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Résumés de présentation par affiche

Poster Abstracts

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Titre :
Oxytocin: A neurohormone link to the epigenetics of early life adversity and suicide

Résumé :
Oxytocin is a mammalian neurohypophysial hormone which acts primarily as a neuromodulator in the CNS. The early development of secure attachments, relationship quality, and the ability to regulate and manage emotions are all instances of psychological resources influenced by the oxytocinergic system. Previous studies have shown that early life adversity might act to disturb the oxytocinergic system during critical developmental periods. A body of literature also supports alterations in the oxytocinergic system as a predisposing factor for suicidal behaviour. Our research looks into the expression of genes regulating the oxytocinergic system in the prefrontal cortex of suicide completers who experienced early life adversity, non-abused suicide completers, and healthy controls. Our gene expression data from the prefrontal cortex indicates an effect of abuse on genes involved in oxytocin metabolism and function. Specifically, suicide completers with a history of early life adversity show a significant upregulation of LNPEP (an enzyme responsible for the breakdown of neuropeptides in the brain), OXTR (oxytocin receptor), and AVPR1B (arginine vasopressin receptor 1 B), when compared to non-abused suicide completers and healthy controls. Recently, several studies have identified epigenetic mechanisms influencing the oxytocinergic system, with an emphasis on methylation. We are therefore investigating methylation via targeted bisulfite sequencing of CpG rich regions within LNPEP, OXTR, & AVPR1B. The practical goals of this research are two fold, first they seek to strengthen the literature on child-abuse and CNS changes in psychiatric disorders, and secondly, to determine whether epigenetic modification of the oxytocinergic system represents a CNS biomarker of early life adversity and later suicidal behaviour.

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Superviseurs :
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Titre :
Attempted suicide among persons who inject drugs in relation to types of substance use: Results from a seven-year longitudinal study in Montréal

Résumé :
Background: Persons who inject drugs (PWID) are known to be at risk of engaging in suicidal behaviours. It is less clear, however, whether use of different substances is associated with varying degrees of risk. We sought to estimate the associations between types of substance use and subsequent attempted suicide in a prospective cohort of active PWID in Montréal. Methods: Between 2004 and 2011, participants completed an interviewer-administered questionnaire eliciting information on socio-demographic factors, substance use patterns and mental health markers. Time-lagged generalized estimating equation analyses were used to model the relationship between self-reported past-month use of cocaine, amphetamine, opioids, sedative-hypnotics, cannabis [regular (≥4 days); occasional (1-3 days); none], alcohol [heavy (≥60 drinks); moderate (1-59 drinks); none], and past six-month suicide attempt. Results: At baseline, of 797 participants (median age: 38.7, 82.0% male), 6.0% reported a recent suicide attempt. Among 4,460 observations collected during follow-up, a further 115 attempts were reported by 8.8% of participants. In multivariate analyses, a positive association was found between regular use of sedative-hypnotics [Adjusted odds ratio (AOR): 1.89; 95% Confidence interval (CI): 1.21–2.95)], occasional use of cannabis (AOR: 1.84; 95%CI: 1.09-3.13), heavy alcohol consumption (AOR: 2.05; 95%CI: 1.12-3.75], and subsequent attempted suicide. No statistically significant association was found for the remaining substances. Conclusion: Use of sedative-hypnotics, cannabis and alcohol, but not cocaine, amphetamine or opioids, appears to be associated with increased likelihood of

later attempted suicide among PWID. Use of soft drugs and alcohol may deserve particular consideration from suicide prevention efforts in this population.

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Titre :
Vulnerability and the ethics of suicide research

Résumé :
The concept of vulnerability is frequently alluded to in suicide research and captures a concern for the protection of patients who face significant psycho-social challenges. These concerns also apply to the relatives of people who have died by or attempted suicide. The Nuremberg Report, adopted in 1947, captured the emerging notion that research subjects are vulnerable and in need of protection. The concept of vulnerability has since been broadly adopted in research ethics and refers to a heightened vulnerability beyond that experienced by all subjects. While it is agreed that vulnerable subjects require special protections, there is a lack of agreement in research ethics about what characteristics render subjects vulnerable and who is owed special protections under the rubric of vulnerability. In the context of suicide research, vagueness and imprecision about vulnerability is particularly problematic. Suicidal populations are often considered to be vulnerable, and their recruitment for research sensitive from an ethics standpoint. The categorical assumption of vulnerability in suicidal populations may serve to harm (e.g., exclusion from research), rather than protect and respect, these individuals and their particular needs. This assumption has likely contributed to the dearth of evidence-based strategies for addressing suicide. We undertook a systematic review of vulnerability in Canadian and international research ethics guidance to assess and examine its conceptual foundations. In this poster, we present the results of this work and wish to discuss with conference attendees how ethical guidance surrounding vulnerability may impact the involvement of suicidal populations in research.

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Titre :
Resting high frequency heart rate variability moderates the relationship between brooding rumination and stress-related increases in depressive symptoms in female students

Résumé :
Several factors influence depression risk. Brooding rumination (B-RUM) predicts the onset and maintenance of depressive disorders. High frequency heart-rate variability (HF-HRV), the fluctuation in time between two consecutive heartbeats, is an index of vagal-mediated parasympathetic tone, and is implicated in the development of mood disorders. This investigation hypothesized that resting HF-HRV moderates the prospective relationship between B-RUM and stress-related changes in depression. The academic stress model is an ecologically valid and standardized model that uses a longitudinal design that encompasses periods of lower and higher stress to examine vulnerability. Method: Baseline measures were collected in the first 4 weeks of the semester (low stress period) using the Depression, Anxiety, and Stress Scale (DASS-21) and the Response Styles Questionnaire (RSQ-B). Resting HF-HRV was measured in the final 2 weeks of the semester (high stress period) and the DASS-21 was repeated. Results: 80 female participants were retained for analysis (age M=20.96, SD=2.10). There was a significant increase in depression over the semester (M=1.01, SD=.401, t=2.255, p=0.013). After controlling for baseline depression, the main effect of resting HF-HRV was not significant (p>0.05), while B-RUM (β=0.34, p=0.01) was related to changes in depression. The interaction term between B-RUM and HF-HRV explained a significant increase in the variance (R2change=0.082, p=0.01). Baseline B-RUM was predictive of change in depression in individuals with low, but not high, HF-HRV. Conclusion: The results confirm that resting HF-HRV moderates the prospective relationship between B-RUM and stress-reactive depression. The interaction between psychological and physiological vulnerability best identified stress-related increases in depression.

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Superviseur :
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Titre :
Improved RRBS Methods with McrBC and MspJI

Résumé :
Reduced representation bisulfite sequencing (RRBS) is widely used in genome wide DNA methylation studies. MspI is used for digestion of genomic DNA in RRBS. This method is very effective in its coverage of a certain percentage of CpG islands (CGIs) on the human genome. However, its coverage outside those CGIs regions is poor. Recent studies have showed that non-CpG methylation as well as CpG methylation outside of CGIs play important roles in DNA methylation studies and those genome regions normally not detected by MspI based RRBS (MspI-RRBS) methods.
Here, we report several methods aimed at improving RRBS for its extended coverage on CpG and non-CpG methylation regions outside MspI-RRBS coverage. These RRBS methods incorporate the use of two methylation dependent restriction enzymes: McrBC and MspJI, which have been used previously in DNA methylation studies. While some methods we reported here preserved original MspI-RRBS coverage profiles and contain additional regions with enriched CpG and non-CpG methylation; other methods explored combined dual restriction enzyme digestion approaches to create RRBS with new profiles. We showed that RRBS libraries constructed by these methods result in more enriched coverage of genome wide DNA methylation information while the sequencing cost increase is minimal.

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Superviseur :
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Titre :
Redox Regulation of SAT1 Activity

Résumé :
Oxidative stress refers to elevated levels of intracellular reactive oxygen species (ROS) such as superoxide anion (O2-), hydrogen peroxide (H2O2), and hydroxyl radicals (OH-). ROS generated in the cell are normally cleared by glutathione peroxidase, thioredoxin, and other oxidation-reduction (Redox) related molecules. Redox signalling refers to free radicals, ROS, and other electronically-activated species that act as messengers in cells. There is a growing list of redox-active enzymes using intrinsic redox changes to control their biological activity.
Here, we found that spermidine/spermine-N1-acetyltransferase 1 (SAT1) contains redox sensitive reactive cysteine residues. Importantly, we discovered that the extremely inducible SAT1 enzyme activity under oxidative stress is governed by a redox regulated SAT1 protein conformation change mechanism. The oxidative stress induced SAT1 activity requires its redox sensitive reactive cysteine residues. We also showed that polyamine analogues induced SAT1 activation via a different mechanism. We identified a potential redox motif or redox switch on SAT1. All drugs targeting SAT1 are polyamine analogues or antagonist-based and are known for their cytotoxic side-effects. Our SAT1 redox regulatory mechanism opened a new avenue for designing high efficacy drugs that do not target SAT1 polyamine substrate binding sites but target SAT1 redox motif instead.

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Titre :
Investigating the Molecular basis of Lesch-Nyhan Disease, a Genetic Cause of Self Harm

Résumé :
Lesch-Nyhan disease (LND) is a rare genetic disorder caused by the disruption of the metabolic gene Hypoxanthine Guanine Phosphoribosyltransferase (HRPT1). LND has a variety of physiological and neurological symptoms including gout, dystonia, intellectual disability, and chronic self-injury. While the genetics of LND are clearly defined, how a disruption of this metabolic gene leads to these complex neurological symptoms remains unknown. To better understand the molecular basis of LND, we have developed novel models of the disorder using neurons differentiated from patient derived induced pluripotent stem cells and HPRT deficient human neural progenitors. Global transcription profiling using RNA sequencing revealed large decreases in many genes involved in adenosine signaling, one of the major neuromodulatory systems in the brain, which are more pronounced in cells from patients expressing self harm than those which do not. This study is the first to use high-throughput transcriptional analysis in a human neuronal model of LND, and the first to associate changes in the adenosine signaling system with disease symptoms.

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Superviseur :
Dr Linda Booij

Titre :
Méthylation périphérique du transporteur de la sérotonine chez l'humain: étude de validation sur l'utilisation des échantillons biologiques non-invasifs, et la pertinence pour la fonction cérébrale

Résumé :
La sérotonine (5-HT) joue un rôle majeur dans de nombreuses psychopathologies, surtout en présence de l'adversité précoce. La méthylation de l'ADN peut être un mécanisme expliquant l'intéraction Gènes-Environnement. Mais, il est impossible de mesurer la méthylation directement dans les cerveau humain vivant. Il faut recourir aux tissus périphériques facilement accessible, tel le sang. Voici les premiers résultats sur la pertinence de la méthylation periphérique dans les gènes 5-HT pour le circuit fronto-limbique. On s'intéresse au gène du transporteur de 5-HT (SLC6A4) vu son rôle important dans la neurotransmission de 5-HT, le développement cérébral et mental.
Méthode: 35 adultes en santé, recrutés d'une cohorte longitudinale suivie depuis l'enfance, ont passé une IRMf, incluant une tâche de traitement émotionnel et des mesures morphométriques. La méthylation a été évaluée avec des procédés de pyroséquençage optimisées et validées (Wang et al., 2012).
Résultats: La méthylation de SLC6A4, dans les sites CpG corrélés avec la synthèse cérébrale de 5-HT (Wang et al., 2012), est associée avec l'adversité précoce, une reduction de l'activation précentrale face aux stimuli négatifs et la diminution du volume fronto-limbique. Présentement, on évalue la stabilité de la méthylation de SLC6A4 dans le temps, les tissus et les types cellulaires (e.g., cellules T/B; la salive; les cellules buccales), et le lien avec la réactivité au stress quotidien.
Conclusion: Nos premiers résultats suggèrent que la méthylation de SLC6A4 peut être un potentiel marqueur de la neurotransmission de 5-HT et du risque de la psychopathologie. L'utilisation d'un tel marqueur periphérique peut aider à identifier les individus à risque de troubles reliés à la 5-HT et concevoir des interventions préventives.

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Titre :
LncRNA CB984582: A potential regulator of miR-1202 and predictor of antidepressant responses

Résumé :
Background: MicroRNAs (miRNA) are small noncoding RNA molecules that regulate the expression of target genes. Our group recently discovered that the miRNA miR-1202 is significantly downregulated in the brains of depressed individuals who committed suicide. Moreover, miR-1202 levels in the blood were found to be predictive of clinical response to antidepressant treatment. Methods: We examined the genomic region surrounding the miR-1202 locus for expressed sequences, and identified a long non-coding RNA (lncRNA), CB984582, which overlaps with miR-1202 and possesses several predicted binding sites for this miRNA. To investigate the relationship between miR-1202 and CB984582, we quantified their expression in several brain regions from suicide completers and healthy controls using quantitative real-time PCR (qRT-PCR). To determine their relationship with antidepressant treatment, we measured expression in vitro following a two-week treatment of neural progenitor cells (NPC) with citalopram or imipramine, as well as in a depressed human cohort treated with citalopram or desvenlafaxine for eight-weeks. Results: CB984582 displayed tissue-specific patterns of expression, supporting a functional role for this lncRNA. In the brain, there was a negative correlation between the levels of CB984582 and miR-1202, where CB984582 displayed significantly increased expression in the brains of depressed individuals. In vitro, CB984582 expression was significantly decreased following chronic antidepressant treatment. Finally, while CB984582 expression in the blood did not change following eight weeks of antidepressant treatment, decreased expression of this lncRNA was a significant predictor of clinical response following treatment. Conclusions: Similar to miR-1202, the expression of CB984582 is dysregulated in the brains of depressed individuals and is responsive to antidepressant treatment in neuronal cells. However, the dissimilar expression patterns of these two RNA across the body, and the lack of change in CB984582 expression following an eight week antidepressant trial, suggest that factors regulating the expression and function of both molecules are important in the pathology and treatment of depression. Ultimately, these results suggest an interaction between miR-1202 and CB984582, and highlight CB984582 as a novel biomarker for treatment response.

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Titre :
Développer, implanter et évaluer une intervention infirmière permettant de soutenir la croissance post-traumatique des endeuillés par suicide

Résumé :
Au Canada, il y a eu 3 728 suicides en 2011. Chaque suicide touche plusieurs personnes auprès desquelles il faut intervenir car à risque de suicide, de stress post-traumatique et de dépression. Toutefois, certains démontrent une croissance post-traumatique (CPT) suite à cet événement (plus grande appréciation de la vie, relations interpersonnelles plus significatives, croyance plus forte en ses forces, vie spirituelle plus riche et changement des priorités face à la vie). Des interventions existent visant la CPT d'autres populations mais aucune pour les endeuillés par suicide (ES). Le but est de développer, implanter et évaluer une intervention permettant la CPT des ES. Nous croyons être en mesure de faire les phases I et II du cadre d'élaboration et d'évaluation des interventions complexes proposé par le MRC. La phase I clarifiera l'intervention et évaluera les préférences en termes de traitement. Des entrevues semi-structurées auprès d'ES (n=20) permettront d'identifier besoins et préférences. Des entrevues auprès d'intervenants (n=10) permettront de connaître ce qui existe et ce qui devrait être fait. Les résultats seront mis en commun avec une recension des écrits afin de développer contenu et modalités d'intervention. La phase II testera faisabilité et acceptabilité de la recherche et de l'intervention. Une étude pilote sera entreprise où les participants (n=30) seront randomisés. Ceci permettra de répondre à des questions concernant le recrutement et l'acceptabilité de la randomisation et de l'intervention. Si le tout s'avère faisable et acceptable, une étude randomisée à devis mixte sera menée par la suite.

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Titre :
Valproic acid in unipolar treatment resistant depression (TRD): A Pilot Study

Résumé :
Objective. About 50% of patients with unipolar depression suffer from treatment-resistant depression (TRD). Animal studies have suggested potential antidepressant properties of valproate (VPA) possibly due to its implication in epigenetic programming. Methods. Fourteen TRD patients (7 males and 7 females; age 19-59) received VPA (375-1000mg/d) in addition to their treatment regimen after previously failing to respond to two or more antidepressant trials and/or different combinations. Clinical response to VPA was investigated prior the treatment (T-0) and after 1 (T-1), 4 (T-4) and 7 (T-7) months of therapy using the Montgomery–Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI). Results: Compared to T-0, VPA significantly decreased MADRS score at T-1 ($P<0.001$), T-4 ($P<0.001$), and T-7 ($P<0.001$) (partial $\eta 2=0.86$). Importantly, MADRS score at T-7 (13.6±1.6, mean±S.E.M.) was closer to the reported value of remission (MADRS<10), and none of the patients relapsed during the observational period. Compared to T-0, VPA also decreased CGI-Severity of illness score at T-1 ($P=0.03$), T-4 ($P<0.001$), and T-7 ($P<0.001$) (partial $\eta 2=0.74$). Conclusions. Antidepressant augmentation with VPA provided substantial clinical improvement and maintenance over a relatively long-term period in a subgroup of patients with severe TRD. VPA thus deserves further exploration in large double-blind clinical trials.

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Titre :
Reduced corpus callosum volume is a specific trait marker of bipolarity, not suicidality

Résumé :
Background: Several studies suggest that reduced corpus callosum volume is associated with history of suicidal gestures, while other studies showed an association with bipolar disorder. It remains unclear if these associations are independent from each other. Here, we investigated corpus callosum volumes in a large sample of patients with mood disorders, with or without a personal suicidal history. Method: A total of 209 male and female euthymic participants were recruited, including 72 patients with major depressive disorder, 64 with bipolar disorder and 73 healthy controls. Among patients, 61 had a history of suicide attempt and 75 had none. Structural scans were acquired with 1.5T magnetic resonance imaging. Surface-based morphometry (Freesurfer) analysis was used to compute the volumes of 5 antero-posterior segments of the corpus callosum. Analyses were covaried for intracranial volume and sample, and controlled for age, education, impulsivity, number of mood episodes, past alcohol/substance use and medication status. Results: There was a significant reduction in the volume of mid-anterior ($F=5.1$, $p=0.007$), central ($F=6.6$, $p=0.002$) and mid-posterior ($F=5.0$, $p=0.008$) corpus callosum in bipolar patients compared to patients with depressive disorders and healthy controls, with medium effect sizes between patient groups (Cohen's d -0.5). These effects were independent from suicidality. In contrast, suicide attempters did not differ from non-attempters. Conclusion: Our study suggests that reduced volume of the central part of corpus callosum may be a trait marker of bipolar disorder among non-elderly adults with mood disorders, independently of suicidality. In contrast, corpus callosum structure may not directly affect the suicidal risk.

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Titre :
Characterizing a genomic map of 5-hydroxymethylcytosine in human brain at single base resolution through next-generation sequencing

Résumé :
The recent discovery that methylated cytosines are converted to 5-hydroxymethylated cytosines (5hmC) by the family of ten-eleven translocation enzymes has sparked significant interest on the genomic location, the abundance in different tissues, the putative functions, and the stability of this epigenetic mark. 5hmC plays a key role in the brain, where it is particularly abundant and dynamic during development. Using AbaSI-Seq, we comprehensively characterize 5hmC in the prefrontal cortices of 24 subjects. We show that, although there is inter-individual variability in 5hmC content among unrelated individuals, approximately 8% of all CpGs on autosomal chromosomes contain 5hmC, while sex chromosomes contain far less. Our data also provide evidence suggesting that 5hmC has transcriptional regulatory properties, as the density of 5hmC was highest in enhancer regions and within exons. Furthermore, we link increased 5hmC density to histone modification binding sites, to the gene bodies of actively transcribed genes, and to exon-intron boundaries. Finally, we provide several genomic regions of interest that contain gender-specific 5hmC. Collectively, these results present an important reference for the growing number of studies that are interested in the investigation of the role of 5hmC in brain and mental disorders. Understanding the differences in the genomic locations of hmC will shed light on the growing debate as to whether hmC represents a novel epigenetic mark or whether it is simply an intermediate product of active DNA demethylation.

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Titre :
Perinatal Depression and its Effects on the Epigenome

Résumé :
Increasing evidence suggests that exposure to stress during critical periods of development (such as in infancy) may increase one's susceptibility to disease risk, including depression. The present research aims to address a potential biological mechanism that interacts with the environment to induce changes in gene expression which may then account for some of the variability surrounding vulnerability to disease and psychopathology. This mechanism is epigenetics; epigenetic profiles may be established early in life when the infant is developing according to signals it is receiving from the maternal environment. Given that perinatal depression affects one in eight pregnant women and depression is believed to influence epigenetic programming, much in the same way that exposure to stress can induce epigenetic changes, we are investigating how depression experienced during pregnancy may be associated with changes to the epigenome in both the mother and child. Specifically, we are examining certain candidate genes associated with maternal behavior, the stress response and sociability; the genes in question are those that regulate the neuropeptides oxytocin (OXT) and vasopressin (AVP). Using a longitudinal design, we followed a cohort of recently pregnant women throughout their pregnancy. We hypothesize that perinatal depression (as measured using the Edinburgh Postnatal Depression Scale) will be associated with increased methylation (hypermethylation) of OXT-related genes and decreased methylation (hypomethylation) of AVP-related genes in both mother and child. The results from this study can facilitate a better understanding of how the maternal environment can exert its influence inter-generationally via epigenetic mechanisms.

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Superviseur :
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Titre :
Epigenetic dysregulation of myelin by childhood maltreatment in the anterior cingulate cortex

Résumé :
Childhood maltreatment (CM) is a global problem of significant proportion, and represents a major risk factor for the emergence of psychopathology into adulthood. Accordingly, our main hypothesis is that CM contributes through epigenetic and gene expression changes to the risk of depression and suicide.

Using brain tissue from the anterior cingulate cortex (ACC), we compared suicide completers with a history of CM with psychiatrically normal individuals with no history of CM. We characterized genome-wide DNA methylation using RRBS, and uncovered a hundred genomic regions where differential DNA methylation is detected as a function of CM. The top 3 most significant regions are located on genes related to oligodendrocytes, the cells responsible for myelination in the central nervous system. To assess the impact of DNA methylation changes, we performed RNA-Seq experiments, and found that a large collection of genes expressed by oligodendrocytes are downregulated following CM. These downregulations were absent in suicide completers with no history of CM, and therefore specifically associate with CM.

To understand how these changes affect myelination, we are currently characterizing the white matter adjacent to the ACC. Myelination index of axons, and the organization of myelin, are investigated using CARS. Myelin proteins are quantified by Western Blot, and oligodendroglial precursors and mature cells are quantified by stereology.

Overall, this project integrates multiple approaches to identify novel pathways epigenetically induced by CM. In particular, our findings point toward a major impairment of myelin following CM, which may represent a pathophysiological mechanism with lifelong consequences.

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Superviseur :
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Titre :
Functional analysis of MAOA gene promoter hypermethylation observed in an offender population with antisocial personality disorder

Résumé :
Persons suffering from antisocial personality disorder (ASPD) present aggressive and impulsive behaviours, have increased probabilities of committing criminal acts and of being incarcerated. Whereas deregulation of the serotoninergic system has been associated with impulsive aggression and antisocial criminality, polymorphisms of the MAOA gene (gene coding an enzyme which contributes to regulate the serotoninergic system) have largely been investigated in context of aggressive and impulsive behaviours. Recent studies have also shown that behaviours could be mediated at a molecular level by epigenetic modifications regulating gene activities. In the present study, we aim to understand the epigenetic mechanisms that could lead to a deregulation the MAOA expression. We have recruited 83 incarcerated offenders with ASPD and 73 healthy controls. We have explored methylation levels of MAOA promoter in blood samples from both groups. The functional effect of methylation on gene expression has been assessed in vitro. Finally, 5-HT levels were quantified in a subset of the case group. We found a hypermethylation of MAOA promoter in the ASPD group compared to control group. Furthermore, in vitro methylation of the MAOA promoter induces a reduction of gene expression. Those data are in agreement with previous studies that had suggested MAOA gene and serotoninergic system in impulsive and aggressive behaviours. Our results also suggest that epigenetic modifications are in part responsible for MAOA dysregulation in a context of ASPD.

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Superviseur :
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Titre :
Epigenetic markers associated with immune activation and mood disorder onset in high-risk adolescents

Résumé :
Bipolar disorder (BD) is a persistent psychiatric illness with typical onset during adolescence. Despite a high estimated heritability, which indicates a significant genetic contribution, molecular genetics and genome-wide association studies have failed to explain all of the variability associated with the illness risk. Epigenetic mechanisms provide a powerful tool to understand the gene by environment interactions seen in complex traits like BD. In both animal and human studies, stable DNA methylation changes associated with early-life experiences have been shown to influence individual differences in neural development and functions relevant to cognition and emotion. Immune activation is also recognized as an independent risk factor predicting mood disorder onset, and is highly interconnected with other physiological systems implicated in BD, including disturbances in neuroendocrine and neurotrophic systems. Our study aims to identify DNA methylation changes in candidate genes associated with immune activation and the onset of mood disorders in a cohort of well characterized, high-risk adolescents. This research is divided into two studies (cross-sectional and longitudinal), and we will assess the methylation status of cytosines in CpG rich regulatory regions of immune-related genes (IL-1b, IL-6, TNF, BDNF and NR3C1) using targeted bisulfite sequencing. This work represents the first cross-sectional and longitudinal studies of peripheral epigenetic markers associated with immune activation and mood disorder onset in the offspring of bipolar parents. Deciphering the relationship between immune activation and the onset of mood disorders in genetically vulnerable youth will provide a clearer understanding of the etiology of BD and provide potential avenues for treatment.

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Superviseur :
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Titre :
Intervening with clients experiencing mental illness and substance use: Patient perceptions of helpful care

Résumé :
Background: It is estimated that 30- 50% of patients with a mental illness also have a substance use disorder. Referred to as having concurrent disorders (CD), this is a suicide-vulnerable group with high levels of unmet needs and difficulty accessing appropriate services. Staff nurses are well-positioned to help persons with CD during psychiatric hospitalization. Further knowledge of the interventions nurses offer as well as the impact nursing has on client health and recovery is required.
Study Purpose: To identify and describe actual or potential nursing interventions, attitudes, and behaviours that are perceived as helpful by clients with concurrent disorders during hospitalization on psychiatric units.
Methods: A qualitative-descriptive research design was used. Individual semi-structured interviews were conducted with twelve participants; all inpatients with CD receiving treatment on psychiatric units.
Results: Helpful nursing was found to occur within four main categories of care: 1) promoting health in daily living; 2) managing substance use in tandem with mental illness; 3) providing a healing environment; and 4) building a therapeutic relationship.
Conclusion: The findings reveal that relational interventions are a powerful component of helpful care with important implications for client health and recovery. Recommendations include tailoring and timing nursing interventions to fit client needs and readiness, and introducing evidence-based responses to substance use as a central activity in the practice of mental health nurses.

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Superviseur :
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Titre :
Deux constructions du phénomène suicidaire. Journalistes et coroners québécois des années 1950

Résumé :
Cette affiche présente deux différents compte-rendus du même évènement, soit la noyade d'un jeune homme dans les eaux du canal Lachine de Montréal, au printemps 1958. En comparant les informations recueillies dans les Archives du Coroner du Québec à celles d'un article publié à l'époque dans un journal hebdomadaire à haut tirage, cette affiche cherche à prendre la mesure de ces deux constructions (juridique et journalistique) de l'évènement suicidaire, tout en examinant la complémentarité de ces différentes sources du point de vue de l'histoire sociale du suicide au Québec.

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Superviseur :
Michel Perreault

Titre :
Evaluation of the STAR Depression and Anxiety program: Patient's Perspectives on Treatment Outcome

Résumé :
The evaluation of Mental Health services places important attention to the assessment of patient's perspectives which allows for a better understanding of treatment outcome from the perspective of the patient. Psychogeriatric developments for the treatment of depression and anxiety are vital as these report the highest prevalence rates. Using patient's perspectives on treatment outcome, this study assessed an ongoing psycho-educational program offered for the treatment of geriatric depression and anxiety. Pre-post measures of symptomatic change (GDS) and recovery were collected in a sample of 34 older adults (age = 71.32±6.456 years). Post -testing data included patient's perceived improvement (PI) rated by clinicians and patients, and clinician impressions on depression (CS-GDS). Data studied the relationship between PI, symptomatic change and recovery. The relationship between patient's PI, the GDS and the CS-GDS, were also examined. Results indicated significant correlations betwefsen pre-post changes of the GDS and patients' PI total score (r =-0.374, N=31, p=0.038) and emotional health subscale (r =-0.412, N=31, p=0.021), added to significant correlations between PI and post-ratings on GDS (r = -0.739, N=33, p=0.000) and CS-GDS (r =-0.475, N=32, p=0.006). Patient's PI and post-measures of recovery, also noted significant correlations (r =0.618, N=34, p=0.000). Results imply that a psycho-educational approach may be an effective tool for the treatment of geriatric depression but not for anxiety. This study served to gain better insight on patient's perspectives on services and to raise the attention on clinician impressions of their patient's. Future studies may further explore the relationship between PI and recovery.

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Superviseur :
Naguib Mechawar

Titre :
Evidence for Increased Microglial Priming and Macrophage Recruitment in the Dorsal Anterior Cingulate White Matter of Depressed Suicides

Résumé :
Background: Despite all the evidence supporting the neuroinflammatory theory of depression, there is currently limited information regarding the state cerebral macrophages in individuals suffering from major depression. The aim of the present study was to examine the morphology and distribution of microglial cells and other cerebral macrophages in the dorsal anterior cingulate cortex (dACC) white matter of depressed suicides and matched nonpsychiatric controls. This region is of particular interest since we previously described the presence of hypertrophic astrocytes in depressed suicides and imaging studies have confirmed its implication in mood disorders.
Methods: Using immunostained sections with the macrophage-specific marker ionized calcium binding adaptor molecule 1 (IBA1), distributions of microglial phenotypes were assessed using stereology and cell morphometry. Blood vessels were characterized as being associated with either a high or a low density of macrophages in IBA1 and CD45-IR sections. The mRNA expression levels were quantified using real time-PCR.
Results: Total densities of IBA1-immunireactive (IR) microglia were statistically similar between groups. However, the relative proportions of primed microglia were significantly increased in depressed suicides. The proportion of blood vessels surrounded by a high density of IBA1-IR macrophages was significantly higher in depressed suicides than in controls (87% vs 42%, respectively). Consistent with these findings, the mRNA expression levels of both IBA1, MCP-1, a chemokine involved in the recruitment of circulating monocytes, and Zona Occludens-1 were significantly upregulated in depressed suicides. Furthermore, the mRNA expression levels of CD45, a marker enriched in perivascular macrophages, showed a significant increased in samples from depressed suicides but the proportion of blood vessels surrounded by a high density of CD45-IR cells was similar between groups.
Conclusion: Our results show evidence of microglial priming and a possible recruitment of macrophages in the dACC white matter of depressed suicides. However, we cannot exclude the possibility of other types of macrophages (including microglia) accounting for the observed increase in macrophages associated with blood vessels. Altogether, these findings suggest that the previously reported depression- and suicide-related increases in circulating pro-inflammatory cytokines may be associated with low-grade cerebral neuroinflammation involving the recruitment of circulating monocytes.

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Superviseur :
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Titre :
DNA methylation in the dorsal and ventral striatum of patients with chronic cocaine dependence.

Résumé :
Background: Multiple genetic and environmental factors interact to determine the risk and trajectory of cocaine dependence, and the expression of addiction-associated genes is likely influenced by environmental factors that leave persistent epigenetic marks on an individual's genome. Recently, several studies have identified epigenetic mechanisms that are associated with long term transcriptional and synaptic changes and with the acquisition of compulsive drug seeking in animal models, but little is known about the role of epigenetics in human cocaine dependence. Of particular interest is DNA methylation as it represents a mitotically stable mark that has been shown to be altered by environmental experience. This study aims to identify genome-wide changes in DNA methylation in two cocaine-relevant regions of the human brain, the dorsal and ventral striatum. Methods: We used Reduced Representation Bisulfite Sequencing (RRBS) on nucleus accumbens and caudate tissue from 25 dependent cocaine users and 25 drug-free and age-matched controls. RRBS is a high throughput sequencing based approach, which enriches for CpG dinucleotides and generates methylation data at base-pair resolution. We will also compare these data to transcriptome-wide RNA sequencing data and deep bisulfite sequencing data in neuronal and non-neuronal nuclei, separated using fluorescently activated cell sorting (FACS). Results: All RRBS libraries contained more than 4 million reads at 10X coverage and over 65% of reads in each library were uniquely aligned to the human genome. After filtering each library for quality and correcting for covariates, we've identified multiple differentially methylated CpG clusters between groups, in both the ventral and dorsal striatum. In addition, we've uncovered regions of hyper- and hypomethylation that are associated with transcriptional dysregulation, in cases versus controls, for follow-up in sorted nuclear fractions.

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Superviseur :
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Titre :
Impact of early life adversity on DNA methylation of the oxytocin receptor gene (OXTR)

Résumé :
Early life adversity is a major risk factor for development of poor mental and physical health later on in life (Grimm et al., 2014). Recent models propose DNA methylation as an underlying molecular mechanism responsible to dynamically translate and imprint these negative environmental experiences in corresponding biological pathways (Szyf & Bick, 2013). This study focuses on the oxytocin receptor gene, OXTR, given the role of the oxytocinergic system in modulation of social behavior and its implications with regards to anxiety and depression. The goal of this study is to examine the effect of early life adversity on CpG methylation frequency in distinct regions of the OXTR, and whether the changes mediate the measured childhood behavior trajectories. We compared, in a unique 27-year longitudinal cohort, adults with high or low early life adversity, their oxytocin receptor gene (OXTR) DNA methylation frequency and teacher and parental rated trajectories of anxiousness and intrusiveness (n=46). The main findings suggest that in females, DNA methylation within Promoter, Intron and Enhancer regions of OXTR is correlated early life adversity (Promoter CpG 3 and 7, $p<0.01$, $p<0.05$, Intron 1 CpG 4 and 5, $p<0.05$, $p<0.01$, Enhancer 1 CpG 2, $p<0.05$). Changes at the reported sites also correlate anxiety and depression trajectory but not aggression. Furthermore, OXTR DNA methylation at Promoter CpG 7 mediated the relationship between early life adversity and subsequent behavioural trajectories ($R2=0.35$, $p<0.05$). This study offers novel regions of interest within OXTR for further investigations; validates past reported findings, and highlights the role of DNA methylation in OXTR in early life adversity and later behavioural measures.

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Superviseur :
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Titre :
Childhood Maltreatment Associates with Long Non-Coding RNAs Differentially Expressed in the Rostral Anterior Cingulate Cortex

Résumé :
Background: Childhood maltreatment (CM) has been strongly associated with the dysregulation of stress response systems. Changes in these systems incurred during early life may lead to lifetime negative consequences contributing to suicide etiology. Long non-coding RNAs (lncRNAs) have been implicated in brain development as well is in various neurodegenerative diseases. Whether lncRNAs play a significant role in translating the effects of CM into biological programs of gene regulation contributing to suicide risk are investigated in this study. Methods: We performed high throughput RNA-sequencing (RNA-seq) in the rostral anterior cingulate cortex (rACC), a region implicated in emotional regulation, of 26 suicides with a history of CM and 24 matched controls without CM. Reverse transcription quantitative polymerase chain reaction (RT-qPCR) was used to validate the expression of the differentially expressed lncRNAs in the original two groups as well as in a third group of 25 suicides without a history of CM. Results: Six differentially expressed lncRNAs were identified from RNA-seq. Validation using RT-qPCR showed there was a significant decrease in the expression of the lncRNA RP11-453F18_B.1 in suicides with CM compared to both controls and a suicides without CM. Additionally, there was a significant increase in the expression of the lncRNA RP11-273G15.2 in suicides with CM compared to the other two groups. Furthermore, the expression of RP11-273G15.2 was significantly correlated with several nearby genes; 4 were lymphocyte antigen 6 genes and 2 were genes encoding zinc finger proteins. Conclusions: Exposure to CM may increase the expression of the RP11-273G15.2 amd RP11-453F18_B.1 lncRNAs in the rACC of suicides. These lncRNAs may be implicated in important cellular processes that contribute to suicide etiology.