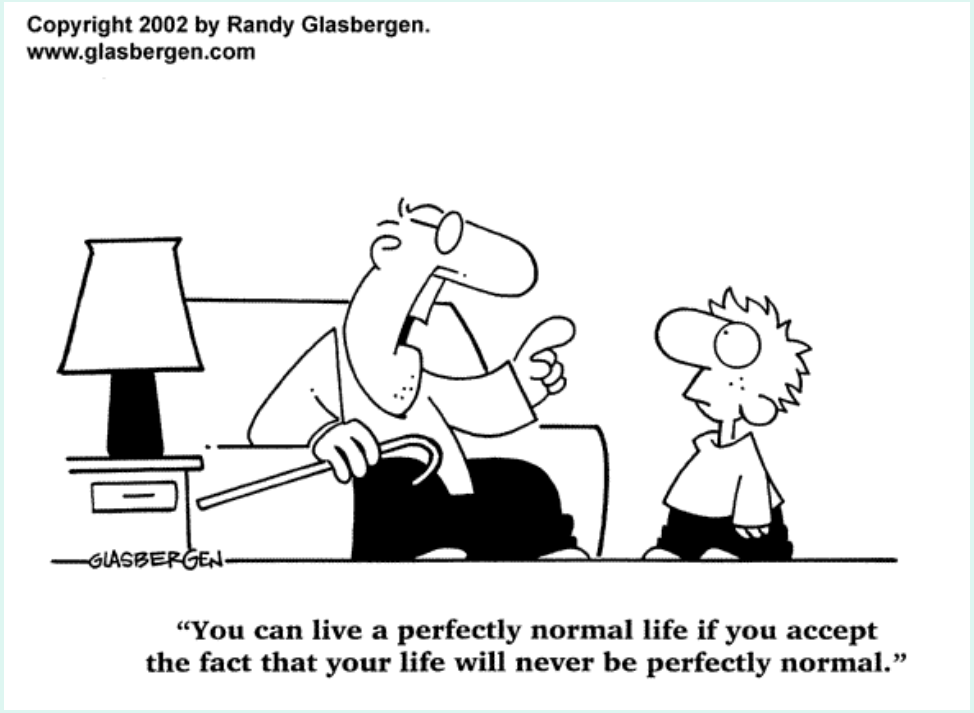
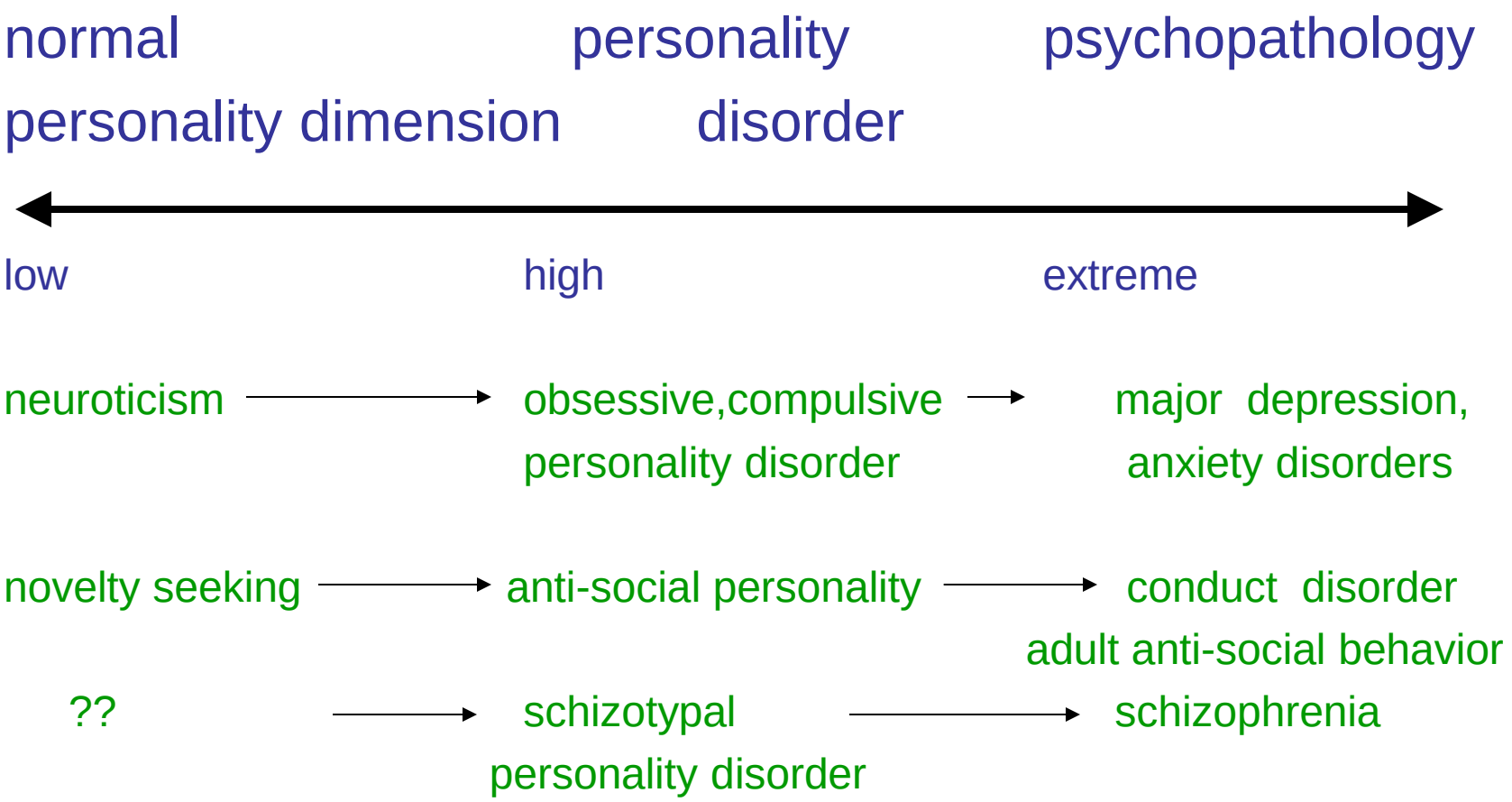


Psych 3102
Introduction to Behavior genetics

Lecture 24

Genetics of personality disorders

- evidence points to continuous variation linking normal personality dimensions with personality disorders and some psychopathologies



A personality disorder is defined as:

a personality trait that causes significant impairment or distress

- not classified as a clinical syndrome
- compared with long-term, early-onset disorders, same axis as mental retardation

Prevalence = 6 – 9% US (rate of having any disorder)

females > males

DSMIV recognizes 10 personality disorders

- 4 studied by behavioral geneticists:

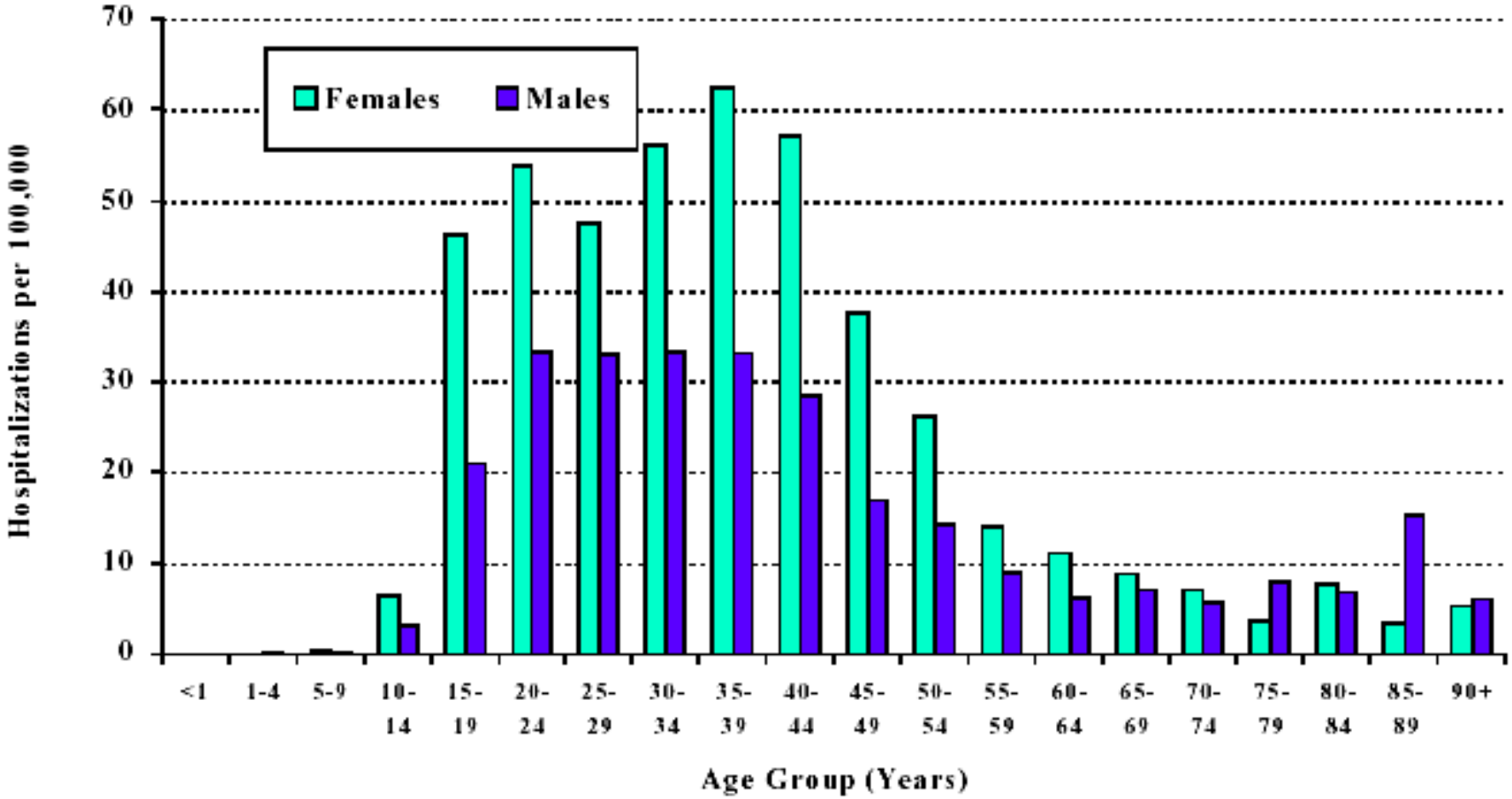
obsessive-compulsive

borderline

schizotypal

antisocial

Figure 5-1 Hospitalizations for personality disorders* in general hospitals per 100,000 by age group, Canada, 1999/2000



* Using most responsible diagnosis only

Source: Centre for Chronic Disease Prevention and Control, Health Canada using data from Hospital Morbidity File, Canadian Institute for Health Information

Borderline personality disorder

- instability & intensity in interpersonal relationships, self-image
- marked impulsivity, potentially self-damaging
- very sensitive to environmental circumstances, fear of abandonment
- reactivity of mood, inappropriate intense anger

70-80% self-injure 10% suicide heterogeneous symptoms

Prevalence = 2-6%

heritability ~ 70% Concordances: MZ=38% DZ=10%

- 70% reported cases are female

epidemiological studies - no difference between male/female rates

males diagnosed with ASPD instead, not diagnosed at all?

Antisocial personality disorder

- psychopathic/sociopathic personality
- at least 18 years old, onset before age 15 (diagnosed as CD)

rate of early-onset CD that persists as ASPD in adulthood =

males 5% females <1%

(symptoms more persistent: 40% males and females)

- criminal record (stealing)
- social disapproval
- irresponsible, irritable
- disregard for truth lying cheating conning
- aggressive lack of empathy
- reckless impulsive aggressive

Prevalence males 4% females 1% (age 13-30)

Good correlation between clinical, legal and personality measures

Table 1

Criteria for Antisocial Personality Disorder

A. There is a pervasive pattern of disregard for the rights of others occurring since the age of 15 years indicated by three or more of the following:
   (1) Failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest
   (2) Deceitfulness, as indicated by repeated lying, using aliases, or conning others for personal profit or pleasure
   (3) Impulsivity or failure to plan ahead
   (4) Irritability and aggressiveness, as indicated by repeated physical fights or assaults
   (5) Reckless disregard for the safety of others or self
   (6) Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations
   (7) Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another person

B. The individual is at least 18 years old

C. There is evidence of conduct disorder with onset before the age of 15 years

D. The occurrence of antisocial behavior is not exclusively during the course of schizophrenia or a manic episode

Source: *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.

Black DW. *Primary Psychiatry*. Vol 8, No 1. 2001.

Table 2

Clinical Symptoms in Antisocial Personality Disorder (%)

Symptoms	Women (n=14)	Men (n=80)	Total (n=94)
Unstable work history	100	82	85
Financial dependency	71	80	79
Arrests	43	81	75
Marital difficulties	93	71	74
Alcohol abuse/dependence	64	74	72
Poor school history (including truancy)	29	79	71
Impulsivity	71	66	67
Promiscuous sexual behavior	93	59	64
"Wild" adolescence	71	60	62
Vagrant	29	65	60
Belligerent	36	61	58
Socially isolated	64	55	56
Lacks remorse	64	36	40
Somatic complaints	36	30	31
Use of aliases	14	31	29
Poor military performance*	—	28	23
Pathological lying	14	16	16
Drug abuse/dependence	14	15	15
Suicide attempts	21	9	11

*No data were reported for women.

Adapted from: Robins LN. *Deviant Children Grown Up.* Baltimore, Md: Williams & Wilkins; 1966.
Black DW. *Primary Psychiatry.* Vol 8, No 1, 2001.

Family and adoption studies

- ASP appears to run in families
- adoption studies indicate similarity within family is due to genes not shared environment

Males: prevalence = 4%

first degree relative risk = 20% whether reared at home or adopted away

Females: prevalence = 1%

first degree relative risk = 10%

suggests higher heritability in females

Twin studies

- population studies
- personality questionnaire NOT diagnosed cases, just antisocial behavior
- similar results from several studies

Rhee & Waldman (2002)

Meta-analysis of 52 twin and adoption studies on antisocial behavior symptoms: broad heritability = 0.41

A = 32%

D = 9%

C = 16%

E = 43%

More recent meta-analyses: heritability 50-60%, shared e 15%

likely that heritability changes with age

Lyons et al (1995)

Longitudinal study, 3000 pairs of male twins

correlations as adults: MZ = 0.47

DZ = 0.27

a^2 = 40%

e^2 = 50%

c^2 = 10%

as adolescents: MZ = 0.39

DZ = 0.33

a^2 = <10%

e^2 = >50%

c^2 =40%

Genetic influences increase, shared e decreases over time

Relationship to other problems

Criminality prison populations ~47% males diagnosed with ASP

~21% females

Danish study

1000+ twin pairs, all male twins born 1881-1910, criminality assessed from police records

Prevalence = 20 - 30% depending on age

Concordances MZ = 51% adult criminality

DZ = 30%

overestimate of gene effect due to participation in crime together by MZ twins?

criminal parents' children adopted away from home had higher levels of ASPD than prevalence, suggests link between criminal behavior/ASPD

- GxE interaction: criminal bio parents + criminal adoptive parents → highest rate of criminality in adopted

From Rhee & Waldman meta analysis (2002)

Criminality A = 33%

D = 42%

E = 25% but based on very small samples

Violent crime convictions (v. large Swedish extended family, twin, adoption study Frisell et al, 2012)

A = 30 – 55% depending on sample and sex

C = 0 – 13% adoptee sample gave 0%

E = rest of variance

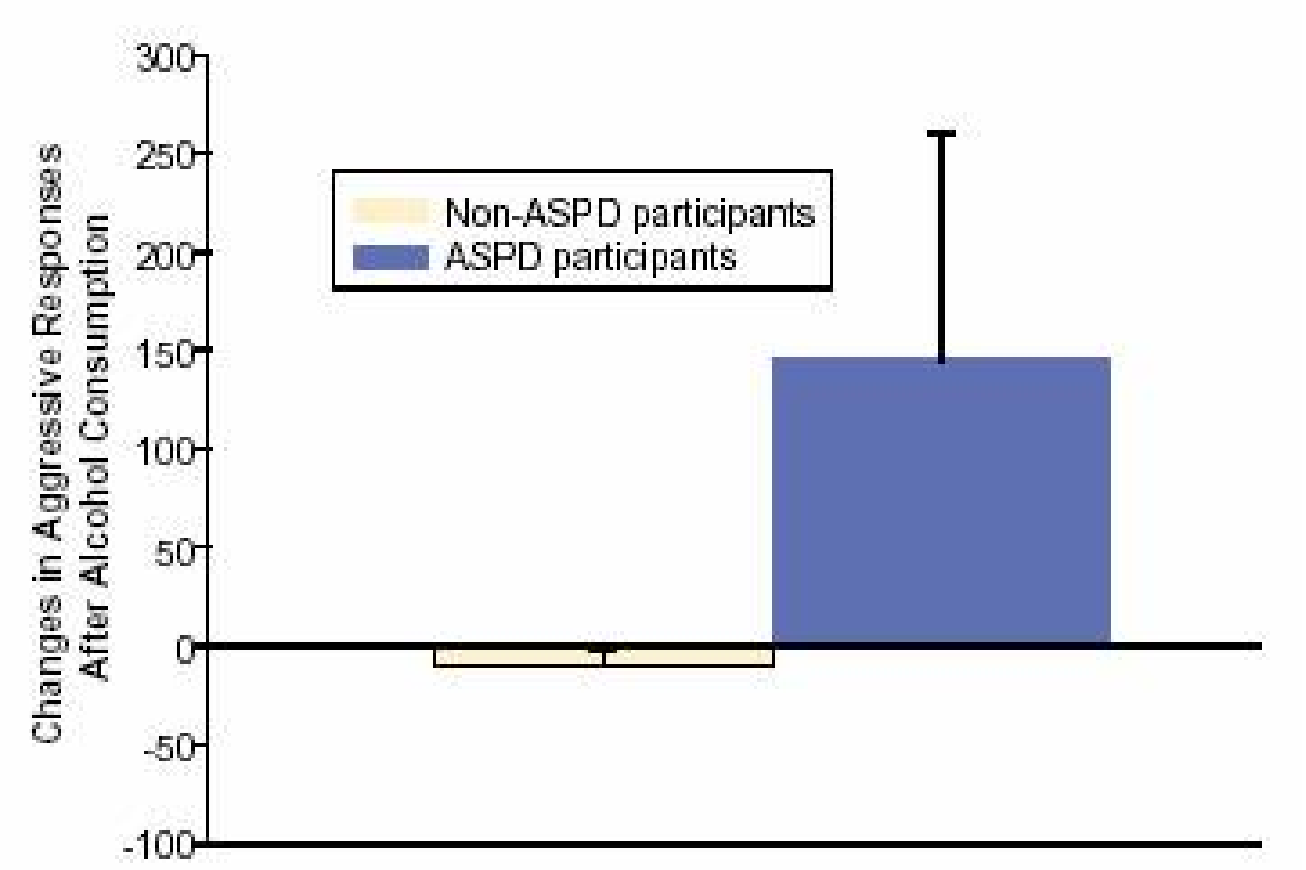
- no evidence for sibling interactions affecting variance
- large assortative mating component r = 0.4 for spouses
- no evidence for gender-specific genes
- significant gender differences in heritability males A = 59% C = 13%

females A = 28% C = 22%

- very similar to antisocial personality disorder in males

Patients in alcohol, other drug abuse treatment programs have higher rates of ASPD than prevalence

Alcohol use may increase aggression in those with antisocial personality disorder



Role of genotype in the cycle of violence in maltreated male children Caspi et al (2002) Science 297

- study provides evidence for a GxE interaction in response of children to abuse

abuse + low MAOA levels → higher rates of ASP in later life

12% of cohort → 44% of cohort's violent convictions

From previous studies:

boys who experience abuse (erratic, coercive, punitive parenting)

have higher risk for CD, ASP, 50% increased risk of becoming criminals, increased risk for violent crime

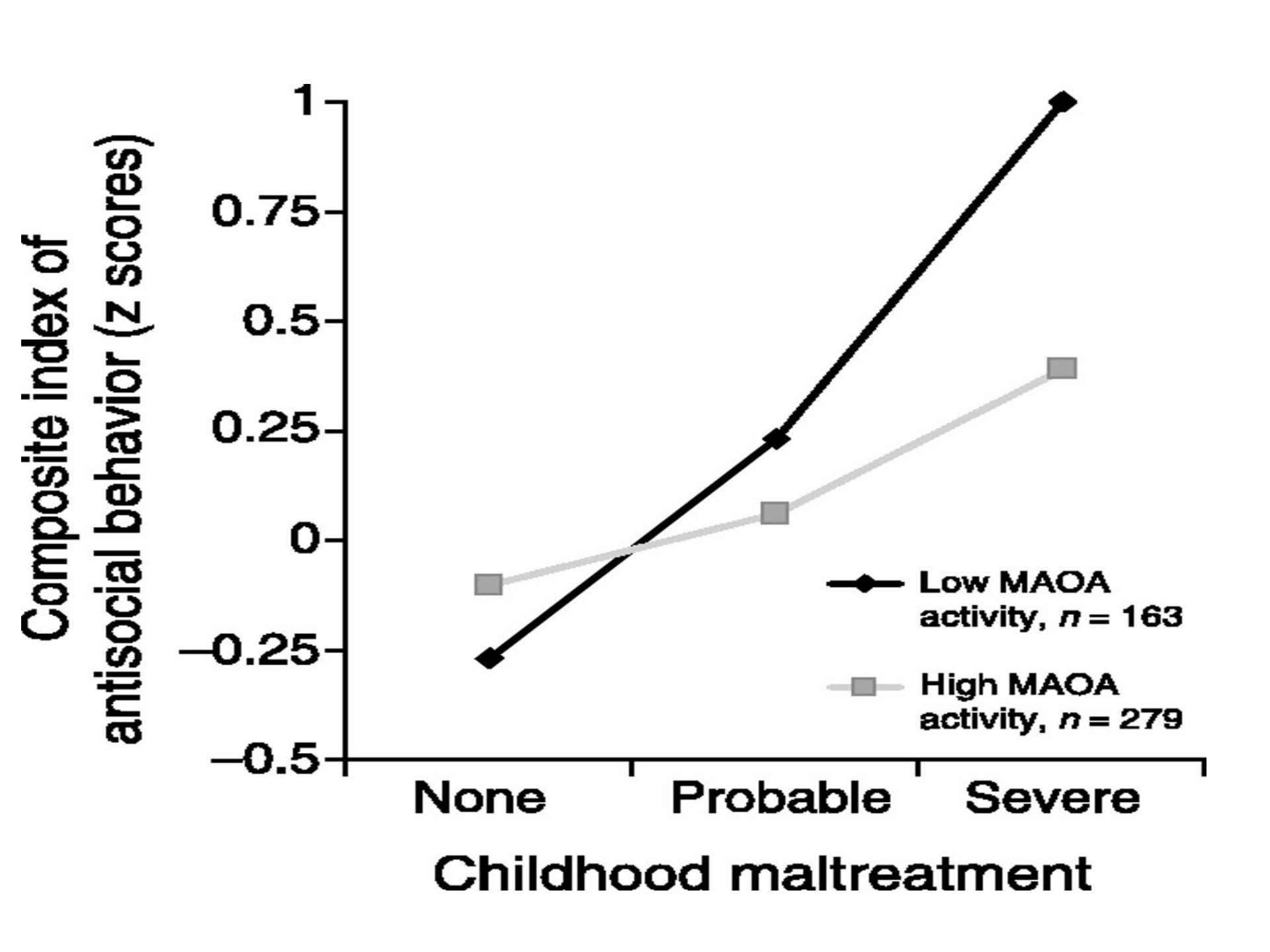
BUT large differences in response, most abused boys do NOT suffer any disorders why the differences in response?

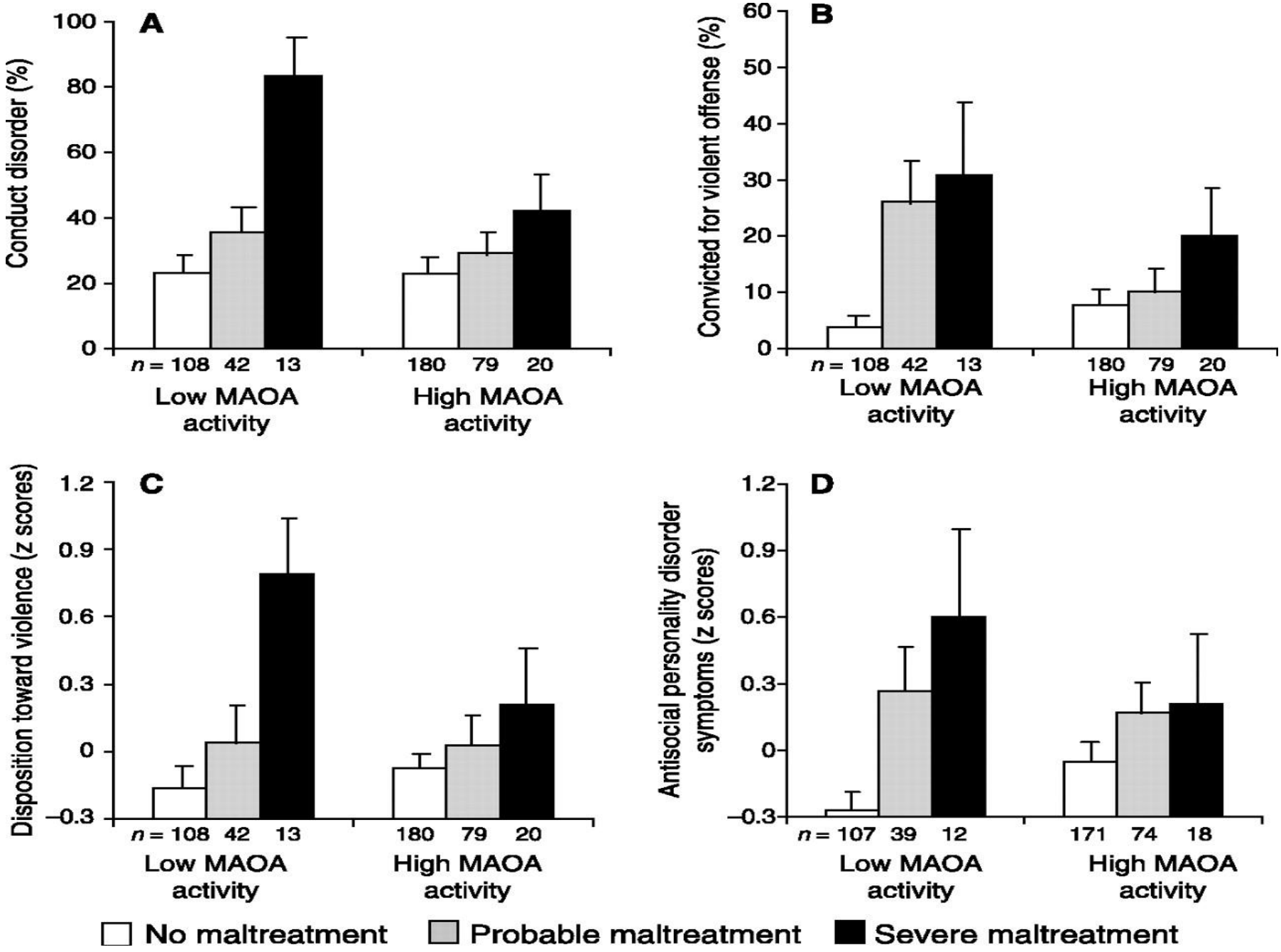
Answer? G x E interaction - variant forms of the MAOA gene moderate the response to maltreatment

MAOA = monoamine oxidase A X chromosome

- an enzyme involved in neurotransmitter metabolism (inactivates NE, serotonin, dopamine)

- increased gene expression lowers risk for ASP and aggression


Composite index of antisocial behavior (z scores)
1
0.75
0.5
0.25
0
–0.25
–0.5
None
Probable
Severe
Childhood maltreatment
Low MAOA activity, n = 163
High MAOA activity, n = 279


A
Conduct disorder (%)
100
80
60
40
20
0
n = 108 42 13
180 79 20
Low MAOA activity
High MAOA activity
B
Convicted for violent offense (%)
60
50
40
30
20
10
0
n = 108 42 13
180 79 20
Low MAOA activity
High MAOA activity
C
Disposition toward violence (z scores)
1.2
0.9
0.6
0.3
0
−0.3
n = 108 42 13
180 79 20
Low MAOA activity
High MAOA activity
D
Antisocial personality disorder symptoms (z scores)
1.2
0.9
0.6
0.3
0
−0.3
n = 107 39 12
171 74 18
Low MAOA activity
High MAOA activity
No maltreatment
Probable maltreatment
Severe maltreatment

Epigenetic effects of abuse during childhood

Nature Neuroscience, 12, 342-348 (2009) McGowan et al

Childhood abuse alters HPA stress responses, increases risk for suicide how?

- brain samples (hippocampus) from suicides showed more methylated DNA in region of gene for receptor for glucocorticoid hormones and fewer glucocorticoid receptors, but only in those who had a history of childhood abuse
- no differences as above seen in suicides with no history of abuse or unabused people who died by other means

supported by previous research on rats (Weaver et al, Nat Neurosci, 7 (2004)

Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions

Torsten Klengel[1], Divya Mehta[1], Christoph Anacker[2], Monika Rex-Haffner[1], Jens C Pruessner[3], Carmine M Pariante[2], Thaddeus W W Pace[4], Kristina B Mercer[5], Helen S Mayberg[4], Bekh Bradley[4,6], Charles B Nemeroff[7], Florian Holsboer[1], Christine M Heim[4,8], Kerry J Ressler[4,5,9], Theo Rein[1] & Elisabeth B Binder[1,4]

Although the fact that genetic predisposition and environmental exposures interact to shape development and function of the human brain and, ultimately, the risk of psychiatric disorders has drawn wide interest, the corresponding molecular mechanisms have not yet been elucidated. We found that a functional polymorphism altering chromatin interaction between the transcription start site and long-range enhancers in the FK506 binding protein 5 (*FKBP5*) gene, an important regulator of the stress hormone system, increased the risk of developing stress-related psychiatric disorders in adulthood by allele-specific, childhood trauma–dependent DNA demethylation in functional glucocorticoid response elements of *FKBP5*. This demethylation was linked to increased stress-dependent gene transcription followed by a long-term dysregulation of the stress hormone system and a global effect on the function of immune cells and brain areas associated with stress regulation. This identification of molecular mechanisms of genotype-directed long-term environmental reactivity will be useful for designing more effective treatment strategies for stress-related disorders.

Epidemiological, family and molecular genetic studies have shown that genetic predisposition as well as stressful or traumatic life events, especially in childhood, are important risk factors for psychiatric disorders, including major depression and post-traumatic stress disorder (PTSD) and that these factors most likely have interactive, rather than additive, effects[1]. Although specific gene × environment interactions have been described[2–5], the molecular basis of gene × environment interaction in mood and anxiety disorders remains obscure. *FKBP5* is an important functional regulator of the glucocorticoid receptor complex[6]. The glucocorticoid receptor is a pivotal nuclear receptor of the stress hormone system mediating the negative feedback of this axis to terminate the stress response after the end of a threat[7]. Dysregulation in this system has been described in stress-related psychiatric disorders and as a long-term consequence of exposure to early life trauma[8,9]. FKBP5 alters glucocorticoid receptor function by decreasing ligand binding and impeding translocation of the receptor complex to the nucleus[10,11]. Furthermore, FKBP5 is part of an intracellular ultra-short negative feedback loop that regulates glucocorticoid receptor activity. Glucocorticoid receptor activation induces *FKBP5* transcription via activation at predominantly intronic steroid hormone response elements[12], leading to increased transcription of *FKBP5*, entailing restrained glucocorticoid receptor activity. We and others have shown that polymorphisms in *FKBP5* (haplotypes including rs1360780, rs9296158, rs3800373 and rs9470080) interact with early trauma or childhood abuse to predict adult PTSD, suicide attempts and major depression[3,13–17]. Here we identified a molecular mechanism for this gene × environment interaction by long-term epigenetic modifications.

RESULTS

rs1360780 moderates the risk for PTSD after early trauma

Previously, we found that the same *FKBP5* polymorphisms that interact with early trauma are also associated with altered induction of *FKBP5* mRNA by glucocorticoid receptor stimulation in peripheral blood[18]. We hypothesized that the associated functional variant lies in or close to glucocorticoid response elements (GREs) in the *FKBP5* locus. Given that the originally genotyped variants are in high linkage disequilibrium over the entire locus, we used genotype data from Illumina OmniExpress Single Nucleotide Polymorphism (SNP) arrays spanning the whole *FKBP5* locus in 192 individuals of the Grady trauma project and imputed all currently known variants using the 1,000 Genomes project data (http://www.1000genomes.org/)[19]. This resulted in 799 polymorphisms imputed with a quality greater than 0.6 and an average quality score of 0.93. Linkage disequilibrium with rs1360780, rs9296158, rs9470080 and rs3800373 was evaluated using the tagger software implemented in Haploview version 4.2. Of the imputed polymorphisms, 48 had an r^2 greater than 0.4 with at least one of the four polymorphisms mentioned above to interact

[1]Max Planck Institute of Psychiatry, Munich, Germany. [2]King's College London, Institute of Psychiatry, Section of Perinatal Psychiatry and Stress, Psychiatry and Immunology, Department of Psychological Medicine, London, UK. [3]McGill Centre for Studies in Aging, Faculty of Medicine, McGill University, Verdun, Quebec, Canada. [4]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia, USA. [5]Howard Hughes Medical Institute, Chevy Chase, Maryland, USA. [6]Atlanta Veterans Affairs Medical Center, Decatur, Georgia, USA. [7]Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, Florida, USA. [8]Institute of Medical Psychology, Charité University Medicine Berlin, Berlin, Germany. [9]Yerkes National Primate Research Center, Emory University, Atlanta, Georgia, USA. Correspondence should be addressed to E.B.B. (binder@mpipsykl.mpg.de) or T.K. (klengel@mpipsykl.mpg.de).

Received 15 June; accepted 1 November; published online 2 December 2012; doi:10.1038/nn.3275

Comorbidity between alcoholism and externalizing disorders

COGA Collaborative study of the Genetics of Alcoholism

- Washington University, St Louis + other centers
- longitudinal study of a sample of high risk offspring of alcoholic parents
- **assessed at ages 13 – 17 n = 1333**

Substantial comorbidity within the sample

Rates of disorders: alcohol dependence 5.2%
conduct disorder 17.8%
ADHD 12.8%
ODD 14.9% (oppositional defiant disorder)

CD, ADHD, ODD all conferred sig. risk for concurrent alcohol dependence

Externalizing disorders - what might cause the comorbidity?

Behavioral disinhibition

Young et al American Journal of Medical Genetics (Neuropsychiatric genetics) 2000

Aim of study – to find evidence for a latent trait termed 'behavioral disinhibition'
- defined as inability to inhibit behavior in spite of social/familial/educational consequences
- an executive function deficit

Analyzed comorbidity among childhood disruptive behavioral disorders:

conduct disorder
ADHD
ASP
early substance abuse

} externalizing behaviors

- co-occurrence shows familial aggregation
- no evidence for large shared environment effects
- possibly pleiotropic genes underlie the comorbidity

population-based twin study n = 334 pairs 12 – 18 years old

DSMIV symptom counts obtained for:

1. conduct disorder
2. ADHD
3. substance experimentation
4. novelty-seeking

<u>novelty-seeking (NS)</u> Cloninger personality dimension

- heritable (30 – 40%)
- tendency to show exploratory activity in pursuit of rewards and avoidance of monotony
- increased levels associated with increased risk for CD ASP ADHD compulsive spending & gambling, criminal behavior, early-onset drinking
- high levels in combination with other traits is also a predictor of well-being, self-transcendence, creativity, exploratory behavior
- lower levels give ability to be well attuned to risks involved with behaviors

Latent trait analysis

– multivariate factor analysis used to determine presence of common factor underlying variation measured in several traits.

- analysis revealed strong evidence for the latent trait
- it accounted for between 16 and 46% of observed variance for the 4 measures (Fig 4)
- it was highly heritable: $a^2 = 0.84$ $e^2 = 0.16$ $c^2 = 0$ (Fig 4)
- latent trait was named ‘behavioral disinhibition’

Other sources of variance for the measures:

7% c^2 for CD 45% c^2 for substance experimentation

5% genetic dominance for ADHD 20% dominance for NS

Journal of Abnormal Psychology
2002, Vol. 111, No. 3, 411–424

0021-843X/02/$5.00 DOI: 10.1037/0021-843X.111.3.411

Etiologic Connections Among Substance Dependence, Antisocial Behavior, and Personality: Modeling the Externalizing Spectrum

Robert F. Krueger, Brian M. Hicks, Christopher J. Patrick, Scott R. Carlson, William G. Iacono, and Matt McGue
University of Minnesota—Twin Cities Campus

A hierarchical biometric model is presented of the origins of comorbidity among substance dependence, antisocial behavior, and a disinhibited personality style. The model posits a spectrum of personality and psychopathology, united by an externalizing factor linked to each phenotype within the spectrum, as well as specific factors that account for distinctions among phenotypes within the spectrum. This model fit self-report and mother-report data from 1,048 male and female 17-year-old twins. The variance of the externalizing factor was mostly genetic, but both genetic and environmental factors accounted for distinctions among phenotypes within the spectrum. These results reconcile evidence for general and specific causal factors within the externalizing spectrum and offer the externalizing factor as a novel target for future research.

Common mental disorders are often correlated with each other, co-occurring at greater than chance rates in both clinical and epidemiological samples (Clark, Watson, & Reynolds, 1995; Lilienfeld, Waldman, & Israel, 1994; Sher & Trull, 1996; Widiger & Sankis, 2000). What is the meaning of this "comorbidity" phenomenon? Krueger and colleagues (Krueger, 1999b, 2002; Krueger, Caspi, Moffitt, & Silva, 1998; Krueger, McGue, & Iacono, 2001) have proposed that this phenomenon may result from common mental disorders acting as reliable indicators of latent factors, or hypothetical core psychopathological processes, that underlie putatively separate disorders.

To date, this hypothesis has been supported by data gathered from unrelated persons. Such data have allowed for multivariate analyses of observed, phenotypic correlations among mental disorders. These analyses have revealed a broad, latent factor linking substance dependence and antisocial behavior disorders in late adolescence and adulthood. Following the lead provided by multivariate analyses of emotional and behavioral problems in children (Achenbach & Edelbrock, 1978, 1984), this factor has been labeled *externalizing* (cf. Kendler, Davis, & Kessler, 1997).

In the analyses presented herein, we extended this line of research by addressing three specific questions in a genetically informative sample. First, what is the etiologic basis for the phenotypic externalizing factor? Second, are there etiologic factors that distinguish among specific externalizing disorders? Third, are disinhibitory personality traits part of the externalizing spectrum?

Robert F. Krueger, Brian M. Hicks, Christopher J. Patrick, Scott R. Carlson, William G. Iacono, and Matt McGue, Department of Psychology, University of Minnesota—Twin Cities Campus.

The Minnesota Twin Family Study is supported in part by U.S. Public Health Service Grants AA00175, AA09367, DA05147, and MH65137.

Correspondence concerning this article should be addressed to Robert F. Krueger, Department of Psychology, University of Minnesota, Twin Cities Campus, N414 Elliott Hall, 75 East River Road, Minneapolis, Minnesota 55455-0344. E-mail: krueg038@umn.edu

The Etiologic Basis of the Externalizing Factor

Recent research suggests the hypothesis that genetic factors play an important role in the etiology of the externalizing factor in adolescence and adulthood. First, many large-scale, well-conducted studies now point to genetic factors in the etiology of specific antisocial behavior disorders (Bock & Goode, 1996; Carey & Goldman, 1997; DiLalla & Gottesman, 1989; Gottesman & Goldsmith, 1994; Krueger, Hicks, & McGue, 2001; Lyons et al., 1995; Rutter, 1997; van den Bree, Svikis, & Pickens, 1998) and substance use disorders (Heath et al., 1997; McGue, Pickens, & Svikis, 1992; Pickens et al., 1991; Prescott & Kendler, 1999; Tsuang et al., 1996). Second, in contrast to earlier adoption studies that suggested genetic differentiation of antisocial and substance use disorders (Bohman, Sigvardsson, & Cloninger, 1981; Cadoret, O'Gorman, Troughton, & Heywood, 1985; Cadoret, Troughton, & O'Gorman, 1987; Cloninger, Bohman, & Sigvardsson, 1981; Crowe, 1974; Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973), a number of recent twin studies have begun to point to common genetic factors linking antisocial behavior and substance use disorders. Grove et al. (1990) presented evidence for substantial genetic overlap between antisocial and alcohol problem symptom counts in a small sample of identical, or monozygotic (MZ), twins reared apart. Pickens, Svikis, McGue, and LaBuda (1995) compared cross-twin correlations between alcohol dependence and antisocial personality in small samples of both MZ and fraternal, or dizygotic (DZ), twins. For male pairs, the MZ cross-twin, cross-trait correlation was similar to the within-person correlation between alcohol dependence and antisocial personality but higher than the DZ cross-twin, cross-trait correlation, suggesting that the phenotypic correlation was partially due to genetic factors shared between alcohol dependence and antisocial personality.

The most extensive and thorough study documenting significant genetic links between antisocial behavior and substance use disorders was reported by Slutske et al. (1998). A sample of 2,682 adult Australian twin pairs retrospectively reported symptoms of childhood conduct disorder and alcohol dependence. Both disorders were substantially heritable; in addition, genetic influences