

Translational Genetics: Import to the Prevention Sciences

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Translational Research

- Basic understanding of the underlying pathophysiology of mental and behavioral disorders.
- Extends basic or clinical research findings to yield a knowledge base for the development of novel, efficacious prevention interventions:
 - Why do some respond well to conventional interventions?
 - Characterize heterogeneous subgroup that does not respond.
 - Do “effective” interventions actually change brain function?

Genetic x Environment Interactions in Risk Behaviors

- A complex interplay of numerous genetic and environmental risk factors clearly is involved.
- Genetic risk factors identified for distinct disorders; e.g., alcoholism, ADHD, CD, impulsivity, drug addiction, aggression, psychopathy
- Expression either occurs or is suppressed in response to social inputs; e.g., influences that promote drug experimentation
- Thus, brain activities resulting from gene expressions likely *mediate* effects of psychosocial influences on behavioral outcomes



Psychogenomics

- Definition: The process of applying genomics and proteomics toward a better understanding of endophenotypes of normal behavior and of brain dysfunction that manifest as behavioral abnormalities.
- Example: In the study of drug addiction, will help to identify genes and their protein products that control reward pathways of the brain and their adaptations to drugs of abuse, as well as variations in these genes that confer genetic risk for addiction and related disorders.
- Ultimate goal: To develop more effective treatments for these disorders as well as objective diagnostic tools, preventive measures, and eventually cures.

Utility of Psychogenomics for Prevention Sciences

- Scientific Utility: Enhances understanding of the cause and pathophysiology of behavioral dysregulation
- Translational Utility: Facilitates the design of interventions that target malleable substrates of genetic expressions
- Evaluation Utility: Identifies neurobiological substrates that provide a mechanistic account of how interventions mediate their effects

Modeling Vulnerability is Complex

- Weak validity of psychiatric diagnoses for identifying gene carriers
- Subjective assessments
- Overlap between disorders
- Complexity of the brain and behavior
- Numerous intervening variables b/t genetic transcription and behavioral consequences
- Phenotypic output from the brain, i.e., behavior, is not simply a sum of all its parts

Thus, need to reduce measures of neuropsychiatric functioning rather than refer to behavioral “macros” when investigating biological and genetic substrates

Translational Prevention Model

- To bridge theoretical gap, study endophenotypes – quantitative neurobiologic correlates of disorders that precede their overt development may have higher reliability than behavioral measures and involve simpler relationships with a smaller number of genes (Frederick and Iacono, 2006)
- Prevention science has a good feel for the most important environmental risk factors
- Knowledge of the genetic risk factors, their neurobiological mechanisms, and environmental interactions can complete the equation and influence prevention efforts
- ☺ **Genetic dissection of behavioral disorders holds promise of dramatic advances in diagnosis, prevention, and treatment**

Whittling Down the Playing Field

- Fewer genes are required to produce variations in traits if phenotypes are:
 - Specialized
 - Represent relatively straightforward and more elementary phenomena
 - Not associated only with behavioral macros or a psychiatric diagnostic entity
- Endophenotypes provide a means for identifying:
 - “downstream” traits or facets of clinical phenotypes
 - “upstream” consequences of genes
 - aberrant genes in polygenic systems conferring vulnerabilities to disorders

Phenotypes that Lend Themselves to Study of Clinical Endophenotypes

- Excessive alcohol use
- Drug addiction
- Affective instability
- Impulsivity
- Aggression
- Emotional information processing deficits
- Reward seeking
- Cognitive disorganization
- Social deficits
- Psychosis



Criteria for Endophenotypes (as markers are not always genetic)

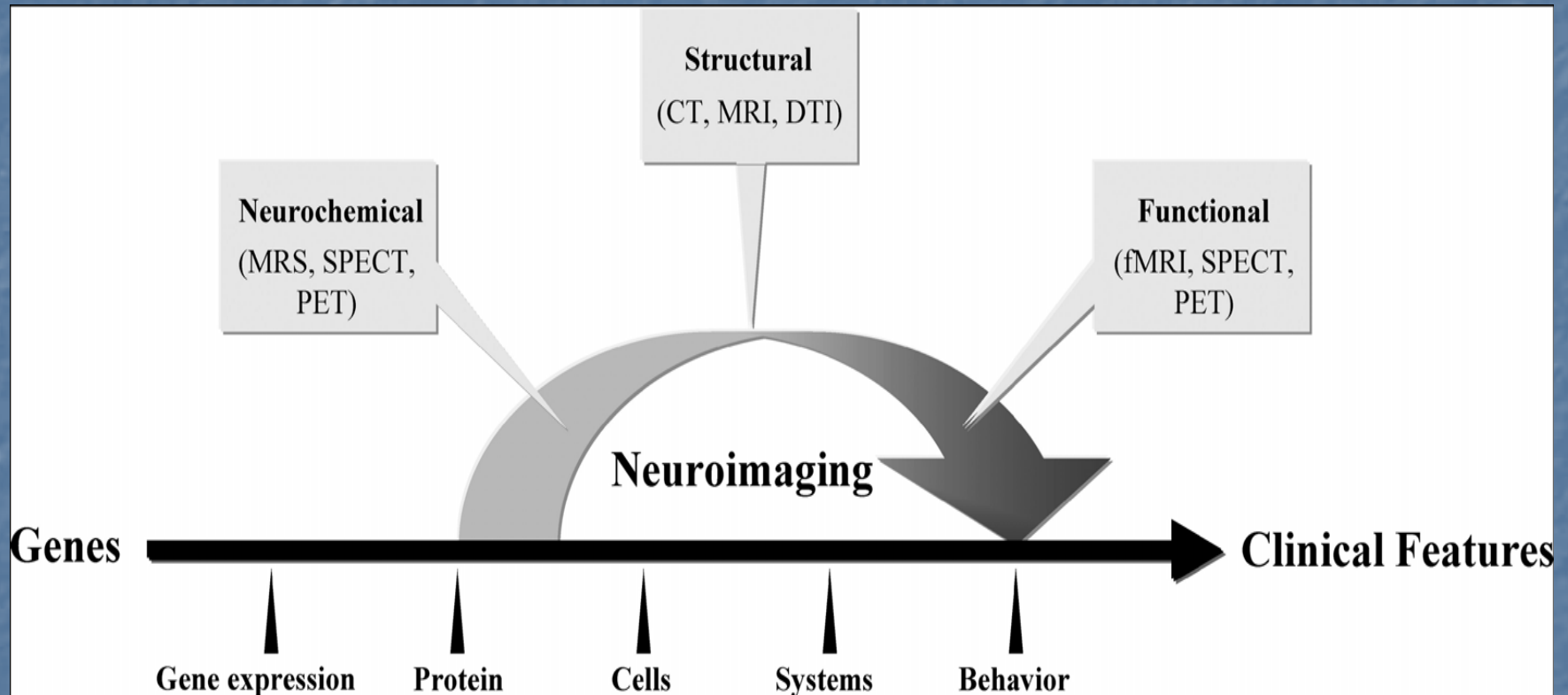
1. Association with illness
2. Heritability
3. State independence (manifests in an individual whether or not illness is active)
4. Cosegregation with illness within families
5. Occurrence in nonaffected family members at a higher rate than the general population

Adopted from: Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;160:636–45.

Our Current Armamentarium to Measure Endophenotypes

- Neurophysiological: EEG, ERP
- Biochemical: NTs, enzymes, modulators
- Endocrinological: stress and sex hormones
- Neuroanatomical: volume, lesion
- Cognitive/neuropsychological
- Neuroimaging: fMRI, diffusion tensor imaging, single photon emission computed tomography, and PET

The Role of Neuroimaging in Investigating Endophenotypes



Adapted from: Callicott JH, Weinberger DR. Brain imaging as an approach to phenotype characterization for genetic studies of schizophrenia. In: Leboyer M, Bellivier F, eds. Psychiatric genetics: methods and reviews. Totowa, NJ: Humana, 2003:227–250.

Phenotype	Endophenotypes	Prevention Implication
Reward Sensitivity	Neural developmental immaturity, hi DA activity, low amygdala activity, hi striatum activity, low motor activity	Typologies for risk assessment, Focus on memories associated with reward, Tailored to adolescents, Alternative rewarding activities
Sensation Seeking	Low MAO activity, dysreg of opioid system, hi DA activity	Risk assessment, arousing media-type programs that capture attention, safe alternative stimulating activities
Associative Processes	Caudate and putamen involvement, possible basal ganglia, ERP differences, cognitive interference	Address implicit and explicit processes, counteract automatic associative effects, teach alternative behaviors that are rewarding, form new associations
Cognitive and Inhibitory Control	Impaired frontally modulated functions, poor connectivity with limbic structures	Include cognitive tasks as part of risk assessment, Focus on decision making and inhibitory skills, cognitive neurorehab component

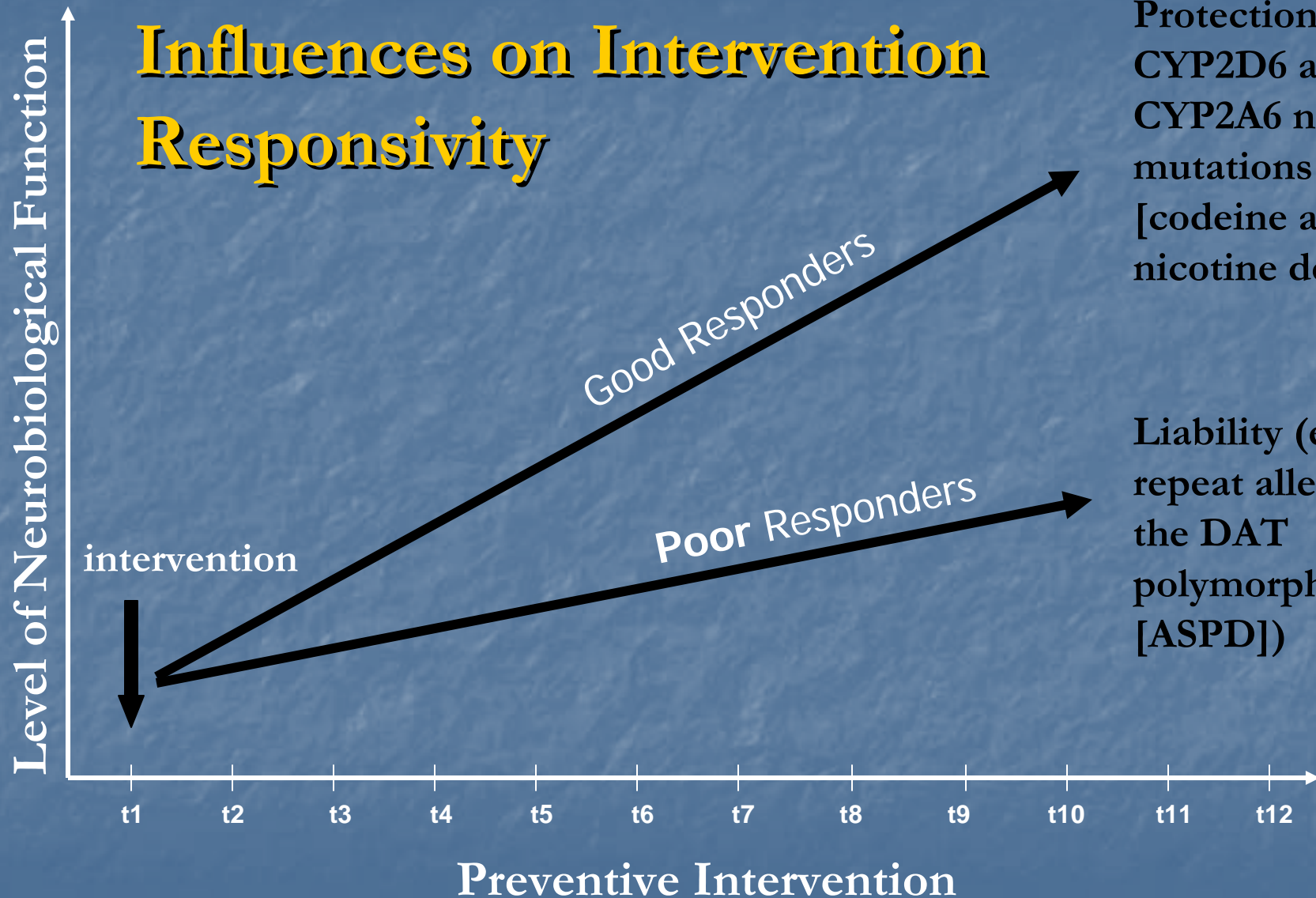
Excerpted from Ames and McBride, 2006

Candidate genes used in association studies with cognition

Gene Name	Abbreviation	Location	Function
Alpha 7 nicotinic receptor	CHRNA7	15q	Cholinergic receptor; attentional gating
Brain derived neurotrophic factor	BDNF	11p	Role in LTP; episodic memory
Catechol-O-methyltransferase	COMT	22q	Involved in degradation of dopamine, notably in prefrontal cortex; executive subprocesses
Dopamine receptor type 4	DRD4	11p	Dopamine receptor with a limbic distribution; attention
Dopamine transporter	DAT1	5p	Reuptake of dopamine at or near the synapse; attention
Monoamine oxidase A	MAOA	Xp	Degradation of dopamine, norepinephrine, serotonin; attention
	OTX1	2p	Transcription factor involved in forebrain development
Semaphorin	SEMA4F	2p	Axonal growth cone guidance
Serotonin 2A receptor	5HT2A	13q	Serotonin receptor with wide forebrain distribution; episodic memory

Terry E. Goldberg and Daniel R. Weinberger (2004). Genes and the Parsing of Cognitive Processes. *TRENDS in Cognitive Sciences* Vol.8 326

Theoretical Model: Genetic Influences on Intervention Responsivity



Protection (e.g., CYP2D6 and CYP2A6 null mutations [codeine and nicotine dep])

Liability (e.g., 9-repeat allele of the DAT polymorphism [ASPD])

“Selective Advertising”

- In the same way that parenting, peer influences, media, and other social conditions may be more effective in promoting risk behaviors among those who are genetically vulnerable...
 - ... the efficacy of any given intervention approach may be contingent on genotype
- Prevention effectiveness can be increased when the intervention targets an individual’s specific liabilities.
- Environmental manipulations matched to an individual’s genotype may effectively reinforce more adaptive and normative endophenotypes and, in turn, phenotypes

Research Questions Remaining for Prevention Science

- What are the *endophenotypes* for various types of risk behaviors?
- What is the *environmental impact* on these neurogenetic mechanisms?
- What are the critical *stages of development* during which psychosocial conditions (e.g., stress) differentially exerts its effects?
- Can understanding gene-brain-environment interactions help *design interventions* that impact at critical points in the developmental trajectory to alter risk status?
- Can environmental interventions alter: a) *genetic expression* (endophenotype) and, b) *behavioral phenotype*?

Measurement Questions

- Can the *impact* of an effective intervention on endophenotype and phenotype be measured?
- Can an integrated dataset incl genetic variants account for more of the *variability in intervention response* than conventional applications?
- What *designs and methods* can be used to identify endophenotypes amenable to prevention interventions and to assess change over time?
- What is the role of *social context* in risk behaviors and how can it be measured?
- What *gender differences* in endophenotypes and their unique interactions with the environment suggest gender-sensitive programming?

Steps to Incorporate Genetic Research into Prevention Practices

- Characterize the myriad of *neurobehavioral liability factors* (endophenotypes)
- Identify *socio-environmental factors and contexts* that potentiate genetic expression of liabilities
- *Disaggregate population* into distinct subgroups based on prevailing liabilities and interacting conditions
- Identify *underlying mechanisms* in differential behavioral responses to social stimuli, incl. interventions
- Enable design of *developmentally sensitive* ecological preventions that promote healthy genetic expression
- Apply *empirically-based* techniques in a variety of settings to enhance neurodevelopment, preventing expression of risk-enhancing phenotypes