

# Families at High Risk for Depression: Anxiety and Startle Response

Virginia Warner, Dr. P.H.<sup>1</sup>

Priya Wickramaratne, Ph.D.<sup>1,2</sup>

Christian Grillion, Ph.D.<sup>3</sup>

Myrna M. Weissman, Ph.D.<sup>1,2</sup>

<sup>1</sup>NYS Psychiatric Institute, Division of Epidemiology

<sup>2</sup>Columbia University, Department of Psychiatry

<sup>3</sup>NIMH, Section Chief, Neurobiology of Fear & Anxiety

# Financial Disclosure

- Dr. Weissman in the past four years, Dr. Weissman received funding from the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Sackler Foundation, the Templeton Foundation and the Interstitial Cystitis Association; and receives royalties from the Oxford University Press, Perseus Press, the American Psychiatric Association Press, and MultiHealth Systems. None of these activities create a conflict.
- Drs. Warner, Grillon, & Wickramaratne have no competing financial interests to declare.

**Evolution of an idea...**

**or**

**How did I get here?**

# What do we know about anxiety and depression?

- Parental MDD increases the risk for offspring MDD and anxiety (2 to 3-fold).
- Strong, consistent association between anxiety and MDD in children and adolescents.
- Onset of anxiety precedes the onset of MDD in community studies as well as clinical studies.
- Early onset anxiety increases the risk for a subsequent onset of MDD and perhaps mediates the association between gender and MDD.

# What do we know about startle response?

- Startle response is a twitch of facial and body muscles evoked by a sudden and intense stimulus.
- Cross species.
- Acoustic startle response is mediated by a pathway in the brain stem which produces a motor or startle response.
- The startle response can be potentiated and sensitized by fear and stress.

# What is known about the association between startle and anxiety, depression and family environment

- Parental history of anxiety disorders is associated with elevated startle magnitude that varies by gender (Grillon, Biological Psychiatry, 1998).
  - Sons - fear-potentiated.
  - Daughters - normal fear-potentiated, significant elevation in anxiety-potentiated.
- Childhood abuse is associated with increased startle reactivity in adulthood ( $P < .01$ ) (Jovanovic, Depression and Anxiety, 2009).

- **Startle reactivity in depressed patients has been shown to be reduced.**
- **However healthy individuals have been shown to demonstrate increased anxiety-potentiated startle following sad mood induction.**
- **Risk for depression due to parental depression is associated with increased anxiety-potentiated startle.**



# What don't we know?

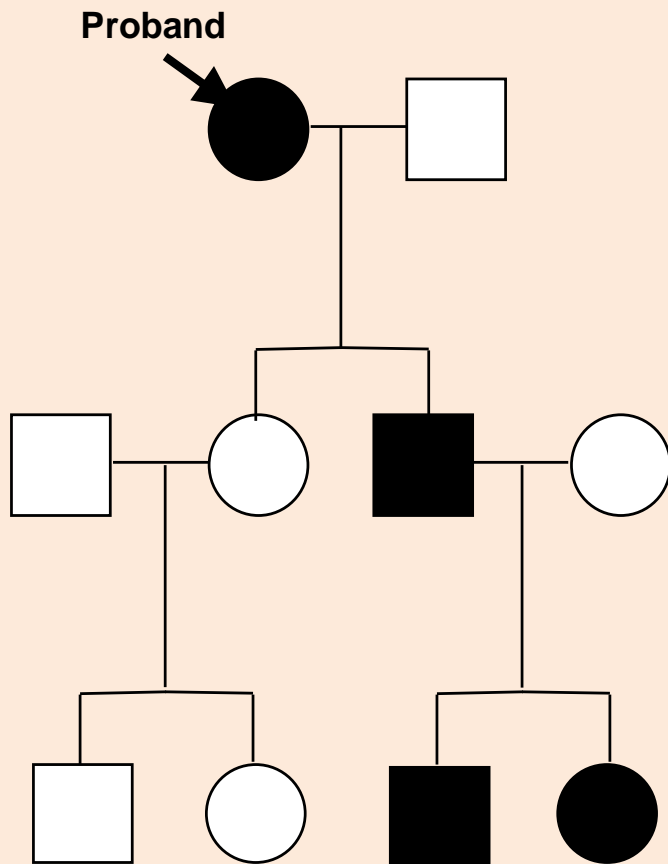
- Are childhood disorders associated with fear stronger mediators of the association between parent and offspring MDD than disorders associated with anxiety?
- Could anxiety-potentiated startle be an endophenotype for a form of depression associated with fear-related disorders?



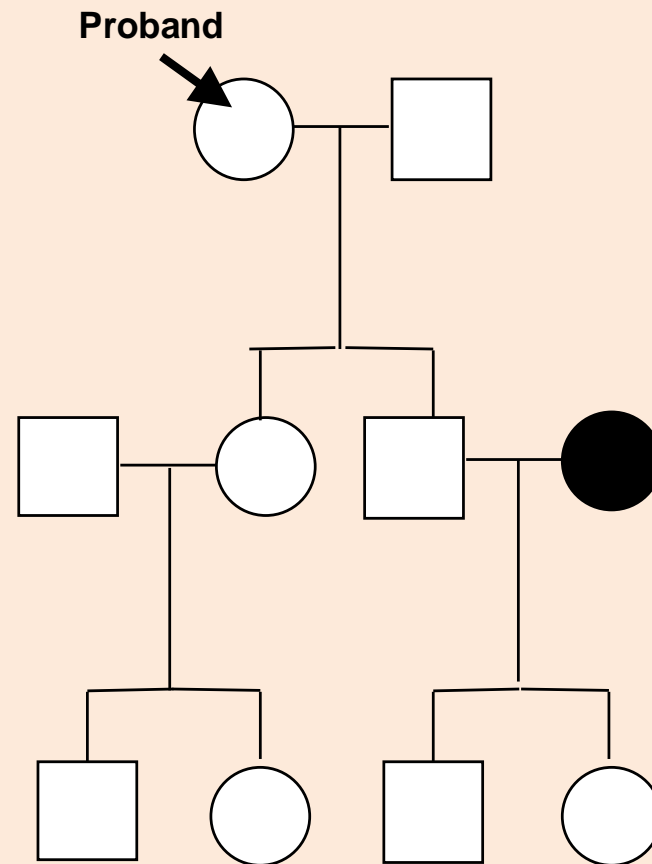
# Design of the Parent Study

- Study design is retrospective cohort with exposure defined by generation 1(G1) depression.
- Three generations studied. Currently starting to assess the 4<sup>th</sup> generation.
- Longitudinal: Five assessments completed over nearly 30 years from childhood to adulthood in 2nd generation. Sixth assessment in progress.
- Three assessments completed over nearly 20 years in 3rd Generation . Fourth assessment in progress.

## High Risk Families



## Low Risk Families



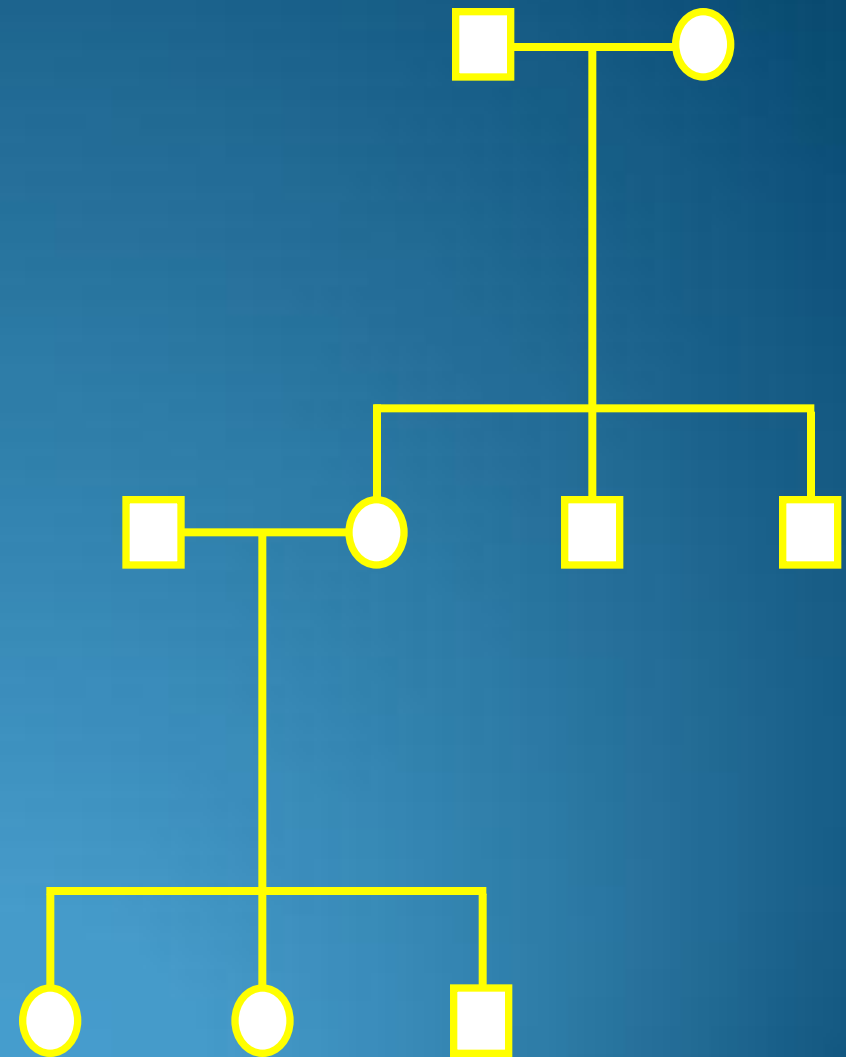
1<sup>st</sup> Generation  
(G1 - Grandparents)



2nd Generation  
(G2 - Parents)



3rd Generation  
(G3 - Grandchildren)



| Generation                           | Generation 1<br>1<br>(Probands) | Years            |                  |                  |                  |                  |                  |
|--------------------------------------|---------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                                      |                                 | Baseline         | Year 2           | Year 10          | Year 20          | Year 25          | Year 30 +        |
|                                      |                                 | Clinical Battery | Clinical Battery | Clinical Battery | Clinical Battery | Clinical Battery | Clinical Battery |
|                                      |                                 |                  |                  |                  | EEG              | MRI              | EEG              |
|                                      |                                 |                  |                  |                  | DNA              | DNA              |                  |
|                                      |                                 |                  |                  |                  |                  |                  |                  |
|                                      | Generation 2<br>2<br>(Children) | Clinical Battery | Clinical Battery | Clinical Battery | Clinical Battery | Clinical Battery | Clinical Battery |
|                                      |                                 |                  |                  |                  | EEG              | MRI              | MRI              |
|                                      |                                 |                  |                  |                  | Startle          | DNA              | EEG              |
|                                      |                                 |                  |                  |                  |                  |                  | DNA              |
| Generation 3<br>3<br>(Grandchildren) |                                 |                  | Clinical Battery | Clinical Battery | Clinical Battery | Clinical Battery |                  |
|                                      |                                 |                  |                  | EEG              | MRI              | EEG              |                  |
|                                      |                                 |                  |                  | Startle          | DNA              | DNA              |                  |
|                                      |                                 |                  |                  |                  |                  | MRI              |                  |

# Samples

## Anxiety and fear-related disorders as mediators - Lifetime

- G2 N=224, all G2 interviewed at Wave 1 or 2 and re-interviewed at Wave 3 or 4.
- G3 N=161, all G3 interviewed at Wave 3 or 4.

## Startle – Wave 4

- 7+ years old, geographic area of the study, and without a hearing impairment or history of seizures, epilepsy, head trauma, or psychosis.
- G2 N=108 had analyzable startle data.
- G3 N=70 had analyzable data.

# Definition of G2 and G3 Fear- and Anxiety Related Disorders

- **FEAR = Phobic or panic disorders (associated with increased activity of amygdala)**
- **ANXIETY/STRESS = Generalized Anxiety Disorder or Overanxious Disorder (associated with activity in the hippocampus, bed nucleus of the stria terminalis - extended amygdala)**

# Startle Methods

- The experiment consisted of three conditions: safe, threat, and intertrial interval (ITI).
- Fear-potentiated startle is measured as the difference between startle during the threat condition minus startle during the ITI condition. Anxiety-potentiated startle is measured during the ITI condition.
- The safe and threat conditions were signaled by 8-sec visual cues (blue circle for safe and green square for threat).
- Half the threat cues were reinforced with an air blast.



## Startle Methods (cont.)

- ITI lasted 18 - 40 sec and occurred between threat/safe signals.
- Six acoustic startle stimuli occurred during each condition (ITI, threat and safe).
- Left and right eye blink reflexes were recorded with electrodes placed under each eye.

**Are childhood disorders  
associated with fear  
stronger mediators of the  
association between  
parent and offspring MDD  
than disorders  
associated with anxiety?**

# Mediation (Pearl, 2010)

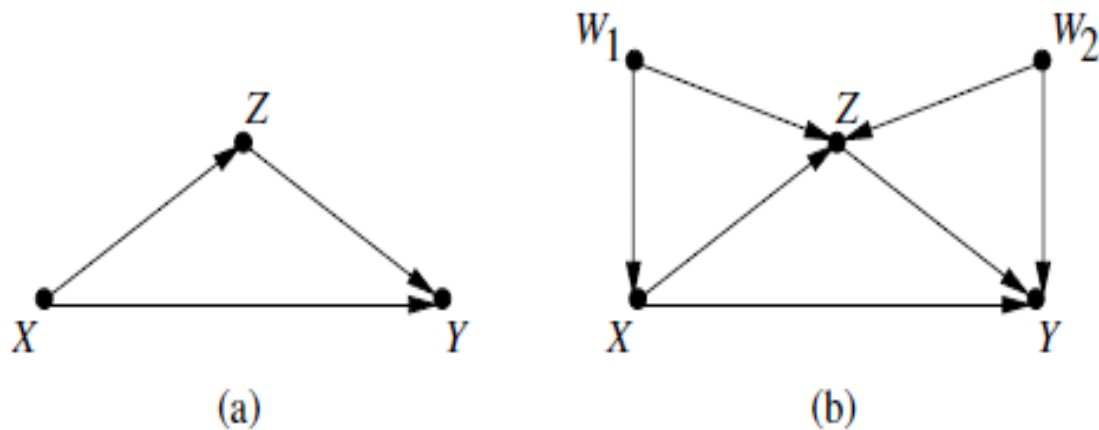
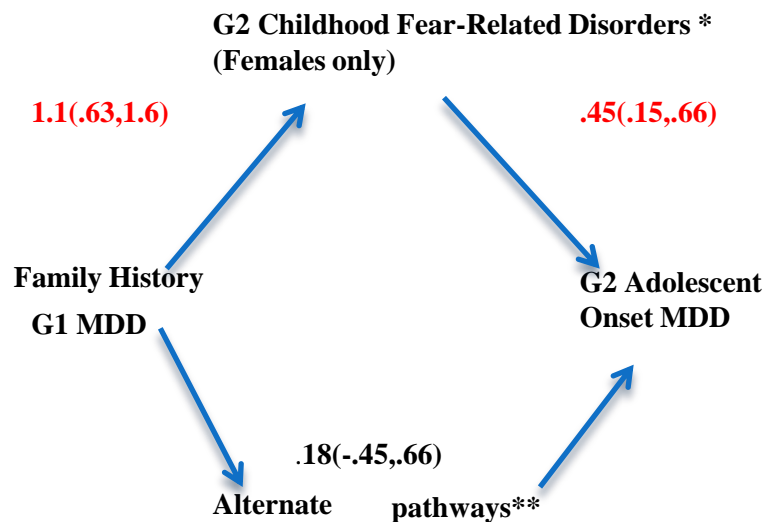
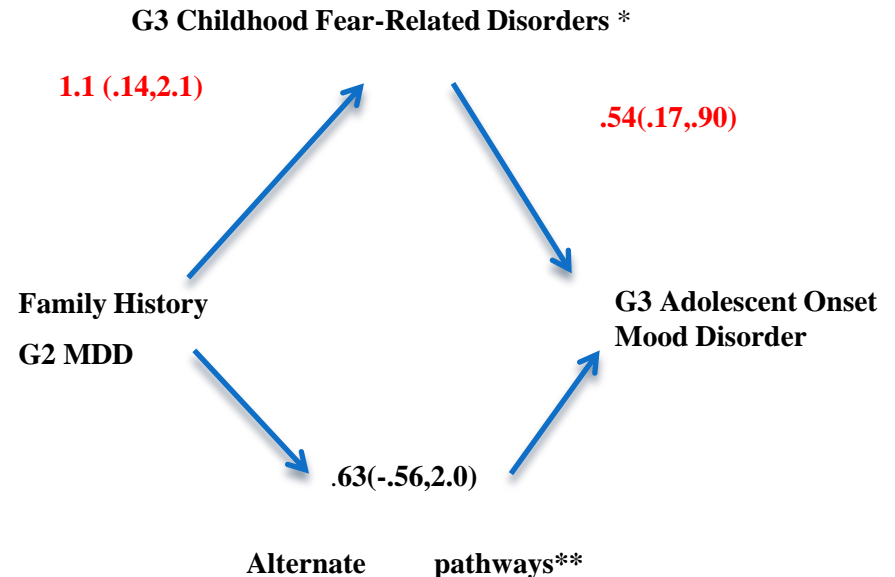


Figure 1: (a) A generic model depicting mediation through  $Z$  with no confounders, and (b) with two confounders,  $W_1$  and  $W_2$ .

# Mediation



TOTAL INDIRECT:  $.50 (.19, .93)$   
 TOTAL ALTERNATE:  $.18 (-.45, .66)$   
 TOTAL:  $.69 (.20, 1.3)$   
 \*Indirect via fear-related disorders  
 \*\* All pathways other than indirect



TOTAL INDIRECT:  $.58 (.005, 1.5)$   
 TOTAL ALTERNATE:  $.63 (-.56, 2.0)$   
 TOTAL:  $1.2 (.62, 2.0)$   
 \*Indirect via fear-related disorders  
 \*\* All pathways other than indirect

# Anxiety-related disorders

- Were associated with G1 and G2 depression.
- Did not mediate the association between G1 and G2 depression.
- Indirect pathway was not significant.

**Could anxiety-potentiated startle  
be measuring an  
endophenotype for a form of  
depression associated with  
fear-related disorders?**

# Endophenotype

- Measured component unseen by the unaided eye along the pathway between genotype and disease.
- Genotype → Activity in fear/anxiety circuitry measured by startle → depression with comorbid fear-related disorders



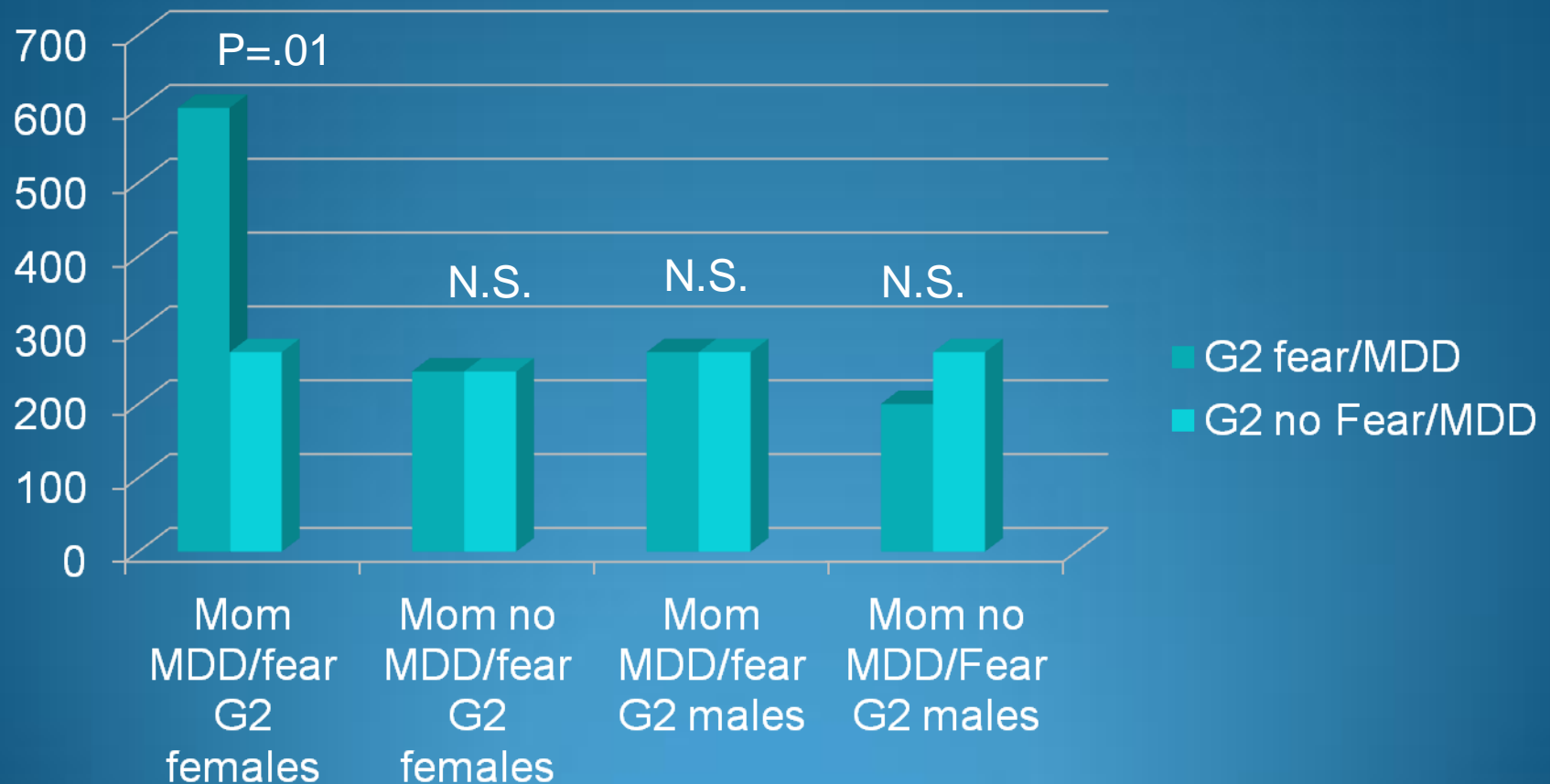
# Why Use High/Low Risk Design For Endophenotypes?

- A true endophenotype should not simply be a disease correlate.
- It should be on the causal pathway to illness – appears before illness was developed.
- Should not arise as a result of illness, should be state independent (observed in subjects who are at risk but not currently ill).
- High-Risk, includes subjects based on their risk rather than presence of illness of interest.

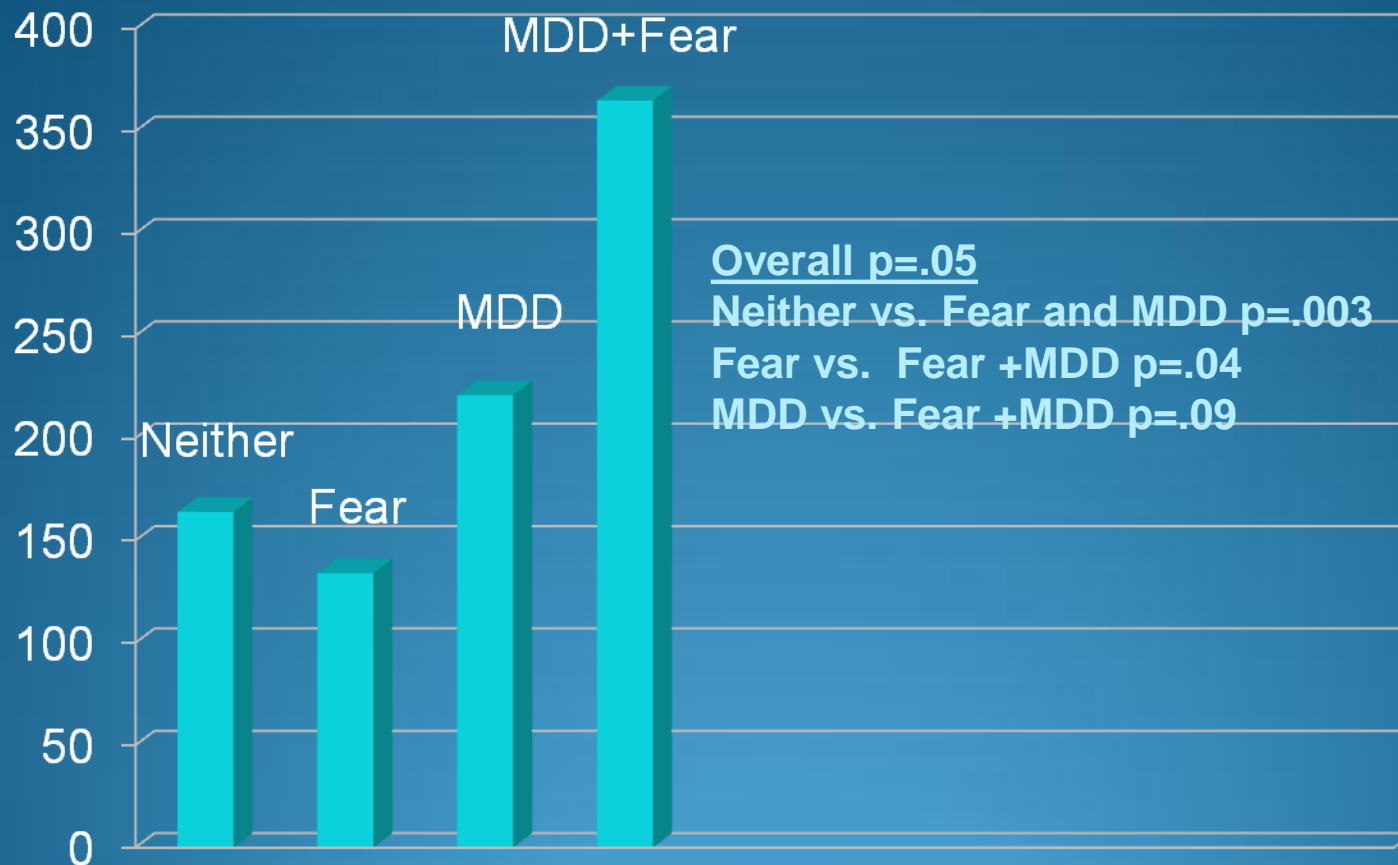
# Summary of Findings

- If the mother (G1) had fear-related depression and if G2 was a female and had fear-related depression, the G2 female had increased anxiety-potentiated startle.
- G2 offspring with parents with fear-related depression had greater anxiety-potentiated startle independent of G2 diagnosis.
- G2 was associated with G3 anxiety-potentiated startle (.39  $p=.004$ ) and correlated within families (.31  $p=.01$ ).
- Anxiety-potentiated startle met some criteria for an endophenotype as defined by Gottesman (2003).

**Figure 1. G2 anxiety-potentiated startle by G2 gender, maternal (G1) fear-related MDD**



**Figure 2. G2 anxiety-potentiated startle by G1 MDD and Fear-related disorders, in absence of G2 fear-related MDD**



**Fear-potentiated startle (in the presence of a threat of an airblast) did not meet criteria for an endophenotype for depression with comorbid fear-related disorders.**

# Genetics - recent, very preliminary results

## In this sample:

- The SS/SL genotype (serotonin transporter) increases the risk for fear-related disorders and enhanced anxiety-potentiated startle.
- Enhanced anxiety-potentiated startle is also associated with a gene (FKBP5) that has been shown to interact with severity of childhood trauma increasing the risk for adult PTSD symptoms (Ressler et. al.,2008).
- Enhanced anxiety-potentiated startle is also associated with brain-derived neurotrophic factor Val66Met which is associated with fear extinction (Frielingsdorf et. al., 2010).
- Again very preliminary data , still small sample.

# What do I think about this?

- The findings are consistent with the findings that post-traumatic stress disorder (PTSD) is associated with enhanced stress responsiveness combined with the dysregulation of fear and dysregulation of fear's inhibition (Ressler, 2010).
- Likely that people in these families exhibit deficits in fear extinction (Graham & Milad, 2011).



# Next Steps

- Trauma and revictimization data (Widom)
- Community stress
- MRI, EEG
- 5-HTT (serotonin), BDNF, FKBP5 genotypes
- Subsequent episodes of disorder
- Fear extinction

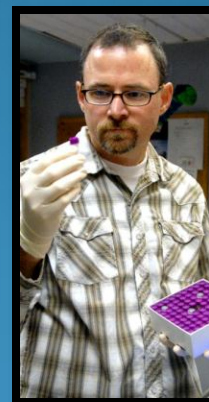
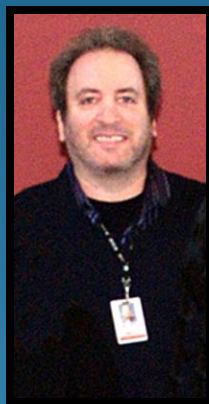
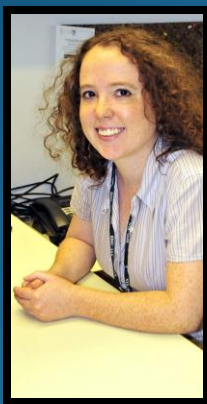
# Lastly...

**Treatment needs to:**

- **Take into account overactive fear circuitry,**
- **stress sensitivity,**
- **and deficits in fear extinction**
- **in families at high risk for fear-related depression.**
- **This could have the potential to decrease the rates of MDD in adolescence.**

# Acknowledgments

This study was funded by the **National Institute of Mental Health** Children at High and Low Risk for Depression (2 R01 MH36197; Weissman, P.I.) and Serotonergic Modulation of Brain Development: Genetic and Pharmacologic Influences on Structure, Function, and Behavior (1P50MH090966; Gingrich, J.; Weissman, M. , P.I. Project 2).



National Institute of Mental Health grant MH36197