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UOJM: PREFACE

Brain Health Research Day 2021 was collaboratively hosted by The University of Ottawa Brain and Mind Research Institute (uOBMRI) and the Neuroscience and Mental Health Trainee Network (NeuMe-TN) at the University of Ottawa Institute of Mental Health Research (uOIMHR) with representation from Carleton University's Department of Neuroscience and The Society for Neuroscience (SfN) Ottawa Chapter. This year's event hosted 253 attendees, including 97 abstract submissions from trainees. Proudly, the annual conference is a collaborative network of representation at all academic levels, and from multiple institutions and associated hospitals: notably the Children's Hospital of Eastern Ontario (CHEO), Savoir Montfort, Élisabeth Bruyère Hospital, the Ottawa Hospital Research Institute/the Ottawa Hospital, the University of Ottawa Heart Institute, l'Université du Québec en Outaouais and The National Research Council of Canada. The planning committee is a group of students and early-career researchers dedicated to enhancing opportunities for networking, collaborations, research, education and training for other trainees and individuals working in the field of neuroscience, mental health, psychology and health. We would like to give special recognition to the student co-chair committee members: Rami Hamati, Ana Santos, Maja Ramljak, Margarita Lui, Pablo Serrano, and Zacharie Saint-Georges, the planning committee: Natasha Hollywood, Candace Fortier and Victoria Racher, as well as the student committee: Jessica Drodge, Bronwen Schryver, Marie Huc, Cecelia Shvetz, Sara Siddiqi and Hyejun Kim. We would also like to thank our scientist co-chairs: Dr. Simon Chen, Dr. Florence Dzierszinski and Dr. Ruth Slack for their oversight of the planning process. This virtual conference could not have been successful without the contributions of all involved. Finally, we would like to thank our sponsors; Brain Health Research Day 2021 was supported by the Canadian Institutes of Health Research's Planning and Dissemination Grant, Carleton University Department of Neuroscience, SfN Ottawa Chapter, and the University of Ottawa Journal of Medicine with the present publication.

Brain Health Research Day Committee

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Development of human iPSC-derived blood brain barrier CHIPs to assess antibody-triggered receptor mediated transcytosis

Li, Y.[1], Sodja, C.[1], Baumann, E.[1], Huang, J.[1], Charlebois, C.[1], Pandian, B.P.[2], Gilbert, A.[3], Stanimirovic, D.[1], Jezierski, A.[1]

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ABSTRACT

Background: The blood-brain barrier (BBB) is the most important biological barrier between the blood circulation and the central nervous system (CNS), it functions as a physical barrier and plays a major role as a transport and metabolic barrier. *In vitro* models of the human BBB are highly desirable for drug development and studies of neurovascular pathology. Human induced pluripotent stem cell (iPSC) derived brain endothelial-like cells (iBECs) have demonstrated a substantial advantage over primary and immortalized brain endothelial cells for BBB modeling.

Methods: We developed a 3D BBB-on-Chip co-culture model using the SynVivo-BBB channel microfluidic technology to model critical components of the BBB. We established iBEC microvessel lumens under physiological *in vivo* shear stress conditions (5 dynes/cm2) in the apical channel of the chips, while human primary astrocytes and pericytes were cultured on the basolateral side separated by a porous 1μm membrane. We deployed this BBB-on-Chip model to study antibody-triggered receptor mediated transcytosis by perfusing the iBEC lumens with a well characterized single domain BBB-carrier FC5-Fc and non-crossing A20.1 control. Leveraging Wes (ProteinSimple), we established protocols for on-CHIP BBB permeability quantification, using anti-Fc and anti-His antibodies, in small sample volumes extracted from the microfluidic channels

Results: Astrocyte, pericyte and endothelial cell co-cultures, coupled with *in vivo* hemodynamic shear stress, enhanced tight junction formation by increased membrane expression of ZO-1 and decreased sodium fluorescein permeability across the iBEC monolayer. We observed similar FC5-Fc transcytosis under 3D static conditions compared to conventional 2D transwell assays; however, a significant increase in FC5-Fc transcytosis was observed under physiological shear stress conditions. Similar BBB crossing of FC5-Fc was observed in *in vivo* brain exposure experiments.

Limitations: This study is limited due to the small volume in the chips. Highly sensitive analytics coupled with small volume size can be used to study the transport mechanism and kinetics.

Conclusions: These findings suggest that 3D BBB-on-CHIP technology can recapitulate the physiological characteristics of the BBB *in vivo* and offer a more predictive platform for assessing antibody transcytosis across the BBB.

Small molecule ice recrystallization inhibitors improve post-thaw functionality and network activity of human induced pluripotent stem cell-derived neurons (iPSC-Ns)

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ABSTRACT

Background: Human induced pluripotent stem cell (iPSCs)-derived neurons (iPSC-Ns) have shown tremendous utility in modeling neurological disease etiologies, and in treating patients suffering with Parkinson's and other neurological diseases. Successful applications of iPSC-Ns in cell therapies relies on effective cryopreservation to deliver high quality cell products to the patient. Current, conventional cryopreservation strategies often result in increased cell death and loss of neuronal activity post-thaw limiting therapeutic applications.

Methods: In this study, we sought to develop a novel cryopreservation strategy to increase viability, recovery and functional network activity of iPSC-Ns exploiting novel ice recrystallization inhibitors (IRIs). IRIs inhibit the growth of crystals during freezing/thawing, resulting in increased post-thaw viability and function-al capacity of cells with specialized functions. We compared two cryopreservation media: a com-mercially available medium (Cryostor® 10, CS10) and CS10 supplemented with a lead IRI devel-oped in our laboratory, N-(2-fluorophenyl)-D-gluconamide (2FA).

Results: Although 2FA did not significantly improve post-thaw viability of iPSC-Ns, it significantly decreased the timeframe towards establishing synchronous synaptic activity at 27 vs 42 days *in vitro* (assessed by mul-tielectrode arrays). iPSC-Ns also retained the expression of key neuronal specific and terminally differentiated markers and displayed expected functional neuropharmacological responses follow-ing treatment with a panel of neuroactive drugs.

Limitations: Developing key enabling technologies to support an effective cryopreservation and an efficiently managed cryochain is fundamental to support the delivery of successful iPSC-derived therapies to the clinic.

Conclusion: Optimizing cryopreservation media formulations with IRI rep-resents a promising technology to improve functional cryopreservation, especially for sensitive iPSC-derived cell therapy products.

Utility and reliability of the CVLT-II

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ABSTRACT

Background: The California Verbal Learning Test-II (CVLT-II) is one of the most common neuropsychological tests used to date. The test provides dozens of supplementary indices that offer information about several cognitive processes by which examinees learn, recall, and recognize words. The current study proposes to examine the utility and reliability of new memory indices (e.g., semantic and serial clustering indices), presented in the CVLT-II, in a healthy older adult sample and compare results to data acquired by Woods and colleagues (2006) in 80 participants.

Methods: Our sample consisted of 52 healthy older adults (13 males, 39 females) aged between 55-91 years old who completed the CVLT-II on two separate time-points (5-weeks interval). To study the reliability and practice effects of both indices, Spearman correlations and a Wilcoxon Test were conducted with an alpha of 0.05.

Results: A Spearman's rho (ρ) correlation coefficient of 0.637 ($p < 0.001$) was obtained between pre- and post-Semantic Clustering, suggesting a strong relationship and comparable to Woods et al. (0.61). For pre- and post-Serial Clustering, a Spearman's rho (ρ) correlation coefficient of 0.496 ($p < 0.001$) was obtained, whereas Woods et al. also obtained a moderate correlation (0.40).

Limitations: This study is limited by the small sample and focus on healthy older adults.

Conclusion: By confirming reliability and validity of the new semantic and serial clustering indices of the CVLT-II, clinicians and researchers can use these measures with confidence. As this study examined healthy older adults, future studies should also be conducted across young healthy controls and clinical populations.

Soluble hTREM2 up-regulates the expression of cytokines in THP-1 cells

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ABSTRACT

Background: Triggering receptor expressed on myeloid cells-2 (TREM2) is a critical innate immune receptor expressed on myeloid-derived cells and binds to ligands such as Apolipoprotein E (ApoE) and bacterial lipopolysaccharides (LPS). TREM2 plays important roles in regulating inflammation and activation of microglia, and its variants are associated with several neurodegenerative diseases. TREM2 can be cleaved from cell membrane as soluble TREM2 (sTREM2), but it is not known whether sTREM2 can induce inflammatory response in myeloid-derived cells.

Methods: THP-1 is a myeloid-derived human monocytic leukemia cell line and was incubated with 100ng/mL LPS (as a positive control), 40μM or 80μM human sTREM2 for 2, 4, 6, and 8 hours, respectively. Non-treated cells were used as another control. Following treatment, RNAs from treated and control groups were purified, quantified, and amplified using real-time RT-qPCR to assess transcript levels of inflammatory cytokines TNF-α, IL-1β, and IL-6, and anti-inflammatory cytokine IL-10.

Results: 100ng/mL LPS strongly stimulated the expression of cytokines TNF-α, IL-1β and IL-10 in THP-1 cells at 2 hours post-treatment but not at other time points. 40μM sTREM2 stimulated the expression of TNF- α and IL-1β at 4 hours post-treatment as compared with control. 80μM sTREM2 strongly stimulated the expression of TNF-α and IL-1β at 2 and 4 hours post-treatment as compared with control. Interestingly, both 40μM and 80μM sTREM2 up-regulated the expression of anti-inflammatory cytokine IL-10 at 6 and 8 hour post-treatment as compared with control.

Limitations: THP-1 cell line is a rudimentary model for macrophages and not necessarily directly translatable to model microglia in neurodegenerative disease but provides insight into how these cells may be functioning in inflammation. Further investigation into primary microglia models or mouse models will provide better information towards understanding this mechanism *in vivo*.

Conclusion: *In vitro*, sTREM2 was capable of up-regulating the expression of pro-inflammatory cytokines TNF- α and IL-1β at the earlier time points but up-regulating the expression of anti-inflammatory cytokine IL-10 at the later time points in THP-1 cells.

Age differences in white matter volume in individuals with gastrointestinal symptoms

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ABSTRACT

Background: Many gastrointestinal disorders share overlapping gastrointestinal symptoms (GIS), which usually begin in early life and persist in adulthood. Adults experiencing GIS display altered in the brain structure. The objective of this study was to determine if GIS-related alterations in brain structure are also present earlier in life.

Methods: Structural brain MR images of 187 participants experiencing GIS and controls from ages 8-21 were provided by the Philadelphia Neurodevelopmental Cohort database. White matter volume (WMV) was analyzed with voxel-based morphometry.

Results: All GIS participants displayed altered WMV compared to age-matched controls. Pre-adolescents experiencing GIS displayed larger WMV in the brainstem and smaller WMV in the caudate nucleus (CN), anterior cingulate cortex (ACC), middle cingulate cortex (MCC), superior temporal gyrus (STG) and the cerebellum. Adolescents experiencing GIS showed larger WMV in the MCC, CN, orbital frontal cortex, precuneus, middle frontal gyrus (MFG), middle temporal gyrus and smaller volumes in the insula, brainstem, percental, supplementary motor area and the cerebellum. Young adults experiencing GIS displayed larger WMV in the insula, STG, CN, hippocampus, amygdala, MFG, MCC, ACC and a smaller volume in the cerebellum.

Limitations: Since this study used a cross-sectional design, causal inferences cannot be drawn. The restricted information about the types of GIS experienced by each participant is also a limitation.

Conclusion: The age-specific structural differences found in this study support the need for further research into neurophysiological effects of GIS. The specific areas that are impacted by living with GIS suggest potential influences on cognitive function and emotion modulation.

Directed differentiation of mouse embryonic stem cells towards blood-brain barrier endothelial cells

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ABSTRACT

Background: *In vitro* blood brain barrier (BBB) models are crucial tools to aid in the pre-clinical evaluation and selection of BBB-crossing therapeutics. Stem cell derived BBB models have recently demonstrated a substantial advantage over primary and immortalized brain endothelial cell models for BBB modeling and maintenance of BBB phenotype in culture. Coupled with recent discoveries highlighting significant species differences in the abundance and function of key BBB transporters, the field is in need of robust, species-specific BBB models for improved translational predictability.

Methods: Mouse embryonic stem cells were directly differentiated into mouse embryonic stem cell–derived brain endothelial cells (mBECs) through a monolayer differentiation protocol.

Results: We have developed a mouse stem cell-derived BBB model, composed of mBECs. These mBECs exhibited barrier formation properties as assessed by high transendothelial electrical resistance, inducible by retinoic acid treatment, up to 500 Ω cm^2. This robust barrier integrity results in restricted sodium fluorescein permeability (0.017 x 10^{-3} cm/min), magnitudes lower than that of Bend3 cells (1.02 x 10^{-3} cm/min) and comparable to that described for human iPSC-derived BECs (0.020 x 10^{-3} cm/min). The mBECs also express key BBB and endothelial specific markers (Cd31, Cldn5, Occludin and Zo1), polarized expression of functional P-gp efflux transporters and receptor mediated transcytosis triggered by antibodies against specific receptors. The battery of antibodies binding species selective or cross-reactive epitopes on BBB receptors that trigger receptor-mediated transcytosis with evaluated in parallel in the mBEC and human iPSC-derived BECs to demonstrate discrimination of species-specific BBB transport mechanisms.

Limitations: Despite optimization of the BEC differentiation protocols, these cells do not fully recapitulate TEER values *in vivo* (>5000) however sill form robust barrier properties to assess BBB permeability of a number of neurotherapetuics.

Conclusion: Since mouse remains the primary species in preclinical studies, the development and deployment of high-quality mouse BBB models is essential to improve translational predictability and aid in de-risking of CNS drug discovery and development pipelines.

Validation of an ecological momentary assessment to measure cognition in major depressive disorder

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ABSTRACT

Background: Cognitive deficits are a core feature of major depressive disorder (MDD) that have negative impacts on functional outcomes. However, it remains challenging to assess these impairments in clinical settings. Smartphone applications provide the opportunity to measure cognitive impairments in an accessible way. While numerous applications have been developed with the goal to assess cognition, none have been validated in MDD.

Methods: Twenty-four individuals with MDD and thirty-three healthy controls were recruited and completed the Trail Making Tests (TMT), and smartphone-based versions, named the Jewels Trail Tests (JTT). We examined the concurrent validity of the JTT and investigated whether these tests discriminated participants with MDD from controls. We also assessed the predictive validity by exploring whether self-reported sleep quality impacted cognition overtime measured by the JTT.

Results: Significant positive relationships between the JTT and TMT were observed, indicating that the JTT is a valid measure of cognition in MDD (p =.04 for JTT A and p < .0001 for JTT B). The cognitive performance of participants with MDD group was higher than the HC group, though the results were not significant (p =.31 for JTT A and p =.14 for JTT B). Higher sleep quality was associated with a better cognitive performance (p =.03 for the JTT A).

Limitations: These are preliminary analyses of an interim sample with small sample size.

Conclusion: Smartphone-based cognitive assessments may be promising in individuals with a mental health disorder, such as MDD.

Elucidating the endogenous distribution, topography and cells-of-origin of α-synuclein in relation to Parkinson's disease

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ABSTRACT

Background: Parkinson's Disease (PD) pathologically presents with Lewy body inclusions throughout the brain, leading to neurodegeneration and ultimately motor and non-motor PD symptomology. Lewy bodies are composed of aggregated a-synuclein protein, and although essential to our understanding of PD, there is limited knowledge of the role of α-synuclein in healthy cells. Due to its cytoplasmic locale, it is difficult to determine which cells natively produce or host α-synuclein. To overcome these issues in visualizing and understanding α-synuclein, we engineered a mouse model that localizes endogenous a-synuclein to the nucleus of cells (SncaNLS-Flag). With this model the topography and cells-of-origin of α-synuclein can be determined in the brain and periphery of mice.

Methods: I performed immunohistochemistry on SncaNLS-Flag tissue to visualize the endogenous distribution of α-synuclein in the brain and periphery. Using machine learning analysis, I determined regions with high α-synuclein expression, which were subsequently co-stained with cell-type specific markers, elucidating the exact cells α-synuclein is present in.

Results: a-synuclein was highly expressed in the olfactory bulb, hippocampus, cerebral cortex, substantia nigra and cerebellum in the brain. Among these regions, there was significant colocalization with α-synuclein in granule, pyramidal, mitral, dopaminergic and layer-specific cortical neurons.

Limitations: The α-synuclein expression profiles were determined via visual analysis, and not controlled to cell counts. Future analysis will correct this by incorporating nuclear analysis as a control.

Conclusion: There are clear, distinct populations of cells with α-synuclein expression throughout the mouse brain and periphery, providing insight into cells most impacted by normal and pathological α-synuclein.

Evaluating the risk of Parkinson's disease with ethno-racial considerations

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ABSTRACT

Background: Inclusion of race/ethnicity in research is essential to delineate research generalizability. Currently no published large-scale studies of multi-factorial ethno-racial differences in Parkinson's Disease (PD) diagnosis/risk exist. Thus, there remains an important need to evaluate the contribution of ethno-racial factors to PD risk profiles. We hypothesize that there may be limited published PD research that incorporate ethno-racial considerations.

Methods: We conducted a targeted literature review on PD risk/diagnosis to assess the contribution of ethno-racial considerations. A PubMed search included articles published between 2000-2020 with MeSH terms of PD, diagnosis, risk factors, incidence, and epidemiology. Selection criteria included: exclusion of reviews/meta-analyses. Following abstract review, 410 articles were selected for full review to quantify inclusion of ethno-racial factors.

Results: Based on the review 52.4% of articles accounted for race/ethnicity. Among these, only 9.8% accounted for ethno-racial factors as an integral part of analysis. A few studies identified significant differences in PD incidence such that African Americans are less likely to be diagnosed with PD than Caucasian individuals. Considering PD genetic vulnerability, the LRRK2 p.G2019S variant was documented in European populations but found absent in an Asian population, while the LRRK2 p.G2385R variant was associated with risk in the Chinese population.

Limitations: Included studies published only in English and between 2000-2020.

Conclusion: Most studies accounted for race/ethnicity, however; only a very small subset conducted stratum-specific analyses with race/ethnicity as an independent variable. Suggested differences across race/ethnicity warrant a need for further studies with diverse cohorts to improve PD risk predictions.

Inhibition of miR-145-5p Improves Clinical Severity of EAE

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ABSTRACT

Background: Multiple Sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS) resulting in neurological dysfunction. Our laboratory has previously shown that the microRNA miR-145-5p is upregulated in MS lesions and this can contribute to the inhibition of oligodendrocyte differentiation. Using experimental autoimmune encephalomyelitis (EAE) as a model for MS, we showed that knockout of miR-145-5p resulted in reduced clinical severity, loss of myelin and immune cell infiltration. We hypothesize that inhibition of miR-145-5p at disease onset with an antisense oligonucleotide (ASO) would result in reduced severity of disease.

Methods: Female mice were induced with EAE and then treated with the miR-145-5p ASO at disease onset. We evaluated disease progression by monitoring clinical severity daily. CNS and lymphoid tissues were collected at onset, peak and chronic timepoints to evaluate molecular and structural characteristics of EAE by RT-qPCR, immunohistochemistry and electron microscopy.

Results: We have shown that our miR-145-5p ASO reduces miR-145-5p expression in lymphoid and CNS tissues following EAE induction. The miR-145-5p ASO resulted in improved clinical severity demonstrated by a reduction in the number of days paralyzed, the score at the chronic timepoint and the number of clinical relapses. The mechanism by which miR-145-5p inhibition improves clinical severity of EAE is not yet known.

Limitations: Only female mice were used since EAE is not optimized in male mice; however, MS is more prevalent in women than men.

Conclusion: The knockout of miR-145-5p resulted in reduced severity of EAE. This study will allow us to assess if a miR-145-5p ASO can reduce severity of disease and if this approach represents a potential treatment for MS.

Modulation of cortical excitability and tolerability of a 30 Hz intermittent theta-burst (iTBS) protocol in healthy adults

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ABSTRACT

Background: TBS is a form of repetitive transcranial magnetic stimulation (TMS) developed to induce neuroplasticity. TBS usually consists of 50 Hz bursts at 5 Hz intervals. When applied intermittently (2 s ON, 8 s OFF), TBS can lead to facilitation of motor evoked potentials (MEPs), although these effects can be quite variable between individuals. Here, our goal was to determine whether a modified version of iTBS consisting of 30 Hz bursts at 6 Hz intervals would lead to more robust and less variable modulation.

Methods: Participants (n=18, young adults) underwent single-pulse TMS to assess corticomotor excitability at baseline as reflected in MEP amplitude (n=20). 30 Hz iTBS was then administered to the left motor cortex (1.7 ON, 8.3 OFF, 600 pulses over 194 s). MEP amplitude was reassessed at 5, 20 and 45 mins post. Safety and tolerability were also assessed with standard questionnaires and the visual analog scale (VAS).

Results: Compared to baseline, MEPs were significantly facilitated up to 45-min post-iTBS (mean 154±74%). Most participants exhibited the expected facilitation (13/18). No serious adverse event was recorded. Participants reported only minor complaints (e.g., scalp discomfort) associated with the intervention and little to no pain (mean VAS score, 1.1± 1.5).

Limitations: Age-related differences could contribute to the variability of TBS responses, warranting investigation of 30Hz/ 6Hz iTBS on a group of healthy older adults.

Conclusion: These observations suggest that 30 Hz/6 Hz iTBS may provide a sound and safe alternative to induce consistent neuromodulatory effects over the commonly used 50 Hz/5 Hz protocol.

Disentangling the cannabis-suicide relationship: examining cannabis use, neuroendocrine profiles, and suicidal behaviour

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ABSTRACT

Background: Cannabis is one of the most commonly used psychoactive drugs among young adults worldwide. Frequent use is associated with elevated risk of suicidal ideation (SI) and suicide attempt (SA), which can predict suicide deaths. However, neurobiological underpinnings mediating an association between cannabis use and suicidal behaviour remain unclear. This study examined cannabis use and the neuroendocrine stress biomarker, cortisol, in relation to SI and SA.

Methods: The association between problematic cannabis use and suicidal behaviour was examined among University students (N=539; Mage=19.4, 23.2% males, 76.3% females). Participants completed questionnaires, including the Cannabis Use Disorder Identification Test-Revised (CUDIT-R), and reported lifetime and past 12-month SI and SA. Blood samples were collected to determine levels of plasma cortisol, quantified by radioimmunoassay.

Results: Problematic cannabis use was significantly associated with lifetime SA, $p = .002$, lifetime SI, $p = .003$, and past 12-month SI, $p = .004$. Levels of cortisol were higher in individuals who reported past 12-month SI, $p = .029$, and lifetime SA, $p = .042$. While a trend was observed between cortisol and lifetime SI, it did not reach statistical significance.

Limitations: The study was limited by the cross-sectional nature precluding any causal relationships.

Conclusion: Problematic cannabis use is associated with increased suicidal thoughts and behaviors, which could be in part due to altered neurobiological stress pathways. These findings highlight potential risks associated with cannabis use and could be considered in the development of public health education initiatives.

Oral contraceptive use and mental health in young women: examining associations to mood states and peripheral biomarkers

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l

ABSTRACT

Background: Oral contraceptives (OC) are used by approximately 30-45% of young females in Canada, and have been linked to mood, hormone and brain alternations. However, evidence is inconsistent re-garding the direction of these effects. Thus, a more comprehensive understanding is needed regard-ing the use of OC in relation to mood states and stress-related physiology.

Methods: The current study examined stress, depression and anxiety symptoms, as well as plasma levels of cortisol and inflammatory factors (C-reactive protein (CRP), Interleukin 6 (IL-6) and tumor necro-sis factor alpha (TNF-a)), according to OC use and menstrual cycle in 388 females aged 17-29 years.

Results: Females using OCs had higher stress, $p = .04$, and depressive symptoms, $p = .03$, compared to non-users. OC users also exhibited higher plasma cortisol, $p < .001$, and CRP, $p = .001$, compared to non-users. In contrast, no differences were found between groups across anxiety scores, IL-6 or TNF-a levels. Moreover, compared to regularly cycling females (not taking OCs), OC users had higher cortisol levels compared to females in the follicular phase, $p < .001$, and higher cortisol and CRP levels compared to females in the luteal phase, $p < .001$ and $p = .02$, respectively.

Limitations: Insufficient sample size for OC subgroups prevented the examination of different forms of contraceptives.

Conclusion: Oral contraceptive use may increase sensitivity to the effects of stress through alerted stress pathophysiology. Ultimately, this could contribute to an increase in vulnerability and susceptibility to psychological disturbances among female OC users.

Elevated and slowed EEG oscillations in patients with post-concussive syndrome and chronic pain following a motor vehicle collision

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ABSTRACT

Background: Mild traumatic brain injury produces significant changes in neurotransmission including brain oscillations. Our objective was to investigate potential quantitative electroencephalography biomarkers in 57 patients with post-concussive syndrome and chronic pain following motor vehicle collision, and 54 healthy nearly age-and-sex-matched controls. We hypothesized that patients would exhibit increased broadband EEG power when compared to controls.

Methods: In this observational study we obtained EEGs from 57 patients with post-concussion syndrome and chronic pain, and 54 healthy nearly age-and-sex-matched controls. Electroencephalography processing was completed in MATLAB, statistical modeling in SPSS, and machine learning modeling in Rapid Miner. Group differences were calculated using current-source density estimation, yielding whole-brain topographical distributions of absolute power, relative power and phase-locking functional connectivity. Groups were compared using independent sample Mann-Whitney U tests. Effect sizes and Pearson correlations were also computed. Machine learning analysis leveraged a post-hoc supervised learning support vector non-probabilistic binary linear kernel classification to generate predictive models from the derived EEG signatures.

Results: Patients displayed significantly elevated and slowed power compared to controls: delta ($p=0.000000$, $r=0.6$) and theta power ($p<0.0001$, $r=0.4$), and relative delta power ($p<0.00001$) and decreased relative alpha power ($p<0.001$). Absolute delta and theta power together yielded the strongest machine learning classification accuracy (87.6%). Changes in absolute power were moderately correlated with duration and persistence of symptoms in the slow wave frequency spectrum (<15Hz).

Limitations: Patients were not medication naïve. This could influence their EEG signals.

Systematic review on the safety and tolerability of transcranial direct current stimulation in children and adolescents

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a safe, tolerable, and acceptable technique in adults. However, there is limited evidence for tDCS safety in youth and a synthesis of pediatric safety studies is not currently available. Our objective was to synthesize objective evidence regarding the safety and tolerability of pediatric tDCS based on the current state of the literature.

Methods: Our search and report used PRISMA guidelines. Our report systematically examined twelve studies purposefully designed to evaluate the safety, tolerability, and acceptability of tDCS in healthy and atypical youth that were submitted to three databases (PubMed, Scopus, and Scholar Portal), from the beginning of the database to November 2019. The following search terms were used: "tDCS child safety", "tDCS child tolerability", "tDCS adolescent safety", and "tDCS adolescent tolerability". Safety considerations were evaluated by studies utilizing neuroimaging, physiological changes, performance on tasks, and by analyzing reported and objective side effects; tolerability via rate of adverse events; and acceptability via rate of dropouts.

Results: We report on 203 sham sessions, 864 active sessions up to 2 mA, and 303 active hours of stimulation in 156 children. A total of 4.4% of the active sessions were in neurotypical controls, with the other 95.6% in clinical subjects..

Limitations: This study was limited by the current evidence being sporadic and scarce.

Conclusion: The presently reviewed literature provides support for the safety, tolerability, and acceptability of tDCS in youth for 120 sessions of 20 min up to 2 mA. Future pediatric tDCS research is encouraged.

Social media use and student mental health during the COVID-19 pandemic

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ABSTRACT

Background: Undergraduate university students are experiencing many academic and non-academic stressors during the COVID-19 pandemic, putting them at a greater risk of experiencing negative mental health outcomes. To connect with peers during the isolation restrictions and cope with the stress of the pandemic, students appear to be increasingly turning to social media.

Methods: Carleton University undergraduate students (N = 806) participated in an online study between September to December 2020. Students completed a series of demographic questions including gender and current mental health diagnosis (MHD), as well as questionnaires assessing depressive symptoms, loneliness scores, social media use and social media addiction (SMA) scores.

Results: Students with a current MHD reported higher stress ($p < .001$), depressive symptoms ($p < .001$), loneliness scores ($p < .001$) and SMA scores ($p = .05$). Similarly, females reported higher stress ($p < .001$), depressive symptoms ($p < .001$), SMA ($p < .001$) and tended to report higher loneliness scores ($p = .06$). Positive associations between SMA scores were found in relation to stress ($p < .01$), depressive symptoms ($p < .01$), and loneliness levels ($p < .01$). The relationship between gender and SMA scores was mediated by depressive symptoms (95% CI {.25, .50}).

Limitations: The cross-sectional nature of these data preclude any causal interpretations.

Conclusion: Females and individuals with a MHD exhibit worse mental health outcomes and greater problematic social media use during the pandemic. Moreover, for females, problematic social media use seems to be explained, in part, by depressive symptomatologies.

Towards conceptual convergence: a systematic review of psychological resilience in family caregivers of persons living with chronic neurological conditions

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ABSTRACT

Background: The demand for informal family caregiving in persons with chronic neurological conditions (CNCs) is increasing. Psychological resilience, which describes the process of maintaining positive adaptations in the face of adversity, may empower and protect caregivers in their role. Still, debate regarding how resilience ought to be described and measured in relation to numerous contextual factors persists. In this systematic review, we narratively synthesize and critically assess the current scientific literature on the concept of resilience in CNC family caregivers to advance the study and clinical applications of resilience under a singular intelligible model**.**

Methods: We sourced peer-reviewed English articles across a variety of health disciplines using relevant search terms comprised of CNCs, family caregivers, and resilience.

Results: A total of 50 studies were retained. Nearly half (44%) of retained studies used trait-based resilience definitions, while a substantial portion (36%) employed a process-based definition. Collectively, authors affirmed that resilience is related to multiple indicators of healthy caregiver functioning (e.g., quality of life, social support, positive coping) as it buffers against negative outcomes of burden and distress. Discordance in relation to the interaction between resilience and demographic, sociocultural, and environmental factors was evident.

Limitations: As a function of the nuance and permeability of resilience across numerous psychological disciplines, it is possible that not all relevant literature was captured in our narrow resilience-focused search strategy. As such, more rare CNC caregiver populations were underrepresented in our synthesis.

Conclusion: This study reveals where inconsistencies in the CNC carer resilience literature predominate and calls for more culturally sensitive and longitudinal approaches within the field. With broad acceptance of the importance of resilience for caregiver wellbeing, future researchers should align their conceptual designs to reflect contemporary resilience process theories and ecological applications.

Sexual dimorphism in a neuronal mechanism of spinal hyperexcitability across rodent and human pathological pain models

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ABSTRACT

Background: The neurobiological underpinnings of sexually dimorphic pain signalling remain unclear in rodents and are virtually unexplored in human preclinical models. Within the pain-processing system, the superficial dorsal horn (SDH) is a critical site of pain modulation. We have recently characterized a pathological-pain pathway in male rat and human SDH neurons where brain-derived neurotrophic factor (BDNF) mediates loss of inhibition and a subsequent potentiation of GluN2B-containing N-methyl D-aspartate receptors (NMDARs). Here, we investigate whether molecular mechanisms of spinal hyperexcitability are conserved between sexes in rodents and humans.

Methods: We studied spinal mechanisms of pain processing using the ex vivo BDNF pain pathology model in rodent and human spinal cord and the *in vivo* Freund's adjuvant (CFA) rodent inflammatory pain model. We paired patch-clamp electrophysiological recordings of synaptic NMDAR responses with ex vivo pharmacology, biochemical approaches, and behavioural testing.

Results: In female rats, NMDAR responses at lamina I SDH synapses are not potentiated by spinal cord ex vivo treatment with BDNF nor in the *in vivo* CFA inflammatory pain model. Parallel biochemical evidence shows no differences in female rodent as well as human models of pathological pain compared to non-pain tissue. Electrophysiology and biochemical investigations in ovariectomized rats suggest hormonal mediation of this sex-difference.

Limitations: It remains unclear whether the BDNF-disinhibition-NMDAR potentiation pathway occurs in females with neuropathic pain.

Conclusion: Neuronal mechanisms of SDH hyperexcitability are sexually dimorphic in rats and humans. This sex-difference in underpinning neurobiological mechanisms of chronic pain has profound implications for the development of novel pain therapeutics.

Exploring clinical and cognitive side effects of electroconvulsive therapy: a case study

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is an effective treatment for severe mental health disorders, but there are often cognitive side effects associated with treatment. Furthermore, research into cognitive and clinical symptoms is inconsistent, highlighting the need for further investigation.

Methods: Eight participants were screened, and two participants receiving ECT for severe mental health disorders were enrolled. Participants one and two were female, 63 and 74 years old, diagnosed with Bi-Polar II and Major Depressive Disorder, respectively. Assessments were administered 72-hours pre-ECT, 72-hours post-ECT, and one-month post-ECT. Clinical interviews included assessments of depression, anxiety, and suicidality. Cognitive assessments included the Montreal Cognitive Assessment (MoCA) and the ElectroConvulsive Therapy Cognitive Assessment (ECCA). Due to COVID-19, assessments were conducted over the phone.

Results: From baseline to one-month post-ECT, there was a 53% and 34% reduction in depression scores, 81% and 34% reduction in anxiety scores, and 81% and 20% reduction in suicidality scores, for participant one and two, respectively. Cognitive scores on the MoCA decreased by 27% for participant two. There was <10% improvement for participant one on the MoCA and both participants on the ECCA.

Limitations: Limitations included protocol modifications due to COVID-19 and difficulty recruiting and retaining participants, resulting in a small sample size.

Conclusion: Preliminary data suggests ECT could improve clinical symptoms, but its effect on cognitive symptoms remain unclear. Once research restrictions are lifted, our full protocol will include data from 60 participants and additional transcranial magnetic stimulation measures to explore neurobiological predictors of response and neural mechanisms of ECT.

Implications of early physical activity on functional connectivity after a pediatric concussion

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ABSTRACT

Background: Physical activity (PA) has been proposed as a treatment to manage concussion symptoms, however, few studies have investigated PA-induced neurophysiological changes following a concussion. Functional connectivity (FC) within the default mode network (DMN) has been proposed as a potential recovery biomarker following pediatric concussion and may provide objective measures of PA-induced changes.

Methods: 92 acutely concussed participants aged 10-17.99 were enrolled in the CHEO emergency department. Participants were randomized to either resume non-contact PA 72 hours post-injury or rest until asymptomatic. Both groups underwent a resting-state fMRI scan at 72 hours (+/-48 hours) and 4 weeks (+/-5 days) post-injury. The bilateral posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) were defined as regions-of-interest. One-way ANCOVAs adjusting for DMN FC of the 72-hour scans and handedness were conducted with the 4-week scans.

Results: No significant differences were found between the PA group (n=30) and the rest group (n=25) in FC between the bilateral PCC and the mPFC at whole brain level threshold of p(uncorrected)<0.001 and cluster threshold of p(FWE)<0.05.

Limitations: Per-protocol analysis is required to investigate group differences in those that have adhered to the intervention.

Conclusion: Children assigned to PA initiation at 72-hours post-injury demonstrated no differences in FC at 4-weeks post-concussion between the bilateral PCC and the mPFC—main hubs of the DMN—in comparison to those resting until asymptomatic. This provides preliminary, objective evidence that early PA reintroduction does not cause adverse changes in brain functional activity following an acute pediatric concussion.

Characterization of synaptic NMDA receptor responses in rat and human spinal pain-processing neurons

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ABSTRACT

Background: Although pathological pain primarily affects women, pain physiology has been studied primarily in male rodents. Nociception involves the neural encoding of noxious stimuli, thus forming the physiological bases of pain perception. The superficial dorsal horn (SDH) of the spinal cord receives sensory input from the periphery and sends the processed and modulated nociceptive signals to the brain. Glutamatergic NMDA receptors (NMDARs) are key players in modulating spinal pain signaling. NMDARs are composed of subunits that each contribute differently to receptor kinetics. In this study, we performed the first-ever analysis of synaptic NMDAR responses in SDH neurons to compare the subunit composition of NMDARs across sex and species.

Methods: We collected viable spinal cord tissue from Sprague Dawley rats and human organ donors of both sexes. We used patch-clamp electrophysiology recording to measure synaptic NMDAR responses. From our recordings, we evaluated the decay constants and the peak amplitude of NMDAR responses.

Results: Both species and sexes showed a wide heterogeneity in spontaneous synaptic responses. The high contribution of GluN2A- and GluN2B-like responses was consistent across sex and species. Interestingly, male human synaptic responses showed higher amplitude than male rats and female humans.

Limitations: Due to methodological differences in slice preparation, rat and human results cannot be directly compared.

Conclusion: The heterogeneity of NMDAR subunit composition across individual synapses in SDH neurons was conserved across sex and species. The amplitude difference between males and female humans shows the importance of inclusion of both sexes in preclinical pain research.

A case study reporting the effect of abruptly stopping and reinstating theta burst stimulation treatment in two patients with major depression

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ABSTRACT

Background: Theta burst stimulation (TBS) has been shown to be effective in treating major depression when applied to the prefrontal cortex. However, the clinical effect of abruptly stopping and reinstating treatment, as in the case of the Covid-19 pandemic, remains unknown.

Methods: A 62-year-old man and a 63-year-old woman, who had been randomly assigned to receive either unilateral or bilateral TBS treatment for depression as part of a clinical trial, were enrolled in the case study. Six weeks of TBS treatment were completed and a six-month maintenance phase had begun when treatment was stopped, in March 2020, due to the pandemic. The Hamilton Depression Rating Scale (HDRS-17), was administered to assess clinical symptoms before, during and after the confinement period, as well as before and after treatment reinstatement.

Results: After TBS treatment, both participants achieved remission level on the HDRS-17, with a 72.7% and a 81.2% reduction in symptoms. During the pandemic, depression symptoms levels showed an average increase of 90% for participant 1 and 233.3% for participant 2. On average, scores did not exceed pre-treatment levels. Reintegration into 4-weeks of treatment was marked by a 25% increase for participant 1 and a 33.3% decrease for participant 2, although their symptoms remained in the "mild depression" category.

Limitations: This observational case study is limited by the small sample size.

Conclusion: Our results are consistent with larger studies showing effectiveness of TBS in treating depression and suggest that TBS may be a protective factor for relapse in periods of great stressors.

Chronic desipramine induces norepinephrine projections to interneurons for recovery in a mouse model of fluoxetine-resistant depression

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ABSTRACT

Background: Reduction in monoamines has been implicated in major depressive disorder, for which serotonin (5-HT) reuptake inhibitors (SSRIs) are the first-line treatment. However, many patients fail to respond, and are switched to augmentation or tricyclic antidepressants (TCAs). To elucidate rational strategies to overcome SSRI-resistant depression (SRD), we generated the cF1ko mice. In these mice, the Freud-1/CC2D1A gene is deleted in adult 5-HT cells leading to reduced 5-HT and SRD phenotype. Here we address the response of cF1ko mice to the TCA desipramine, targeting 5-HT and norepinephrine systems.

Methods: cF1ko and wild-type mice chronically treated with desipramine were examined using behavioral tests. Brain-wide NE projections, synapses and chronic cellular activation were detected by immunofluorescence for the norepinephrine transporter (NET), synaptophysin and FosB, respectively, with GAD67/gephryn or CaMKII/vGluT1-2/PSD95 used to detect GABAergic interneurons, glutamatergic neurons or post-synaptic densities, respectively.

Results: Desipramine treatment restored depression-/anxiety-like behaviour of cF1ko mice to wild-type levels. Desipramine increased locus coeruleus NE neuronal activity and induced full recovery in NE innervation targeting interneurons to restore activity in the mPFC and BLA.

Limitations: Only one treatment condition was tested.

Conclusion: cF1ko mice with reduced 5-HT activity show alterations in NE corticolimbic-projections. Desipramine-induced behavioural recovery was associated with restored NE innervation of interneurons in the mPFC and BLA. These results suggest that treatment of patients with reduced 5-HT function or SSRI non-response with antidepressants targeting NE, like TCAs or SNRIs, may be an effective alternative to SSRIs. The cF1ko mice provide a clinically relevant genetic model of SSRI-resistance to further investigate the efficacy and mechanisms of alternative antidepressant approaches.

Sex-specific changes in salivary cortisol with repeated ketamine infusions for depression

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ABSTRACT

Background: Ketamine is a novel antidepressant strategy that has been shown to rapidly reduce depressive symptoms and suicidal ideation in a significant proportion of individuals with major depressive disorder. Given the hypothalamic-pituitary-adrenal (HPA) axis abnormalities seen in depression, this study aimed to investigate the effects of a short course of repeated ketamine infusions on cortisol, the final product of the HPA axis.

Methods: Saliva samples were available from 29 participants with treatment-resistant depression that completed a repeated ketamine infusion clinical trial. Salivary cortisol levels were measured from samples collected at waking, 30 minutes after waking and 60 minutes after waking. Area under the curve (AUC) was calculated as an aggregate index of cortisol exposure both with respect to the ground (AUCG: index of total hormone output) and with respect to increase (AUCI: index of intensity of response).

Results: Prior to ketamine treatment, salivary cortisol AUCI was significantly lower in males than females ($p=.024$). With ketamine treatment however, this was reversed and AUCI increased in males that responded to ketamine treatment ($p<.05$). There was also a sex-specific change in AUCG with repeated ketamine infusions ($p<.05$); AUCG increased in males following repeated infusions and decreased in females.

Limitations: Study was limited by sample size ($n=29$) and lack of control group.

Conclusion: This study found that ketamine treatment impacts morning cortisol output (AUCG) and intensity of cortisol awakening response (AUCI) in a sex-dependent manner. Further research on the sex-specific impact of ketamine treatment on the HPA axis is warranted.

Light intensity-dependent antidepressant actions of acute and chronic optogenetic stimulation of raphe serotonin neurons in a mouse model of post-stroke depression

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ABSTRACT

Background: Post-stroke depression (PSD) occurs in one third of stroke survivors, negatively impacting stroke recovery. SSRIs are the first-line treatment for depression but require three weeks before antidepressant effect and are only 50% effective in clinic. We hypothesize that direct stimulation of the serotonin (5-HT) system can overcome these issues and tested this in a mouse PSD model.

Methods: Transgenic Pet1-ChR2 mice expressing channelrhodopsin in 5-HT neurons were given a unilateral ischemic lesion to the medial prefrontal cortex to induce a PSD phenotype and implanted for light stimulation of the raphe. To test acute effects of 5-HT activation, one week after stroke mice underwent three anxiety and two depression tests with light stimulation. To determine the chronic effects of 5-HT activation, mice underwent one week of daily 5-HT stimulation in home cage after stroke before undergoing the same behavioural testing.

Results: Stimulation under acute settings produced a light intensity-dependent anxiogenic effect and a significant antidepressant effect. Chronic stimulation showed no changes in anxiety and a persistent pre-stimulation antidepressant effect as well as acute antidepressant effect.

Limitations: The present protocol inducing system-wide 5HT activation may trigger conflicting activity from antagonistic circuits.

Conclusion: These data suggest that acutely direct activation of the 5-HT system produces an immediate light intensity-dependent antidepressant effect, while repeated activation can induce a persistent antidepressant effect. Further work to determine regions activated with chronic optogenetic activation for direct targeting to induce the antidepressant response may elucidate targets for clinical brain stimulation treatments.

Descriptive analysis of research productivity in Canadian neurosurgeons

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ABSTRACT

Background: Scholarly activity is becoming an increasingly important aspect of neurosurgical training in Canada. Post graduate and fellowship training opportunities have been utilized by trainees to augment academic productivity. However, modifiable and non-modifiable determinants of future research proclivity have not been studied comprehensively in the current literature. Thus, we sought to identify demographic and training measures on research productivity.

Methods: A retrospective bibliometric review was conducted on a cohort of 338 actively practicing Canadian neurosurgeons as of August 2020. Publications were manually curated as basic/translational or clinical. Clinical papers were further classified by research quality using a published tier-based system.

Results: Approximately half of Canadian neurosurgeons held a graduate degree (48.9%). A total of 11,139 Canadian neurosurgical publications were identified via Medline, where 80.7% were clinical. Negative binomial modelling using surgeons' highest graduate degree, fellowship status, Canadian medical training, and gender demonstrated that a PhD predicted a surgeon's basic-science publications ($p<0.0001$) and that fellowship training was associated with first-authorship ($p<0.0001$) and high-quality clinical publications ($p<0.0001$). Gender and training institutions were nonsignificant predictors.

Limitations: The study limited inclusion to currently active neurosurgeons, therefore publication activity of retired or temporarily inactive neurosurgeons was not included.

Conclusion: This is the first study to examine the research productivity amongst all actively practicing neurosurgeons in Canada. Our findings have important implications for allocation of research funding and recruitment imperatives. This work also informs career choice and planning for trainees at all levels of neurosurgical training.

Ventriculoperitoneal shunt infection rate in developed versus developing countries: a systematic review

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ABSTRACT

Background: Ventriculoperitoneal shunting (VPS) is the commonest treatment for hydrocephalus. However, perioperative infections remain the most common complication in neurosurgery. Given that national socioeconomic status may influence other health related outcomes, we sought to compare VPS infection rates between developed and developing economies.

Methods: A systematic review was conducted using PubMed to identify articles reporting the infection rates associated with ventriculoperitoneal shunt insertion. PRISMA guidelines were followed and key words included "infection rate", "ventriculoperitoneal shunt" and "VPS''. Countries were stratified as 'developed economies' or 'developing economies' according to the United Nations 2019 classification.

Results: A total of 345 papers were identified, in which 68 were included for qualitative and quantitative analysis. Among these, 42 articles classified as being from developed economies and 26 from developing economies. The most prevalent etiology of hydrocephalus were hemorrhagic and congenital in both developed and developing nations. The average infection rate was 8.65% in developed nations and 11.18% in developing nations ($p = 0.20$).

Limitations: The study did not calculate the infection rate per procedure which may have underestimated our findings. Reporting biases or limited follow up may also under describe true complication rates.

Conclusion: Despite technological and presumed medical evolution in developed economy nations, these advancements do not translate into improved VPS infection rates. These negative findings remain highly valuable as they suggest that infection rates may not be modified by resource availability alone, but by other latent factors.

An unbiased proteomic approach to mapping the TDP-43 interactome in the context of ALS

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ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative movement disorder in which an RNA-binding protein, TDP-43, mislocalizes and pathologically accumulates from its normal nuclear locale to the cytosol.Given that the subcellular localization and expression of TDP-43 is tightly regulated and affected by its protein-protein interactions (PPIs), we posit that identifying novel interactors of wild-type and mutant TDP-43 could reveal insight into networks involved in driving neurodegeneration in ALS.

Methods: Using CRISPR/Cas9, our lab has generated knockin cell lines expressing GFP-tagged wildtype (WT) and an ALS-causing mutant (Q331K), in the endogenous TARDBP locus (coding for TDP-43). We have shown that the Q331K mutation causes loss-of-function and mislocalization of TDP-43. We have performed immunoprecipitation coupled to mass spectrometry (IP-MS) on this cellular tool to elucidate interactors of WT- and Q331K, TDP-43.

Results: Our data has shown that there is an overall loss of interactors with TDP-43Q331K mutation, and we have identified 46 proteins to be shared or distinct interactors of TDP-43WT. From this dataset, we have used bioinformatic approaches to shortlist and validate 14 candidates using IP-western blot. From this, we are characterizing the effects of knockdown and overexpression of 4 top hits (PABPC1, HNRNPC, DDX39b and ELAVL1) using cellular and biochemical approaches.

Limitations: Given the non-neuronal nature of our knock-in cell line, future characterization of top validated hits will be completed using neuronal cultures and spinal cord samples from ALS mouse models.

Conclusion: Using this unbiased approach, we will identify TDP-43 protein-protein interactions and characterize their roles in cellular functions in the context of ALS, giving insight into pathways involved in driving neurodegeneration.

The effects of stressor controllability on social incentive stimuli and the role of serotonin

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ABSTRACT

Background: Stress is a well-known risk factor for anhedonia, which often encompasses impaired social functioning. The lack of control over stress appears critical to its deleterious consequences, and serotonin modulates the interaction between stressor controllability and responses to social rewards. The current study in male Sprague-Dawley rats explored the effect of uncontrollable stress on responses to social incentive stimuli and clarified the possible involvement of serotonin in mediating this interaction.

Methods: The effects of inescapable foot-shocks on preferential investigation of a conspecific and a compartment that previously housed the conspecific were assessed in a Y-apparatus in subjects administered the selective serotonin reuptake inhibitor escitalopram (ESC; 0, 5 or 10 mg/kg). In-vivo microdialysis was used to measure serotonin tissue stores in the dorsal hippocampus after exposure to inescapable foot-shocks and ESC (0 or 5 mg/kg).

Results: It was found that rats exposed to inescapable foot-shocks did not display increased investigation of the previously paired social compartment, and this impairment was reversed by ESC administration. Foot-shock exposure did not significantly alter investigation of the conspecific. Moreover, serotonergic tissue stores were significantly elevated by ESC in rats exposed to inescapable foot-shocks.

Limitations: This study was completed only in male rats and was limited to acute ESC administration.

Conclusion: These results suggest that psychophysical stress and reactivity to social rewards are linked and possibly regulated by serotonergic mechanisms.

In vivo characterization of cortical noradrenergic activity during motor learning using an optical noradrenaline sensor

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ABSTRACT

Background: The locus coeruleus (LC) projects ubiquitously to cortex, and noradrenaline (NA) exerts neuromodulatory control on cortical excitation and inhibition. NA has an important role in motor processes, and recent work in our lab revealed dysregulation in LC-NA function as a culprit of motor-related deficits in Autism Spectrum Disorder (ASD).

Methods: To characterize changes in NA levels during motor learning in awake, behaving mice, I employed a newly developed optical NA sensor, combined with *in vivo* two-photon imaging, to visualize spatiotemporal activation patterns of NA in the motor cortex (M1). This approach allows us to track and chronically image the same M1 region over multiple days, permitting the characterization of NA activity throughout the entirety of the motor learning process.

Results: I found that NA levels increase significantly during the initial phase of learning, which coincides with structural-functional plastic changes previously reported in M1 during early motor learning. NA activity returns to baseline levels as mice develop their movement strategy. Now, we are investigating NA dynamics in the 16p11.2 deletion $^{(+/-)}$ mouse model of autism using the same paradigm.

Limitations: The nature of this rodent study precludes direct conclusions regarding human ASD, but can nonetheless provide valuable insight for clinical applications to improve diagnostic criteria for motor-related dysfunction in ASD.

Conclusion: Together, results of these experiments will offer a novel glimpse into the dynamics of NA activity in M1 during motor learning in wild-type and 16p11.2$^{+/-}$mice.

Co-expression and distribution of MCH, CART and NK3R in the mouse hypothalamus

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ABSTRACT

Background: Melanin concentrating hormone (MCH) neurons are hypothalamic cells important for energy balance and sleep regulation. Subpopulations of MCH cells can be marked by coexpression of cocaine- and amphetamine-regulated transcript (CART) or neurokinin 3 receptor (NK3R). Transcriptomic studies have indicated that one-third of MCH neurons coexpress both CART and NK3R, but the distribution of this MCH subpopulation has not yet been mapped in the mouse brain.

Methods: We quantified the proportion of MCH neurons that coexpress CART and/or NK3R, and we mapped the distribution of these cells to mouse Allen Reference Atlas templates. We identified MCH neurons by native EGFP fluorescence (EGFP-f) in Mch-cre;L10-Egfp mice, and performed immunohistochemical staining to identify CART and NK3R.

Results: In total, 49% of cells counted expressed EGFP-f (MCH) only. These were most commonly found within the lateral hypothalamus. In contrast, 47% of EGFP-f neurons coexpressed CART and were more common in the medial hypothalamus. Of these EGFP-f/CART+ cells, half of them coexpressed NK3R, which appeared equally throughout the medial and lateral hypothalamus. Less than 4% of EGFP-f neurons coexpressed NK3R only.

Limitations: Only one mouse brain was analyzed thus far, and we found a small cluster of EGFP-f cells (4%) were not MCH-immunoreactive and may represent ectopic expression.

Conclusion: These results indicate a robust heterogeneity of MCH cells. We will expand our analysis of the CART+ and CART/NK3R+ subpopulations by defining their electrical fingerprints so we are able to characterize the heterogenous nature of the MCH population based on their neurochemical and electrical properties.

Identifying therapeutic leads for GLUT1 deficiency syndrome through a high throughput FDA drug Screen

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ABSTRACT

Background: Glucose transporter 1 deficiency syndrome (GLUT1-DS), also known as De Vivo syndrome, is an autosomal dominant progressive genetic disorder caused by mutations in solute carrier 2A1 (SLC2A1) gene, encoding glucose transporter 1. Typically, a de novo disabling mutation in a single allele, results in a ~50% decrease, or haploinsufficiency, in cerebral endothelial GLUT1 levels. The resulting impaired blood-brain barrier (BBB) glucose transport leads to low glucose levels in the cerebrospinal fluid (CSF) or hypoglycorrhachia, in turn resulting in severe neurodevelopmental delay seen in infancy.

Methods: We have conducted a high-throughput screen on endothelial cells for GLUT1 upregulation using an FDA-approved drug library and several small molecules previously reported to upregulate GLUT1. The impact of upregulating agents detected in the screen on glucose transport in a disease model cell line derived from induced pluripotent stem cells (iPSC) differentiated into iPSC induced brain endothelial cells (iBECs) will be assessed. Post *in vitro* validation, the drugs will be tested in SLC2A1+/- mice.

Results: Our initial screen identified a number of potential new leads which are currently being validated; it would appear that GLUT1 levels are pharmacologically inducible. Upregulating agents found in the literature (e.g. berberine and deferoxamine) induced GLUT1 but only at concentrations higher than the pharmacologic range attainable in humans. Fluoxetine may be an exception in this regard, although cytotoxic at GLUT1 inducing levels *in vitro* experiments (e.g. 20 uM), such levels are readily attainable *in vivo*.

Limitations: The drug concentrations that are effective *in vitro* may be greater than clinically attainable for brain endothelial cells *in vivo*. In addition, as with all such screens, results in vitro may not translate to functional upregulated protein *in vivo.*

Conclusion: The SLC2A1 gene is highly inducible and a small molecule has the potential to target and upregulate the GLUT1 transporter as a pharmacological approach to GLUT1-DS.

A GABAergic pathway from the zona incerta dopamine cells to the superior colliculus

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ABSTRACT

Background: The zona incerta (ZI) comprises a group of dopaminergic cells in the hypothalamus that coexpress the vesicular GABA transporter (vGAT), thus they may release dopamine and/or GABA. The superior colliculus (SC) receives dopaminergic and GABAergic ZI projections, but it is not known if these projections arise from ZI dopamine+vGAT cells.

Methods: To determine if ZI dopamine+vGAT cells innervate the SC through GABA and dopamine, we transfected *Th-cre* cells in the medial ZI with a cre-dependent adeno-associated virus encoding channelrhodopsin (ChR2)-mCherry then performed whole-cell recordings from SC cells residing within the mCherry-labeled terminal field.

Results: ZI projections were observed throughout the SC rostrocaudally but were predominantly localized to the medial SC region. Photostimulation of ChR2-labeled terminals within the SC produced optogenetically-evoked inhibitory postsynaptic currents (oIPSC) with an average amplitude of 19.0±7.6 pA and latency of 5.1±0.3 ms. The oIPSC was abolished by the GABA-A receptor antagonist bicuculline but persisted in the presence of tetrodotoxin and 4-aminopyradine. Additionally, SC cells innervated by ZI *Th-cre* cells are also dopamine-sensitive and may be stimulated or inhibited by dopamine.

Limitations: Virus transmission may transfect *Th-cre* neurons in adjacent hypothalamic nuclei though these regions are not known to innervate the SC.

Conclusion: ZI dopamine+vGAT cells innervate the SC via monosynaptic GABA release. Ongoing studies will determine the mechanisms underlying ZI-mediated dopamine responses at the SC, including whether ZI *Th-cre* cells also innervate the SC by dopamine release.

Characterizing the involvement of the LPAR1 pathway in impaired adult neurogenesis of an Alzheimer's disease mouse model

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ABSTRACT

Background: Alzheimer's disease (AD), marked by a serious and progressive decline in cognitive abilities, is a severely debilitating disease that is becoming an increasing concern in our current healthcare climate. Defects in neurogenesis have been shown to exist in AD and aggravate the neuropathology and cognitive deficits associated with the disease. Study of the underlying mechanisms behind these defects can reveal promising and novel avenues of therapy.

Methods: We performed an *in vivo* characterization of neural stem and progenitor cell (NSPC) defects of the triple transgenic mouse model of AD (3xTG) through immunohistochemistry. Bulk RNA sequencing was subsequently used to determine molecular targets and cellular pathways potentially underlying the identified cellular defects, which were then validated *in vivo*.

Results: Immunohistochemistry characterization revealed defects in the total number of 3xTG NSPCs at both the early and later stages of neurogenesis. However, there was also a decrease in the proportion of later stage 3xTG NSPCs, suggesting the cells are confronted with defects that prevent their effective progression through neurogenesis. Bulk RNA sequencing revealed defects in the LPAR1 pathway, which is involved in pertinent cellular functions. *In vivo* characterization of LPAR1 expression validated the dysregulation of this pathway in 3xTG mice.

Limitations: Expression of upstream and downstream targets have yet to be characterized which is necessary to support our conclusions.

Conclusion: LPAR1 appears to be a promising approach to rescue the cellular defects observed in 3xTG neurogenesis. Further characterization and manipulation of this pathway can reveal a novel therapeutic strategy for AD.

Multi-tensor tractography of suicide ideators versus attempters using a free water diffusion model

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ABSTRACT

Background: The neurobiological factors distinguishing suicide ideators from suicide attempters are understudied. Preliminary investigations have indicated the use of spatially and temporally specific neuroimaging modalities to illustrate circuit-level dysfunction in psychiatric disease, including depression and suicide. Diffusion Tensor Imaging (DTI) provides the opportunity to identify white matter microstructural correlates associated with suicide attempt history.

Methods: DTI data was obtained from N=34 patients with treatment-resistant depression (TRD; n=19 suicide ideators, n=15 suicide attempters). Multi-tensor tractography was performed using a combined 2-tensor Unscented Kalman Filter and free water correction model. Fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) were calculated for the resulting tensor from an atlas of 58 deep white matter and 16 superficial white matter tracts.

Results: Multi-tensor tractography revealed significantly reduced FA in 8 association, 7 projection, 5 superficial and 1 commissural white matter tract; reductions in FA were accompanied by a significant increase in RD and MD in suicide attempters ($p<0.05$).

Limitations: Future investigations are encouraged to include larger samples and a healthy volunteer group for statistical comparison. Use of additional white matter atlases may allow for further exploration of neuronal white matter.

Conclusion: DTI analysis revealed significantly altered diffusion metrics in suicide attempters compared to suicide ideators, suggesting a potential relationship between white matter integrity and suicide in TRD.

Influence of chronic childhood adversity on the relationship between the gut microbiota, diet quality, and affective symptoms in adulthood

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ABSTRACT

Background: Vulnerability to depression (MDD) and anxiety (AD) promoted by childhood adversity has been suggested to be associated with gut microbiota changes that persist to adulthood. Evidence indicates that poor diet quality influences symptom severity. The associations between gut microbial status, poor diet, and severity of anxiety and depressive symptoms are bidirectional, in which a pathology-promoting microbial signature or poor diet could increase symptom severity, and in which depressive and anxiety symptoms could influence microbiota status and dietary choices. We examined if childhood adversity and diet quality influenced the relationships between gut microbiota and symptoms severity in the context of depression and anxiety.

Methods: Individuals with a diagnosis of MDD and AD, and healthy controls completed questionnaires assessing severity of depressive and anxiety symptoms, childhood adversity, and dietary patterns. Participants provided a stool sample to determine gut microbiota composition using species targeted PCR.

Results: A poor quality diet was related to more severe depressive symptoms only in individuals with moderate-to-severe childhood trauma. Importantly, high levels physical neglect, the most common form of childhood adversity, was driving associations between diet quality with depressive and anxiety severity. Our clinical cohort showed decreased amounts of the anti-inflammatory bacterium Faecalibacterium prausnitzii, but the association with increased depressive symptoms and loss of this bacterium was moderated by high scores of physical neglect.

Limitations: Full 16S rRNA microbiota sequencing has not yet been completed to confirm relationships with bacterial abundances and symptom severity.

Conclusion: These data suggest that experiencing chronic physical neglect early in life might trigger developmental changes in the gut microbiota that may impact mood in adulthood, and that diet quality may influence symptom severity.


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