From genes to behavior:

How electrophysiological studies can provide insight into autism and other disorders

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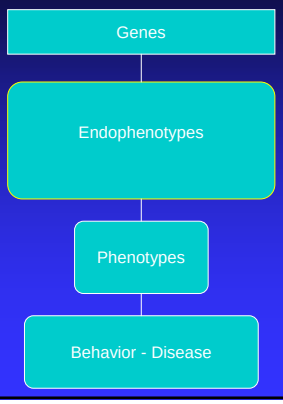
Behavioral diagnosis of PDDs

- Typically diagnosed around 3 years of age
- Can be reliably diagnosed at 18 months
- Retrospective home video studies and behavior studies in "at risk" infants distinguish at 12 months
- Pattern of behavioral change
  - 6 and 12 months
  - 12 and 18 months
- 4:1 ratio of males to females
- Social class distribution resembles that of the general population
- Equivalent distribution across racial and ethnic boundaries

Part 1: From Genes to Behavior



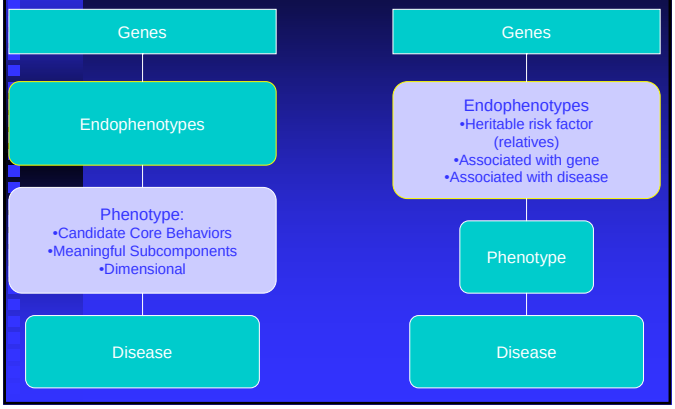
Genes

- 2q
- 7q - Language
  - FoxP, WNT2, HOXA1, HOXB1
  - RELN - neuronal signaling, synaptic transmission, plasticity
- 15q
  - Prader-Willi, Angelman Syndrome region
- X
  - FMR1 - Fragile X
  - MeCP2 - Rett's
  - NLGN2, NLGN3 (neuroligins)
- GABA receptor subunits (4q12; 5q34-35; 6q15; 15q12)
- Serotonin transport genes
- Differ by sex (male vs female affected families)
- Differ by parent of origin

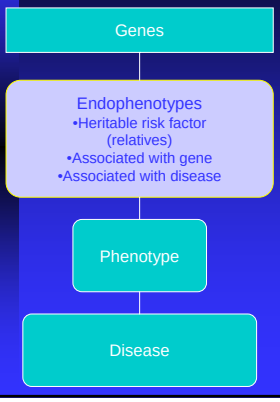
- Aarskog syndrome (X)
- Angelman Syndrome (15q)
- Cornelia de Lange Syndrome (5)
- Fragile X (X- FMRP gene)
- Hypomelanosis of Ito
- Moebius syndrome
- Neurofibromatosis
- PKU
- Prader Willi Syndrome (15q)
- Rett Disorder (X- MeCP2 gene)
- Smith Lemli Opitz Syndrome (11q)
- Sotos Syndrome
- Tourette Syndrome
- Tuberous Sclerosis
- Williams Syndrome (7q)

http://www.exploringautism.org/genetics/articles.htm

Intermediate steps

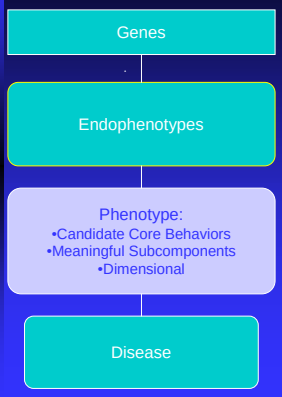


Endophenotype



- Neurophysiology
  - EEG/ERP
- Biochemistry
  - Grey matter choline compounds
  - Serotonin
- Neuroanatomy
  - White matter
  - Mini columns
  - Brain growth
  - Cerebellum, Superior temporal sulcus, Fusiform gyrus, MTL, Amygdala

Phenotype



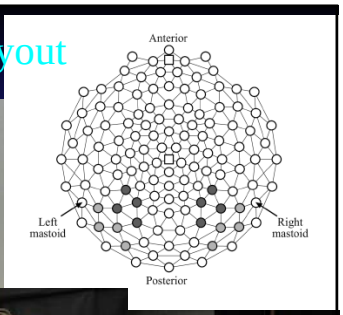
- "Social Processing"
  - Face memory
  - Voice/tone
  - Emotion id and use
  - Social motivation
  - Social expressiveness
- Behavioral flexibility
- Language/conversation
- Executive functioning
- Global/local processing

Part 2: Electrophysiological insights

EEG vs. ERP

- EEG - electroencephalogram
  - "Spontaneous" background activity
  - Reflects the state of the brain
  - Induced
  - Not time locked
- ERP- "event related" "evoked"
  - Time locked to a stimulus or behavior
  - Averaged

Sensor Net Layout



- ERPs - latency, amplitude, & topography
- EEG - frequency, power, & topography
- Coherence (connectivity)

Can EEG/ERP be used as endophenotypes? – Other disorders

- Heritability
  - Alcoholism (Almasy et al., 1999; Martin et al., 2005)
    - Theta 40-60%, Linked to 7
    - P300 amp & latency
  - Twins (Anokhin et al., 2004; Katsanis et al., 1998; Smit et al., 2005; vanBeijsterveldt van Baal, 2002)
    - Frontal N2/P3 amplitude 60%
    - P300 amp 50%
    - P300 lat 51%
    - EEG peak alpha power 77%
- At risk pop.
  - Dyslexia
    - Auditory ERP - phoneme processing
  - Alcoholism
    - Reduced amplitude P300 to novelty
  - Schizophrenia (relatives)
    - Prolonged latency

Part 2b: Insights into autism

N170 across development

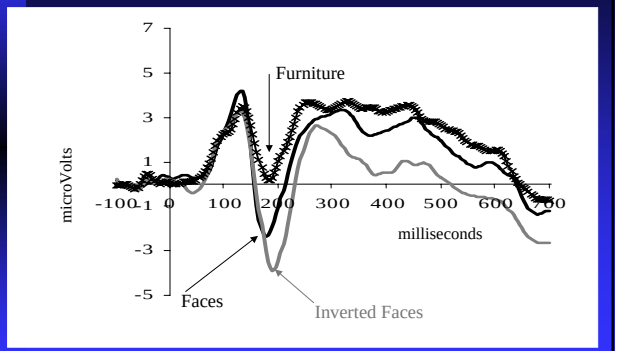
- ERP component that is elicited by Faces.
- Adults
  - Latency 140 to 170 msec
  - Greater & faster to faces than other stimuli
  - Right lateralized
- Children 3 to 11 years
  - Latency 280 msec --> 180 msec
  - Right lateralized

Bentin et al., 1996; Taylor et al., 1999; 2001; Webb, Dawson et al., 2006

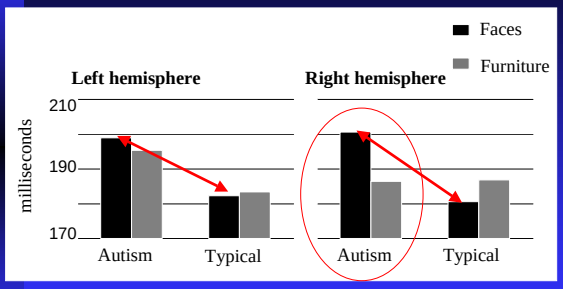
ERPs- Event Related Potentials

- Model –
  - Collection during stimuli / task known behavioral impairment
  - Autism - Face Processing
    - Face memory is phenotype of disorder
    - Identify stage of disruption

N170



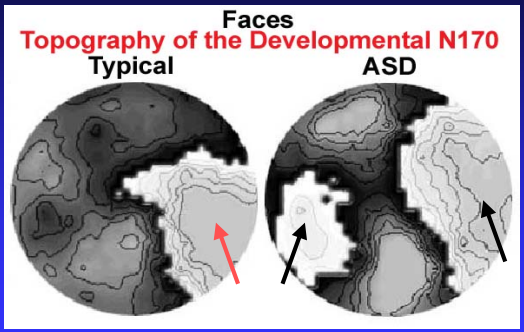
N170 -
Adults and Adolescents with ASD



- In ASD, slower response to faces
- In ASD, faster RT response to furniture than faces

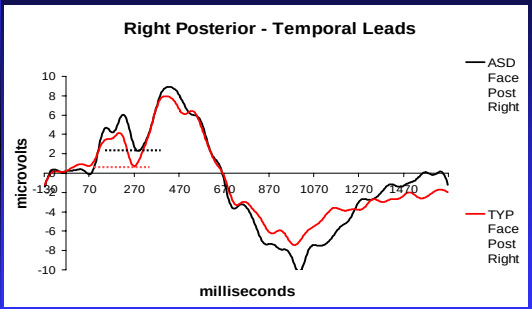
McPartland, Dawson, Webb, Panagiotides, & Carver, 2005

Precursor N170-
3 to 4 year olds with ASD



Dawson, Webb et al. (2004)

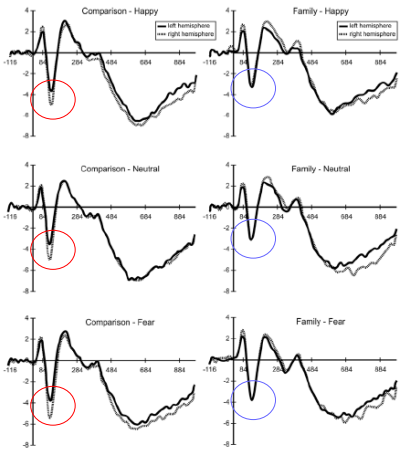
Precursor N170-
3 to 4 year olds with ASD



Webb, Dawson, Panagiotides, & Bernier (2006)

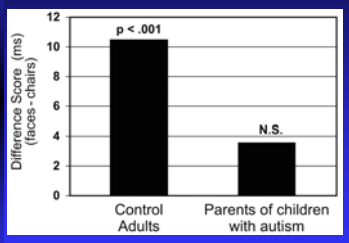
N170 -
Parents of children with ASD

- Lack of right hemisphere specialization



Dawson, Webb, Estes, Munson & Faja (in review)

N170 -
Parents of children with ASD



- In controls faces < furniture
- In parents, faces = furniture

Dawson, Webb, Wijsman, Schellenberg, Estes, Munson & Faja, 2005

EEG Power

- Collection during resting or active state
- Model – Target processes that have known EEG correlates & known behavioral deficits
  - Autism – Imitation
    - Imitation deficits (behavior) in ASD
    - Identify abnormalities in neural patterns underlying observe/ imitate

N170 - Endophenotype?

- Delayed temporal processing & abnormal cortical specialization
- Populations:
  - 3 to 4 year olds, 6 year olds, Adolescents & Adults, Parents (multiplex families)
- Related to behavior - yes
- Risk Factor - ?
- Heritable - ?

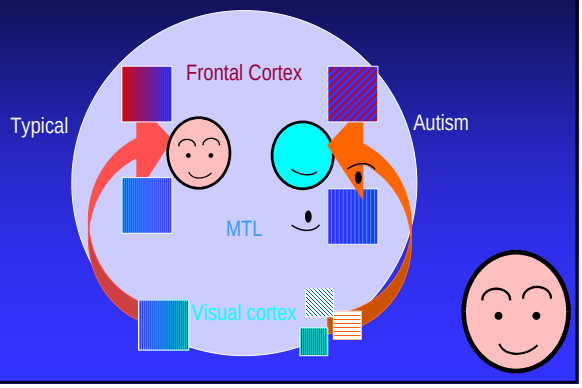
Imitation & Mu

- Mu = 8 to 13 Hz over central leads
  - Execute, Observe, Imitate - Muthukumaraswamy et al., 2004
  - Ratio of power relative to resting
  - Log transformed due to non-normality or ratio data
  - Negative value representing attenuation

EEG Power (wavelet)

- Collection during resting or active state
- Model – Target processes that have known EEG correlates
  - Autism – Feature (temporal) Binding
    - Parts based processing bias behavioral phenotype of ASD
    - Identify abnormalities in neural patterns that may contribute

Temporal binding



Temporal binding & gamma

- Temporal binding
  - Neurons that respond to the same object are tagged by their temporal correlation during firing (Milner, 1974; von der Malsburg, 1981).
- Assessed by EEG Power in gamma band (30 to 80 Hz)
- Feature Binding (Muller et al., Tallon Baudrey et al.)
- Central coherence (Brock et al., 2001)

Feature Binding thru temporal binding

- Binding of actual items to create additional (illusory) item
  - Kanisza figures
  - Mooney Faces

  - Increase in gamma over visual cortex to perception of "illusory figures"
    - ~ 50 to 100 msec after stim onset

Temporal Binding- Circuitry formation

- Binding of active neural regions to accomplish task efficiently
  - Delayed match to sample
    - Multiple stimuli types
    - Encoding
    - Delay (working memory)
    - Retrieval and Response

Mu / Gamma - Endophenotypes ?

- ASD mu atypical
- ASD gamma typical (~)
- Atypical binding of frontal-occipital regions.

- Related to behavior – Yes (mu)
- Risk factor - ?
- Heritable - ?

EEG - active state

- Mu –
  - Lack of mu atttenuation during action observation
- Gamma –
  - Increase in gamma activity during working memory
  - Failure to link neural circuitry

EEG Connectivity

- Collection during resting or active state
- Model: Theoretical description of neural systems / anatomy & behavior.
  - Autism
    - Individuals with autism have known white matter abnormalities
    - Proposed deficit in long range connections

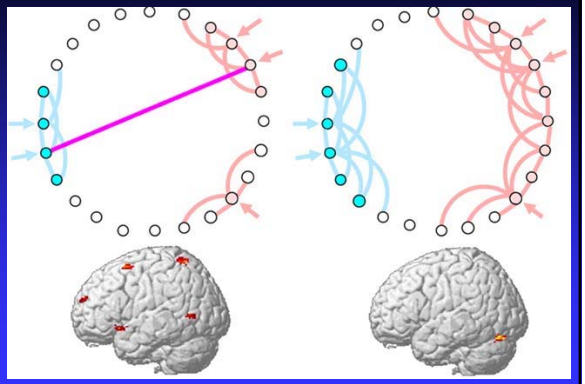
Connectivity

- Coherence
  - Phase relations between two EEG signals
  - Squared correlation coefficient, expressed as a function of frequency
  - Coherence reflects the transmission of neural signals along axonal projections. (Nunez, 1981)

Connectivity - Endophenotype?

- Band specific differences
- Relation between frontal and parietal/occipital
- Related to behavior –
  - Theoretically - yes
- Heritable -
  - Schizophrenia / Twins - yes
- Risk factor - ?

Connectivity



Belmonte, Allen, Beckel-Mitchener, Boulanger, Carper, & Webb, 2004

Conclusions, ASD

- Temporal slowing during early processing stages
- Lack of or atypical cortical specialization
- Alterations in resting and active state EEG
- Disrupted connectivity

Part 3: Implications

Implications for therapy

- Does intervention lead to
  - More efficient processing?
    - Latency
    - Amount of activation
  - Connectivity?
  - Compensation or normalization?

Differentiation of disease states

- Common phenotypes
  - Face processing/memory
  - Attention
  - Working memory

Collaborators

- Geraldine Dawson PhD
- Elizabeth Aylward PhD
- Andreas Keil (University of Konstanz, Germany)
- James McPartland PhD (Yale)
- Mike Murias PhD
- Heracles Panagiotides PhD
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- Kristen Merkle
- Megan Paul
- Audrey Quinn
- Jessica Shook