Neurophysiological Endophenotypes, CNS Disinhibition and Risk for Alcohol Dependence and Related Disorders

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Henri Begleiter
Distinguished Professor of Psychiatry & Neuroscience
Sept. 11, 1935 – April 6, 2006
COGA ASCERTAINMENT + PROTOCOL

- Proband recruited from inpatient or outpatient treatment units (n=9265/1,227 families)
  - Must meet criteria for DSM-III-R alcohol dependence and Feighner definite on direct interview with SSAGA
- For genetic study: densely affected families
  - Must have at least two additional 1st degree relatives who also meet criteria for alcohol dependence on direct interview (n=2282/262 families)
  - Assess additional biological relatives
- Control families recruited from the general population (n=1240/227 families)
  - Blood sampling: DNA, cell lines
  - Endophenotype: brain oscillations (EEG/ERP/ERO)
Endophenotypes

- Endophenotypes (or intermediate phenotypes) reflect more proximal effects of genes than diagnostic categories, and hence they provide a more powerful strategy in searching for genes involved in complex psychiatric disorders.
  (Gottesman & Gould, 2003)

- “Ideally, we should perform molecular genetic studies, not on psychiatric diagnoses, which reflect distal, variable effects of genes, but on neurobiological measures that reflect more proximal effects of genes involved in the genetic predisposition for psychiatric disorders.”
  (Tsuang & Faraone, 2000)
Advantages of using Quantitative Biological Risk Factors (*ENDOPHENOTYPES*) in search for genes in complex disorders

- Closer to gene action involved in the predisposition for the disorder
- Genetically simpler than clinical endpoints
- Quantitative traits provide more power to localize and characterize disease susceptibility genes
- Identify relatives of affected individuals who would be considered unaffected with typical diagnostic systems including offspring at risk before the onset of illness

(reviewed by Porjesz and Begleiter, 2006)
Brain oscillations as endophenotypes

- Reflect ensembles of neurons firing in synchrony and represent the basic mechanism of neural communication.
  - High frequencies: are involved in short range communication
  - Low frequencies: longer range communication between brain areas.
- Reflect the dynamic millisecond by millisecond balance between excitation and inhibition in the brain neural networks.
Brain oscillations as endophenotypes

- **Resting**: eyes closed EEG
- **Active**: during sensory + cognitive tasks

Event Related Potentials (ERP)
Event Related Oscillations (ERO)

- Selected brain oscillations that differentiate between *alcoholics* and controls, and *high risk offspring* and controls
Brain oscillations as endophenotypes

- Brain oscillations are **highly heritable**

<table>
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<tr>
<th>Frequency band</th>
<th>Mean $h^2$ (Mz/Dz)</th>
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<tbody>
<tr>
<td>Delta (1.5-3.5 Hz)</td>
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<tr>
<td>Theta (4-7.5 Hz)</td>
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<td>Beta (13-25 Hz)</td>
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(Van Beijsterveldt et al., 1996)

- They are under **genetic control** and are modulated by genes controlling neurotransmitters in the brain.
Increased resting beta power in abstinent alcoholics + offspring at high risk

- Antecedes development of alcoholism: “trait” not “state” measure
- Index of **CNS disinhibition**: involved in genetic predisposition toward alcohol dependence
- Provides good endophenotype

HR (high risk) minus LR (low risk) Beta power:
(Rangaswamy et al., 2002; 2004)
LINKAGE ANALYSIS RESTING EEG: BETA

N=1553/250

GABRA2, GABRA4, GABRB1, GABRG1

Porjesz et al., PNAS, 2002
SNPs across the cluster of GABA_A receptor genes

Significant LD for SNPs only in GABRA2

β EEG linkage/disequilibrium due to GABRA2

- **Homozygotes** for the rarer genotype (15%) of the rs279836 SNP in the GABRA2 gene have significantly increased EEG Beta 2 compared to individuals with all other genotypes. (i.e. manifest more CNS disinhibition)

* p < 0.0001

N = 220 743 499

rs279836 genotype
Beta-rhythm, CNS Disinhibition, GABA + Alcoholism

- Beta rhythm is due to balance in networks of excitatory pyramidal cells and inhibitory interneurons that involve GABA$\textsubscript{A}$ action.
- Increased beta in alcoholics and high risk offspring indicates imbalance in excitation/inhibition (CNS disinhibition).
- Alterations of GABA$\textsubscript{A}$-benzodiazepine receptors in alcoholics and high risk offspring (e.g., Volkow et al., 1995; Abi-Dargham et al., 1998; reviewed by Krystal et al., 2006)
ENDOPHENOTYPE APPROACH

Same GABRA2 receptor gene is also involved in risk for Alcohol and Other Substance Dependence, Conduct Disorder (COGA: Edenberg et al. 2004; Dick et al. 2006; Agrawal et al., 2006)

This finding provides a biological hypothesis relating CNS disinhibition to genetic risk for alcoholism and related disorders:

- Variations in the GABRA2 receptor gene affect brain oscillations and level of neural excitation
- Imbalance in excitation/inhibition
- CNS disinhibition is involved in the genetic risk for alcoholism and related disorders

Independent replications: e.g., Covault et al. 2004, 2007; Lappalainen et al. 2005; Fehr et al. 2006; Soyka et al. 2007; Matthews et al., 2007
EEG COHERENCE

- Measure of cortical synchronization in neural networks (the phase consistency of electrodes over time)
- Indexing the functional relation, communication, between populations of neurons (coupling between brain regions)
- Modulated by genes controlling neurotransmitter action as pacemaker in inhibitory circuits
- Heritable (Chorlian et al., 2007)
EEG High Theta (6-7 Hz) Coherence between Alcoholics and Controls

- Significant increases in EEG high theta coherence in alcoholics, particularly posterior, at parietal-occipital regions
- Similar findings in high risk offspring of alcoholics (Chorlian, Rangaswamy, et al., 2007)
Linkage with Resting EEG
High Theta (6-7 Hz)
Coherence

**GABA-A**

SNPs across cluster of
GABA-A receptor genes
(Rangaswamy, in preparation)
Significant linkage and association of EEG high theta (6-7 Hz) coherence and CHRM2 (Muscarinic Acetylcholine Receptor M2)

• Both the GABAergic and cholinergic systems are important in the function of local inhibitory circuits, which are essential for cortical synchronization.
• Localizing genes helps unravel neural substrates.
• Dysfunction in coherence in alcoholics and High Risk
P300 (P3) amplitude of the event-related potential (ERP) provides a good endophenotype for alcohol dependence and other disinhibitory disorders

- Reduced P300 amplitude in abstinent alcoholics and high-risk offspring
  - Does not recover with prolonged abstinence
  - Precedes the development of alcoholism
P3 IS NOT A UNITARY PHENOMENON

- Multiple sources of activity: parietal and frontal cortex (including anterior cingulate).

- The P300 is composed of different frequencies: primarily posterior delta (1-3 Hz) and frontal theta (4-7 Hz).

- **Theta** oscillations have been associated with memory processes and attention. **Delta** oscillations are related to signal detection and decision making.

- These oscillations are **heritable** and are modulated by **genes** controlling neurotransmitters in the brain. → **endophenotypes for genetic analysis**
Event-Related Potential (ERP) vs. Event-Related Oscillation (ERO)

This figure depicts grand-averaged ERP waveforms (left) and bandpass filtered ERP waveforms (right) with different frequency band ranges.

**Theta ERO:**
- Memory processes
- Attention
- Fronto-limbic or cortico-hippocampal interactions

**Delta ERO:**
- Decision making
- Generated by cortico-cortical interactions
- Prominent after target stimuli

➢ This figure depicts grand-averaged ERP waveforms (left) and bandpass filtered ERP waveforms (right) with different frequency band ranges.
Theta and Delta EROs underlying P3 are reduced in alcoholics

(Jones et al., 2006)

Control: N=100, 29.6±5.7 yrs; Alcoholic: N=100, 30.0±5.3 yrs (male, right handed)
Theta and Delta EROs underlying P3 are reduced in offspring of alcoholics in COGA.

Theta and Delta EROs are more sensitive than P3 in discriminating between HR and LR.

(Rangaswamy et al., 2007)
Significant linkage on Chromosome 7 with frontal Theta ERO to visual targets

CHRM2

Waves 1 & 2,
N=1320/240

(Jones et al., 2004)
Association of 27 SNPs within and flanking **CHRM2** gene in Caucasian families
(Measured Genotype + QPDT)

**THETA ERO (frontal)**

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**DELTA ERO (Parietal-occipital)**

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**• Cholinergic system modulates P3**

**• M2 receptors inhibit presynaptic release of acetylcholine**

-> inhibition of irrelevant networks

**• Theta + delta depend on level of acetylcholine (muscarinic activation)**

(Jones et al., 2004; 2006)
Because of role of muscarinic cholinergic 2 receptor gene, \textit{CHRM2}, in brain oscillations (endophenotype), evaluated whether \textit{CHRM2} involved in risk for alcoholism

- Significant linkage and association with DSM-IV alcohol dependence + major depressive disorder (Wang et al., 2004)
- Comorbid alcohol and drug dependence—more severe form of disorder (Dick et al., 2007)

Replication by other groups

- \textit{CHRM2} gene predisposes to alcohol dependence, drug dependence and affective disorders (Luo et al., 2005)
Significant linkage on Chromosome 7 with frontal Theta ERO to visual targets

\[ F4 \text{ max}=3.72 \text{ at 162 cM} \]

Waves 1 & 2
N=1320/240

GRM8 chr 7q31.3-q32.1 (mGluR8)

Jones et al., 2004
Glutamate and EROs

- The major neurochemical substrates contributing to theta and delta rhythms and P3 involve strong GABAergic, cholinergic and glutamatergic system interactions.
- We already have evidence that a cholinergic muscarinic receptor gene (\textit{CHRM2}) is involved in event-related theta oscillations underlying the P3.
- To assess the potential association between SNPs in a glutamate receptor gene and the quantitative trait of event-related theta band energy during processing of target visual signals.
The **GRM8** is a member of the Group III metabotropic glutamate receptors (**GRM4**, **GRM6**, **GRM7** and **GRM8**), which are linked to the inhibition of the cyclic AMP cascade but differ in their agonist selectivities.

Substances acting as agonists of group III mGlu receptors were shown to produce an anxiolytic-like effect after intrahippocampal administration to rats. (Palucha and others 2004)

Administration of the mGlu8 receptor agonist has also been shown to suppress alcohol self-administration and cue-induced reinstatement of alcohol seeking in preclinical study. (Backstrom and Hyytia 2005)
## Association of SNPs in GRM8 with theta EROs

<table>
<thead>
<tr>
<th>SNP</th>
<th>b.p. position</th>
<th>Location</th>
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Significance Level: p<0.05 p<0.01 p<0.001 p<0.0001

Data present the p-value of the FBAT. (Chen et al., under revision)
## Association of SNPs in GRM8 with Alcohol Dependence

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- p<0.05
- p<0.01
- P<0.001
- p<0.0001

Data present the p-value of the FBAT. (Chen et al., under revision)
### Association of SNPs in GRM8 with theta EROs at Frontal, Central, and Parietal Regions and Alcohol Dependence

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Significance Level:
- p<0.05
- p<0.01
- p<0.001
- p<0.0001

Data present the p-value of the FBAT. (Chen et al., under revision)
Low visual P3 amplitude is not specific to risk of alcohol dependence but is characteristic of many disinhibitory conditions.

- Substance abuse
- Antisocial Personality Disorder
- Conduct disorder
- Attention Deficit Hyperactivity Disorder

(Reviewed by e.g., Porjesz et al., 2005)
Alcohol dependence is a disorder of disinhibition

- Characterized by **disturbed impulse regulation**, and “termination pathology” i.e. inability to terminate behavior at an appropriate point in time.
- These traits are **not unique to alcoholism**, but are fundamental to other psychiatric disorders.

Clinical manifestations of disinhibition:

- Impulsivity
- Alcohol dependence
- Drug dependence
- Conduct disorder
- Oppositional disorder
- Mania
- Attention Deficit Hyperactivity Disorder

---

**Is there a common genetic diathesis?**
OVERLAPPING GENETIC COMPONENTS OF DISINHIBITORY PSYCHIATRIC DISORDERS

Externalizing

Alcohol Dependence  Substance Dependence  Antisocial Personality  Conduct Disorder

Common underlying genetic liability involving impulse control

(Kendler et al., 2003)
Alcohol-dependent subjects show an increased level of impulsivity trait (BIS)

Significant negative correlations between VP3 amplitude and impulsivity. (Chen et al., 2007)
Alcoholics showed significantly reduced activation in anterior cingulate, cingulate gyrus, medial gyrus, and superior frontal gyrus with LORETA* during the processing of visual targets.

Controls

Alcoholics

*low-resolution brain electromagnetic tomography

• High Impulsive subjects, regardless of diagnosis, showed significantly reduced activation during the processing of target visual signal in the same frontal regions. (Chen et al., 2007)
Conclusions

- Genetically influenced differences in susceptibility involve neural disinhibition and impulsivity.
  - Involves frontal lobe functions
  - Influences a range of outcomes including externalizing and mood disorders, alcoholism and abuse of other substances.
Conclusions (continued)

- These findings underscore the utility of electrophysiology and the endophenotype approach in the genetic study of psychiatric disorders.
- Many of the same genes important for the expression of the endophenotypes help in identification of genes that increase the susceptibility for risk of alcohol dependence and related disorders.
Acknowledgment

The Collaborative Study on the Genetics of Alcoholism (COGA)

Co-Principal Investigators:

B. Porjesz  
SUNY Downstate Medical Center

V. Hesselbrock  
University of Connecticut

H. Edenberg  
Indiana University

L. Bierut  
Washington University

Nine different centers where data collection, analysis, and storage take place:

University of Connecticut (V. Hesselbrock)

Indiana University (H.J. Edenberg, J. Nurnberger Jr., P.M. Conneally, T. Foroud)

University of Iowa (S. Kuperman, R. Crowe)

SUNY Downstate (B. Porjesz)

Washington University in St. Louis (L. Bierut, A. Goate, J. Rice)

University of California at San Diego (M. Schuckit)

Howard University (R. Taylor)

Rutgers University (J. Tischfield)

Southwest Foundation (L. Almasy)

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In memory of Henri Begleiter and Theodore Reich, Principal and Co-Principal Investigators of COGA since its inception. We are indebted to their leadership in the establishment and nurturing of COGA, and acknowledge with great admiration their seminal scientific contributions to the field.

Dr. Andrew C. Chen receives support from the American Psychiatric Association/ American Psychiatric Institute for Research And Education/ NIMH PMRTP Award, 2006-2008
The P300 represents a measure of CNS processing of salient stimulus information (including attention and memory). P3(00) reflects an index of CNS inhibition. The low P3 amplitude indicates a state of disinhibition.
The S-transform TFR

- Time-Frequency Representation (TFR) used to *localize* the spectral content of *non-stationary* time-series.
- The S-transform TFR (Stockwell, 1996) is a *generalization* of the STFT (Portnoff, 1980) and an *extension* to the Continuous Wavelet Transform (Goupillaud, 1984).
- The S-transform provides frequency dependent resolution (multi-resolution) while simultaneously localizing the complex components of the signal.

\[
ST(f, \tau) = \int_{-\infty}^{\infty} h(t) \frac{|f|}{\sqrt{2\pi}} e^{-(\tau-t)^2 f^2 / 2} e^{i2\pi ft} dt
\]