



8th Annual

## Yale NEA-BPD Conference

*Impulsivity, Aggression, and Legal Involvement*

Friday, May 4, 2012; 8:30 AM - 4:45 PM

# BORDERLINE PERSONALITY DISORDER: IMPULSIVITY, AGGRESSION, & LEGAL INVOLVEMENT

FRIDAY MAY 4, 2012

8:30 AM - 4:45 PM

Mary S. Harkness Memorial Auditorium, Sterling Hall of Medicine

333 Cedar Street, New Haven, CT

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CLEARVIEW  
TREATMENT PROGRAMS  
CENTERS FOR BORDERLINE PERSONALITY AND DISORDERS

## **Neurobiology of Impulsive Aggression in BPD**

**Antonia S. New MD**



## The Neuroscience of Aggression in Borderline Personality Disorder

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## Stigma in BPD

- Doubts about the validity of the diagnosis
- Complex nature of the symptoms
- Relative refractoriness to treatment, leaving the mental health professional to feel helpless.
- The disorder has as a cardinal symptom, anger and interpersonal disruptiveness, making it difficult to form a therapeutic alliance with the patient

## Validity Criteria for a Psychiatric Disorder

- **a careful delineation of symptoms**
- information about the course of illness
- evidence of familial clustering
- predictable treatment response, especially to somatic treatments
- biological markers

Robins and Guze, 1970

## Factor Analyses of BPD Symptoms

- Early studies showed three factors:
  - disturbed relatedness (unstable relationships, identity disturbance and chronic emptiness)
  - behavioral dysregulation (impulsivity, suicidality/self-mutilatory behavior)
  - affective dysregulation (affective instability, inappropriate anger and efforts to avoid abandonment)
- Subsequent analyses confirmed factors but showed the three factors were highly correlated with one another ( $r = .90, .94, \text{ and } .99$ )

(Sanislow et al, 2000, 2002)

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## Empirical Evidence about BPD: Course and Prognosis

- The completed suicide rate in BPD approaches 10%; with 75% attempting suicide at least once
- Elevated risk of: physical illnesses, cigarette smoking, medical emergency room visits, motor vehicle accidents, violence to others and occupational and psychosocial dysfunction
- A naturalistic longitudinal study over 16 years showed that 78% BPD patients achieve 8 year sustained remission and 40% achieved recovery (1/3 remitting in first two years).
- "Recovery" defined as remission + at least one stable close relationship and ability to work or go to school fulltime

## Parental Survey Data

- ⊙ 234 female BPD offspring compared to 87 non-BPD sisters
- ⊙ Parents report significantly more moodiness starting in first year of life in BPD than non-BPD sibs, and a trend for more sensitivity and poor self-soothing
- ⊙ Interpersonal difficulties manifest in elementary school
- ⊙ Impulsivity, aggression, and self-destructive behaviors dominate in adolescence

Goodman et al., 2010

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## Twin Studies in Borderline Personality Disorder

- An early small study showed high heritability for dimensions of BPD, especially for direct assaultiveness (Torgerson et al., 1984)
- Recent twin studies show high heritability (0.50-0.79) for borderline personality disorder itself (Torgerson et al., 2000; Kendler et al., 2009)
- An additional 10% of the variance may come from common environmental factors

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Robins and Guze, 1970

## Absence of a Robust Response to Somatic Treatments

- ⊙ This leaves patients without the benefit of effective pharmacology, AND impedes and avenue of understanding the biology of the disease

We will get back to this briefly and you will hear more about this later today!

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Robins and Guze, 1970

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## Words from an e-mail I received

- "I have lived with symptoms of Borderline for most of my teen years and all of my adult life. I am 33... I began showing symptoms around the age of 15, but did not enter treatment until I was 25. My parents never noticed a problem. I was just a moody, bad kid...not a teen who needed help. It was after several messed up "relationships" that I got help for myself."
- About the move of BPD to Axis I: "I think that the stigma surrounding borderline is bad enough, but having it on the Axis I would mean (in the US anyway) more people might get treatment for it".
- "I also think that if it was moved, there might (might) be more research dollars invested into it and certainly more education for families. My family has turned their back on me because they feel that I am doing things "on purpose", and that I am "manipulative" ... Perhaps if they understood that it has much more of a biological cause, or that it was in the same category as other "important" illnesses like "depression"....maybe my family would have cared a bit more than they did before they gave up."

## So why focus on impulsive aggression?

- It appears to be highly associated with other symptoms of BPD
- It is often the symptoms domain most associated with hospitalization, poor employment history and interpersonal disruptions
- Focuses on a rather objectively measured behavior

## Models for BPD

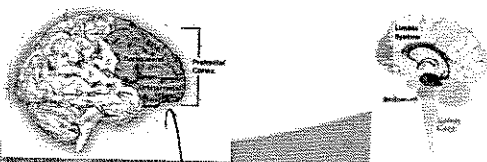
- Prefrontal-limbic disconnect: similar to model in anxiety disorders
- A serotonergic model
- Habituation Failure: difficulty quieting emotional responses
- A developmental model

Prefrontal-limbic disconnect

## DYSINHIBITION: A FOCUS ON AGGRESSION

## Primate Studies

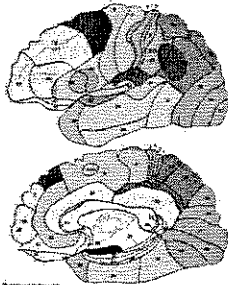
- Primates: ablation of the posterior orbitofrontal cortex (OFC) bilaterally results in hyperactivity and aggression (Pribram & Bragshaw, 1953)
- Increase in social aggression in rhesus monkeys after bilateral chemical lesioning of the amygdala (Izquierdo, A. et al., 2005)



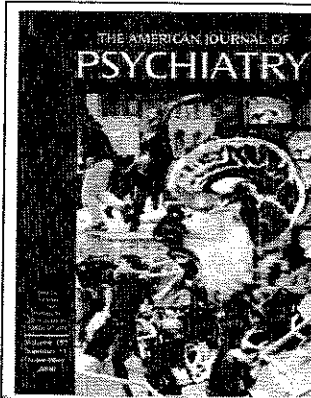
## Brain Injury and Aggression

- Phineas Gage: damage to anterior and mesial orbital cortex and anterior cingulate, left >right (Damasio, 1994)
- Angry outbursts associated with damaged OFC in patients with frontotemporal dementia with hypoperfusion (Miller et al, 1997)
- Injury to medial PFC early in childhood can result in disinhibited aggression later in life (Anderson & Silver, 1998)

## Neuroanatomy of Violence: PET and Aggression



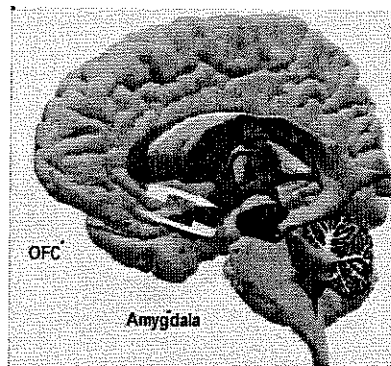
- Decreased metabolism in medial cortex and OFC (BA 32, 12, 11) in murderers (Raine et al, 1994, 1997)
- Decreased metabolism in OFC (BA 11) in aggressive behavior and in posterior OFC in perpetrators of domestic violence (George et al, 2004)



Anger induction in normal men showed increased rGMR in the left anterior cingulate gyrus (BA 24) and orbital frontal cortex (Pietrowsky et al, 2000)

## <sup>18</sup>FDG PET in BPD

- Decreased metabolism in patients with BPD compared to healthy volunteers in anterior, and medial frontal regions at rest (BA 9, 10, 32, 46) (De La Fuente et al 1997; Soloff et al, 2000)
- Increased metabolism in female patients with BPD in frontal and anterior cingulate regions at rest (BA 32, 8, 10) (Juengling et al 2003).
- Female patients with BPD had increased activation in frontal pole (BA 9 & 10) bilaterally and decreased activation in right ventromedial cortex (BA 24 & 32) compared to controls in response to abandonment scripts (Schmahl et al 2003; Schmahl et al, 2004).



Orbitofrontal cortex (OFC) part of coordinated limbic circuit that controls aggressive responding.

## Aggression Provocation: Point Subtraction Aggression Paradigm (PSAP)

- Subjects play a "confederate"
- They can press one of three buttons:
  - A: gain points for money
  - B: remove points from the other player (aggressive responding)
  - C: protect yourself from the other
- Provocation occurs when the "other" takes points from the subject. (PFI: provocation free interval)

## Subjects

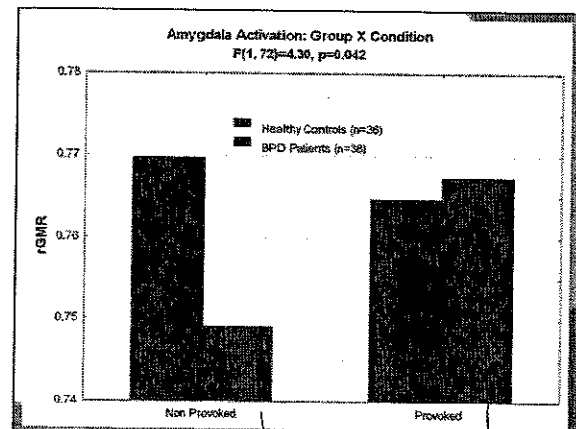
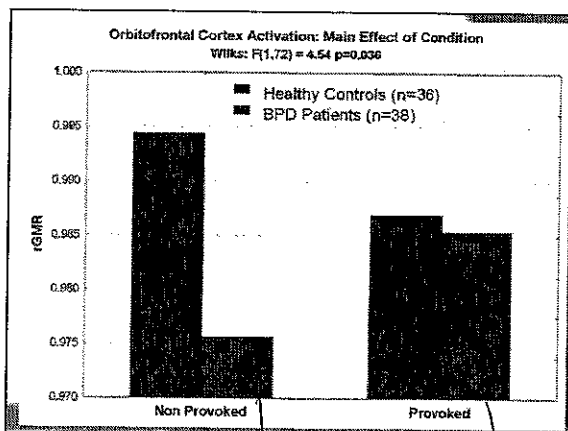
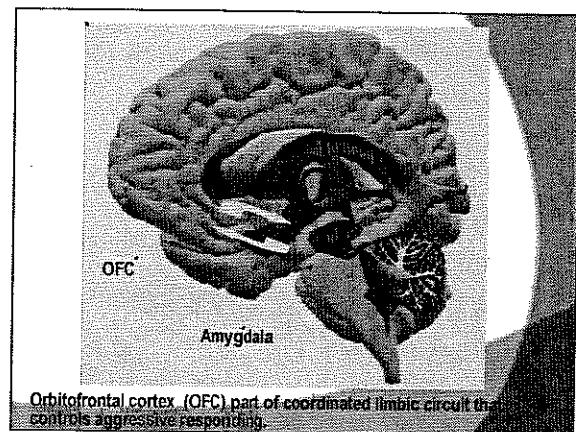
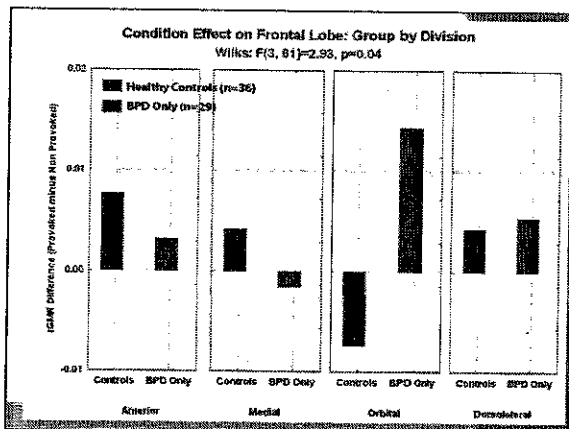
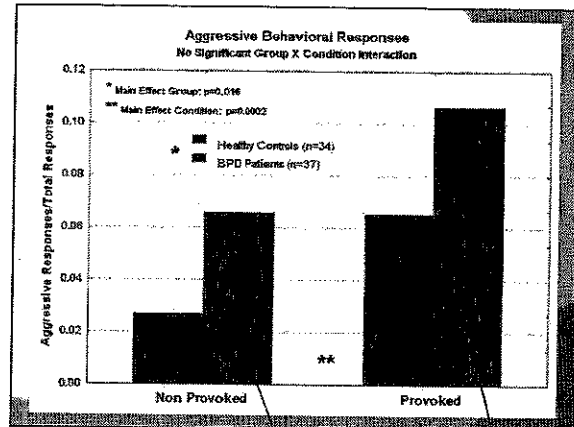
- BPD-IED group (n=38):
  - Met criteria for IED-R
  - Met DSM-IV criteria for borderline personality disorder
- Healthy Controls (n=36):
  - no personal or first degree relative with a history of psychiatric disorder
- All medically healthy and off medication for at least 6 weeks
- No substance abuse for 6 months

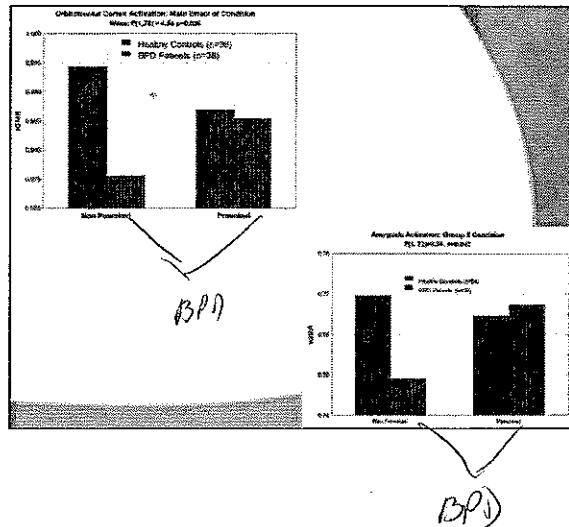
New et al, 2008

## Method

- All subjects underwent 2  $^{18}\text{F}$ FDG PET scans, control (non provoked with  $\text{pfi}=\infty$ ) and active (provoked with  $\text{pfi}=62.5$ ) PSAP task, counterbalanced for order
- All underwent structural MRI for co-registration

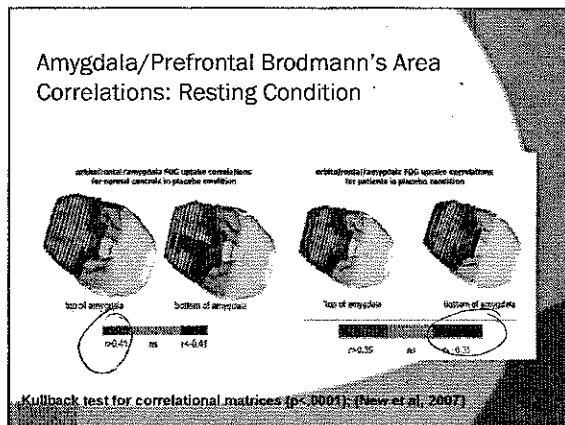
Pushers button (ATTACK)





## Hypothesized Circuitry

- ◉ If PFC plays a modulatory role in regulating negative emotion as manifested by amygdala activity, then
  - Controls should have positive correlations between amygdala and PFC
  - This coordination might be disrupted in BPD



## SEROTONERGIC MODEL

## Serotonin and Aggression

- ◉ Neuroendocrine probes of serotonin show blunted response to serotonergic agents: eg m-CPP and fenfluramine
- ◉ Low metabolite levels in plasma and CSF of 5-HIAA in aggressive patients with personality disorders
- ◉ SSRIs decrease aggression in non-depressed subjects.

## Serotonin Receptor Availability in OFC

- ◉ Orbitofrontal 5-HT<sub>2A</sub> receptor availability is increased in patients with personality disorder and current physical aggression compared with patients without current physical aggression and healthy control subjects
- ◉ No significant differences in 5-HT<sub>2A</sub> receptor availability in other brain regions
- ◉ OFC 5-HT<sub>2A</sub> receptor availability correlated, specifically, with a state measure of impulsive aggression. (Rosell et al., 2010)



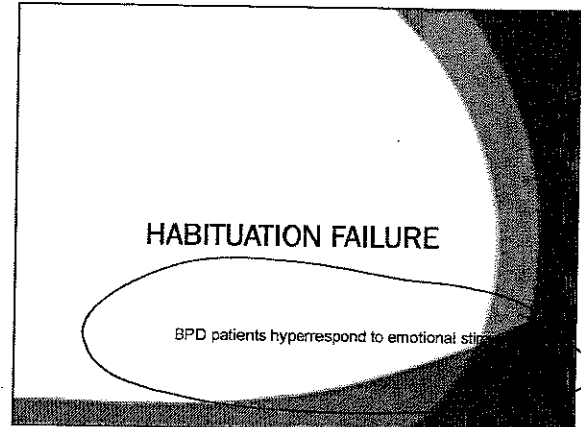
### Serotonin Genotype Influences Response to SSRIs

Genotype	Responders (n=10)	Nonresponders (n=10)	P < 0.05
5-HTT			
LL	9 (90.0)	7 (70.0)	0.210
SL	1 (10.0)	3 (30.0)	
SS	0 (0.0)	0 (0.0)	
5-HT <sub>2A</sub>			
AA	6 (60.0)	6 (60.0)	0.809
AG	4 (40.0)	4 (40.0)	
GG	0 (0.0)	0 (0.0)	
5-HT <sub>2C</sub>			
AA	9 (90.0)	4 (40.0)	0.106
AG	1 (10.0)	6 (60.0)	
GG	0 (0.0)	0 (0.0)	
5-HT <sub>1B</sub>			
LL	10 (100.0)	10 (100.0)	0.587
SL	0 (0.0)	0 (0.0)	
SS	0 (0.0)	0 (0.0)	
5-HT <sub>1D</sub>			
LL	7 (70.0)	10 (100.0)	0.004
SL	1 (10.0)	0 (0.0)	
SS	2 (20.0)	0 (0.0)	
5-HT <sub>2B</sub>			
AA	14 (140.0)	17 (170.0)	0.619
AG	1 (10.0)	4 (40.0)	
GG	0 (0.0)	0 (0.0)	
5-HT <sub>2D</sub>			
LL	7 (70.0)	6 (60.0)	
SL	0 (0.0)	0 (0.0)	
SS	0 (0.0)	0 (0.0)	

Table 2. Genotype frequencies in responders (n = 22) and nonresponders (n = 27) to a 12-week fluoxetine treatment.

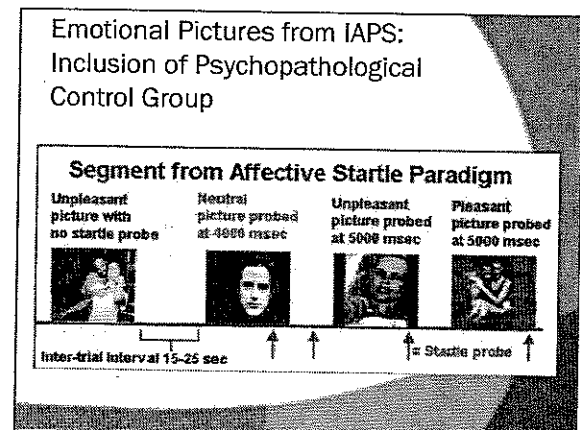
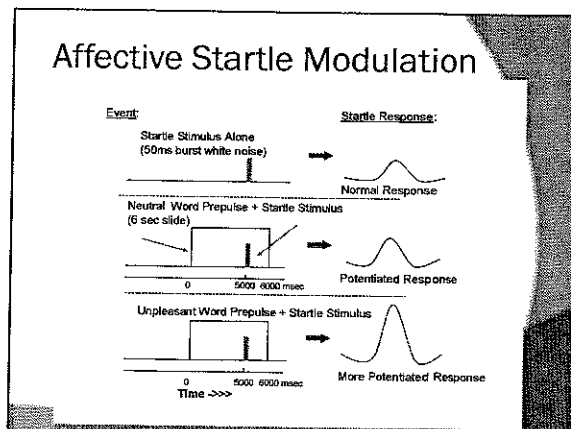
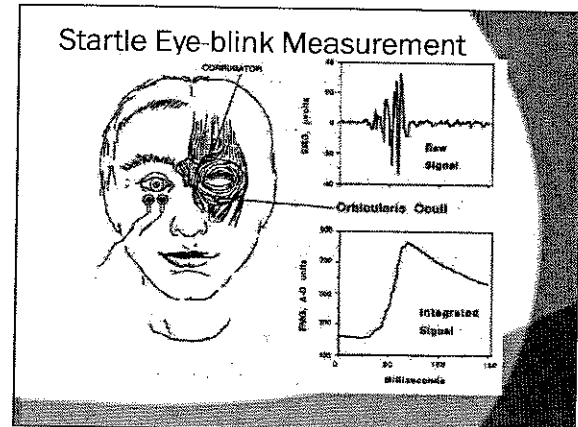
Fluoxetine response in impulsive-aggressive behavior and serotonin transporter polymorphism in personality disorder: Silva, Hermas, Iltis, Patricia, Solari, Aldo, Villalón, Juan, Jara, Sonia, Romero, María, Galegüer, Felipe, Martínez, María.

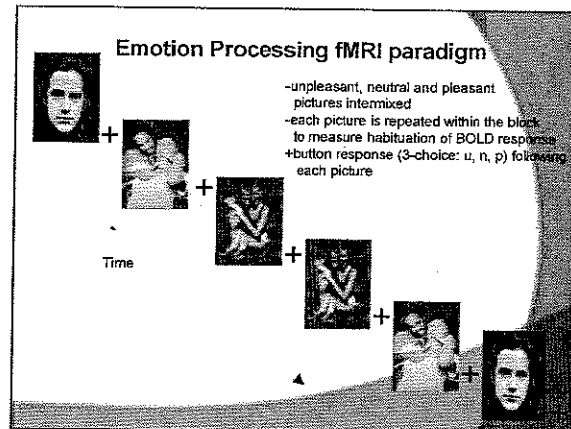
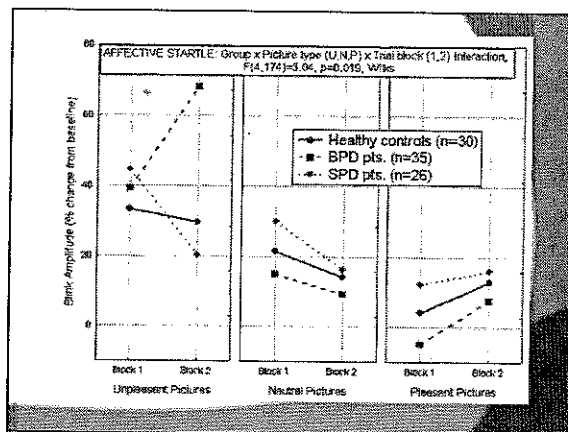
Psychiatric Genetics, 20(1):25-33, February 2012.



### Startle Eye Blink Modification: an objective measure of affect response

- Measurement of intensity of blink via contraction of orbicularis oculi in response to sound burst
- Emotion can influence this intensity: negative emotion in healthy controls enhances intensity



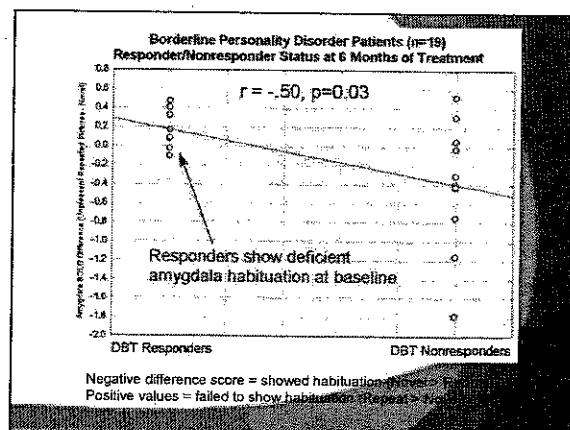


## Habituation Failure in BPD

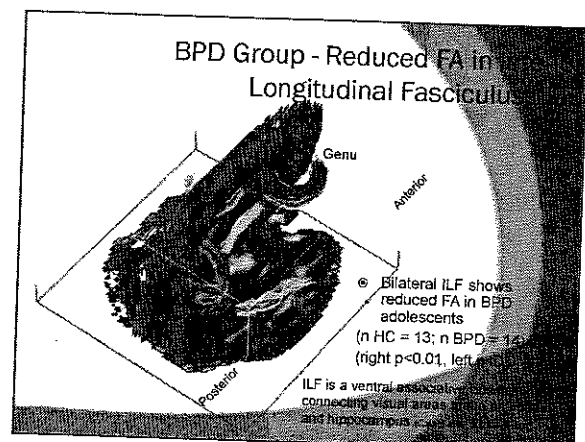
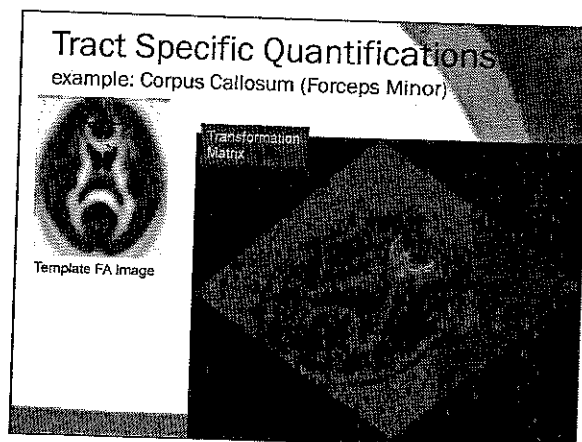
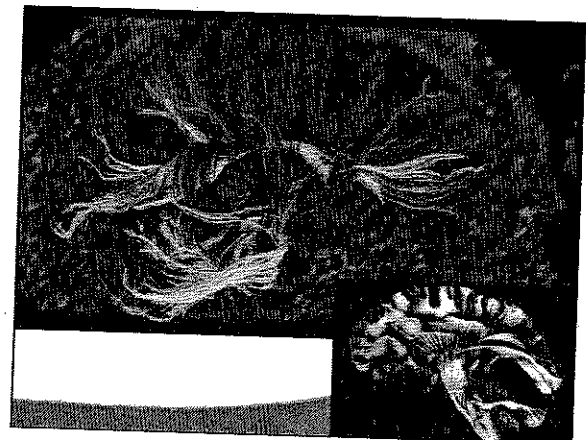
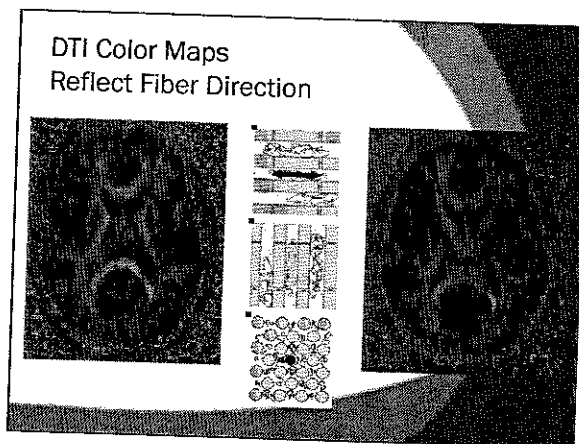
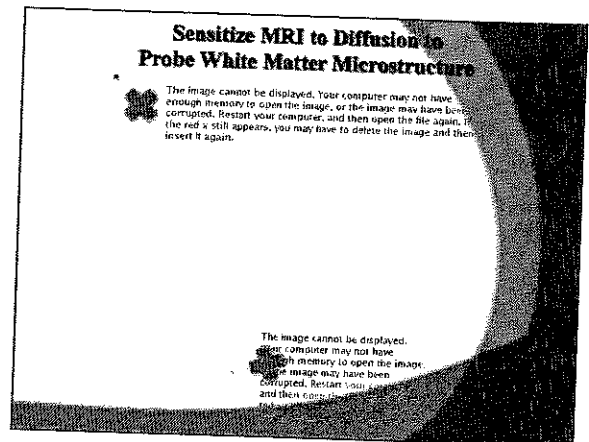
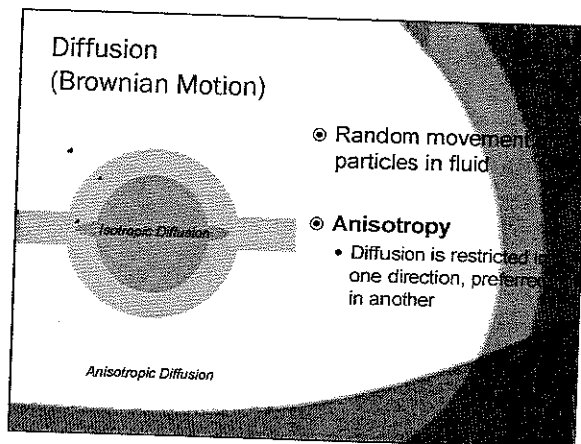
- Controls and SPDs respond less to second exposure of an emotionally unpleasant stimulus, while BPD patients responded more. This failure of normal habituation to emotional stimuli appears to be specific to BPD.
- Amygdala BOLD response potentiation related to severity of BPD symptoms, except dissociation (may be a protective symptoms as has been previously postulated).

## Clinical Implication

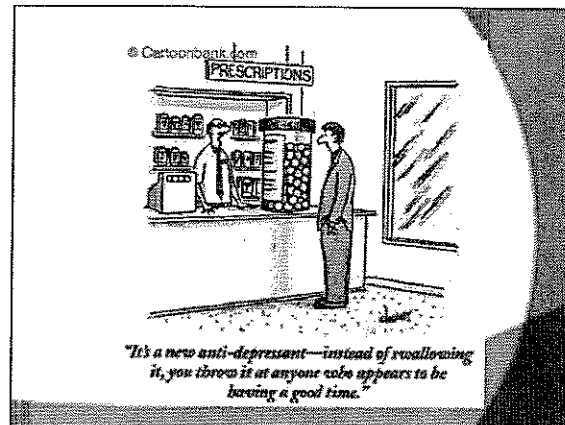
- This suggests that psychotherapies that focus on reviewing painful memories may worsen, not help BPD.
- Mentalization and DBT, which focus on skills in the present may employ better strategies.



## A preliminary Study of Adolescent BPD DEVELOPMENTAL MODEL



## TREATMENT OF AGGRESSION IN BORDERLINE PERSONALITY DISORDER

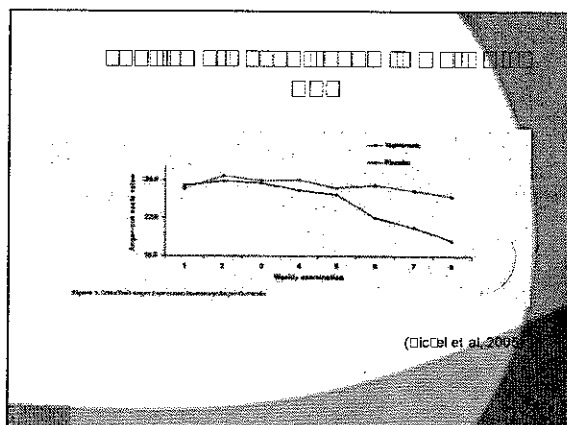


### Limitations of Pharmacotherapy in BPD

- There are simply no pharmacological treatments that put individuals with borderline personality disorder in remission
- This differs from treatments for many other psychiatric disorders in which some individuals are brought into remission.
- Reported quite high placebo response rate in BPD. Long duration and placebo controlled trials much more valuable than open label trials.

### Classes of Medications

- **Antidepressants** Clinical trials show drug placebo response for fluoxetine (Coccaro & Davoussi, 1993) and fluvoxamine (Dinne et al, 2002), especially in impulsivity and aggression. Less change for intrapsychic pain.
- **Mood Stabilizers** Superior to placebo in particular in reducing aggression; Divalproex (Hollander et al, 2005) Topiramate in female (Dicke et al, 2004; 2005; Loew et al, 2003; 2005) and male BPD (Dicke et al, 2003) and Lamotrigine (Tritt et al, 2005)



### Classes of Medications (cont)

#### Atypical Antipsychotics

- **Olanzapine** placebo in Clinical Global Impression as early as 4 weeks into treatment, but substantial weight gain seen (Bogenschut et al, 2004)
- **Olanzapine vs. Fluoxetine vs. combination** Both arms with olanzapine better in decreasing aggression and dysphoria than the fluoxetine arm
- **DBT with olanzapine vs. placebo** Olanzapine placebo in depression, anxiety, and impulsivity aggressive behavior (Soler et al, 2005; Linehan et al, 2003)

APA Treatment Guidelines      It isn't all about pharmacology

- **Psychosocial interventions** are an important part of the treatment of bipolar disorder.
- **Psychoeducation** is a key component of psychosocial intervention.
- **Family therapy** is a key component of psychosocial intervention.
- **Individual psychotherapy** is a key component of psychosocial intervention.
- **Group psychotherapy** is a key component of psychosocial intervention.
- **Self-help** is a key component of psychosocial intervention.
- **Relapse prevention** is a key component of psychosocial intervention.
- **Long-term management** is a key component of psychosocial intervention.

- ~~only TFP significantly predictive~~
- **Impact** younger years may impact future brain development
- adverse childhood effects common in BPD patients
- Prolonged exposure tends to hurt BPD patients more than help,
  - ↳ opposite true w/ PTSD