Is Suicide Genetic?
In Search of Intermediate Phenotypes

David A. Brent, M.D.

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Will Address These Questions:

- Why is this topic clinically relevant?
- What is evidence for family transmission (FT)?
- What intermediate phenotypes might explain FT?
- What is the role of trauma in FT?

Objectives

- Participants will be familiar with the results of family-genetic studies of suicidal behavior
- Participants will be familiar with possible mechanisms by which familial suicidal behavior is transmitted.
- Participants will be familiar with clinical implications for treatment and prevention of suicidal behavior

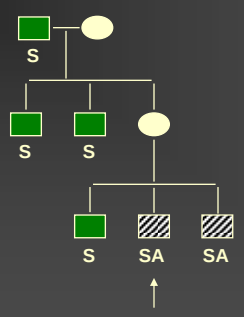
Psychopathology & Suicidal Behavior

- Majority who attempt and complete psychiatrically ill
- But, few who have mental disorder attempt or complete suicide
- Therefore, psychopathology may be (relatively) necessary, but not sufficient

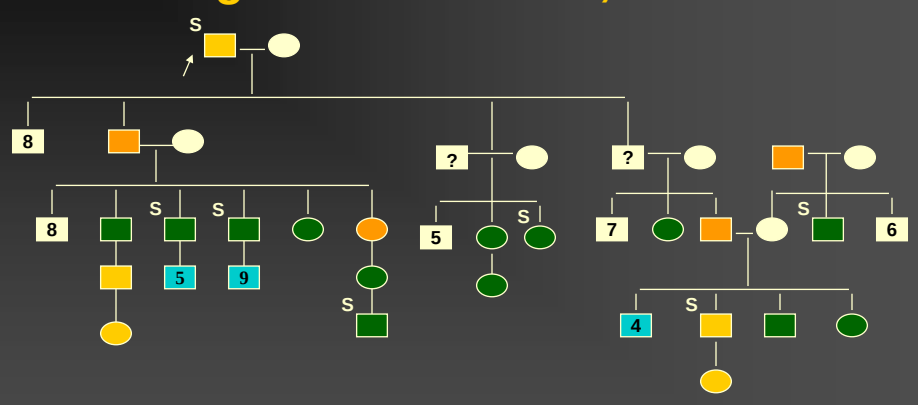
Why Focus on Familial Factors?

- Suicide is familial
- Identification of familial factors can aid in:
  - Understanding genetic and environmental factors above and beyond psychopathology that contribute to suicide
  - Prevention
  - Treatment

A Perplexing Pedigree



Egeland & Sussex, 1985*



Bipolar
Unipolar
Other Affective

? Unknown Status
S Suicide
Total Normal

*Egeland & Sussex, 1985

Adoption Studies: Schulsinger et al., 1979

Adopted	Index Cases	Suicide/Biological Relatives	Suicide/Adopted Relatives
Suicide	57	12/269*	0/148
Controls	57	2/269	0/150

* $p<0.01$

Twin Studies of the Genetic Epidemiology of Suicidal Behavior

Study	N	Gender	Concordance (%)		Concordance (AOR)		Heritability (%)	
			MZ	DZ	MZ	DZ	Ideation	Attempt
Statham	5995	Both	23.1	0	3.8	__	43	55
Glowinski	3416	Female	25	12.8	5.6	4.0	__	48
Fu	7744	Male			12.1	7.4	43 36*	30 17*

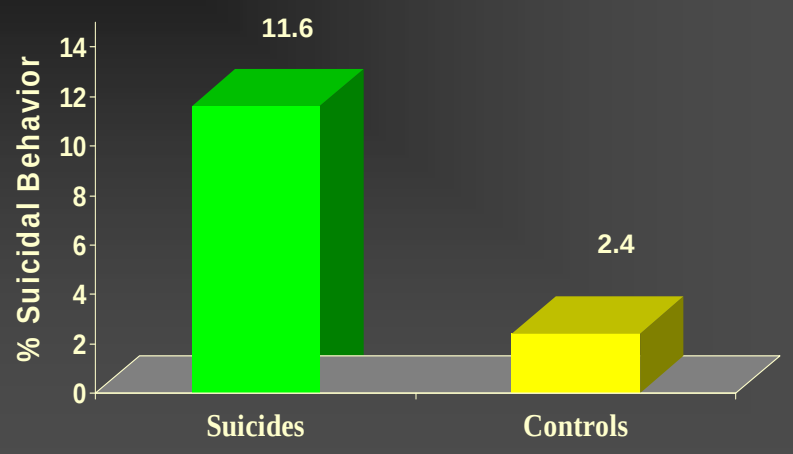
***Adjusted for transmission of other risk factors**

Familial Aggregation of Suicidal Tendencies*

- 58 adolescent suicide completer probands
- 55 community controls
- 4 direct interviews with first-degree relatives per family

*Supported by the National Institute of Mental Health (MH43366)

Rates of Suicidal Behavior in First-Degree Relatives of Suicide Victims and Controls



Brent et al., 1996

Risk for Suicidal Behavior in First-Degree Relatives Adjusting for Other Psychiatric Conditions

Characteristic	OR	95% CL
Attempt/Completion	4.3	1.1 - 16.6
Proband Any Axis I	16.3	9.5 - 28.0

Family Studies: Suicide Probands

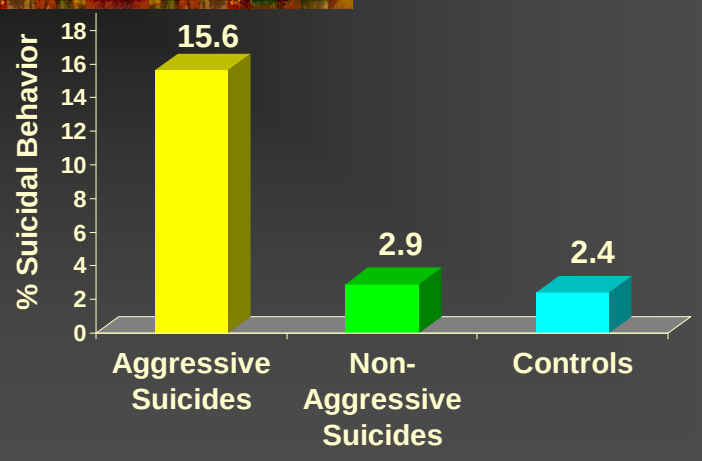
Author	Year	Proband	OR
Tsuang	1983	Patient suicides	3.8
Egeland	1985	Amish suicides	4.6
Gould	1996	Adolescent suicides	4.4-4.7*
Brent	**1996**	**Adolescent suicides**	**4.3***
Cheng	2000	Adult suicides	5.0*
Powell	2000	Inpatient suicides	4.6*
Tsai	2002	Bipolar Suicides	15.1*
Kim	2005	Male suicides	10.6

*Adjusted OR

Risks of Familial Suicidal Ideation [OR (95% CL)]

	Familial Psychopathology	Controlling for Uncontrolled
First-degree relatives	1.9 (1.0-3.7)	1.6 (0.5-5.1)
Second-degree relatives	1.8 (1.0-3.0)	1.0 (0.4-2.3)

Rates of Suicidal Behavior in First-Degree Relatives Role of Proband Impulsive Aggression



Brent et al., 1996

Family Study of Male Suicides*

- Family study of 25 male suicides and 25 age-matched controls
- Rate of aggression in 1° relatives OR=3.97
- Overall AOR=10.4 for FH suicidal behavior
- AOR in Cluster B suicides = 14.84
- AOR for depressed suicides = 4.90
- Rate of ideation not significantly increased

Kim et al., 2005

Summary: Relationship Between Transmission of Suicidal Behavior and Mood Disorder

- Suicidal behavior is familially transmitted
- Transmission distinct from Axis I disorder
- But, attempt almost always occurs in the context of mood and/or substance abuse
- Greater family loading associated with greater impulsive aggression, which mediates transmission of suicide attempt

Familial Pathways to Early-Onset Suicidal Behavior

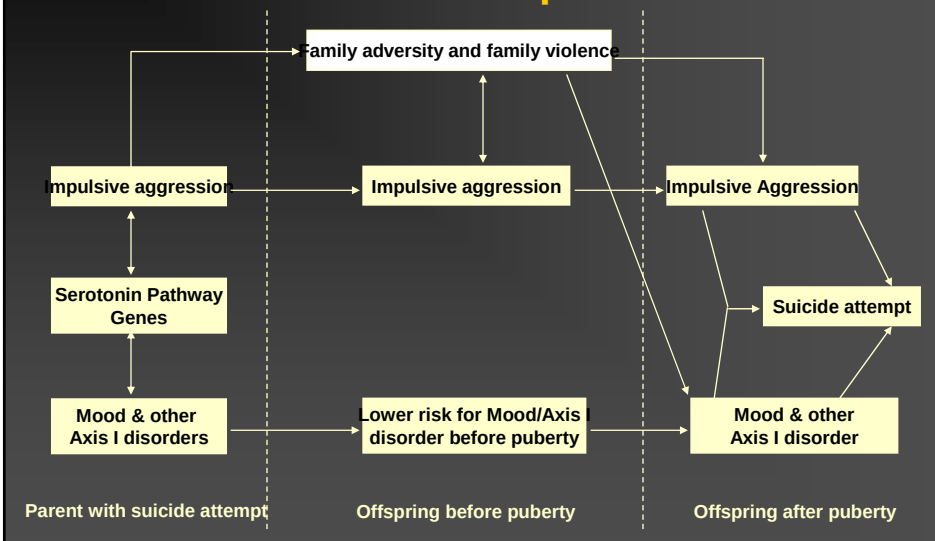
WPIC
David Brent, M.D.
Susan Beers, Ph.D.
Boris Birmaher, M.D.
David Kolko, Ph.D.
Nadine Melhem, Ph.D.
Jamie Zelazny, B.S.N.
Carol Agee, B.A.
Samantha Davis, M.S.W.
Joan White-Gjesfjeld, M.S.W.
Haishin Ozawa, MS
MH56612

NYSPI
J. John Mann, M.D.
Maria Oquendo, M.D.
John Keilp, Ph.D.
Laurence Greenhill, M.D.
Barbara Stanley, Ph.D.
Beth Brodsky, Ph.D.
Steven P. Ellis, Ph.D.
Ben Everett, Ph.D.
Marielle Palop, B.A.
Adrienne Tin, Ph.D.
Ainsley Burke, Ph.D.
MH56390

Goals

- Examine precursors of suicidal behavior in a cohort at high familial risk
- Identify clinical and biological phenotypes that may mediate transmission of suicidal behavior, independently and in interaction with early childhood adversity (ECA)
- Identify genes that alone, and in interaction with ECA, map to intermediate phenotypes and suicidal behavior

Familial Pathways to Early-Onset Suicide Attempt



Sample

- Probands – Adults with MDD who have children (in custody)
- Mainly inpatients
- Either attempters (lethality ≥2) OR
- Never attempters
- Offspring and other biological parents

Sample Sources

	Attempter	Non-Attempter
Probands	81	55
Offspring (≥ age 10)	183	116

Proband Characteristics: Axis I Lifetime Diagnoses (%)

	Attempter (n=81)	Non-Attempter (n=55)
Unipolar Major Depression	84.0	89
Dysthymia	11.1	12.5
Bipolar I/II	8.6	9
Any Anxiety	57.5	55.4
PTSD	36.2	15 *
ADHD	6.2	1.8
Alcohol or Substance Abuse/Dependence	53	36

*$p \leq .01$

Proband Characteristics: Axis II Lifetime Diagnoses (%)

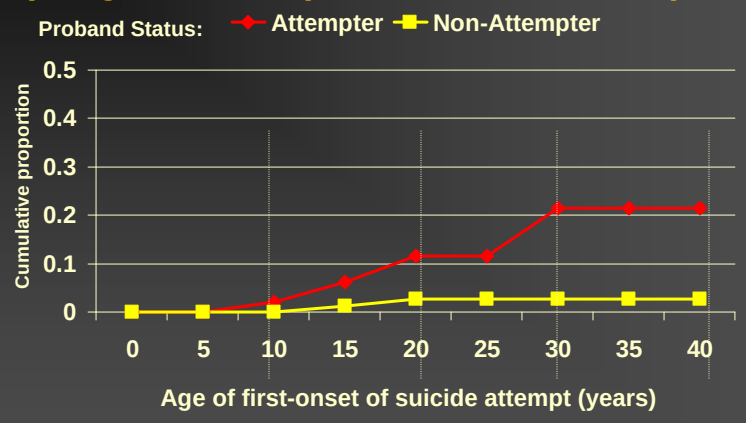
	Attempter (n=81)	Non-Attempter (n-75)
Cluster A	2.6	1.9
Cluster B	36.8	8.0 *
Borderline	34.2	3.7 *
Cluster C	8.2	11.1

*p≤.0001

Offspring: Lifetime Axis I Disorder (%)

	Attempter (n=183)	Non-Attempter (n=116)
Any Disorder	58.6	51.7
Any Mood Disorder	34.8	37.9
Unipolar Depression	25.5	31.0
Dysthymia	3.5	5.7
Bipolar I/II	1.4	1.1
Any Anxiety	23.4	15.9
Alcohol or Substance Abuse/Dependence	29.3	23.9
ADHD	15.6	9.0

Cumulative Proportion of Suicide Attempt Among Offspring of Attempters vs Non-Attempters



Generalized Savage: $\chi^2 = 7.89$, $p = .005$
OR = 6.2, 97.5% CI, 1.2 to 33.4

Brent et al., 2002

Risk Factors for Offspring Suicide Attempt

	Attempter (n=19)	Non-Attempter (n=213)	OR	*p*
Proband Characteristics				
Proband attempt, % yes	89.5	58.7	6.0	.008
Proband sexual abuse	**78.9**	**24.4**	**11.6**	**<.0001**
Offspring Characteristics				
Sex, % female	89.5	44.6	10.6	.0002
Race, % white	47.4	72.3	2.9	.023
Any mood disorder (lifetime)	**84.2**	**31.6**	**11.6**	**<.0001**
Any alcohol/substance (lifetime)	**57.9**	**24.4**	**4.3**	**.002**
Cluster B	31.3	6.6	6.4	.007
Offspring sexual abuse	42.1	3.8	18.5	<.0001
Psychological aggression, M ± SD	18.4±9.1	6.4±6.2	1.2	<.0001
Cohesion, M ± SD	42.1±11.3	55.8±11.7	0.91	.004
Impulsivity/Aggression				
Buss Durkee & CHI, M ± SD[a]	**0.73 ± 0.84**	**-0.09 ± 0.97**	**2.4**	**.0009**

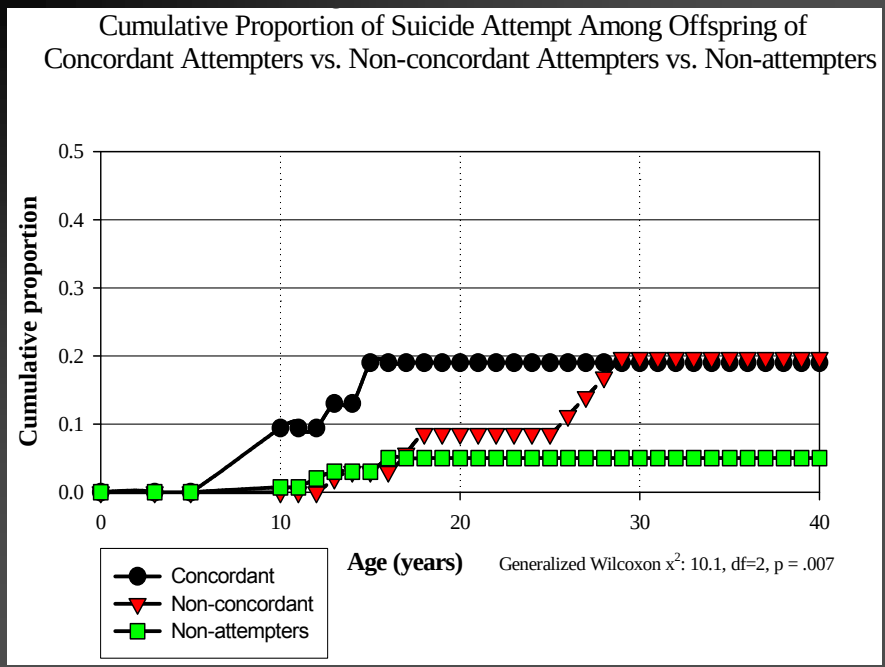
Note: OR indicates odds ratio; M, mean; SD, standard deviation; CHI, Children's Hostility Inventory.

Brent et al., 2002

Number of years between proband and offspring suicide attempt

Impact of Family Loading for Suicidal Behavior on Transmission

Proband Status	Proband (n)	Offspring (n)
Attempter, concordant sibling	19	41
Attempter, no concordant siblings	73	186
Non-attempter, no siblings with attempt	73	166



Prospective Analysis*

- 365 offspring of 212 mood-disordered probands
- 54.2% attempters
- Followed 1-6 years

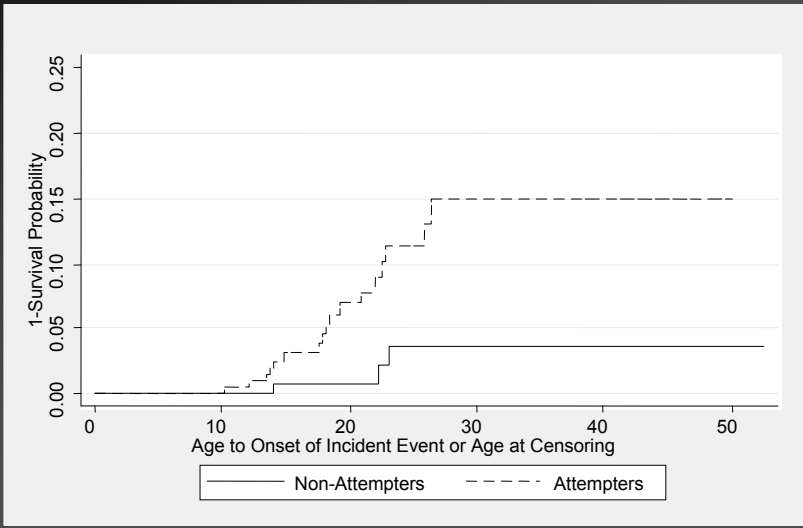
*Melhem et al., submitted

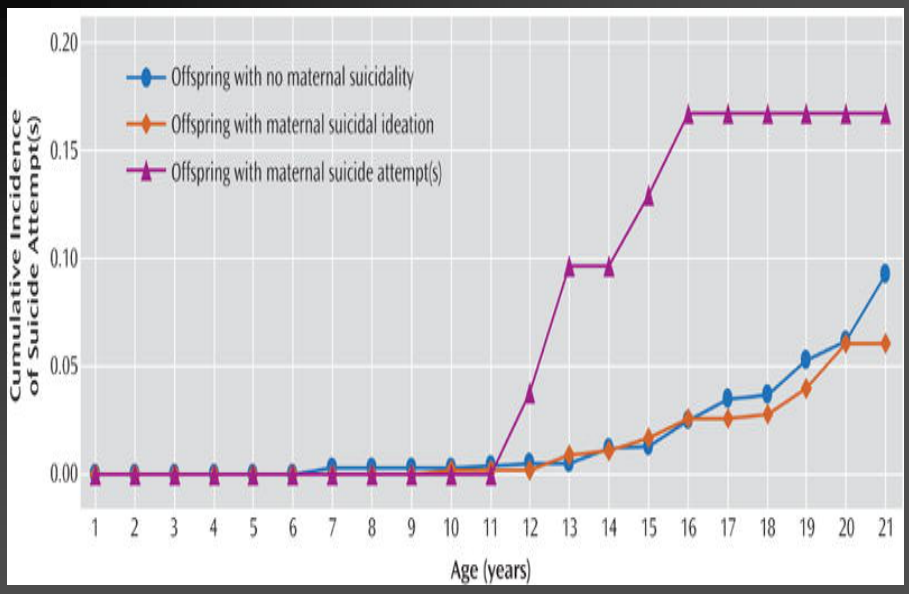
Incident Rate for Offspring of Attempters vs. Non-Attempter*

- 8.3% vs. 1.9% (RR = 4.4, 1.3-14.8)
- Time to event earlier

*Melhem et al., submitted

Kaplan Meier Survival Curve by Proband Attempt Status





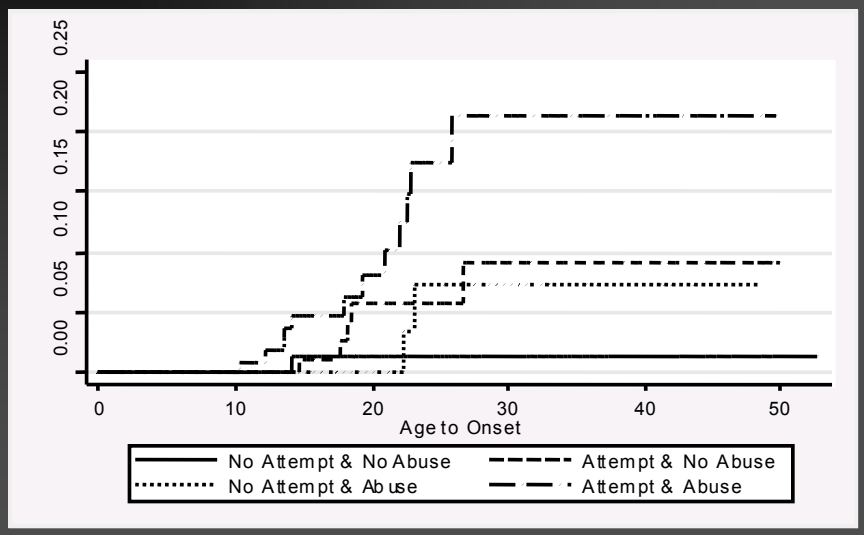
Lieb et al., 2005

Multivariate Prediction of Incident Effect*

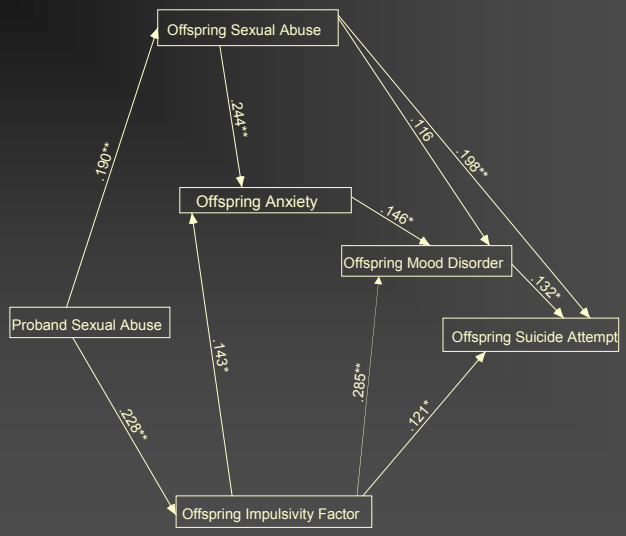
Time	Variable	OR	
Baseline	Proband sexual abuse	6.2	1.4-26.8
Baseline	Offspring mood disorder	7.0	1.5-32
Closest	Offspring mood disorder	4.5	1.2-18
Overall	Offspring proportion of time in mood episode	β=1.28	.26-2.30
Worst	Offspring ideation	β=.29	.002-.57
Worst	Offspring impulsive aggression (time to event)	β=.88	.39-1.37

*Melhem et al., submitted

Kaplan Meier Survival Curve by Proband Attempt and Abuse

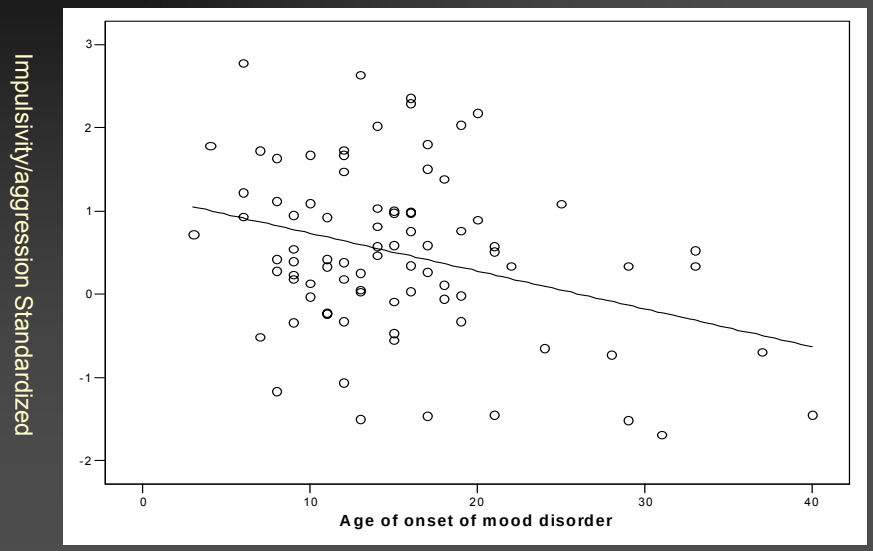


Cross-Sectional Path Analysis for Transmission of Mood Disorder and Suicide Attempt

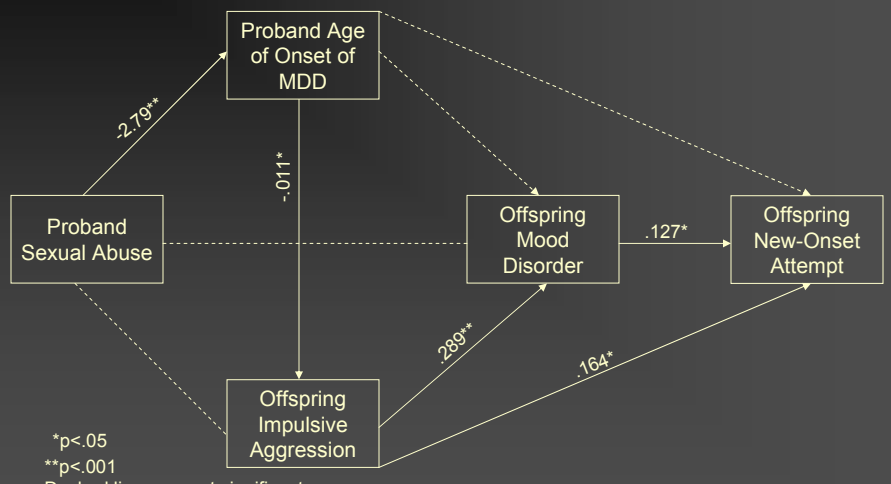


Correlation between age of onset of mood disorder and impulsivity factor

Correlation between Age of onset of mood disorder and impulsivity/Aggression

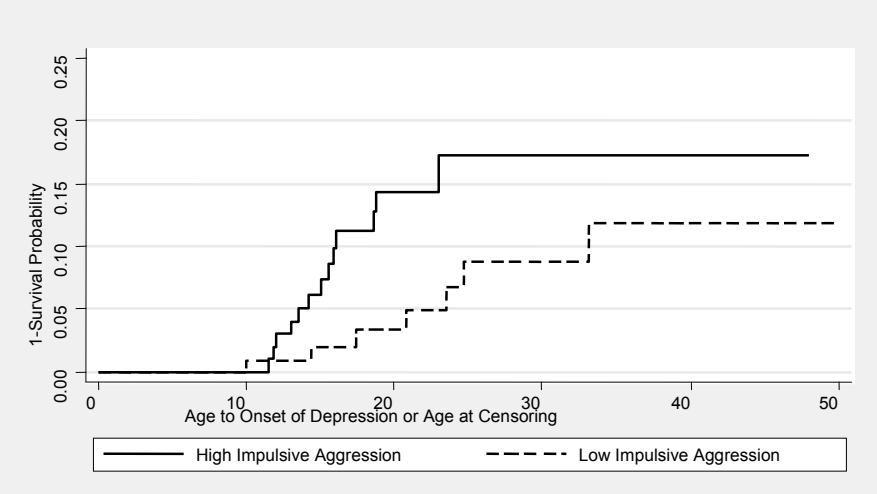


Prospective Path Analysis: Parent Abuse and Offspring Suicide Attempt



*p<.05
**p<.001
Dashed lines are not significant.
χ^2=0, df=0 (just identified model), p cannot be computed.
The model fits the data perfectly.

Kaplan Meier for Age to Onset of Depression by Impulsive Aggression

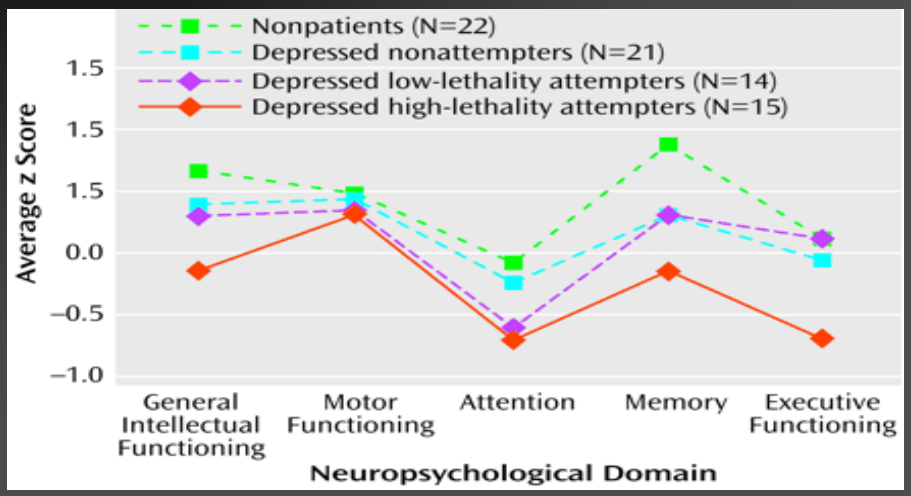


Wilcoxon test: chi2(1) = 5.13, Pr = 0.024

Early-Onset Mood Disorder

- Familial (r = .29); Mondimore, 2006
- Related to abuse and anxiety
- But still familially transmitted after control for abuse, anxiety
- Suicide attempters have earlier age of onset of mood disorder (23.5 vs. 27.3 years, p < .03)

Neuropsychological Domain Scores of Depressed Patients With No History of Suicide Attempts, Depressed Patients With Low- and High-Lethality Previous Attempts, and Nonpatient Comparison Subjects*



*Keilp et al., 2001

Memory and Executive Functioning in Offspring of Attempters and Non-Attempters

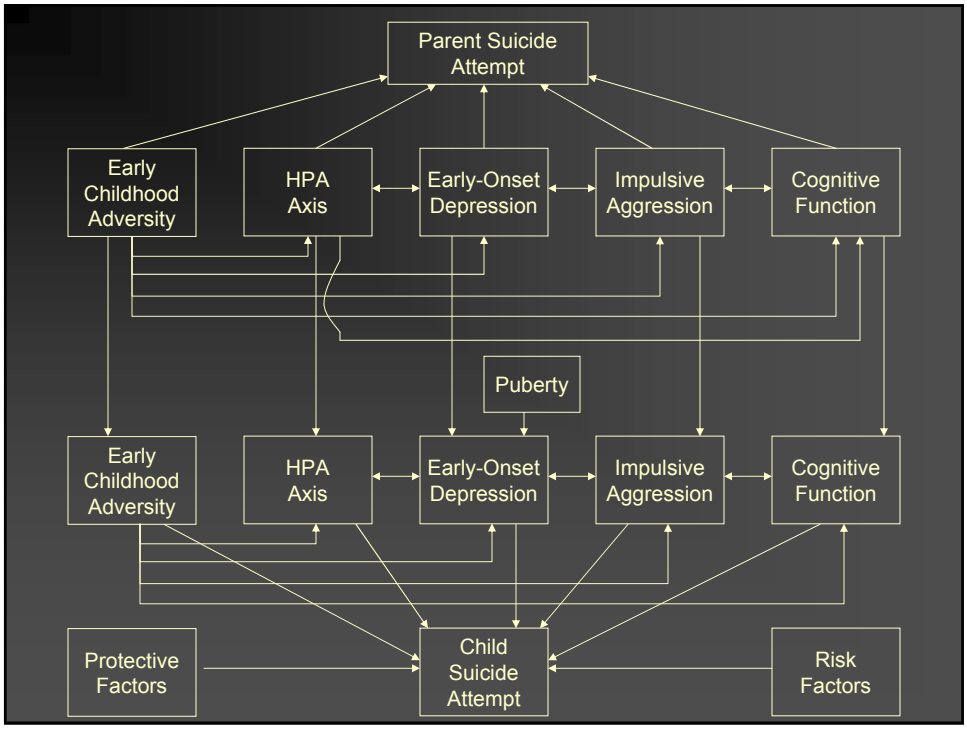
- Impairment similar to probands on memory (Bushke Selective Reminding Task) and executive function (Wisconsin Card Sort Test)
- BSRT Delay Recall (p = .009) and WCST (category, p = .023)
- Persist after control for PPVT, depression, other covariates
- Parent-child correlations (r's .18 to .32)

Summary

- Suicidal behavior is familially transmitted
- Four possible intermediate phenotypes
- Early maltreatment in parent and child probably has impact on intermediate phenotype
- Phenotypes may be interrelated

Intermediate Phenotypes and Familial Transmission of Suicidal Behavior

	A>N	AO>NO	F.T.	Pred.	Mediate	CG
Impulsive aggression	•	•	•	•	•	+
Early-onset mood disorder	•	•	•	•	?	+
Neuropsychological function	•	•	•	?	?	+
Cortisol response to stress	•	•	?	?	?	?
Early maltreatment	•	±	•	•	?	N/A



Role of Parental Sexual Abuse

- May increase risk of abuse in child
- Related to early-onset depression (EOD) in parent
- Early-onset depression in parent transmitted to child via impulsive aggression (IA)
- IA leads to EOD and suicide attempt in offspring

Impulsive Aggression (IA) and Early-Onset Depression (EOD)

- IA precedes EOD in time
- Is it a predictor, a precipitator, or a “forme fruste?”

Implications for Research

- Must assess stressful life events like abuse in genetic studies
- Need to assess and refine physiologic and psychological endophenotypes
- Is impulsive aggression the first manifestation of early-onset mood disorder?

Implications for Treatment

- Target impulsive aggression as well as depression
- Careful assessment, and when appropriate, treatment of intergenerational trauma
- Treatment of parental disorders
- Problem-solving via alternative neural pathways?

Implications for Prevention

- High risk families: high family loading for suicidal behavior, early-onset mood disorder, abuse, impulsive aggression
- Will prevention or delay of onset of depression reduce impulsive aggression?
- Can we interrupt familial transmission of suicide attempters in high risk families through prospective enhancement of protective factors?
- Will targeting early manifestations of IA decrease risk for mood disorder?