inducer of the heat shock response, proved to be a less effective inducer of Hsps compared to celastrol which shows promise as a potential pharmacological agent to counteract protein misfolding, a central feature of neurodegenerative diseases. (Supported by grants from NSERC to Ian Brown who holds a Canada Research Chair [Tier I] in the Neurobiology of Stress)

Research Theme: Cognition and Behavior

I remember μ : The effects of methadone and heroin on memory retrieval in rats

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In humans, methadone is a long-acting opioid agonist used to treat opioid dependence. Although widely prescribed, little is known about possible side effects of methadone on learning and memory when administered acutely or chronically. In these experiments, we compared the effects of acute and chronic methadone, as well as the effect of acute heroin on memory retrieval in rats, and assessed whether deficits on memory tasks are attributable to motor or emotional side effects.

Experiment 1 assessed the effect of acute methadone (0, 1.25, 2.5 or 5 mg/kg SC) on the retrieval of an appetitive spatial memory task motivated by Froot Loops in a 10-arm parallel maze. Acute methadone impaired performance, but this was attributable to dose-dependent changes in motor activity. In the few rats injected with the highest doses that did move, memory accuracy was not affected. Experiments 2 & 3 examined the effects of acute methadone (0, 1.25, 2.5, or 5 mg/kg SC) and heroin (0, 0.03, 0.3, 3 mg/kg SC) on memory retrieval in an aversive spatial task (Barnes maze) motivated by escape from a bright light and loud acoustic stimulus. The highest dose of methadone impaired memory retrieval, independent of motor deficits. In fact, in this task, rats injected with the highest dose of methadone moved more than rats injected with lower doses and controls. However, rats treated with the highest methadone dose also displayed emotional hyper-reactivity as indicated by enhanced acoustic startle. Contrary to methadone, heroin had no effect on memory accuracy, although the highest dose increased latency to complete the task and total distance moved. Further, heroin had no effect or decreased acoustic startle reactivity. Experiment 4 explored the effects of steady-state methadone (SSM) (0, 10, 30, 55 mg/kg/day) administered via osmotic mini pumps on memory retrieval in the Barnes maze, as well as on acoustic startle reactivity and locomotion. SSM had no effect on memory retrieval or startle reactivity, and had no effect or enhanced locomotor activity.

These experiments suggest that neither acute methadone nor heroin have effects on accuracy of memory retrieval, but both opioids can induce performance deficits on memory tasks by altering motor behaviour and reactivity to aversive stimuli. When methadone is administered in rats to mimic steady-state maintenance, no effects on memory retrieval, locomotion or emotionality are noted. Supported by NSERC

Analysis of smoking cessation drug, Bupropion, in rats to determine its effects on foetal and infant development in three behavioural paradigms

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Foetal and infant development has been shown to be impaired in pregnant and nursing mothers who smoke. Children born to smoking mothers are exposed to over 4000 chemicals including nicotine¹. Foetal and neonatal exposure to nicotine results in an increased incidence of cognitive and behavioural disorders, due to nicotine neuroteratogenicity²⁻⁴. Bupropion (BUP) is a smoking cessation drug that has been shown to inhibit dopamine uptake, inhibit the neuronal nicotinic receptor and act as an atypical antidepressant. BUP in human trials has been shown to be effective for smoking cessation and as an antidepressant; however its effects on foetal and infant development are unclear⁵.

In this pilot study, female Wistar rats were administered 5mg/kg/day or 10mg/kg/day of BUP for 2 weeks prior to mating until weaning. Female and male offspring were then behaviourally analyzed for sensorimotor gating, social interaction and locomotor activity at 8 weeks of age. Deficits in sensorimotor gating, measured through Pre Pulse Inhibition (PPI), are indicative of neurological disorders such as schizophrenia and Alzheimer's disease. Locomotor activity was measured for 4 hours following an amphetamine challenge. Altered locomotor activity is suggestive of behavioural supersensitivity and parallels overall changes in the activity of dopamine neurons. Social interaction was recorded in an open chamber setting to measure traits of anxiety and social isolation. Offspring of mothers administered BUP had no deficits in PPI, social interaction or locomotor activity when compared to controls. These preliminary results indicate that offspring of female rats administered BUP during mating, pregnancy and nursing exhibited no behavioural abnormalities in three behavioural paradigms.

In this pilot study, BUP has shown to act as a neurologically safe drug during pregnancy and infant development in three behavioural paradigms that are indicative of dopaminergic action. On these grounds BUP has shown promise to act as a viable replacement for nicotine replacement therapy.

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Research Theme: Cognition and Behavior

Serotonergic modulation of startle is influenced by social status in Wistar rats

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The acoustic startle response (ASR) is a protective reflex to a brief acoustic stimulus and serves to prepare an animal for a fight or flight response. The ASR can be attenuated through habituation or prepulse inhibition (PPI). These startle attenuation processes are important measures of sensory filtering, which is important to everyday life in humans and animals to prevent sensory flooding and cognitive fragmentation. Deficits in habituation and/or PPI are seen in many human neuropsychiatric disorders characterized by disrupted sensory filtering.

There is conflicting literature about the effect of serotonin on startle. The intent of this experiment was to study the effect of a systemic increase of serotonin on startle and startle modulations in rats, taking into account their social status. We hypothesize that serotonin disrupts PPI while it does not affect habituation, and that dominant and subordinate animals are affected differently by SSRI treatment because they have different natural levels of serotonin due to their different aggression levels.

Rats were observed fourteen times (2x per day) and dominant and submissive behaviours were recorded during both light and dark cycles. During each observational period, a scoring system was used to determine the dominant and subordinate rat for each cage pair. After all behavioural testing was complete the results were tallied to determine the overall dominant animal in each cage. Acoustic startle testing was performed four times: The first was a control, after an injection of saline. The second was after a single subcutaneous injection of 10mg/kg clomipramine hydrochloride, a common serotonin reuptake inhibitor (SSRI), and served as acute SSRI testing. The SSRI injections were continued for two weeks, every twelve hours and a chronic SSRI startle test was performed. After a recovery period of two weeks, a final startle test was conducted. Each test consisted of a block of 30 identical startle habituation trials, and a block of PPI trials with various prepulse intensities (0dB, 75dB, or 85dB) and two interstimulus intervals (ISI, 30ms or 100ms) at a pseudorandomized order. Baseline startle amplitudes, habituation scores, and prepulse inhibition percentages were calculated and analyzed.

Baseline startle amplitudes increased throughout the injection protocol and reached a maximum after the recovery period in all rats. Habituation and PPI (85 db prepulse) was increased in subordinate rats after chronic treatment with clomipramine, but not in dominant rat. However, with a 75 dB prepulse, increased PPI was observed in dominant rats after acute and chronic SSRI treatments and in subordinate rats after chronic treatment only. This effect was only significant with a short ISI, not with 100 ms ISIs.

Our results suggest that social status and protocol parameters (prepulse intensity/ISI) play an important role in studies involving serotonergic modulation of startle, and they have to be taken into account when setting up an experiment.

Research Theme: Disorders of the nervous system

BDNF mRNA concentration is elevated in a mutant mouse model of bipolar disorder and does not correlate with reduced manic-like behaviour following exercise

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Bipolar disorder (BD) is a debilitating chronic mental illness of unknown etiology. It is characterized by manic or elevated mood states that are interspersed among depressive episodes. Serum BDNF is reportedly decreased in BD patients experiencing a manic or depressive episode and in euthymic patients in the late stage of BD, but not those in the earlier stages. Together, these studies implicate reduced BDNF in both the acute changes of mood state as well as the progression of BD. In contrast, aerobic exercise is a potent upregulator of BDNF and is a well established neuroprotector, neuromodulator and antidepressant.

Mice who carry an inactivating mutation in the neuron-specific $\alpha 3$ isoform of the Na⁺,K⁺-ATPase membrane pump, known as *Myshkin* mice, have recently been shown to display a behavioural phenotype that is very similar to that of bipolar patients in a manic state. Interestingly, the manic phenotype of these *Myshkin* mice was abolished following 6 weeks of wheel running. *Myshkin* runners exhibited reduced exploratory behaviour in an open field, decreased risk taking behaviour in an elevated plus maze and light-dark box and improved pre-pulse inhibition. Based on this evidence, we hypothesize that *Myshkin* mice will have reduced BDNF compared to wild-type mice and that the normalization of behaviour in *Myshkin* mice following exercise is mediated by an elevation in BDNF.

12 *Myshkin* mice and 12 wild-type control mice were housed 2 or 3 per cage and divided into sedentary or running groups. Running mice had unlimited access to a running wheel for 6 weeks, while sedentary mice were housed in cages with a stationary wheel. Running normalized the behavior of *Myshkin* mice. Real-time PCR was used to quantify BDNF and β -actin mRNA expression in the hippocampus and cortex of all mouse populations to determine whether levels of BDNF differed between wild-type and *Myshkin* mice and between runners and non-runners. We found that contrary to our hypothesis, *Myshkin* mice did not exhibit decreased BDNF mRNA compared to wild-type mice. Furthermore, although wild-type runners showed a trend towards increased BDNF when compared to wild-type non-runners, running had no effect on BDNF mRNA levels in *Myshkin* mice. Our BDNF data conflict with the proposed role for the neurotrophic factor in recovery from mania. It is important to note that our studies examine BDNF mRNA in brain rather than serum BDNF protein as assayed in human studies. Brain BDNF mRNA levels may differ from peripheral BDNF levels or may not reflect protein levels. Lastly, the effect of running on *Myshkin* behavior may not be mediated by BDNF. The common mood stabilizers lithium and valproate, for example, both normalize behaviour, but only lithium increases BDNF protein in the brain. Further studies are needed to elucidate the molecular underpinnings responsible for the beneficial effects of aerobic exercise on *Myshkin* mouse behaviour.

Research Theme: Disorders of the Nervous System

Increased USVs positively associated with number of copies of *Gtf2i*, a gene deleted in WBS

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Williams Beuren Syndrome (WBS) is a developmental disorder caused by the hemizygous deletion of genes on chromosome 7q11.23. WBS has a neurocognitive profile, that includes low IQ, visuospatial deficits, strength in expressive language, hypersociability, and non-social anxiety. By contrast, duplication of this region (Dup7q11.23) results in speech and language deficits and social anxiety, including maternal separation anxiety. *Gtf2i* is one of the 26 genes commonly deleted/duplicated in WBS, and analysis of individuals with atypical deletions have implicated this gene in the neurocognitive profile. We have generated mice with reduced or increased genomic copy number of *Gtf2i* and corresponding changes in mRNA and protein expression, to examine the effects of altering the dosage of this gene. We have found that postnatal day 7 (P7) mouse pups with either heterozygous or homozygous duplication of *Gtf2i*, show increased separation induced ultrasonic vocalizations (USVs), in contrast to P7 pups with heterozygous deletion of *Gtf2i*, that exhibit reduced separation USVs. Furthermore, preliminary USV data in adult mice show that male mice with reduced *Gtf2i* copy number exhibit reduced mating-associated USVs when paired with females, whereas mice with increased *Gtf2i* copy number exhibit hypersociability. These results suggest that GTF2I plays a significant role in the anxiety and social behaviour phenotypes seen in patients with WBS and Dup7q11.23.

Research Theme: Development

Developmental distribution of NMDA receptor subunit mRNA in auditory brainstem of rat

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To compute interaural sound level differences, principal neurons of the lateral superior olive (LSO) integrate converging excitatory inputs from the cochlear nucleus with inhibitory inputs from the medial nucleus of the trapezoid body (MNTB). This computation requires precise tonotopic organization, and major functional tonotopic refinement is accomplished during the first postnatal week. During this period of refinement, synapses in the nascent inhibitory MNTB-LSO pathway release glutamate, which may mediate developmental plasticity through NMDA receptors (NMDARs). The GluN2A and GluN2B NMDAR subunits confer widely different properties on NMDARs, substantially affecting plasticity.

We assessed postnatal developmental expression of these NMDAR subunits in the LSO and MNTB using quantitative in situ hybridization in tissue from 10 litters, ages postnatal day 1 to 36 (P1-36). In the LSO, GluN1 expression was stable P1-15, and declined by ~50% between P15 and P36 (adult). GluN2A expression increased 100% P1-P15 whereas GluN2B expression decreased 70% P1-36, with GluN2A/2B ratio increasing 3-fold between P8 and P15. In the MNTB, GluN1 expression increased 50% from P1 to a peak at P15 and subsequently declined to P1 levels at P36. GluN2A was expressed earlier and at higher levels in the MNTB than in LSO, and the rise in GluN2A/2B ratio occurred earlier in MNTB, between P1 and P8. These data corroborate electrophysiological results showing high levels of functional GluN2B in the first postnatal week and point to a GluN2B >> GluN2A subunit switch at P8, similar to the subunit switch seen in other areas of the nervous system.

Research Theme: Cognition and Behavior

The effects of progesterone and metabolite allopregnanolone on social learning in female mice

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The social transmission of food preferences (STFP) in rodents involves a naïve “observer” animal developing a food preference for a novel food that it smells on a “demonstrator” animal’s breath, allowing the observer to avoid the costs of individual trial-and-error learning. Performance on this task in female mice is related to the phase of the estrous cycle, likely due to different circulating and brain levels of gonadal hormones such as progesterone and estrogens. Progesterone is a neurosteroid that acts through progesterone receptors in the brain, but can also act through conversion to several metabolites. One of the most important is allopregnanolone (AP), a positive allosteric modulator of the GABA_A receptor. Both progesterone and AP affect cognitive functions and social behaviour; and the effects of progesterone could be mediated by AP. We therefore tested the effects of acute administration of progesterone and AP on STFP before (1 hour before for progesterone, 20 minutes for AP) or immediately after the demonstrator-observer social interaction. The observer mice were treated with 10, 20, and 40 mg/kg progesterone or 5, 10, and 20 mg/kg AP. Mice in the control group were treated with sesame oil (progesterone vehicle) or 2-hydroxypropyl- β -cyclodextrin (AP vehicle). Mice treated with the highest doses of progesterone prior to learning showed a prolonged preference for the demonstrated food, while those treated with the same doses after learning had impaired performance. The middle and high doses of AP administered pre-acquisition shortened the duration of the food preference, while the lowest dose prolonged the preference. All doses of post-acquisition AP prolonged the preference for the demonstrated food. The different effects of the two drugs on this task suggest that progesterone affects performance not only through its conversion to AP, but also through other neural mechanisms (e.g. interactions with neurotransmitter systems, and/or protein synthesis). Pre-acquisition progesterone and AP may have also affected behaviour during social interaction, which is essential for learning a food preference.

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Hot or Not: The effect of response inhibition on affective value and incentive-salience of motivationally-relevant stimuli

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Motivation-related processes are critical to determining thought and behaviour. However, these processes may be modulated by attentional and response-related cognitive processes. Specifically, visual stimuli that indicate that a motor response must be withheld are later given more negative affective evaluations than stimuli that do not require any response inhibition (the inhibitory devaluation effect). Although neutral and mildly affectively positive and negative images are emotionally devalued when associated with an inhibited response, it is not clear whether the same effect is seen when the to-be-inhibited stimuli automatically invoke a strong motivational response. These experiments use a series of Go/Nogo tasks, in which Nogo images serve as a “do not respond” cue, to demonstrate a decrease in affective ratings for the Nogo images even when those images initially invoked strong approach motivation. In Experiment 1, participants first played a Value Learning game in which selecting red (or green) images allowed them to win money, while selecting green (or red) images resulted in losing money. They then performed a Go/Nogo task with either the previous-rewarding or previously-losing images as Nogo (inhibited) images. Results indicated that inhibition of both reward-linked and loss-linked stimuli lead to emotional devaluation, although the effect was more robust for loss-linked images. Experiment 2 used sexually-appealing images of males and females as Go and Nogo cues to demonstrate that images of both a participant’s preferred and non-preferred sex were emotionally devalued when shown as a Nogo cue. This inhibitory devaluation may index changes in the emotional valence of the inhibited stimulus, in its motivational value, or both. Experiment 3 examined the effect of having previously inhibited a category of images (either motivationally-relevant or non-relevant) on the motivation to act towards these stimuli. Male participants who inhibited images of attractive females were later less likely to press a button in order to see more images of that type than participants who did not inhibit these images. This demonstrates that attentional and response-related cognitive processes may modulate not only the affective valence associated with a stimulus, but also its motivational value, directly affecting behaviour.

Research Theme: Cognition and Behavior

A Computational model of reading acquisition and developmental dyslexia

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Dual-route computational models of reading have been successful in simulating human performance in word recognition tasks, but they do not have the necessary learning mechanisms to simulate the developmental progression of reading acquisition. The proposed research addresses this issue by incorporating a self-organizing learning system within a Connectionist Dual Process model of reading, which is currently the most successful model of word reading. An outline for the proposed learning system will be presented and demonstrate how it will enable the model to simulate the development of a child's mental lexicon for spoken and written words. An additional goal is to describe how particular processing deficits arise within the reading system and can result in dyslexic reading impairments. Validation of the model's accuracy is based on the model's ability to simulate the reading performance patterns of both dyslexic and non-impaired developing readers.

Research Theme: Disorders of the Nervous System

Diabetes as risk factor in Alzheimer's disease. Evaluation of the brain in a type 2 diabetes (t2d) rat model combined with Alzheimer

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The purpose of this work is to evaluate the relationship of diabetes as a risk factor for Alzheimer's disease (AD). Worldwide, 3.2 million diabetes-related deaths are reported annually and is estimated that 30 million have AD with 4.6 million new cases annually. A very well-known factor related to AD is age but other risk factors are hypertension, stroke and other vascular pathologies. Amyloid beta protein (Abeta) and neurofibrillary tangles (NFT) are the hallmarks of AD in post-mortem nervous tissue. Diabetes leads to cognitive decline. Abeta, the main pathogenic factor in AD development, is eliminated by glycation end products and degraded by the insulin degrading enzyme. In addition a metabolic change in the regulation of insulin stimulates secretion of Abeta and promotes brain inflammation with changes in glucose metabolism. Hyperglycaemia is able to induce synapse plasticity and leads to cognitive decline. Glycation of tau protein promotes production of NFT. Upregulation of inflammatory mediators and kinases as result of inflammation lead to disruption of mitochondrial function and reactive oxygen species are released inducing cell death and apoptosis. In this project a rat model of spontaneous onset type 2 diabetes (Zucker diabetes fatty rats, ZDF) is combined with a model of AD induced by injection of the peptide fragment of Abeta (Abeta25-35) in the lateral ventricles. The aim of this work is evaluate the presence of different cell markers related to neurodegeneration, oxidative stress and neuroinflammation, insulin receptors and growth factors in different brain regions. The hypothesis is that the combined models of AD and diabetes will result in much greater neuropathology and cognitive impairment than either condition alone. OX6 is a neuroinflammation detector by mean of microglia activation. ZDF Abeta rats showed a high number of microglia cells in the hippocampus, corpus callosum and thalamus. ZDF sham rats showed a high presence of microglia in thalamus and lower amount in hippocampus and corpus callosum. Lean Abeta, the control group of this rat model, showed a high number of cells in the hippocampus with fewer in the corpus callosum and thalamus. Lean sham rats had few or no microglia in the brain regions examined. These results demonstrate that type 2 diabetes leads to neuroinflammation in vulnerable regions of the brain and that the combined diabetic/AD model exacerbates this condition.

Research Theme: Cognition and Behavior

Rapid regulation of learning by the novel GPER/GPR30 estrogen receptor

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G protein-coupled estrogen receptor 1 (GPER/GPR30) is a novel, membrane bound, estrogen receptor (ER) capable of mediating rapid signaling events in response to estrogen. Chronic treatment of G-1, a selective GPER agonist, enhanced the rate of acquisition of a spatial learning task in ovariectomized rats. Previously, our lab demonstrated that ER α agonist propyl pyrazole triol (PPT) and ER β agonist diarylpropionitrile (DPN) affected social recognition, object recognition and object placement learning within a rapid time scale (Phan A et al., *Endocrinology*, 2011, in press). The fact that GPER is expressed in areas of the adult rat brain important for learning and memory such as the hippocampus and forebrain, suggests that GPER could mediate rapid estrogenic effects on learning. Therefore, we used ovariectomized CD1 female mice to investigate the effects of a GPER selective agonist, G-1 at 0, 1, 6, 10 or 30 μ g/kg, on social recognition, object recognition and object placement learning, within 40 min of subcutaneous drug administration. Results show that social recognition was improved at the 6 μ g/kg dosage and object placement learning was improved at the 6 μ g/kg and 10 μ g/kg dosage. The analysis of the effects on object recognition is on going. These preliminary results suggest that GPER, in addition to ER α and ER β , is involved in rapid estrogen-mediated learning. These results also support the role of GPER as an estrogen receptor important in non-genomic signaling. To the best of our knowledge, this is the first report of the rapid effects of GPER on learning and memory.

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Research Theme: Development

Dynamic protein expression patterns during embryonic development in the chick cerebellum

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The cerebellum is a functionally complex region of the brain associated with the refinement and coordination of motor skills. Although the details of cerebellar development are well understood in mammals for groups such as birds far less is known. We used western blot analysis and immunohistochemistry to characterize three antigens commonly used to describe cerebellar morphology in a broad range of species: calbindin, calretinin and zebrin II. We documented the expression of these antigens throughout chick embryogenesis from E10 to E20. Calbindin immunostaining identifies the initial appearance of immature Purkinje cells in dense clusters at E10. Calbindin-positive Purkinje cells mature (forming extensive dendritic arbors; ~E14) and become reorganized into a uniform monolayer asynchronously across the cerebellum (from posteromedial to anterolateral). Calretinin-positive cells include subsets of interneurons, mossy fiber terminals and Purkinje cells beginning at E12.5. Calretinin expression is dynamic, peaking at E16 and then diminishing at later embryonic timepoints. Zebrin II expression is restricted to Purkinje cells, beginning at E14. Similar to Calbindin, Zebrin II-positive Purkinje cells first appear asynchronously across the cerebellum. By late embryogenesis (E16) Zebrin II is globally expressed. Ultimately, some of these Purkinje cells secondarily become Zebrin II-negative, revealing a conserved pattern of parasagittal stripes. We conclude that the dynamic and asynchronous antigen expression patterns characteristic of cerebellum development in the chick closely resembles those seen in mammals.

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Research Theme: Neural Excitability, Synapses, and Glia: Cellular Mechanisms

The psychoactive inhalant toluene disrupts synaptic transmission at perforant path – dentate gyrus synapses in the anesthetized rat in vivo

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Toluene, a psychoactive volatile organic solvent commonly found in adhesives, paint products and gasoline, is inhaled for its euphoric and intoxicating effects. Toluene inhalation additionally results in cognitive disturbances including impairments in learning and memory, suggesting that toluene may change the physiology of neurons in the hippocampus – specifically within the dentate gyrus of the hippocampus, which serves as an entry point for the processing of memory information in the brain. In the present study we tested the hypothesis that toluene modifies synaptic transmission at perforant path – dentate gyrus synapses. Multi-channel extracellular field potential recordings were performed in anesthetized male and female Long Evans rats (n=40; 60 to 105 days old) *in vivo*; field potentials were evoked in the granule cell layer of the dentate gyrus via stimulation of the fibres of the ipsilateral perforant path. Exposure to toluene vapour increased the rise slope of the field potential and reversibly potentiated population spike amplitude while decreasing its latency to peak in all female and most male rats. Paired-pulse analyses revealed that toluene vapour increased field potential rise slope paired-pulse ratios, while prolonging the recovery time of population spike amplitudes during repeated activation. A toluene-evoked decrease in the power of the hippocampal theta rhythm was measured via power spectral analysis. Our results demonstrate that toluene disrupts synaptic transmission at perforant path – dentate gyrus synapses, and provides one potential explanation for the behavioural deficits noted following exposure to toluene vapours.

Research Theme: Cognition and Behavior

Assessing crossmodal object recognition in a rat model of schizophrenia

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Animal models are commonly used to investigate the neural bases of schizophrenia-like behaviour in order to gain a greater understanding of the disease in humans. The cognitive symptoms of schizophrenia include a reduced ability to integrate multisensory information. We have recently developed a crossmodal object recognition task for rodents that could prove to be highly sensitive to such a cognitive deficit. The crossmodal object recognition task assesses the ability of rats to recognize an object visually when they have only previously explored the object tactually. In the current study, we used the crossmodal object recognition task to examine multisensory integration in a rat model of schizophrenia (using sub-chronic administration of MK-801, a non-competitive NMDA receptor antagonist). Rats received twice daily systemic (ip) injections of either MK-801 or saline for seven days. Following a seven day washout period, the animals were tested in the crossmodal and unimodal (tactile or visual) object recognition tasks. Rats that received the MK-801 treatment were impaired on all object recognition tasks (tactile only, visual only, and crossmodal) when the delay between sample and test phases was 1 hour. To further assess the sensitivity of the crossmodal task, we shortened the time between initial sampling of objects and the recognition test to 30 sec; in this experiment a selective impairment in crossmodal object recognition was seen in the MK-801 treated rats, with no impairment in the tactile-only or visual-only tasks. These results indicate the high sensitivity of the crossmodal task to cognitive deficits in these animals, and are consistent with findings indicating impairment in multisensory integration in schizophrenia. In two additional experiments, we assessed the potential for remediation of these impairments with nicotine. Smoking occurs with a high prevalence among schizophrenic patients, and studies with rat models of the disease have shown that nicotine can reduce some of the cognitive symptoms induced by NMDA receptor antagonism. When nicotine was administered systemically prior to the sample phase, the impairment in all three tasks with a 1 hour delay was attenuated. In addition, with the shorter retention delay, MK-801 rats given nicotine performed significantly better on the crossmodal task compared to control animals receiving nicotine. These results support recent suggestions that nicotinic receptor agonism may provide a fruitful treatment option for cognitive impairment in schizophrenia and, further, suggest that nicotinic receptors, or the systems affected by them, may be hypersensitive in animals that have received subchronic administration of NMDA receptor antagonists. Continuing assessment of these animal models using the crossmodal object recognition paradigm should further elucidate the neural bases of these cognitive effects.

Research Theme: Disorders of the Nervous System

Association of MET C allele and cortical thickness in autism spectrum disorder

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Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental condition characterized by impairments in behavioral flexibility, social interaction, and communication. Appropriate social behavior depends on the wiring together of relevant sensory and cognitive neural circuits during development. Several functional variants in the gene encoding the MET receptor tyrosine kinase are associated with ASD and a basic mechanistic hypothesis relating *MET* gene function to ASD has been proposed: Decreased MET protein expression during development increases the risk of ASD-relevant circuit miswiring. Recent work shows highly divergent patterns of MET/Met protein expression in the neocortex of primates compared with rodents. In the mouse neocortex, Met expression is broadly distributed. In the macaque, however, robust MET is localized to the posterior cingulate, inferior temporal, posterior parietal, and visual cortices, including face-processing regions. This pattern is consistent with the particular importance of vision in the social milieu of primates, and suggests a conserved developmental function of the MET receptor in facilitating the connectivity between limbic and neocortical circuits that gives rise to appropriate social behavior. The *MET* promoter variant, rs1858830, is a common G-to-C single nucleotide polymorphism (SNP) that results in the reduction of gene transcription and transcription-factor binding; the *MET* C allele has been consistently associated with both social and communication phenotypes of autism. Given that MET receptor tyrosine kinase signalling plays a critical role in neurodevelopment—likely by facilitating connectivity across socially-relevant neural circuits—we aim to investigate the down-stream influence of the *MET* C allele on morphological characteristics of brain regions involved in social processing of visual information. We will employ magnetic resonance imaging (MRI) to investigate the genotype-phenotype associations of the *MET* C allele with cortical thickness in developing autistic brains (n= 16, mean age= 14.94) compared to age and gender-matched controls. MR images will be acquired using a GE short-bore 3-T MRI system (General Electric Healthcare, Milwaukee, WI) and a standard eight-channel head coil. Anatomic MRIs will be processed using the CIVET pipeline via the CBRAIN distributed neuroimaging platform. T1 images will be registered to the ICBM152 nonlinear sixth generation template using a 12-parameter linear transformation, corrected for inhomogeneity using the N3 technique, and tissue-classified. Deformable models will then be used to create the white/gray matter and gray matter/cerebrospinal fluid interfaces for each hemisphere separately, resulting in four surfaces of 40 962 vertices each. Distances between the white and gray surfaces will be determined using the Laplacian method. Finally, the thickness data will be blurred using a 20-mm surface-based diffusion-blurring kernel in preparation for statistical analyses. Statistical analyses will use the Surfstat package in MatLab. We hypothesize the *MET* C allele will confer risk for decreased cortical thickness in associative brain regions involved in the integration of visual social stimuli including the associative visual cortices, inferior temporal cortices, parahippocampal gyrus, the posterior cingulate cortex, and in the pars triangularis. These data will contribute to the evaluation of the afore-mentioned hypothesis relating *MET* gene function to ASD.

Research Theme: Cognition and Behavior

The effects of chronic social stress in adolescence on adult sexual behaviour in male rats

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Previous research has demonstrated that male sexual behaviour consists of two distinct components, motivation and performance. These behaviours do not emerge until adolescence when the brain is undergoing extensive maturation. In rodents, exposure to chronic stress during critical periods of development has been shown to have long-term programming effects that are observable in adulthood. Therefore, we hypothesized that social stress in adolescence would cause impairment to both sexual motivation and performance in adult male rats. Between postnatal day (PND) 30 and 45 male Long-Evans rats were exposed daily to social instability stress (SS). Beginning at PND 84, SS and control (CTL) males were paired with a sexually receptive female for five sessions to measure copulatory ability. Only sessions 1 and 5 were included in the analysis. Sessions occurred once every three days, except between sessions 4 and 5 where an additional three days were used to measure sexual motivation via a partner preference paradigm. The results of the copulation tests demonstrated that CTL males displayed significantly more mounts compared to SS males during session 1 ($p = .035$). However, no differences in sexual performance were observed on session 5. The results of the partner preference test indicated that CTL males did show a greater preference for a receptive female than an unreceptive female compared to SS males ($p < .001$). These results suggest that chronic stress administered during adolescence may have long-term effects on sexual motivation, but not performance.

Research Theme: Sensory and Motor systems

Physiological and morphological specificity of the medial olfactory bulb region in the sea lamprey

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In the olfactory bulb of the sea lamprey, medial located mitral cells are part of an oligosynaptic pathway that transits through the posterior tuberculum to reach locomotor command neurons, whereas nonmedial mitral cell axons mostly project to forebrain structures. In this study we compare properties of odour specificity and mitral cell morphology between this medial region and the remaining olfactory bulb regions. Multi-unit responses to odours in an *ex vivo* preparation revealed that the medial region was responsive to basic amino acids, lamprey sex pheromones, and migratory pheromones while the lateral region was responsive only to amino acids. These properties support previous findings of diverse odour qualities triggering olfactory-locomotor transformation through the medial region of the olfactory bulb and suggest that the remaining bulbar regions exhibit chemotopy. The dendrites and cell bodies of the medial mitral cells were confined to the glomerular layer compared to the cell bodies of non-medial mitral cells, which were located largely proximal to the glomerular layer. Although the cell morphology did not differ between the medial and non-medial mitral cells, the medial somata were larger. These findings show unique neurophysiological and neuroanatomical properties in the medial region of the olfactory bulb that is involved in olfactory-locomotor transformation. Funding provided by the GLFC and NSERC.

Research Theme: Cognition and Behavior

Dissecting the neural architecture of reversal learning: Overcoming avoidance versus inhibiting responding

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Reversal learning is the ability inhibit or switch responding to an object when the object-reward contingency changes. Reversal learning deficits are related to behavioural abnormalities such as impulsiveness and disinhibition, and a number of psychiatric disorders. A range of neural regions play a role in this process, including dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), and inferior frontal gyrus (IFG). However, the specific functional contribution of these regions has been elusive. A recent pharmacological manipulation in marmosets demonstrated that reversal learning involves multiple, neurochemically dissociable, components including inhibiting a response to a previously rewarding stimulus, and overcoming avoidance of a previously punished stimulus.

We used fMRI and an experimental task adapted from a recent neurochemical study in marmosets to parse neural responding to subprocesses of reversal learning during choice and feedback trial components. Error-feedback processing was associated with increased activity in dmPFC, dlPFC, and IFG whether participants were overcoming avoidance, inhibiting responding, or performing classic response reversal. Reduced activity in medial prefrontal cortex (mPFC) was associated with error-feedback processing for response inhibition but not overcoming avoidance. Conversely, there was significantly greater activity in anterior dmPFC during error-feedback processing in overcoming avoidance compared to response inhibition. A conjunction analysis confirmed that a striking overlap in activity was observed across the three conditions in IFG, dlPFC, and dmPFC.

Our results suggest that this approach has implications for models of prefrontal function and neurocognitive perspectives on a range of psychiatric disorders associated with reversal learning impairments. The results are consistent with conceptualizations of IFG function that emphasize resolving competition for motor responding rather than purely response inhibition. Furthermore, our results along with results in non-human primates suggest that these processes represent neuroanatomically similar but neurochemically distinct processes.

Research Theme: Disorders of the Nervous System

Striatal CRP40 injection reverses parkinsonian phenotype in 6-OHDA rats

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Introduction/Purpose: The neurotransmitter, dopamine (DA), is found in both the peripheral and central nervous system (CNS). Due to its effects on specific receptors, DA is a primary neurochemical mediator of movement and behaviour. Likewise, irregularities in DA activity have been implicated in the abnormal movements and behaviours seen in patients with Parkinson's disease (PD).

This study examined the potential of catecholamine regulated protein 40 (CRP40) as a therapeutic in PD. This area of investigation proves quite promising as our lab has shown, previously, that CRP40 is a multifunctional protein with the ability to bind catecholamines. This function may represent a potential component in the overall regulation of DA, and suggests that CRP40 may have a fundamental impact on CNS DA levels and, consequently, DA-dependent movements and behaviours in PD. Pharmaceutical studies show that DA can modulate CRP40 expression. Animal studies show that knockdown of CRP40 in the medial prefrontal cortex causes deficits in DA-dependant behaviours. Thus, it is possible that CRP40 can also modulate DA levels; a functional property that could be exploited as a potent therapeutic for DA-dysfunctional diseases like PD.

Methods: All animals were lesioned hemi-laterally at the substantia nigra using cytotoxic 6-hydroxydopamine (6-OHDA) and cannulated to the striatum on the same side as the lesion. The characteristic behavioural test for this 6-OHDA model of PD is the apomorphine-induced rotations test. The rotations test involves a subcutaneous injection of apomorphine to each rat, causing the animals to turn compulsively, contra-lateral to the lesion. All rats were also tested for sensorimotor gating deficits using the Prepulse Inhibition (PPI) test, and for locomotor activity trends using the locomotor activity test.

Once baseline data was collected, rats were placed under gaseous anaesthesia and injected via cannulae with one of the five treatments listed below. Animals were then re-tested, using the rotations, PPI and locomotor activity tests. All rats were sacrificed on day 15 post-injection. Fresh brain tissue was collected and flash frozen. DA analysis was done by HPLC.

Treatment Groups:

- G1 (n=3):** 6-OHDA lesioned animals, CSF injected;
- G2 (n=3):** lesioned animals, CRP40 plasmid injected;
- G3 (n=2):** lesioned animals, CRP40 protein injected;
- G4 (n=3):** controls: non-lesioned, CSF injected.

Results: Before treatment, all 6-OHDA rats rotated significantly more during the rotations test compared to non-lesioned controls. Animals in treatment group **G2** rotated significantly less after treatment, and animals in treatment group **G3** reversed in rotation at first, then stopped rotating all together after treatment. No other treatment group showed a significant change from baseline in the rotations test, after treatment. No animals showed any significant change in performance in the PPI and locomotor activity tests after treatment. HPLC revealed a significant increase in DA at the substantia nigra and striatum of **G2** rats only after treatment.

Conclusions: This study examined the effect of CRP40 injection on the behavioural phenotypes seen in the 6-OHDA rat model in order to explore the possible use of CRP40 as a therapeutic for PD. The results reinforce our original hypothesis that CRP40 has an impact on CNS DA levels, and has potential as a therapeutic for patients with PD.

Research Theme: Disorders of the Nervous System

The effects of nicotine on incentive learning and motivation in rats

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Persistence in tobacco smoking behavior is influenced by the effects of nicotine, the primary psychoactive ingredient in tobacco, on reward related processing. It is hypothesized that nicotine acts as a reinforcer by enhancing the incentive value of other, non-nicotinic reward stimuli. Responding for conditioned reinforcement (CR) provides a means to test such a hypothesis in animal models. Rats are trained to associate a light-tone stimulus with primary reinforcement. After such Pavlovian training, incentive motivation evoked by the CS is assessed by requiring rats to acquire a novel lever-pressing response for response-contingent presentations of the CS, now a CR. This study assessed the effects of nicotine on reward-related processing during (a) the acquisition of a conditioned stimulus (CS)-unconditioned stimulus (UCS) association and (b) motivated operant responding for the CS. Three groups of water-deprived rats were trained in 30 minute sessions for 13 days in a Pavlovian conditioning procedure to associate a tone-light cue (CS) with the delivery of 0.05 mL of water (UCS). CS-UCS stimuli were presented on a random-time 60s schedule of reinforcement. Two groups of rats received either daily saline ($n = 12$) or daily nicotine (0.4 mg/kg; $n = 12$) injections prior to Pavlovian conditioning training. A third group ($n = 12$) received nicotine injections (0.4 mg/kg), 2.5 hours after each session. Nicotine prior to Pavlovian conditioning sessions enhanced discriminated approach responding relative to the saline condition ($p < .05$). The nicotine-after group also showed enhanced discriminative approach compared to rats in the saline condition, but this difference did not reach statistical significance. Next, the effects of saline or three dose levels of nicotine (0.1, 0.2, and 0.4 mg/kg) on responding for the tone-light CR was assessed on four separate test days, counterbalanced across individual rats. All doses of nicotine elevated responding for CR in rats that received daily nicotine injections 2.5 hours after Pavlovian conditioning training ($p < .05$). Additionally, the 0.4 mg/kg dose of nicotine elevated responding for CR in the animals that received nicotine injections prior to Pavlovian approach sessions ($p < .05$). There was no effect of nicotine on CR responding in the nicotine-naïve rats. Together, these data support a role for nicotine in (a) enhancing the salience of reward stimuli during the acquisition of a cue-reward association and (b) elevating the incentive motivation of a cue previously associated with primary reinforcement. Furthermore, these data support emerging evidence that nicotine dependence is maintained because of the reinforcement-enhancing effects of nicotine on other reward stimuli.

Research Theme: Disorders of the Nervous System

Emotional conflict in offspring of bipolar parents - preliminary fMRI findings.

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Background: Pediatric Bipolar Disorder (BD) is a debilitating psychiatric illness whose diagnosis in its early stages can be challenging due to the overlapping in symptoms and comorbidity with other pediatric psychiatric illnesses. Finding neurobiological markers of risk for BD among vulnerable children may aide the clinical approach to such patients. This experiment proposes to detect functional neurocircuitry differences in children at high-risk for BD by examining fMRI activation patterns through a modified emotional-Stroop task. **Methods:** This imaging paradigm, developed by Etkin et al. (2006), uses fearful or happy faces presented with either the matching or mismatching word (fearful or happy) to create reliable activation patterns of emotional conflict and resolution. Verified in adults, this study proposes the task to be an effective method for activation in children as well. The proposed experiment includes 15 healthy controls and 45 offspring with a parent that has BD (Of these: 15 will have BD, 15 will be diagnosed with other pediatric psychiatric illness (high risk kids), and 15 without any psychiatric illness). **Results:** To date, 3 controls and 3 high risk children have been scanned. Preliminary results show a significant decrease in activation of prefrontal areas including medial frontal and middle frontal gyrus (Broadmann Areas 9 and 10, with $p < 0.001$) in high risk kids when resolving emotional conflict. **Conclusions:** These preliminary results suggest that the decrease in emotional conflict resolution capabilities seen in the high risk group can be partially attributed to lower functioning in these prefrontal areas.

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Research Theme: Disorders of the Nervous System

Exploring the common pathway between stroke and AD: Mass spectrometry imaging of gangliosides.

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Alzheimer's Disease (AD) and stroke show a high co-morbidity as they share common risk factors as well as certain underlying pathogenic features. Experimentally they have been shown to converge and act synergistically at the neuroinflammatory cascade in an adult-onset rodent model. Gangliosides, which are a member of the glycosphingolipid family, are differentially expressed in the outer cell membrane of all vertebrate cells and are particularly abundant in the brain. One species in particular, GM1, has shown an age-dependent accumulation in the dentate gyrus and the entorhinal cortex, two key areas implicated in AD pathology. GM1 is able to bind soluble amyloid and seed the fibrillization of amyloid, which is believed to be a critical step in AD pathogenesis. Mass spectrometry imaging is an innovative technique which affords a holistic view of multiple ganglioside species, and can be complemented by targeted immunohistochemical staining for specific ganglioside species. It is hypothesized that a combined adult-onset model of AD and stroke will alter the distribution of GM1 which will correlate with amyloid load and neuropathology, providing a mechanistic link to the enhanced neuroinflammatory response. Adult male Wistar rats will receive bilateral intracerebroventricular injections of the toxic β -amyloid fragment $A\beta_{25-35}$ and a unilateral endothelin-1 injection into the striatum. After 21 days their brains will be removed and either fresh-frozen, or perfused with paraformaldehyde. Fresh-frozen brains will be analyzed via matrix-assisted laser desorption/ionization (MALDI) imaging to visualize and quantify ganglioside distribution and immunohistochemical staining to assess neuropathology, while perfused brains will be analyzed via immunohistochemistry to provide complementary visualization of ganglioside distribution and neuropathology.

Research Theme: Sensory and Motor Systems

The effect of dorsal foot anaesthesia on gait control

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Many advances have been made in the recent past regarding the contribution of skin receptors to kinesthetic information. However, it is still not entirely clear to the extent at which this proprioceptive information is critical for precision in motor tasks or whether this involvement is uniform throughout the body. The purpose of this study was to determine if the skin on the dorsum of the foot altered gait and obstacle avoidance strategies. A 30cm² area of skin over the ankle joint was covered with a topical anaesthetic and participants completed an assortment of unobstructed and obstructed walking trials for both full cutaneous (control) and reduced sensation (anaesthetised). We hypothesized that with reduced sensory cues from the skin, there would be an over compensation of toe clearances over the ground and obstacle, as well as a greater degree of ankle movement during the swing phase of gait. As a result of the anaesthetic, there were no statistically significant differences between the sensation trials. However, ground clearances were slightly increased with reduced skin input and a range of responses were portrayed from the subjects for obstacle trajectories. The substantial variation among results that yielded no significance indicated that perhaps skin at the ankle does not play as pertinent of a role during gait. However further research is required to confidently rule out functional involvement of the dorsal skin during locomotion and obstacle avoidance.

Research Theme: Cognition and Behavior

Cholinergic involvement in the association of object features across sensory modalities

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The neurotransmitter acetylcholine (ACh) has been shown to have an important role in learning and memory, particularly for encoding new information. More recently, the cholinergic system has been implicated in the formation of associations between stimuli across sensory modalities. Using our newly developed version of the conventional spontaneous object recognition (SOR) paradigm, we investigated the role of ACh in crossmodal object recognition and object feature binding in rats. Using a crossmodal matching (CMM) task, we previously reported that rats are able to use tactile representations of an object acquired in a sample phase to recognize a visual presentation of that object in a subsequent choice phase 1 hour later. In the current study, we demonstrate that the administration of the muscarinic receptor antagonist scopolamine prior to the visual choice phase significantly disrupts crossmodal object memory. Interestingly, this effect is unique to CMM as pre-choice injections of scopolamine in the standard SOR task, or in unimodal (tactile or visual) versions of the object recognition task, produced no deficits. The most parsimonious interpretation of these results suggests that ACh is required in the choice phase of the CMM task to facilitate encoding of the novel visual information and possibly to compare the visual features of the object to the stored tactile representation of that same object. Conversely, in the sample phase of SOR, both the tactile and visual properties of the object have been encoded together, forming a multimodal representation and subsequently eliminating the requirement for ACh in the choice phase. Following from this, in our next experiment we tested the hypothesis that forming an explicit crossmodal association of the object prior to the CMM task would depend on ACh. To achieve this, we modified the CMM task by increasing the retention delay between the sample and choice phases, resulting in impaired CMM performance. However, simultaneous pre-exposure to the visual and tactile properties of the sample object rescued the ability of animals to perform the CMM task with the longer retention delay. Here we show that blocking muscarinic receptors with scopolamine prior to this pre-exposure phase prevents the usual facilitation of crossmodal object recognition, possibly by preventing the formation of a multimodal object representation. Taken together, our results suggest an important role for the cholinergic system in forming complex associations of object properties across sensory modalities.

Research Theme: Sensory and Motor Systems

The expression of the GABA_BR1 and GABA_BR2 receptor subunits in the rat's central auditory structures

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The GABA_B receptor is one of the major subtypes of GABAergic receptors and it makes an important contribution to neural responses in many brain structures. A functional GABA_B receptor is a heterodimer consisting of two subunits, i.e., GABA_BR1 and GABA_BR2. Presynaptic GABA_B receptors can regulate the release of neurotransmitters including glutamate and GABA. Postsynaptic GABA_B receptors can increase the opening probability of potassium channels, causing membrane hyperpolarization.

We conducted immunohistochemical and western blotting experiments to determine the level and distribution of the GABA_BR1 and GABA_BR2 subunits in the rat's major central auditory structures. Results revealed that both subunits were abundant in layers I through V of the auditory cortex, with the levels being the highest in the layers II and III. Other structures showing relatively high levels of expression included the medial geniculate nucleus, the dorsomedial and the lateral parts of the inferior colliculus, and the molecular and fusiform cell layers of the dorsal cochlear nucleus. Levels of expression were intermediate or low in the ventral region of the inferior colliculus and in brainstem auditory structures including the nucleus of the lateral lemniscus, the superior olivary complex, and the ventral cochlear nucleus. Immunoreactivities to antibodies of the two subunits had similar regional distributions and cellular localizations in major auditory structures. For both subunits, labeled cell bodies were found in all of the major auditory structures including their subdivisions. Neuropil labeling was strong in areas with high overall level of immunoreactivity.

Our results are in agreement with the fact that a functional GABA_B receptor consists of a GABA_BR1 and a GABA_BR2 subunit. The results also suggest that the contribution of GABA_B receptors to responses of auditory neurons is dependent on specific structures and locations within these structures.

Research Theme: Cognition and Behavior

The influence of arousal on social acceptance and decision-making in persons with and without MHI

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Social acceptance and attitudes towards others is a sophisticated social integration tool for inclusion and persons with acquired brain injury (ABI) are often socially isolated relative to their cohort (McLellan, Bishop, & McKinley, 2010). Similarly, individuals in the community often reveal substantial prejudgements towards this population (e.g., Seniuk & Good, 2008). Persons with traumatic ventromedial prefrontal cortex (VMPFC) injury are riskier in their decision making, physiologically underaroused, and do not respond to emotional feedback – e.g., their ‘gut’ feeling (e.g., Yechiam et al., 2005). As a result, they often have difficulty with social acceptance and integration. This research explores the effects of physiological arousal on social acceptance and attitudes as a measure of sophisticated form of social decision-making. University students, grouped according to having a history of mild head injury (MHI) or not, listen to background emotion-laden music or white noise (as a means of manipulating physiological arousal) while reading vignettes depicting a character who portray pro- or adverse-social behaviour and who was responsible, or not, for his/her predicament. Attitudes toward the character are measured. The results are examined as a function of the participant’s MHI status, level of physiological arousal (i.e., electrodermal response, heart rate), and valence of the arousal manipulation. Implications for biases towards persons who have ABI, and how to ameliorate it, are discussed.

Research Theme: Disorders of the Nervous System

Stress-induced localization of HSP70 proteins to centrosomes (Microtubule Organizing Centers-MTOCs) in cultured human neuronal cells

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The centrosome is a cellular organelle that serves as the main Microtubule Organizing Center (MTOC) in animal cells. In neurons, centrosomes play key roles in the organization of the cytoskeleton and cellular polarity that is required for neurite outgrowth. Given that it is essential to preserve centrosome structure and function during periods of stress, we examined whether proteins of the *HSP70* gene family localize to centrosomes in differentiated human neurons grown in tissue culture. Hsps are known to be induced by stressful stimuli and play important roles in cellular repair and protective mechanisms. Stable lines of human SH-SY5Y neuronal cells were established that expressed YFP-tagged protein products of two human inducible *HSP70* genes (*HSPA1A* and *HSPA6*) and a constitutively expressed member (*HSPA8*). Following heat shock at 43°C for 20 minutes, confocal microscopy demonstrated that the two YFP-tagged inducible HSP70 proteins rapidly moved into centrosomes and co-localized with the MTOC marker protein, gamma tubulin. The two inducible HSP70 proteins were detected in centrosomes immediately after the heat shock period and strong co-localization signals persisted up to 3 hours post-heat shock and were greatly reduced by 6 hours. In contrast, the protein derived from the constitutively expressed *HSPA8* gene did not localize to centrosomes at any time point. The transient association of stress-inducible members of the *HSP70* gene family with centrosomes in differentiated human neurons suggests that these proteins may be involved in repair and protection mechanisms that preserve microtubule organizing centers (MTOCs) in neurons during periods of cellular perturbation. (Supported by grants from NSERC to Ian Brown who holds a Canada Research Chair [Tier I] in the Neurobiology of Stress)

Research Theme: Sensory and Motor Systems

Vestibular modulation of compensatory reactions during forced perturbation

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Introduction: Falls are one of the leading causes of injury in older adults and lead to severely diminished independence. In Canada, the direct cost of these falls is approximately \$2.4 billion each year (1).

A key feature of stable balance is the ability to recover from any external perturbations (e.g. trip, slip, push). Stepping and grasping (e.g. reach to a surface/handhold for support) reactions are particularly prevalent and effective responses to recover balance, and are the only recourse in the event of a sizeable balance perturbation. My research will focus on the guidance of compensatory grasping responses.

The nature and control of these reactions are unique: grasping responses are executed very rapidly, beginning as early as 100 milliseconds following a perturbation (2). Despite the speed of the response, compensatory grasping is not a simple stereotyped reaction. The arm trajectory from the immediate outset is accurately directed to an available handhold, and is also immediately adapted for the perturbation-induced body motion (e.g. reaching further if the body is falling away from handhold) (3).

It is unknown what sensory feedback is utilized to rapidly guide the response. Eye movements to fixate environmental features do not typically accompany responses to perturbations (4), nor would the longer latency of visual feedback suggest it could be utilized so rapidly. Rather, a combination of somatosensory and vestibular feedback is likely utilized to guide the reaching response. The vestibular system itself may be of particular importance, as it provides direct feedback of body motion relative to the external environment, and has sufficiently rapid latency (60 msec (5)) to guide compensatory grasping reactions.

Aim: To determine the role of the vestibular system in grasping responses during forced perturbations.

Methods: This project will compare grasping reflexes in reaction to balance perturbations that require stepping with and without galvanic vestibular stimulation (GVS). GVS is a painless, safe method of influencing vestibular input. Harnessed subjects will stand on a hexapodal robotic platform that will evoke grasping reactions via perturbations to balance. Moveable handholds will vary position about the subject, and participants will be able to visually identify the new location prior to the perturbation. Optotrak Certus® (Northern Digital Inc., Waterloo, Canada) will be used to capture movement information.

Expected Results: It is hypothesized that the vestibular system will play a key role in sensing body motion in order to shape the reach trajectory to available handholds.

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Serotonin transactivates platelet-derived growth factor receptor type beta in neuronal cells

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Serotonin (5-HT) is an important neurotransmitter in the central nervous system that has been linked to a variety of neurological and psychiatric diseases including schizophrenia, depression and anxiety. The platelet-derived growth factor receptor type β (PDGFR β) is a mitogenic receptor tyrosine kinase important for both neuronal development and survival. Our previous studies have shown that PDGFR β conveys neuroprotective effects to excitotoxic neurons. PDGFR β can be transactivated by a variety of factors in numerous cell types including smooth muscle, fibroblasts, CNS endothelial cells, neurons and glial cells. Transactivation of a growth factor receptor involves activation/phosphorylation of the receptor in the absence of its ligand. We present evidence that 5-HT transactivates PDGFR β in the neuronal cell line SH-SY5Y. As measured by western blotting with anti-phospho-PDGFR β antibodies, application of 5-HT that resulted in PDGFR β activation was dose-dependent and led also to the activation of ERK 1/2. Treatment with the serotonin analog, 5-carboxamidotryptamine (5-CT), also resulted in PDGFR β phosphorylation. Pretreatment with selective serotonin reuptake inhibitors (SSRIs) fluoxetine or citalopram prevented 5-HT-induced PDGFR β activation. The non-receptor tyrosine kinase c-Src was also involved, since pretreatment with the c-Src inhibitor PP2 completely blocked 5-HT-induced PDGFR β transactivation. In addition, treatment with neutralizing antibodies against PDGF-BB ligand failed to attenuate 5-HT-induced PDGFR β activation. Thus, transactivation of PDGFR β by 5-HT in neuronal cultures may be responsible for the mitogenic effects of 5-HT and potentially other neurotransmitters as well. These studies may explain how neuronal communication via neurotransmitters contributes to neuronal viability. In addition, by understanding the mechanistic pathway of PDGFR transactivation, each step in the pathway becomes a potential drug targets for activating the mitogenic and neuroprotective effects of PDGFR β , which may be useful in treating neurodegenerative disorders.

Research Theme: Sensory and Motor Systems

Olfactory properties of round goby putative pheromones: an electro-olfactogram study

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Fishes widely employ the olfactory sense for communication in most aspects of their life, but particularly reproduction. The round goby, *Neogobius melanostomus*, is a small highly successful invasive fish in the Great Lakes, and it is hypothesized that the reproductive male (RM) of the species releases compounds that may act as reproductive pheromones, attracting reproductive female (RF) round gobies to the males' nests. I have investigated the olfactory properties of several steroids that have been identified as released by RM round goby and are putative pheromones. By recording summed generator potential responses from the olfactory epithelium (electro-olfactogram, EOG), I show that female responses to methanol-extracted steroids from RM conditioned water increased following treatment of the RM with gonadotropin releasing hormone, but not saline. In addition, there was a correlation between female reproductive status (as measured by gonadosomatic index) and response to NRM (but not RM) urine. Using EOG I confirmed that female gobies detect the novel steroids 11-oxo-etiocholanolone (11-O-ETIO) and 11-O-ETIO-3-sulfate, but not 11-O-ETIO-17-sulfate or 11-O-ETIO-3-glucuronide, all of which are released by RM round gobies. Additional electro-physiological experiments demonstrated that these steroids act upon separate olfactory receptor mechanisms and are transduced via both cAMP and IP₃. Therefore, considering their olfactory potency and specific receptor mechanisms, we conclude that 11-O-ETIO and 11-O-ETIO-3-s are putative pheromonal compounds in the round goby.

Research Theme: Development

Developmental Expression of Neuroligin and Neurexin mRNA in the Fragile X Mouse

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Introduction: Fragile X Syndrome is caused by a silencing of the *FMR1* gene and leads to dysregulation of synaptic mRNA translation in the brain. Patients present with symptoms including anxiety, susceptibility to seizures, and a host of autistic behaviours. In fact, up to 25% of Fragile X patients are diagnosed with autism and 2% to 6% of autism patients have a mutation in the *FMR1* gene. Recent genetic studies in autism have implicated a role of synaptic proteins in this neurodevelopmental disorder. Specifically, the neuroligins, synaptic adhesion molecules, and their presynaptic partners, the neurexins, are susceptibility genes in the autism spectrum. Neuroligin-neurexin interactions are important to synaptic maturation and contribute to the formation of both excitatory and inhibitory synapses. In addition, it has been reported that neuroligin-I RNA is associated with FMRP (Dahlhaus et al., 2010, Beh Brain Res, 208:96). Our preliminary data shows upregulation of neuroligin-I mRNA in male adult *fmr1*^{-/-} somatosensory cortex and hippocampus.

Methods: In the current study, we examined the expression of the neuroligins and neurexins gene families during postnatal development in wildtype (FVB.I29P2(B6)) and *fmr1*^{-/-} mice.

Results: In wildtype mice, gene expression of neuroligins is maximal during synaptic maturation and reduces to adult levels by three weeks of age, while gene expression of neurexins show a more dynamic profile during early life. Analysis of changes in gene expression in *fmr1*^{-/-} mice is ongoing.

Conclusion: This research will further our understanding of the shared neurobiology between autism and Fragile X Syndrome.

Research Theme: Disorders of the Nervous System

Effect of oxygen-glucose deprivation on hippocampal slices prepared from adolescent and adult rats

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Stroke is a leading cause of death and disability in Canada, yet, despite the development of hundreds of potential therapies, no treatment is currently available. One major reason for the lack of an effective therapy is the uncertainty about how stroke affects the brain; for example, whether the brain might become more susceptible to stroke-related damage over the life span. To begin addressing some of the gaps in our understanding, we characterised a pre-clinical model system wherein hippocampal slices were exposed to oxygen-glucose deprivation (OGD), and then used the model to examine how the age of an animal might affect outcome from ischemic insult. Slices were harvested from male Sprague-Dawley rats at either 7-8 weeks of age (adolescent) or 25-35 weeks of age (adult). After 15 minutes of OGD and a 3 hour recovery period, slices were immersed in a 2,3,5-triphenyltetrazolium chloride (TTC) solution. The reduction of TTC by mitochondria produces a reaction product within the tissue that can be extracted and quantified with spectrophotometry to provide a measure of slice viability. Regardless of animal age, the level of TTC reduction in slices challenged with OGD was approximately half of that observed in slices maintained under control conditions. Our data indicate that we can reliably measure the effect of OGD upon acutely prepared hippocampal slices, and suggest that the decrease in hippocampal viability caused by a stroke-like insult may not differ between these two age groups.

Does the cerebellum modulate the electromyogenic response to vestibular stimulation?

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Introduction: The vestibular system works in conjunction with other sensory systems to maintain balance. Composed of otolith organs and semicircular canals, it is able to evaluate accelerations of the head and generate rapid reflexive responses. Galvanic vestibular stimulation (GVS) manipulates the firing of these peripheral vestibular afferents by passing a current through the mastoid processes. This in turn causes an illusory sensation of movement and a distinct muscular response in the form of a short (SL) and medium latency (ML) activation seen in the muscles used for balance [1].

The cerebellum, a comparator of sensory systems, is used in the coordination, precision and accurate timing of motor activity. Since it receives direct input from the vestibular system, it is predicted to integrate information from all sensory sources before dispatching an appropriate postural response. With the use of constant theta burst stimulation (cTBS), a stream of rapid magnetic pulses, it is possible to stimulate the cerebellar cortex, producing long term depression, reducing its function [2].

Aim: To determine if the cerebellum modulates the SL and ML electromyogenic response to GVS.

Methods: Ten to fifteen healthy subjects will be tested with no prior history of neuromuscular disease. While standing quietly on an AMTI™ force plate (Advanced Mechanical Technology Inc., MA, USA), with their eyes closed, subjects will receive 240 short duration GVS pulses (25ms stimulus, 800ms interstimulus interval) through an A395 Linear Stimulus Isolator™ (World Precision Instruments Inc., FL, USA). EMG will be collected bilaterally from the soleus and tibialis anterior with a Bortec AMT-8 EMG system (Bortec Biomedical Ltd., AB, Canada). Subjects will then be seated as they receive 600 cTBS (three bursts at 50Hz, repeated every 200ms) over the Vermis using a transcranial magnetic stimulator (Magstim Rapid2™ system; Magstim Company Ltd., Wales, UK) for 40 seconds to induce cerebellar inhibition [2]. Finally, the same GVS protocol will be repeated to assess any changes in EMG activity.

All data will be collected on previously coded LabView software™ (National Instruments Co., TX, USA).

Expected Results: The short latency response produced by vestibular stimulation is expected to maintain its size and duration following cTBS stimulation. The medium latency response, which is thought to be associated with a postural sway response[1], is expected to be diminished or completely abolished following the reduction of the cerebellar contribution.

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The role of full-field visual flow in the coordination of balance and focal voluntary movements

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Introduction: Vision is central to guiding motor actions, including balance and targeted actions of the arm. Past studies have demonstrated that motion of the visual background, termed visual flow (VF), provides important feedback for controlling posture and goal-directed movement. VF rapidly and profoundly influences postural sway, and has actually been shown to cause falls in the elderly¹. With respect to voluntary focal movement (e.g. reaching to grasp an object), full-field VF has been shown to rapidly modulate the trajectory of reaching behaviours with very short latency (~100 ms) in a direction consistent with that of background motion². It is believed that these rapid reaching responses occur at latencies that preclude cortical involvement. Thus, it has been proposed that goal-directed reaching adjustments are regulated via rapid-latency transcortical feedback loops³. While some maintain that the reaching response is due to a shift in the internal representation of the goal induced by VF⁴, others believe that these aiming behaviours are adjusted according to the visual motion of the background².

Rationale: Although focal movements and posture have been fairly well studied independently, the influence of VF on goal-directed pointing from standing posture has yet to be examined. The roles of central and peripheral vision in the control of these processes requires further attention as well.

Aim: The aim of the proposed study is to determine how posture and focal voluntary movements of the upper limb are coordinated during motion of the surrounding visual field.

Methods: From standing posture, participants will point to targets flashed in the central visual field. VF will be presented on large screens, which will be placed directly in front of and on either side of the subject. VF occurrence will be varied within and between the central and peripheral areas. EMG, kinematics and GRF analysis will determine whether VF induces similar spatial changes at the same latencies in both the goal-directed action and posture.

Expected Results: If VF elicits rapid-latency transcortical modulation on both reach trajectories and postural sway, it would suggest that the CNS controls goal-directed pointing and postural activity as a combined entity. However, if the responses occur at different latencies or in an uncoordinated fashion, it would provide evidence to support the notion that goal-directed actions and balance operate under separate control processes.

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Research Theme: Cognition and Behavior

Physiological and neurobehavioural effects of mephedrone (4-MMC)

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The novel synthetic cathinone derivative 4-methylmethcathinone (4-MMC) has rapidly grown in popularity among recreational drug users since its introduction in 2007. This amphetamine-like drug, termed mephedrone, remains the subject of great controversy in the UK where its unresolved legal status and numerous reports regarding the drug's harmful effects and related deaths have bombarded the media. The substance has always been defined as controlled in Canada; however its prevalence is currently unknown. The present study characterized the physiological (e.g. temperature, body weight), and neurobehavioural effects (i.e., food and water consumption, locomotor activity, anxiety, memory, and place conditioning) of 4-MMC (doses up to 18 mg/kg, i.p.) in male Sprague-Dawley rats. Preliminary results revealed that 4-MMC induced hyperactivity, increased body temperature, increased anxiety, but yielded no conditioned place preference or avoidance. The effects of 4-MMC alone (doses up to 3 mg/kg) and when combined with delta-9-tetrahydrocannabinol are presently being examined using a delayed match-to-position (DMTP) operant task. Preliminary findings revealed that 4-MMC disrupts choice accuracy and reduces the number of trials completed in the DMTP task. A survey of undergraduate students at Wilfrid Laurier University revealed relatively low usage of 4-MMC (0.8%). Results suggest that 4-MMC induces stimulant-like effects, but appears to be devoid of rewarding properties, at least under the conditions examined in the present study. These findings are at odds with anecdotal reports suggestive of high abuse potential. Additional experiments in progress will provide a more detailed analysis of the effects of 4-MMC on memory.

Research Theme: Development

An examination of MicroRNA expression during caudal spinal cord regeneration in the Newt, *Notophthalmus viridescens*

Amanda Lepp, PhD Candidate, Graduate Studies in Biological Sciences; Robert Carlone, PhD, Brock University

Adult urodele amphibians possess the unique ability to regenerate a number of lost structures such as limbs and spinal cord following tail amputation. Caudal tail regeneration begins with the formation of a blastema, and outgrowth occurs as ependymal cells that line the central canal of the spinal cord proliferate and extend as an ependymal tube. Regeneration requires rapid global changes in gene expression, and one current focus involves identifying molecules and signalling pathways that contribute to the formation of the tail blastema, as well as outgrowth and patterning of the regenerating spinal cord. MicroRNAs (miRNAs) are attractive candidates as regulators of regeneration in the urodele; they are small non-coding RNAs that regulate gene expression at the translational level. Recent efforts in our lab have focused on identifying miRNAs in the newt, *Notophthalmus viridescens*, which exhibit differential expression in response to injury that may contribute to caudal spinal cord regeneration after tail amputation. We have identified several miRNAs that are expressed in the intact tail, but are downregulated in response to injury, including miR-133a, miR-124, miR-132 & miR-203. Expression of miR-133a is significantly decreased following tail amputation, and expression appears to be localised to the ependymal layer surrounding the central canal in the intact spinal cord. Analysis of the putative downstream effectors of miR-133a in the regenerating caudal tail of the newt is currently underway.

Regulation of food intake during unlimited access to highly palatable food

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We explored the effects of daily access to either Oreo cookies (food high in sugar and fat that is typically employed as “junk food” in research with rodents) or Quaker Oats plain rice cakes (food nutritionally devoid of sugar and fat) on weight gain and consumption of standard rat chow in non-food restricted male Sprague Dawley rats. In Experiment 1, taste reactivity (TR) was employed to determine whether Oreos and rice cakes differed in palatability. For TR, subjects received intraoral (IO) infusions, hence, for the purpose of testing these foods were pureed into a liquid solution. Rats (n=24) received a 5-minute habituation session to acclimatize to the IO infusion procedure and 24 hours later the TR test. At test, rats were placed into the chamber, attached to the infusion pump, and infused with either Oreo (n=12) or rice cake (n=12) solution at a rate of 0.5ml/minute. Their orofacial reactions were recorded and hedonic responses to infusions of either food (measured by frequency of tongue protrusions (extensions of the tongue out of the front or side of the mouth)) were scored. In Experiment 2, 32 rats were assigned to either the chow fed only (n=6), chow + rice cake (C+RC; n=6), or chow + Oreo (C+O; n=20) group. In addition to standard rat chow which was made available ad lib, rats in the C+O and C+RC groups received a single Oreo (12 grams (g)) or rice cake (12g) in their home cages daily for 12 consecutive days, which served as a baseline for testing. During the test phase, the quantity of food made available was increased each day from 12g, to 24g, 36g, and then maintained at 48g for six consecutive days. Finally, in Experiment 3, rats were assigned to either the chow fed only (n=11) or C+O (n=12) group, and for the latter group, in addition to ad lib rat chow, subjects received 72 g of Oreo in their home cage daily for 27 consecutive days. Oreos were more palatable than rice cakes, as the frequency of hedonic reactions were significantly higher following infusions of Oreos. During the baseline and testing phase of Experiment 2, both rice cake and Oreo fed rats regulated their chow consumption in response to the addition of these foods. Consumption of chow was significantly reduced in both groups compared to the chow fed only rats and group differences in weight gain were not observed. In the test phase when the quantity of food escalated from 12-16 grams, rats in both the C+RC and C+O group consumed all of the food; however, when 48 grams was made available individual differences in consumption (as evidenced by remaining food the next day) were revealed. Similarly, in Experiment 3, Oreo fed rats significantly reduced their intake of rat chow in response to the addition of Oreos to their diet; however, following 16 days of unlimited access to Oreos, those rats weighed significantly more than chow fed only rats and this effect was observed on each subsequent day of testing. Taken together, prolonged unlimited access to Oreos engenders significant weight gain in rats. Initially, animals regulate their intake of both chow and food, but overtime, they consume more calories than required to sustain normal growth as measured against the chow fed only rats. Research in our laboratory has previously found that preference for Oreos but not rice cakes is predictive of enhanced drug-seeking and sensitivity to the motivational properties of cocaine. The availability of Oreos and rice cakes in these studies (12 grams per day for four days) did not have a significant impact on measures such as weight gain or regulating food intake. Data from the experiments described above provide a set of parameters from which we can design future experiments to explore how these factors may influence the relationship between highly palatable foods and drugs of abuse.

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Research Theme: Disorders of the Nervous System

Effect of nerve growth factor on endothelial nitric oxide synthase expression in PC12 cells in the context of Alzheimer's Disease.

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Introduction: Nerve growth factor (NGF) is a neurotrophin that has been investigated as a treatment for Alzheimer's disease (AD). The purpose of this study is to determine how endothelial nitric oxide synthase (eNOS) expression is regulated by nerve growth factor.

AD is a progressive neurodegenerative disorder, afflicting 1 in 11 individuals above the age of 65 and 50% of individuals above the age of 85. Patients suffering from AD typically display memory loss, disorientation and a decrease in cognitive function as a result of cholinergic neuron cell death in the basal forebrain. The cellular and molecular characteristics of AD include extracellular amyloid plaques, a result of elevated levels of beta-amyloid, and intracellular neurofibrillary tangles caused by hyperphosphorylated tau proteins. NGF, which maintains the health of cholinergic neurons, has been reported to regulate the expression of genes involved in these pathologies.

Nitric oxide synthase (NOS) is commonly expressed in all tissues types including neurons. The NOS enzymes control the production of nitric oxide (NO) which is associated with modulating the NGF-mediated expression of several AD-related genes and proteins, including choline acetyltransferase, amyloid precursor proteins and tau proteins. In addition, a decrease in the levels of the endothelial isoform of nitric oxide synthase (eNOS) has been postulated to reduce expression of low-density lipoprotein related-receptor protein (LRP), ultimately reducing the clearance of beta-amyloid from extracellular space. Despite the correlations between eNOS/NO and AD-related genes and proteins, the mechanisms in regulating eNOS expression are not known.

Methods: To determine how eNOS expression is regulated, eNOS mRNA and protein levels were measured in cell extracts of control and NGF treated PC12 cells using reverse transcriptase (RT)-polymerase chain reaction (PCR) and western blot analysis, respectively. NGF has been consistently reported to induce the expression of many of the AD-related genes in PC12 cells via the TrkA signalling pathways. Therefore, the effect of TrkA signalling pathway inhibitors on NGF-mediated increases in eNOS mRNA and protein levels is also being examined. To evaluate transcriptional regulation of eNOS, various promoter fragments of eNOS have been amplified using PCR and are currently being ligated into a PGL3 expression vector to determine the location of NGF regulatory elements on the eNOS promoter. In future studies, site-specific mutagenesis can be performed on the NGF-responsive eNOS promoter fragments to determine the transcription activation sites. Following this, eNOS mRNA and protein stability will also be measured using actinomycin D and cyclohexamide to inhibit transcription and translation respectively.

Results: eNOS mRNA and protein were successfully detected in cell extracts of PC12 cells. When compared to untreated cells, the addition of NGF increased the expression of eNOS at the mRNA and protein level. Interestingly, proteins levels were increased significantly after 24 hours of NGF treatment while mRNA expression increased following 48 hours of NGF exposure. The increase in eNOS mRNA levels suggests that NGF may be regulating eNOS expression in part through transcription. Therefore, eNOS promoter analysis studies were initiated. Several fragments of the eNOS promoter have been successfully amplified using PCR (500, 1000, 2000 and 3000 base pair fragments) and the ligation process is currently underway. The eNOS-pGL3 basic constructs will then be transfected into PC12 cells and luciferase activity measured in control and NGF-treated cells.

Research Theme: Sensory and Motor Systems

Combining sensory protection and electrical stimulation for prevention of muscle atrophy following peripheral nerve injury: histology

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Purpose:

If musculature is denervated for several months or more, such as after suffering proximal peripheral nerve damage, the muscle undergoes irreversible atrophy and becomes unreceptive to reinnervation. Sensory protection (connecting an afferent sensory nerve to distal stump of the severed motor nerve) improves force generation and muscle function after reinnervation and improves morphological, histological and molecular measures in the absence of contractile activity. Electrical stimulation of denervated muscle is also known to improve muscle function. This project seeks to determine whether the combination of sensory protection with electrical stimulation of denervated muscle preserves the histological properties of the muscle more than either approach individually.

Content:

We compared the average muscle fibre area for both fast and slow twitch fibres to demonstrate that sensory protection combined with electrical stimulation is the superior choice for preserving muscle fibre area during periods of prolonged denervation.

Methodology:

Male Lewis rats were randomly assigned to one of six surgical groups: sensory protected with and without electrical stimulation, denervated with and without electrical stimulation, and immediate motor nerve repair with and without electrical stimulation. After three months, the gastrocnemius muscle of denervated and sensory protected groups was repaired with the peroneal (motor) nerve. Following three more months to allow recovery, the rats were sacrificed and gastrocnemius muscle tissues were collected for histological assessment. Frozen muscle tissue was sectioned and myofibrillar ATPase staining was carried out at pH 10 to distinguish slow twitch and fast twitch fibres. Average area of slow and fast twitch fibres was evaluated for each experimental condition.

Results:

Animals treated with both electrical stimulation and sensory protection exhibited fast twitch muscle fibres that were significantly larger in area than the fast twitch muscle fibres of sensory protected alone or denervated groups with and without stimulation. Slow twitch fibres that had been sensory protected and electrically stimulated were larger in area than sensory protected alone and denervation without stimulation, although there was no significant difference compared to stimulated alone. Thus, sensory protection combined with electrical stimulation is highly effective at preserving fast twitch muscle fibres, although it is no more protective than electrical stimulation alone for slow twitch fibres. We conclude that due to the protection of fast twitch fibres by sensory protection with electrical stimulation and the protection of slow twitch fibres by electrical stimulation, sensory protection combined with electrical stimulation is the superior choice for protecting muscles from atrophy during periods of prolonged denervation.

An ERP investigation of tonal versus phonemic influences on spoken word recognition in mandarin chinese

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When hearing spoken words, speakers of tonal languages like Mandarin Chinese must process not only the individual sounds that make up the words (phonemes), but the tone in which the words are articulated as well in order to access their meaning. This is because tone, or the pitch in which a syllable is articulated, signifies meaning in Mandarin; for example, the word 'ma' can mean 'mother', 'hemp', 'horse', or 'to scorn', depending on whether the syllable is articulated in a high tone (tone 1), a rising tone (tone 2), a low-dipping tone (tone 3), or a sharply falling tone (tone 4). Despite the prevalence of tonal languages like Mandarin among the world's speakers, most current theories and models of word recognition do not account for the role of tone in the word recognition process, as they have been developed using data from non-tonal languages such as English and Dutch. To update these theories and models, we need to know in particular when tonal information is accessed during spoken word recognition (especially in relation to phonemes), and also if a listener's expectation of an upcoming tone can guide his or her word recognition in the same way that expectation of upcoming phonemes can. To investigate these questions, we employed a picture/word matching task, in which native Mandarin speakers (N = 19) saw pictures of items that set up expectations of upcoming auditory words, and then heard words that either matched these expectations or violated them. In particular, the mismatches were of the following nature: segmental (see 'hual', hear 'hua4'), cohort (see 'hual', hear 'hui1'), rhyme (see 'hual', hear 'gual'), tonal (see 'hual', hear 'jing1'), and unrelated (see 'hual', hear 'lang2'). We recorded event related potentials (ERPs) during presentation of the auditory words and looked at how two ERP indices – one of sublexical processing (phonological mapping negativity; PMN), and the other of lexical processing (N400) – were modulated by mismatches. The segmental and cohort conditions addressed the question of when tonal information is accessed during word recognition, as violations were signaled at a similar point in time within the syllable, yet the type of information signaling the divergence was different: tonal information signaled the violation in the segmental condition, whereas phonemic information signaled the violation in the cohort condition. Results showed that the segmental condition showed a modulation in the PMN window, which was earlier than the onset of modulation in the cohort condition, which did not occur until the N400 window. This suggests that tonal information was accessed very early during the unfolding of auditory stimuli, and was used to guide word recognition as soon as it was signaled, in just the same way that phonemes were. However, different amplitudes and cortical distributions of component modulation between the two conditions suggest that potentially different mechanisms might underlie tonal versus phonemic processing. The rhyme and tonal conditions addressed whether a listener's expectation of an upcoming tone can guide his or her word recognition in the same way that expectation of upcoming phonemes can; that is, whether there is feedback based on expected tones and expected phonemes in Mandarin spoken word recognition. Both the rhyme and tonal conditions showed an attenuated late N400 component compared to completely unrelated words, suggesting that upcoming expectations guided subsequent bottom-up recognition of phonemes and/or tones. These results are discussed with respect to current theories of spoken word recognition, and suggest several modifications that need to be made to these theories so that they can accommodate the tonal languages spoken by a large proportion of the world's speakers.

Research Theme: Disorders of the Nervous System

Exercise and neurogenesis in a mouse model of Alzheimer's disease.

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Alzheimer's disease (AD) is a neurodegenerative disorder resulting from a progressive loss of neurons leading to cognitive impairment and disruption of adult neurogenesis. Several non-invasive treatments are being developed to reduce the rate of neuronal degeneration. For example, it has been shown that exercise influences adult neurogenesis, synaptic plasticity, and cognitive functions in healthy adults and recent epidemiological studies suggest that exercise potentially benefits AD patients as well. However, we have only begun to understand the effects exercise has on pathology, plasticity, and cognition in AD mouse models.

Here we evaluated the effects of moderate voluntary exercise on cognitive function by giving AD mice access to running wheels for 30 and 60 days and assessing their functional recovery with a battery of behavioural tests. Our results to date from a Y-maze behavioural task show an improvement in maximum alternation, an index of spatial working memory, in transgenic running animals suggesting that running may improve memory function in those mice after 60 days of exercise ($p=0.04$, $n=5$). Results obtained from the open field behavioural test showed no difference in anxiety levels and locomotor activity in tested groups.

In summary, we were able to show that exercise can improve spatial working memory in an AD mouse model. Subsequent research in these animals will test whether moderate exercise has a positive effect on adult neurogenesis by assessing the number of cells labelled at the onset of exercise (cell differentiation) and after several weeks of exercise (cell proliferation). Exercise has the potential to improve cognition even when cognitive impairment results from different neuropathological events.

The microbiome is necessary for normal gut intrinsic primary afferent neuron excitability

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Introduction: Recently there has been profound interest in the role of intestinal microbiota in gut-brain communication. Germ free (GF) mice are bred and maintained without exposure to bacteria of any kind, and thus provide a valuable research tool to investigate whether the presence of a gut microbiome affects the development of the functional constitutive state of the enteric nervous system (ENS) neurons. Here we examine if GF mice differ from their conventionally-reared specific pathogen-free (SPF) counterparts in terms of intestinal intrinsic primary afferent neuron (IPAN) excitability.

Methods: Segments of jejunum from 8 week old GF and SPF mice were placed in a silastic-lined recording dish filled with carbogenated Krebs. The segment was opened, pinned flat, and mucosa, submucosa and circular muscle were dissected away exposing the myenteric plexus. Intracellular recordings in current clamp mode were obtained from these neurons by impaling cells with sharp microelectrodes. Action potential (AP) firing thresholds, the number of APs fired at 2x threshold along with other membrane characteristics were measured in IPANs.

Results: Membrane parameters (mean \pm s.e.m., n) for SPF vs GF mice were: membrane potential decreased from $-63 \pm 2, 7$ vs $-78 \pm 2, 9$ (mV) ($P=0.03$); Threshold was $181.4 \pm 47.4, 7$ vs $288.9 \pm 90.4, 9$ (pA) ($P=0.3$); AP amplitude was $84.4 \pm 2.9, 7$ vs $89.4 \pm 7.8, 9$ (mV) ($P=0.9$); AP $\frac{1}{2}$ width was $2.4 \pm 0.2, 7$ vs $2.6 \pm 0.2, 8$ (ms) ($P=0.5$); slow afterhyperpolarization (sAHP) amplitude was $-5.5 \pm 0.6, 6$ vs $-9.7 \pm 2.0, 9$ (mV) ($P=0.08$); sAHP duration increased from $3.3 \pm 0.9, 7$ vs $6.2 \pm 1.1, 9$ (s) ($P=0.05$). Number of APs fired during a 500 ms depolarizing current pulse at two times threshold intensity was $2.7 \pm 0.5, 7$ vs $1.9 \pm 0.2, 9$ ($P=0.1$).

Conclusion: The absence of bacteria lowered the resting membrane potential for the afterhyperpolarization (AH) cells and extended the AP sAHP. Both of these measures indicate the potential for decreased IPAN firing in response to adequate sensory stimuli, which could possibly underlie the abnormal gut function previously reported in GF mice. This is the first work to show that commensal intestinal microbiota are necessary for normal excitability of gut sensory neurons.

Research Theme: Cognition and Behavior

Nicotinic receptor activation in perirhinal cortex and hippocampus facilitates aspects of object memory

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Research involving object recognition tasks has significantly improved our understanding of medial temporal lobe (MTL) memory functions, with specific contribution to knowledge regarding perirhinal cortex (PRh) and hippocampal (HPC) involvement in object memory processing. Extensive evidence now indicates that PRh is the principle MTL structure involved in object recognition memory, with cholinergic input to the PRh also strongly implicated in this process. Conversely, the HPC seems to be involved in spatial recognition processes that are not essential to the recognition of objects per se. Evidence indicates that nicotinic acetylcholine receptors (nAChR) play a facilitative role in memory. This study further investigated the role of nAChR in object recognition and spatial recognition memory using the spontaneous object recognition (SOR) and object-location (OL) tasks, respectively. In the SOR task, normal rats preferentially explore a novel object over a familiar object in a choice phase, which occurs some time after a familiarization (sample) phase with one of the objects; the OL task is similar, except that the objects are identical in both phases and one is placed in a new spatial location in the choice phase. In Experiments 1 and 2, systemic pre-sample nicotine dose-dependently facilitated SOR and OL performance, respectively, compared to vehicle conditions in which performance was at chance with a 72-h retention delay between the sample and choice phases. Experiments 3-6 investigated the potential involvement of PRh and HPC in these systemic effects. In Experiment 3, intra-PRh infusions of nicotine significantly facilitated SOR. Somewhat surprisingly, the results of Experiment 4 suggested a possible facilitative effect of intra-HPC nicotine on SOR performance. Experiments 5 and 6 indicated facilitative effects on OL performance caused by intra-PRh and intra-HPC nicotine administration, respectively. These results not only demonstrate that nAChR activation can facilitate performance on object recognition and object-location memory tasks, but suggest that these effects are mediated by nAChR action in both PRh and HPC. This study indicates that, although PRh and HPC are functionally distinct, they can interact to enhance performance on tasks for which they are not entirely necessary. These findings therefore support the view of functional independence and interactivity of MTL structures.

Research Theme: Disorders of the Nervous System

Altered balance of proteolytic isoforms of pro-brain-derived neurotrophic factor in autism

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Recent genetic studies suggest defects in synaptic development and plasticity may lead to autism. Brain-derived neurotrophic factor (BDNF) plays a critical role in synaptogenesis and synaptic plasticity. BDNF is synthesized as a large precursor, proBDNF, which can be processed into either a truncated form or into mature BDNF, which is neurotrophic. ProBDNF and mature BDNF have opposing activities and roles in the brain, but truncated BDNF has unknown biological activity. Previous studies reported increased BDNF-immunoreactive protein in autism, although neither the mechanism of this increase nor the responsible BDNF protein isoform was investigated.

In the present study, BDNF levels were assayed in post mortem fusiform gyrus, a cortical area that has been implicated in the impairments in face recognition and perception of autism. BDNF mRNA was examined by real-time RT-PCR in tissue from 9 autism and 14 control subjects. BDNF protein was examined in 9 autism samples and 9 controls using Western blotting and ELISA. BDNF mRNA levels were unchanged in the autism group compared to controls. However, total BDNF-like immunoreactive protein, measured by ELISA, was increased in autism compared to controls. Western blotting revealed increased proBDNF, reduced truncated BDNF and a trend towards increased mature BDNF levels in autism compared to controls. In conclusion, these data demonstrate that increased levels of BDNF-immunoreactive protein in autism are not transcriptionally driven. Increased proBDNF and reduced truncated BDNF implicate defective processing of proBDNF to its truncated form. This leads to distortion of the balance between the three isoforms of BDNF which could lead to changes in connectivity and synaptic plasticity and hence behaviour. Defective proteolytic maturation is a possible new mechanism for altered synaptic plasticity leading to autism.

Research Theme: Cognition and Behavior

The effects of chronic estrogen receptor Alpha and Beta specific agonists on social leaning of a food preference in female CD1 ovariectomized mice

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Social learning provides an adaptive advantage, allowing individuals to reduce the risks associated with trial-and-error learning by acquiring information from conspecifics. The social transmission of food preference paradigm (STFP) involves an ‘observer’ acquiring a food preference for a novel food after a brief interaction with a recently fed ‘demonstrator’. Previous work in our laboratory has shown that estrogens are involved in the STFP in mice. Acute administration of PPT, an estrogen receptor alpha (ER α) agonist, blocked the preference for the demonstrator food, while non-selective estrogen estradiol benzoate (EB) and an ER beta (ER β) agonist prolonged the food preference. Similarly, chronic EB administration also prolonged the preference for the demonstrator’s food. However, the effects of chronic administration of the ER-specific agonists on the STFP are presently unknown. In the current experiment, mice were either not implanted (sham group) or implanted with Silastic capsules containing sesame oil vehicle, PPT or DPN during their ovariectomy, 10-15 days prior to testing. Doses of 3, 6, 12, and 24 μ g per mouse were administered for each of the agonists. On experiment day, demonstrator mice were placed in cages with a specific flavoured food and allowed to feed for 1 h. Demonstrators were then returned to their home cage and the interaction with the paired observer was videotaped for 30 min. The observer mouse was then placed in an observer choice test cage with food of two flavours available, both of which were novel, but one being the food fed to their demonstrator. It was found that chronic administration of both ER α agonist PPT and ER β agonist DPN prolonged the preference for the demonstrator food to 2-3x the duration of the preference observed in the vehicle and sham controls. Physiological effects of the treatments were also analyzed, specifically assessing the histomorphology of the uterus, a “classical” ER α sensitive tissue. Up to 12 μ g, PPT dose dependently increased the height of the luminal epithelium, which only occurred at the highest dose of the ER β selective ligand, DPN. Comprehensive analysis of the behavioural interaction is currently being performed to determine if the nature of the social interaction modulated the STFP. The effects on the demonstrator food preference are very similar to those obtained using EB, a non-specific estrogen, suggesting that there may be a reduction in the selectivity of the two receptor agonists upon chronic exposure to the drug, or that the chronic activation of one ER may be affecting the expression of the other. Results of this study will contribute to the current knowledge and research on hormone replacement therapy administration.

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Research Theme: Cognition and Behavior

Many-to-one matching with temporal and hedonic samples in rats

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In Experiment 1, rats were trained in a symbolic delayed matching-to-sample task to discriminate 2-s and 8-s of tone by responding to either a stationary lever or a moving lever.

During delay testing, rats exhibited a strong choose-long bias, indicating that they were timing from the onset of tone until the entry of levers into the chamber. Many-to-one (MTO) training was then given in which for one group of rats (S-F), the short sample and the food sample were associated with responding to one comparison lever and the long sample and the no-food sample were associated with responding to the alternative lever. For the other group of rats (L-F), the mapping of duration and hedonic samples was reversed. In both groups, the retention functions for duration samples continued to exhibit a strong choose-long bias. However, the retention functions for hedonic samples differed. In the S-F group, accuracy decreased more rapidly on trials initiated by a food sample, than on trials initiated by a no-food sample. In the L-F group, accuracy decreased more rapidly on trials initiated by the no-food sample, than on trials initiated by the food sample. The nature of the response bias exhibited by rats after initial training with duration samples, as well as the opposing asymmetries for hedonic samples exhibited after MTO training differ significantly from those previously reported in pigeons. In rats, the response bias exhibited at long delays for duration samples appears to provide the basis for responding to the hedonic samples introduced subsequently in the MTO mapping. In addition to coding for food or no-food rats may have also timed the hedonic samples. On trials initiated by hedonic samples timing may have continued until entry of the levers into the chamber and rats may responded on the basis of a strong temporal representation rather than a weaker memory trace of food or no-food. Future research will examine the effect of training with hedonic samples prior to the introduction of duration samples as well as using mediated-transfer designs to assess the presence or absence of common-coding for hedonic and duration samples.

Research Theme: Cognition and Behavior

Progesterone receptor expression in relation to male Mongolian gerbil parental and social behaviours

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Mongolian gerbils (*Meriones unguiculatus*) are biparental rearing mammals that live in small family units consisting of one reproductive male, one reproductive female and their offspring. Progesterone is a sex hormone that has multiple functions in the body and has known associations with parental and sexual behaviours. We investigated the link between brain progesterone receptors (PR) and various social behaviours in gerbils. We focused on two areas that are known to express PRs; the medial preoptic area (MPOA), which has been associated with parental behaviour, and the ventral medial nucleus of the hypothalamus (VMN), which has been associated with sexual behaviours. Various behavioural tests were run on the Mongolian gerbils to test for parental care and other social behaviours, as well as various physiological measurements of the gerbils were taken. The brains of the gerbils were then removed, sliced and immunohistochemistry was performed to stain for progesterone receptors. The quantification of progesterone receptor density in three subsections of the MPOA and the VMN was completed using ImageJ software. Correlations between PR density and the behavioural measures were then analyzed using SigmaStat. Surprisingly, in all brain areas examined, males had a significantly higher density of progesterone receptors than females. Gerbils were given a choice between a chamber with their pups or an empty chamber, PR expression in the MPOA correlated negatively with the amount of time males spent with their pups and positively with the empty chamber. Similarly, PR expression in the MPOA correlated negatively with time spent with pups but positively with time spent with mate when given a choice between the two. These correlations suggest that high levels of PR in the MPOA may be associated with a decrease in parental behaviours. Funded by NSERC.

Research Theme: Cognition and Behavior

Repeated inhibition of a visual stimulus leads to increasingly negative evaluations of its emotional tone: Evidence from a Go/No-go task

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Inhibition is thought to aid goal-directed behaviour by suppressing perceptual and response-related processing of stimuli that might otherwise interfere with task performance. Growing evidence suggests that inhibition has affective consequences for such stimuli. Items from which attention or a behavioural response has been withheld subsequently receive more negative affective ratings than stimuli that become the target of attention/response. Here we investigated whether such effects are relatively transient or may instead accumulate in memory. Does repeatedly inhibiting an item have a cumulative effect on its subsequent evaluation? To address this question, we used a paradigm combining response-inhibition and affective evaluation tasks and manipulated the number of times each item was inhibited (No-go item) or was the target of a response (Go item). Participants viewed abstract patterns that were primarily yellow or blue in colour and pressed the spacebar for images of one colour (Go) while withholding from responding for images of the other colour (No-go). Each image was presented as a No-go or Go item a total of one, three or six times throughout the study. Participants were subsequently asked to rate the pleasantness of these images along with previously-unseen novel patterns. Results showed more negative ratings for No-go items than for novel or Go items, reflecting devaluation of previously inhibited stimuli. Moreover, the magnitude of this inhibitory devaluation was found to significantly increase with the number of times each stimuli had been previously inhibited. Ratings of Go items were not affected by number of prior exposures. We interpret these findings as evidence that the negative affective status of an inhibited item is encoded into memory along with perceptual and response-related representations of an item. Subsequent inhibition of the same item may therefore result in an accumulation of negative affect that may help to bias attention and behavioural-responses away from items that might otherwise interfere with goal-directed behaviour.

Research Theme: Disorders of the Nervous System

STII: a potential guard against A β oligomers' toxicity

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Stress Inducible protein I (STII) is secreted by astrocytes and binds to PrP^C to induce multiple signalling pathways that are involved in neuronal and astrocyte protection and differentiation. To evaluate a possible involvement of STII in degeneration we examined STII expression in a transgenic mouse model of Alzheimer's disease (APP^{Swe}/PS1 Δ 9). Six-month old APP^{Swe}/PS1 Δ 9 mice have normal levels of STII mRNA whereas protein levels are decreased by 50%. To understand the consequences of reduced STII levels for pathology induced by A β oligomers, we treated wild-type and heterozygous STII knockout cultured cortical astrocytes with A β oligomers. Cell death was evaluated 24 and 48 hours after treatment using the live/dead kit. Our results show that astrocytes derived from heterozygous STII knockout mice have 50% decrease in STII expression. Moreover, astrocytes, with reduced STII expression, were more sensitive to the toxicity induced by A β oligomers. Significantly more mutant astrocytes died after 48 hours of A β oligomer treatment than non-treated astrocytes. In contrast, cell death in astrocytes that are not treated with A β oligomers was identical for mutant and wild type astrocytes. Our results suggest that STII plays an important role in protection of astrocytes against A β oligomer induced cell death.

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Research Theme: Cognition and Behavior

Rapid effects of intrahippocampal delivery of 17 β -estradiol on object placement learning in female mice

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Estrogens have been implicated in multiple physiological and behavioural functions, including the modulation of learning and memory. This modulation can occur through genomic means, typically occurring on a time frame upwards of several hours or days; or this modulation can take place via non-genomic means in a rapid fashion (minutes to hours). Previous experimentation has proved that pre-learning systemic 17 β -estradiol injections were able to enhance learning and memory in a rapid manner, in paradigms assessing the recognition of a novel social stimulus, a novel object or a novel object's location. Similarly, estrogen receptor (ER) agonists PPT (ER α) and DPN (ER β) were shown to facilitate object placement learning in mice, with PPT, but not DPN, facilitating also social and object recognition. This suggests similar mechanisms underlay ER α and ER β regulation of learning about the location of objects. The involvement of the hippocampus in various spatial learning paradigms makes it a likely candidate for estrogenic effects in the object placement paradigm. Accordingly this experiment was designed to determine the role of the dorsal hippocampus in 17 β -estradiol's rapid learning effects in the object placement paradigm. Microinjections of 17 β -estradiol into the hippocampus of young adult ovariectomized female CDI mice (50nM, 100nM, and 150nM at a volume of 0.05 μ L) were performed, 15min prior to testing in an object placement paradigm. As in the systemic experiments, this paradigm was completed within 40min of microinjection and the results were ethologically analyzed. We found that administration of 100nM of 17 β -estradiol improved object placement learning in these female mice within the rapid 40min time frame. Thus, it appears as if the role played by 17 β -estradiol on object placement learning is mediated, to some degree, by the dorsal hippocampus.

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Research Theme: Cognition and Behavior

The development of ultrasonic vocalizations in long-evans rat pups

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Previous research has shown that rat pups primarily elicit 40 kHz distress calls when isolated in order to induce maternal retrieval and care behaviour. Around weaning, these calls are replaced by 22 kHz aversive and 50 kHz appetitive calls. Of particular interest is the 50 kHz call type, which is thought to be reflective of a positive affective state. To date, no research has been conducted to examine the development of the 50 kHz call in very young pups. It was therefore the aim of the present study to track the development of this call type in preweanling rats through early adolescence, in order to further our understanding of this behavioural marker of positive affect. Sonographic analyses were conducted on the ultrasonic vocalizations of ten Long Evans rat pups recorded from PND 4 to PND 40. Appetitive stimuli in the form of heterospecific hand play or “tickling” was administered during 2-minute play sessions in order to maximally induce 50 kHz calling. Acoustic parameters of peak frequency, bandwidth and call duration were analyzed across this development period to determine when 50 kHz calls are first reliably produced in young rats. Vocalizations were further categorized by acoustic characteristics to identify possible 50 kHz call subtypes. It was found that pups emit 50 kHz calls prior to weaning, and the calls have flat or sweep type sonographic characteristics. After weaning, a steady increase in frequency-modulated calls was observed with a dominating trill-type. Eye opening and weaning make dramatic changes in development of pup vocalizations. Supported by NSERC of Canada.

Research Theme: Cognition and Behavior

Effects of driving experience and visibility on driving performance

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When visibility is reduced, the risk of collision increases for everyone regardless of driving experience. Trick, Lochner, Toxopeus and Wilson (2009) found that elderly drivers reduce their speed when driving in fog, whereas young novice drivers do not and, consequently, have more collisions. Two hypotheses may explain these findings: a) aging causes deterioration in performance, or b) as elderly drivers are typically more experienced, they have a better understanding of the risks associated with fog. In this study we controlled for age by testing drivers under the age of 35 in order to determine whether experience or age-related impairment account for the speed reduction observed. We compared two groups of drivers: novices (less than one year of experience) and experienced drivers (over five years of experience). Using a driving simulator, participants drove through three scenarios: one practice, and one for each condition of visibility (clear and fog). Experienced and novice drivers reduced their speed to the same overall speed in fog, but the difference was greater for experienced drivers as they drove faster in clear visibility. In clear visibility novices adhered to the speed limit and only reduced their speed slightly in fog. This suggests that novices will adhere to the rules of the road even when adjustments in their behaviour would be advised. Driving experience can to some extent account for the speed reduction observed in Trick et al. Driver education curricula should promote awareness of the risks associated with driving in fog and implement the appropriate behavioural modulation strategies.

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Research Theme: Sensory and Motor Systems

Examination of the effects of cooling the footsoles on the electromyographic responses in the upper and lower limbs following galvanic vestibular stimulation

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Introduction: The maintenance of balance in a standing human requires the integration of sensory information from many sources including vision, somatosensory and vestibular inputs. Equilibrium is best maintained if all sensory modalities are available, however, the body can re-weight sensory importance if an input becomes unreliable [1]. Both vestibular and skin information are known to contribute to standing equilibrium control [2]. The combined contribution from these two sources is unknown, although loss of one is often related to augmentation of the other [2].

Aim: The project aimed to establish whether skin information is important in the ability to generate a vestibular evoked balance response.

Methods: Ten healthy subjects were instructed to stand quietly on a force platform. They received bipolar, binaural galvanic vestibular stimulation (GVS; 2mA square pulse) with their head facing to the side. The GVS stimulation profile consisted of 200, 25ms stimuli (interstimulus interval 800ms) randomized for either anode or cathode front. Hypothermia-induced anesthesia was then used to remove sensation from the skin of the foot sole, after which all GVS conditions were repeated. Electromyographic (EMG) responses in the soleus, tibialis anterior, deltoid and triceps muscles were recorded using silver silver/chloride (Ag Ag/Cl) surface electrodes. Short (SL) and medium (ML) latency responses to the GVS perturbation were evaluated before and following skin anesthesia. Changes in centre of pressure were also recorded to highlight balance responses. EMG data were spike trigger averaged to assess the changes in the vestibular evoked EMG response pre and post anesthesia.

Results: GVS evoked clear biphasic muscle responses in the soleus muscle at latencies around 40-60 ms (SL) and 90-100ms (ML). In the control conditions, the SL response sizes ranged from 3.71 to 18.92% ($7.46 \pm 1.18\%$) and ML responses ranged from 5.79 to 58.79% ($25.84 \pm 4.53\%$) when expressed as a percentage of the mean pre-stimulus (50ms) background EMG. There was no significant change in the amplitude of the SL ($t \text{ stat} = -0.599, P = 0.56$) or the ML ($t \text{ stat} = -1.99, P = 0.072$) response between *control* and *iced* conditions, however there was an obvious trend of increasing ML amplitude, reaching a mean response size of $33.72 \pm 6.43\%$ after icing. Force plate data demonstrated the minimal influence of this GVS stimulus protocol on inducing a sway response in either the anterior-posterior or medio-lateral directions and this remained consistent during the iced trials.

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Research Theme: Disorders of the Nervous System

Moral reasoning performance in patients with bipolar disorder

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Moral reasoning encompasses judgments surrounding moral issues and moral behaviour, and determines whether actions meet personal and societal moral expectations. Preliminary evidence suggests that relative to healthy controls, patients with bipolar disorder (BD) show deficits on several inter-related social cognitive tasks, including theory of mind and emotion comprehension. Systematic investigations examining other aspects of social cognition, including moral reasoning, have not been conducted in psychiatric populations. In the present study, BD patients and their matched controls completed a previously validated moral reasoning task: a modified version of the moral and cognitive dilemmas task used in previous studies of moral reasoning. Participants also received standardized measures of social functioning. BD patients showed decrements (i.e., lower developmental ratings following standardized scales of moral reasoning) in moral reasoning relative to matched controls; performance on a cognitive control task was also impaired in the patient group. A higher illness burden was associated with diminished moral reasoning performance. Deficits in social cognition among patients with bipolar disorder appear to extend across various domains and may relate to cognitive deficits associated with an extended course of illness.

Research Theme: Cognition and Behavior

Computer visualizations: the influence of spatial ability, depth cues, and interactivity on learning visuospatial information

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Computer visualizations are increasingly common in education across a range of subject disciplines, including anatomy. Despite optimism about their educational potential, students sometime have difficulty learning from information presented in these visualizations. The purpose of this study is to examine the relationship between computer visualizations and learning, and to explore a range of factors that influence learning from computer visualizations. Three major factors are considered: (1) the type of visual depth cues in the display, (2) the level of interactive control permitted by the system, and (3) participants' level of spatial ability. Participants (n=60) of differing spatial ability (high, low) studied a tubular array of anatomy-like objects in one of three visual conditions (3D, 2D, control) and one of two interactive conditions (active, passive). Prior to and after the learning phase, participants' knowledge of the tubular objects were assessed using a multiple-choice test involving the mental rotation of the tubular objects, the identification of the objects in 2D cross-sections, and the localization of planes or levels where these cross-sections were taken. Results indicate a main effect of spatial ability on performance. Individuals with high spatial ability performed better than those with low ability regardless of the type of depth cue and level of interactivity. When the effects of prior anatomy knowledge were controlled, a significant interaction effect between spatial ability and depth cues was found. Specifically, those with high spatial ability can learn with either 2D or 3D computer visualizations, while those with low ability appear disadvantaged while learning with 3D visualizations.

Research Theme: Disorders of the Nervous System

Amphetamine sensitization induced by carbachol in ventral Subiculum in mice

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In rats, amphetamine-induced locomotion can be sensitized by ventral Hippocampal (vHPC) stimulation, or blocked by either vHPC or ventral Subiculum (vSUB) lesions. Carbachol, a cholinergic agonist, or glutamate administered to the vSUB activates dopamine release in the nucleus accumbens and/or locomotor behavior. To extend these findings we injected carbachol (0.5 µg/0.5 µl) or saline into the left vSUB of mice, 24 hours prior to amphetamine (2 mg/kg i.p.). Carbachol in vSUB increased locomotion for 60 min vs. saline, and this effect was reduced by atropine (30 µg/0.5 µl). Amphetamine-induced locomotion increased by over 4 fold after pre-exposure to carbachol vs. saline in the left vSUB. This sensitization of amphetamine was reduced when carbachol was co-infused with atropine. Viral transfection of the M5 gene into the left vSUB prior to treatment with carbachol did not change amphetamine-induced locomotion. Our study supports theories that amphetamine sensitization and schizophrenic delusions involve activation of the left vHPC and vSUB. As such, this amphetamine test in mice may be used to evaluate genes related to schizophrenia, and testing antipsychotic drugs that target ventral hippocampal systems supporting amphetamine sensitization.

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Research Theme: Cognition and Behavior

The interaction of arousal, musical context, and task difficulty on recognition

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The influence of music on learning has been a growing area of research in psychology. While some researchers have reported that music can impede learning, others have claimed that music can facilitate it. The present study looked at the interaction of musical context (music played during studying, music played during testing, or music played during both studying and testing), valence (positively or negatively valenced music), arousal (high or low arousal music), and task difficulty (easy or hard task) on the recognition of face-name pairs. During the study phase, participants were presented with a series of randomly selected face-name pairings. In the subsequent test phase, participants were presented with the same face-name pairs, but some of the pairs were changed. Participants were asked to indicate if the pairings during the test phase matched the ones they saw during the study phase. Throughout the task, different selections of music with varying levels of valence and arousal, and sometimes no music, were played in the background. Results showed no main effect of musical context, valence, arousal, and task difficulty but revealed a significant three-way interaction between arousal, musical context, and task difficulty on recognition performance. On the easy task, performance was better for high arousal music compared to low arousal music when it was presented only during study or only during test. On the hard task, recognition was better for high arousal music compared to low arousal music when presented only during the test phase, but the effect was reversed when music was presented only during the study phase. Relative to silence, when music was present during both study and test, arousal did not have an effect on recognition on the easy task or the hard task. Listening to high arousal music has more beneficial effects during test or during study but not when music is presented during both for easy tasks. However, listening to high arousal music is only beneficial during testing, but not during studying for harder tasks.

Post-synaptic mechanism underlying neuropeptides effect in *Drosophila melanogaster*

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Nerve cells use a diverse array of signalling molecules to transmit information. One important class of such molecules are neuropeptides (short chains of amino acids). Approximately 50 neuropeptides have been identified in humans, and several hundred have been identified in invertebrates. One such neuropeptide found in the fruitfly, *Drosophila melanogaster*, is DPKQDFMRamide. This peptide is a member of perhaps the largest super-family of neuropeptides, the FMRamide-like peptides. DPKQDFMRamide has previously been shown to elicit modulatory effects on motorneurons and muscles fibers of *D. melanogaster*. The peptide is known to work through a G-protein coupled receptor (GPCR), but; the mechanisms through which the peptide induces its post-synaptic effects remain unclear. We have previously demonstrated that the peptide's action is strongly calcium-dependent, as an L-type calcium channel blocker inhibited the peptide from inducing myogenic contractions in the body-wall of third instar *Drosophila* larvae. The present work extends such studies by further examining the role of L-type calcium channels in modulating synaptic transmission at the neuromuscular junction. Using third instar larvae of *D. melanogaster*, we show that DPKQDFMRamide decreases the input resistance of muscle fibers by 21% ($P < 0.05$). Co-application of DPKQDFMRamide and nifedipine inhibits the reduction in input resistance, suggesting that the peptide-induced changes in input resistance are dependent upon L-type selective channels. We next sought to determine whether this effect on postsynaptic input resistance contributes to the peptide's ability to potentiate excitatory junctional potentials (EJPs). DPKQDFMRamide induced a 60% increase in EJP amplitude in the muscle fibers investigated. Nifedipine, which blocked the reduction in input resistance, did not enhance the peptide's ability to increase EJP amplitude. Instead, nifedipine reduced the peptide's ability to increase EJPs (from 60% enhancement to 40% enhancement). These data suggest that while the effects of the peptide-induced changes in input resistance are dependent upon L-type calcium channels, the potentiation of EJPs are not. This suggests that the peptide elicits differential effects pre- and post-synaptically which might utilize multiple signalling pathways. Future work will examine intracellular signalling pathways involved in mediating the L-type calcium channel dependent, peptide induced effects. Supported by NSERC

Research Theme: Neural Excitability, Synapses, and Glia: Cellular Mechanisms

Local field potentials in the dorsal cortex of the inferior colliculus evoked by tone bursts presented at low probabilities

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Animals are regularly exposed to multiple acoustic stimuli in the natural environment. Novel sounds (i.e., sounds presented at low probability) in the environment usually carry information important for animal behaviours. Neurons sensitive to novel sounds have been found in auditory structures including the auditory cortex, thalamus, and midbrain. The inferior colliculus (IC) is an important midbrain auditory structure consisting of three major subdivisions, i.e., the central nucleus (ICc), the dorsal cortex (ICd), and the external cortex (ICx). Studies using single unit recording techniques have found that neurons in the IC generate a stronger action potential discharge in response to a sound presented at a low than a high probability (Perez-Gonzalez et al., 2005; Malmierca et al., 2009; Lumani and Zhang, 2010).

We conducted *in vivo* neurophysiological/neuropharmacological experiments to determine: (1) if the neural sensitivity to novel sounds in the ICd can be revealed by local field potential recordings, and (2) whether the GABA_A receptor contributed to the neural sensitivity to novel sound in the ICd.

Sounds were presented to the ear contralateral to the recording site of an anesthetised rat using an earphone. An auditory oddball stimulus paradigm was used to elicit auditory novelty responses. This stimulus consisted of a train of tone bursts constructed by embedding one tone burst (an oddball stimulus, presented at a low probability) in a sequence of another tone burst (a standard stimulus, repetitively presented).

Our results show that the response evoked by a tone burst presented as an oddball stimulus has a significantly larger amplitude than that evoked by the same tone burst presented as a standard stimulus. The difference in the amplitudes of the two responses increased with the reduction of the presentation probability of the oddball stimulus, the increase of the rate of sound presentation, and the increase in the frequency difference between the oddball and standard tone. Bicuculline (an antagonist of GABA_A receptors) increased the amplitudes of neural responses in the ICd but did not completely abolish the neural sensitivity to oddball sounds. Our results indicate that the neural sensitivity to novel sounds in the ICd can be revealed by using field potentials, and the inhibition mediated by GABA_A receptors is not the sole factor that contributes to the neural sensitivity to novel sounds in the ICd.

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Research Theme: Cognition and Behavior

Affective influences on physiological arousal in persons with and without MHI

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Music has been shown to evoke strong emotional responses (Zetner, Grandjean, & Scherer, 2008), and can increase one's physiological arousal; one's level of arousal, in turn, has been shown to influence cognitive performance (Jefferies, Smilek, Eich, & Enns, 2008; Schellenberg, 2005). Persons with injury to the ventromedial prefrontal cortex (VMPFC) are physiologically underaroused relative to their cohorts, and similar effects have been observed for those with mild head injury (MHI; Baker & Good, 2009). This study investigated the influence music, with both positive and negative valence, had on arousal in individuals with MHI and their subsequent performance on decision-making. University students were randomly assigned to one of 3 conditions (positive music, negative music, white noise) and performed various cognitive decision-making tasks while their physiological state was being continuously recorded (i.e., electrodermal response, heart rate). On the basis of their results from a demographic questionnaire, students are classified as either reporting having a previous MHI or not. Changes in physiological arousal as a function of affective valence and any corresponding enhancement or alteration in decision-making performance between MHI and no-MHI cohorts is assessed. This research highlights the important implications of music and arousal enhancement with respect to therapy or treatments that could alleviate affective, decision-making, and arousal impairments in those with MHI.

Research Theme: Neural Excitability, Synapses, and Glia: Cellular Mechanisms

Toluene inhalation evokes widespread c-Fos expression in the adult rat brain

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Toluene is a psychoactive chemical inhaled for its euphoric effects. Toluene inhalation is additionally associated with a variety of short- and long-term changes including impairments in cognition, memory deficits, and motor dysfunction. Such diverse behavioural outcomes suggest a myriad of brain structures may be implicated in the effects of toluene, yet to date there has been no systematic examination of the brain structures activated by toluene vapours. In the present study we examined the functional activation of neurons throughout the brain by assessing immunoreactivity for the immediate early gene c-Fos. Adult rats were exposed to toluene vapour (5000 ppm – an abuse-relevant concentration) or control conditions for 0, 5, 10, or 30 minutes. 1.5 hours later rats were anesthetized and then perfused transcardially. Cryoprotected brains were sectioned, slices were immunostained with a c-Fos antibody, and cells showing c-Fos immunoreactivity were quantified via brightfield microscopy. Numerous brain regions implicated in reward and addiction were activated by toluene, including the ventral tegmental area, the nucleus accumbens, subnuclei of the amygdala, and specific regions within the hypothalamus. Immunoreactivity was further observed in areas of the brain associated with motor function, including select regions of the cerebellum as well as the motor cortices. Finally, c-Fos immunoreactivity was noted in the medial and lateral entorhinal cortices, but not in the hippocampus itself. Our results reveal the extent of neural activation associated with exposure to abuse-relevant concentrations of toluene vapour, with patterns of neural immunoreactivity consistent with behavioural outcomes of toluene exposure.

Who's Got the Rhythm?: Individual Differences in Rhythmic Abilities

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Rhythm has been studied in many different ways. Links between certain factors (e.g. short-term auditory memory, musical training) and possessing rhythmic ability have been hypothesized. Although some studies have investigated how certain factors contribute to rhythmic ability, none have included a range of factors within the same study. The current study examines a set of factors that are hypothesized to contribute to individual differences in rhythmical ability including: auditory short-term memory, temporal structure detection ability (or the ability to “feel the beat”), basic timing abilities, and musical training. Participants completed five separate tests that measured individual aptitude for each of the hypothesized factors mentioned above. First, a standard auditory digit span test determined participants’ digit span. Second, a duration discrimination test asked participants compare two tones and determine if the second tone was shorter or longer. Third, the Beat Alignment Test (BAT) had participants determine if beeps superimposed over a song were on or off beat with the song. Fourth, a musical training questionnaire determined the level of musical training. Finally, the Rhythm Reproduction Test had participants reproduce rhythms that differed in beat (beat or non-beat conditions) and length (short, medium or long). The first four tests assessed factors hypothesized to contribute to rhythmic ability: the digit span test measured auditory short-term memory; the duration discrimination test measured basic timing abilities; the Beat Alignment Test measured the ability to detect temporal structure; and the questionnaire assessed years of musical training. The scores from these tasks were used to predict performance on the Rhythm Reproduction Test. A 2x3 repeated measures ANCOVA was used to analyze the relationship between individual differences in rhythm reproduction ability and the other variables. The two factors included beat (2) and length (3) and all other variables scores were entered as covariates. The results revealed that beat rhythms were reproduced more accurately than nonbeat rhythms, and shorter rhythms were reproduced more accurately than longer rhythms. A significant three-way interaction was also revealed between beat, duration discrimination, and Beat Alignment Test scores. The interaction demonstrated that for beat rhythms, basic timing ability positively correlated with rhythm reproduction ability regardless of ability to detect temporal structure. However, for nonbeat rhythms, for those participants with a better ability to detect temporal structure, basic timing ability correlated with rhythm reproduction ability. This relationship disappeared for those with a weak ability to detect temporal structure. Overall, the results suggest that beat, length, basic timing abilities, and the ability to detect temporal structure contribute to individual differences rhythmic ability.

Changes in tactile spatial acuity over development: from pre-pubescence into adulthood

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The question of whether, and if so how, tactile spatial acuity (TSA) changes during childhood has been largely disregarded in the literature. Only two groups have investigated this question, with equivocal results^{1,2,3}. We predicted that children would have better TSA than adults by virtue of their diminutive digits⁴. Under the reasonable assumption that receptor number is fixed from early childhood into adulthood, the smaller fingertips of children may possess finer TSA than adult fingertips because tactile receptors in the skin might necessarily become more sparsely distributed as the fingertips grow (maintaining adequate receptive field coverage). Indeed, tactile receptors appear fully mature in function by ages 5-7 years⁵. Apart from physical changes in the periphery, age-related cortical maturation (e.g. myelination) may also influence acuity^{1,2,3}. We are performing a cross-sectional study to track the developmental course of TSA in children (ages 6-16 years), using our fully-automated tactile testing apparatus⁶. In addition, we are measuring several physical properties of the fingertip to determine whether these influence TSA. These candidate variables are: surface temperature, hydration, elasticity and sebum content of the skin, and fingertip surface area, volume and sweat pore spacing. Preliminary results suggest that acuity indeed worsens with age; however, more data are needed to make stronger conclusions about the effects on TSA of age, finger size and the additional candidate variables we are measuring.

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Research Theme: Cognition and Behavior

THC does not affect Arc expression in the CA1 region of the hippocampus

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Several lines of evidence suggest the involvement of CBI receptors in certain forms of learning and memory as well as in hippocampal synaptic plasticity. Similarly, the activity-regulated immediate early gene *Arc* is involved in enduring plasticity and memory consolidation. It is well established that following spatial exploration, hippocampal neurons express *Arc* in an environment-specific manner such that they can reliably label cells that express place fields. Taking advantage of *in situ* hybridization for *Arc* mRNA and catFISH cellular imaging technique, we investigated CBI receptor activity modulates place cell-related *Arc* expression in the CA1 region of the hippocampus. F344 rats were habituated to handling and injection (saline) prior to the behavioral test. On test day, rats received either a single injection of Δ^9 -tetrahydrocannabinol (THC) at several doses (0.2, 1.0, or 5.0 mg/kg) or vehicle (saline). The rats were placed back in their home cages and 25 min later were exposed to an open-field environment for 5 min. Immediately following this exploration session, rats were sacrificed. Control groups consisted of a negative control group consisted of undisturbed rats sacrificed immediately after being removed from their home cages. Preliminary data reveal no change in *Arc* induction following spatial exploration, although it remains possible that subtle changes have occurred.

Research Theme: Sensory and Motor Systems

Influence of Area 5 on the neural circuitry within the primary motor cortex assessed using TMS

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Brodmann's area 5 (BA 5) has direct connectivity with primary motor cortex (MI), is largely dedicated to the representation of the hand and may have evolved with the ability to perform skilled hand movement. The present study examined the influence of BA 5 on MI neural circuits before and after theta-burst stimulation (TBS) over right hemisphere BA 5. Using single and paired-pulse TMS, measurements of motor evoked potentials (MEPs), short interval intracortical inhibition (SICI), intracortical facilitation (ICF) and resting motor threshold (RMT) were examined for the representation of the first dorsal interosseous muscle (FDI) for MI bilaterally. Transcranial magnetic stimulation was performed using BiStim-2/Magstim 200² stimulators and a MagPro stimulator for the paired and single pulse paradigms and TBS, respectively. Surface EMG was recorded from the FDI muscle on the right and left hands. Preliminary results indicate that BA 5 influences MI excitability such that MEP amplitude is increased without changing intracortical circuits SICI or ICF. Collectively, the data suggest that BA 5 alters MI output directed to the hand by influencing select MI neural circuits. Targeting BA 5 via TBS is a novel mechanism to powerfully modulate activity within MI and may provide an avenue for investigating hand control in healthy and clinical populations.

Research Theme: Sensory and Motor Systems

Tactile perception on the hand following Theta-burst TMS over the primary somatosensory cortex

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Fine motor control of the hand relies on intact somatosensory integration and feedback. Impaired hand movements are observed in patient groups where touch perception and processing within the primary somatosensory cortex (SI) is abnormal. Repetitive transcranial magnetic stimulation (rTMS) involves trains of multiple stimuli to the same cortical area that act to alter cortical excitability. When applied over SI, rTMS modulates tactile perception and cortical physiology. Continuous theta-burst stimulation (cTBS) is a form of rTMS that involves the application of low-intensity short duration pulses which induces physiological changes to the underlying cortex. The effect of cTBS on tactile perception is unknown. The goal of present study was to examine changes in temporal and spatial tactile psychophysics to reveal whether cTBS can modify touch perception. In separate experiments, temporal discrimination threshold (TDT) and amplitude discrimination were measured from the right hand before and for up to 35 minutes following real or placebo cTBS over left SI. Compared to pre-cTBS values, TDT was elevated immediately following cTBS (3-6) minutes and at later intervals (11-18 minutes post). The spatial measure of tactile perception was also measured over the same time course and compared to pre-cTBS values showed tactile impairments for up to 18 minutes. These experiments reveal that cTBS over SI impairs tactile acuity in both space and time on the contralateral hand. The effects lasts for up to 18 minutes and subsequent measures return to pre-cTBS levels. This work is important in indentifying means to modulate cortical excitability and has potential for clinical application.

Research Theme: Sensory and Motor Systems

Striato-pallidal divisions receive topographical input from the ventral midbrain in the fire-bellied toad *Bombina orientalis*

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Dopaminergic projections from the midbrain to the forebrain have been implicated in various aspects of reward and learning. A homologue of the mammalian mesolimbic dopaminergic pathway has been proposed in amphibians, but projections from the midbrain to the forebrain are not well described in this group. Recent behavioural evidence showing that fire-bellied toads (*Bombina orientalis*) are highly sensitive to reward conditions prompted the present investigation of pathways connecting the midbrain to the striato-pallidal systems of the telencephalon. Knowledge of these pathways will help set the stage for investigations of the neural substrate of reward and learning in *Bombina*. Retrograde tract-tracing using biocytin applications to either the ventral or dorsal striato-pallidal systems was used to investigate their afferents from the midbrain. Results indicate a topographical organization of midbrain neurons projecting to either the ventral or dorsal striato-pallidum. More neurons projecting to the ventral striato-pallidum are found in the ventral tegmentum of the midbrain, whereas more neurons projecting to the dorsal striato-pallidum are found in the posterior tuberculum. However, both application sites often result in the labelling of a small proportion of neurons in both midbrain regions. This situation is reminiscent of the organization of mammalian mesolimbic and mesostriatal pathways, but further work is necessary to confirm the neurochemistry of these pathways.

Research Theme: Neural excitability, synapses and Glia: Cellular mechanisms

Investigating the role of retinoid receptors in retinoic acid-mediated growth cone turning

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Retinoic acid (RA), an endogenous vitamin A metabolite, has been implicated in neuronal regeneration in addition to its well-known functions in axial patterning and neurogenesis. Classically RA is known to bind to two nuclear receptors, the retinoic acid receptor (RAR) and the retinoid X receptor (RXR), which modify gene expression. Recent data from our lab using the pond snail, *Lymnaea stagnalis*, has suggested a novel, non-genomic role for the RXR in mediating growth cone turning. Specifically, the RXR was shown to be present in the growth cone and a RXR agonist was able to mimic the RA-induced growth cone turning. More recently, a novel RAR has been cloned from *Lymnaea*, despite belief that invertebrate non-chordates did not possess RARs. Much like the RXR, this receptor is also found in the growth cones of regenerating neurons. In this study we aimed to determine, using pharmacological blockers for RAR and RXR, the extent to which each of these receptors might mediate the effects of endogenous RA in chemoattraction. Specifically, both 9-*cis* RA and all-*trans* RA isomers produce similar growth cone turning responses. Though both isomers can bind to vertebrate RARs, only 9-*cis* RA binds to vertebrate RXRs. Interestingly, antagonists for both the RAR and RXR independently blocked the growth cone turning responses to both 9-*cis* and all-*trans* RA in our study, suggesting different binding affinities of these receptors compared to vertebrate retinoid receptors. Furthermore, these data suggest that the novel invertebrate RAR may also play a non-genomic role in mediating growth cone turning in response to RA. Whether the RAR and RXR are working independently or in conjunction with one another when mediating this growth cone response, has not yet been determined.

Delineating the neural circuitry underlying crossmodal object recognition in rats

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Previous research has indicated that the perirhinal cortex (PRh) and posterior parietal cortex (PPC) contribute to spontaneous tactile/visual crossmodal object recognition in rats. Specifically, PRh seems to provide crucial visual information processing, while the PPC may contribute similarly to tactile information. Moreover, these two cortical regions have been shown to interact functionally to mediate crossmodal object representation in rats. However, it remains to be explored if these areas alone are sufficient for crossmodal object recognition, or if another region might facilitate comparison between the two object representations. The prefrontal cortex (PFC) receives extensive polymodal projections and has been widely implicated in crossmodal cognition and might therefore underlie either a unitary multimodal representation or comparison mechanism that allows for integration of object information across modalities. The hippocampus (HPC), however, also receives polymodal projections from both the PRh and PPC, and HPC lesions have been known to impair other object recognition tasks. Accordingly, two separate crossmodal object recognition tasks were implemented to assess HPC and PFC contributions to crossmodal cognition. A variation of the spontaneous object recognition task was employed, taking advantage of the rat's innate preference to explore novel objects over familiar objects. In the crossmodal matching task (CMM), rats explore two identical objects in a darkened red-light environment, which limits their exploration to only tactile information. Then, after an hour delay, they are given a choice between a novel object and the familiar object, both placed behind transparent barriers in normal lighting, necessitating the use of visual information to discriminate between the objects. To control for potential sensory impairments caused by the lesions, visual-only and tactile-only object discriminations are used as control tasks. In the crossmodal association task (CMA), rats are briefly pre-exposed to the sample object in normal lighting conditions so that both tactile and visual information are available simultaneously. Pilot studies have demonstrated that without the pre-exposure, a 3 hour delay between the sample and choice phase abolishes crossmodal object recognition. Simultaneous pre-exposure to tactile and visual object information seems to change how the object is represented in the brain, and CMA might therefore involve different regions than the CMM task. Bilateral HPC lesions did not significantly impair CMM or CMA task performance, suggesting that the HPC is not necessary for either task. However, large bilateral PFC lesions impaired both CMM and CMA tasks. Furthermore, the PFC can be divided into sub regions, including orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC). By performing selective lesions to these sub regions, dissociation was found between the tasks: OFC lesions selectively impaired CMM, but not CMA, whereas mPFC lesions failed to disrupt performance on either task. These experiments provide greater insight into the neural bases of object memory representations and the dynamic nature of memory processes in the mammalian brain.

Multiple exposures of therapeutic ultrasound results in increased peak antinociceptive effects in segmentally related myofascial trigger points

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Introduction: Therapeutic ultrasound (US) is a common therapeutic modality used to treat a wide range of musculoskeletal conditions⁵ and may be effective in the treatment of myofascial pain⁷. Myofascial pain syndrome (MPS) is characterized by the formation of hyperirritable muscular loci called myofascial trigger points (MTPs)¹. Previous research has shown that one dose of US applied to an MTP reduces pain by up to 45% locally⁶ and up to 31% in segmentally linked MTPs⁷. We aim to explore treatment protocols to optimize this antinociceptive effect in the management of MPS. Thus, we will investigate the hypothesis that two equal therapeutic doses of US evoke enhanced antinociceptive effects when compared with a single dose (temporal summation). To date, no group has investigated the summative effects of multiple US exposures on the magnitude and duration of MTP antinociception.

Methods: 20 young, healthy subjects will be recruited from the student population of the University of Guelph. Inclusion criteria are the presence of clinically identifiable MTPs² located within the right infraspinatus (IS) and supraspinatus (SS) muscles. Findings from a confidential health history and physical examination will provide the basis for exclusion. Qualified subjects (n=20) will be randomly allocated to test (n=10) or control (n=10) groups.

Prior to commencing the study, each subject will be trained on the left side to recognize the onset of a deep or sharp pain which represents the pain pressure threshold (PPT), measured using a pressure algometer (Chatillion DFE). Data capture (NI LabView 2010) of PPT readings from the IS MTP will occur before US intervention for baseline readings and at 3, 6, 9, 12, and 15 minutes after each US. The control group administered a control intervention (5 minute sham US) followed by the test (5 minute dose; 1 MHz; 0.5 W/cm², pulsed wave, 50% Duty Cycle) and the test group will be given the test intervention twice.

Expected Results: According to previous research⁷, we expect to observe a peak antinociceptive effect of 31% after one dose of US. Owing to the effects of temporal summation, we expect to observe both increased peak (5 minutes after the second application of US) and increased duration (significantly increased for the full 15 minute record period) of antinociceptive effects in the group receiving two doses compared to the group receiving one dose.

Conclusion and Relevance: Myofascial pain syndrome is a very common musculoskeletal pain condition with a significant physical and financial impact on society accounting for up to 90% of patients treated in pain clinics³ and approximately \$47 billion per year in direct health care costs in the United States⁴. Ultrasound has demonstrated the ability to reduce MTP pain. However, optimal intervention protocols have not been established. Therapeutic ultrasound is an easy to implement and cost-effective therapeutic modality; accordingly, it may play an important role in the conservative management of myofascial pain syndromes.

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Research Theme: Homeostatic and Neuroendocrine Systems

Immune-brain cross-talk influences sex differences in stress reactivity

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Sexual dimorphism in behaviour and risk of psychiatric illness is an important topic for today's neuroscientists. Current literature demonstrates that immune-brain crosstalk influences stress-related behaviours. Our group has focused on the role of the adaptive immune system using T cell deficient and germ-free mice and demonstrated that loss of adaptive immune function leads to reduced anxiety-like behaviour. This anxiolytic phenotype is related to changes in gene expression of NMDA receptor subunits within the limbic system. Here we further assessed differences in stress circuitry in response to repeated restraint stress (daily for 10 d) in wild type and T cell receptor deficient mice (TCR β -/- δ -/-). Radioimmune assay revealed elevated basal plasma corticosterone levels in TCR deficient mice. Repeated restraint stress reproducibly elevated plasma corticosterone, with increased levels in WT female mice compared to WT male mice. TCR mice lacked this sexual dimorphism in peripheral stress reactivity, and yet centrally, upregulation of CRH mRNA in the hypothalamus following restraint was exaggerated in TCR mice. CRH receptor expression was also differentially regulated between sexes. Restraint stress elevated hippocampal CRHR2 mRNA expression in WT males but not females. In TCR animals, CRHR1 mRNA expression was elevated in the hippocampus of males whereas females had increased expression of CRHR2 mRNA. Sex differences were also observed in the expression of NMDA receptor subunits in the amygdala and hippocampus. NR2A mRNA was increased in the hippocampus of TCR males and females following restraint. NR2B mRNA expression was elevated in the amygdala of TCR males compared to WT males following restraint. Overall, male and female TCR mice display an exaggerated stress response, though each have distinct alterations to the stress axis and glutamatergic system. These data suggest that adaptive immune system crosstalk has lasting consequences on the development of CNS stress circuitry.

Research Theme: Cognition and Behavior

Decision-making strategies in persons with and without MHI

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Mild head injuries (MHI) are known to be highly prevalent even in high functioning university students (DeBono & Good, 2008; Segalowitz & Lawson, 1995), despite being substantially underrepresented in the medical community (Tellier et al., 1999). In particular, the orbitofrontal/ventromedial prefrontal cortices (VMPFC) are highly vulnerable to biomechanical injuries (Wallis, 2007) and, in more severe brain injuries, result in impaired social decision-making despite preserved intellectual ability (Bechara et al., 1996; Bechara et al., 2000). This study examined decision-making under conditions of uncertainty (i.e., simulated gambling) in University students using the Iowa Gambling task. Disadvantageous card selection choice (i.e., evidenced by slower transition from disadvantageous to advantageous choices leading to less gain - similar to that observed with persons of traumatic VMPFC injury, Yechiam et al., 2005), as well as explicit strategy awareness is examined as a function of reported MHI history and concomitant physiological arousal (i.e., electrodermal response, heart rate). These relationships have implications for the neuropsychological and neurological continuum between MHI and more severe traumatic brain injuries.

Research Theme: Cognition and Behavior

Cannabidiol may attenuate vomiting and nausea by acting as an indirect 5-HT_{1A} agonist

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Cannabidiol (CBD), a non-intoxicating component of cannabis suppresses cisplatin-induced vomiting in *Suncus murinus* (house musk shrew; Kwiatkowska et al., 2004) and reduces lithium chloride (LiCl)-induced conditioned gaping in rats (a selective measure of conditioned nausea; Parker & Mechoulam, 2003), but the mechanism of action mediating these effects is unknown. We investigated the involvement of somatodendritic 5-hydroxytryptamine 1A (5-HT_{1A}) auto-receptors in CBD's anti-emetic/anti-nausea effects, as evidence suggests its involvement in the neuroprotectant and anxiolytic properties of CBD.

A series of experiments were conducted to examine the action of CBD at the 5-HT_{1A} receptor, using the 5-HT_{1A} antagonists WAY100135, and WAY100635 in later experiments, to block the anti-emetic/anti-nausea effects of CBD in shrews and rats respectively.

Cannabidiol (5 mg/kg) suppressed nicotine-, LiCl-, and cisplatin (20 mg/kg)-induced vomiting in the shrew, and LiCl-induced conditioned gaping in rats. The anti-emetic/anti-nausea effects of CBD were reduced by systemic pretreatment with WAY100135. As well, the more selective 5-HT_{1A} receptor antagonist, WAY100635, administered systemically or intracranially into the dorsal raphe nucleus (DRN), a site of somatodendritic 5-HT_{1A} autoreceptors, interfered with the suppressed conditioned gaping produced by CBD in rats. When administered intracranially into the DRN, CBD completely abolished LiCl-induced conditioned gaping in rats. In addition, CBD was found to display significant potency at enhancing the ability of the 5-HT_{1A} receptor-selective agonist, 8-OH-DPAT, to stimulate [³⁵S]GTPγS binding to rat brainstem membranes *in vitro*. Furthermore, in combination CBD (0.5 mg/kg) and 8-OH-DPAT (0.005 mg/kg) synergistically reduced conditioned gaping, but these doses alone were not effective.

These results suggest that the anti-emetic/anti-nausea effects of CBD may be mediated by increasing activation of 5-HT_{1A} somatodendritic auto-receptors in the DRN, perhaps by reducing the release of forebrain 5-HT.

Research Theme: Disorders of the Nervous System

Microfluidic chambers for culture of basal forebrain cholinergic neurons

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Basal forebrain cholinergic neurons (BFCNs) are the major cholinergic output of the CNS. Degeneration of BFCNs is a feature of aging and of diseases of the aging brain such as Alzheimer's disease. Atrophy of BFCNs and loss of their connections correlate strongly with the degree of dementia in Alzheimer's disease. It has been suggested that memory deficits in Alzheimer's disease may arise from lack of appropriate trophic support of BFCNs. The neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are target-derived neurotrophic factors for BFCNs and work to promote growth, maintenance and survival of these neurons. During aging and age-related diseases, the expression or effective transport of these neurotrophins in BFCNs is compromised. Significant literature supports deficits in BDNF expression and NGF transport as significant contributors to the cholinergic atrophy observed in aging and in Alzheimer's disease.

The objective of this research is to develop the culture of BFCNs of different ages in microfluidic chambers and to use this novel culture system to explore the effects of aging and disease on neuronal survival and axonal transport. The method uses a microfluidic platform to allow the cell bodies in one chamber to extend neurites into a separate chamber across grooves that can be microscopically imaged. BFCNs from embryonic (E18) and postnatal (P1-3) rat brains are cultured in NGF, BDNF, or both, and cultures are monitored by immunostaining for neurotrophin receptor (TrkA, TrkB) and cholinergic marker expression and for amount of outgrowth into the axonal compartment. These cultures are also used to visualize axonal transport using BDNF-GFP. Preliminary work suggests that embryonic as well as postnatal BFCN cultures, particularly TrkB+ neurons, will grow extensive axons through the microfluidic platform into the axonal chamber. In addition, E18 BFCN cultures in microfluidic chambers have proved to be a reliable system to visualize and measure the axonal transport of BDNF-GFP.

Long-term objectives of this research include successfully culturing BFCNs and demonstrating transport of neurotrophins within these neurons, as well as examining the effects of aging on transport, signaling, and synapse integrity with target neurons.

Research Theme: Cognition and Behavior

The role of the anterior cingulate cortex in the consolidation of fear memories

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The anterior cingulate cortex (ACC) is implicated in the consolidation of contextual fear memories. Here, we tested whether we could enhance consolidation by increasing the excitability of ACC neurons following contextual fear training. To do this we used herpes simplex virus (HSV) to overexpress the dominant negative form of the KCNQ2 gene (dnKCNQ2). The KCNQ2 gene encodes a protein subunit that is an integral component of a slow-activating voltage-gated potassium channel. Thus, overexpression of dnKCNQ2 disables this channel, reduces afterhyperpolarization, and increases the overall excitability of infected neurons. C57Bl/6Jx129 mice were subjected to contextual fear conditioning. One day after training (0.5 mA shock) mice were injected with HSV-dnKCNQ2 or an HSV control vector containing red fluorescent protein (RFP) into their ACC. Mice were tested 7 days later, for 3 consecutive days. We found that mice infected with HSV-dnKCNQ2 exhibited higher freezing levels compared to control mice, suggesting that an increase in excitability in the ACC strengthens the consolidation of a contextual fear memory.

Research Theme: Cognition and Behavior

c-Fos expression during acute administration of cocaine and heroin

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Using c-Fos as a marker of neural activation, the present study aims to shed light on the nature of neural activity that occurs when rats receive cocaine or heroin within a place conditioning context. Following a single conditioning trial with cocaine (0, 3, 10, or 20 mg/kg) or heroin (0, 0.03, 0.3, or 1 mg/kg), c-Fos density was examined in regions known to be implicated in learning and memory, including regions of the mesocorticolimbic dopamine system, the serotonergic pathway, the cholinergic pathway, as well as the central grey. c-Fos density increased with increasing doses of both cocaine and heroin in all regions examined. Further, c-Fos expression differed between the cocaine and heroin groups in all regions except the ventral tegmental area, lateral tegmentum, and anterior cingulate cortex, with heroin demonstrating greater c-Fos expression in all regions except the basolateral and central amygdala. These findings suggest that the regions examined are all involved in the learning and memory that occurs when a rat receives a single injection of cocaine or heroin, and this enhancement of neural activity appears to occur in a dose-dependent manner. The differential levels of c-Fos expression between the heroin and cocaine groups in the regions of interest suggest the pattern of activation across these regions differs between the two drugs. This may be due to differential mechanisms of inducing c-Fos expression.

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Access conditions, excessive behaviours and addiction in older male rats

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Access conditions can have profound effects on consumption, beyond those driven by need. Non-deprived young adult rats consume excessive amounts of weak (4%) sucrose solutions when it is provided discontinuously (every third day) but consume much smaller amounts when given ad lib access (Hewitt & Eikelboom, 2008). When access conditions are made equivalent (giving all rats alternate day access) rats in the discontinuous group continue to show significantly higher consumption for prolonged periods of time. This long lasting differential consumption has been suggested as a factor in the development of addiction. Age has been suggested as another susceptibility factor for addiction. Parts of the young brain are not fully developed potentially making it more vulnerable to addiction (Dayan, Bernard, Ollicac, Mailhes, & Kermarrec, 2010). We were curious if the sucrose consumption differences would be evident in older rats.

Older male Sprague-Dawley rats (retired breeders $n=16$ aged 9-12 months) were randomly assigned to ad lib (AL) or every fourth day (24h) discontinuous access (D) to 4% sucrose for four cycles. The average first day's consumption was $183.1 \pm 22.2g$ SE and $178.8 \pm 22.7g$ for AL and D rats respectively. The AL rats showed a slight decrease in consumption tapering off and remaining constant ($151.7 \pm 8.6g$) across the following 16 days. D rats showed a marked increase in consumption from their first exposure reaching stability across the last two exposures ($252.3 \pm 19.4g$). Like young rats, older rats consume 4% sucrose excessively when given discontinuous access.

Another excessive behaviour only evident in younger rats is wheel running; young rats run over 5000 wheel turns a day while older rats run approximately 1000 (Looy & Eikelboom 1989). Would these older rats show low wheel running and would discontinuous access to a running wheel elevate this running. Half the rats in AL and D groups were assigned to either ad-lib or discontinuous access (every fourth day) to a running wheel for four cycles or 16 days. Rats in the continuous group showed the typical low levels of running (688 ± 111.8 wheel turns per 24 h) similar to previous findings (Looy & Eikelboom, 1989). Every fourth day access to a running wheel had no significant effect on wheel running (1033 ± 317.7 wheel turns per 24 h across the four cycles). We then increased the non-running period in the discontinuous group to every eighth day for 2 cycles (16 days). Running remained low (1023 ± 288.5 across two cycles, while continuous exposure running remained low as well). In older rats discontinuous wheel access did not increase running.

Discontinuous access to 4% sucrose is enough to drive an addiction-like consumption pattern in aged rats, but discontinuous access to running wheel had no effect on running. Short and long access to a substance can also effect consumption. Repeated six hour access to cocaine produces increasing consumption in rats, but repeated one hour exposure does not (Ahmed & Coob, 1998). Long (4h) but not short (1h) access to a running wheel produces increasing running (Eikelboom & Lattanzio, 2003). Preliminary results suggest short and long sucrose access results in similar consumption levels. Access conditions can have significant but differential effects on the various models of excessive behaviours but why is not clear.

Research Theme: Cognition and Behavior

Gender differences in modulations of acoustic startle response in Sprague Dawley rats

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Habituation is characterized by a gradual decrease in response to a repeated, irrelevant stimulus. In rodents, habituation can be studied using the acoustic startle response (ASR). ASR can be further modulated by prepulse inhibition (PPI), where the presentation of a subthreshold pre-stimulus decreases an organism's behavioural response to a subsequent high intensity stimulus. While gender differences in habituation and PPI have been observed in association with several disorders, such as bipolar disorder and schizophrenia, they have not thus far been extensively studied in a healthy model. Pre-existing gender differences have important implications for characterizing diseases on the basis of non-associative learning deficits. Furthermore, female subjects are often excluded from non-associative learning experiments due to potential effects of hormonal fluctuations on startle modulations. The focus of this study was to investigate any gender differences in startle modulations with the hope of addressing any experimental concerns with the use of females in nonassociative learning experiments.

This experiment observed short term habituation and PPI in male and female Sprague Dawley rats from PND 12 to PND 40. Habituation was assessed through the presentation of a high intensity (105db) acoustic stimulus for twenty trials, with stimulus duration of 20ms per trial. PPI was measured through exposure to a prepulse of three possible intensities (0 db, 75 db, 80 db) for duration of 4 ms, followed by exposure to the pulse (105 db), with an ISI of 50ms.

There was no significant difference in prepulse inhibition between genders. Similarly, there was no significant gender difference in habituation; however a trend suggesting that males exhibit greater habituation than females was noted.

This experiment indicates that perhaps due in part to the adaptive nature of non-associative learning, habituation and prepulse inhibition are not significantly affected by gender differences.

Research Theme: Disorders of the Nervous System

Over-expression of the SIRT3 Sirtuin protects differentiated PC12 cells from degeneration induced by oxidative stress and trophic withdrawal

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SIRT3 is a mitochondrial sirtuin whose deacetylase activity regulates several facets of mitochondrial function. In non-neuronal cells SIRT3 over-expression increases cellular respiration efficiency, and decreases levels of reactive oxygen species. In this study, we tested whether the over-expression of SIRT3 in differentiated PC12 cells, a model of sympathetic neurons, would affect their sensitivity to oxidative stress. Our results show SIRT3 over-expression decreased basal mitochondrial membrane potential and reactive oxygen species levels in unchallenged cells without altering mitochondrial morphology. When subjected to acute glucose deprivation (GD) or acute oxygen-glucose deprivation (OGD) differentiated PC12 cells over-expressing SIRT3 displayed significantly lower levels of cytotoxicity both at the end of the insult, and after 20 hours of normal media replacement. Further, SIRT3 over-expression protected differentiated PC12 cells from apoptosis induced by trophic withdrawal. Collectively, these data indicate that an elevation of SIRT3 is sufficient to protect neurons from cytotoxic insults, and add to the growing evidence that SIRT3 could be targeted for neurodegenerative intervention.

Research Theme: Cognition and Behavior

The effect of asymmetrical sample training on retention functions for hedonic samples in rats

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Rats trained in delayed matching-to-sample to discriminate sample stimuli consisting of the presence of food or the absence of food show more forgetting of the food sample than of the no-food sample. According to the single code/default strategy, rats code only the food sample and make the response correct for the no-food sample by default when there is no memory of the food sample. The purpose of this study was to examine how asymmetrical training with only one sample prior to two-sample training, and illumination conditions during the intertrial interval and the delay interval, would affect retention functions for samples of food and no-food. Rats were divided into two groups and each group was initially trained with only the food sample or the no-food sample prior to the introduction of the second sample. Following introduction of the second sample, delay tests were conducted. The retention functions obtained from delay testing were not affected by whether the food sample was trained first or the no-food sample was trained first. While illumination conditions during the intertrial interval and the delay interval appeared to have some effect on the retention functions, for most of the test conditions the retention functions were parallel, suggesting that rats coded both the food sample and the no-food sample. Transfer tests, in which features of the food and no-food sample were manipulated, confirmed that features of the no-food sample were coded in memory. While previous research in both pigeons and rats indicates that symmetrical sample training produces nonparallel retention functions consistent with a single code/default strategy, the current study in rats shows that asymmetrical sample training produces parallel retention functions which are consistent with the coding of both food and no-food samples.

Research Theme: Disorders of the Nervous System

Curcumin: a potential therapeutic for tardive dyskinesia?

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Background: The use of antipsychotics to treat schizophrenia can result in the development of movement disorders including abnormal-oro facial movements (AOFM) and with chronic treatment tardive dyskinesia (TD). While the mechanisms of induction of AOFMs are unclear, oxidative stress (OS) remains a dominant hypothesis. OS can result from excessive dopamine oxidation and the consequent formation of free radicals. These free radicals have been shown to cause neuronal death by caspase dependant and independent mechanisms in animals and humans. The anti-oxidant curcumin, an extract of turmeric, has been reported to have significant therapeutic effect in patients with Parkinson's disease. Thus, the goal of this study was to explore the oxidative stress hypothesis of AOFMs and TD and to determine whether curcumin can prevent AOFMs in rats.

Methods: Four groups of rats (n=8) were used: haloperidol vehicle with curcumin vehicle; haloperidol with curcumin vehicle; curcumin with haloperidol vehicle; curcumin and haloperidol. Rats were administered haloperidol (2mg/kg) via intra-peritoneal injections daily and curcumin (200mg/kg) orally. AOFMs were counted at baseline, day7 and day14. Rats were sacrificed on day 14, and striata removed for proteomic analysis.

Results: At day14 there was a significant increase in AOFMs following haloperidol treatment, this was reversed by concurrent curcumin treatment. Proteomic analysis identified an up-regulation of anti-apoptotic molecule BclXL following curcumin treatment.

Conclusion: Curcumin can be therapeutic in the treatment of AOFMs, supporting a role for oxidative stress in the development of AOFMs. While the underlying mechanism remains unknown, it is probable that BclXL is implicated. However, the limitations of this model were inconsistencies in the incidence of VCMs beyond day 14, thus haloperidol decanoate administered via intramuscular injection was demonstrated to provide an alternate and arguably more favourable model for future chronic investigations.

Research Theme: Cognition and Behavior

The MAGL inhibitor, JZL184, attenuates LiCl-induced vomiting in the *SUNCUS MURINUS* and 2AG attenuates LiCl-induced nausea-like behavior in rats

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The endogenous cannabinoid, anandamide, has been shown to suppress toxin-induced vomiting in a number of emetic species (Darmani, 2002; Van Sickle *et al.*, 2001; Parker *et al.*, 2009), as well as reduce lithium chloride (LiCl)-induced conditioned gaping in rats (a selective measure of conditioned nausea; Cross-Mellor *et al.*, 2007). However at present, only a few studies have evaluated the effects of the endogenous cannabinoid, 2-arachidonoylglycerol (2AG), on emesis, while its effect on nausea-like behaviors in rats remains unknown. We investigated the role of 2AG, as well as inhibition of its inactivating enzyme, monoacylglycerol lipase (MAGL), in the regulation of nausea and vomiting using a shrew (*Suncus murinus*) model of emesis and LiCl-induced conditioned gaping in rats.

A series of experiments evaluated the effects of pretreatment with the selective MAGL inhibitor, JZL184, as well as exogenous 2AG prior to administration of the emetogenic drug, LiCl. JZL184 (0, 16, 40 mg/kg), dose-dependently suppressed vomiting in the shrew in response to LiCl, and this effect was reversed by pretreatment with the CBI antagonist/inverse agonist, AM-251. The ability of JZL184 to selectively inhibit MAGL in shrew brain tissue was observed using competitive activity based protein profiling (ABPP). Pretreatment with exogenous 2AG (0, 0.5, 1.25, 2.0 mg/kg) dose-dependently suppressed LiCl-induced nausea-like behavior (conditioned gaping) in rats, however, the anti-nausea-like effects of 2-AG were not reversed by pretreatment with AM-251 or the CB2 antagonist, AM-630. Instead, pretreatment with the cyclooxygenase (COX) inhibitor, indomethacin, reversed the ability of 2-AG, as well as its downstream metabolite, arachidonic acid (AA), to suppress LiCl-induced conditioned gaping. On the other hand, when rats were pretreated with a high dose of JZL184 (40 mg/kg), the suppression of conditioned gaping by 2AG was partially reversed by AM251. The suppression of conditioned gaping was not due to interference with learning because the same dose of 2AG did not modify the strength of conditioned freezing to a shock-paired tone.

These findings suggest that manipulations that result in an elevation of 2AG may have anti-emetic/anti-nausea potential, and that downstream metabolites of 2AG and AA may be partially responsible for mediating the anti-nausea effects of exogenous administration.

The influence of skin thickness and hardness on touch and vibratory thresholds across the human foot sole

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Background: Glabrous skin on the soles of the feet contains specialized mechanoreceptors, which provide proprioceptive and tactile feedback to the central nervous system (CNS). The ability of the skin to provide sensory feedback is dependent on the type and distribution of receptors as well as the properties of the surrounding tissue. The skin on the soles of the feet has been shown to contain an even distribution of cutaneous receptors [1] despite having areas of variable sensitivity [2]. Vibratory thresholds have been shown to vary across the foot sole and skin thickness has been proposed to account for this variability [3][4]. Different classes of skin receptors are known to be preferentially activated by specific stimulation frequencies [5]; however the influence of skin thickness on the attenuation of vibratory stimuli and the resulting location specific tactile and frequency specific vibratory perception remains unknown. When discussing skin as a sensory organ it is crucial to understand the morphological factors which may influence perceptual thresholds.

Purpose: To establish the influence of skin thickness and hardness on touch and vibratory perceptual thresholds across the foot sole.

Hypothesis: Perceptual thresholds will show regional variability, and receptor specificity that relate to differences in skin thickness and hardness.

Methods: 20 young healthy adult subjects will be recruited to participate in this study. Skin thickness, hardness, temperature as well as touch and vibratory thresholds will be determined on the right foot at five foot sole locations: great toe (GT), fifth metatarsal head (5MT), lateral arch (LA), medial arch (MA) and heel (H). Subjects will lay prone with their leg flexed and 90° and supported in a brace. *Skin thickness* will be measured using high-frequency B-Mode ultrasonography (>20 MHz). The thickness of the epidermis, dermis and hypodermis will be determined. *Skin hardness* measurements will be taken using a hand held durometer (Rex Gauge, model 1600, type OO). Four measurements will be averaged at each site. *Touch thresholds* will be assessed using monofilaments (Semmes-Weinstein). At each test site, a monofilament with the largest applied pressure (g/mm²) will be delivered perpendicularly to the test site first, followed by monofilaments in order of decreasing pressures. Touch threshold will be determined to be that of the monofilament with the lowest applied pressure, which is correctly perceived at least two thirds of the time. *Vibratory thresholds* will be determined across 4 frequencies (3, 25, 65, and 250Hz) delivered by a mini shaker (Bruel & Kjaer 4810) with a 6mm diameter probe. Each frequency will be applied for 2 seconds and the subject will depress a trigger when they perceive the vibration. Stimulus amplitudes will increase or decrease based on subject response until the lowest perceived amplitude is achieved.

Significance: Establishing the influence of skin thickness and hardness on perceptual thresholds will enhance the understanding of how skin characteristics can alter sensory transmission and tactile perception. Ultimately this research can be applied to facilitate improvements in therapy for patients who have impaired balance and gait ability as a result of decreased sensory feedback from the skin.

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Research Theme: Cognition and Behavior

Candidate plasticity gene 15: temporal patterns of activation

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Activity-induced genes play an important role in promoting neuroplasticity by way of their protein products. One such gene product, candidate plasticity gene 15 (*cpg15*, also known as neuritin) is thought to enhance plasticity by promoting synaptogenesis through axon arbor elaboration and neurite extension in various brain regions (Nedivi et al., 1996).

It has been determined that *cpg15* is expressed in multiple brain regions including the cortex, hippocampus, thalamus, retina and olfactory bulb (Hevroni et al., 1998, Corriveau et al., 1999, Nedivi and Lee, 2002). Following expression, *cpg15* has been implicated in various neurite survival roles, as well as nurturing localized neuromuscular synaptogenesis, advancing existing pre-synaptic axon growth, and promoting dendritic and axon arbor elaboration (Cantalops et al., 2000, Naeve et al., 1997, Harwell et al., 2005). For instance, it has been shown that *neuritin* plays a key role in dictating branch dynamics of axon arbor elaboration and synaptogenesis at neuromuscular junctions in presynaptic motor neurons. Using time-lapse imaging of *Xenopus Laevis* tadpoles, one study described a clear role for *cpg15*, in which its expression significantly impacts motor neuron axon terminal arbor elaboration by increasing synapse density and increasing the rates at which new branches are added (Javaherian and Cline, 2004).

This gene product may play a similar role in promoting the restructuring of central connections. Investigating this *in vivo*, however, requires knowledge of the time course with which this gene product is expressed following neuronal activity. The aim of the present study was to determine at what point and for how long hippocampal *cpg15* is induced following neuronal activity. Rats separated into 15 minute intervals received electroconvulsive stimulation spanning a 180 minute timeframe. Using fluorescent *in situ* hybridization and confocal microscopy, *cpg15* transcripts within the dentate gyrus (DG) and CA1 and CA3 layers of the hippocampus were labeled and quantified. Preliminary results indicate that activity-induced *cpg15* expression begins as early as 45 minutes following stimulation and persists for at least 180 minutes. This suggests a potential role for CPG15 in early stages of hippocampus-dependent learning and consolidation.

Research Theme: Disorders of the Nervous System

PAOPA, a novel antipsychotic drug devoid of side effects associated with currently prescribed typical and atypical antipsychotics

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Schizophrenia (SZ) is a mental disorder that affects 1.1% of the world's population, and is characterized by disturbances in a variety of behaviours, ¹. Antipsychotic drugs (APDs) are the current treatment for patients with schizophrenia. All APDs bind to the dopamine D2 receptor, and the efficacy of APDs to treat symptoms of SZ is directly correlated to their occupancy at the dopamine D2 receptor. However, while treating symptoms of SZ, APDs also cause an array of debilitating side effects. Treatment with first generation of 'typical' APDs can lead to movement disorders including parkinsonism, akathisia, and tardive dyskinesia ², while treatment with the second generation of 'atypical' APDs can cause metabolic complications, such as weight gain, agranulocytosis, and increased risk of type 2 diabetes mellitus ². Drugs currently in the market are undoubtedly largely insufficient to effectively treat SZ, and the need for a safer and more effective therapeutic is in high demand.

PAOPA (3(R)-[(2(S)-pyrrolidinylcarbonyl) amino]-2-oxo-1-pyrrolidineacetamide), an analogue of a naturally occurring brain tripeptide L-prolyl-L-leucyl-glycinamide, is a newly developed drug for the treatment of SZ. Unlike APDs, PAOPA modulates the dopamine D2 receptor at an allosteric site. This novel drug has shown its therapeutic benefits in several established preclinical models of SZ in our lab. In order to determine if there are any adverse metabolic and extrapyramidal side effects that are associated with current APDs, we evaluated the safety profile of PAOPA under a strict regime of testing. These studies were undertaken to determine if PAOPA caused 1) neurological abnormalities, and b) metabolic toxic effects.

Male Sprague Dawley rats were injected intraperitoneally for both 40 days and 8 days at 5, 10, and 100 times the effective dose (1mg/kg) of PAOPA or saline. Rats were observed for extrapyramidal side effects. Blood glucose and insulin levels were measured. Behavioural testing revealed no abnormalities generally associated with conventional APDs. PAOPA's haematological and biochemical profile revealed no toxic effects on liver and kidney functions, blood cells, blood pressure, and various other biochemical parameters. In addition, necropsy and histopathology findings showed no abnormalities on examined animals.

Preclinical screening has demonstrated PAOPA to be a safe and potential novel therapeutic drug which offers a number of distinct advantages over conventional drugs, including the absence of adverse and toxic side effects that are commonly associated with conventional APDs. The development and transition of this new drug into clinical studies will significantly improve health care both in Canada and worldwide.

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Research Theme: Development

AMPA Receptor trafficking: a mechanism of excitatory synaptic plasticity

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Introduction: Research into the molecular basis of synaptic plasticity has revealed that the activation of both N-Methyl-D-Aspartate (NMDA) and alpha-amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid (AMPA) is key in the regulation of excitatory mediated plasticity. In particular, it is the trafficking of AMPA receptors that has been implicated in synaptic plasticity regulation. The brain is most plastic during the critical period in early life, and little plasticity is believed to occur in adulthood.

Methods: We used quantitative Western blot analysis to characterize the developmental expression of four proteins (PICK, GRIP, GluR2, and PhosphoGluR2) involved in AMPA receptor trafficking in the rat primary visual cortex and frontal cortex. We further extended the experiment to include cortical tissue of monocularly deprived adult rats as well as those treated with Prozac to see the effect of these manipulations on AMPA receptor trafficking.

Results: We found significant differences in the trajectories of AMPA receptor proteins between the two cortical areas throughout development. Prozac has been shown to reinstate plasticity in the adult visual cortex; however, treating the animals with Prozac did not appear to have any effect on the AMPA receptor protein expression. However, monocular deprivation caused an upregulation of proteins in the primary visual cortex.

Conclusion: The effect of monocular deprivation on the expression of AMPA receptor proteins is consistent with synaptic scaling, a compensatory homeostatic mechanism that occurs in response to a lack of sensory input to the deprived eye. This suggests the presence of excitatory mediated plasticity in the adult brain.

Research Theme: Sensory and Motor Systems

Do the olfactory subsystems of red-legged salamanders cooperate in prey detection? An analysis of brain responses to soluble and volatile cues

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Terrestrial salamanders of the genus *Plethodon* are among many vertebrates possessing both main olfactory and vomeronasal systems, which are thought to detect volatile and soluble olfactory cues, respectively. However, recent work showed a high amount of convergence between the two olfactory subsystems at the level of the central nervous system, suggesting that they could play complementary roles. For this study, immunocytochemistry against c-Fos was used as an indirect marker of neuronal activity to assess the brain regions activated by olfactory input. The salamanders were stimulated with either soluble or volatile prey cues, or with both together. Soluble cues were obtained by rinsing a beaker which had held crickets, and volatile cues came from a paper tissue placed in the beaker. Soluble prey cues were applied to the nasolabial grooves using a fine-tipped pipetter, while a 20-ml syringe was used to apply air laced with prey volatiles near the snout of salamanders. Treatment was followed by a 120 minute survival period followed by anaesthesia, brain dissection and immunocytochemistry against c-Fos. Cells positive for c-Fos were counted in all brain regions that displayed consistent labelling. Counts were made visually by an observer blind to the experimental treatments, and then automated counting was performed in the olfactory bulbs for confirmation. This work is still in progress. Under the assumption that each olfactory subsystem is stimulated specifically by soluble or volatile olfactory cues, we predicted that a limited number of brain regions would respond specifically to the volatile or soluble cues, whereas most brain regions activated should respond to both types of cues due to central convergence, with some regions possibly showing synergistic or inhibitory responses.

Cutaneous sensitivity in unilateral trans-tibial amputees

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Introduction: After partial lower limb amputation, the residual limb becomes the primary site of interaction with the prosthetic, and as a result, the soft tissue of the residual limb becomes subjected to significant loading forces which would normally be supported by the feet. In addition, amputation reduces the sensory feedback to the central nervous system (CNS), which when present used for control of gait and posture [1]. One important component of this afferent feedback is obtained from cutaneous skin receptors in the foot sole which relay information regarding pressure, skin stretch and vibration. Previous research in upper limb amputees has shown changes in tactile perception sensitivity when compared to the unamputated limb [2], and further research in upper limb amputees has suggested these changes are due to central and not peripheral changes [3]. While findings in upper limb amputees illustrate an interesting change in skin sensitivity, it is not known how cutaneous information altered with lower limb amputations given the role of skin in balance and posture. In addition to any central changes which may occur, the residual lower limb may also experience peripheral changes and soft tissue deformation due to the new challenge of weight bearing. Some early work has shown changes in tactile sensitivity in the residual lower limb [4] but has not fully examined a wide range of sites or utilized additional tools to accurately identify sensitivity levels.

Aim: to examine skin sensitivity and perception thresholds in the residual limb of unilateral trans-tibial amputees, and compare these values to the intact limb as well as to thresholds in matched control subjects.

Methods: Subjects screening will involve a written questionnaire to determine details of amputation and prosthetic use prior to testing. Various skin sites on the residual limb and homologous sites on the intact limb will be examined in amputees in addition to sites on the intact plantar foot. Similar sites will be tested in both legs of control subjects. Testing modalities will include tactile perception and vibration. Tactile perception will be assessed using Semmes-Weinstein nylon monofilaments using a dual-step technique designed by Berquin et al [5]. Vibration detection will be assessed in a range of 2Hz-200Hz using a vibrating shaker device (Bruel and Kjaer, Denmark), with the lowest positive response indicating threshold level.

Expected Results: Both increased and decreased skin sensitivity at the residual limb could have serious implications. Decreased sensitivity may have pathological consequences, since pressure sensitivity is necessary for detection of excessive loading that can lead to tissue degradation. Increased sensitivity may indicate mechanisms similar to those in upper limb amputees, which has been due to central changes. Increases in sensitivity seen here may reflect an adaptation of the CNS to increase sensory feedback at the residual lower limb for control of gait and balance. The concept of central change would be further supported by changes in sensitivity on the unamputated limb.

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Measuring tactile spatial acuity: a simple but rigorous alternative to the flawed two-point test.

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Weber long ago measured tactile spatial resolution as the distance between two contacts to the skin necessary to evoke the sensation of distinct points (Weber, 1835). The classic two-point task remains popular to this day, particularly in clinical settings: calipers of increasing tip-separation are applied to the skin until the patient responds “two.” Contrary to the belief that this task rigorously measures spatial acuity, critics note that task performance depends upon a subjective criterion for responding “two” (Craig and Johnson, 2000). In an attempt to prevent criterion effects, some investigators use a two-interval forced-choice (2IFC) procedure, stimulating the skin with both one and two points, in random order, and asking the subject which interval contained two. Unfortunately, this version of the task may provide a non-spatial neural population response magnitude cue (Johnson and Phillips, 1981) arising from surround suppression: two closely spaced points elicit fewer action potentials than does a single point of equal indentation (Vega-Bermudez and Johnson, 1999). Here we compare the 2IFC two-point task to an equally easily performed alternative task, 2IFC horizontal-vertical (HV) discrimination, in which the subject is stimulated with two points, once along the skin’s medial-lateral axis (horizontally) and once along the proximal-distal axis (vertically). We assess both tasks on the fingertip, finger base, palm, and forearm, and we correlate task performance with an anatomical measure associated with receptive field spacing (Peters et al. 2009). Preliminary data indicate that HV discrimination, unlike the two-point task, provides a rigorous measure of tactile spatial acuity.

Is vestibular information calibrated to a visual reference frame to facilitate recovery from a perturbation?

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Introduction: Balance during quiet standing is regulated through sensory feedback from the vestibular, somatosensory and visual systems. Galvanic vestibular stimulation (GVS) is a technique used to directly stimulate the vestibular system, creating an illusory sense of head movement that results in reflexive postural adjustments observed as an upper body segment roll and whole body shift in centre of pressure (CoP) toward the anode electrode [1]. Vestibular input is shown to modulate the amplitude of postural responses by providing a reference signal for gravitational vertical. This signal, in conjunction with somatosensory information, allows for accurate alignment of the body after a disturbance to standing posture [2]. Recently, it has been shown that the tonic firing of vestibular afferent input is calibrated to a visual reference frame during a gait navigation task [3]. It is yet to be determined whether vestibular information is also calibrated to a visual reference frame during postural responses to a perturbation.

Aim: The objective of the current project is to determine whether vestibular information is calibrated to a visual reference frame to facilitate recovery from a perturbation.

Methods: The application of two main stimulation profiles will assist in establishing whether vestibular evoked postural responses are generated relative to a visual reference frame. Subjects will be instructed to stand relaxed on a motion platform with their eyes closed. Both profiles will use bipolar binaural GVS at an intensity 3x threshold. In the first profile, GVS will be delivered at the onset of a platform translation and will continue for 8 seconds [2]. In the second profile, subjects will receive GVS for 8 seconds while standing with their eyes closed. They will then be instructed to open their eyes and 'recalibrate' their altered body position to vertical using a visual reference. Following the recalibration, subjects will be instructed to close their eyes, at which time the support surface will undergo a translation perturbation. Control trials will consist of subjects receiving a translation perturbation in the absence of a GVS signal. Perturbations will be randomly sequenced, low-velocity translations of a custom motion platform in the frontal plane to the left or right. Segmental and whole body centre of mass (CoM) displacements will be captured using a 3D motion capture Optotrak™ system (Northern Digital Inc., Ontario, Canada) and electromyography (EMG; Bortec Biomedical Ltd., Alberta, Canada) will be recorded bilaterally from tibialis anterior, medial gastrocnemius, soleus, and gluteal muscles. CoP displacement during individual trials will be calculated from information captured by a Kistler™ forceplate (Kistler Instruments Inc., New York, USA) secured to the motion platform.

Expected Results: It is proposed that vestibular evoked postural responses will be elicited relative to the new recalibrated vertical position. We hypothesize this will be demonstrated by the following: the amount of postural sway elicited during the recalibration trials will be significantly less than the sway induced during the GVS-translation trials.

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- [3] Sturnieks et al. (2005) *Gait and Posture* 21(Suppl 1) S30 Vestibular input is calibrated to a visual reference frame during walking.

Research Theme: Disorders of the Nervous System

Cortical thickness analysis in major depressive disorder: correlations between structure and function

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Introduction/Background: Structural abnormalities in major depressive disorder (MDD) have been identified in various brain regions, however, little is known about the causal relationship between structure, function, and the emergence of neuropsychiatric symptoms. Recently, localized changes in cortical thickness have been proposed as a putative brain-based endophenotype of major depression. The mechanism that leads to changes in cortical thickness are thought to involve dysregulation of the hypothalamic-pituitary-adrenal axis as well as disturbances in normal cellular resilience, leading to loss of synapses, atrophy and ultimately to volume losses in the cerebral cortex.

Purpose: The aim of this study is to compare cortical thickness in various MDD populations and to correlate cortical thickness with both cognitive functioning and symptoms of depression.

Methods: Cortical thickness analysis will be performed on T1-weighted anatomical magnetic resonance images (MRI) obtained from a 3-Tesla MRI scanner at St. Joseph's Healthcare, Hamilton. Automated methods for classifying tissue, segmenting brain structures, and measuring thickness values at each 1 mm point of the cerebral surface will be used. Non-depressed individuals with a first-degree relative with depression, treatment-naïve patients in their first episode of depression, patients who have experienced multiple (three or more) episodes of depression, and healthy volunteers are included.

Expected Area of Findings: We hypothesize that the cortical areas responsible for emotion regulation will be affected as a function of chronicity. Based on the literature, we expect to find regionally specific thinning in the dorsolateral prefrontal cortex, the right parietal cortex, and reduced volumes in the bilateral hippocampus. In addition, we predict regional thickening in the medial prefrontal cortex and the anterior cingulate cortex. We will also examine the cognitive correlates of these structural changes, including verbal working memory, rumination, and default-mode activity.

Discussion: Findings may have implications in differential diagnosis, identifying novel therapeutic targets, and early intervention strategies.

Research Theme: Cognition and Behavior

Effects of the 5-HT_{2C} agonist mCPP in the quinpirole sensitization rat model of obsessive-compulsive disorder (OCD)

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Introduction: Previous research from our laboratory has shown that in the quinpirole sensitization rat model of OCD, checking behaviour has the attribute of being compulsive because it possesses at least two distinct features: heightened vigor of motor performance, and heightened concentration or focus on the task of checking¹. The literature indicates that such attributes of behaviour are modulated by serotonergic receptors, and specifically, that 5-HT_{2C} receptor agonism reduces locomotion² while 5-HT_{2C} receptor antagonism decreases focus on task performance³. The present study asked how 5-HT_{2C} agonism would modulate the vigor and focus of compulsive checking. We hypothesized that co-treatment with a 5-HT_{2C} agonist would produce a seemingly paradoxical effect on quinpirole-induced compulsive checking: both a reduction in the vigor of performance and an increase in the focus on checking. **Methods:** Four groups of rats were tested: two experimental groups were co-treated with quinpirole (0.125 mg/kg) and the 5-HT_{2C} agonist meta-chlorophenylpiperazine (mCPP; 0.625 mg/kg or 1.25 mg/kg); one control group was co-treated with quinpirole and saline while the last group served as saline controls. Rats underwent a chronic sensitization procedure on the open-field according to our standard protocol⁴. **Results:** Following chronic sensitization, quinpirole+saline rats showed the expected larger vigor and focus on checking compared to saline controls. Quinpirole+mCPP rats (both doses) showed a decrease in vigor compared to quinpirole controls as well as an increase in focus, albeit the latter effect was evident only during the early portion of the sensitization regimen. **Discussion:** Thus, the present results support the hypothesis that vigor and focus of compulsive checking are differentially modulated by 5-HT_{2C} receptors. Furthermore, considering that this effect was observed in rats co-treated with a D₂/D₃ agonist, the present findings highlight the importance of 5-HT_{2C} modulation of dopaminergic systems that may be relevant for pharmacotherapy of OCD.

¹ Dvorkin A, et al. (2010). Features of compulsive checking behavior mediated by nucleus accumbens and orbital frontal cortex. *European Journal of Neuroscience*, 32(9), 1552-63.

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Research Theme: Cognition and Behavior

Depletion of serotonin in the insular cortex by 5,7-Dihydroxytryptamine (5,7-DHT) lesions attenuates conditioned nausea in rats

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Keywords: nausea, learning, lesion, taste avoidance, aversion, insular cortex, serotonin

Although rats do not vomit, they display conditioned gaping reactions when re-exposed to a flavor previously paired with a nauseating treatment. The insular cortex (IC) is a site of gustatory and visceral input, suggesting it may be an important site of taste-illness associations. IC lesions have been reported to attenuate the strength of taste avoidance, but its effects on conditioned gaping are relatively unknown. Depletion of forebrain serotonin attenuates the establishment of conditioned gaping but not taste avoidance. Experiment 1 investigated the effect of bilateral 5,7-Dihydroxytryptamine lesions of the rat insular cortex on conditioned gaping and taste avoidance. After recovery, rats began the taste reactivity test and were intraorally infused with 0.1% saccharin solution for three conditioning/testing trials and immediately injected (i.p.) with lithium chloride. During the trials the rats' disgust reactions were recorded. 5,7-DHT IC lesions significantly reduced conditioned gaping but not taste avoidance relative to controls. Experiment 2 investigated the effect of the serotonin 5-HT₃ antagonist ondansetron (OND), delivered to different regions of the insular cortex on conditioned gaping. Immediately before both taste reactivity conditioning trials, rats were intracranially infused with 1 ug/ul OND to either the Gustatory Insular Cortex (GIC) or Visceral Insular Cortex (VIC). The rats' disgust reactions were recorded and afterward the rats were injected with lithium chloride. At test, no OND was administered. Pretreatment of OND to the GIC and VIC showed a double dissociation. Infusion to the VIC reduced conditioned gaping but did not disrupt taste avoidance and infusion to the GIC had no effect on gaping but did interfere with taste avoidance. Serotonin depletion of the insular cortex reduced gaping, a model of nausea. The double dissociation indicates that gaping and taste avoidance are mediated by different regions of the IC. The results suggest that activation of the 5-HT₃ receptors in the VIC produce nausea resulting in gaping reactions, but activation of the 5-HT₃ receptors in the GIC are necessary for the production of conditioned taste avoidance. These results indicate that the VIC may be a site responsible for the generation of nausea. The taste reactivity test can be used as a nausea prescreening tool for new pharmacological treatments.

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Research Theme: Cognition and Behavior

Role of the medial prefrontal cortex in NMDAR-dependent modulation of sensorimotor gating

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Prepulse inhibition (PPI) of the acoustic startle response is a paradigm commonly used as an operational measure of sensorimotor gating, a pre-attentive process which is disrupted in schizophrenic patients. NMDA antagonist-induced PPI disruption has become a model for the study of the cognitive symptoms of schizophrenia and sensorimotor gating deficits. However, the mechanism by which NMDA antagonists exert their effects has yet to be elucidated. Evidence suggests that medial prefrontal cortex (mPFC) lesions occlude the PPI disrupting effects of systemically administered NMDA antagonists. Furthermore, NMDA receptors are expressed by the startle mediating neurons of the caudal pontine reticular nucleus (PnC). This study aims to examine the possible roles of the medial prefrontal cortex (mPFC) and the caudal pontine reticular nucleus (PnC) in NMDA antagonist-induced prepulse inhibition deficits in rats.

Sprague-Dawley rats received injections of the general NMDA antagonist MK-801, the NR2B subunit specific antagonists ifenprodil or Ro25-6981, or vehicle (0.9% saline) either systemically or locally into the mPFC or the PnC through chronically implanted bilateral cannula. PPI was tested with different prepulse levels and different interstimulus intervals. Both MK-801 and Ro25-6981 disrupted PPI when administered systemically. MK-801, but not Ro25-6981, also increased baseline startle. When administered locally into the dorsal region of the mPFC (prelimbic cortex) MK-801 and ifenprodil caused a potent disruption of PPI, however administration of MK-801 and ifenprodil to the ventral mPFC (lower prelimbic cortex or infralimbic cortex) had no significant effect on PPI. When administered to the PnC, MK-801 and ifenprodil had no effect on PPI. Baseline startle was not affected by any local injection.

In summary, we show that NMDA antagonists can affect PPI through blocking NR2B receptors in the prelimbic mPFC, but not in the infralimbic mPFC.

Current and future studies aim to dissociate the seemingly variable effects of NMDAR antagonists depending on dorsoventral extent in the mPFC with respect to their effect on PPI, and to evaluate the mechanisms by which NMDAR affect modulation of PPI in the mPFC in order to potentially better understand the pathophysiology of schizophrenia.

Research Theme: Neural Excitability, Synapses, and Glia: Cellular Mechanisms

Retinoic acid's influence on regeneration following an *in situ* nerve crush injury

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The vitamin A metabolite, retinoic acid (RA), has been well studied for its role in CNS development and neurite outgrowth. Additionally, both RA signalling proteins, the retinoic acid receptor (RAR) and retinoid X receptor (RXR) have been found to play a role in vertebrate nerve regeneration. We have previously shown that molluscan dopaminergic neurons that have undergone a nerve crush injury exhibited significantly more neurite outgrowth following exposure to RA over 24 hours. Interestingly, this outgrowth occurred proximally to the site of the nerve crush injury. Furthermore this RA-mediated outgrowth appeared to be crush-dependent, as no outgrowth was observed in CNSs that did not receive the nerve crush injury. Since RA is known to auto-regulate its receptors, our current work first sought to determine whether exposure to RA during a nerve crush injury could alter the expression of either the RAR or RXR. In preliminary studies utilizing western blotting we show that this does not appear to be the case, suggesting that RA's morphological effects on outgrowth may not require global changes in RAR or RXR expression in the CNS. Since we have previously shown that the RXR can be found in neurites and extending growth cones (Carter et al., 2010) we next utilized immunohistochemistry to determine whether the RXR had localized to the site of nerve injury. Our data show that the expression of the RXR at the crush site remained unchanged when compared to uncrushed CNSs. Interestingly, we do however show an increase in RXR expression at the transected nerve endings. This upregulation does not appear to be dependent on RA, but is dependent on the nerve crush injury. This work suggests that the RXR may be operating in a nongenomic capacity at the site of transected nerve endings, though its role at this site is yet to be determined.

Research Theme: Cognition and Behavior

Non-symbolic numerical magnitude processing in the brain: the role of surface area

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Introduction:

The human brain demonstrates a striking ability to process a wide range of symbolic and non-symbolic numerical information. The capacity to process non-symbolic numerical information is often indexed by the ability to discriminate between sets containing different numbers of items. When using such comparison tasks, researchers are faced with the fact that there exists a tight association between numerical magnitude and non-numerical physical variables (e.g. surface area) that are correlated with the total number of items in each set. To mitigate these confounds researchers have developed strategies to control for continuous variables, whereby non-numerical variables are systematically varied between trials in such a way that they are, on average, not reliably predictive of numerical magnitude. This approach presumes that neurocognitive mechanisms engaged during non-symbolic numerical magnitude processing are insensitive to trial-by-trial variations of continuous variables. In the present study we investigate the extent to which variables continuous with numerical magnitude affect brain activation patterns during numerical magnitude processing.

Method:

Functional imaging data were acquired on a 3T MRI scanner. Stimuli consisted of two intermixed dot arrays displayed on a grey background. Participants were asked to decide whether there are more yellow or blue dots on the screen. In half of the trials overall surface area was equated between the dots (SC; size controlled), whereas, in the other half surface area was perfectly correlated with numerical set size (NSC; non-size controlled). In addition, numerical ratio (larger set/smaller set) was varied across trials. A total of 19 adults (mean age 23.8) participated in the present study. Whole-brain, random effects general linear model analyses were carried out to reveal brain regions exhibiting a parametric effect of ratio across conditions, as well as regions demonstrating a differential effect of ration between conditions

Results:

A significant effect of numerical ratio for both SC and NSC was found in front-parietal as well as occipital regions. Within the parietal lobe, numerical ratio modulated the activation of the posterior intraparietal sulcus (IPS) of the left hemisphere as well as the right superior parietal lobe (SPL).

The contrast of the two conditions revealed a difference in the parametric effects of numerical ratio in SC and NSC conditions in the right IPS. This difference was characterized by a significant ratio effect for the NSC but not SC condition.

Discussion:

The present finding demonstrates that continuous physical variables – such as surface area - influence brain activation during non-symbolic numerical magnitude processing in a region that is currently postulated to host the core representation of numerical magnitude (Dehaene et al., 2003). If, the IPS is modulated by non-numerical variables that are continuous with numerical magnitude, it is likely that results of studies in which different non-numerical variables are controlled by means of averaging, reflect an interaction between numerical and non-numerical information. Against this background, our data encourage greater efforts to characterize the interplay between variables continuous with numerical magnitude that allows for non-symbolic numerical magnitude comparison.

Research Theme: Disorders of the Nervous System

Brain injury and mortality correlating to post-stroke seizures in 18-20 month old C57 black mice model of hypoxia ischemia

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Stroke occurs primarily in the aging population. Post-stroke seizures are known to be associated with poor prognoses but are poorly understood. Thus, we examined these post-stroke seizures in aging C57 black mice (18-20 months) using a model of hypoxia-ischemia (HI). The animals received a permanent occlusion of the right common carotid artery and were then exposed to a systemic hypoxic episode (8% O₂ for 30 min). Of 26 aging mice examined, 9 exhibiting severe seizures encountered mortality within 24 hours post HI and suffered extensive brain injury in the hemisphere ipsilateral to the carotid artery occlusion. Contrarily, 17 mice lacking such seizures survived for several weeks post HI and had variable brain injuries. We suggest that severe early seizures are a major contributing factor to mortality and that the HI model is suitable for the investigation of post-ischemic seizures in aging animals.

Research Theme: Cognition and Behavior

Viral transfection of the M5 Gene in wildtype mice enhances morphine-induced locomotion in VTA Sites, but blocks morphine-induced locomotion in RMT sites.

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Mesopontine cholinergic neurons activate tegmental dopamine (DA) neurons via nicotinic and M5 muscarinic receptors. In rats, ventral tegmental area (VTA) muscarinic receptors are needed for brain-stimulation reward or food reward sensitivity, and for morphine-induced DA output. M5 knockout mice emit fewer ultrasonic vocalizations (USVs) during mating, and show less locomotion or DA output in response to morphine than wild-type mice. Using a Herpes simplex virus, the M5 receptor gene was transfected into the VTA or rostromedial tegmentum (RMT) of wild-type mice along with a green fluorescent protein (GFP) marker gene. M5 transfection into VTA DA and non-DA neurons increased morphine-induced locomotion at both 10 and 30mg/kg doses. Immunocytochemistry showed increased M5 receptors in HSV-M5-GFP infected neurons. M5 transfection into RMT inhibited morphine-induced locomotion at 10mg/kg and especially at 30mg/kg. Transfection of the excitatory M5 receptor in RMT is hypothesized to excite GABA neurons that inhibit VTA DA neurons. Immunocytochemical staining of GAD67 co-localized with the transfected HSV-M5-GFP. These results support previous evidence that the RMT is a critical inhibitory system for DA-reward functions, and provides new evidence that RMT is especially important for controlling opiate functions.

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Research Theme: Sensory and Motor Systems

The functional effects of sensory protection combined with neuromuscular electrical stimulation in denervated muscle

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Specific Purpose: Poor muscle and nerve functional recovery after nerve damage is a serious clinical problem. Immediate surgical repair of the damaged nerves is the best option for recovery but is not always possible or successful. Long term denervation leads to severe muscle atrophy, coupled with a loss of muscle spindles, force, motor function and an increase in tissue collagenization and fibrosis. Due to these factors, functional recovery following delayed reinnervation is poor. The purpose of this study was to investigate the effects of two different treatments on functional recovery of denervated muscle.

Content: Our previous work demonstrated that suturing a sensory nerve to the distal motor nerve stump (called sensory protection) significantly improves muscle weight, force, morphological and histological aspects as well as preserving muscle spindles. More recently, we have shown that one month of electrical stimulation of denervated muscle also significantly increases muscle weight, force, and fiber area. We used a novel, clinically relevant paradigm where muscles were stimulated for only 1 hour per day, contrary to the typical 24 hour per day paradigms used by others. We hypothesized that the combination of sensory protection and electrical stimulation will enhance functional recovery more than either of these treatments alone.

Methodology: Rat gastrocnemius muscles were denervated by cutting the tibial nerve, and the peroneal nerve was then sutured to the distal tibial stump either immediately or following 3 months of treatment (electrical stimulation, sensory protection, or both). The muscles were allowed to recover for 3 additional months, and then functional measurements were taken and muscles excised. These measurements included muscle weight, force, contractile properties, and motor unit estimation. The contralateral, unoperated limb served as a control.

Results: The results showed that all treatment groups had significantly higher muscle weight, force and motor unit counts when compared to the untreated group (denervated). Contraction times were unchanged in the stimulated groups. However, half relaxation times were significantly higher in the sensory protected stimulated group compared to both immediate repair groups. Interestingly, weight, force and motor unit counts did not significantly differ between treated groups although the sensory protected stimulated group had higher mean values in all of the tests. The lack of statistical significance may be attributed to the small sample size in this group. Because the combination of the two treatments was not significantly different than either treatment alone, our hypothesis is currently not supported. It may be that electrical stimulation and sensory protection work through a similar mechanism, and future work will address this question. Nevertheless, this study demonstrates that either electrical stimulation or sensory protection significantly improves functional measures following delayed nerve repair. The combination of the two treatments also shows promising results. The use of any of these therapies may provide new options for clinical treatment of denervated muscle.

Research Theme: Sensory and Motor Systems

A Bayesian ideal observer model for tactile spatial perception

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Is human tactile spatial perception optimal? We constructed a Bayesian ideal observer that performs optimally on tactile spatial tasks, and compared the performance of the ideal observer to that of humans tested previously on the same tasks.

We used a continuum mechanics model (Phillips & Johnson, 1981) to simulate the firing rates of a population of slowly adapting type-I primary afferents (SAI) in response to a square wave grating indented statically for 1s into the skin. We introduced firing rate noise typical of either SAIs (low variability) or primary somatosensory cortical neurons (high variability, Poisson). The ideal observer optimally decoded these firing rates using Bayesian model comparison to perform grating orientation discrimination and grating detection tasks.

When we fed the ideal observer SAI firing rates, its performance overwhelmingly surpassed human perception; when we fed it cortical firing rates, its performance worsened considerably but still surpassed human perception. Thus, human tactile spatial perception is suboptimal in that humans do not make full use of the information carried by either primary afferents or primary somatosensory cortical neurons.

When we fed the ideal observer only the action potentials evoked during a short (e.g., 200ms) initial portion of the stimulus, its performance approached human levels. Thus, humans may perceive suboptimally because they do not integrate sensorineural information over the entire stimulus-presentation period. Alternatively, humans may derive tactile spatial inferences from the activity of higher-order cortical neurons, whose receptive fields may be larger, and/or firing rates more variable, than those of primary somatosensory cortical neurons.

Research Theme: Cognition and Behavior

Sexual behaviour in tachykinin knockout mice

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Aims: Tachykinin peptides influence complex social behaviours in mice. In this study we investigated whether removal of genes for TAC1-encoded peptides substance P (SP) and neurokinin A (NKA) and the TAC4-encoded peptide hemokinin-1 (HK-1) as well as their preferred receptor neurokinin-1 (NK-1R, encoded by TACRI) influence sexual behaviours by using tachykinin knockout mice as model systems.

Methods: TAC1^{-/-}, TAC4^{-/-} and TACRI^{-/-} mice were compared to C57BL/6 wild type control mice. To exclude the possibility of compensatory mechanisms such as SP/NKA compensating for the lack of HK-1 and vice versa, we generated TAC1/4^{-/-} “double knockout mice”, deficient for both TAC1 and TAC4-encoded peptides. To test whether mutant mice respond to social odours of the opposite sex in a similar fashion, we used the female urine sniffing test. We performed the olfactory habituation/dishabituation test to test whether an animal can smell and is able to differentiate odours. Ultrasonic vocalizations (USVs) were investigated in male-female mating studies.

Results: Male mice deficient for the NK-1R (TACRI^{-/-}), but not for its ligands SP/NKA and/or HK-1 (TAC1^{-/-}, TAC4^{-/-} and the newly generated TAC1/4^{-/-} mice), exhibited an impairment of olfactory investigation of female urine. The decreased olfactory investigation of female urine in TACRI^{-/-} mice was not due to an inability to smell or distinguish different odours as they showed similar patterns of olfactory habituation and dishabituation as wild-type mice. Compared to controls, male TACRI^{-/-} mice displayed significantly reduced vocalizations and sexual behaviours towards females.

Conclusions: NK-1R signalling facilitates olfactory investigation of female urine and sexual behaviour including increased USVs. The lack of change in these behaviours in mice deficient for SP/NKA and/or HK-1 suggests that NKB may play a role in these pathways.

Research Theme: Sensory and Motor Systems

Sex differences in auditory sensitivity in the round goby, *Neogobius melanostomus*.

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Sensory neurons often show differences in response properties between sexes, partially driven by differences in circulating hormone levels. Differential sensory responses may affect the reception of signals from conspecifics and are often greatest when individuals are in a reproductively mature condition. Examination of neural response differences can reveal important insights into a species' communication system by providing information on which sex is most sensitive to a given signal and how signal reception may change in a mating context. The current study examined the potential effects of sex and reproductive condition on auditory sensitivity in the round goby. Round gobies breed in high density aggregations, with males guarding nests and producing low frequency (150–180 Hz dominant frequency) vocalizations that both males and females can localize. Auditory sensitivities in both sexes were assessed in reproductive and non-reproductive individuals using auditory evoked responses to a vocalization segment and to tone pips that ranged from 100 to 600 Hz. Females were more sensitive than males in response to the vocalization segment and in response to tone stimuli across their hearing range. Reproductive females were more sensitive to the vocalization segment than non-reproductive fish from either sex. These results suggest that hearing sensitivity in the round goby is sexually dimorphic and that the capacity for detection of conspecific vocalizations improves with reproductive maturation in females.