Genetics of Borderline Personality Disorder

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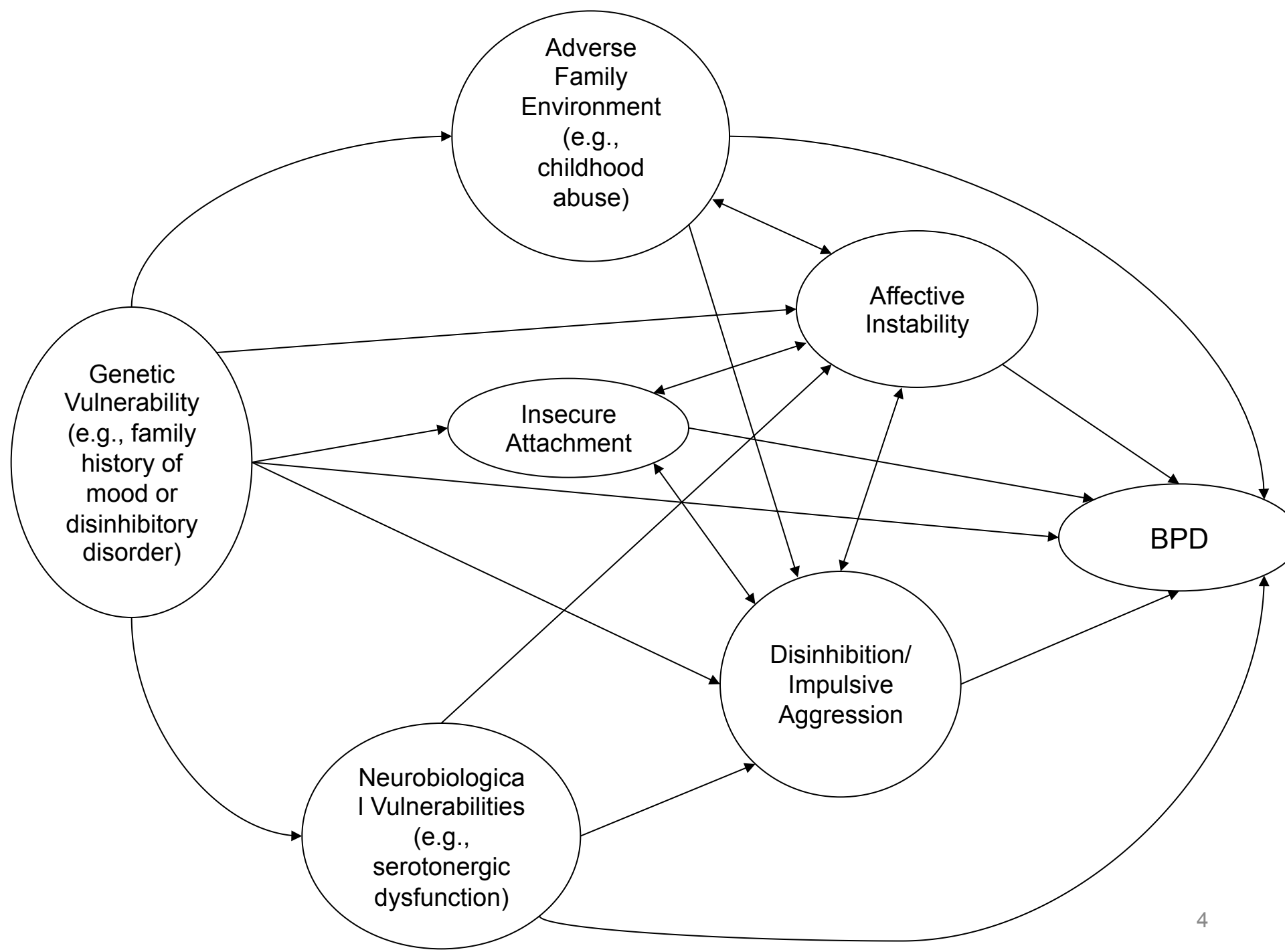
DSM-IV Diagnostic Criteria for Borderline Personality Disorder (APA, 2000)

- Frantic efforts to avoid real or imagined abandonment
- Unstable and intense interpersonal relationships
- Persistently unstable self-image
- Impulsivity in at least two areas that are potentially self-damaging (e.g. sex and substance abuse)
- Suicidal behavior, gestures, or threats; Self-mutilating behavior
- Affective instability due to a marked reactivity of mood
- Feelings of emptiness
- Inappropriate and intense anger
- Stress-related dissociative symptoms

Borderline Personality Disorder
Etiology

- A comprehensive model of the etiology of BPD includes the influences of genetics and family history, neurobiological factors, adverse environmental conditions, and personality factors.
- Figure 1 depicts a conceptualization of how these influences may interact and lead to the development of BPD symptoms
- Unidirectional and bidirectional effects.


Adverse Family Environment (e.g., childhood abuse)
Affective Instability
Genetic Vulnerability (e.g., family history of mood or disinhibitory disorder)
Insecure Attachment
BPD
Disinhibition/ Impulsive Aggression
Neurobiological Vulnerabilities (e.g., serotonergic dysfunction)

Evidence for genetic effects

- Family studies
- Adoption studies
- Twin studies
- Candidate gene studies
- Genome wide association studies
- Gene-Environment studies
- What is inherited?

Borderline Personality Disorder
Family Studies

- Family studies report increased rates of BPD in the relatives of individuals with BPD compared to relatives of control probands (e.g., Baron et al. 1985; Johnson et al. 1995; Zanarini et al. 2004; Bandelow et al. 2005; Zanarini et al. 1988; Loranger et al. 1982).

- Prevalences/morbidity risks for BPD in relatives of BPD probands ranged from 9.1% (Bandelow et al. 2005) to 24.9% (Zanarini et al. 1988).

Borderline Personality Disorder Family Studies (cont.)

- Prevalence of individual borderline symptoms or features in relatives of BPD probands.
- Silverman et al. (1991)
  - prevalence rates for **affective and impulsive personality disorder traits** were significantly higher in the relatives of BPD probands than in the relatives of probands with other personality disorders or in the relatives of schizophrenic probands.
- Zanarini et al. (2004)
  - in first degree relatives of BPD patients, the prevalence rates of five (**inappropriate anger, affective instability, paranoia/dissociation, general impulsivity, and intense, unstable relationships**) were significantly higher in first degree relatives of BPD patients than in first degree relatives of axis-II comparison subjects.

Borderline Personality Disorder
Family Studies (cont.)

- Limitations
  - Sample sizes small, varying from 17 (Baron et al. 1985) to 83 BPD probands (Loranger et al. 1982)
  - Often not representative of the population (e.g. Loranger et al. 1982 assessed only female BPD probands).
  - Information on psychopathology of relatives was derived from the BPD probands themselves (e.g., Zanarini et al., 2004).

  - Family studies CANNOT RULE OUT ENVIRONMENTAL INFLUENCES

Borderline Personality Disorder
Adoption Studies

- Very compelling design

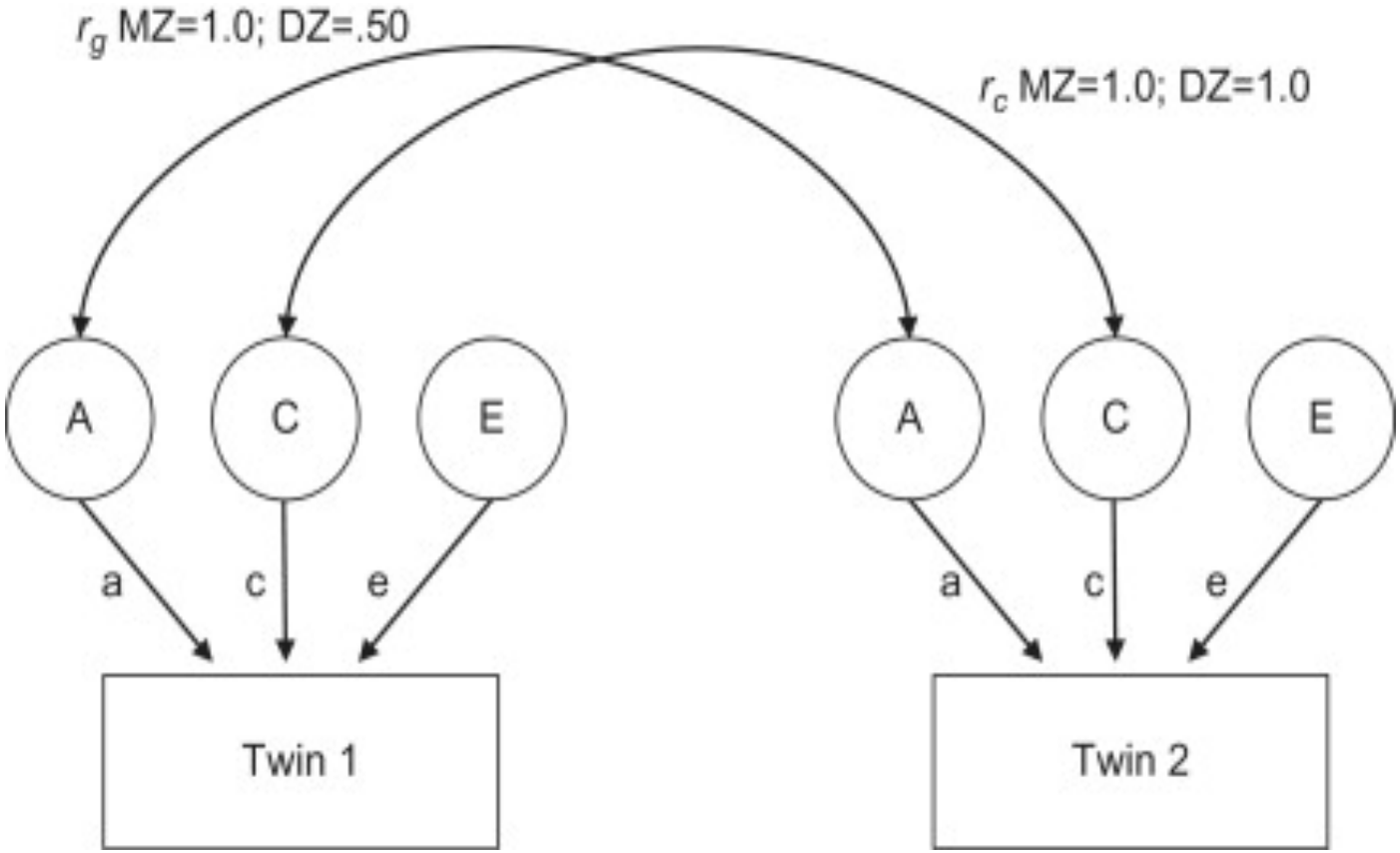
- Genetic influences from biological parents; no environmental influence from biological parents (not raised in this home)
- Environmental influences from foster home (and unique environment).
- Foster siblings outcome can be used in comparison; same shared environment.

- Unfortunately, no adoption studies of BPD

Borderline Personality Disorder
Twin Studies

- Family studies cannot disentangle the effects of genes from the effects of environment shared by family members, social interaction and cultural inheritance.
- Twin studies can disentangle the effects of common environment and genes by making use of the different genetic relatedness of monozygotic (MZ) and dizgotic (DZ) twins.
- MZ twins are genetically (nearly) identical while DZ twins and siblings share on average 50% of their segregating genes.
- If genetic factors are important for a trait, MZ twins must be more similar than DZ twins or other first degree relatives.
- If MZ twins are as similar as DZ twins, familiality is mainly due to common environmental factors.

Univariate genetic model



Borderline Personality Disorder Twin Studies (cont.)

- Few twin studies on BPD available using structured interviews.

- Torgersen et al. (2000) found a concordance rate for definite BPD at 35% for MZ pairs and 7% for DZ pairs.
  - h^2=.69
  - A number of methodological problems with this study (including the sampling of those who were being treated for a mental disorder, the small number of twin pairs, and the interviewers' awareness of both zygosity and diagnostic status of the co-twin.

- Torgersen et al, (2008): approx 1400 twin pairs
  - h^2 estimate for BPD=.35

Borderline Personality Disorder
Twin Studies (cont.)

- Twin studies using self-report questionnaire measures of BPD

- Distel et al. (2008) were able to assess BPD features in 5,496 twins (1,852 complete pairs) between the ages of 18 and 86 years from the Netherlands, Belgium and Australia.
  - Results showed that genetic influences explained 42% of the variation in BPD features in both men and women.
  - The heritability was equal between the three countries suggesting no interaction between genotype and country.

Borderline Personality Disorder
Twin studies

Distel at al. (2008), Psychological Medicine

	A	E
Netherlands	42.3%	57.7%
Belgium	42.5%	57.5%
Australia	41.6%	57.8%

Estimates constrained to be equal

A=42.2%; E=57.8%

Borderline Personality Disorder
Twin Studies (cont.)

- Twin studies using self-report questionnaire measures of BPD
- Torgersen et al. (in press)
- ~2,800 Norwegian Twins; used items from the Dysfunction Personality Questionnaire that tapped BPD criteria.
- Heritability of questionnaire scores estimated to be .46

Borderline Personality Disorder
Twin Studies (cont.)

- Limitations:
- Aggregate effect of genes only
- Cannot identify specific genetic influences
- Equal shared environments for MZ versus DZ twins assumed

Borderline Personality Disorder
Candidate gene studies

- Most candidate genes are functional genes that have biological consequences related to the trait, disorder or disease.
- Reduced serotonergic function in anger (Giegling et al. 2006), aggression (Siever 2008), suicidal behaviour (Bah et al. 2008; Zaboli et al. 2006) and impulsivity (Passamonti et al. 2008; New et al. 1998), and increased serotonergic function in emotional lability (Hoefgen et al. 2005) have led to several **serotonergic candidate genes for BPD**.
- Tryptophan hydroxylase (TPH) and the serotonin transporter gene (5-HTT), are the most studied candidate genes.

Borderline Personality Disorder
Candidate gene studies

- There is some evidence that **dopamine (DA) dysfunction** may be associated with BPD. DA dysfunction is associated with emotional dysregulation, impulsivity and cognitive-perceptual impairment (for a review see Friedel 2004), three important dimensions of BPD.
- Joyce et al. (2006) found a significant replicated association between the 9-repeat allele of dopamine transporter 1 (dopamine active transporter, DAT1) and BPD in depressed patients.

Borderline Personality Disorder
Candidate gene studies

- Genes involved in the production of **monoamine oxidase-A (MAOA),** which degrades amongst others 5-HTT and DA, are suggested to be involved in BPD because it is shown to be associated with aggression (Buckholtz and Meyer-Lindenberg 2008), impulsivity (Manuck et al. 2000) and mood lability (Furlong et al. 1999).
- To test whether MAOA is also associated with the BPD diagnosis Ni et al. (2007) genotyped two MAOA polymorphisms (promoter VNTR and rs6323) in 111 BPD patients and 289 control subjects.
- A high frequency of the high activity VNTR alleles and a low frequency of the low activity haplotype was found in BPD patients suggesting that the high activity allelic variant may play a role in the etiological development of BPD.

Borderline Personality Disorder
Candidate gene studies

- **Some Limitations inherent in the candidate gene approach**:
- Must have a good understanding of the function of a candidate gene
- Most traits/features are influenced by many genes, each contributing only a very small amount to overall genetic risk
- Therefore, need extremely large samples to detect these very small effects, and have to target the "correct" genes
- Gene variants that are relevant will be missed if they are not within the specific gene region of investigation

Borderline Personality Disorder
Genome wide association studies

- Genome wide association (GWA) studies. GWA searches the whole genome for small variations (single-nucleotide polymorphisms; SNPs) that occur more frequently in people with a particular disorder than in people without the disorder.

- Each study can look at thousands of SNPs at the same time.

- However, association analysis measures statistical associations, cannot be used to test for causality, and is prone to population stratification. Cases and controls should ideally come from the same population.

Borderline Personality Disorder
Genome wide association studies

- Large samples are required, and most findings for other disorders have not been replicated.

- Only a small percentage of the variance in the phenotype explained (<5%); only **common** genetic variants detected

Borderline Personality Disorder Gene-Environment Studies

- Three major ways that genes and environment can jointly influence the overall vulnerability to psychopathology.
  - First, an individual's liability for a disorder may be the sum of the contributions of genes and environment (**the additive model**).
  - Second, genes and environment may interact, such that genes control the sensitivity to the environment or, alternatively, one can say the environment controls gene expression (**the gene-environment interaction model; GxE**).
  - Third, genes and environment can be correlated such that genes influence environmental exposure (**the gene-environment correlation model; rGE**).

Borderline Personality Disorder
Gene-Environment Studies

- Gene-environment interaction (GxE) implies that genes determine the degree to which a subject is sensitive to an environment. In the presence of interaction, individuals with a 'sensitive' genotype will be of greater risk to develop BPD if the predisposing environment is present, than individuals with an 'insensitive' genotype.

- GxE can be detected by determining if the heritability of BPD varies in groups with different environmental conditions (for example, experiencing sexual abuse).

Borderline Personality Disorder Gene-Environment Interaction

- Many studies purporting to find GxE effects on a phenotype are unable to do so definitely for one or more of the following reasons:
  - (1) the number of participants is much too small to reliably detect GxE effects (effects which are notoriously small);
  - (2) factors that are considered "environmental" may actually be under some degree of genetic influence (i.e., a gene-environment correlation);
  - (3) "environments" are measured retrospectively and imprecisely; and
  - (4) the inadequate scaling of environments (i.e., how these are quantified) can lead one to conclude that a GxE effect exists when in fact it does not.

Borderline Personality Disorder Gene-Environment Interaction

- There is no strong, replicated empirical evidence yet supporting a gene-environment interaction (GxE) model of liability to borderline pathology. Regardless of whether….
  - Studies have examined genetic underpinnings of features of BPD (impulsivity, emotional sensitivity, anger and aggression, suicidal behavior)
  - Studies have examined the BPD phenotype itself (via questionnaire or interview)

Borderline Personality Disorder Gene-Environment Correlation

- Distel et al. (2011) tested the GxE and rGE models in a large twin/sibling sample.
- rGE, the correlation between the genetic influence on environmental risk factors and the genetic influence on BPD traits
- Twin and sibling pairs from the Netherlands and Belgium (n=6368).
  - Participants self-reported their symptoms of BPD, using the Personality Assessment Inventory-Borderline Scale (PAI-BOR), and
  - the experience of SLEs (i.e., divorce, car accident, assault, robbery, and job loss).

Borderline Personality Disorder
Gene-Environment Correlation (cont.)

- Distel et al. (2011)
- Evidence suggested significant **gene-environment correlation** for divorce/break-up, violent assault, sexual assault, and job loss and borderline personality.
- That is, *the genes influencing borderline features increased the likelihood of being exposed to these adverse life events.*
- However, it is not possible to determine the direction of causality.

What is inherited or under genetic control?

- Neurobiological Vulnerabilities (serotonin, dopamine, endogenous opioid system)
- Personality traits: impulsivity/aggression and emotional dysregulation
- Adverse life events
- Attachment styles?

Borderline Personality Disorder Personality

Distel et al. (2009)

- All genetic variance in borderline personality is shared with FFM personality traits (esp. with N and A)
- 33% of environmental effect is NOT shared with FFM traits
- Unique environmental influence may influence normal personality → borderline personality

The future of genetics research for BPD

- Well-designed, large twin and family studies that assess the aggregate effects of genes.
- In order to reliably characterize a G-E effects, it is necessary to use very large samples (thousands).
- It is necessary to also evaluate gene-environment correlation effects, and a failure to do so could lead to erroneous conclusions about a GxE effect

The future of genetics research for BPD (cont)

- Great need for improved measures of environmental influences (prospective, cumulative, and proximal)
- The genes that have been considered include a relatively small range of candidate genes, whose status as risk factors for BPD is uncertain.
- There are no large scale genome wide association (GWA) studies yet for BPD.

Borderline Personality Disorder
Final Comments

- The expression of BPD features is genetically mediated, although genetic factors cannot explain the entire picture.
- These issues can only be addressed with extremely large population-based samples and clinical case-controls.
- Research on the genetics of BPD is a very important next step
- Identifying genes that influence the development of BPD will help to develop better strategies to diagnose, treat and prevent the disorder.
- Our measures of environmental influences are woefully inadequate.

Thank you!

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Further reading

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