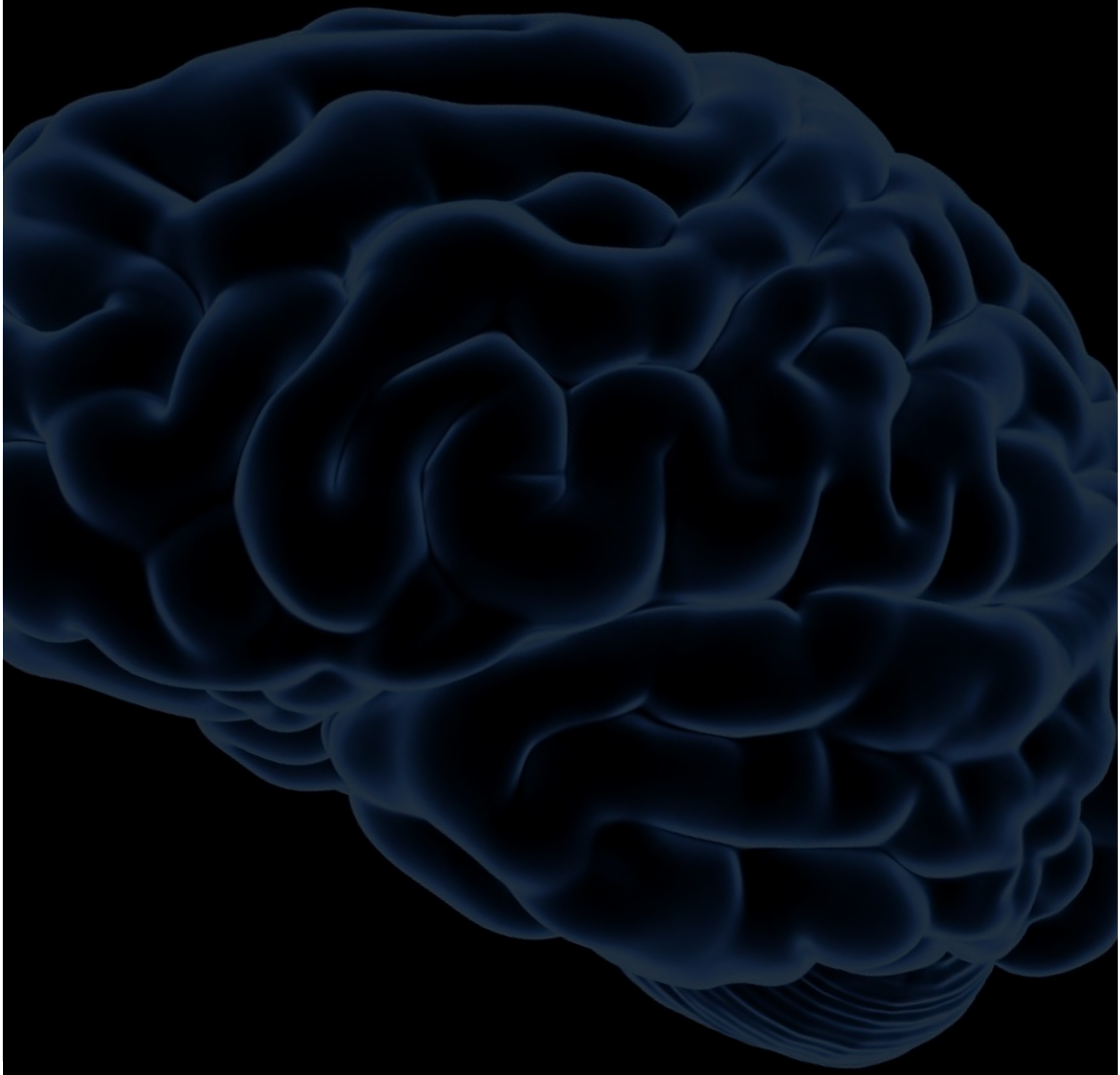
Friday September 9th, 2016 - 8:30 - 4:00

NEURO RETREAT

at the Isabel Bader Centre



NEURO RETREAT

Centre for Neuroscience Studies

Queen's University

Friday September 9th 2016

Isabel Bader Centre

8:30 – 9:00am ***Registration with coffee and breakfast***

9:00 – 10:00am ***Keynote Speaker***

Dr. Sheena Josselyn
Senior Scientist, Neurosciences & Mental Health
Associate Professor, Physiology, University of Toronto
Canada Research Chair, Molecular and Cellular Cognition

10:00 – 12:00pm ***3 Minute Theses***

10:00-10:07am **THE EFFECTS OF HYPOTHERMIA ON SPREADING DEPOLARIZATION ONSET TIME AND SEVERITY IN THE RAT CORTEX – ESTABLISHING IF CORTICAL NEURON SUSCEPTIBILITY TO ISCHEMIC DAMAGE IS AN EVOLUTIONARILY CONSERVED SURVIVAL TACTIC.** Donovan, V. A., & Andrew, R.D. (Abstract # 1)

10:07-10:14am **CORTICO-BASAL ATROPHY INCREASE ANTICIPATORY SACCADE BEHAVIOUR AND DIRECTION ERRORS IN ANTI-SACCADE CONDITION.** Vaca-Palomares, I., Fernadez-Ruiz, J., Coe, B. C., Brien, D., & Munoz, D. P. (Abstract # 2)

10:14-10:21am **NOVEL ASSESSMENT TOOL FOR FASD BASED ON EYE MOVEMENT BEHAVIOURS.** Thompson, S., Flannigan, K., Dennys, K., Loock, C., Oberlander, T., & Reynolds, J. (Abstract # 3)

10:21-10:28am **GENE THERAPY CORRECTION OF AB-VARIANT GM2 GANGLIOSIDOSES IN A MOUSE MODEL USING ADENO-ASSOCIATED VIRUS SEROTYPE 9.** Vyas, M., Osmon, K., Thompson, P., & Walia, J. S. (Abstract # 4)

10:28-10:35am **USING EYE MOVEMENTS TO IDENTIFY EARLY BIOMARKERS OF DISEASE PROGRESSION IN PARKINSON'S DISEASE PATIENTS WITH AND WITHOUT LRRK2 GENE MUTATIONS.** Morris, J. E., Brien, D. C., Coe, B. C., Visanji, N., Ghate, T., Lang, A. E., Marras, C., & Munoz, D. P. (Abstract # 5)

10:35-10:42am **SLEEP ARCHITECTURE IN DEPRESSED PATIENTS TREATED WITH DESVENLAFAXINE.** Javinsky, T., & Milev, R. (Abstract # 6)

10:42 – 10:49am **EXAMINING DIFFERENCES IN HIPPOCAMPAL THETA IN RELATIONS TO ANXIETY.** Ou, C., & Dringenberg, H. (Abstract # 7)

10:49-10:56am **EPIGENETIC REGULATION OF GENE EXPRESSION IN PROLIFERATING INTESTINAL SMOOTH MUSCLE CELLS AND ENTERIC NEURONS.** Bonafiglia, Q. A., & Blennerhassett, M. G. (Abstract # 8)

10:57-11:04am **PATTERNS OF BEHAVIOURAL IMPAIRMENT IN TRANSIENT ISCHEMIC ATTACK AND AMYOTROPHIC LATERAL SCLEROSIS PATIENTS.** Simmatis, L., Appaqaq, S., Peterson, J., Demers, M. J., Moore, K. D., Scott, S. H., & Jin, A. Y. (Abstract # 9)

11:04 – 11:11am **THE EFFECTS OF INTERMITTENT THETA-BURST STIMULATION ON COGNITION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER.** Liu, Y., & Milev, R.M. (Abstract # 10)

11:11 – 11:18am **SELECTIVITY AND ATTENTION: CONTEXT PROMOTES INFANTS TO ENCODE FEATURES OF GOAL OBJECTS.** Robson, S. J., & Kuhlmeier, V. A. (Abstract # 11)

11:18 – 11:25am **USING EYE MOVEMENTS TO ESTABLISH A NORMATIVE DATABASE OF CONTROL SUBJECTS ACROSS THE LIFESPAN.** Smorenburg, M., Yep, R., Coe, B., Brien, D., & Munoz, D. (Abstract # 12)

11:25 – 11:32am **PROTEASE-MEDIATED EFFECTS OF COMMENSAL BACTERIA ON NOCICEPTIVE DORSAL ROOT GANGLIA.** Sessenwein, J., Petrof, E. O., Allen-Vercoe, E., Vanner, S. J., & Lomax, A. E. (Abstract # 13)

11:32 – 11:39am **THE OPTIMALITY OF DECISION MAKING DURING MOTOR LEARNING.** Moskowitz, J. B., & Flanagan, R. (Abstract # 14)

11:39-11:46am **EXECUTIVE FUNCTIONING AND EMOTIONAL PROCESSING DEFICITS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND BIPOLAR DISORDER.** Yep, R., Marin, A., & Munoz, D.P. (Abstract # 15)

11:46-11:53am **INHIBITORY CONTROL IN ALZHEIMER'S DISEASE, MILD COGNITIVE IMPAIRMENT, AND HEALTHY AGING: AN FMRI STUDY.** Luedke, A. C., Fernandez-Ruiz, J., Garcia, A., & Munoz, D. P. (Abstract # 16)

11:53 – 12:00pm **THE EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION ON OLFACTORY DEFICITS ASSOCIATED WITH DEPRESSION.** Taalman, H. C., Milev, R. V., Liu, Y. Q., & Choi., E. (Abstract # 17)

12:00-1:00pm ***Lunch***

1:00 – 2:00pm ***Full Talks***

1:00 – 1:15pm **BRAIN TISSUE OXYGENATION DURING THE RESUSCITATIVE PHASE OF CRITICAL ILLNESS AND ITS ASSOCIATION WITH NEUROLOGICAL DYSFUNCTION.** Wood, M., Maslove, D., Muscedere, J., & Boyd, J. G.

1:15-1:30pm **DEACTIVATION OF PMd AND A5 IMPAIRS FEEBACK CONTROL DURING VOLUNTARY MOTOR ACTIONS.** Takei, T., Lomber, S. G., Cook, D. J., & Scott, S. H.

1:30– 1:45pm **PRECLINICAL SAFETY AND EFFICACY OF INTRAVENOUS ADMINISTRATION OF ADENO-ASSOCIATED VIRAL VECTOR EXPRESSING A NOVEL HEXOSAMINIDASE ENZYME – IMPROVED PHENOTYPE IN ADULT MOUSE MODEL SANDHOFF DISEASE.** Osmon, K. J. L., Woodley, E., Thompson, P., Karumuthil-Melethil, S., Gray, S.J., & Walia, J.S.

1:45 – 2:00pm **VISUOMOTOR PROCESSING DURING UNIMANUAL AND BIMANUAL REACHING.** de Brouwer, A. J., Jarvis, T., Gallivan, J. P., & Flanagan, R.

2:00-3:00pm ***Career Workshop***

Dr. Chase Figley, PhD
Associate Professor, Radiology, University of Manitoba
Principal Investigator within the Neuroscience Research Program at the Kleysen Institute for Advanced Medicine

Dr. Courtney Green, PhD
Medical Research & Guideline Specialist at the Society of Obstetricians & Gynecologists of Canada

Dr. Jonathan Diamond, PhD
Associate at Well Grounded Real Estate & Founder of Kingston Tutoring Co.

Dr. Jordan Leitch, MSc, MD
Anesthesiology Resident, Kingston General Hospital

3:00-4:00pm ***How to write a proposal workshop***
Chair: Dr. Ken Rose

Dr. Jason Gallivan, PhD
Assistant Professor
Previous holder of NSERC Banting Postdoctoral Fellowship Award & CIHR Postdoctoral Award

Catherine Normandeau, 4th Year PhD
Current holder of CIHR Vanier Scholarship, previous holder of Frederick Banting & Charles Best (CIHR) Canada Graduate Scholarship

Chloe Soutar, 3rd Year PhD
Current holder of NSERC Postgraduate Scholarships-Doctoral Program

Mathew Smorenburg, 2nd Year MSc
Current holder of Frederick Banting & Charles Best (CIHR) Canada Graduate Scholarship

4:00 - onwards ***Beer with Profs!***

Conference Abstracts

3 Minute Theses

THE EFFECTS OF HYPOTHERMIA ON SPREADING DEPOLARIZATION ONSET TIME AND SEVERITY IN THE RAT CORTEX – ESTABLISHING IF CORTICAL NEURON SUSCEPTIBILITY TO ISCHEMIC DAMAGE IS AN EVOLUTIONARILY CONSERVED SURVIVAL TACTIC. **Donovan, V. A., & Andrew, R.D. (Abstract # 1)**

Previous studies have demonstrated that following traumatic brain injury (TBI), higher cortical neurons are more susceptible to damage than brainstem neurons - often resulting in persistent vegetative state (PVS). Present in humans, rodents and insects, it is believed that this is an evolutionarily conserved survival tactic. In order to confirm this theory, we developed a multi-faceted study that will eventually incorporate Northern Leopard frogs (Rana pipens) as an additional link on the evolutionary timeline. First, data was collected on juvenile male Sprauge-Dawley rat brain slices to establish the effects of hypothermia on the initiation and severity of the ischemic penumbra. Light Transmittance (LT) imaging was used to determine depolarization onset time and change in neuronal integrity (dendritic beading/cell swelling) following perfusion with an oxygen-glucose deprived (OGD) solution at varying hypothermic temperatures (22^{o}C, 27^{o}C, 32^{o}C, and 35^{o}C). Initial findings showed decreased temperatures resulted in a delayed spreading depolarization (SD) onset time as well as reduced neuronal damage. This preliminary data is to be compared with that of frogs in future experimental procedures. We hope to establish if frogs are more like warm-blooded animals or cold-blooded insect with regards to SD and temperature. In addition, we hope to establish if OGD induced susceptibility in frogs is similar to rodents at the selected varying hypothermic temperatures. Clinically speaking, this research could provide further insight into the underlying mechanisms of why higher cortical neurons are more susceptible to ischemic damage, and if this damage can be delayed, reduced or prevented with therapeutic hypothermia.

CORTICO-BASAL ATROPHY INCREASE ANTICIPATORY SACCADE BEHAVIOUR AND DIRECTION ERRORS IN ANTI-SACCADE CONDITION. **Vaca-Palomares, I., Fernadez-Ruiz, J., Coe, B. C., Brien, D., & Munoz, D. P. (Abstract # 2)**

Introduction: Eye movements (EM) can be classified as anticipatory saccades (AS). AS depends on processes like response inhibition involved in the experimental task, can be triggered prior to the arrival of the visual information to the oculomotor system and could involves the corticostriatal loops (CSL) modulating cognitive-flexible behaviours. The inhibition of AS reflects cognitive-flexible mechanisms. To understand the participation of CSL in AS is useful to study Huntington's disease (HD) which basal ganglia (BG) degeneration leads to impairments in EM. We hypothesize a high proportion of AS and saccade direction errors. Methods: We assessed EM in 23 HD patients and 23 healthy controls (CO) age- and gender-matched. We used the Interleaved Anti-Pro-saccade Task to examine the suppression of reflexible movements and the execution of flexible-voluntary commands, and structural magnetic resonance imaging (MRI) to

map neurodegeneration. In the pro-saccade condition (PRO) participant has to make an automatic saccade to a target, whereas in anti-saccade condition (ANTI) the participant has to suppress an automatic saccade and instead make a voluntary saccade to the opposite side of the target. Results: The Mixed-design ANOVA (between HD-CO, within ANTI-PRO) showed that the increased AS-ANTI ($p=0.002$) and direction errors-ANTI ($p=0.000$) was due to patients' behaviour. Pearson's analysis showed a positive correlation ($p=0.035$) between AS-ANTI and direction errors-ANTI. MRI analysis showed associations ($p<0.05$) between neural atrophy in cerebral areas involving CSL and AS-ANTI and direction errors-ANTI. Conclusion: BG degeneration produces an increase in AS that in turn leads to high direction errors in highly response inhibition conditions.

NOVEL ASSESSMENT TOOL FOR FASD BASED ON EYE MOVEMENT BEHAVIOURS. **Thompson, S., Flannigan, K., Dennys, K., Loock, C., Oberlander, T., & Reynolds, J. (Abstract # 3)**

Background: Fetal alcohol spectrum disorder (FASD) is the leading known cause of preventable developmental disability among Canadians, affecting at least 1% of the population in Canada. A diagnosis of FASD requires collaboration from a multidisciplinary team and can be a lengthy process frequently involving long wait times. It is therefore apparent that new screening tools are needed to facilitate more rapid assessments of brain dysfunction that could streamline the diagnostic and referral process.
Methods: The use of eye tracking technology as a screening tool for children with FASD will be investigated in a two-stage process (1) a validation study and (2) a prospective study. In both the proposed studies, children/youth will complete four eye-tracking tasks, which measure automatic and voluntary eye movement responses, spatial working memory and visuospatial skills. Based on previous work, the following hypotheses will be tested: (1) Eye movement tasks are a sensitive and specific screening tool that can be used to identify brain injury associated with prenatal alcohol exposure; and (2) Eye movement control tasks will reveal specific functional biomarkers that will inform state-of-the-art machine learning models to reliably and efficiently discriminate between children with FASD and typically developing control children.
Results: Thirty children with FASD and twenty typically developing controls were recruited and tested in the validation study. The results of the sensitivity and specificity analysis will be presented and discussed.
Conclusions: This research will demonstrate the potential of eye tracking technology to be a reliable and valid screening tool for FASD.

GENE THERAPY CORRECTION OF AB-VARIANT GM2 GANGLIOSIDOSES IN A MOUSE MODEL USING ADENO-ASSOCIATED VIRUS SEROTYPE 9. **Vyas, M., Osmon, K., Thompson, P., & Walia, J. S. (Abstract # 4)**

GM2-gangliosidoses are a group of neurodegenerative diseases affecting the brain. They are characterized by rapid neurological deterioration and death before 4-years of age. GM2-ganglioside is normally degraded in a cell's lysosomes through the action of three gene products, HEXA, HEXB, and GM2A. A defect in any one gene can result in a deficiency of HEX-A

activity toward GM2-ganglioside, which then cannot breakdown. The most rare form is characterized by a mutation in the GM2A-gene that encodes the GM2-activator protein, a required co-factor for the breakdown of GM2-gangliosides by the protein Hex-A. Currently, there is no cure for this disease. GM2A mouse models provide an animal model to study potential therapies for the GM2-gangliosidosis. An effective viral vector known as Adeno-associated virus serotype 9 (AAV9) has improved approaches for gene therapy. The aim of this study is to be able to give a one-time treatment, by injecting an AAV9 viral vector therapy at a dose of 1 x 1011 vector genomes per mouse, into 1-day old pups via the superficial temporal vein, to correct GM2-gangliosidoses AB variant. We hypothesize that an optimized AAV9 treatment can correct GM2-gangliosidosis AB variant in mice. Behavioural, biochemical and molecular analysis will be performed at 20-week and 60-week end-points. The development of such an improved approach for GM2-gangliosidosis would provide a step forward towards the goal of clinical gene therapy.

USING EYE MOVEMENTS TO IDENTIFY EARLY BIOMARKERS OF DISEASE PROGRESSION IN PARKINSON'S DISEASE PATIENTS WITH AND WITHOUT LRRK2 GENE MUTATIONS. **Morris, J. E., Brien, D. C., Coe, B. C., Visanji, N., Ghate, T., Lang, A. E., Marras, C., Munoz, D. P. (Abstract # 5)**

In some patients with Parkinson's disease (PD), variations of the Leucine-rich repeat kinase 2 (LRRK2) gene have been associated with the development of the disease. Patients with PD exhibit specific behavioural deficits when preforming saccadic eye movement tasks. There are also significant disruptions of modulated pupil responses via voluntary movement preparation in patients with PD during these tasks. It is unclear whether LRRK2 mutation carriers before they manifest PD symptoms (non-manifesting carriers) exhibit the same discrepancies as patients with PD. By exploiting these known behavioural and pupillary variations, saccade tasks may be used as a diagnostic tool to help differentiate between the healthy population and pre-PD patients. We conducted interleaved pro- and anti-saccade tasks with age-matched controls, patients with idiopathic PD, and non-manifesting carriers. The pro-saccade task (look at the peripheral visual stimulus) assesses the basic sensory-motor processing of eye movements via automatic tendencies to look at salient visual stimuli, whereas the anti-saccade (look in the opposite location of peripheral visual stimulus) task assesses inhibition of this automatic response and requires a generation of a voluntary command to look in the opposite location. Interestingly, preliminary analysis revealed no significant behavioural differences between the controls and non-manifesting carriers. However, there were significant pupil differences between controls and non-manifesting carriers and patients with PD. More specifically, there is a significant difference in baseline pupil size, and pupil constriction size. Further analysis is essential to identify pre-symptomatic behavioural biomarkers of PD that accurately predict disease and thus lead to earlier PD detection.

SLEEP ARCHITECTURE IN DEPRESSED PATIENTS TREATED WITH DESVENLAFAXINE. **Javinsky, T., & Milev, R. (Abstract # 6)**

Sleep disturbances are a common symptom of major depressive disorder (MDD) and frequently include reduced time in slow wave sleep (SWS), increased time in rapid eye movement (REM)

sleep, and shortened REM latency. Previous research has shown that some antidepressants are capable of improving sleep quality by normalizing these architectural changes through their effects on serotonin and norepinephrine. The goal of this study is to assess the acute and long-term changes in sleep architecture and quality that occur after the introduction of desvenlafaxine in patients with MDD, as well as to correlate these changes with measures of illness severity. This is a randomized, controlled, double-blinded study. Participants who were currently experiencing a major depressive episode were recruited from the community via paper and online advertisements and assigned to receive a placebo or desvenlafaxine for 4 weeks. Sleep architecture was assessed by ambulatory polysomnography while sleep quality and mood were measured by a series of clinical scales. These measures were recorded at baseline, 3-5 days after randomization to measure acute effects, and 28-31 days after randomization to measure long-term effects. Given the data from previous studies, we expect to find an acute deterioration in sleep quality due to the initial increase in norepinephrine, followed by an improvement at the long-term measurement. We expect these improvements to correlate with decreased depression severity. The data from this study could aid in improving the management of sleep disturbances, thus enhancing the overall treatment of MDD given the importance of sleep in healing and recovery.

EXAMINING DIFFERENCES IN HIPPOCAMPAL THETA IN RELATIONS TO ANXIETY. **Ou, C., & Dringenberg, H. (Abstract # 7)**

Anxiety disorder impacts 1 in 20 people in Canada. Women are twice as likely to develop an anxiety related disorder in comparison to their male counterparts. Over the past decade animal research focusing on anxiety and anxiolytic drugs have been primarily geared towards males. Hippocampal theta is an oscillatory, rhythmic activity pattern (4-14 Hz frequency range) generated by the hippocampal formation in rodents and other mammals. Theta activity is thought to play a role in movement, as well as learning and memory. Interestingly enough, hippocampal theta activity also appears in rats during fear conditioning and other anxiety-inducing situations indicative of a link between theta and “fear/anxiety” states. Currently, female rat models have not been used to examine anxiety in the context of the theta suppression model. Our goal is to examine anxiety in female adolescent rats and compare these findings to male adolescent rats in the elevated plus maze, a recognized animal model of anxiolytic drug action. We hypothesize that rats expressing higher levels of “anxiety-like” behaviors (reduced open arm exploration in the elevated plus maze) will exhibit higher frequencies of hippocampal theta activity, thus supporting the link between theta activity and anxiety proposed on the “theta-suppression model of anxiolysis.” When male adolescent rats were given Buspirone (10mg/kg, i.p.) there was a decrease in anxiety and theta activity within the reticular formation. Understanding behavioral and electrophysiological differences of sex in rodent models can elucidate biological and behavioral basis of anxiety.

EPIGENETIC REGULATION OF GENE EXPRESSION IN PROLIFERATING INTESTINAL SMOOTH MUSCLE CELLS AND ENTERIC NEURONS. **Bonafiglia, Q. A., & Blennerhassett, M. G. (Abstract # 8)**

Intestinal inflammation causes proliferation of smooth muscle cells (ISMC), contributing to dysmotility symptoms observed in inflammatory bowel disease (IBD). Prolonged proliferation of ISMC results in loss of their normal contractile phenotype, characterized by decreased expression of smooth muscle marker proteins SMA and SM22, and glial cell-line derived neurotrophic factor (GDNF). GDNF expression by proliferating ISMC is essential for survival and growth of enteric neurons within the myenteric plexus. Consequently, loss of contractile proteins and GDNF expression contributes to the cellular basis of intestinal dysfunction in IBD. The mechanism behind proliferation-induced ISMC phenotypic switching is currently unknown. We hypothesize that epigenetic changes to gene expression may underline these progressive changes. This was investigated in cultured rat ISMC treated with agents that reverse histone acetylation (trichostatin; TSA) or DNA methylation (5-azacytidine; AZA). Outcomes were evaluated using western blotting, immunocytochemistry, RT-PCR and functional assays.
Both AZA and TSA treatment increased SMA and SM22 mRNA and protein expression. Furthermore, media isolated from AZA- and TSA-treated high passage ISMC showed increased support of neuronal survival and axonal outgrowth, evidence for an increase in GDNF expression. We conclude that epigenetic changes, primarily DNA methylation and histone deacetylation, account for ISMC altered phenotype. The outcomes of AZA and TSA treatment suggest that modulation of an epigenetic component of smooth muscle phenotype could be a novel therapeutic option in treating dysmotility in IBD patients.

PATTERNS OF BEHAVIOURAL IMPAIRMENT IN TRANSIENT ISCHEMIC ATTACK AND AMYOTROPHIC LATERAL SCLEROSIS PATIENTS. **Simmatis, L., Appaqaq, S., Peterson, J., Demers, M. J., Moore, K. D., Scott, S. H., & Jin, A. Y. (Abstract # 9)**

Background: Transient ischaemic attack (TIA) and amyotrophic lateral sclerosis (ALS) both cause specific and distinct behavioural impairments. Motor impairment in TIA is associated with an elevated stroke risk and executive function impairment in ALS is associated with reduced survival time. Robotic assessment could provide information about motor behaviour deficits which escape clinical scores. The KINARM exoskeleton robot will be used to detect specific impairments in TIA and ALS which could identify high-risk patients.
Methods: Twenty-four patients with TIA/minor stroke and 17 patients with ALS were recruited from Kingston General Hospital. Robotic assessment was performed using the KINARM exoskeleton's 8 standard tasks. Clinical assessments included: Behavioural Inattention Test (BIT;TIA), Purdue pegboard test (PPB;TIA), Montreal cognitive assessment test (MoCA;TIA), Chedoke-McMaster stroke assessment (CMSA;TIA), National Institutes of Health Stroke Scale (NIHSS;TIA), Frontal Assessment Battery (FAB;ALS), and ALS Functional Rating Scale (ALSFRS;ALS).
Results: Cognitive tasks were failed by 24-86% of TIA patients and 0-88% of ALS patients. Motor domain deficits occurred in 8-29% of TIA patients and 18-69% of ALS patients. TIA patients appeared neurologically normal on NIHSS (score=0) but the majority had CMSA abnormalities.

FAB was abnormal in 10/17 ALS patients and ALSFRS was <40 in 13/17 ALS patients.
Conclusions: ALS patients and TIA patients displayed different patterns of motor and cognitive impairment. CMSA detected motor impairment in TIA and ALSFRS detected functional impairment in ALS. KINARM assessment was able to provide additional specific information about the nature of the underlying deficits which may be useful for future therapeutic decision-making.

THE EFFECTS OF INTERMITTENT THETA-BURST STIMULATION ON COGNITION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER. **Liu, Y., & Milev, R.M. (Abstract # 10)**

People with MDD often struggle with cognitive impairments such as decreased executive functioning, attention, concentration, speed of processing, and working memory. The brain areas associated with cognition, such as the prefrontal cortex and hippocampus are negatively affected by depression. Currently, there is a lack of treatment options for improving cognition in depressed patients. Therefore, we are exploring the therapeutic potential of an emerging treatment called intermittent theta-burst stimulation (iTBS).
Methods: We are hoping to recruit 10 healthy controls and 15 MDD patients. Patients will be receiving 21 days of iTBS treatment. At baseline, controls and patients will complete a cognitive battery including four tasks (Digital Symbol Substitution Test, Trial Making Test A and B, n-back task and International Shopping List Task). Patients will complete it before and after treatment, and at the one month follow up. Patients will be completing the n-back task during their fMRI scans before and after the iTBS treatment.
Predicted Outcome: MDD group will perform significantly better on the cognitive tasks after iTBS treatment and at the 1 month follow up compared to baseline. The results will also be similar to the controls at baseline. MDD group will show changes in functional connectivity and resting-state activity.
Research Impact: The preliminary evidence from our study will add to the understanding of the short and long term effects of iTBS treatment on the brain. We hope to provide more knowledge for health care professionals, and allow better care to be delivered to patients.

SELECTIVITY AND ATTENTION: CONTEXT PROMOTES INFANTS TO ENCODE FEATURES OF GOAL OBJECTS. **Robson, S. J., & Kuhlmeier, V. A. (Abstract # 11)**

Selective attention plays an important role in determining what it is about the world that we notice, and what we are able to later recall, by highlighting parts of the visual scene and suppressing others. Context influences selective attention; the same action can be incredible or unremarkable depending on who is involved, and when and where it occurs. For instance, infants pay more focused attention to a target object when other objects (distractors) are present in the scene as opposed to when they are absent (Ruff, Capozzoli, & Saltarelli, 1996). Infants also show better memory for a target when they suppress a distractor (Markant, Worden, & Amso, 2015).
Infants can see others' object-directed actions as goal-directed, as being 'about' a particular object. This has been demonstrated by habituating infants to repeated selection of one object from a pair, and seeing that infants look longer towards a later inconsistent action (Woodward,

1998). When the second, unselected object is not present in the initial phase of the study, though, infants no longer show this effect (Luo & Baillargeon, 2005). What remains unclear is if the identity of the second object matters to infants, or if the mere presence of this object as a distractor that engages selective attention, enhancing the features of the target and suppressing the identity of the distractor.
In the following study, we examine the influence of both the presence and the identity of a distractor object on 9-month-old infants' recall of a target of an actor's reach.

USING EYE MOVEMENTS TO ESTABLISH A NORMATIVE DATABASE OF CONTROL SUBJECTS ACROSS THE LIFESPAN. **Smorenburg, M., Yep, R., Coe, B., Brien, D., & Munoz, D. (Abstract # 12)**

As the brain ages, cognitive abilities such as executive function and memory decline. In order to differentiate neurodevelopmental and neurodegenerative disorders from normal development/aging as early as possible, cognitive decline due to normal aging needs to be understood. The oculomotor system is an effective model to probe brain function through analysis of saccadic eye movements. We used a video-based eye tracker capable of measuring saccade performance on an interleaved pro- and anti-saccade task in subjects aged 5-85 years. The interleaved pro- and anti-saccade task requires subjects to generate anti-saccades (voluntary eye movement away from stimulus) or pro-saccades (automatic eye movement toward stimulus) depending upon an on-screen colour instruction. This interleaved task requires that subjects dynamically update goal-directed objectives on a trial-by-trial basis, amplifying the effects of potential cognitive dysfunction. Subjects over 60 years had significantly more direction errors, increased reaction times, and increased latencies to initiate anti-saccades. Compared to pro-saccades, which were relatively stable across all ages, anti-saccades were significantly affected as age increased. These results provide insight into normal cognitive ability and changes that take place across the healthy lifespan, providing a baseline to evaluate saccade deficits and abnormalities caused by neurological disorders.

PROTEASE-MEDIATED EFFECTS OF COMMENSAL BACTERIA ON NOCICEPTIVE DORSAL ROOT GANGLIA. **Sessenwein, J., Petrof, E. O., Allen-Vercoe, E., Vanner, S. J., & Lomax, A. E. (Abstract # 13)**

Background: The mucosal barrier that separates the microbiota from the nervous system is disrupted during gastrointestinal (GI) inflammation. It is presently unknown whether translocation of bacteria during GI inflammation modulates visceral sensation and thereby contributes to pain. The primary aim of this study was to determine if a defined community of 33 commensal GI microbes (MET-1) alters the excitability of mouse dorsal root ganglion (DRG) neurons.
Aims: To determine whether supernatant containing the secretory products of MET-1 altered the excitability of DRG neurons, and identify the intracellular signaling pathways involved. In addition, we sought to identify candidate bacterial mediators of this effect.
Methods: DRG neurons were dissociated from C57Bl6 male mice and incubated overnight in sterile MET-1 supernatant (1:10 – 1:10,000 dilution in sterile media) or sterile control media, in

the presence or absence of various inhibitors. Current and voltage clamp experiments were performed after 24 hours.
Results: MET-1 decreased the excitability of DRG neurons in a concentration-dependent manner by significantly increasing rheobase. 1:100 MET-1 was used in subsequent experiments. The resting membrane potential of DRG neurons was hyperpolarized by MET-1, -68 mV (n=7; MET-1) vs. -58 mV (n=30; controls), $p < 0.05$; Mann-Whitney test. In addition, MET-1 increased voltage-gated K+ current ($p<0.001$; 2 way ANOVA). Addition of a nuclear factor kappa B (NFκB) inhibitor (SC-514, 20 μM) or an ERK1/2 inhibitor (PD 98059, 30 μM) blocked the effects of MET-1. A bacterial protease inhibitor cocktail (1:10,000) abrogated MET-1 effects on DRG neurons. The serine protease inhibitor (FUT-175, 50 μM), but not inhibitors of cysteine proteases, acid proteases, metalloproteases, or aminopeptidases, abolished the effects of MET-1. The serine protease, cathepsin G (100 nM) recapitulated the effects of MET-1 on the excitability of DRG neurons. Blocking protease activated receptor (PAR) 2 (GB83, 10μM) or PAR4 (P4pal10, 10μM) did not block the effects of MET-1 on the excitability of DRG neurons.
Conclusion: Serine proteases secreted by MET-1 can directly impact the function of DRG neurons, through NFκB and ERK1/2-dependent pathways. On the basis of these observations, pain signaling may be modulated by microbiota-neuronal interactions.

THE OPTIMALITY OF DECISION MAKING DURING MOTOR LEARNING. **Moskowitz, J. B., & Flanagan, R. (Abstract # 14)**

In our daily lives, we often must predict how well we are going to perform in the future based on an evaluation of our current performance and an assessment of how much we will improve with practice. Such predictions can be used to decide whether to invest our time and energy in learning and, if we opt to invest, what rewards we may gain. We investigated whether people are capable of tracking their own learning (i.e. current and future motor ability) and exploiting that information to make decisions related to task reward. Participants learned a novel target aiming task in which they were rewarded for target hits. Every five trials, they could choose a target size which varied inversely with reward value. Although participants' decisions deviated from optimal, a model suggested that they took into account both past performance, and predicted future performance, when making their decisions. The results of this experiment suggest that people are capable of tracking their own learning and using that information to make sensible decisions related to reward maximization.

EXECUTIVE FUNCTIONING AND EMOTIONAL PROCESSING DEFICITS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND BIPOLAR DISORDER. **Yep, R., Marin, A., & Munoz, D.P. (Abstract # 15)**

Despite distinct differences in age of onset and core symptoms, attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) share cognitive and emotional processing deficits that can make differential diagnoses difficult. In order to better characterize these two disorders, we compared ADHD and BD performance on a saccade paradigm designed to assess both executive functioning and emotional processing. Performance on this task may identify subtle differences between ADHD and BD that traditional clinical assessments are not sensitive

enough to capture. 9 healthy controls, 6 ADHD, and 8 BD individuals performed an interleaved pro/antisaccade task (look towards vs. look away from a visual target, respectively) in which the gender of emotional faces acted as the directional cue to perform either the pro or antisaccade. Saccadic reaction time and direction error performance was significantly worse on antisaccade trials compared to prosaccade trials, with ADHD and BD groups trending toward making more direction errors than controls on the antisaccade task. The presentation of emotional stimuli had the greatest impact on the BD group, who was significantly slower on antisaccade trials when emotional stimuli, as compared to non-emotional stimuli, were presented. The findings presented here suggest that executive dysfunction is a key deficit in both patient groups, and that it is further impaired in the BD group when recruitment of emotional processing systems is also required. Further characterization of how these processing systems interact in ADHD and BD could be used to develop psychiatric endophenotypes to help improve diagnoses.

INHIBITORY CONTROL IN ALZHEIMER'S DISEASE, MILD COGNITIVE IMPAIRMENT, AND HEALTHY AGING: AN FMRI STUDY. **Luedke, A. C., Fernandez-Ruiz, J., Garcia, A., & Munoz, D. P. (Abstract # 16)**

Alzheimer's disease (AD) and mild cognitive impairment (MCI) are associated with cognitive changes including response inhibition, commonly measured using the Stroop task. While increases in neural activity have been reported in healthy adults compared to young adults as a means of compensation during the Stroop task, whether AD and MCI leads to a further increase in activity during a task of inhibition remains unclear. The goal of this work is to elucidate the relationship between inhibitory control in AD and MCI using fMRI and Stroop interference (conflict between stimulus word and colour e.g. green written in yellow).
16 mild AD (74.6 ± 7.6 years), 16 age-matched controls (74.5 ± 7.6 years), and 12 participants with MCI (64.4 ± 9.3 years) completed a rapid event-related version of the Stroop task. We contrasted incongruent minus congruent conditions at stimulus onset to investigate neural activity related to Stroop interference within each group. Mean beta weights were extracted from ROI's associated with inhibitory control in frontal and parietal cortices, including the anterior cingulate cortex (ACC), and inferior frontal gyrus (IFG) for group comparison. Stroop interference (incongruent – congruent reaction time), and number of errors were calculated. There were significant group differences on Stroop interference and number of incongruent errors. The AD group had a significantly greater Stroop effect, and made more incongruent errors, compared to the MCI and control groups.
Overall there were differences between groups in interference related activity in several ROI's. The ACC, a key area implicated in the Stroop task, showed greater activity in the incongruent compared to congruent condition in controls and MCI, however no differences were found in AD. In addition, the controls also had greater incongruent compared to congruent activity bilaterally in the insula, and right supramarginal gyrus compared to AD and MCI. The MCI group had greater incongruent activity in the superior frontal gyrus compared to AD and MCI. Thus, the controls had a greater number of areas with increased activity for the incongruent compared to congruent condition, suggesting those areas are important for intact inhibitory control during the Stroop task. While MCI had some similarities to controls, the AD group did

not show differences in incongruent versus congruent activity in many key areas relating to inhibitory control.
Despite similar behavioural performance on the Stroop task, the MCI group differed slightly in activity relating to inhibitory control compared to the control group, which may suggest early changes not yet detectable behaviourally in the Stroop task. The AD group showed less Stroop interference related activity, and reduced Stroop performance, suggesting altered inhibitory control in AD.

THE EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION ON OLFACTORY DEFICITS ASSOCIATED WITH DEPRESSION. **Taalman, H. C., Milev, R. V., Liu, Y. Q., & Choi., E. (Abstract # 17)**

Recent research in the field of depression has found a relationship between depression and deficits in olfactory function. Such research has found an improvement in olfactory improvement with successful pharmacological treatment. However, it is unknown if a similar effect can be observed in patients receiving transcranial magnetic stimulation (TMS). Our objective is to determine if depressed individuals have a baseline dysfunction and exhibit improved olfactory sensitivity and identification after receiving a series of TMS. We aim to recruit twenty individuals that will receive TMS and ten controls. Before the commencement of their treatment and 7-14 days after the final treatment, patients will be assessed using Sniffin' Sticks Expanded Test to measure olfactory threshold, discrimination, and identification, Montgomery-Asberg Depression Rating Scale (MADRS), Snaith-Hamilton Pleasure Scale (SHPS), and Beck Depression Inventory (BDI). The control group will consist of age and gender matched healthy participants. The pilot study conducted by the Department of Psychiatry found no difference between control and depressive individuals in sensitivity to olfactory stimuli. However, individuals with poor olfactory identification showed effective restoration with treatment of TMS and a correlation between olfactory identification and baseline MADRS scores. Given these results, we expect that TMS patients will have olfactory scores similar to that of controls in the threshold and discrimination tests but an observable difference between groups in the identification test. Overall, we hope to determine the relationship between olfactory functioning and depression as they may provide valuable insight into diagnostic and treatment tools, the quality of life and everyday functioning.

Full Talks

BRAIN TISSUE OXYGENATION DURING THE RESUSCITATIVE PHASE OF CRITICAL ILLNESS AND ITS ASSOCIATION WITH NEUROLOGICAL DYSFUNCTION. **Wood, M., Maslove, D., Muscedere, J., & Boyd, J. G.**

BACKGROUND: Acute and chronic neurological dysfunction is common among critically ill patients, and may be related to hypoxemia and hypoperfusion. We used near infrared spectroscopy (NIRS), a potential proxy for cerebral perfusion, to measure brain tissue oxygenation (BtO2) and investigate its association with physiological/hemodynamic parameters, as well as its association with subsequent cognitive dysfunction.
METHODS: Adult patients were enrolled if they required mechanical ventilation for >24 hours, and/or vasoactive agents. Patients were excluded if they had previous cognitive dysfunction, or a life expectancy <24 hours. BtO2 was measured with the FORESIGHT monitor for the first 24-72 hours of ICU admission. Blood samples were drawn as per usual clinical practice.
RESULTS: Correlation analysis between BtO2 and hemodynamic parameters was highly variable, however, there was a significant association between hemoglobin and BtO2 ($r=0.347$, $P<0.01$). Furthermore, both delirious and comatose patients had significantly lower BtO2 levels relative to intact patients ($P<0.001$). Of the critical illness survivors who were assessed at 3 months, 45% were impaired on Immediate Memory, 70% on Visuospatial/Constructional, 10% on Language, 30% on Attention, 45% on Delayed Memory, and 65% on Total Score.
CONCLUSIONS: Delirious patients exhibited the lowest BtO2 recordings and demonstrated a significant association between Hb and BtO2. However, BtO2 and its association with hemodynamic parameters was highly variable. A large proportion of survivors demonstrated cognitive impairment, however, there is insufficient data to conclude that impairment is associated with poor BtO2.This study offers potential insight into some of the physiological mechanisms associated with the development of acute neurological dysfunction.

DEACTIVATION OF PMd AND A5 IMPAIRS FEEBACK CONTROL DURING VOLUNTARY MOTOR ACTIONS. **Takei, T., Lomber, S. G., Cook, D. J., & Scott, S. H.**

Neurophysiological studies implicate a broad network in frontoparietal cortex in sophisticated feedback corrections to mechanical perturbations, but the specific role of each region is unknown. Here we investigated the function of dorsal premotor cortex (PMd) and parietal area 5 (A5) in feedback control by combining a neural deactivation (cooling deactivation) in non-human primates with a model simulation. To give functional implications to the behavioral results, we generated an optimal feedback control model to observe how deactivations (i.e. reductions) of model parameters impacted feedback responses. Results showed that deactivation of “feedback controller” impaired both response speed and accuracy, whereas deactivation of “state estimator” impaired only accuracy but not speed of the response. Next, we trained a rhesus monkey to perform a unilateral arm postural task, in which the monkey was required to maintain arm posture while responding to mechanical perturbations. Under normal conditions, the monkey made a quick and accurate perturbation response to return to

the original position. When we deactivate PMd, the monkey showed impairments in both response speed and accuracy. On the other hand, when we cooled A5, monkey showed impairment of response accuracy, but not response speed. These results suggest that PMd and A5 have different functions in feedback control: feedback controller and state estimation, respectively. This study demonstrates for the first time that feedback processing for voluntary control involves cortical circuits beyond primary motor cortex.

PRECLINICAL SAFETY AND EFFICACY OF INTRAVENOUS ADMINISTRATION OF ADENO-ASSOCIATED VIRAL VECTOR EXPRESSING A NOVEL HEXOSAMINIDASE ENZYME – IMPROVED PHENOTYPE IN ADULT MOUSE MODEL SANDHOFF DISEASE. **Osmon, K. J. L., Woodley, E., Thompson, P., Karumuthil-Melethil, S., Gray, S.J., & Walia, J.S.**

GM2-gangliosidosis stems from HexosaminidaseA (HexA) enzyme deficiency. In humans, HexA is the sole enzyme able to catabolize GM2-ganglioside (GM2); deficiencies can result in severe neurodegeneration and death. HexA is comprised of 2 subunits (α, β). Recently, Tropak et al. (2016), created a variant subunit, named μ, by combining the stabilization and catalytic properties of the human β- and α-subunits, respectively. The μ-subunit, coded by HEXM, forms a functional homodimer (HexM) able to hydrolyse GM2. In this study, we examined the efficacy of scAAV9/HEXM IV injections in 6 week old Sandhoff disease (SD, β-subunit knock-out) mice at two doses: 2.5E+12 vg (LOW, n=17) or 1.0E+13 vg (n=15). Another cohort (n=16) received IV mannitol (3g/kg) prior to LOW injection. Some mice from LOW cohorts were euthanized at 16 week for tissue comparisons to untreated SD mice; the remainder were monitored until the humane endpoint. Analyses of survival, behaviour and biochemical parameters were performed. Untreated SD mice had a 16 week humane endpoint; subsets from the scAAV/HEXM treatment groups are surviving well past 60 weeks, with one mouse still alive at 88 weeks, a highly significant survival benefit. Analyses are ongoing. Preliminary results show that scAAV/HEXM delayed onset of the SD phenotype particularly in combination with IV mannitol. This study is the first to show an IV gene transfer using a scAAV/HEXM vector can provide survival and behavioural benefit in adult SD mice.

VISUOMOTOR PROCESSING DURING UNIMANUAL AND BIMANUAL REACHING. **de Brouwer, A. J., Jarvis, T., Gallivan, J. P., & Flanagan, R.**

Throughout the day, we effortlessly reach and grasp for objects to perform a wide variety of tasks. Visual feedback supports rapid, automatic corrections to errors that can occur due to external events or noise in the motor system. Using both hands to perform a task introduces complexity, because errors can occur at different locations, and gaze can only be directed to one location at a time. The aim of this study is therefore to examine how the visuomotor system corrects for visual errors in hand position during unimanual and bimanual reaching. This was investigated in an experiment in which healthy participants performed reaching movements from two starting positions to two visual target positions, while gaze was fixated at one of the targets. We used a virtual reality setup in which direct vision of the participants' hands was removed and the hand positions were represented as two visual cursors that were aligned with the hands. We artificially introduced visual errors in hand position by shifting the

cursor locations, so that we could measure how the motor system corrects for these errors. The results showed that corrections were stronger during unimanual reaches compared to bimanual reaches suggesting that there may be limited resources for the processing of visuomotor errors. We also found that corrections were stronger when the perturbed hand was directed towards the fixated target compared to the non-fixated target. Thus, fixating reach targets may confer an advantage in terms of visuomotor error processing.