



Introduction

FAMILIAL TRANSMISSION OF BPD AND ITS PHENOTYPES

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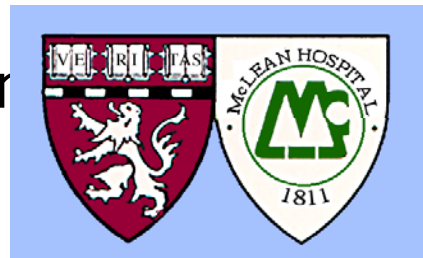
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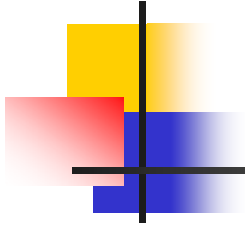
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- Personality traits are often heavily genetic (Tellegen et al. 1988; Jang et al. 1996; Pedersen et al. 1988; Bergeman et al. 1993; Kendler et al. 1993)



Background

- Robins and Guze (1970)
- One of five parameters to the validity of a psychiatric disorder
 - Heightened prevalence of disorder in first-degree relatives
 - Disorder “runs” in families



BPD Family History Studies

- 9 Studies
- 12.6% FDR's have BPD
- BPD Coaggregates with impulse spectrum disorders (ASPD, Alcohol/Substance Abuse)
- BPD may coaggregate with MDD
- BPD does not coaggregate with Schizophrenia, Bipolar I



Preliminary Study

- Family history study of the prevalence of DSM-III-R and DSM-IV BPD
- Relatives of BPD probands vs. relatives of OPD probands
- DSM-III-R: 13% vs. 7.8%
- DSM-IV: 16.1% vs. 9.1%
- Both comparisons were significant

Zanarini et al., 2004



Family History vs. Family Study

- Family history: information about diagnoses of relatives is provided by patient (proband)
- Family study: information is provided by direct interview of relative



Methodologic Strengths

- Direct interview of relatives
 - No bias due to indirect reports
- Larger sample than any previous family interview study
- Comparison probands with MDD and non-BPD “normal” population
- Comparison probands matched on age, SES, minority status
- Comparison probands not selected to be free of psychiatric disorders; that is, not “super-normals”
- Diagnoses made by operational criteria using reliable raters with semi-structured diagnostic interview



Prior Family Studies

(adequately sized, direct assessments)

- Mood Disorders N = 10
- Anxiety Disorders N = 8
- Schizophrenia N = 9
- Alcohol/Substance Abuse N = 5

Merikangas & Swendson, 1997



Sample

Proband Group

	BPD	No BPD	MDD
Probands	117	118	80
Relatives	285	305	186



Familiarity of BPD



Familiality of BPD

- BPD vs. Non-BPD
- Probands matched on SES, ethnicity, (but not age BPD 23.4, Non-BPD 25.5; $p < .001$)
- Relatives matched on SES, ethnicity, age, and gender



Probands I

- All probands are female and between the ages of 18-35
- Those in BPD group: met both DIB-R and DSM-IV criteria for BPD
- Those in Non-BPD group: met neither criteria set for BPD



Probands II

- BPD probands
 - 52.1% were inpatients and other 47.9% were from the community
- Non-BPD probands
 - 2.5% were inpatients and 97.5% were from the community



Proband Axis I Comorbidity

	BPD Probands	Non-BPD Probands	Chi-square Value	P-value
Mood Disorder	92.3 (N=108)	15.3 (N=18)	140.3	<0.001
Substance Use Disorder	47.9 (N=56)	8.5 (N=10)	45.11	<0.001
Anxiety Disorder	46.2% (N=54)	12.7% (N=15)	31.7	<0.001
Eating Disorder	47.0 (N=55)	6.8 (N=8)	48.5	<0.001



Proband Level of Comorbidity

- BPD Probands
 - 3% without lifetime axis I psychopathology
- Non-BPD Probands
 - 74% without lifetime axis I psychopathology



Relative Axis I Comorbidity

	Relatives of BPD Probands	Relatives of Non-BPD Probands	Chi-square Value	P-value
Mood Disorder	34.7 (N=99)	26.2 (N=80)	5.05	0.025
Substance Use Disorder	29.1 (N=83)	17.7 (N=54)	10.77	0.001
Anxiety Disorder	27.4% (N=78)	25.9% (N=79)	0.16	0.687
Eating Disorder	5.6% (N=16)	6.2% (N=19)	0.10	0.752



Results: DSM-IV BPD

Disorder	Relatives of BPD Probands	Relatives of Non-BPD Probands	Odds Ratio (95% CI)	P-value
DSM-IV BPD	13.0% (N=37)	9.2% (N=28)	1.5 (0.83, 2.6)	0.18



Results: DIB-R BPD

Disorder	Relatives of BPD Probands	Relatives of Non-BPD Probands	Odds Ratio (95% CI)	P-value
DIB-R BPD	10.5% (N=30)	3.0% (N=9)	4.1 (1.9, 9.0)	<0.001



Results: DIB-R and DSM-IV BPD

Disorder	Relatives of BPD Probands	Relatives of Non-BPD Probands	Odds Ratio (95% CI)	P-value
DIB-R and DSM-IV BPD	10.2% (N=29)	2.6% (N=8)	4.5 (2.0, 10.0)	<0.001



Main Findings I

- BPD is more common among the first-degree relatives of those with BPD than among the first-degree relatives of those without BPD



Main Findings II

- Prevalence of BPD is lower in this family study than in most family history studies
- Do probands exaggerate relative psychopathology or do FDRs minimize their psychopathology?



Limitations

- Lifetime axis II diagnoses are somewhat difficult to assess
- Not all relatives in family interviewed*
- Not all families willing to join study*



Caveats

- Cannot determine if this aggregation is due to genetics, environmental factors, or some combination of the two
- Twin studies are needed to separate these etiological factors



Conclusions

- DIB-R BPD aggregates strongly in families
- DSM-IV BPD displays weaker (if any) familial aggregation



Implication for DSM-V

- Definition of the BPD phenotype requires the presence of symptoms in three or more of the core sectors of borderline psychopathology.
- They also suggest that the DSM-IV criteria are too broad to identify BPD phenotype.



Familiarity of Phenotypes



“Core” BPD Phenotypes

- Affective Instability
- Impulsivity
- Interpersonal Instability



Prototypes of the Phenotypes for BPD

- Emotional (“hyperbolic” temperament)
 - Fearful/angry, chronically depressed, dysphoric
 - Readiness to shift from anxiety to depression
- Behavioral
 - Acts without concern for consequences (often self-injurious)
 - Externalizes
- Interpersonal (“hypersensitivity”)
 - Intolerant of aloneness
 - Insecure attachments characterized by longings for closeness and fears of rejection or abandonment



The Affective Phenotype I

- Factor analytic support (Hurt, Clarkin, Sanislow)
- Linked to theories of emotional dysregulation (e.g. Linehan, Livesley)
- Explains co-occurrence with affective disorders



The Affective Phenotype II

- Familial:
 - (Silverman et al. 1991, Zanarini et al. 2004)
- Heritability
 - 0.45 (Jang et al. 1996)



The Impulsive Phenotype I

- Factor analytic support
- Linked to theories of behavioral dyscontrol (e.g., Links)
- Explains co-occurrence with ASPD and Alcohol/Substance Abuse



The Impulsive Phenotype II

- Familial
 - (Silverman et al. 1991, Zanarini et al. 2004)
- Heritability
 - 0.28-0.56 (Gottesman et al. 1983; Reiss et al. 2000; Jang et al. 1998)



The Interpersonal Phenotype I

- Factor analytic support
- Linked to theories of failed attachment interpersonal hypersensitivity (e.g. Gunderson, Fonagy, Masterson, Benjamin)
- Explains co-occurrence with HPD, NPD, DPD, and PTSD



The Interpersonal Phenotype II

- Familial
 - (Zanarini et al. 2004)
- Heritability
 - 0.48 (Jang et al. 1996)



Main Analysis

- To assess the association that is induced by familial factors for a given trait assess 2 associations
- Statistical model assesses level of trait in relative and level of trait in corresponding proband
- Presence of association implies presence of causal familial factors



Measures of Effect

- Difference in level of trait in relative associated with a 1-unit increase in level of trait in proband
- Difference in level of trait in a relative of a proband with BPD vs. a relative of a proband without BPD

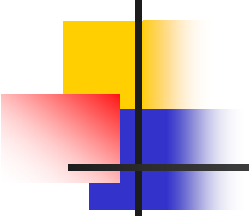


DSM-IV Phenotypes

- Affect
 - Anger
 - Emptiness
 - Reactivity
 - Score: 0-6
- Impulsivity
 - Self-harm/suicidality
 - Two other forms of impulsivity
 - Score: 0-4
- Interpersonal
 - Stormy relationships
 - Frantic efforts to avoid abandonment
 - Score: 0-4

Familial Aggregation of Core Phenotypes of BPD by DSM-IV Criteria

(based on analysis of 590 relatives of BPD (N = 285)
and non-BPD (N = 305) probands)



Measure	Estimate* (95% CI)	p-value
Affective	0.20 (.05, 0.36)	0.011
Impulsive	0.05 (-0.04, 0.13)	0.28
Interpersonal relationships	0.12 (-0.03, 0.26)	0.12

*Estimated mean increase in measure in relative for each increase of 1 in measure in proband, adjusted for relative's age, sex, race/ethnicity and type (parent or sibling)



DIB-R Phenotypes I

- Affect
 - Depression
 - Helplessness/hopelessness/worthlessness
 - Anger
 - Anxiety
 - Loneliness/emptiness
 - Score: 0-10
- Impulsivity
 - Substance abuse
 - Promiscuity
 - Self-mutilation
 - Suicide threats/attempts
 - Other forms of impulsivity
 - Score: 0-10




DIB-R Phenotypes II

- Interpersonal
 - Intolerance of aloneness
 - Abandonment/engulfment/annihilation concerns
 - Counterdependency
 - Stormy relationships
 - Undue dependency/masochism
 - Manipulation/devaluation/sadism
 - Demandingness/entitlement
 - Serious treatment regression
 - Countertransference problems/"special" treatment relationships
 - Score: 0-18

Familial Aggregation of Core Phenotypes of BPD by DIB-R Criteria

(based on analysis of 590 relatives of BPD (N = 285)
and non-BPD (N = 305) probands)



Measure	Estimate* (95% CI)	p-value
Affective	0.27 (0.13, 0.43)	< 0.001
Impulse action	0.17 (0.06, 0.29)	0.003
Interpersonal relationships	0.24 (0.13, 0.36)	< 0.001

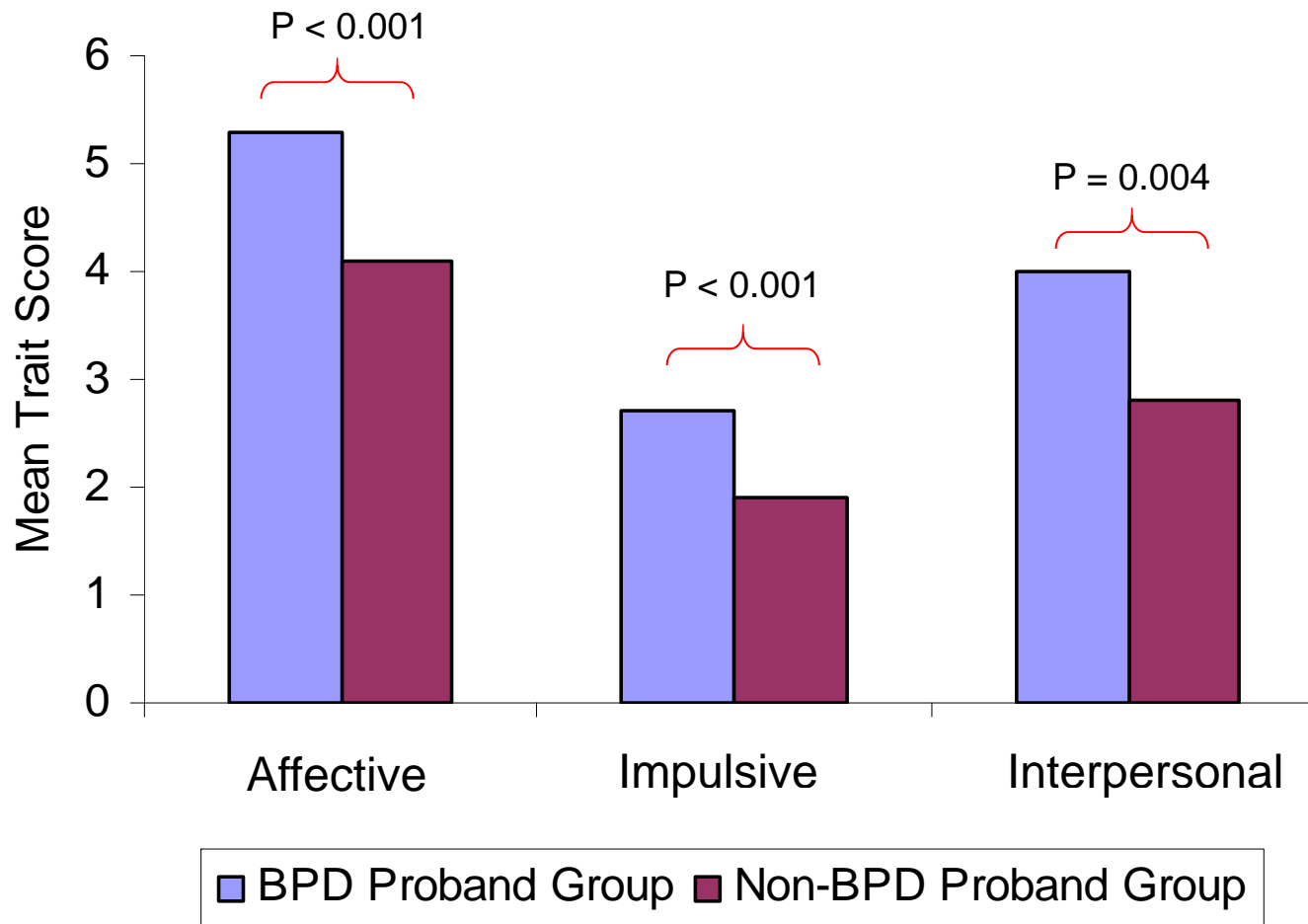
*Estimated mean increase in measure in relative for each increase of 1 in measure in proband, adjusted for relative's age, sex, race/ethnicity and type (parent or sibling)

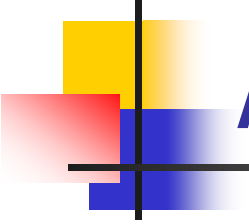


Secondary Analysis I

- To assess whether BPD traits are common in the relatives of probands with BPD compared with relatives of probands without BPD

DIB-R Phenotypic Trait Scores in Relatives of BPD Probands vs. Relatives of Non-BPD Probands





Interpersonal Phenotype as Attachment

- No studies of aggregation of attachment in families to date
- Familial aggregation accounts for relationship of attachment styles of members within a family
- Relates to both parents and siblings



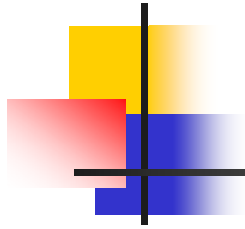
BPD & Attachment

- 13 Studies. Very inconsistent sampling, methods, designs limit conclusions (Agrawal et al. '04)
- AAI-based studies find "*unresolved*" and "*preoccupied*" Self-report based studies find "*fearful*" and "*preoccupied*"
- Overview: BPD characterized by intense longings for closeness but intense fears of dependency or rejection
- Adults with such attachments have had "*disorganized/disoriented*" attachments to their mothers as children and "ambivalent"



Current Study: Assessment

- Relationship Questionnaire (RQ; Bartholomew & Horowitz, 1991)
 - Self-report
 - Current relationships
 - Four paragraphs describing attachment styles on a 7 pt Likert scale



RQ Attachment Styles

Models of Self (dependence)

Positive (low)

Negative (high)

Positive (low)
Models of Other (avoidance)

Negative (high)

SECURE Comfort with intimacy and autonomy	PREOCCUPIED Preoccupied with relationships
DISMISSING Dismissing of intimacy	FEARFUL Fearful of intimacy Socially avoidant

Bartholomew & Horowitz, 1991



Results

Attachment Style	Estimate* (95% CI)	P-value
Preoccupied	0.14 (0.04, 0.24)	0.005
Secure	0.08 (-0.04, 0.19)	0.20
Fearful	0.04 (-0.07, 0.16)	0.46
Dismissing	0.05 (-0.08, 0.18)	0.43

*Estimated mean increase in measure for each increase of 1 in measure in proband adjusted for relative's age, sex, ethnicity, and type (parent or sibling)



Main Finding

- Very little evidence for familial aggregation of attachment styles except for the **preoccupied style**
- The preoccupied style of attachment distinguishes BPD subjects from non-BPD subjects



Significance of Finding

- Attachment preoccupation- vulnerability factor of BPD or another way of measuring the interpersonal phenotype- aggregates in families



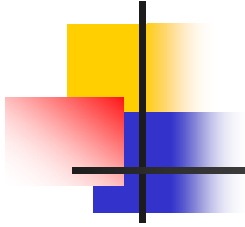
Significance of Finding

- Preoccupied individuals deal with distress by
 - Minimizing distance from attachment figures
 - Hyperactivate attachment
 - Clinging, hypervigilant, controlling behaviors
 - Exacerbates distress



Significance of Finding

- Aggregation suggests familiarity but does not sort out contributions of genetics and environment
- Preoccupation with attachment may represent a psychobiological diathesis to BPD (Gunderson & Lyons-Ruth, 2008)
 - Constitutional diathesis to relational reactivity



- The preborderline child has an innate hypersensitivity to interpersonal interactions that:
 - shapes early caretaking
 - predisposes to making interpersonal stressors traumatic



Conclusion I

- First rigorous demonstration of these phenotypes' familiarity
 - supports theories that they "drive BPD's engine"
 - can help explain patterns of co-occurrence
 - impels search for endophenotypes



Limitations

- sample (incomplete), female
- measures (validity, alternatives)
- other analyses
- phenotypes (others)
- haven't looked at BPD vs. MDD and Non-BPD controls separately



“Candidate” BPD Phenotypes

- Aggressivity
- Anxiousness
- Cognitive Dysregulation



Overall Conclusion

- All three phenotypes need to be represented in the DSM definition of BPD