ABSTRACTS

Opening keynote I

KN-01 | Cracked not broken: The Kevin Hines story
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Kevin shares his story of hope and celebration of life. Kevin Hines is a mental health advocate, global speaker, best-selling author, documentary filmmaker and entrepreneur who reaches audiences all over the world with his story of an unlikely survival and his strong will to live. Two years after he was diagnosed with bipolar disorder (at 19 years of age), he attempted to take his own life by jumping from the Golden Gate Bridge. He is one of only thirty-four (less than 1%) to survive the fall and he is the only Golden Gate Bridge jump survivor who is actively spreading the message of living mentally healthy around the globe.

Keynote II

KN-02 | Deconstructing the neurobiology of bipolar disorders as a bridge to novel therapeutics
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Growing evidence from both animal and human clinical studies supports the hypothesis that the underlying pathophysiology of depressive and bipolar disorders implicate dysfunction across a wide array of systems, including the immune system as well as the monoaminergic and glutamatergic pathways. More specifically, depression is a multidimensional brain and body disease characterized by disturbances in mood, reward mechanisms, cognitive biases, circadian rhythms, and activity levels. In addition, there are alterations in cytokines, adipokines, bone markers, brain circuit function, and homeostatic regulation mechanisms. Because depression is a heterogenous condition, it is possible that not all the components or dimensions of the “depression syndrome” might result from the same pathophysiology. Because traditional behavioral ratings of depression reflect the variety of symptoms, effects localized to just some aspects of the disorder may not be detected. The focus on diagnostic entities, rather than the component constructs, has likely limited attempts to understand the biology of mental illness. A more dimensional approach to the study of the pathophysiology of our disorders, is a potential solution to this issue. In an exploratory factor analysis of a variety of depression ratings collected in patients with either major depressive disorder or bipolar depression, we found that the best solution comprised eight unidimensional factors: Depressed Mood, Tension, Negative Cognition, Impaired Sleep, Suicidal Thoughts, Reduced Appetite, Anhedonia, and Amotivation. Importantly, a differential pattern of response, both to a rapid acting antidepressant agent and placebo, was observed across these unidimensional constructs (factors). In other words, the use of these unidimensional constructs may reveal patterns of neurobiology not observed with traditional scoring of individual instruments. The empirical identification of unidimensional constructs creates more refined scores that may elucidate the connection between specific symptoms and underlying pathophysiology. Our studies are integrated with multimodal technologies (MRI, MEG, PSG, proteomics, metabolomics, and blood biomarkers) obtained longitudinally in patients with severe and/or TRD before, during, and after an experimental intervention, thus permitting us to contrast the biology in the same individual when depressed, in remission, and again upon relapse. The resulting data has led to important insights across units of analysis, from the cellular through circuits to self-report. The data is anticipated to enhance our ability to identify biomarkers for stratification by distinct depression subtypes relevant to clinical response.
Keynote III

KN-03 | Trajectories of emerging illness in the high-risk offspring of bipolar parents: what we have learned over two decades of research and future directions

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Bipolar Disorder runs in families and the single most robust risk factor predicting illness onset remains a confirmed family history of illness in a first degree relative. Therefore, children of affected parents are an identifiable and informative high-risk population. Longitudinal observation of high-risk children over the risk period provides the unique opportunity to study the determinants of risk and pathways to illness onset without the confounding effects of burden of illness or treatment. In this talk I will provide an overview of key findings from the Canadian Flourish High-Risk Offspring study, which started over 2 decades ago. These findings will be discussed in light of the findings from numerous independent high-risk offspring studies from around the world. Knowledge gaps and future important directions stemming from this collective body of work will be highlighted and hopefully stimulate an active discussion at the end of the presentation.

Keynote IV

KN-04 | Interrogating disease biology of bipolar disorder using patient-derived cells

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Background and Aims: Recent advances in cellular reprogramming of stem cells and their neuronal differentiation provide exciting new avenues to investigate the disease biology of bipolar disorder. We are using a variety of approaches, including cellular and subcellular morphological studies, gene expression studies and metabolomic studies with patient-derived cells.

Method: We collected dermal fibroblasts from patients with bipolar disorder and generated induced pluripotent stem cells (iPSCs). We undertook metabolomic studies by measuring polar and nonpolar metabolites in fibroblasts from subjects with bipolar I disorder and matched healthy control subjects, under normal conditions and with two physiologic perturbations - low-glucose media and exposure to dexamethasone - in order to identify disease-specific cellular vulnerabilities that are unmasked with cellular stressors.

Results: Metabolites that were significantly different between bipolar and control subjects showed distinct separation by principal components analysis methods. The most statistically significant findings were observed in the perturbation experiments. Under low-glucose condition and with exposure to dexamethasone, the most significant difference was found in α-aminoadipate, which was consistently lower in bipolar subjects.

Conclusion: Studies of patient-derived cells, including primary tissue and iPSC-derived neurons, provide new opportunities to interrogate the disease biology of bipolar disorder using a variety of methods. Our metabolomic study in the presence of cellular stress implicates α-aminoadipate as a possible stress-related biomarker in bipolar disorder. This is an intriguing finding given the known role of α-aminoadipate in modulation of kynurenic acid in the brain, especially as abnormal kynurenic acid levels have been implicated in bipolar disorder.

Keynote VI (Advocacy)

KN-05 | Identifying the origins of emotional disorders

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Background and Aims: The emergence and onset of emotional disorders, such as anxiety, depression and bipolar disorders remains a mystery. These disorders are a prelude to serious lifelong illnesses that often take hold in adolescence and early adulthood. By understanding the precursors and early signs of emotional changes that forecast the
development of psychiatric disorders it may be possible to alter illness trajectory or even achieve true prevention.

**Method:** This keynote will review research pertaining to these questions and present the findings from novel research that has examined the neural correlates of emotional disorders, in a unique set of studies conducted over a period of several years, involving adolescents aged 12 to 18 years old. The presentation will focus on findings from fMRI scans performed on nearly 300 school-aged children in Sydney (Australia).

**Results:** The extant literature has been systematically synthesised to provide a suitable backdrop against which data from a series of fMRI studies conducted from 2010 to 2017 is presented. Analyses from this body of research reveal nascent but discernible changes in brain function across both task-related and resting state fMRI involving recognised emotional and cognitive neural networks.

**Conclusion:** Insights that can be drawn from these studies, and the implications and clinical impact of these findings, especially with respect to future research and potential avenues of treatment, will be discussed.

### Keynote VII (Advocacy)

**KN-06 | Early intervention in bipolar disorder**

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Bipolar disorder is a recurrent disorder that affects more than 1% of the world population and usually has its onset during youth. Its chronic course is associated with high rates of morbidity and mortality, making bipolar disorder one of the main causes of disability among young and working age people. The implementation of early intervention strategies may help to change the outcome of the illness and avert potentially irreversible harm patients with bipolar disorder, as early phases may be more responsive to treatment and may need less aggressive therapies. Early intervention in bipolar disorder is gaining momentum. Current evidence emerging from longitudinal studies indicates that parental early-onset bipolar disorder is the most consistent risk factor for bipolar disorder. Longitudinal studies also indicate that a full-blown manic episode is often preceded by a variety of prodromal symptoms, particularly subsyndromal manic symptoms, therefore supporting the existence of an at-risk state in bipolar disorder that could be targeted through early intervention. There are also identifiable risk factors that influence the course of bipolar disorder, some of them potentially modifiable. Valid biomarkers or diagnosis tools to help clinicians to identify subjects at high-risk of conversion to bipolar disorder are still lacking, although there are some promising early results. Pending more solid evidence on the best treatment strategy in early phases of bipolar disorder, physicians should carefully weigh the risks and benefits of each intervention. Further studies will provide the evidence needed to finish shaping the concept of early intervention.