Highlights of the Collaborative Programs of Excellence in Autism (CPEAs)

1996-2003

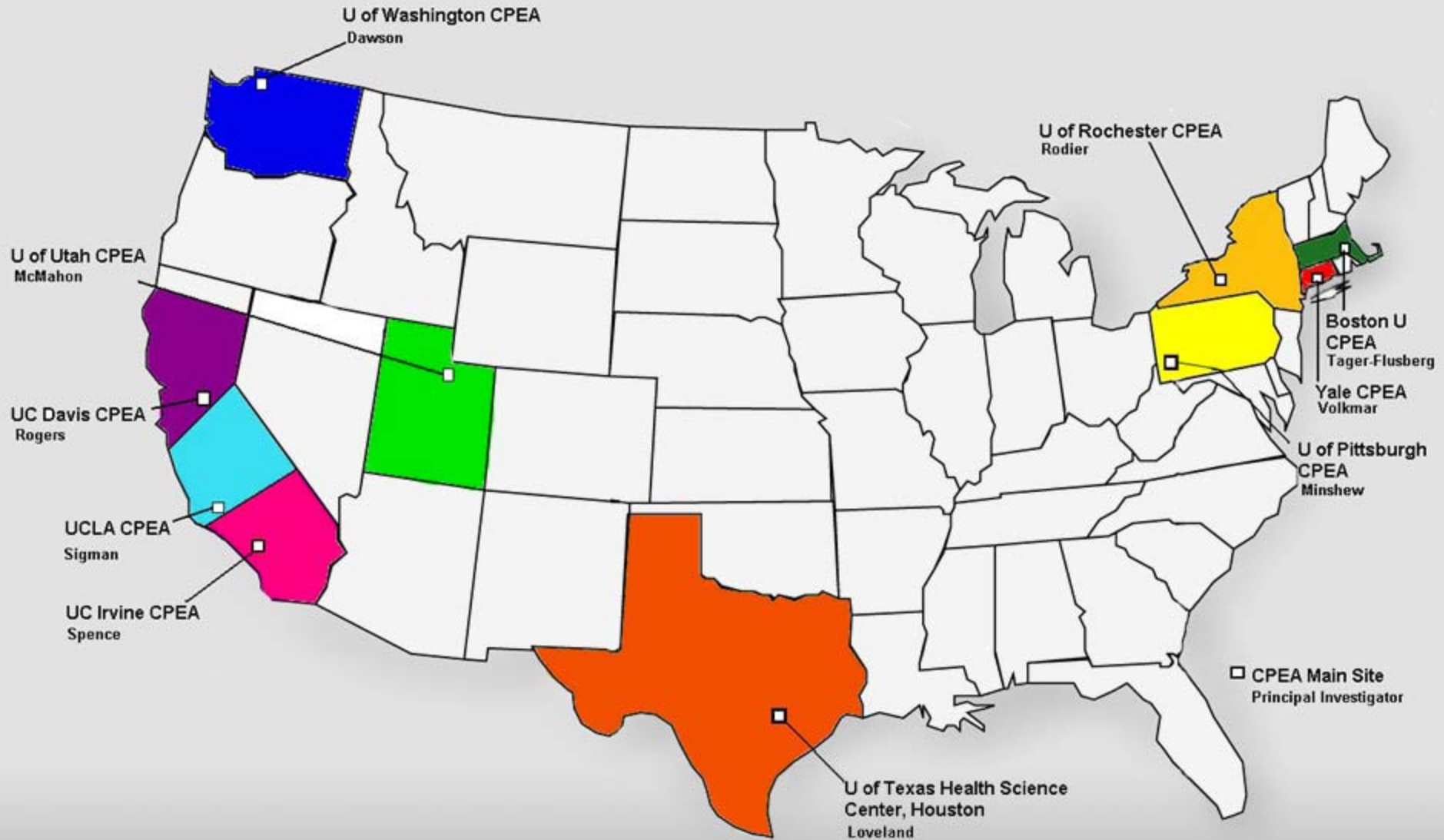### Funded by

National Institute of Child Health and Human Development   **and**   **National Institute on Deafness and Other Communication Disorders**

National Institutes of Health   **U.S. Department of Health and Human Services**

CPEA sites and PIs

Participants evaluated in CPEA projects

Participants	Number evaluated
Autism Spectrum Disorder	2,227
Developmental Delay/Specific Language Impairment	422
Family Members/ Typical controls	1,363
TOTAL	4,020

Diagnosis and early detection

- **Diagnostic methods for toddlers and young children**
- **Symptoms identified in infants younger than one year of age**
- **Differential diagnosis and overlap with other disorders: Fragile X syndrome, specific language impairment, mental retardation, attention deficit/hyperactivity disorder**
- **Longitudinal stability of diagnosis**

Characterizing phenotype and course

- **Core social deficits identified: Social orienting, imitation, emotion processing, and face processing.**

- **Regression and its relation to outcome examined.**

- **Abnormal movements of the face identified.**

- **Language subtypes defined.**

Broader phenotype

- **Reliable quantitative measure of broader phenotype symptoms in parents and siblings developed.**

- **Young siblings found to have social-communicative differences.**

- **Parents demonstrate altered face processing on neurocognitive and ERP measures.**

- **Parents found to have abnormal amygdala and hippocampal volumes.**
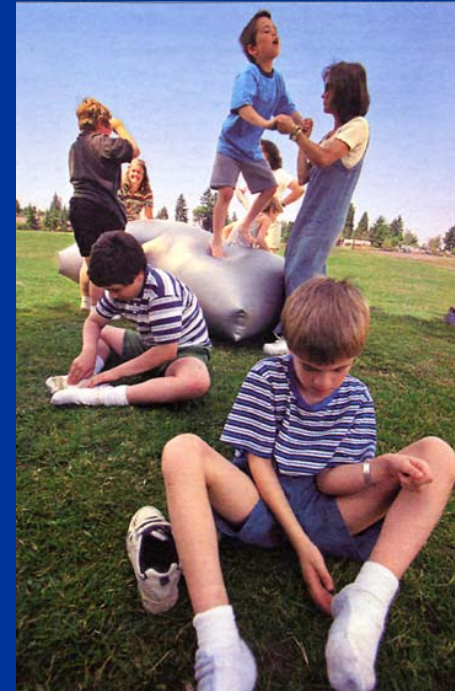
Brain structure and development

- **Specific abnormalities in brain structure development and chemistry identified:**
  - **Early enlarged cerebral volume followed normal volumes by age 6 to 18 years;**
  - **Cerebrospinal fluid, white and grey matter abnormalities;**
  - **Abnormalities in white matter in the corpus callosum;**
  - **Smaller left planum temporale, atypical asymmetry; and**
  - **Atypical development of amygdala structure.**
- **Amygdala volume is associated with severity of symptoms and outcome.**

Brain dysfunction in autism

- **Neuropsychological deficits identified:**
  - **Prefrontal impairments (e.g., spatial working memory, attention shifting, response inhibition);**
  - **Medial temporal lobe impairments (e.g., tasks tapping amygdala, hippocampus);**
  - **Face processing impairments; and**
- **Nature of face processing deficits clarified and extensively studied.**

Brain dysfunction in autism

- **fMRI studies show:**
  - **Prefrontal cortex and cingulate abnormal during spatial working memory.**
  - **Fusiform face area not activated during face processing.**
  - **Atypical activity in brain regions related to word processing.**
  - **Decreased activity in regions related to prosodic cues and facial emotions.**
  - **Less synchronization across cortical areas indicating functional underconnectivity.**
- **New software and analysis methods developed.**
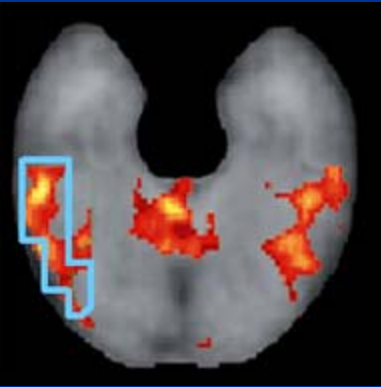
Brain dysfunction in autism

- **ERP/MEG and eye-tracking studies show:**

  - Very young children with autism have abnormal ERP responses to faces, emotions, and speech.

  - Children with autism versus Fragile X show different ERP responses to auditory stimuli.

  - Individuals with autism use alternative gaze patterns in social situations (via eye tracking).

  - Auditory processing abnormality demonstrated using MEG.

Animal models

- **Animal lesion studies clarify role of early lesions of the amygdala and orbital frontal cortex in development of autism-like symptoms.**

- **Parallel deficits in eye blink conditioning in autism spectrum disorder (ASD) and in animals with prenatal valproate exposure (which affects Hoxa1 expression).**

Etiology

- **Phenotypic consequences of chromosome 15q duplications are variable.**

- **Positive association found for TPH2, a brain-expressed tryptophan hydroxylase gene.**

- **Large deletions in chromosomes discovered in autism multiplex fa**

- **Candidate gene list for ASD deve from studies of chromosomal rearrangements.**

Etiology

- **Sample of > 250 multiplex families assembled for linkage analysis.**

- **HOXA1 G allele discovered as marker for ASD and association with macrocephaly.**

- **Gene Gbx2, which has an association with ASD, discovered to be a target of Hoxa1 allele.**

- **A second drug – mosoprostil- fo which exposure is associated wi Moebius syndrome and autism discovered.**

Intervention

- **Factors related to longitudinal outcome identified.**

- **Randomized clinical trial (RCT) demonstrates large effects on joint attention and symbolic play from a short-term intervention.**

- **Important role of parental behavior in promoting children's language demonstrated.**

- **Two RCTs show that secretin is not effective for reducing symptoms of autism.**

CPEA Network Projects 1996-2001

Effectiveness of secretin for autism	Unis AS et al., *Journal of the Am Academy of Child & Adolescent Psychiatry.* 41(11): 1315-21, 2002. Owley T. et al. Multisite, Double-Blind, Placebo-Controlled Trial of Porcine Secretin in Autism. *Journal of the Am Academy of Child and Adolescent Psychiatry, 40(11)*: 1293-1299. (2001).
Regression and vaccines in autism	Luyster R, et al. *Developmental Neuropsychology.* In press Richler J, et al. (submitted). *Journal of Autism and Developmental Disorders.*
DNA collection on autism probands	Ongoing data collection for next 5 years
HOXA gene and autism	Devlin B. et al. *American Journal of Medical Genetics. 114(6):667-72,* 2002
Reelin gene and autism	Devlin B. et al. *Ameriacn Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 2004. 126B:46-50.*
Deletions in autism families	Yu CE. et al. *American Journal Human Genetics* 2002 July; 71(1):100-115
Head circumference in autism	Data analysis in progress.
Cognitive profiles in preschool aged children with autism	Munson et al. Manuscript in preparation.
Executive functions in autism	Ozonoff S, et al. *Journal of Autism and Developmental Disorders.* 2004, 34:2; 139-150.
Language function in autism	Tager-Flusberg H, et al. under review. *Journal of the Academy of Child and Adolescent Psychiatry*
Cognitive Profiles in Children	Joseph RM. et al. *Journal of Child Psychology and Psychiatry*, 2002 43:6; 807-821