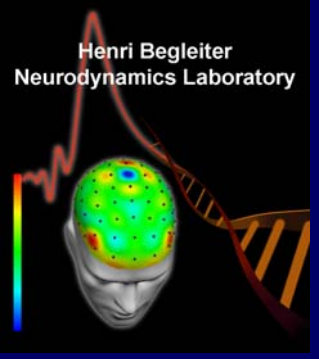

Neurophysiological Endophenotypes, CNS Disinhibition and Risk for Alcohol Dependence and Related Disorders

Prof. Bernice Porjesz
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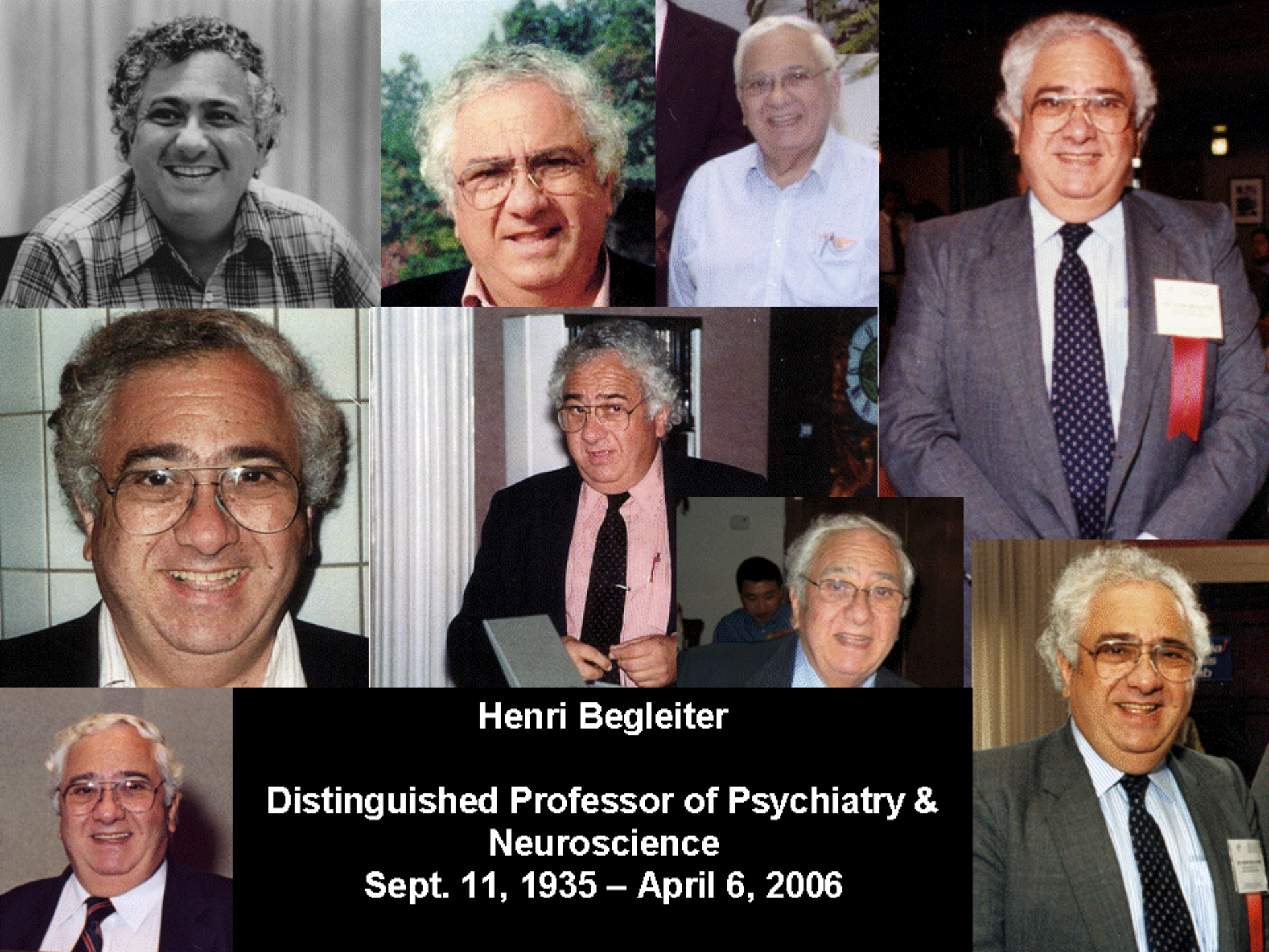
Assistant Professor of Psychiatry, SUNY Downstate
Attending Psychiatrist, University Hospital of Brooklyn



Henri Begleiter

Distinguished Professor of Psychiatry & Neuroscience

Sept. 11, 1935 – April 6, 2006


COGA
ANALOX INSTRUMENTS
COGA

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)

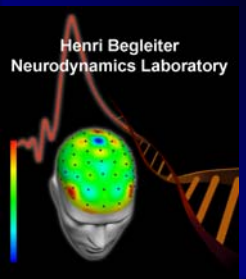
Endophenotypes

- 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."

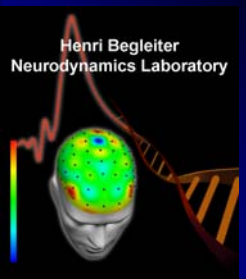
  (Tsuang & Faraone, 2000)



Advantages of using Quantitative Biological Risk Factors (*ENDOPHENOTYPES)* in search for genes in complex disorders

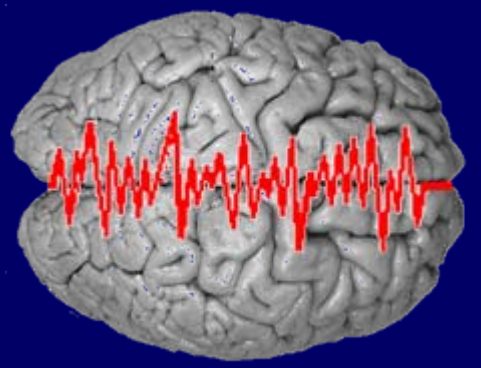
- Closer to gene action involved in the predisposition for the disorder
- Genetically simpler than clinical endpoints
- Quantitative traits provide more power to localize and characterize disease susceptibility genes
- Identify relatives of affected individuals who would be considered unaffected with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

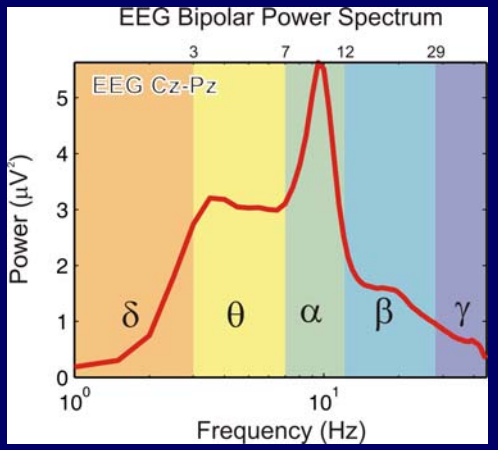
(reviewed by Porjesz and Begleiter, 2006)

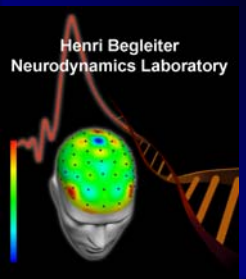


Brain oscillations as endophenotypes

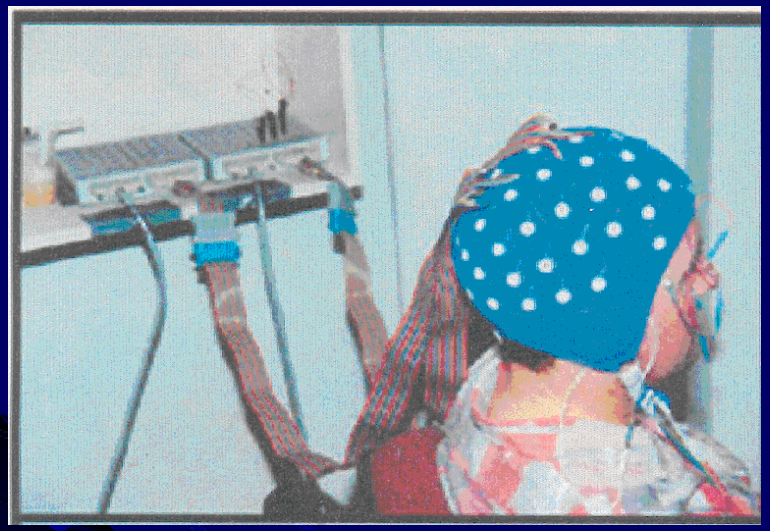
- Reflect ensembles of neurons firing in synchrony and represent the basic mechanism of neural communication.
  - High frequencies: are involved in short range communication
  - Low frequencies: longer range communication between brain areas.
- Reflect the dynamic millisecond by millisecond balance between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







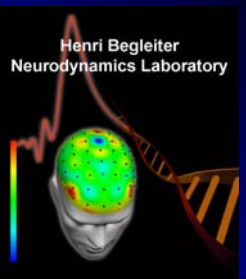
Brain oscillations as endophenotypes



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

  Event Related Potentials (ERP)

  Event Related Oscillations (ERO)



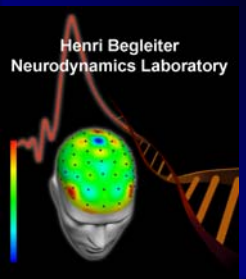
➢Selected brain oscillations that differentiate between ***alcoholics*** and controls, and ***high risk offspring*** and controls

Brain oscillations as endophenotypes

- Brain oscillations are highly heritable

Frequency band	Mean h^2 (Mz/Dz)
Delta (1.5-3.5 Hz)	76%
Theta (4-7.5 Hz)	89%
Alpha (8-12.5 Hz)	89%
Beta (13-25 Hz)	86%

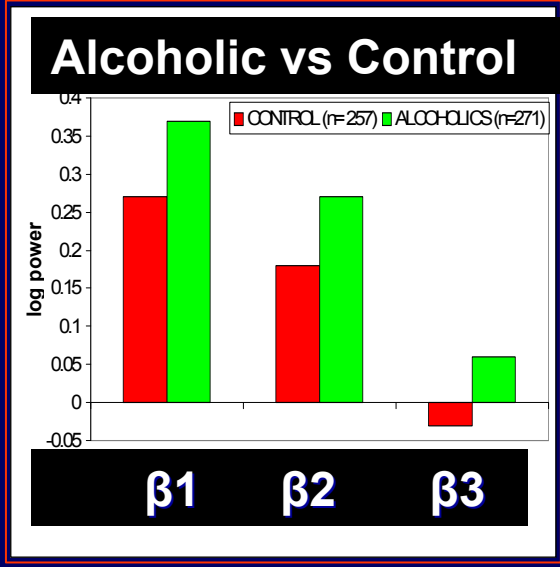
(Van Beijsterveldt et al., 1996)

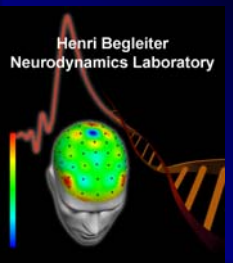


➢They are under genetic control and are modulated by genes controlling neurotransmitters in the brain.

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



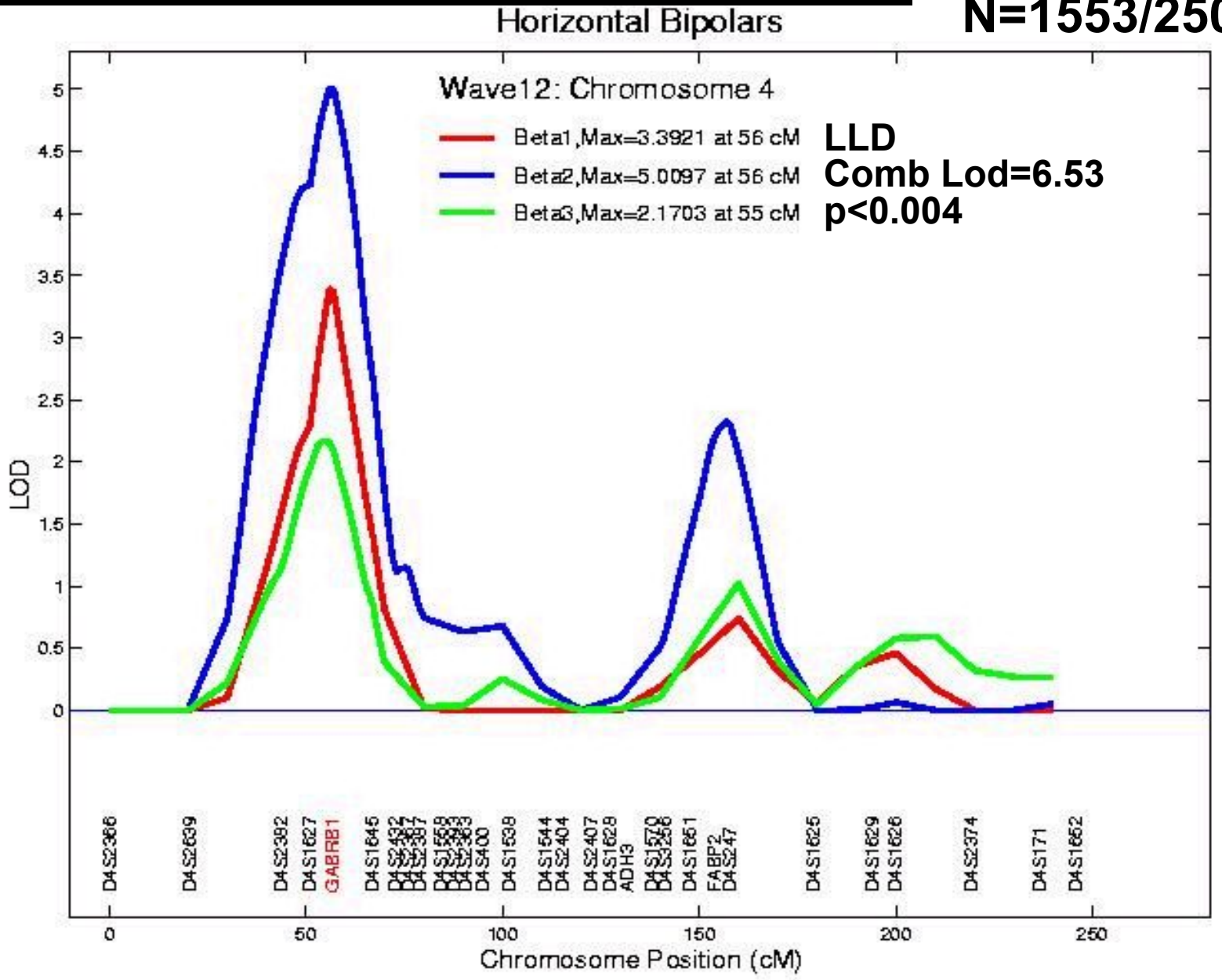


HR (high risk) minus LR (low risk) Beta power:

(Rangaswamy et al., 2002; 2004)

LINKAGE ANALYSIS RESTING EEG: BETA

N=1553/250

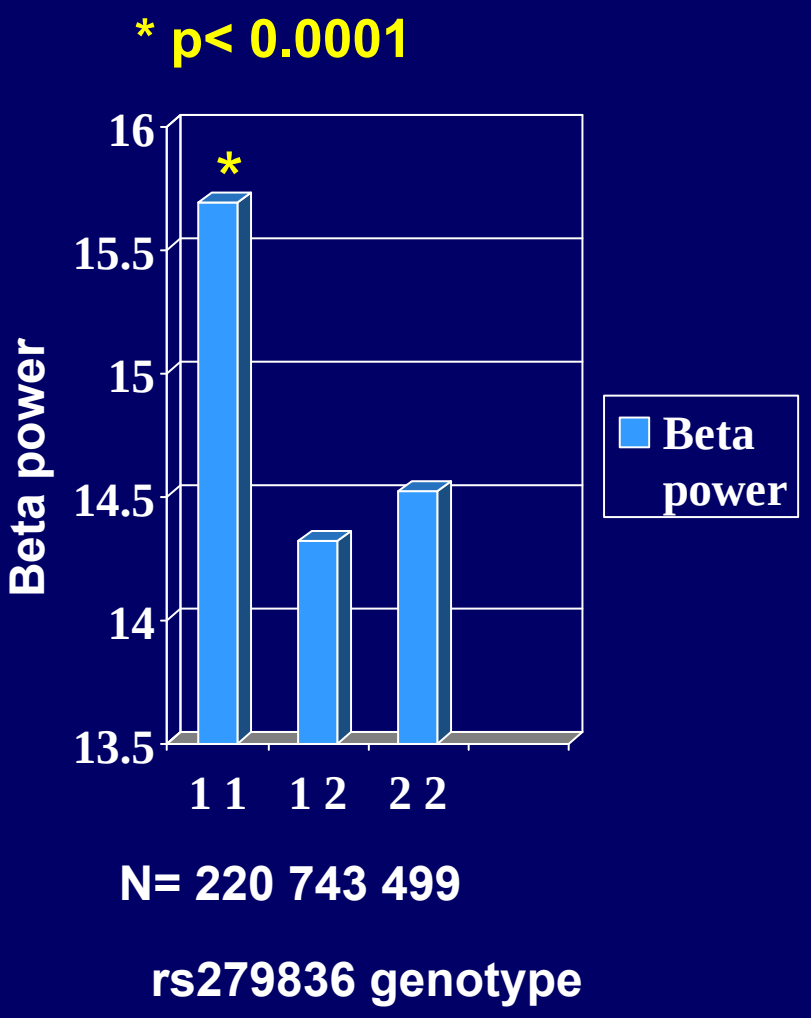


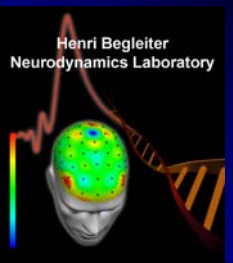
GABRA2, GABRA4, GABRB1, GABRG1

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*

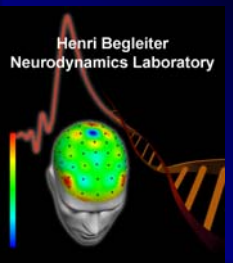
- **Homozygotes** for the rarer genotype (15%) of the rs279836 SNP in the *GABRA2* gene have significantly **increased EEG Beta 2** compared to individuals with all other genotypes. (i.e. manifest **more CNS disinhibition**)





Beta-rhythum, CNS Disinhibition, GABA + Alcoholism

- Beta rhythm is due to balance in networks of excitatory pyramidal cells and inhibitory interneurons that involve $GABA_A$ action.
- Increased beta in alcoholics and high risk offspring indicates imbalance in excitation/inhibition (CNS disinhibition).
- Alterations of $GABA_A$-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)

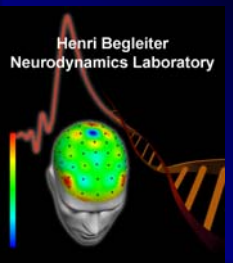


ENDOPHENOTYPE APPROACH→
Same *GABRA2* receptor gene is also involved in risk for Alcohol and Other Substance Dependence, Conduct Disorder

(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:

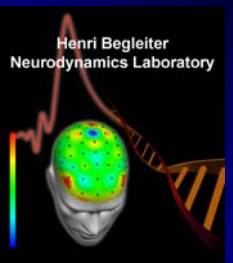
- Variations in the *GABRA2* receptor gene affect brain oscillations and level of neural excitation
- Imbalance in excitation/inhibition
- CNS disinhibition is involved in the genetic risk for alcoholism and related disorders



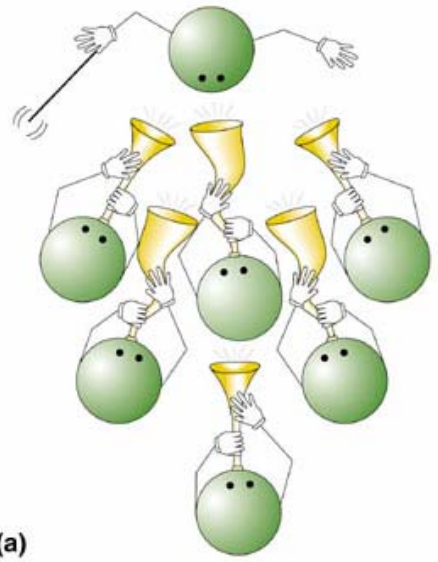
Independent replications: e.g., Covault et al. 2004, 2007; Lappalainen et al. 2005; Fehr et al. 2006; Soyka et al. 2007; Matthews et al., 2007

EEG COHERENCE

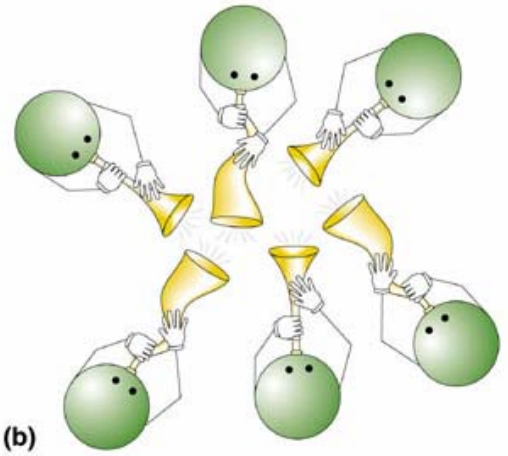
- Measure of cortical **synchronization in neural networks** (the phase consistency of electrodes over time)
- Indexing the functional relation, **communication**, between populations of neurons (coupling between brain regions)
- Modulated by genes controlling neurotransmitter action as pacemaker in inhibitory circuits
- Heritable (Chorlian et al., 2007)



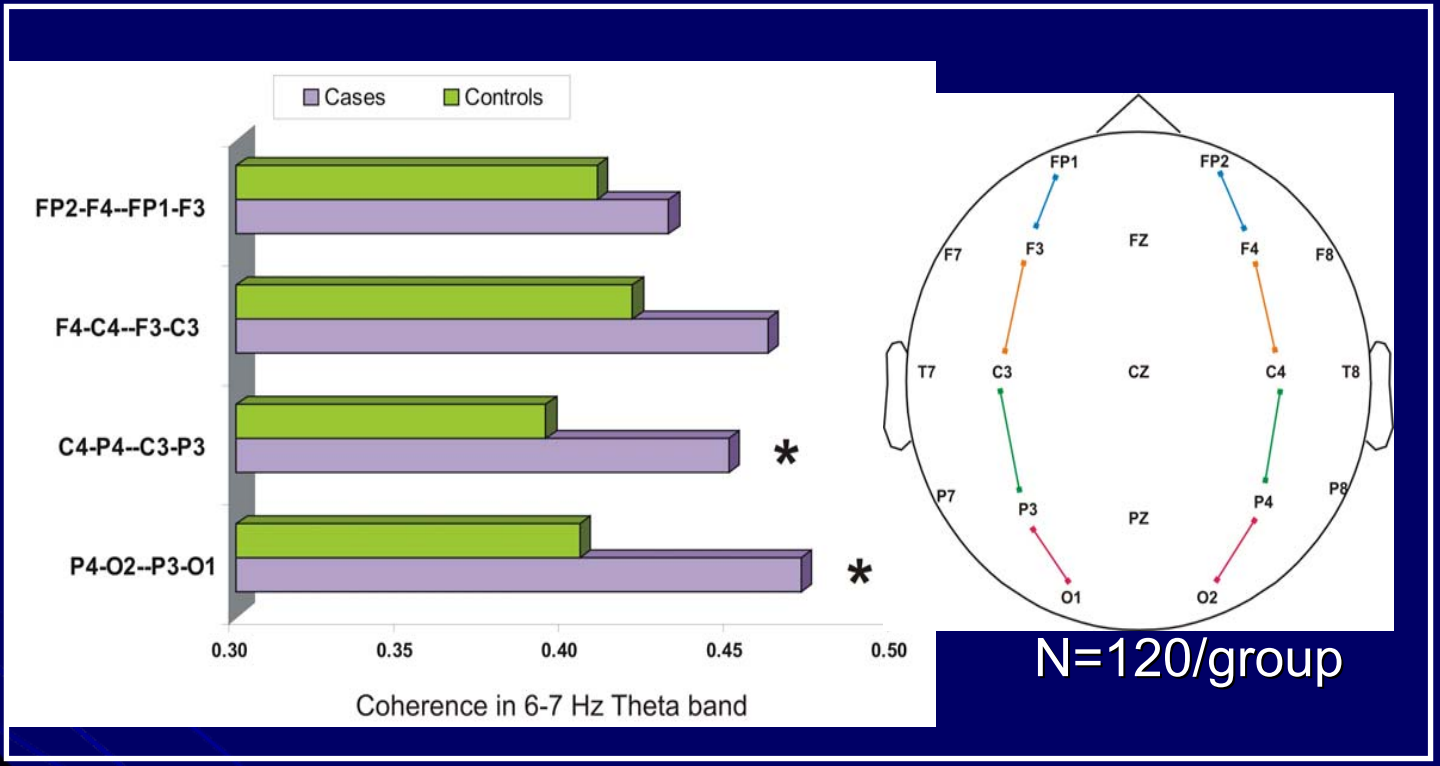
PACEMAKER:



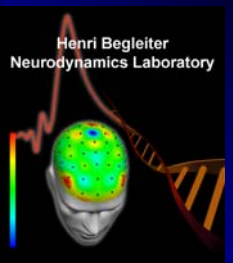
MUTUAL COORDINATION:



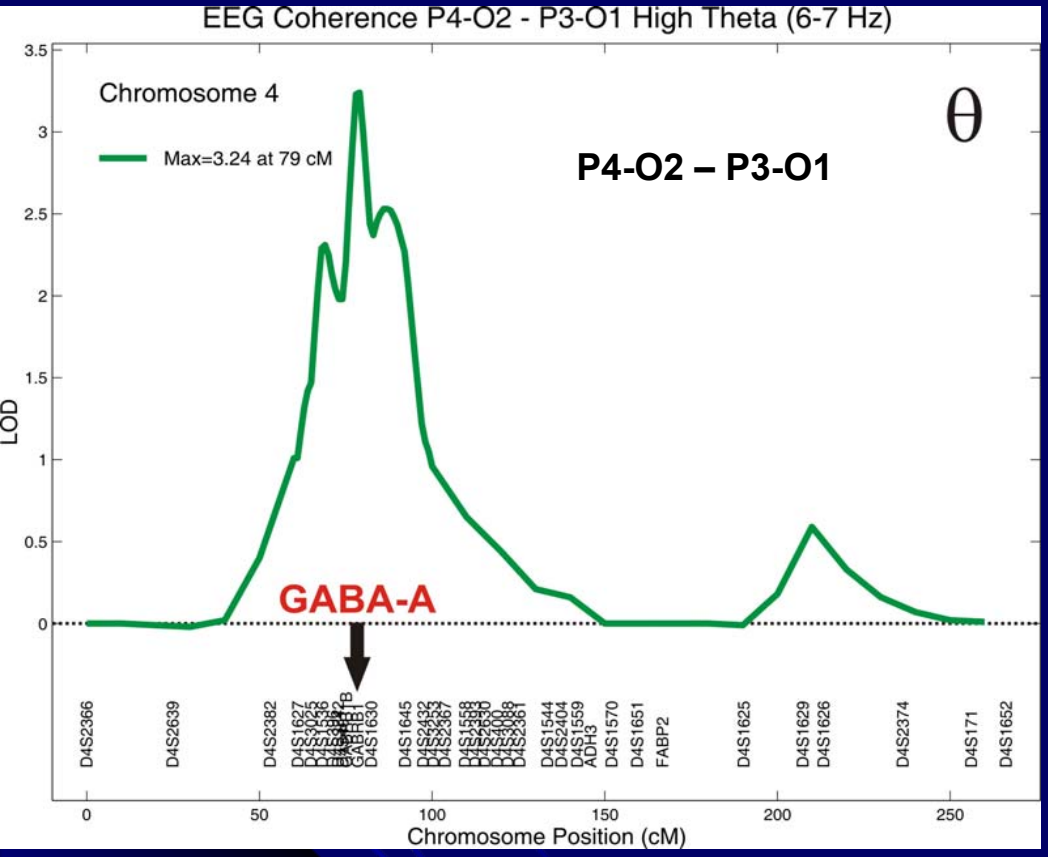
EEG High Theta (6-7 Hz) Coherence between Alcoholics and Controls

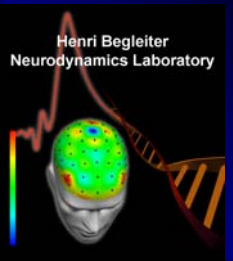


- Significant increases in EEG high theta coherence in alcoholics, particularly posterior, at parietal-occipital regions
- Similar findings in high risk offspring of alcoholics
  (Chorlian, Rangaswamy,et al., 2007)



Linkage with Resting EEG High Theta (6-7 Hz) Coherence





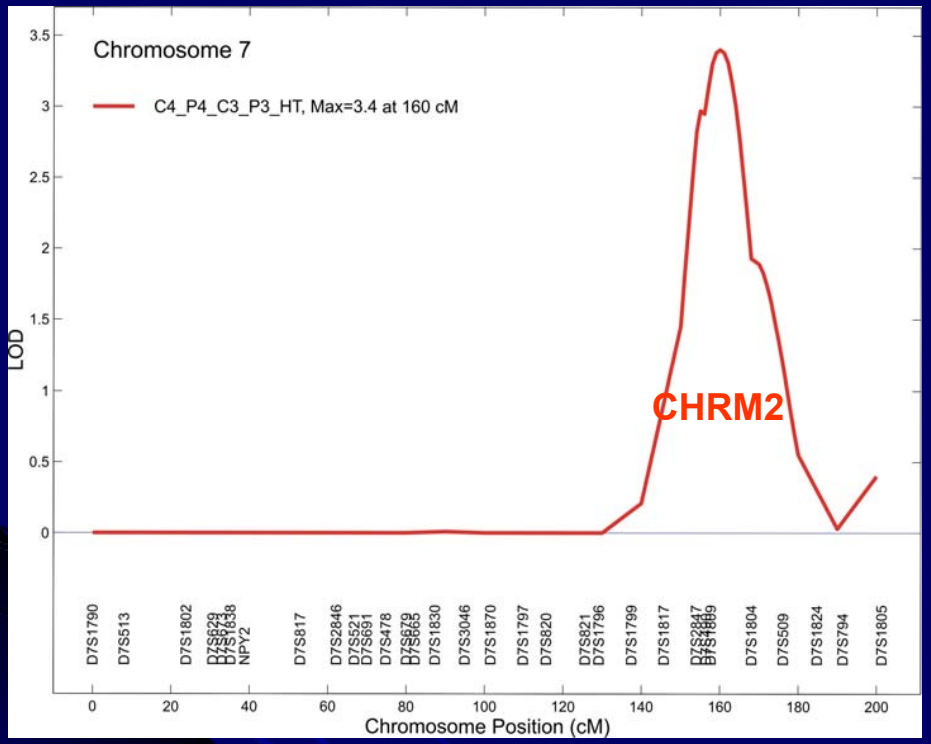
SNPs across cluster of GABA-A receptor genes

(Rangaswamy, in preparation)

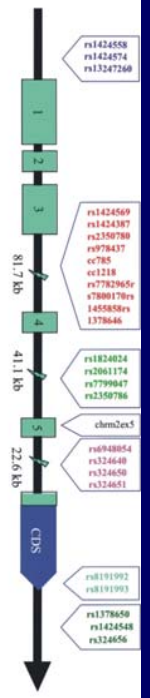
GABRA2 Association analysis

GABRA2		Posterior Theta Interhemisperic Coherence		Edenberg et al. (2004)	
SNP	Type	mg	qpdt_ave	AlcDep	EEG-β
rs490434	3'	0.03	0.0004	.0052*	0.64
rs576666	3'	0.001	0.0001	0.095	0.067
rs531460	3'	0.0004	0.0005	.022*	.024*
rs561779	3'	0.0003	0.0005	.048*	.044*
rs495818	3'	0.0003	0.001	.022*	.034*
rs497068	3'	0.001	0.0003	.0069*	0.26
rs572227	3'	0.001	0.001	.038*	.019*
rs573400	3'UTR	0.0005	0.005	0.062	0.27
rs541418	Intron 9	0.007		.020*	0.1
rs481311	Intron 9	0.001	0.002	0.076	0.17
rs507788	Intron 9	0.002	0.001	.031*	.068*
rs532780	Intron 9	0.005	0.0002	0.079	.016*
rs548583	Intron 9	0.005	0.0003	.012*	.028*
rs10938435	Intron 9	0.003	0.001	0.103	0.56
rs496650	Intron 8	0.01	0.03	0.054	0.75
rs540363	Intron 8	0.007	0.007	.044*	0.49
rs526752	Intron 8	0.003	0.0002	0.12	0.07
rs530329	Intron 8	0.001	0.0008	.034*	.048*
rs483160	Intron 8	0.004	0.0001	0.15	.036*
rs279871	Intron 7	0.001	0.016	.0004*	.049*
rs279869	Intron 6	0.004	0.013		
rs279867	Intron 6	0.003	0.00005	0.24	.05*
rs279866	Intron 6	0.001	0.002	.029*	.037*
rs1808851	Intron 6	0.007			
rs279863	Intron 5	0.006	0.0002	.017*	.011*
rs279861	Intron 5	0.002	0.0008	.037*	.045*
rs279858	Exon 5	0.002	0.05	.0087*	0.22
rs175931	Intron 4	0.004	0.0006	0.1	0.071
rs279843	Intron 4	0.01	0.006	.049*	0.3
rs279845	Intron 4	0.02	0.004	.013*	.011*
rs279846	Intron 4	0.03	0.0009	.017*	.012*
rs183961	Intron 4	0.02	0.001	.038*	.014*
rs1440130	Intron 4	0.02	0.0009	.013*	.017*
rs279826	Intron 4			.0008*	0.25
rs11503016	Intron 4			.014*	0.7
rs279827	Intron 3	0.03	0.0007	.0068*	.016*
rs279828	Intron 3	0.03	0.004	.0086*	.02*
rs279834	Intron 3	0.03	0.04	.015*	.027*
rs279836	Intron 3	0.02	0.002	.0071*	.0066*
rs279837	Intron 3	0.03	0.05	.035*	0.064
rs279841	Intron 3	0.04	0.008	.038*	.018*
rs189957	Intron 3	0.01	0.0003	.053*	0.27
rs1442059	Intron 3		0.002	.034*	.018*
rs1442061	Intron 3			0.37	0.24
rs1442062	Intron 3			0.22	0.13
rs11503015	Intron 3			0.76	0.57
rs11503014	Intron 0			0.91	0.97
rs3756007	Intron 0			0.99	0.98
rs894269	5'			0.097	0.84
rs1372472	5'				
rs2165607	5'			0.44	0.67
rs1545234	5'			0.41	0.62

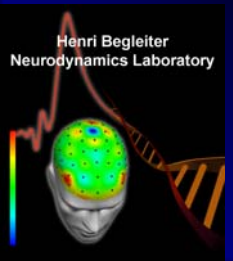
Significant linkage and association of EEG high theta (6-7 Hz) coherence and *CHRM2* (Muscarinic Acetylcholine Receptor M2)



	CHRM2 SNP	QPDT (sum)	QPDT (avg)
	rs1424558	0.49350	0.53640
	rs1424574	0.35110	0.44660
upstream of exon 1	rs13247260	0.60570	0.22790
	rs1424569	0.36160	0.36310
	rs1424387	0.20060	0.11800
	rs2350780	0.14600	0.07425
	rs978437	0.38080	0.09993
	cc785	0.06530	0.28720
	cc1218	0.03358	0.06465
	rs7782965	0.09095	0.04509
	rs7800170	0.00777	0.01463
	rs1455858	0.19430	0.06319
intron 3-4	rs1378646	0.09175	0.06671
	rs1824024	0.16600	0.04226
	rs2061174	0.02047	0.00771
	rs7799047	0.02306	0.01211
intron 4-5	rs2350786	0.08900	0.11950
exon 5	chrm2ex5	0.63450	0.77350
	rs6948054	0.02640	0.01937
	rs324640	0.01409	0.00346
	rs324650	0.03288	0.02253
intron 5-6	rs324651	0.02641	0.25460
	rs8191992	0.01437	0.00724
3' UTR	rs8191993	0.00523	0.00233
	rs1378650	0.00962	0.01006
	rs1424548	0.25490	0.23580
downstream of exon 6	rs324656	0.03406	0.06319

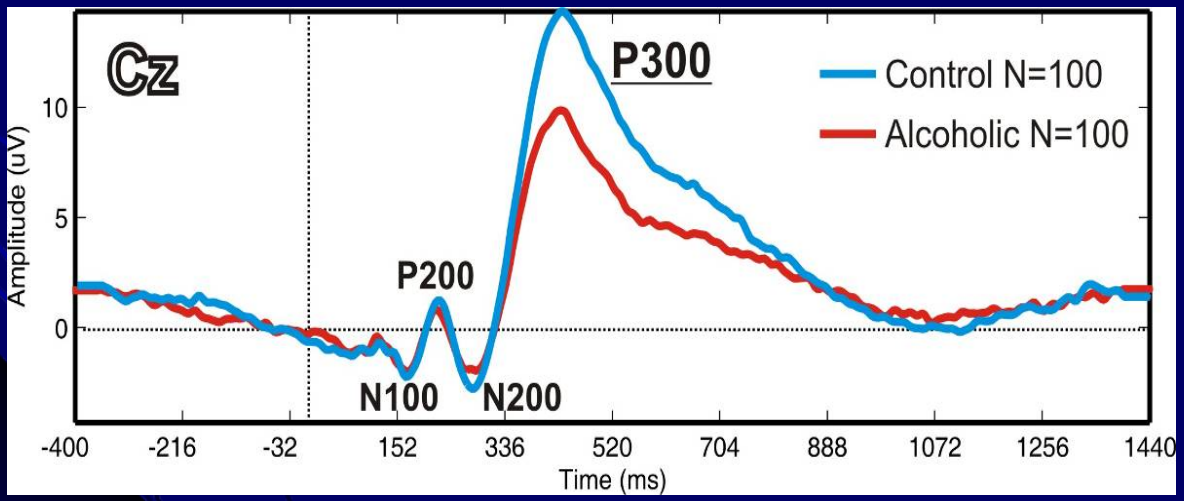


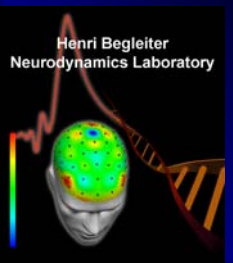
- Both the GABAergic and cholinergic systems are important in the function of local inhibitory circuits, which are essential for cortical synchronization.
- Localizing genes helps unravel neural substrates.
- Dysfunction in coherence in alcoholics and High Risk



P300 (P3) amplitude of the event-related potential (ERP) provides a good endophenotype for alcohol dependence and other disinhibitory disorders

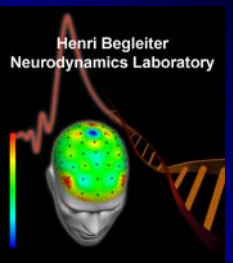
- Reduced P300 amplitude in abstinent alcoholics and high-risk offspring
- Does not recover with prolonged abstinence
- Precedes the development of alcoholism



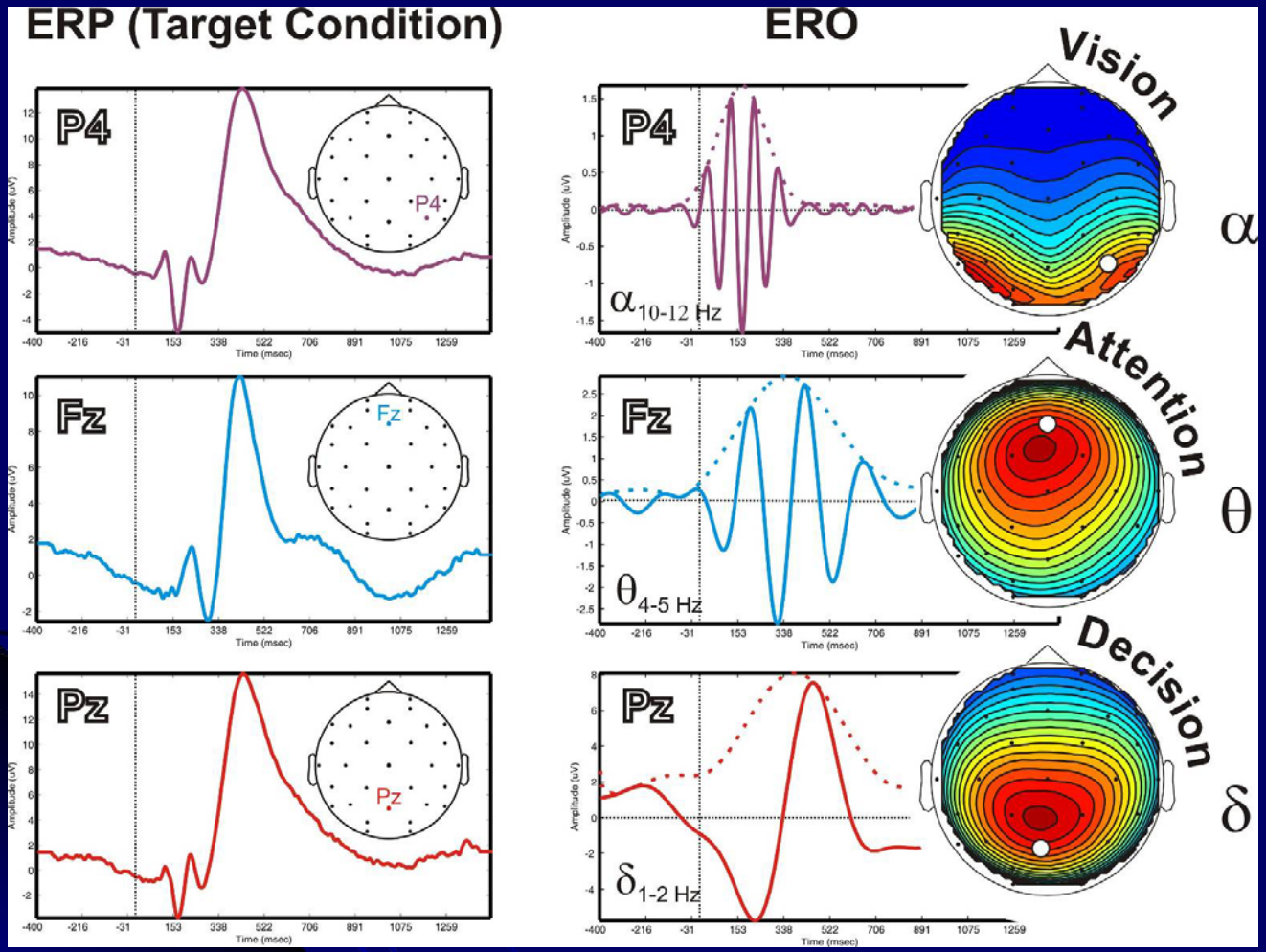


P3 IS NOT A UNITARY PHENOMENON

- **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)



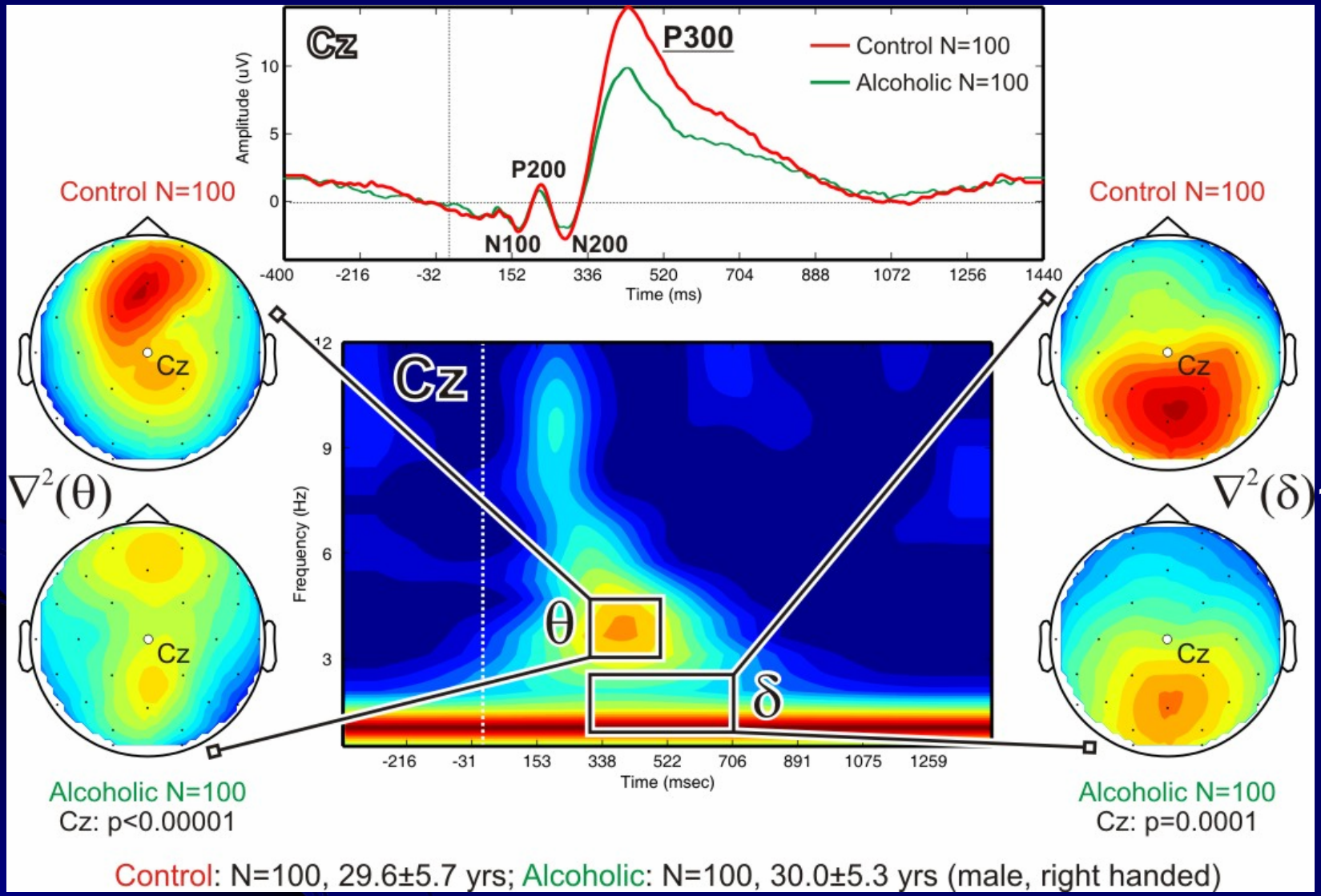
Theta ERO:
- Memory processes
- Attention
- Fronto-limbic or cortico-hippocampal interactions

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

Henri Begleiter
Neurodynamics Laboratory

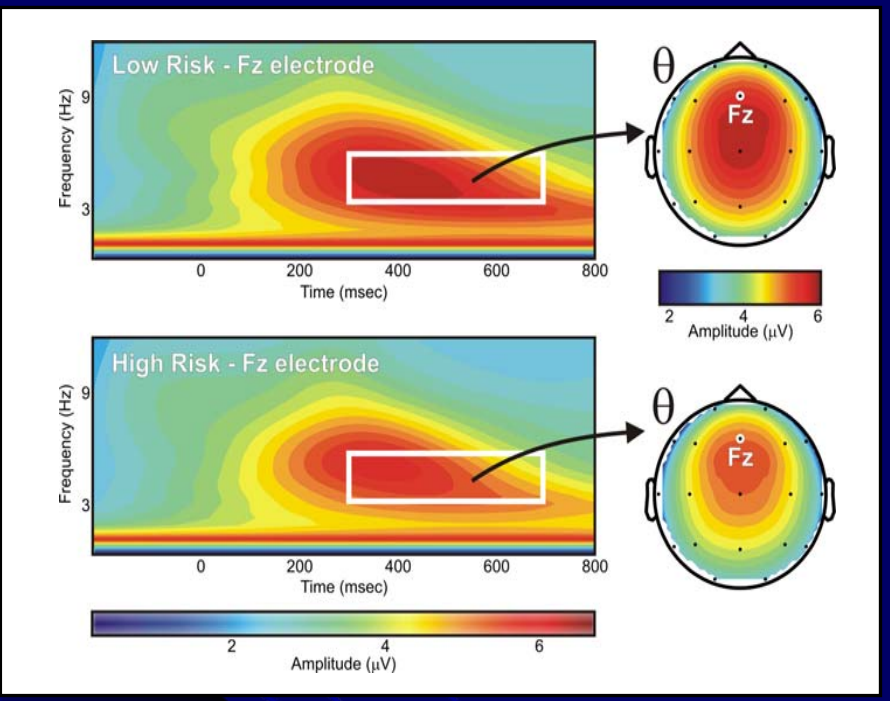
➢ This figure depicts grand-averaged ERP waveforms (left) and bandpass filtered ERP waveforms (right) with different frequency band ranges.

Theta and Delta EROs underlying P3 are reduced in alcoholics



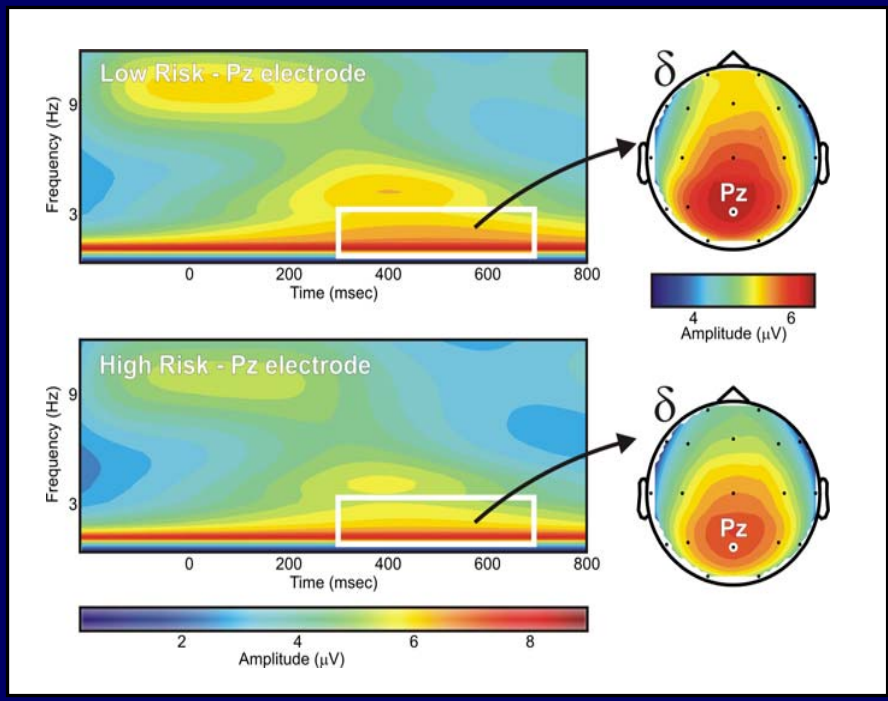
(Jones et al., 2006)

Theta and Delta EROs underlying P3 are reduced in offspring of alcoholics in COGA



Low Risk (LR)

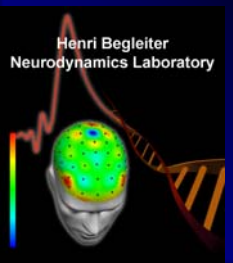
High Risk (HR)



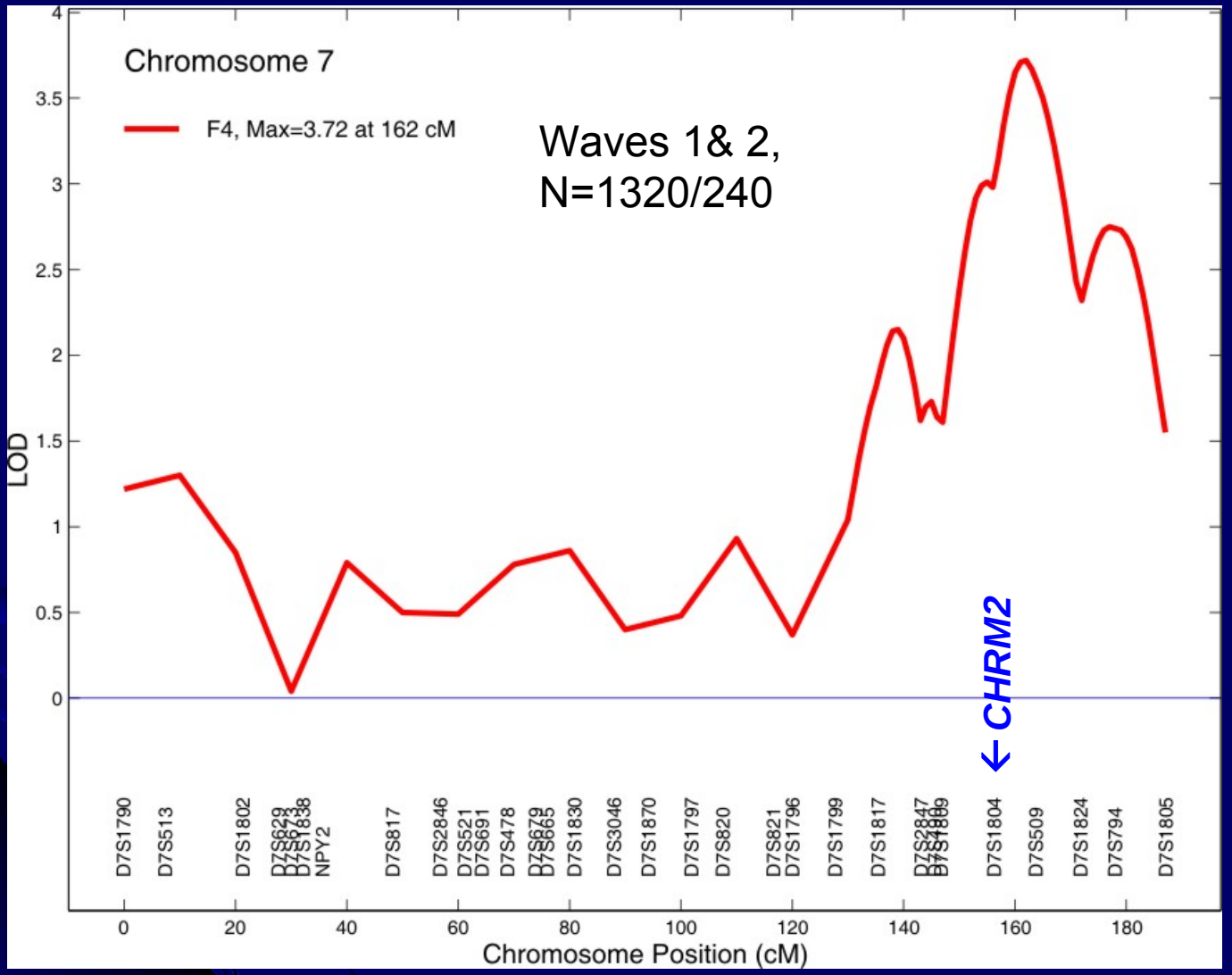
THETA **DELTA**

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



(Jones et al., 2004)

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Association of 27 SNPs within and flanking *CHRM2* gene in Caucasian families

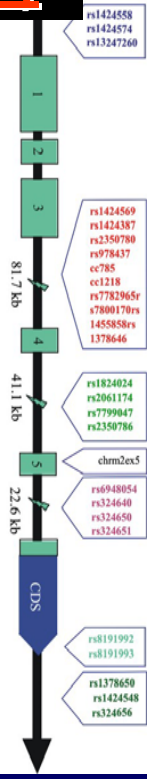
(Measured Genotype + QPDT)

THETA ERO (frontal)

	snp	F3			Fz			F4		
		mg	ave	sum	mg	ave	sum	mg	ave	sum
	rs1424558		0.024	0.161		0.043	0.355		0.060	0.459
upstream of exon 1	rs1424574		0.801	0.744		0.754	0.458		0.592	0.490
	rs13247260		0.319	0.497		0.719	0.652		0.747	0.842
	rs1424569		0.650	0.445		0.894	0.520		0.822	0.413
	rs1424387	0.028	0.370	0.094	0.042	0.309	0.074	0.034	0.184	0.057
	rs2350780		0.266	0.409	0.037	0.185	0.245	0.008	0.296	0.690
	rs978437	0.007	0.004	0.006	0.002	0.011	0.010		0.012	0.029
	cc785		0.206	0.673		0.491	0.496		0.339	0.660
	cc1218	0.039	0.196	0.229	0.018	0.241	0.191	0.011	0.161	0.156
	rs7782965	0.012	0.006	0.010	0.006	0.023	0.020	0.018	0.025	0.064
	rs7800170		0.210	0.172	0.033	0.214	0.110	0.016	0.147	0.112
	rs1455858	0.002	0.009	0.009	0.000	0.025	0.013	0.001	0.020	0.019
intron 3-4	rs1378646	0.003	0.008	0.007	0.001	0.032	0.012	0.004	0.018	0.025
	rs1824024	0.001	0.002	0.010	0.000	0.018	0.024	0.001	0.013	0.066
	rs2061174	0.031	0.002	0.023	0.008	0.010	0.013	0.019	0.005	0.020
	rs7799047	0.037	0.013	0.039	0.013	0.034	0.045	0.030	0.023	0.069
intron 4-5	rs2350786	0.017	0.004	0.044	0.006	0.017	0.034	0.012	0.014	0.073
exon 5	chrm2ex5		0.820	0.496		0.686	0.365		0.502	0.255
	rs6948054	0.034	0.003	0.030	0.008	0.013	0.020	0.019	0.007	0.029
	rs324640		0.539	0.425		0.862	0.369		0.908	0.512
	rs324650		0.615	0.396		0.530	0.298		0.732	0.490
intron 5-6	rs324651		0.929	0.416		0.726	0.285		0.649	0.258
	rs8191992		0.954	0.675		0.705	0.325		0.850	0.274
3'UTR	rs8191993		0.932	0.621		0.380	0.937		0.487	0.630
	rs1378650		0.035	0.093		0.059	0.044		0.045	0.035
downsteam of exon 6	rs1424548		0.045	0.036		0.105	0.028		0.058	0.018
	rs324656		0.684	0.663		0.374	0.527		0.775	0.223

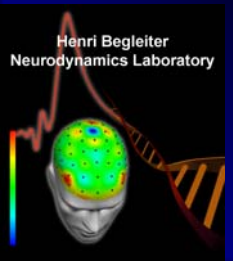
DELTA ERO (Parietal-occipital)

	snp	P3			O1		
		mg	ave	sum	mg	ave	sum
	rs1424558		0.717	0.734		0.867	0.481
upstream of exon 1	rs1424574		0.814	0.795		0.541	0.462
	rs13247260		0.757	0.547		0.517	0.453
	rs1424569		0.431	0.287		0.469	0.260
	rs1424387		0.299	0.371		0.234	0.232
	rs2350780	0.011	0.377	0.131		0.780	0.314
	rs978437	0.016	0.172	0.057	0.046	0.200	0.027
	cc785	0.010	0.247	0.016		0.114	0.020
	cc1218	0.015	0.020	0.029		0.021	0.022
	rs7782965	0.007	0.613	0.225	0.032	0.574	0.128
	rs7800170	0.004	0.021	0.033	0.017	0.015	0.017
	rs1455858	0.022	0.543	0.200		0.559	0.122
intron 3-4	rs1378646	0.007	0.471	0.278	0.043	0.578	0.222
	rs1824024	0.026	0.524	0.109		0.445	0.061
	rs2061174		0.884	0.698		0.672	0.297
	rs7799047		0.709	0.876		0.900	0.394
intron 4-5	rs2350786		0.601	0.573		0.510	0.416
exon 5	chrm2ex5		0.060	0.252		0.022	0.135
	rs6948054		0.962	0.863		0.638	0.413
	rs324640	0.005	0.022	0.021	0.004	0.023	0.011
	rs324650	0.008	0.052	0.043	0.011	0.022	0.029
intron 5-6	rs324651		0.195	0.007		0.172	0.021
	rs8191992	0.003	0.006	0.009	0.039	0.014	0.010
3'UTR	rs8191993		0.365	0.529		0.789	0.616
	rs1378650	0.009	0.049	0.090		0.113	0.176
downsteam of exon 6	rs1424548		0.689	0.432		0.999	0.804
	rs324656		0.012	0.101		0.039	0.131



- Cholinergic system modulates P3
- M2 receptors inhibit presynaptic release of acetylcholine
  - ->inhibition of irrelevant networks
- Theta + delta depend on level of acetylcoholine (muscarinic activation)

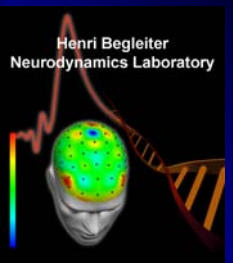
(Jones et al., 2004; 2006)



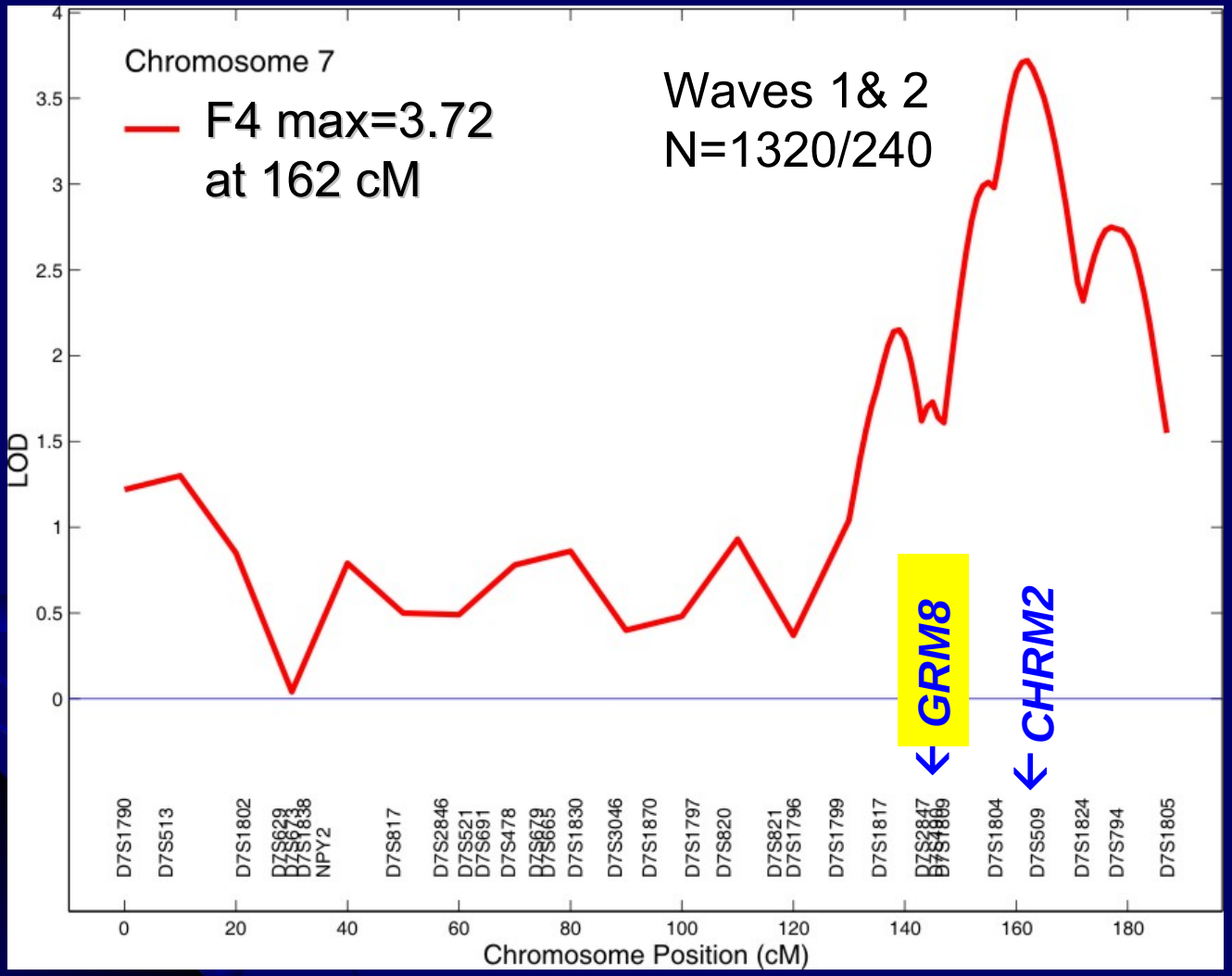
EVIDENCE FROM COGA PROJECT THAT *CHRM2* GENE INVOLVED IN CLINICAL DIAGNOSES

- Because of role of muscarinic cholinergic 2 receptor gene,*CHRM2,* in brain oscillations (endophenotype), evaluated whether *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
  - *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



GRM8 chr 7q31.3-q32.1 (mGluR8) Jones et al., 2004

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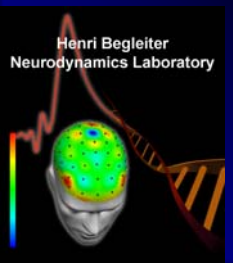
Glutamate and EROs

- 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 (*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.



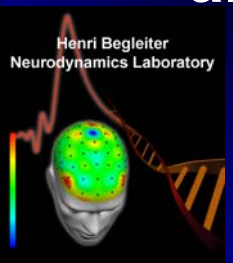
GRM8 chr 7q31.3-q32.1 (mGluR8)

- 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.

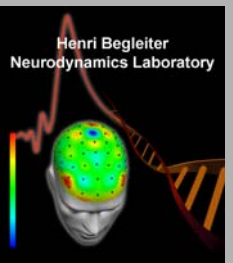
(Backstrom and Hyytia 2005)



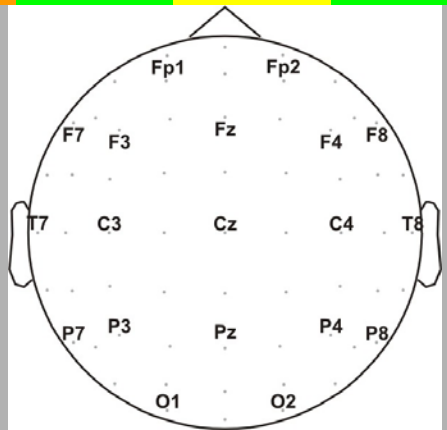
Association of SNPs in *GRM8* with theta EROs

SNP	b.p. position	Loca-tion	Frontal F3	Frontal Fz	Frontal F4	Central C3	Central Cz	Central C4	Parietal P3	Parietal Pz	Parietal P4
RS2402816	125785127	intron7	0.093351	0.252568	0.093892	0.118173	0.14569	0.024175	0.379564	0.149178	0.158817
RS2299459	125789319	intron7	0.000242	0.000858	0.000135	0.000225	0.00027	0.00005	0.000658	0.000318	0.001146
RS1158720	125802257	intron7	0.000553	0.0016	0.000389	0.000356	0.00068	0.000191	0.001271	0.002041	0.006588
RS769198	125843397	Exon7	0.148956	0.164083	0.190267	0.176354	0.14539	0.22199	0.339653	0.254789	0.222664
RS7797602	125881778	intron6	0.000151	0.000318	0.000087	0.000275	0.00036	0.000103	0.00096	0.001005	0.003023
RS2402820	125891649	intron6	0.025128	0.049439	0.012641	0.074566	0.14073	0.041059	0.058175	0.077618	0.084461
RS1074728	125906795	intron6	0.096584	0.216603	0.114742	0.091394	0.09409	0.021838	0.134333	0.074237	0.15928
RS4731323	125917981	intron6	0.005013	0.012996	0.006684	0.005948	0.00978	0.002702	0.011203	0.006601	0.015576
RS1361991	125932593	intron6	0.214853	0.360647	0.380487	0.319222	0.21013	0.127477	0.579042	0.29104	0.27828
RS2299495	125950918	intron6	0.085667	0.112744	0.1531	0.026541	0.04064	0.145957	0.011396	0.028879	0.032381
RS2299498	125951878	intron6	0.486164	0.767491	0.647005	0.797503	0.80816	0.418746	0.785061	0.556374	0.379391
RS10256873	125962243	intron6	0.935112	0.735431	0.971051	0.51099	0.47389	0.981567	0.269095	0.385705	0.586868
RS1361995	125966008	intron6	0.00035	0.000996	0.000603	0.000133	0.00014	0.000057	0.000532	0.000298	0.000768
RS10487457	125970841	intron6	0.001119	0.002741	0.001726	0.000218	0.00042	0.000121	0.001015	0.000857	0.002111
RS10487459	125972206	intron6	0.000718	0.002283	0.001359	0.000228	0.0003	0.000098	0.001097	0.000693	0.001935

Significance Level: p<0.05 | p<0.01 | P<0.001 | p<0.0001

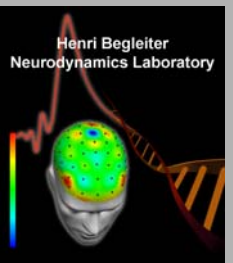


Data present the p-value of the FBAT.
(Chen et al., under revision)



Association of SNPs in *GRM8* with Alcohol Dependence

SNP	b.p. position	location	DSM-IV	ICD-10
RS2402816	125785127	intron7	0.096978	0.122487
RS2299459	125789319	intron7	0.723224	0.938865
RS1158720	125802257	intron7	0.713209	0.940422
RS769198	125843397	Exon7	0.947598	0.936858
RS7797602	125881778	intron6	0.605235	0.781739
RS2402820	125891649	intron6	0.683155	0.465489
RS1074728	125906795	intron6	0.133743	0.200811
RS4731323	125917981	intron6	0.149046	0.532717
RS1361991	125932593	intron6	0.017395	0.032223
RS2299495	125950918	intron6	0.489521	0.77779
RS2299498	125951878	intron6	0.024236	0.046078
RS10256873	125962243	intron6	0.038377	0.203827
RS1361995	125966008	intron6	0.058406	0.036781
RS10487457	125970841	intron6	0.070355	0.03734
RS10487459	125972206	intron6	0.072757	0.040956



Significance Level: p<0.05 | p<0.01 | P<0.001 | p<0.0001

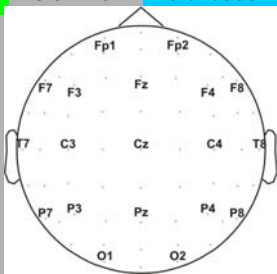
Data present the p-value of the FBAT.

(Chen et al., under revision)

Association of SNPs in *GRM8* with theta EROs at Frontal, Central, and Parietal Regions and Alcohol Dependence

SNP	b.p. position	Loca-tion	F3	Frontal Fz	F4	C3	Centrl Cz	C4	P3	Parietl Pz	P4	DSM-IV	ICD-10
RS2402816	125785127	intron7	0.093351	0.252568	0.093892	0.118173	0.145693	0.024175	0.379564	0.149178	0.158817	0.096978	0.122487
RS2299459	125789319	intron7	0.000242	0.000858	0.000135	0.000225	0.000272	0.00005	0.000658	0.000318	0.001146	0.723224	0.938865
RS1158720	125802257	intron7	0.000553	0.0016	0.000389	0.000356	0.000679	0.000191	0.001271	0.002041	0.006588	0.713209	0.940422
RS769198	125843397	Exon7	0.148956	0.164083	0.190267	0.176354	0.145386	0.22199	0.339653	0.254789	0.222664	0.947598	0.936858
RS7797602	125881778	intron6	0.000151	0.000318	0.000087	0.000275	0.000363	0.000103	0.00096	0.001005	0.003023	0.605235	0.781739
RS2402820	125891649	intron6	0.025128	0.049439	0.012641	0.074566	0.140728	0.041059	0.058175	0.077618	0.084461	0.683155	0.465489
RS1074728	125906795	intron6	0.096584	0.216603	0.114742	0.091394	0.094091	0.021838	0.134333	0.074237	0.15928	0.133743	0.200811
RS4731323	125917981	intron6	0.005013	0.012996	0.006684	0.005948	0.009776	0.002702	0.011203	0.006601	0.015576	0.149046	0.532717
RS1361991	125932593	intron6	0.214853	0.360647	0.380487	0.319222	0.210134	0.127477	0.579042	0.29104	0.27828	0.017395	0.032223
RS2299495	125950918	intron6	0.085667	0.112744	0.1531	0.026541	0.040644	0.145957	0.011396	0.028879	0.032381	0.489521	0.77779
RS2299498	125951878	intron6	0.486164	0.767491	0.647005	0.797503	0.808164	0.418746	0.785061	0.556374	0.379391	0.024236	0.046078
RS10256873	125962243	intron6	0.935112	0.735431	0.971051	0.51099	0.473886	0.981567	0.269095	0.385705	0.586868	0.038377	0.203827
RS1361995	125966008	intron6	0.00035	0.000996	0.000603	0.000133	0.000141	0.000057	0.000532	0.000298	0.000768	0.058406	0.036781
RS10487457	125970841	intron6	0.001119	0.002741	0.001726	0.000218	0.00042	0.000121	0.001015	0.000857	0.002111	0.070355	0.03734
RS10487459	125972206	intron6	0.000718	0.002283	0.001359	0.000228	0.000297	0.000098	0.001097	0.000693	0.001935	0.072757	0.040956

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



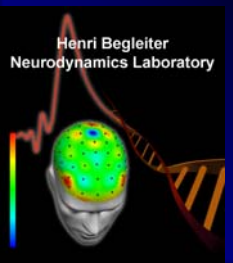
Data present the p-value of the FBAT.

(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)



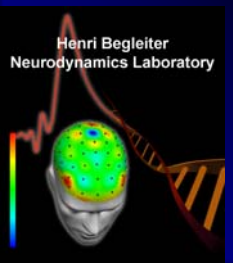
Alcohol dependence is a disorder of disinhibition

- 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.

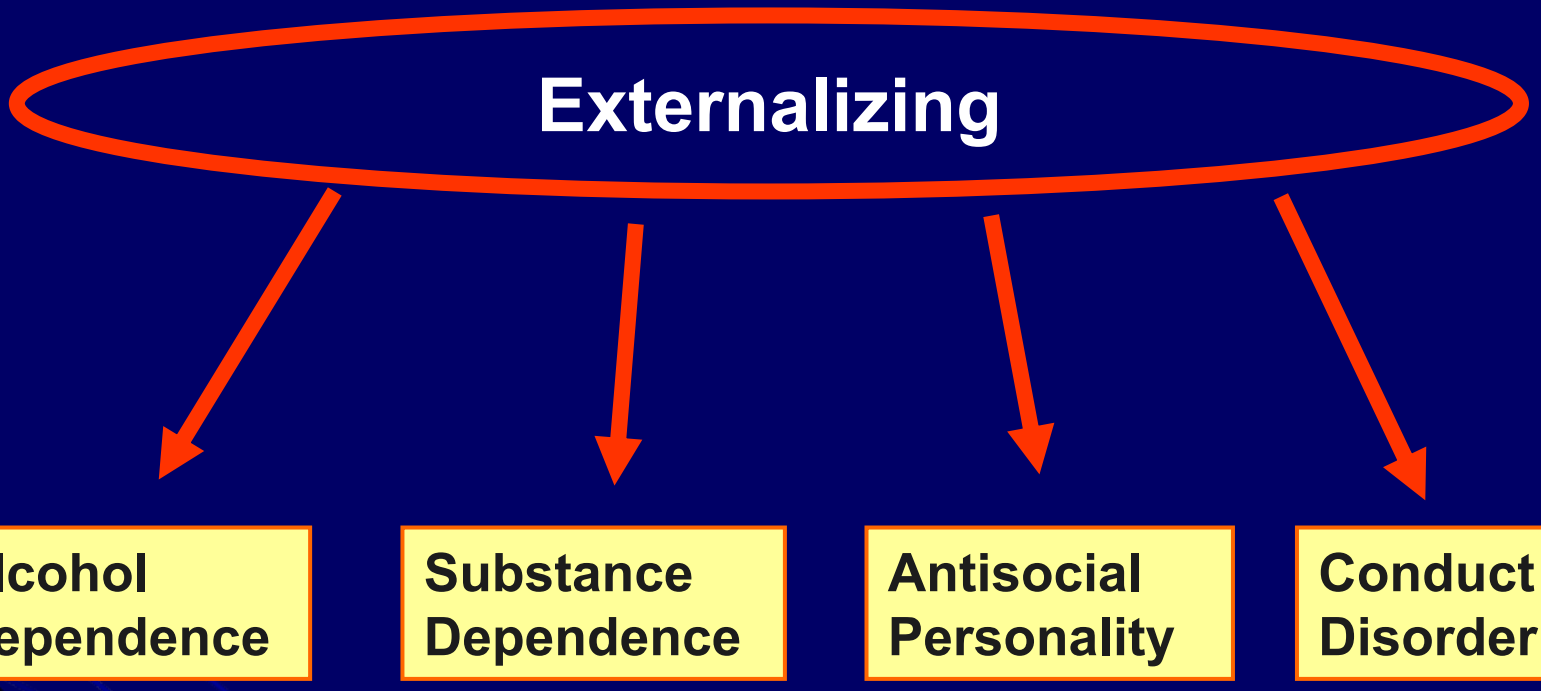
Clinical manifestations of disinhibition:

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



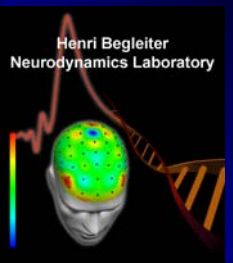
Is there a common genetic diathesis ?

OVERLAPPING GENETIC COMPONENTS OF DISINHIBITORY PSYCHIATRIC DISORDERS

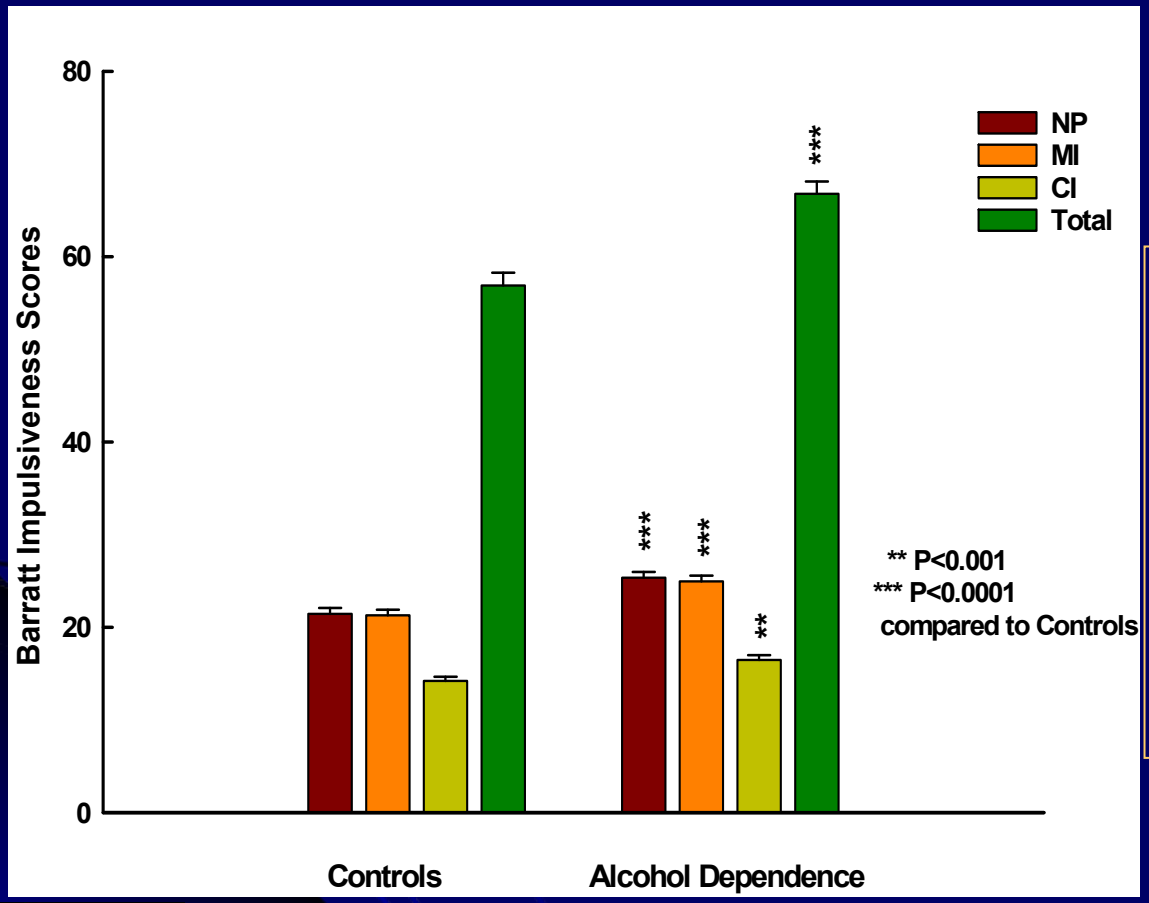


Common underlying genetic liability involving impulse control

(Kendler et al., 2003)



Alcohol-dependent subjects show an increased level of impulsivity trait (BIS)



Total score + Subscales:

NP= Non-Planning

MI= Motor Impulsiveness

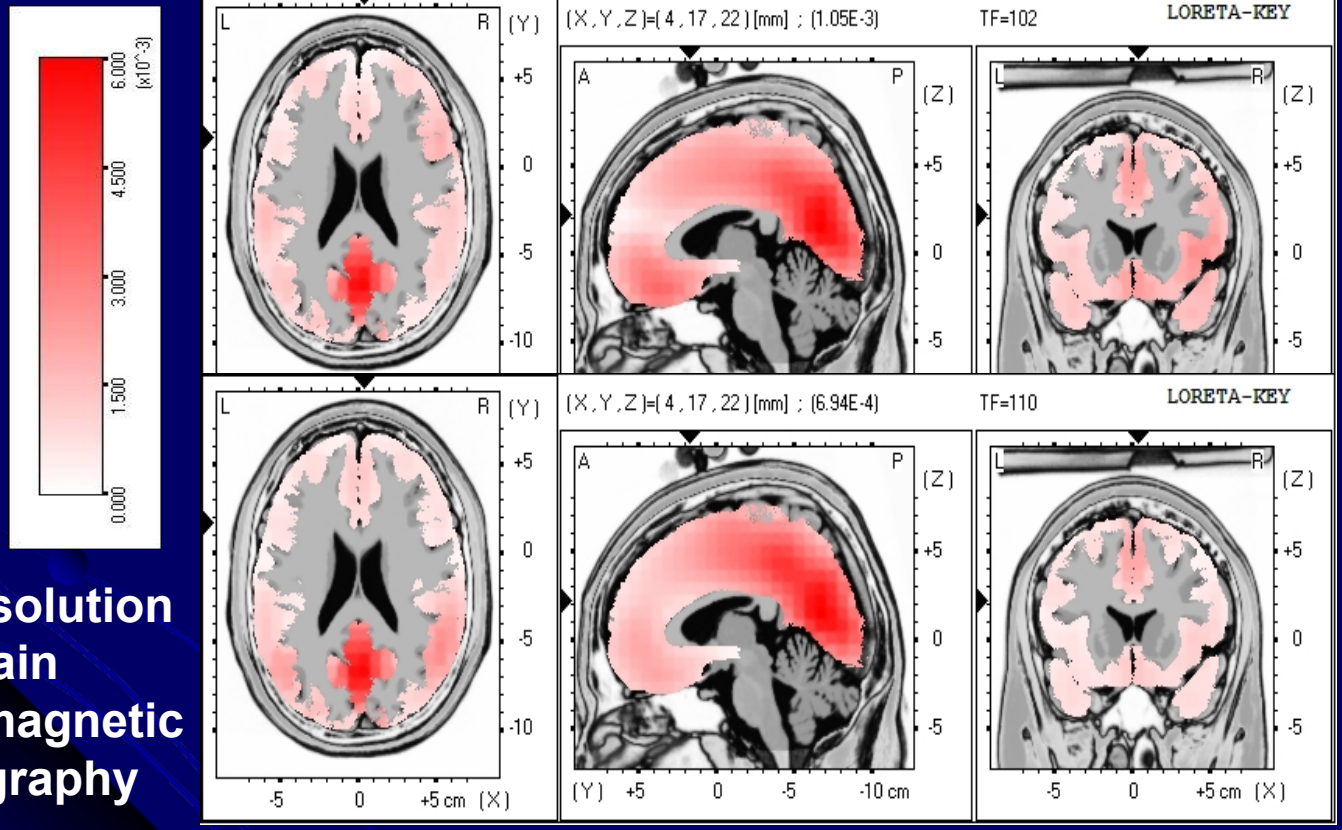
CI= Cognitive Impulsiveness

(Attentional Impulsiveness)

Henri Begleiter
Neurodynamics Laboratory

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

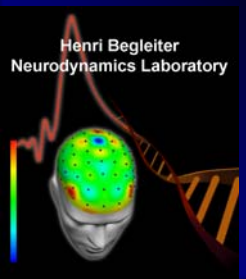
Alcoholics

*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)

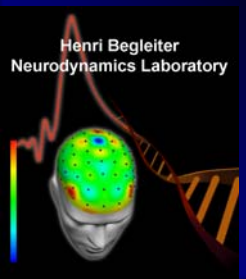
Conclusions

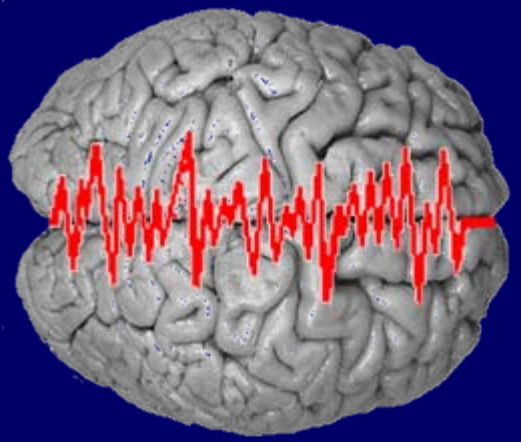
- Genetically influenced differences in susceptibility involve neural disinhibition and impulsivity.
  - Involves frontal lobe functions
  - Influences a range of outcomes including externalizing and mood disorders, alcoholism and abuse of other substances.



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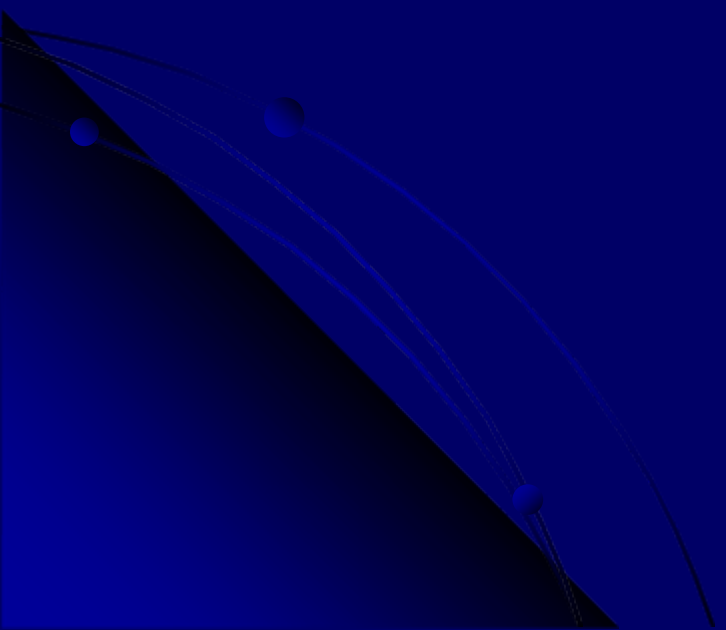
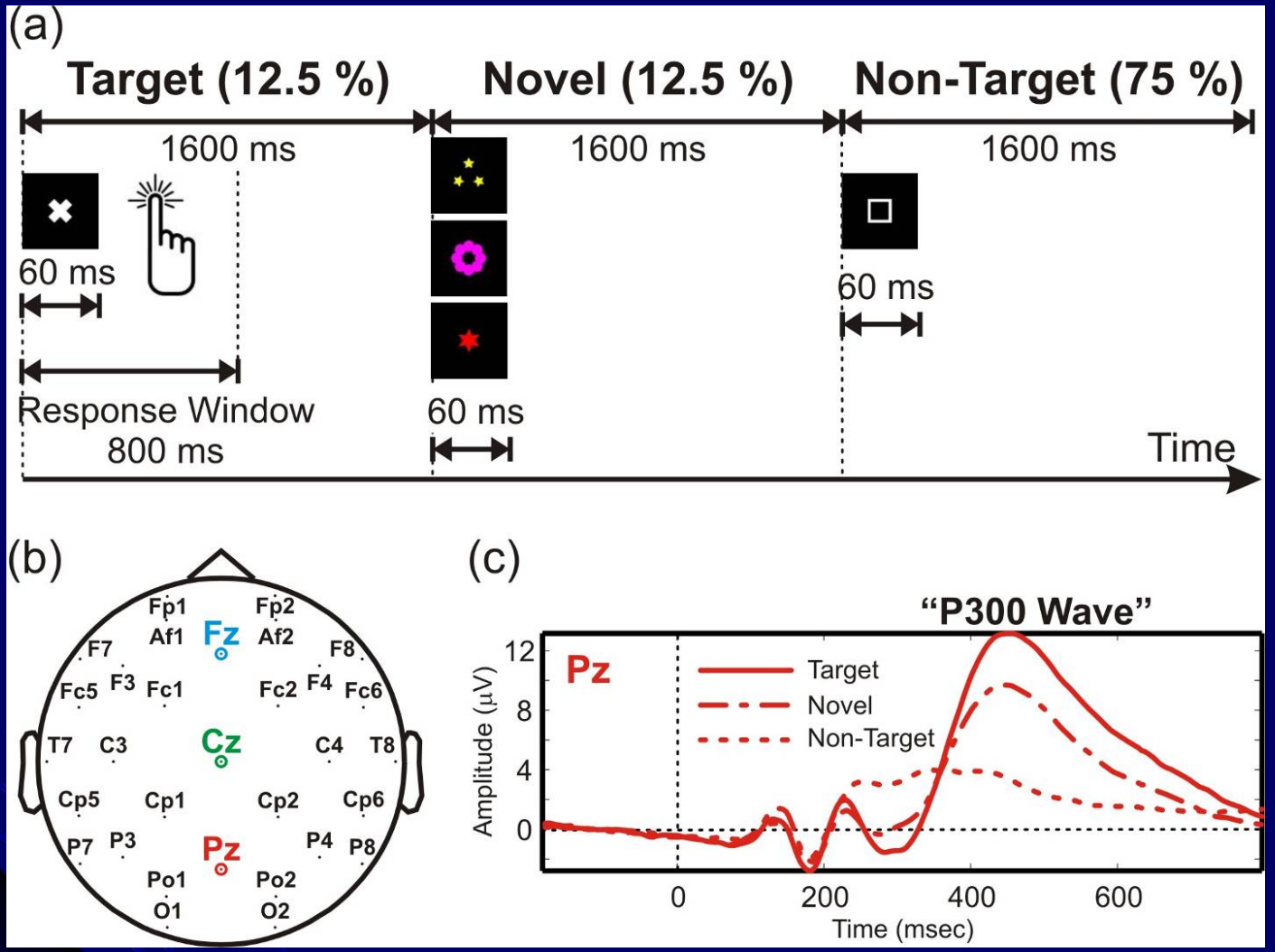
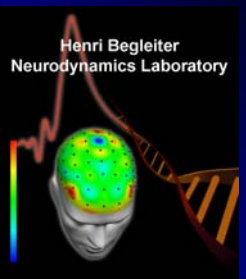
In memory of Henri Begleiter and Theodore Reich, Principal and Co-Principal Investigators of COGA since its inception. We are indebted to their leadership in the establishment and nurturing of COGA, and acknowledge with great admiration their seminal scientific contributions to the field.

- Dr. Andrew C. Chen receives support from the American Psychiatric Association/ American Psychiatric Institute for Research And Education/ NIMH PMRTP Award, 2006-2008



Visual Oddball Experiment





- 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.

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