From genes to behavior: How electrophysiological studies can provide insight into autism and other disorders

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Part 1: From Genes to Behavior

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

Genes

- 2q
- 7p - Langrange
- 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

Genetic syndromes:

- Aarskog syndrome (X)
- Angelman Syndrome (15q)
- Cornelia de Lange Syndrome (5)
- Fragile X (X-FMRP gene)
- Hypomelanosis of Ito
- Mobius syndrome
- Neurofibromatosis
- PKU
- Prader-Willi Syndrome (15q)
- Ron Disorders (X-MeCP2 gene)
- Smith-Lemli-Opitz Syndrome (13q)
- Sotos Syndrome
- Tourette Syndrome
- Tuberous Sclerosis
- Williams Syndrome (7q)

http://www.exploringautism.org/genesis/articles.html
Intermediate steps

Genes

Endophenotypes

Phenotype:
• Candidate Core Behaviors
• Meaningful Subcomponents
• Dimensional

Disease

Endophenotype

Genes

Endophenotypes

• Heritable risk factor (relatives)
• Associated with gene
• Associated with disease

Phenotype

Disease

Part 2: Electrophysiological insights

Phenotype

Genes

Endophenotypes

Phenotype:
• Candidate Core Behaviors
• Meaningful Subcomponents
• Dimensional

Disease

Neurophysiology
• EEG/ERP

Biochemistry
• Grey matter choline compounds
• Serotonin

Neuroanatomy
• White matter
• Mini columns
• Brain growth
• Cerebellum, Superior temporal sulcus, Fusiform gyrus, MTL, Amygdala

“Social Processing”
• Face memory
• Voice/tone
• Emotion id and use
• Social motivation
• Social expressiveness

Behavioral Flexibility
• Language/conversation
• Executive functioning
• Global/local processing
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

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; van Beijsterveldt 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

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 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

N170

-5 -3 -1 1 3 5 7
-100 0 100 200 300 400 500 600 700 milliseconds
0.001 0.01 0.1 1 10 100 1000 microVolts

Faces Inverted Faces Furniture
N170 -
Adults and Adolescents with ASD

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

Precursor N170-
3 to 4 year olds with ASD

- Lack of right hemisphere specialization

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

Dawson, Webb et al. (2004)


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

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

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
  - 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 (Müller et al., Tallon-Baudry et al.)
- Central coherence (Brock et al., 2001)

Temporal binding & gamma

- 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 attenuation during action observation
- Gamma –
  - Increase in gamma activity during working memory
  - Failure to link neural circuitry

EEG Connectivity

- Collection during resting or active state
  - 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 - ?

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

Differentiation of disease states

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

Implications for therapy

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

Collaborators

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