

Abstract

Due to familial factors, younger siblings of children with Autism Spectrum Disorder (ASD) are at an increased risk for developing the disorder^{1,2}. Although behavioral symptoms of ASD typically emerge during a child's second year,³ recent work on younger siblings demonstrates that prodromal features of ASD are present already within the first months of life. These features include atypical attention toward stimuli relevant to social engagement, such as faces and speech sounds.^{4,5} Similar deficits were observed in clinic-referred toddlers suggesting continuity of social attention impairments in ASD from prodromal to early syndromal stages.^{6,7} This presentation will review: (1) the methodological underpinnings of prospective high-risk sibling studies and findings on patterns of autism onset in infancy, and (2) experimental studies on endo- and exogenous attention to multimodal social stimuli conducted during prodromal and early syndromal stages of the disorder.

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Speaker 2: Gianluca Esposito, Italy

Title: Atypical infant cries among incipient ASDs, developmentally delayed individuals, and language-impaired individuals

Abstract

To better understand social communication during early human development, a growing literature is assessing the vocal production of children with Autism Spectrum Disorders (ASD). Previous studies have provided preliminary evidence that disruptions in cry acoustics may be part of an atypical vocal signature of autism early in life.

In the current research we investigate the acoustic characteristics of cries elicited during real life events as well as cries elicited in experimentally standardized social interaction contexts (i.e. the Strange Situation Procedure -SSP).

Using these approaches, we found that 15-month-olds at high risk for ASD had atypical acoustical patterns of distress vocalization (e.g. shorter cry utterances, higher fundamental frequencies). Then, next step was to assess using multiple neuroimaging and electrophysiological techniques (EEG, fMRI, TMS,

EKG, EMG, GSR, etc) the effect on parental perception of ASD distress vocalizations. Perceived distress engendered by ASD cries related to increased activation in brain regions associated with emotional processing.

Speaker 3: Elodie Ey, France

Title: Subtle abnormalities in the vocal behavior of mouse pups mutated in *Shank2*

Elodie Ey, Thomas Bourgeron

Abstract

Mutations in genes coding for synaptic proteins were shown to increase susceptibility to autism spectrum disorders (ASD)^{1,2}. Recently, the synaptic scaffolding protein PROSAP1/SHANK2 has been associated with ASD³⁻⁶. The mouse model lacking *Shank2* displayed abnormal glutamatergic receptor expression and neurotransmission. Abnormalities in body weight as well as in vocal behavior emerged in the first two weeks of life of *Shank2*^{-/-} pups. We highlighted a different profile in the emission rate of pup isolation calls between *Shank2*^{-/-} mice and their wild-type littermates. We did not highlight any significant genotype-related differences in the vocal repertoire used, in the organization of call types and in the acoustic structure. In this mouse model, subtle abnormalities in usage of ultrasonic vocalizations during development precede impairments in social communication in adulthood. Indeed, in adult *Shank2*^{-/-} mice, impairments in social interactions emerged together with abnormalities in usage and structure of ultrasonic vocalizations^{7,8}. Together with other mouse models of ASD, the *Shank2*^{-/-} mice provide a comprehensive framework to identify new knowledge-based treatments.

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Speaker 4: Noboru Hiroi, USA

Title: Structure and function of neonatal social communication in a genetic mouse model of autism

Abstract

A critical step toward understanding autism spectrum disorder (ASD) is to identify both genetic and environmental risk factors. A number of rare copy number variants (CNVs) have emerged

as robust genetic risk factors for ASD, but not all CNV carriers exhibit ASD and the severity of ASD symptoms varies among CNV carriers. Although evidence exists that various environmental factors modulate symptomatic severity, the precise mechanisms by which these factors determine the ultimate severity of ASD are still poorly understood. Here, using a mouse heterozygous for *Tbx1* (a gene encoded in 22q11.2 CNV), we demonstrate that a genetically-triggered neonatal phenotype in vocalization generates a negative environmental loop in pup-mother social communication. Wild-type pups used individually diverse sequences of simple and complicated call types, but heterozygous pups used individually invariable call sequences with less complicated call types. When played back, representative wild-type call sequences elicited maternal approach, but heterozygous call sequences were ineffective. When the representative wild-type call sequences were randomized, they were ineffective in eliciting vigorous maternal approach behavior. These data demonstrate that an ASD risk gene alters the neonatal call sequence of its carriers and this pup phenotype in turn diminishes maternal care through atypical social communication. Thus, an ASD risk gene induces, through atypical neonatal call sequences, less than optimal maternal care as a negative neonatal environmental factor.

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S21: Schizophrenia: Oxidative Stress and Inflammation in Schizophrenia: Functional consequences

Chair: Patricio O'Donnell, USA

Co-Chair: Svetlana Ivanova, Russia

Speaker 1: Vibeke Catts, Australia

Title: Relationship between inflammatory cytokines, oxidative stress and astrogliosis markers and prefrontal grey matter volume in schizophrenia subgroups

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Abstract

The objectives of the current study were to determine the extent to which previously identified increased expression of cytokines in a subgroup of individuals with schizophrenia (40%) relate to markers of oxidative stress, astrogliosis and grey matter volume reductions in postmortem tissue. We utilized a collection of dorsolateral prefrontal cortex tissue from 37 individuals with schizophrenia and 37 controls. Total glutathione was measured using a fluorometric assay. Protein levels of glutathione peroxidase (GPx) and the catalytic subunit of glutamate cysteine ligase (GCLC) were determined by Western blotting. Astrogliosis was assessed by measuring mRNA expression levels of glial fibrillary acidic protein (GFAP) using qRT-PCR, and by examining the morphology of GFAP-positive astrocytes in immunostained sections. Cortical volumes were determined in a subset of 28 individuals with schizophrenia and 22 controls using photographs of fixed postmortem sections and Cavalieri's probe. GFAP mRNA, astrocyte morphology, GPx and GCLC protein levels were not significantly different between people with schizophrenia and controls overall. The diagnosis of schizophrenia was associated with decreased levels of reduced glutathione and reduced cortical volume. Individuals with schizophrenia who also had increased expression of inflammatory cytokines in the PFC displayed an exacerbated pathology, including decreased levels of reduced glutathione, increased GFAP mRNA, hypertrophic astrocyte morphology, and reduced grey matter volume, particularly in the superior frontal gyrus, relative to individuals with schizophrenia with low levels of inflammatory cytokines and unaffected controls. We conclude that the subgroup of individuals with schizophrenia who had elevated cytokines also show evidence of ongoing oxidative stress vulnerability and neurodegenerative processes such as astrogliosis and cortical volume loss. This has implications for clinical trials of novel therapeutics in schizophrenia, as membership of an inflammatory subgroup may influence treatment response.

Speaker 2: Celso Arango

Title: Inflammation and oxidative stress in early onset psychosis: functional and therapeutic relevance

Speaker 3: Patricio O'Donnell, USA

Title: Oxidative stress in prefrontal cortical interneurons in animal models

Patricio O'Donnell, Jan Cabungcal, Kim Q. Do Pfizer, University of Maryland

Abstract

Immune molecules and redox pathways are receiving increasing attention for a possible role in pathophysiology of psychiatric disorders. A cell population that may present enhanced vulnerability to the deleterious effects of these mechanisms is the parvalbumin-positive fast spiking interneurons in cortical circuits. This cell population is thought to be affected in schizophrenia, as post-mortem data consistently reveals changes that can be explained by loss of function in these neurons. Remarkably, several different animal models that produce schizophrenia-relevant behavioural deficits such as altered prepulse inhibition of the acoustic startle response converge in showing alterations in this interneuron population. We explored whether oxidative stress was present and whether antioxidant treatment could reverse deficits in one such model, rats with a neonatal ventral hippocampal lesion (NVHL). This model produces animals