derived neurons. GO pathway analysis of miRNAs significantly elevated in BP derived neurons indicate that these miRNAs regulate a wide variety of cellular processes, including proliferation, cell junction and extracellular matrix organization, chromatin modification, mRNA processing, and carbohydrate metabolism. We use a luciferase assay to validate the targets of these miRNAs, which will then be overexpressed in iPSC derived cells to determine their effects on neuronal behavior.

To determine if our results are restricted to neurons we examined differences in the behavior of astrocytes derived from BP and C individuals. After differentiation as astrospheres, precursors were passaged and expanded in FGF-2 and EGF producing a population of astrocytes which were positive for the glial precursor marker CD44. Expression of S100beta, and the glutamate transporters EAAT1 and EAAT2 were markedly lower in BP astrocytes, and cell doubling times at early passage number were greater in BP cells. These differences in gene expression and behavior suggest that BP astrocytes are functionally distinct from control astrocytes. Current investigations are in progress to examine gliotransmitter expression and behaviors in co-culture.

We have identified differences in calcium signaling in BP vs C neurons; BP neurons are more active than those derived from Control patients. Remarkably, lithium pre-treatment significantly reduced calcium transients and wave amplitude in BP neurons to Control levels, providing a tractable model system to examine the response of iPSC-derived neurons to pathway perturbagens and treatments involved in BP. One of those is ketamine, which we are applying to brain organoids derived from iPSC to determine their response to this therapeutic. Additional work is examining the effects of increased CACNA1C expression associated with the AA allele of rs1006737 – the strongest and most replicated association with bipolar disorder – in neuronal differentiation and function. AA carrier BP cells are undergoing gene editing to revert the mutant genotype to GG, and their calcium signaling and differentiation potential assessed. The overarching goal of our research is to identify novel disease phenotypes and mechanisms involved in bipolar disorder, with the long term goal of improving treatment.

Disclosure

Nothing to disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.630

PREDICTING CONVERSION TO BIPOLAR DISORDER IN A PROSPECTIVE LONGITUDINAL GENETICALLY HIGH-RISK SAMPLE

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Abstract

Objective: Our group has previously reported differences in the clinical, genetic and neuroimaging (structural and functional MRI, DTI) profiles of young people at increased genetic risk of bipolar disorder, compared to control subjects from families without mental illness. Identification of clinical, genetic and neuroimaging features that predict later 'conversion' to bipolar disorder (BD) in those at high genetic risk (HR) would assist in early intervention. This study aimed to investigate whether clinical features (such as lifetime depressive, anxiety or behavioural disorders) or genetic/neuroimaging findings predict later development of hypo/mania.

Method: 287 12-30 year-old participants (163 HR with a first-degree relative with DSM-IV BD, and 124 controls) were assessed at baseline and 12-monthly follow-ups for up to six years.

Results: Nineteen HR subjects later developed either threshold (n=8; 4.9%) or sub-threshold (n=11; 6.7%) hypo/manic episodes. A prior history of MDEs was associated with an increased risk of later conversion to threshold BD (hazard ratio=13.9, $p<.05$). Anxiety disorders did not predict later occurrence of hypo/mania. Behavioural disorders (including ADHD) predicted sub-threshold but not threshold episodes. After accounting for this risk, the presence of >4 'Probabilistic' depressive features was associated with a further seven-fold increase in the risk of conversion to threshold BD (hazard ratio=6.9, $p<.05$). Those features most strongly associated with such conversion were psychomotor retardation and $>$ 5 MDEs. Data on the predictive capacity of genetic (polygenic risk scores) and neuroimaging findings will be presented.

Conclusions: In one of few prospective studies of predictors of conversion to BD in HR subjects, both a history of MDEs and >4 'Probabilistic' features predicted later development of threshold episodes of hypo/mania, and hence may constitute 'targets' for early intervention.

Disclosure

Nothing to disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.631

MITOCHONDRIAL DYSFUNCTION PLAYS A ROLE IN IMPAIRED NEURONAL DIFFERENTIATION IN SCHIZOPHRENIA

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Abstract

Schizophrenia (SZ) is conceptualized as a neurodevelopmental disorder, involving dysfunction of dopaminergic and glutamatergic systems as well as of mitochondria. Among the major obstacles in studying pathological processes in SZ are the inaccessibility of the brain and inability to study brain processes prior to the onset of this disorder. Animal models of the disease can shed light on possible developmental aberration in the disease. An additional attractive experimental tool to study neurodevelopmental impairments together with mitochondrial dysfunction in SZ, is differentiation of induced pluripotent stem cells (iPSC) into neurons.

iPSC from SZ patients and healthy controls were reprogrammed from hair follicle keratinocytes and differentiated into dopaminergic and glutamatergic neurons. Mitochondria were assessed by analyzing mitochondrial membrane potential, network dynamics and apoptosis markers. The effect of transferring isolated active normal mitochondria (IAN-MIT) into SZ- iPSCs was studied. Furthermore, mitochondrial complex I subunits expression was followed in brains of neonatal ventral hippocampal (nVH) damage rat model of SZ.

SZ-derived dopaminergic cells showed severely impaired ability to differentiate, whereas glutamatergic cells were unable to maturate. Mitochondrial complex I driven respiration was impaired in SZ-derived keratinocytes and iPSC along with perturbations in mitochondrial membrane potential and in mitochondrial network in neurons. However, amending mitochondrial function by IAN-MIT transfer improved differentiation of SZ-iPSC derived glutamatergic neurons. In prefrontal cortex, but not the cingulate cortex, of nVH damage rat model of SZ we observed a significant prepubertal increase and postpubertal decrease in mitochondrial complex I subunits. No such change was observed in neonatal exposure to hypoxia rat model.

Our study shows perturbations in neural differentiation and mitochondrial function, which are interconnected and of relevance to early neurodevelopmental processes in SZ.

Disclosure

Nothing to disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.632

Concurrent Symposia Session 15:

APPLYING NEUROIMAGING AND NEUROCOGNITIVE ENDOPHENOTYPES FOR PSYCHIATRIC GENE DISCOVERY

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Overall Abstract

A number of genome-wide significant quantitative trait loci (QTL) have been localized for affective and psychotic illnesses. However, these findings explain only a small portion of the genetic variance predisposing psychiatric disorders and have yet to result in true gene identifications. QTL localizations from linkage or genome wide association analyses indicate that a gene/variant of interest is present in a potentially large chromosomal region but do not identify the underlying causal gene/functional variants. Yet, progress in elucidating the pathophysiology of major mental disorders, and subsequent treatment interventions, is predicated on causal gene identification. In this symposium, we focus on an alternate strategy for gene discovery based on the use of quantitative endophenotypes. An endophenotype is a heritable trait that is genetically correlated with disease liability and can be measured in affected and unaffected family-members, providing greater power to localize disease-related genes than affection status alone. Given that most quantitative endophenotypes vary within the normal population, unselected samples can be used to identify genes influencing these traits. Genes that influence endophenotypes are empirically-supported candidate genes for mental illnesses and can be directly verified in clinically selected samples. John Blangero will open the symposium by providing novel statistical methods for the direct estimation of genetic liability and apply that method to endophenotypes for major depression. Next, Raquel Gur will describe work from the Philadelphia Neurodevelopmental Cohort focused on cognitive and brain changes in normal and pathological development. Godfrey Pearlson will explore the use of parallel ICA methods for nominating genetic networks for endophenotypes in schizophrenia and bipolar disorder. Finally, David Glahn will discuss the use of whole genome sequence data and quantitative endophenotypes for gene discovery in affective and psychotic disorders.