Accomplishments from the NICHD/NIDCD Collaborative Programs of Excellence in Autism (CPEAs)

Research highlights from each site

National Institute of Child Health and Human Development (NICHD)

University of California, Los Angeles (UCLA): Marian Sigman, P.I.

The Bases for Communication and Social Deficits in Children with Autism:

- Joint attention skills are critical for future language acquisition in children with autism (Sigman, Kasari, Siller).
- High-functioning children with autism can engage normative neural networks for understanding emotions and communicative intent when their attention is explicitly directed toward relevant social cues (Bookheimer, Dapretto, Wang).
- The failure to attend to implicit cues is associated with mirror neuron system dysfunctions (Dapretto, Bookheimer).
- In children with 15q duplications, a more severe autism phenotype is correlated with increasing copy number of the gene rich region on chromosome 15q 12-13 (Schanen).

Boston University / Massachusetts General Hospital CPEA

- Language subtypes in autism are important for predicting different patterns of brain asymmetry and useful for genetic studies.
- Children with autism show developmental changes in theory of mind, which are correlated with language, but also predict symptom severity in the social and communication domains.
- Behavioral and neurobiological bases of face processing in autism are associated with differences in attentional patterns to social stimuli and are independent of language.

Utah Autism Program

- Replicated 3q25-27 linkage (single large pedigree, 7 affected)
- Current and future work on large pedigrees
- Found association between autism & TPH2 (repetitive behavior)
- Superior temporal gyrus gray matter appears to decrease abnormally with age in adolescents with high-functioning autism
- Diffusion-tensor imaging shows evidence of abnormal white matter microstructure in corpus callosum (CC)—Abnormal findings appear driven by radial diffusivity, and CC radial diffusivity is related to processing speed in cases and controls
- Measles antigen not increased in cases vs. controls
- Reported similar rates of broad autism phenotype (BAP) in regression and early onset families
- High correlation between Social Responsiveness Scale (SRS) and Broader Phenotype Autism Symptom Scale (BPASS)
- Gilliam Autism Rating Scale (GARS) reliability

University of Texas Health Science Center, Houston CPEA

Orbitofrontal-Limbic Dysfunction in Autism:

- Two fronto-limbic brain circuits are developmentally dysfunctional in autism (orbitofrontal-amygdala circuit and dorsolateral prefrontal-hippocampus circuit).
- Social emotional and social cognitive skills in autism have distinct and predictable relationships to the orbitofrontal-amygdala circuit and dorsolateral prefrontal-hippocampus circuits.
- Experimental neonatal brain lesions in monkeys indicated that the orbital frontal cortex, but not the amygdala, may play a critical role in the quality of infant/mother relationships, and that dysfunction of this structure may result in pervasive impairments of social interactions and reciprocal relationships later in life as found in autism.
- The role of the medial orbital frontal cortex in flexible decision-making in monkeys is related to an inability to use information from bodily states to modify behavioral choices—a deficit that could be related to self-regulation problems observed in autism.

University of Pittsburgh, Carnegie Mellon University, University of Illinois Chicago CPEA

- Autism is a disorder of complex information processing that broadly affects cognition & the brain.
- Categorization processes that organize social & non-social information are impaired throughout life.
- Neural analogue is alterations in functional connectivity with compensatory reliance on elementary visual systems.
- Oculomotor studies show frontal circuitry growth into adulthood in autism suggesting potential for enhancement.
- Widespread alterations in cortical topography or specialization with lack of fine tuned responses to stimuli.

University of California, Davis, University of Colorado Health Sciences Center CPEA: Sally J. Rogers, P.I.

Definition and Development of the Neuropsych Phenotype in Autism

- Onset: Data from parent report, genomic, and immunology data suggest four categories: early onset, developmental plateau, regression, and mixed (early symptoms plus regression) (Ozonoff)
- Neuroimaging: (1) Structural and functional imaging of auditory cortex IDs left hemisphere differences; (2) Hippocampal enlargement found in parents of children with autism, points to familiality (Rojas)
- Imitation: (1) Imitation of object actions at age 2 strongly related to general outcomes at ages 8-11; (2) Performance effects of small changes in tasks don't fit with a general imitation deficit (Rogers) (Hepburn)

University of Rochester CPEA

- HOXA1 - Identified Hoxa1 as a candidate gene for autism susceptibility. Others now report that homozygous inheritance of a mutation of this gene is the cause of a syndrome that includes autism.
- Visual orientation and eyeblink conditioning - Identified and confirmed two functional anomalies that discriminate autism from other CNS disorders.
- Valproate-exposed rat model - Developed an animal model that reproduces many features of neuroanatomy reported in autism and shows eyeblink conditioning abnormalities exactly parallel to the behavior of human cases.
- Misoprostol - Discovered an environmental factor that increases the risk of autism after exposure in the sixth week postconception.

University of Washington CPEA Highlights

- Genome-wide linkage scan revealed strong support for an autism gene on chromosome 7 and compelling evidence for genes on chromosomes 3, 4, and 11. Different linkage patterns were found for males versus females and for early versus late onset autism.
- Quantitative trait locus analyses established heritability of specific autism traits.
- Studies of event-related potential (ERPs) to social and linguistic stimuli in young children with autism showed early abnormalities in face and phonemic processing.
- A longitudinal study of brain structure and chemistry revealed, at age 2-3 years, enlarged cerebral volume, enlarged amygdalar volume, reduced corpus collosum volume, and atypical hippocampal shape differences. By age 6, cerebral enlargement was no longer apparent. Reduced gray matter chemical concentrations of NAA indicated that autism is associated with decreased rather than increased cellular density.
- In a study of home videotapes, the first objective evidence of autistic regression was documented.

Yale / Chicago / Michigan CPEA

- Difference in brain in face processing in fusiform face area
- Eye tracking studies of social information processing
- International Molecular Genetics Study of Autism Consortium (IMGSAC)
  - Confirmation 15q11-q13 duplication
  - New linkage peak chromosome 11
- Stability of early diagnosis and predictors
  - Stability of early diagnosis for autism, PDD-NOS less reliable
  - Diagnostic predictors: verbal IQ, Autism Diagnostic Observation Scale (ADOS)/Autism Diagnostic Interview repetitive behaviors, ADOS social deficits
  - Language scores at 3 predict Verbal IQ at 9, age 2 & 3 scores predict Vineland socialization