Insights into Borderline Personality Disorder

Neurobiological Research and Clinical Interventions

National Education Alliance for Borderline Personality Disorder
and
The Mount Sinai School of Medicine
and
NAMI-NYC Metro

Welcome

to
Goldwurm Auditorium

Saturday
October 21
and
Sunday
October 22, 2007

NEA BPD

6th Annual Family Perspectives Conference

CONFERENCE HANDBOOK

Insights into Borderline Personality Disorder Neurobiological Research and Clinical Interventions

Goldwurm Auditorium The Mount Sinai School of Medicine

PROGRAM

Saturday, October 20, 2007

8:00 am Registration and coffee

8:30-9:15 ***Welcome and Opening Remarks***
Recognition of Wayne S. Fenton: Presentation of the Herb Pardes, MD Award for Advancing the Research Agenda
Perry D. Hoffman, PhD
Herbert Pardes, MD
Ellen Stover, PhD

Moderator for the Day: Larry J. Siever, MD

9:15-10:15 ***Neuroimaging Studies of Emotion Processing in BPD***
Harold W. Koenigsberg, MD

10:15-10:30 Break

10:30-11:30 ***Trauma and Disassociation in Borderline Personality Disorder*** Christian Schmahl, MD

11:30-12:30 ***Serotonin-2A Receptor Binding in Borderline Personality Disorder*** Paul H. Soloff, MD

12:30-1:45 Lunch

1:45-2:45 ***Borderline Personality Disorder: Isn't It time for a New Name?*** *Antonia New, MD*

2:45-3:45 ***Neurobiology and Treatment of Aggression in Personality Disorder*** Emil F. Coccaro, MD

3:45-4:00 Break

4:00-5:00 ***Implications for Treatment***
Overview and Moderator, Larry J. Siever, MD
Panelists
Emil F. Coccaro, MD Harold W. Koenigsberg, MD
Antonio New, MD Christian Schmahl, MD Paul H. Soloff, MD

5:00 Closing Remarks and Adjourn

NEUROIMAGING STUDIES OF EMOTION PROCESSING IN BPD

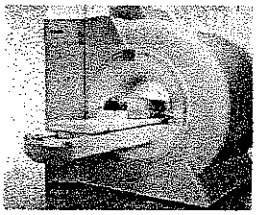
HAROLD W. KOENIGSBERG, MD

PROFESSOR OF PSYCHIATRY
MOUNT SINAI SCHOOL OF MEDICINE
JAMES J PETERS VA MEDICAL CENTER

Bio

Harold W. Koenigsberg, M.D., is Professor of Psychiatry at Mount Sinai School of Medicine. He has had a longstanding research and clinical interest in borderline personality disorder (BPD), is coauthor of two books on the treatment of borderline personality disorder, and has published widely on the neurobiology, phenomenology and treatment of the disorder. He is currently studying the emotional instability characteristic of borderline personality disorder. To better understand the neurobiology of emotional instability, he is using functional magnetic resonance imaging (fMRI) methods to identify brain networks activated as borderline patients process emotional stimuli. He is also studying the role of second messenger systems in emotional instability in BPD. A principal area of his interest is in the interaction between the neurobiologic and psychosocial components of the personality disorders. In addition, Dr. Koenigsberg is principal investigator of an NIMH funded neuroimaging study of cognitive processing in schizotypal personality disorders and in schizophrenia.

- **fMRI Scanner**



- **Affective Instability is a hallmark feature of Borderline Personality Disorder.**
  - It accounts for much of the *Sturm und Drang* and ongoing interpersonal turmoil in the borderline patient's life.
  - It is associated with many of the individual symptoms of BPD:

TABLE 3. Pearson Correlations of Borderline Personality Disorder Criteria with Affective Instability and Impulsive-Aggression.

BPD Criterion Item	Affective Instability Factor	*p* Value	Impulsive-Aggression Factor	*p* Value
Unstable Relationships	.126	.127	.308*	.000
Impulsiveness	.000	.997	.310*	.000
Affective Instability	.345*	.000	.305*	.000
Inappropriate Anger	.273*	.001	.307*	.000
Suicidal Threats, Gestures, Acts	.262*	.001	.005	.952
Identity Disturbance	.272*	.001	.074	.367
Chronic Emptiness, Boredom	.275*	.001	.080	.333
Avoiding Abandonment	.055	.505	.164	.046

*$p < .00625$.

Koenigsberg et al J Pers Disorders 2001

- **Affective Instability in BPD**
  - Mood shifts from baseline to: depression, anxiety, anger
  - Moods last hours, rarely days
  - Are responsive to interpersonal situations
    - Rejections
    - Abandonment
    - Losses
    - Envy
    - Abuse

➢ Affective Instability Measured with the Affective Lability Scale

TABLE 3. Affect Lability and Intensity Among Patients With Borderline Personality Disorder and Those With Other Personality Disorders

	Score			
	Patients With Borderline Personality Disorder (N=41)		Patients With Other Personality Disorders (N=104)	
Affect Measure	Mean	SD	Mean	SD
Affective instability dimension (from the Affective Lability Scale)[a]				
Labile depression	1.66	0.44	1.36	0.55
Labile elation	1.40	0.45	1.12	0.53
Labile anxiety	1.59[b]	0.63	1.13	0.66
Labile anger	1.65[b]	0.67	0.99	0.74
Depression/anxiety oscillation	1.97[b]	0.60	1.47	0.78
Depression/elation oscillation	1.39	0.55	1.06	0.58
Affect Intensity Measure[c]	3.65	0.50	3.41	0.57

Koenigsberg et al. Am J Psychiatry 2002

➢ Genetics of Affective Instability

- Twin studies point to the importance of genetic and environmental influences on BPD *(Skodal et al 2002)*
- There is a strong genetic component to Affective Instability.
- Affective Instability Runs in Families of BPD patients ***(Silverman et al 1991)***
- Twin studies show substantial heritability

Table 1. Heritability of Borderline Traits

Borderline trait	Heritability co-efficient
Anxiousness	44
Affective lability	45
Cognitive dysregulation	49
Identity problems	53
Insecure attachment	48
Submissiveness	45

(Skodal et al 2002)

- **Differences in Brain Activity in BPD?**

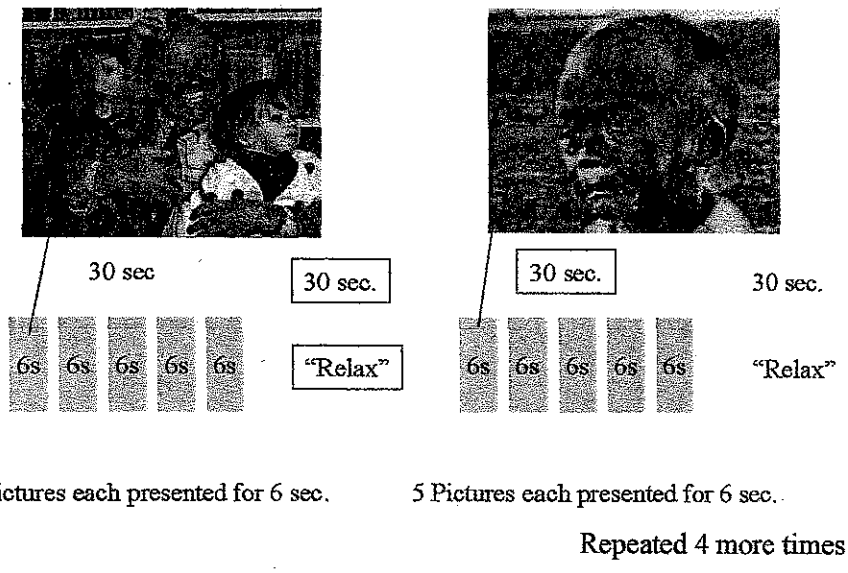
  Do borderline patients who are affectively unstable show a different pattern of brain activation than healthy volunteers when performing an emotion processing task ?

- **Borderline patients and normal controls are shown emotion-inducing pictures while in the fMRI scanner**
  - They are instructed to look at the pictures and allow themselves to feel whatever emotion is generated by the picture (passive viewing paradigm)
  - The pictures are selected from the International Affective Pictures System ***(Lang et al.)***

- **Sample Characteristics**

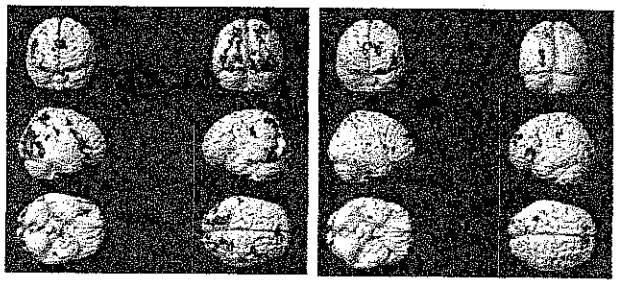
	BPD Subjects	Healthy Controls
N	19	17
Age	34.9 ± 11.1	31.2 ± 10.6
Male/Female	12/7	9/8

- **Stimulus Presentation Design**



- **Differences in Brain Activation Between Borderline Patients and Healthy Volunteers When Viewing Negative vs Positive Emotional Pictures**

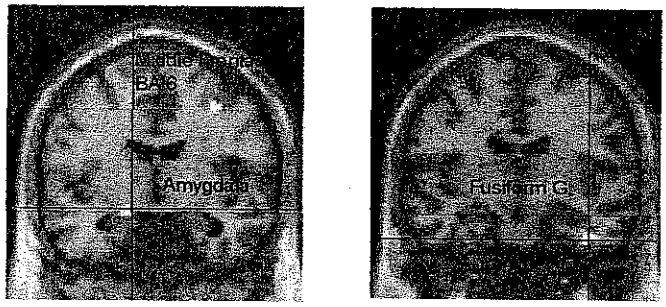
Borderline Patients *Healthy Volunteers*



Koenigsberg et al

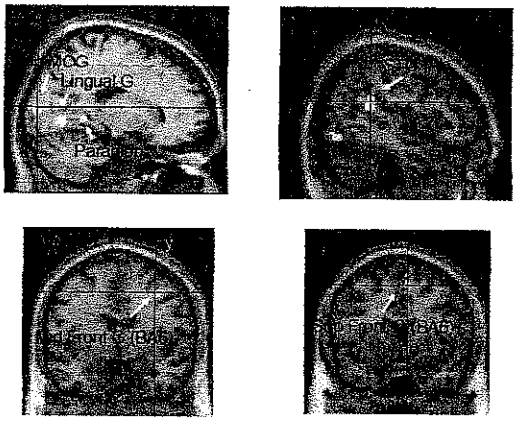
- **Negative Scenes vs. Rest**

- **Clusters of Significantly Different Activation to <u>Negative</u> Scenes vs. Rest BPD > HC**



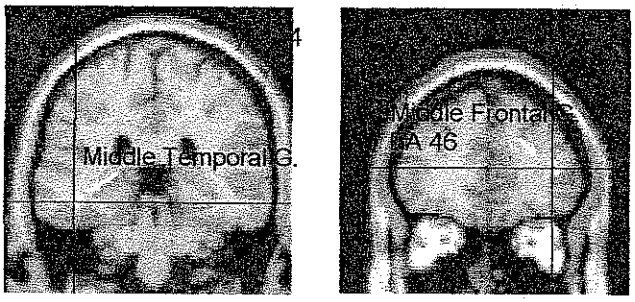
p < .01, k=20
(Koenigsberg et al, submitted)

- **Clusters of Significantly Different Activation to <u>Negative</u> Scenes vs. Rest BPD > HC**



(Koenigsberg et al, submitted)

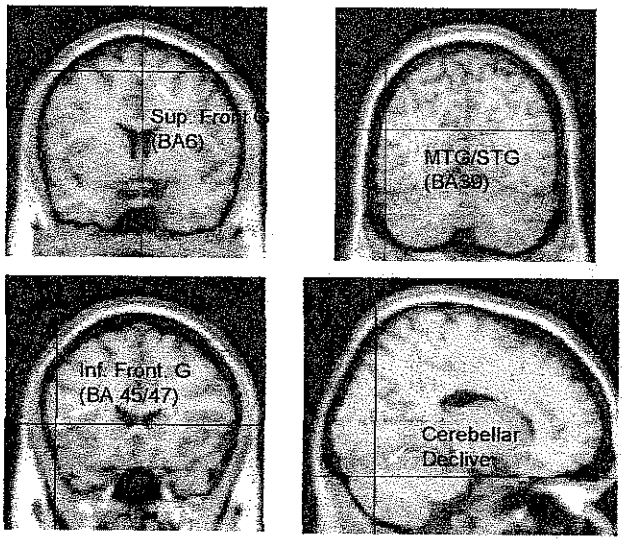
- **Clusters of Significantly Different Activation to <u>Negative</u> Scenes vs. Rest HC> BPD**



(Koenigsberg et al, submitted)

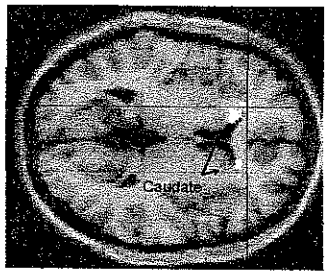
- **Positive Scenes vs. Rest**

- **Clusters of Significantly Different Activation to <u>Positive</u> Scenes vs. Rest BPD > HC**



p< .005, k=20
(Koenigsberg et al, submitted)

- **Clusters of Significantly Different Activation to <u>Positive</u> Scenes vs. Rest HC > BPD**



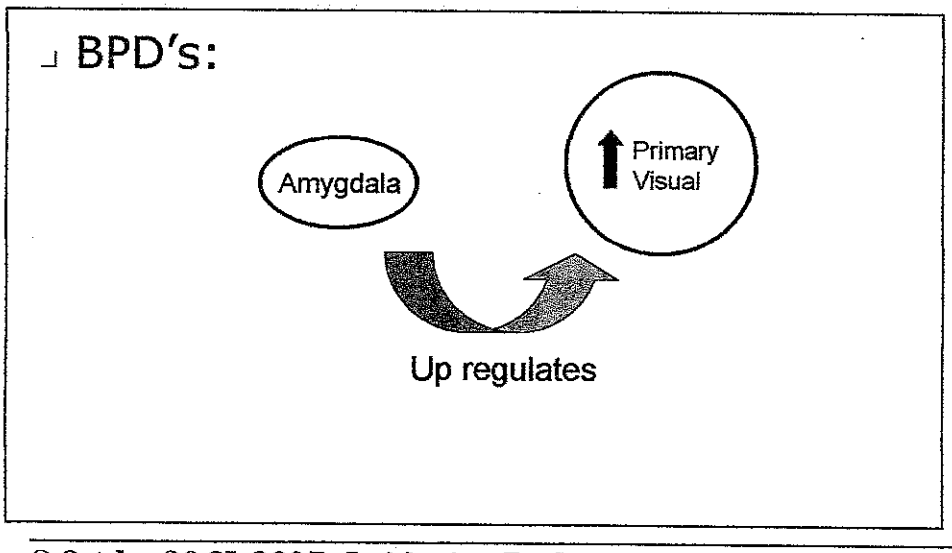
p< .005, k=20
(Koenigsberg et al, submitted)

- **Regions of greater brain activation in borderline patients**
  - When viewing negative pictures (compared to rest) BPD patients show more activation than healthy controls in:
    - Primary visual areas
    - Amygdala and Fusiform Gyrus
    - Superior temporal gyrus (STG)
    - Premotor cortex (BA6, MFG & SFG)

- **Regions of greater brain activation in healthy volunteers**
  - Healthy volunteers respond to negative pictures with greater activation than BPD's in:
    - the insula
    - middle temporal gyrus
    - middle frontal gyrus (BA46).

- **Responses to positive pictures**
  - BPD patients respond to positive pictures with greater activiation than HC's in the premotor cortex (SFG-BA6), superior temporal gyrus, inferior frontal gyrus and cerebellar declive.
  - Healthy volunteers respond to positive pictures with greater activation than BPD's in the caudate bilaterally.

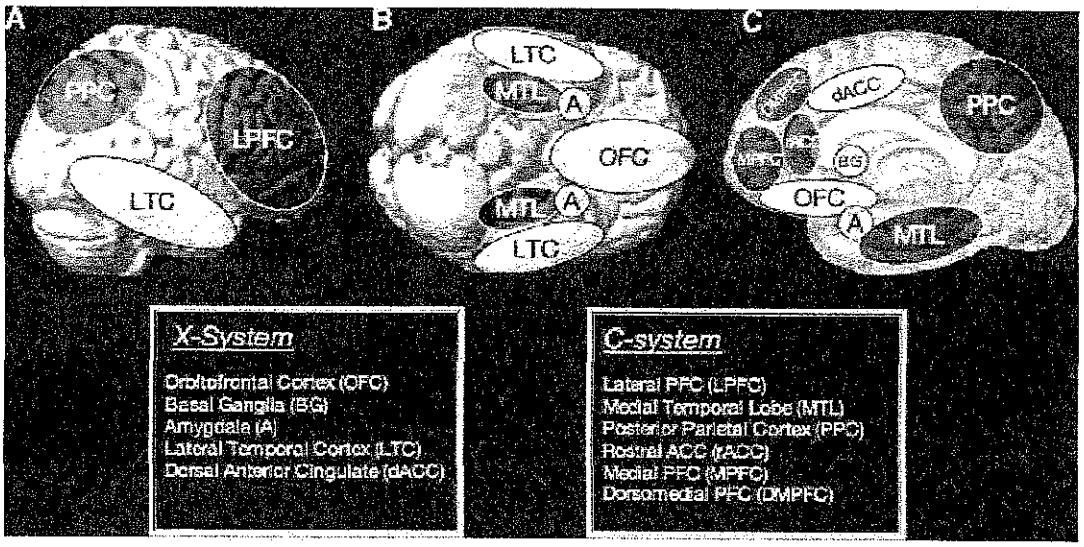
- **Amygdala and Primary Visual Cortex**



➢ Reflexive and Reflective Neural Systems Underlying Social Perception -- Satpute & Lieberman (2006)

Table 1 – Features associated with X- and C-systems

X-system	C-system
Parallel processing	Serial processing
Fast operating	Slow operating
Slow learning	Fast learning
Non-reflective consciousness	Reflective consciousness
Phylogenetically older	Phylogenetically newer
Representation of symmetric relations	Representation of asymmetric relations
Representation of common cases	Representation of special cases
	Representation of abstract concepts (e.g., negation, time)



➢ Superior Temporal Gyrus

- The Superior Temporal Gyrus (STG) is activated in BPD's more than HC's when reacting to negative and positive pictures.
- The STG has been implicated in "reflexive" (automatic and fast) perception of social scenes, identification of actions and attribution of mental goals to individuals' behaviors (Allison et al 2000, Satpute & Lieberman 2006).
- Thus, BPD patients may tend to react more reflexively to social cues than healthy controls.

- **MTG and Prefrontal Systems**

  - Healthy volunteers respond to negative pictures with greater activation than BPD's in the middle temporal gyrus (MTG) and lateral frontal gyrus (BA46).

  - These regions have been implicated as part of the "reflective" system for social cognition ***(Satpute & Lieberman 2006).***
    - The MTG plays a role in the retrieval of episodic memories than may be used to assess social cues and plan responses.
    - The lateral prefrontal cortex is involved in causal reasoning and emotional control.

- **Caudate**

  - The caudate, which is activated in HC's more than in BPD's when viewing positive social images, has been implicated in pleasurable social-emotional experiences such as romantic love ***(Fisher et al 2006).***

- **Emotional Control Mechanisms in BPD:**

  Conscious Cognitive Reappraisal Experiment

- **Aim of the reappraisal experiment:**

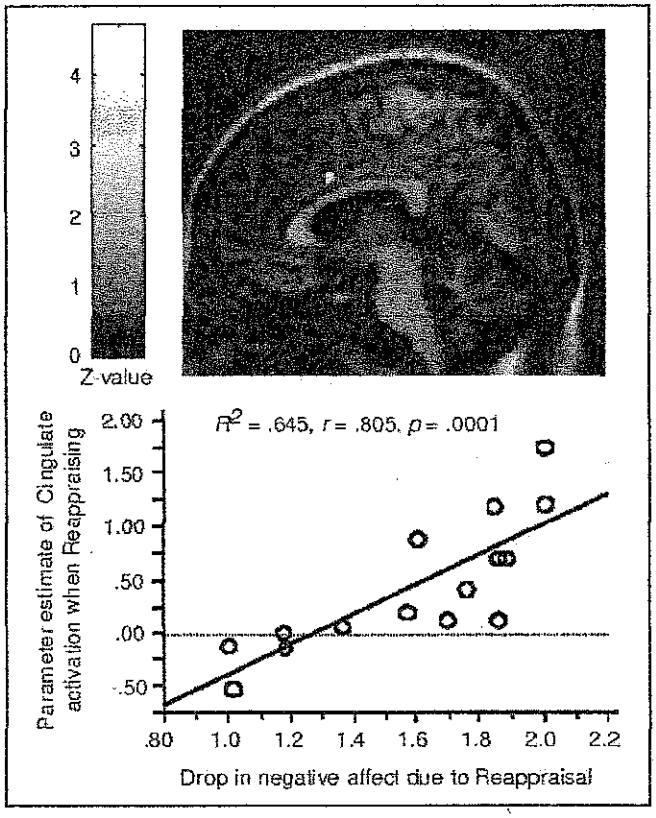
  - Compare brain regions brought into play during conscious efforts to suppress negative emotional experience in BPD vs healthy subjects

- **The Cognitive Reappraisal Task:**

  - Following Ochsner et al (2004), subjects are trained to look at pictures evocative of negative emotions and to decrease their negative reactions by psychically distancing themselves from the scene.

  - "Assume the role of a clinical detached observer or see the scene as though you are an anthropologist."

- **Region in Anterior Cingulate Where the Activity Correlates with a Reduction in Negative Affect During Conscious Reappraisal**



from Ochsner et al 2002

- **IPS and TPJ**

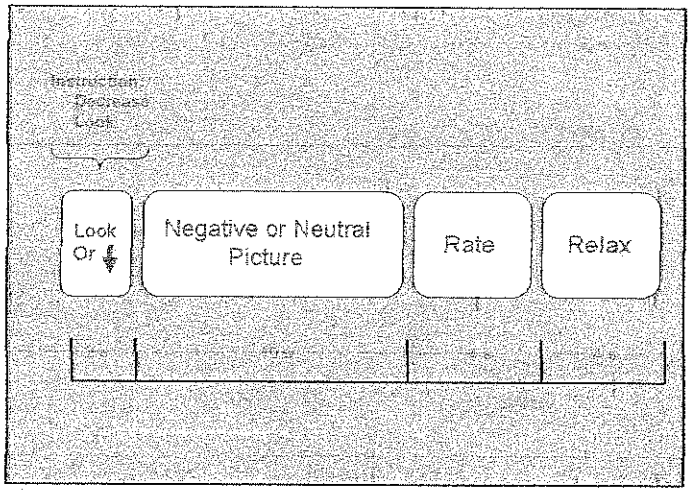
  - BPD's do not activate the Intraparietal Sulci (IPS) and Temporoparietal Junction (TPJ) as much as HC's when attempting to suppress

  - The IPS and TPJ are involved selective attention to the visual field [IPS = top-down; TPJ = bottom-up] (Hahn, Ross, Stein, Neuroimage 2006)

- Possible Implication:

  - May account for HC's better ability to cognitively "detach" from negative emotion. Perhaps these systems play a role in such defenses as isolation.

➢ Design of the Reappraisal Experiment



➢ Sample Characteristics Reappraisal Experiment

	BPD Subjects	Healthy Controls
N	~~8~~ 18	~~8~~ 16
Age	32.6 ± 10.4 ~~26.7±7.0~~	31.9 ± 7.7 ~~28.0±7.8~~
Male/Female	14/7 4/4	8/8 4/4

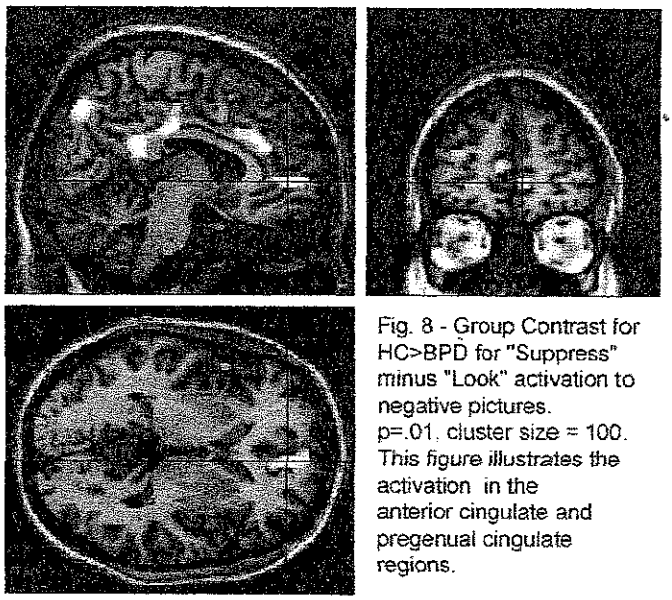
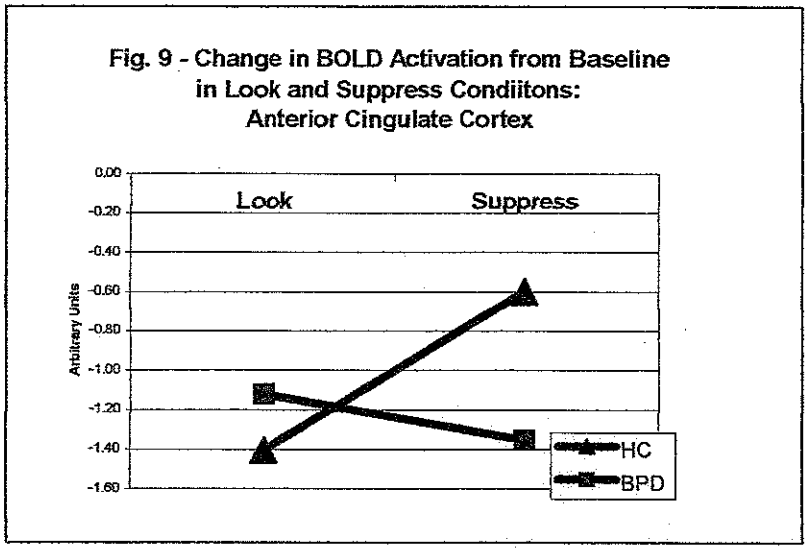


Fig. 8 - Group Contrast for HC>BPD for "Suppress" minus "Look" activation to negative pictures. p=.01, cluster size = 100. This figure illustrates the activation in the anterior cingulate and pregenual cingulate regions.

Brain Regions Where BPD Patients Activate *Less* than Healthy Controls When Attempting to Suppress Negative Emotion

- Anterior Cingulate
- Pregenual Anterior Cingulate
- Intraparietal Sulci
- Temporoparietal Junction (trend)

➢



➢ **Brain Regions Where BPD Patients Activate *More* than Healthy Controls When Attempting to Suppress Negative Emotion**

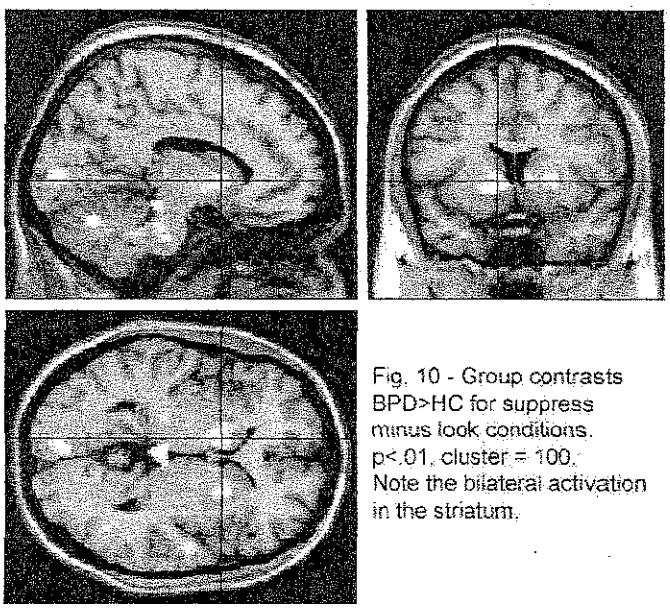


Fig. 10 - Group contrasts BPD>HC for suppress minus look conditions. p<.01, cluster = 100. Note the bilateral activation in the striatum.

■ **Striatum**

➢ **IPS and TPJ**

- BPD's do not activate the Intraparietal Sulci (IPS) and Temporoparietal Junction (TPJ) as much as HC's when attempting to suppress
- The IPS and TPJ are involved selective attention to the visual field [IPS = top-down; TPJ = bottom-up] ***(Hahn, Ross, Stein, Neuroimage 2006)***

➢ **Possible Implication:**

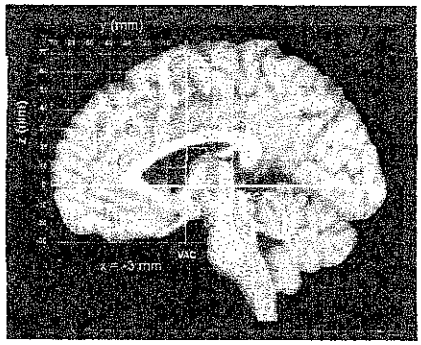
- May account for HC's better ability to cognitively "detach" from negative emotion. Perhaps these systems play a role in such defenses as isolation.

- **Cingulate Cortex**

  - BPD's do not activate the pregenual anterior cingulate and anterior rostral cingulate as strongly as HC's when attempting to suppress

- **Possible Implications:**
  - BPD's lack the ability to recruit brain regions typically employed by healthy subjects in the cognitive control of emotion
  - Failure to mobilize the anterior rostral cingulate may reflect impaired conflict monitoring/resolution in BPD

- **BPD Patients Underactivate the Anterior Cingulate Cortex when Trying to Suppress**



  - Possible Implications:
    - BPD's lack the ability to recruit brain regions typically employed by healthy subjects in the cognitive control of emotion
    - Failure to mobilize the anterior rostral cingulate may reflect impaired conflict processing in BPD

- **Splitting and Borderline Personality**

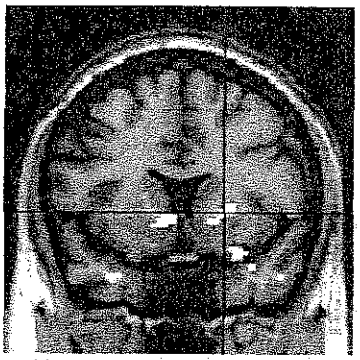
  - Splitting is a pattern of seeing the world in black or white terms
  - People are "all good" or "all bad"
  - i.e. it is hard to integrate conflicting qualities together

- **Conflict Monitoring/Resolution and Splitting**

  - Tasks which involve integrating conflicting information all show activation in the anterior rostral cingulate zone
  - Conflict Monitoring – The ACC responds to conflict and recruits additional cognitive resources to reduce conflict in subsequent performance (Botvinick, Cohen.Carter, 2004)
  - In BPD's
    - ↓ ACC activation → impaired conflict monitoring/resolution → splitting ?

➢ BPD Patients Activate Striatum More than Controls when Trying to Suppress

- Possible Implications:
  - Basal ganglia are activated in the initiation of movement
  - Could ready activation of the striatum be related to BPD's readiness for "acting-



N = 18 BPD; N = 16 HC

➢ Summary – Neurobiology of Emotion Processing

- When processing negative emotions borderline patients do not employ the same brain networks that healthy controls do
- When attempting to reduce their negative reactions to emotional scenes borderline patients call into play different brain networks than healthy controls do

---

Collaborators

Larry J. Siever, M.D.
Jin Fan, Ph.D.
Isak Prohovnik, Ph.D.
Hedok Lee, Ph.D.
Kevin Ochsner, Ph.D.
Scott Pizzarello
Kevin Guise
Xaiodong Guo, Ph.D.
Cheuk Tang, Ph.D.
Lucia Tecuta
Christine Dorantes
Antonia New, M.D.
Marianne Goodman, M.D
Hu Cheng, Ph.D.

TRAUMA AND DISSOCIATION IN BORDERLINE PERSONALITY DISORDER

CHRISTIAN SCHMAHL, MD

DEPT. OF PSYCHOSOMATIC MEDICINE AND PSYCHOTHERAPY
CENTRAL INSTITUTE OF MENTAL HEALTH
MANNHEIM, GERMANY

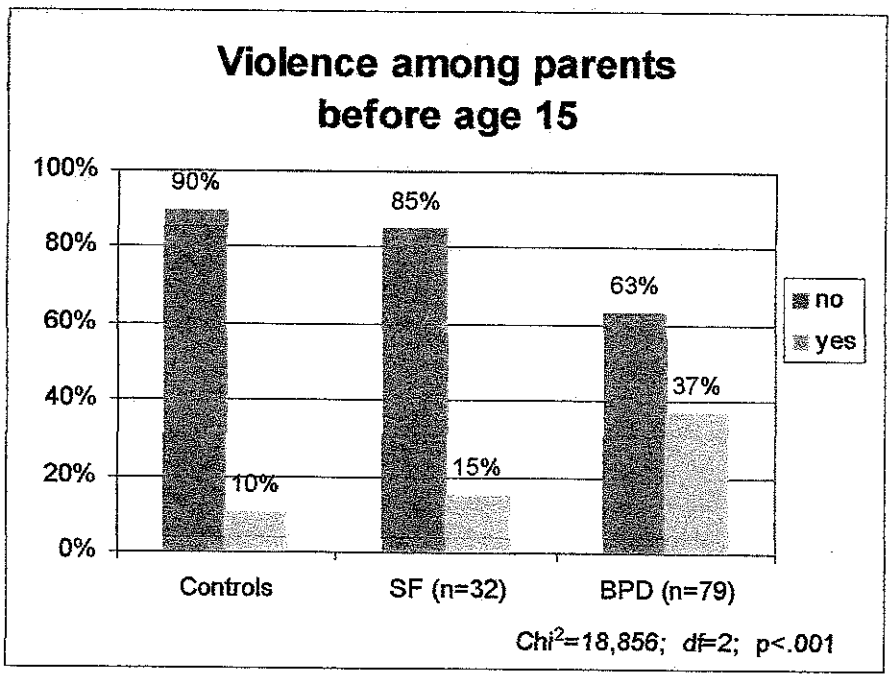
Bio

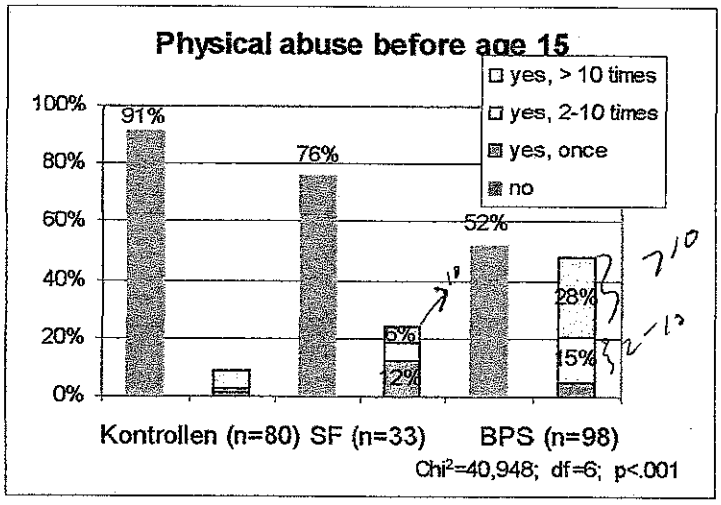
Christian Schmahl received his M.D. at Giessen Medical School and did his residency in Psychiatry at Freiburg Medical School where he was also trained in dialectical behavior therapy by Martin Bohus, M.D.. He spent a one-year research fellowship at Yale and Emory University mentored by J. D. Bremner, M.D. with a training in neuroimaging. Since 2003 he is Assistant Medical Director and Research Coordinator at the Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Mannheim. In 2003 he received a Young Investigator Award of the Borderline Personality Disorder Research Foundation, in 2004 he received the Young Investigator`s Award of the National Education Alliance for Borderline Personality Disorder, and in 2005 the First Price for Pain Research of the German Society for the Study of Pain. He has published 39 articles and 11 book chapters

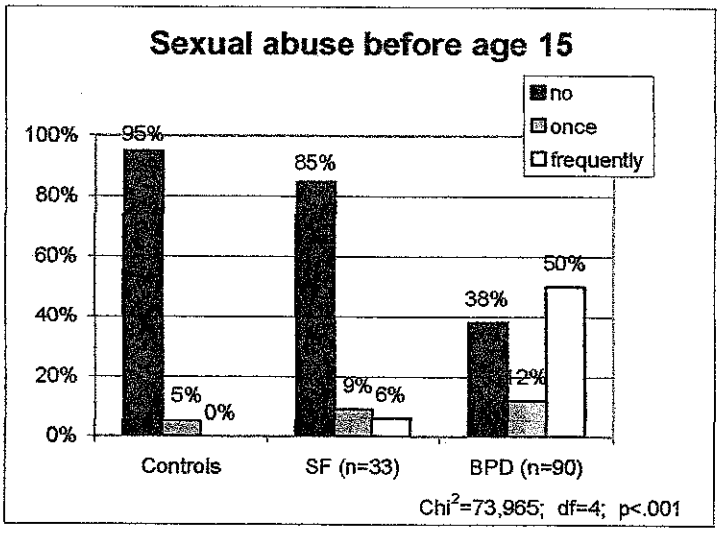
Abstract

Dissociative symptoms are frequently observed in patients with borderline personality disorder and are thought to be related to high levels of stress, particularly traumatic stress, in this population. Traumatic Stress can have an important influence on brain structure and brain function; neural correlates of dissociation are largely unknown. We developed a questionnaire for the assessment of dissociative states and measured dissociative symptoms as well as stress levels. In several studies, we investigated structural alterations following traumatic stress as well as functional correlates of traumatic remembrance in BPD. To investigate neural correlates of dissociative responses, we used script-driven imagery of individual stressful life situations during fMRI. We found a strong association between stress and dissociative symptoms in patients with BPD. Hippocampal as well as amygdala volume reduction were consistently shown in BPD. During traumatic remembrance, dysfunctional prefrontal metabolism was found, and during induced dissociation amygdala deactivation was the most prominent finding.

- **Overview**
  - BPD and traumatic stress
  - Traumatic stress and brain morphology
  - Neural processing of (traumatic) stress
  - Stress and dissociation
- **Etiology of BPD**
  - Genetic Influence
    (Torgersen et al. 2000)
    - appr. 60% of variance explained
  - Traumatic Stress (Zanarini 2000)
    - Sexual violence (appr. 35-70%)
    - Physical violence (appr. 50%)
    - Neglect (appr. 80%)
-





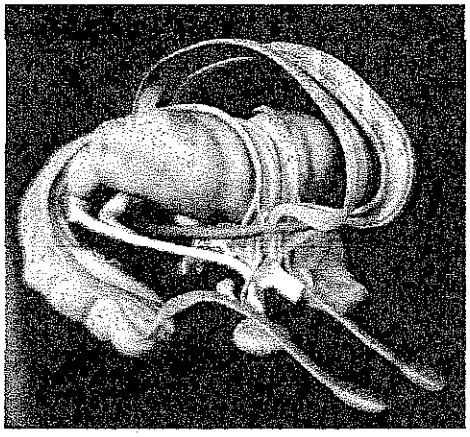


- **Differences between patients with and without PTSD**

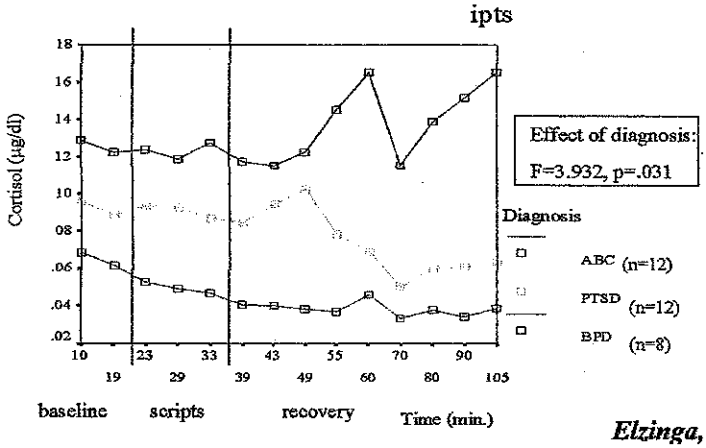
	BPD+PTSD n=65	BPD n=74	PTSD n=26
Sexual Abuse	35%	5%	24%
Physical Abuse	50%	28%	15%
Verbal Abuse	73%	40%	73%
Emotional Abuse	81%	45%	65%
Neglect	90%	82%	80%

Zlotnick et al., JNMD, 2003

➢ Traumatic stress and brain morphology



➢ Cortisol reactivity to traumatic remembrance



Elzinga, Schmahl and Bremner, submitted

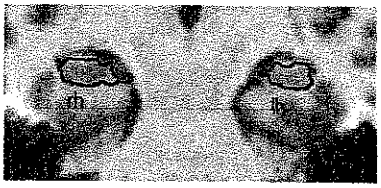
➢ Hippocampal volume reduction in PTSD and BPD

Disorder	Number of Studies	General Findings
Schizophrenia	76	↓/↔ hippocampi bilaterally
Alzheimer's disease	56	↓ hippocampi bilaterally; marker for temporal lobe degeneration
Normal controls	44	Hippocampal volume is dependent on gender, handedness, and age
Major depression	20	↔/recently ↓ hippocampi bilaterally have been demonstrated
PTSD	14	↓/↔ smaller hippocampi bilaterally
Alcoholism	9	↓/↔ hippocampi bilaterally
Bipolar disorder	7	↓/↑ hippocampal volume
BPD	3	↓ hippocampi bilaterally

Geuze et al., Mol Psychiatry 2005

- **Hippocampal and amygdala volumes in BPD**

Hippocampus *Amygdala*



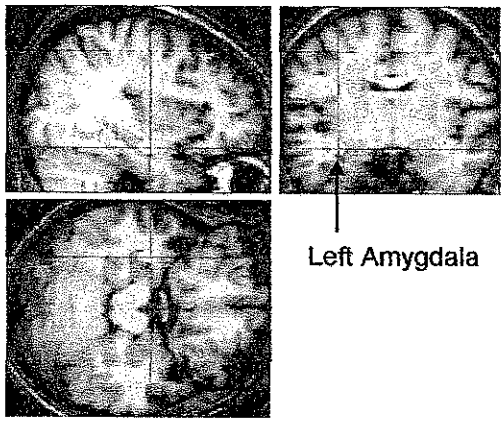
Hippocampus -13,1 % ($p<0.05$)
Amygdala -21,3 % ($p<0.05$

Schmahl et al., Psychiatry Res: Neuroimaging 2003

- **Hippocampus and amygdala are smaller in BPD**

	Hipp. Volumen	Amygdala Volumen
Driessen et al. 2000	- 15,8 % (p < .001)	- 7.6% (p = .04)
Tebartz van Elst et al. 2003	- 20,5 % (p = .03)	- 24 % (p = .004)
Brambilla et al. 2004	18,9% (p < .01)	- 15,5% (ns)
Irle et al. 2005	- 17,0 % (p < .001)	n.u.

- **Voxel-based morphometry**



Rüsch et al., Neuroimage 2003

➢ Volume reduction in prefrontal regions

- 26 % reduction of the right anterior cingulate cortex
- 24 % reduction of the left orbitofrontal cortex

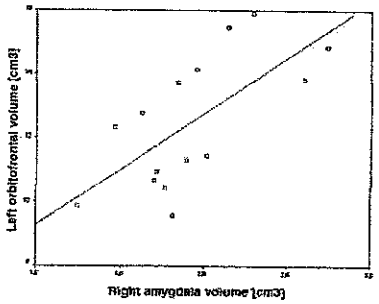
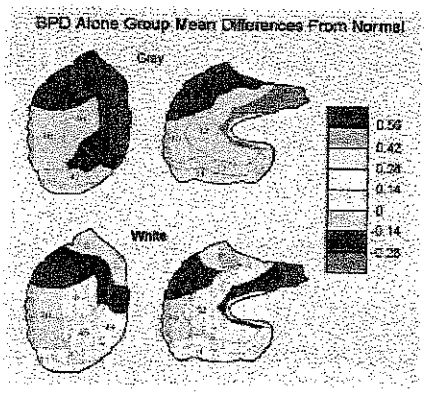


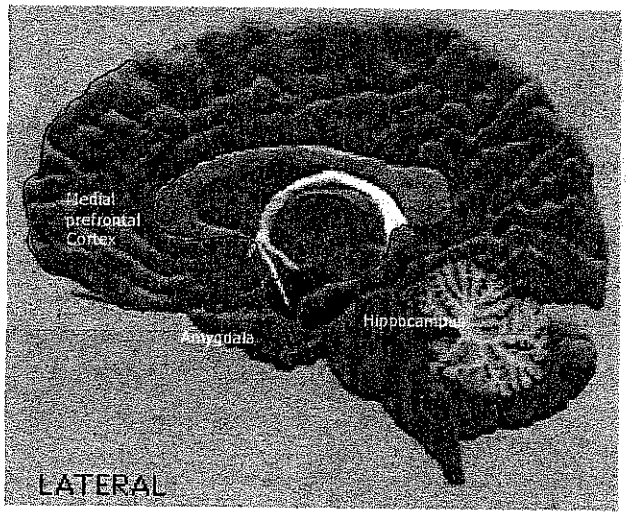
Figure 3. Positive correlation between left orbitofrontal and right amygdala volumes.

Tebartz van Elst et al., Biol Psychiatry 2003

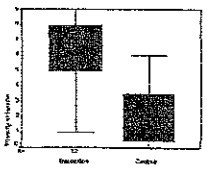


Hazlett et al., Biol Psychiatry 2005

➢



➢ Emotional stress



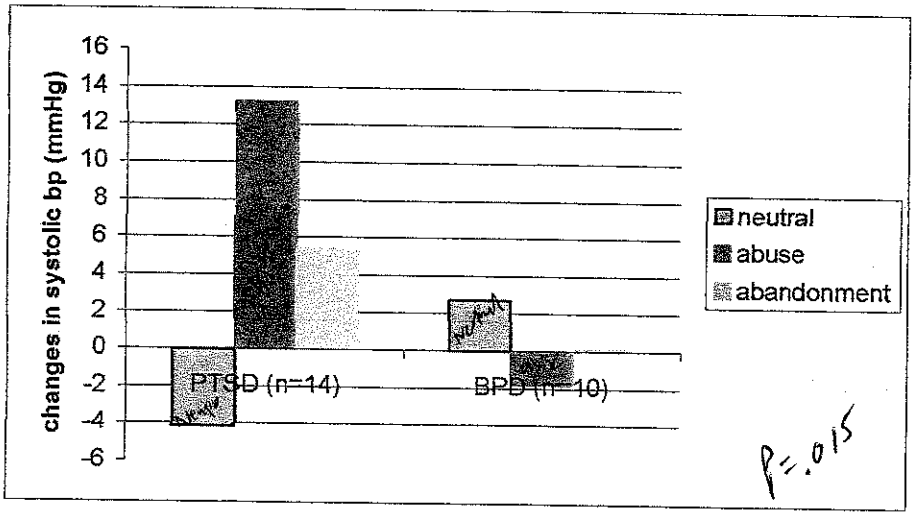
Stiglmayr et al., 2001

Herpertz et al., Biol Psychiatry 2001

- **Neural processing of traumatic stress in BPD**
  - High rates of traumatic childhood events, incl. sexual and physical abuse (Zanarini et al. 2000)
  - But: Emotional abuse and neglect can be equally detrimental to outcome as compared to sexual and physical abuse (Bremner et al. 2000, Zlotnick et al. 2003)
  - Fears of abandonment are an integral part of the BPD symptomatology

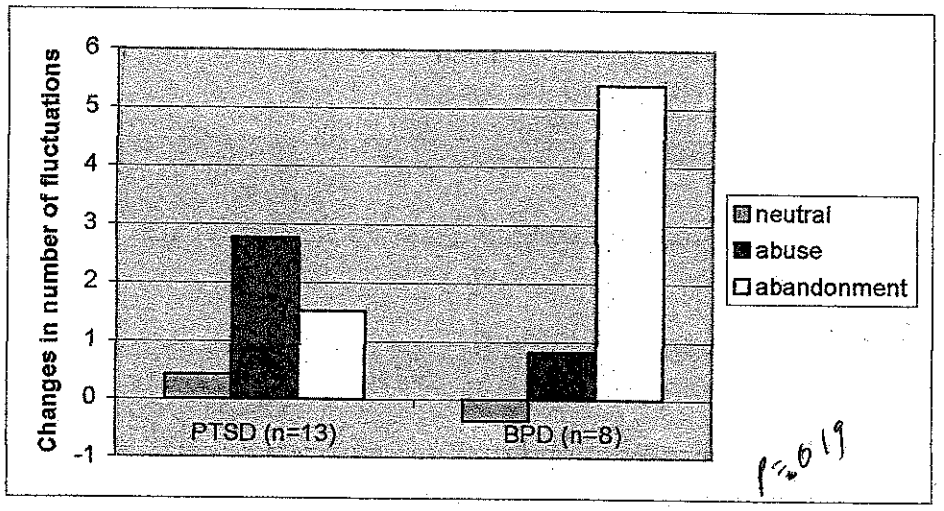
- **Physiological and neural correlates of abuse and abandonment remembrance**
  - Patients with BPD, PTSD, and controls
  - All had sexual and/or physical abuse before age 18
  - Script-driven imagery method:
    - Personalized script of a severe childhood sexual or physical abuse event (traumatic script),
    - Personalized script of an abandonment situation
    - Standardized neutral script
  - Readout:
    - Psychophysiology (skin conductance, blood pressure)
    - Oxygen-PET

- **Effects of abuse and abandonment remembrance on blood pressure**



Schmahl et al., Psychiatry Res 2004

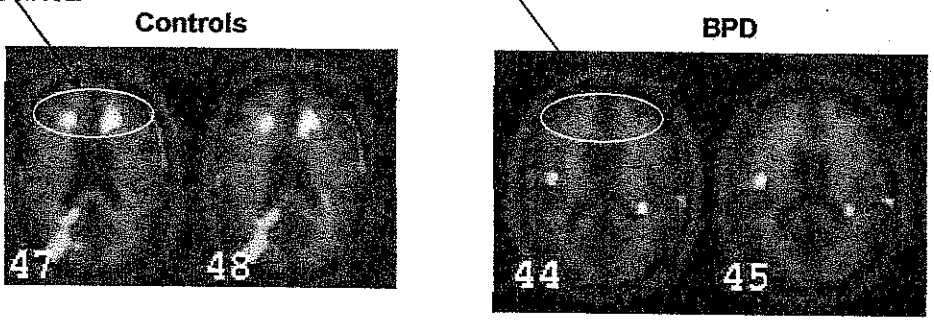
- **Effects of abuse and abandonment remembrance on skin conductance**



Schmahl et al., Psychiatry Res 2004

- **Frontal activation during abuse remembrance**

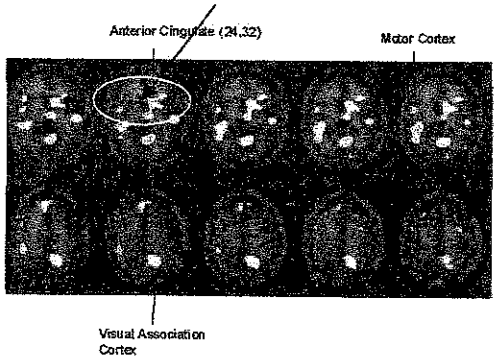
Medial Prefrontal Cortex



Schmahl et al., Biol Psychiatry 2004

- **Abandonment remembrance**

Deactivation



➢ Traumatic remembrance in BPD without PTSD

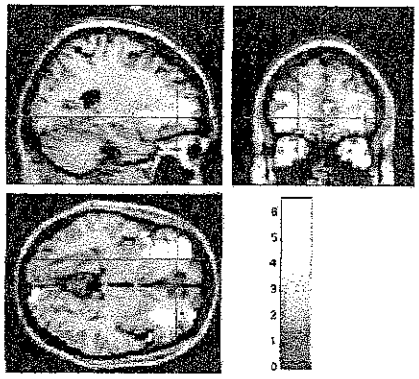


Figure 1. Brain regions showing increased activity associated with the recall of traumatic autobiographical episodes compared with negative but nontraumatic episodes in $n = 6$ female patients with BPD but without PTSD (thresholded for display at $T = 3.0$). Right-sided: the sides of the hemispheres are as given; bottom: the right hemisphere is at the bottom; colored columns: numbers are T-values. BPD, borderline personality disorder; PTSD, posttraumatic stress disorder.

Driessen et al., Biol Psychiatry 2004

➢ Traumatic remembrance in BPD with comorbid PTSD

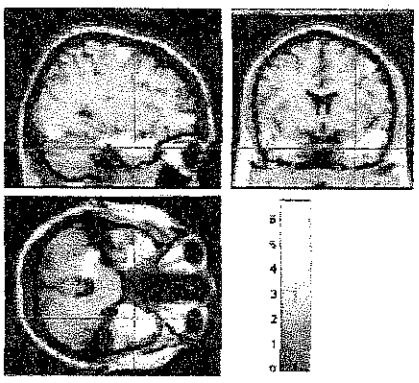
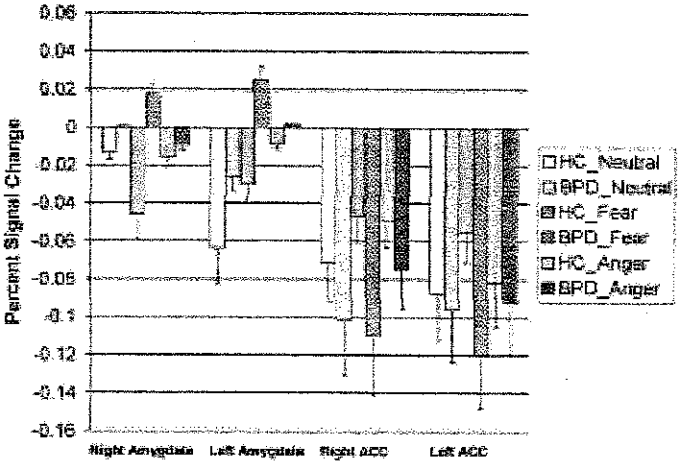
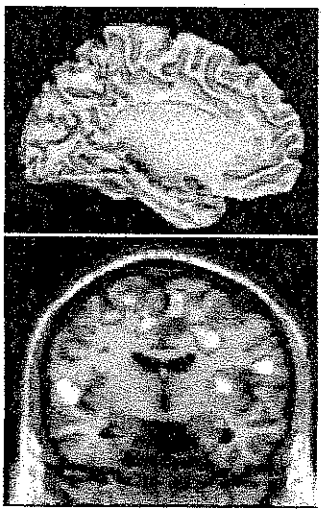


Figure 2. Brain regions showing increased activity associated with the recall of traumatic autobiographical episodes compared with negative but nontraumatic episodes in $n = 6$ female patients with BPD and with additional PTSD (thresholded for display at $T = 3.0$). Right-sided: the sides of the hemispheres are as given; bottom: the right hemisphere is at the bottom; colored columns: numbers are T-values. BPD, borderline personality disorder; PTSD, posttraumatic stress disorder.

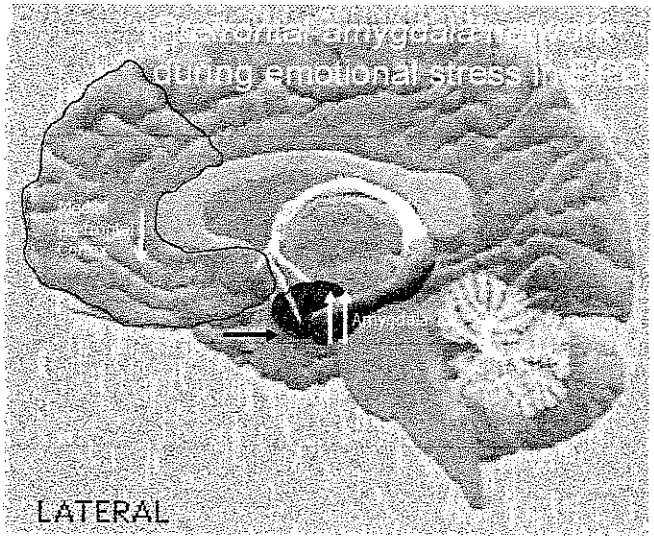
Driessen et al., Biol Psychiatry 2004

➢ Increased amygdala and decreased ACC activity

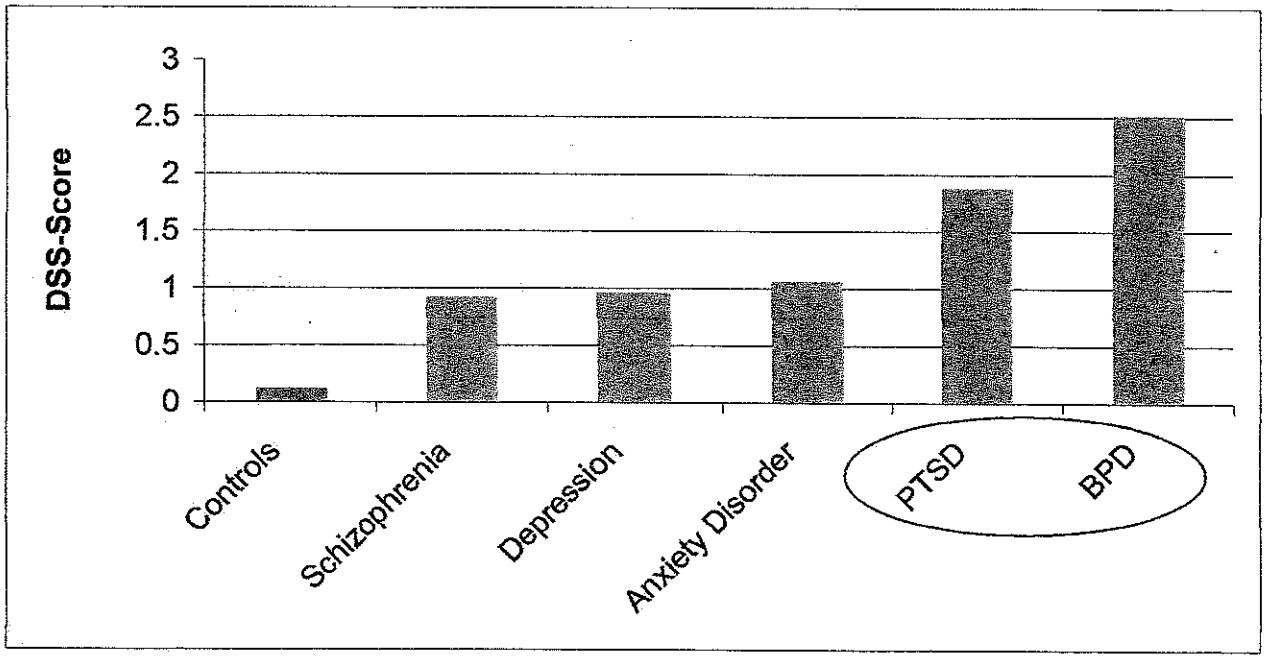




Minzenberg et al., Psychiatry Res: Neuroimaging 2007

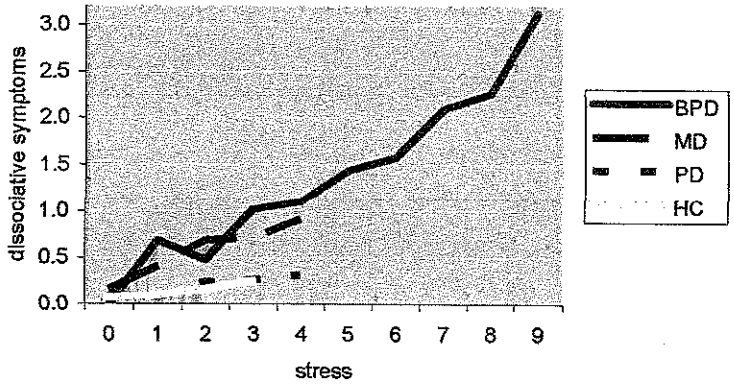


- **Stress and Dissociation**
  - Dissociative symptoms comprise depersonalisation, derealisation, and reduced sensory processes
  - In patients in BPD, these symptoms are frequent and related to emotional stress
- **Dissociation in Psychiatric Disorders**

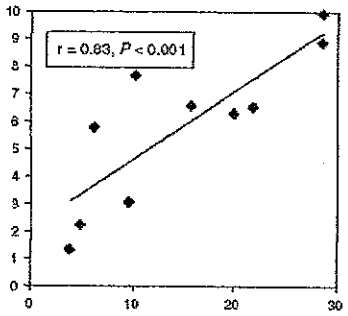


Stiglmayr et al., Psychoth Psych Med Psychol 2003

➢ Stress, Dissociation and Analgesia



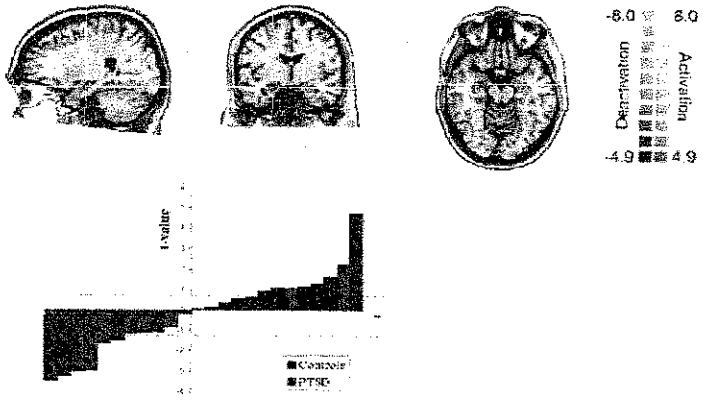
Ebner-Priemer et al., under review



Ludäscher et al., Psychiatry Res 2006

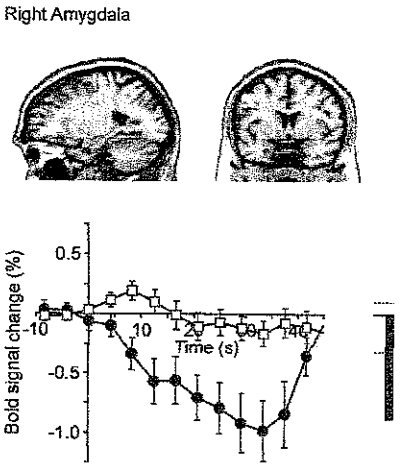
➢ Analgesia in stress-related disorders and deactivation of the amygdala

PTSD



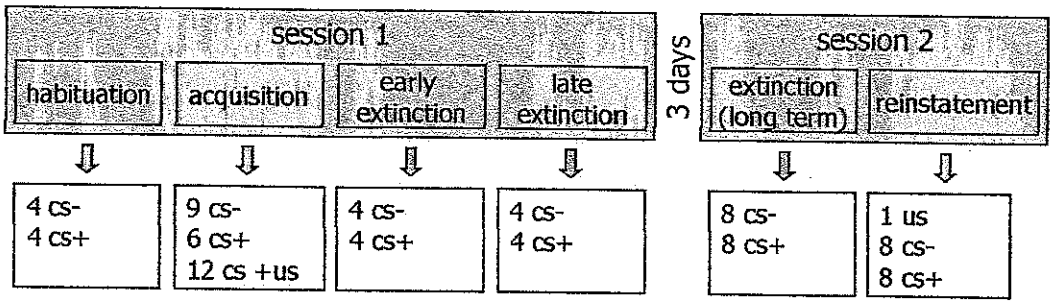
Geuze et al., Arch Gen Psychiatry, 2007

BPD



Schmahl et al., Arch Gen Psychiatry, 2006

➢ Disturbed learning processes in dissociative BPD patients

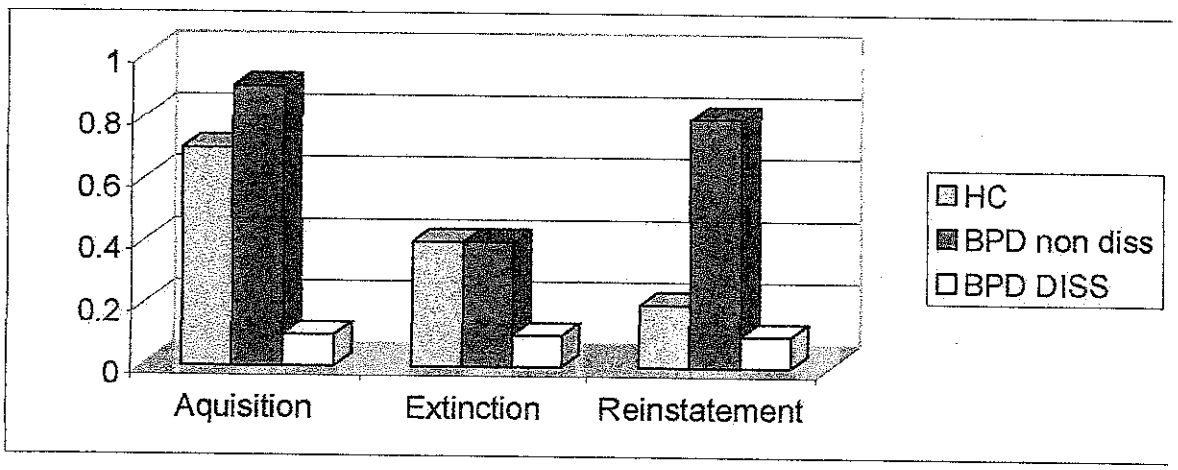


Standard aversive conditioning paradigm
CS+/ CS-: neutral graphic pattern
US: aversive baby cry (95 dB/ 3,5 s.)
delay conditioning: CS 600ms, US 3,5s after 500ms
dependent variables: SCR, valence, arousal
confounding variable: dissociation (cut-off >2.0)

Participants n= 65
BPD: 32
HC: 33

Exclusion: medication, MD

➢ Disturbed learning processes in dissociative BPD patients



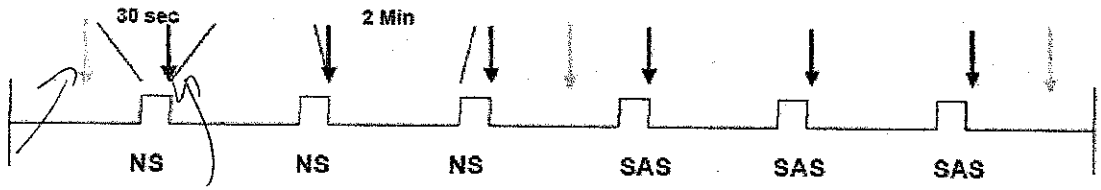
➢ Measurement of acute dissociation (DSS-4)

- Short version of the DSS for the use in fMRI/laboratory experiments
- Four items:
  - ➢ Depersonalization
  - ➢ Derealization
  - ➢ Somatoform dissociation
  - ➢ Analgesia
- High correlation between DSS-4 and DSS (r = .952; Ebner-Priemer, unpublished)

- **fMRI - pilot study**
  - Ten patients with Borderline Personality Disorder acc. to DSM-IV
  - All free of psychotropic medication
  - Preparation of two individualized scripts
    - Emotionally neutral situation
    - Stress-associated, dissociation-inducing situation

NS - Neutral Script
SAS - Stress emotional Scripts

- **Dissociation: Script-driven imagery**



Pain sensitivity

DVI

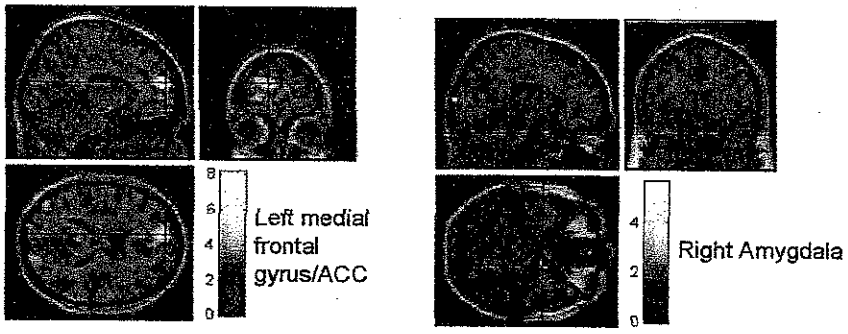
↓ Pain sensitivity

↓ Dissociation

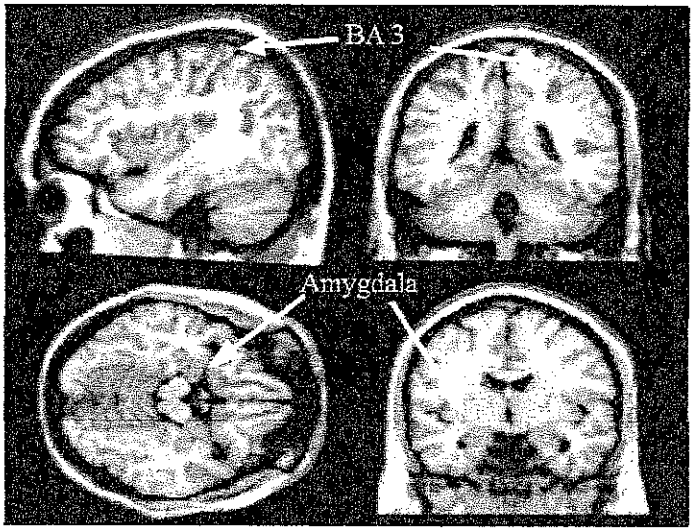
NS: Neutral script
SAS: Stress-associated script

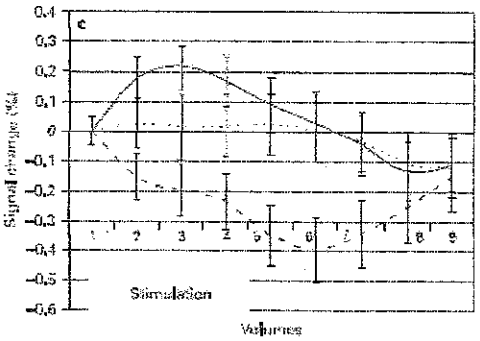
	Neutral script	Stress-associated script	t-test (2-sided): p-value
Dissociation (**n=10**) (1=low, 9=high)	1.54 ± 0.70	3.15 ± 1.51	0.007
Pain sensitivity (**n=7**) (1=low, 9=high)	6.14 ± 1.68	3.86 ± 2.54	0.007

- **Fronto-limbic activation patterns during induced dissociation**

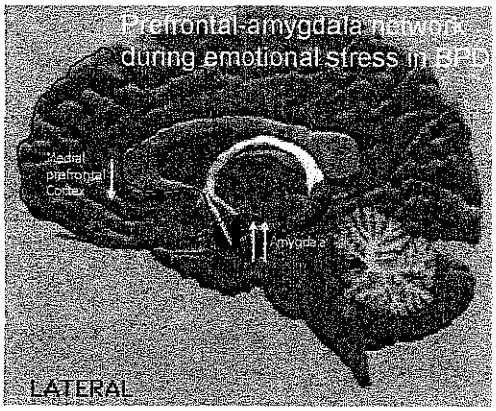


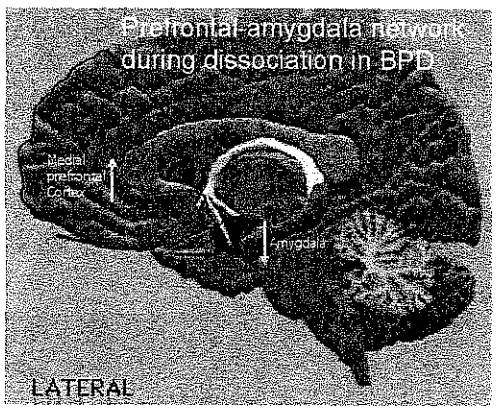
- **Similar findings during hypnotically induced depersonalization**





Roeder et al., Psychother Psychosomatics 2007

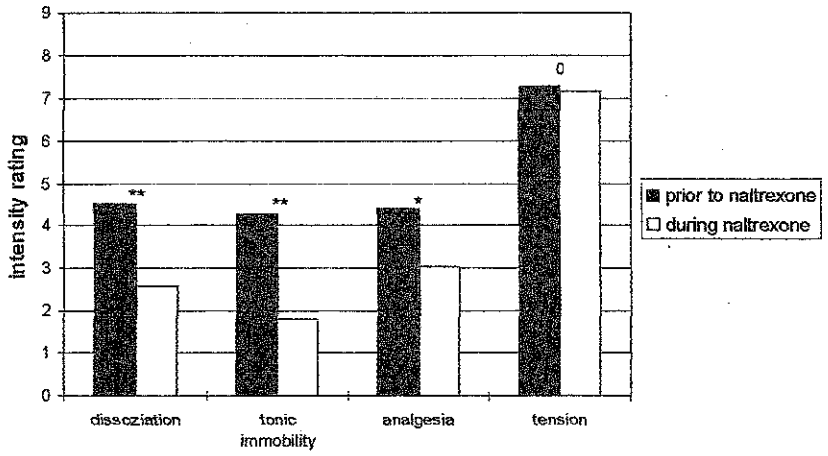
- 

- 

➢ Stress and Dissociation

- Dissociative symptoms comprise depersonalisation, derealisation, and reduced sensory processes
- In patients in BPD, these symptoms are frequent and related to emotional stress
- Disturbed information processing, memory, and learning
- Is dissociation a dysfunctional anti-stress mechanism?

➢ MInfluence of Naltrexone on Dissociative Symptoms



Bohus et al., J Clin Psychiatry 1999

➢ Implications for treatment

- Traumatic Stress is a frequent etiological factor in BPD, but BPD is not only a complex form of PTSD
- Disturbed prefrontal-limbic circuits are a potential correlate of emotional dysregulation and a target for emotion regulation treatment
- Dissociation disturbs learning processes and therapies based on new emotional learning

Thanks to Coworkers and Collaborators

CIMH, Dept. of
Psychosomatic Medicine:

- Martin Bohus
- Gabriele Valerius
- Iris Klossika
- Petra Ludaescher
- Anja Jochims

- Rolf-Detlef Treede, Wolfgang Greffrath (University of Mannheim, Germany)
- Erich Seifritz (Sanatorium Kilchberg, Switzerland)
- Ruth Lanius (University of Western Ontario, Canada)
- J. Douglas Bremner (Emory University, Atlanta, USA)

5HT2A RECEPTOR BINDING IN BORDERLINE PERSONALITY DISORDER

PAUL H. SOLOFF, MD

PROFESSOR OF PSYCHIATRY
WESTERN PSYCHIATRIC INSTITUTE AND CLINIC
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE

NIMH GRANT MH 48463
AMERICAN FOUNDATION FOR SUICIDE PREVENTION

Bio

Paul H. Soloff, MD is Professor of Psychiatry at the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine. Dr. Soloff received his medical training at the University of Pittsburgh, interned at the University of Michigan and completed his psychiatric training at the Massachusetts Mental Health Center. For over 25 years, he has been actively involved in clinical research involving patients with Borderline Personality Disorder(BPD), and has written many papers and book chapters concerning the pathology and pharmacotherapy of BPD. With support from the NIMH, he conducted several of the earliest controlled drug trials involving patients with BPD. He was a member of the APA Task Force which wrote the Guidelines for the Treatment of Patients with BPD. His recent research addresses the clinical, psychosocial and biologic predictors of suicidal behavior in BPD. With support from NIMH and AFSP, he has conducted neurobiologic investigations using the radioligand [^{18}F] altanserin to assess binding potential of the serotonin-2A receptor and its role in impulsive and suicidal behavior in BPD.

Objectives

- ✓ At the conclusion of the presentation, the learner will appreciate the relevance of the serotonin-2A receptor to the study of suicidal behavior.
- ✓ Current studies on the binding potential of the serotonin –2A receptor in BPD will be presented, using [18-F] altanserin binding and Positron Emission tomography.

Presentation Outline

Background

Post-mortem studies in suicide victims demonstrate an increase in the number of post-synaptic 5HT2a receptor binding sites in areas of prefrontal cortex (PFC). Impulsive subjects with BPD, a group at high risk for suicidal behaviors, have diminished metabolic responses to serotonergic activation in related areas of PFC. We conducted a study of the binding potential of the 5HT2a receptor in impulsive BPD subjects, assessing the relationship of receptor binding to impulsivity, aggression and suicidality .

Method

19 BPD subjects (14F,5M), defined by DIB and IPDE interviews, were compared to 21 healthy control subjects (11F, 10M). [^{18}F] altanserin was used with PET neuroimaging to measure 5HT2a receptor binding potential (BP) across 10 pre-defined cortical Regions of Interest (ROIs). Subjects were also assessed for Axis I co-morbidity, depressed mood, impulsivity, aggression, suicidality and histories of childhood abuse.

Results

Among female subjects, altanserin binding was <u>increased</u> in BPD compared to control subjects in all 10 ROIs. The 12 female BPD subjects with histories of prior suicide attempt had greater BP in HIP, medial temporal cortex (which includes HIP), and occipital cortex, with a near-significant trend in lateral orbital frontal cortex. Non-depressed female BPD subjects had significantly increased BP values in the hippocampus (HIP) compared to depressed female BPD and control subjects. Male BPD subjects had <u>decreased</u> BP values across all 10 ROIs compared to control subjects, with significantly decreased BP values in areas of PFC and HIP. Control males had significantly greater BP than control females in HIP and lateral orbital frontal cortex.

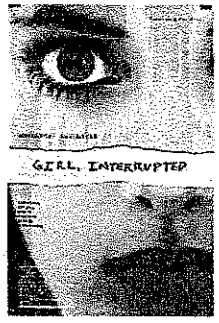
Conclusions

5HT2a receptor function in HIP may play a role in dysregulated behavior in BPD. Gender differences in 5HT2a receptor binding are significant and may mediate different behaviors in male and female subjects.

Collaborators

- Julie C. Price, Ph.D
- Carolyn C. Meltzer, MD
- Anthony Fabio Ph.D
- Guido K. Frank, MD
- Walter H. Kaye, MD

➢ Focus on Suicidal Behavior in BPD



Suicidal behavior…
Self-mutilation…
" the borderline patient's "behavioral specialty."

(Gunderson and Ridolfi,2001)

➢ BPD and Suicidal Behavior

- 1/2 of parasuicides admitted to hospital have BPD *(Soderberg,2001)*
- Over 1/3 of community suicides have BPD *(Isometsa et.al. 1996, Runeson et.al. 1989).*
- Among BPD inpts: 72.6% attempted suicide, an average of 3.3 lifetime attempts. *(Soloff et.al, 1994)*
- Completed suicide rate for BPD: 3% - 10%, ave. age 37 yrs. *(Paris & Zweig-Frank,2001)*

➢ 5HT and Suicidal Behavior

In suicides, high lethality attempters, and impulsive BPD (indep. of suicidal behavior):

- Decreased CSF 5-HIAA
- Blunted prolactin response to FEN, m-CPP
- Inverse relationship between impulsivity/aggression and response to FEN

➢ Imaging methods in BPD

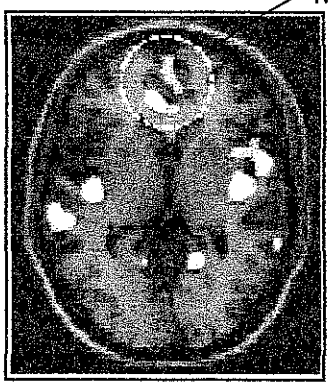
- Structural MRI (ROI or VBM)
- f-MRI (e.g. Ekman faces)
- PET: FEN, m-CPP, behavioral paradigms, radioligands (e.g. 5HT receptors, transporter binding sites)
- Magnetic resonance spectroscopy
- Diffusion tensor imaging (MRI-based, white matter tractography)

Regions of Interest for Affect and Behavior Regulation

- PFC: cognitive control of emotion, esp. orbital-frontal and ventromedial PFC; emotional processing and working memory, esp. DLPFC
- ACC: monitor and modulate emotional intensity
- Amygdala: recognition of aversive faces, fear conditioning,
- Hippocampus: emotional memories, reconcile internal state and external reality (Wall & Messier,2001).
- Disruption in circuits involving these fronto-temporal functions = affective dysregulation and impulsive-aggressive behavior

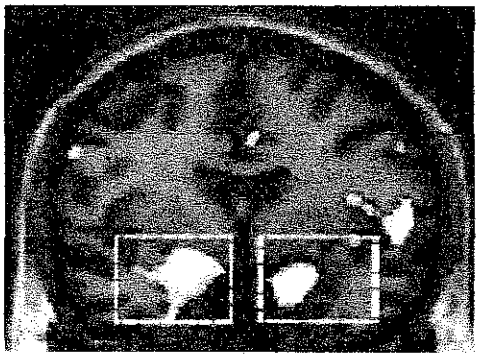
A Voxel-Based-Morphometry Study in BPD

A. BPD (34) vs. Healthy Controls (30)



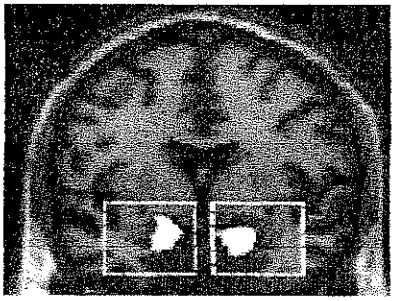
- BPD (22 females, 12 males); HC (19 females, 11 males)
- ANCOVA with age, gender
- Significant **reductions in grey matter concentrations in BPD** compared to HC subjects in:
  - Ventral anterior cingulate gyrus, bilaterally
  - Medial temporal lobe bilaterally (Parahippcampal gyrus, uncus, amygdala)

A. BPD (34) vs. Healthy Controls (30)



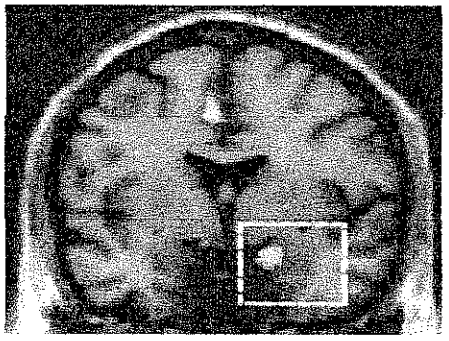
- BPD (22 females, 12 males; HC (19 females, 11 males)
- **Significant reductions in gray matter concentration in BPD** compared to HC in the medial temporal lobe [inset: (Cluster peaks: *t*59 =4.51, x=19 (-19), y=-1, z=-20 (Uncus)

B. Female BPD vs. Healthy Controls



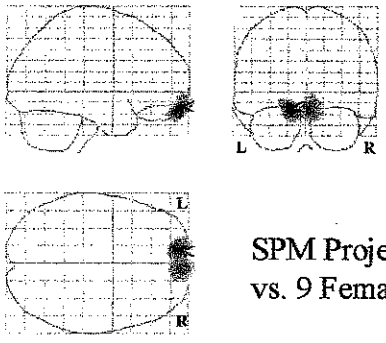
- BPD (n=22); HC (n=19)
- ANCOVA with age
- Significant reductions in gray matter concentration in medial temporal lobe in female BPD compared to female HC. (Cluster peaks: $t37$ =4.94, x=17 (-17) y=-1, z=-19)

C. Female BPD with childhood Sexual Abuse vs. Non-abused Female BPD Subjects

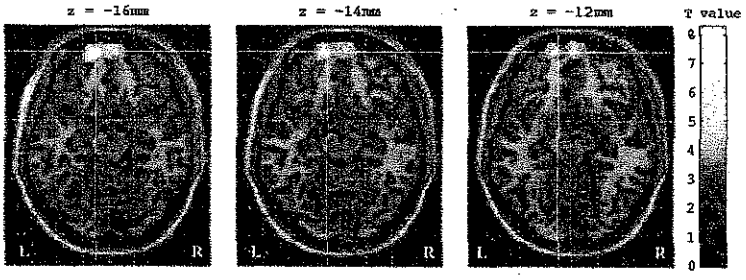


- Abused (n=8); Non-abused (n=14) BPD Females
- ANCOVA with age
- Significant reductions in gray matter concentration in medial temporal lobe in sexually abused compared to non-abused female BPD subjects. (Cluster peaks: $t18$ =4.44, x=19 y=-1, z=-18)

FDG UPTAKE IN BPD LESS THAN CONTROLS



SPM Projections: 13 Female BPD vs. 9 Female Controls



SPM Projection images and overlay of the SPM map on 3 slices of a T1 weighted MR image in MNI Atlas space. N = 22, 2 groups, 1 covariate, 19 df. Images displayed at an uncorrected significance level (height threshold) of $p<0.001$ and cluster size (extent threshold) of 190 voxels. MR images are displayed in neurologic orientation, ie., R. corresponds to the right side.

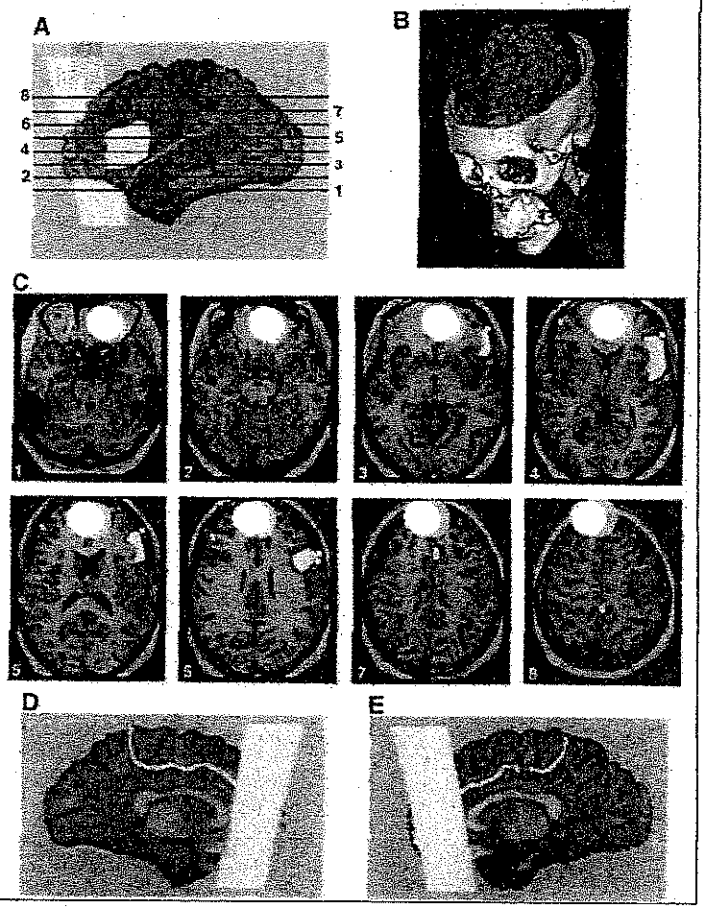
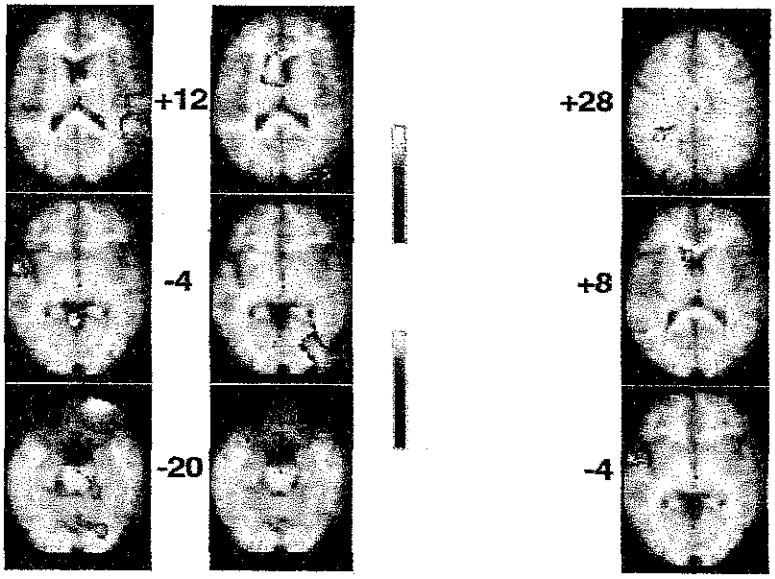


Fig. 5. Normal brain fitted with the five possible rods. The best rod is highlighted in solid white [except for (**B**), where it is shown in red]. The areas spared by the iron are highlighted in color: Broca, yellow; motor, red; somatosensory, green; Wernicke, blue. (**A**) Lateral view of the brain. Numbered black lines correspond to levels of the brain section shown in (**C**). (**D** and **E**) Medical view of left and right hemispheres, respectively, with the rod shown in white.

➢ Pilot Studies: response to d,l FEN



PET

Brain response drugged with PEN.

- **The 5HT2A receptor in suicide: post-mortem studies**

  - Increased post-synaptic 5HT2A receptor number in ventral lateral and orbital frontal cortex,
  - Decreased binding to the 5HT transporter
    - ***(Refs: Arango et.al. 1997, Mann and Stoff 1997)***

less transmissions ~~signals~~
more "windows open" to receive
area of brain deals w/ inhibitions.

- **M 5HT2A receptor**

  - In subjects with chronic suicidal ideation, or self harm behaviors (all BPD± MDD), [18F] setoperone binding to 5HT2A is directly related to scores on a Dysfunctional Attitude Scale independent of depressive sx severity .
  - d-FEN reduced Dysfunctional Attitudes in controls independent of depressed mood
  - Dysfunctional Attitudes (e.g. "negatively biased views of oneself, the world and the future") are inversely related to serotonergic agonism ***(Meyer et.al. 2003).***

- **Hypotheses**

  - a.) Decreased serotonergic agonism in PFC results in post-synaptic upregulation of 5HT2A receptor number, or increased receptor sensitivity.
  - b.) Diminished serotonergic agonism in PFC is associated with impulsivity, aggression, and increased risk of suicidal behavior.

- **Study Design**
-

  - Female and male , 18 – 46 years
  - Axis I: SCID, Axis II: IPDE,
  - BPD dx by IPDE, DIB-R (Impulse Action Patterns = 3 (max.scaled score) required)
  - LHA,TCI at intake; HamD-24, BDHI, BIS, one week before scan.
  - Exclusions: lifetime Schiz, Schizo-Aff, delusional D/O, bipolar (I or II), MDD with psychosis, organic mood disorders
  - Controls: no lifetime Axis I or II.
  - Med free, incl. BCP: (actual> 2mo.) , drugs/ETOH: (actual>5 days, mean (s.d.)17.5 (14.5). Neg UA/preg day of scan

Study Design

- [18F] Altanserin: radioligand/ antagonist, binds to 5HT2A (>95%), and, minimally to 5HT2C receptors.
- MRI for co-reg. on 1.5T Signa, ECAT HR+ PET scanner
- [15O] H2O for CBF;
- [18F] Altanserin (10 mCi). 90 min PET acquisition with arterial sampling

Study Design

- ROIs:
  - anterior cingulate(ANC,BA32): pregenual (PRG,BA24/32), subgenual (SUG,BA25)
  - lateral orbital-frontal (LOF,BA45/47), medial orbital frontal (MOF, BA11), medial frontal cortex (MFC,BA9/10),
  - medial temporal cortex (MTC): hippocampus (HIP), amygdala (AMY).
  - occipital (OCC), thalamus (THL), cerebellum (CER)

Study Design

- Primary analysis by linear Logan graphical method; secondary (confirmatory) analysis by 4 compartment (4C) model. (Price et.al.2001)
- Binding Potential = DVR-1 where DVR is ratio of DV value for an ROI to the DV value of the reference region (cerebellum)
- Corrected for partial volume ("atrophy") effect due to CSF (Meltzer et.al.1999)
- BP values (rt./lt.) for each ROI pooled for 1st analysis; post-hoc analyses on significant ROIs to minimize Type I error.

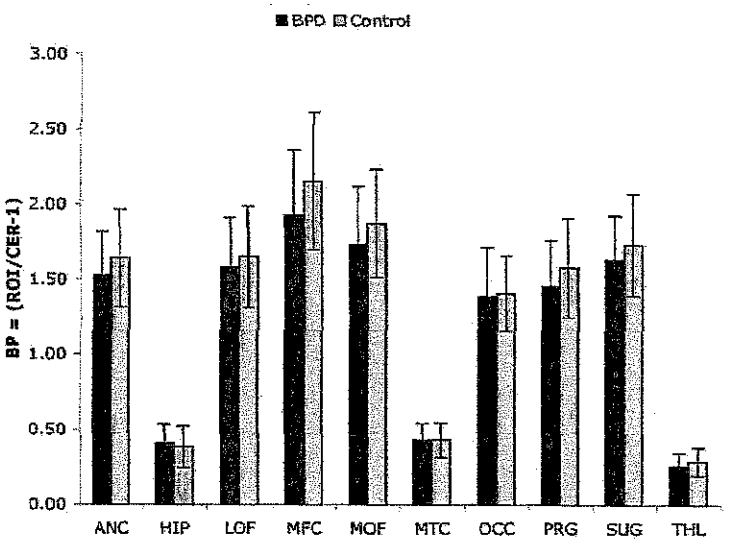
Study Design: Statistical methods

- K-S 1-sample test for normality, Levine for homogeneity
- Group comparisons for each ROI by Mann-Whitney U test.
- ANCOVA with age as covariate (Ln transform as needed).
- Pearson correlation; Regression models: group, age, gender, psychological tests as independents; BP values for each ROI as dependents.

- **Results: Total Sample (n=40)**

  - BPD = 19 (14F, 5 M), Controls = 21 (11F, 10 M)
  - Age (yrs.): range 18-46, mean (s.d.): 26.6 (8.2)
  - BPD current co-morbidity: MDD (5F), Dysthymic Disorder (3F,3M), Depression NOS(1F), SUD (7F,1M), Anxiety Disorder (2 M)
  - BPD Attempters: (12F,3M), range 0-7 attempts, mean (s.d.) = 2.0 (2.1).
  - BPD Sex abuse: (5F, 1M), Phys. abuse (6F,3M)
  - BPD > Con: BIS (p. <.001), HamD (p.<.001), but not LHA (p.=0.1. No diffs for: age, BMI, days from onset of menses to PET.

- **[18F] Altanserin Binding in Borderline Personality Disorder (19) and Control Subjects (21)**



Pooled Gender Samples: BPD (14F, 5M) vs. Control (11F, 10M)
Logan BP values with atrophy correction; Mann-Whitney U Test, 2 tailed.

- **Results: Total Sample (N=40)**

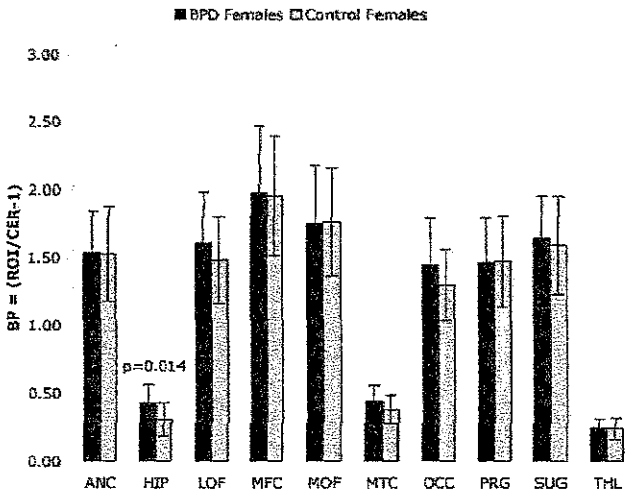
  - No significant group differences in any ROI with age covaried, but group x sex interactions significant in 5 ROIs.
  - Regression models with group, age, sex, psychological variables as independents; BP values in ROIs as dependents:
  - No significant contribution from BIS, LHA, HamD, BUSSTOT, TCI variables.
  - ATTEMPTER status contributes to HIP (p.043)
    - (also, ANOVA with age: BPD > HC (F 12.3, p.034.)

- **Results: Females only**
  - BPD (14) vs HC females (11):
  - Age: range 19 -46 yrs, means (s.d.): BPD 27.7(8.2), HC 27.3(10.6)
  - No sig. diff: age, ht, wt, BMI, days from onset of menses.
  - BPD comorbidity: 5 MDD, 3 Dysthymic, 1 Depression nos,7 SUD,
  - 12 past suicide attempters, lifetime mean 2.5 (2.1) attempts, 5 sex abuse, 6 physical abuse

- **Females only (n = 25)**
  - No significant group differences in:
    - nonspecific binding (CER DV) by either Logan or 4 C method
    - CSF partial volume correction factors
    - CBF for any ROI
    - metabolite levels at 60 and 90 min. post-injection
  - BP inversely related to age in BPD and HC.

- **Females only (n = 25)**
  - Altanserin binding in BPD females > HC in all 10 ROIs
  - Effect of group on BP, with age cov:
    - HIP*: lt. p.009, rt. p.03,
    - OCC: lt. p.02, rt. p.009
    - MTC: lt. p.03, rt. p.98,
    - LOF: lt.p.11, rt. p .08.
  - *Only HIP significant in both Logan and 4C analyses

- **[18F] Altanserin Binding in Female Borderline Personality Disorder (14) and Control Subjects (11)**



Logan BP values with atrophy correction
Mann-Whitney U Test, 2 tailed

- **Females only**
  - Effect of MDE on BP, with age covaried:
  - HIP ($F(2,24) = 9.10$, p.001).
  - 9 Non-Depressed BPD (0.46±15) > 5 Dep. BPD (0.39±12) >11 HC (0.31±.12)
    - Non-Depressed BPD vs.HC (p.001)
    - Non-Depressed vs.Depressed BPD (p.008)
    - Depressed BPD vs HC: (p.ns.)

- **Results: Females only**
  - For 12 Attempters, results even more robust:
  - BPD > HC in:
  - HIP (p.001), MTC (p.046), OCC (p.025), [LOF (p.08)].
  - BP not related to Ham-D, abuse hx, lifetime number of suicide attempts

- **Females only (n=25): Correlations**

HIP + Novelty Seeking: r = 0.56 p.007

HIP + Harm Avoidance: r = 0.51, p.01

-(HA2) fear of uncertainty r = 0.50, p.02

-(HA4) fatigability r =0.42, p.04

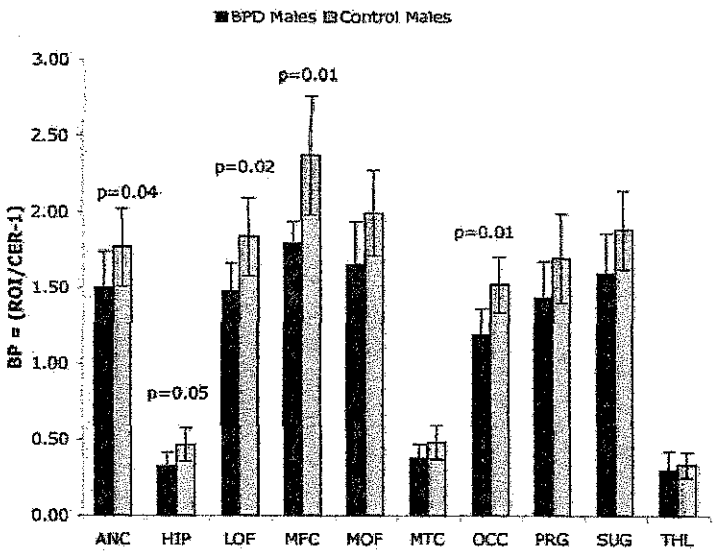
HIP + Reward Dependence: r = 0.65, p.001

HIP + BDHI-total r = 0.43, p.003 [Ind. (r = 0.46, p.02), Neg (r = 0.44, p.03), Res (r = 0.42, p.04), Ver (r = 0.50 p.01)]

- **Females only (n=25): Regression**
  - However, in Regression models with group, age, and personality variables as independents, BP values in ROIs as dependents:
  - BIS, LHA, BDHI and TCI variables ***do not contribute significantly to variance of BP values in any ROI.***

- **Males only**
  - N = 5 BPD vs. 10 Healthy Controls
  - No MDD . Axis I co-morbidity: dysthymic d/o (3), ETOH dep.(1), anxiety d/o (2).
  - Results: BP values for BPD < HC in:
    - ANC, HIP, LOF, MFC, OCC (Mann-Whitney U).
    - Analyses restricted to these 5 ROIs
  - ANOVA, with age covaried: BPD < HC in:
    - MFC (p.02), OCC (p.01), [trends in LOF (p.06), HIP (p.08)]

- **[18F] Altanserin Binding in Male Borderline Personality Disorder (5) and Control Subjects (10)**

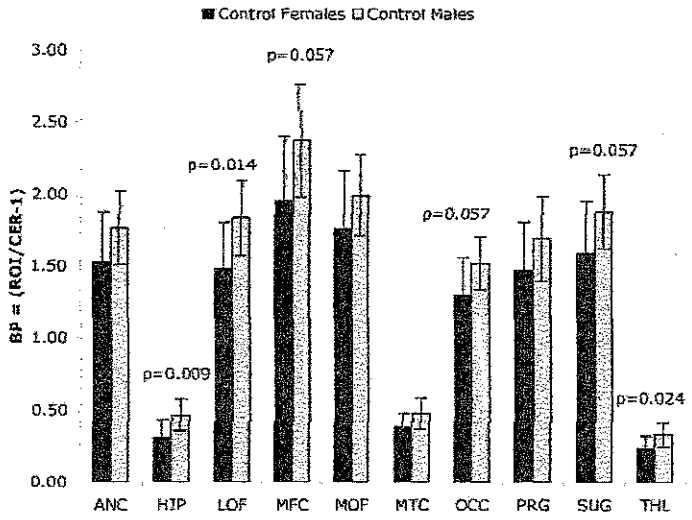


Logan BP values with atrophy correction
Mann-Whitney U Test, 2 tailed

- **Males only (n=15): Correlations**
  - BIS: inversely with MFC (-0.68, p.005), LOF(-0.65, p.009).
  - LHA: inversely with OCC (-0.52, p.05)
  - BDHI total: inversely with HIP (-0.66,p.008), LOF (-0.53, p.04), MFC (-0.58, p.025),OCC (-0.74, p.002), ANC (-0.59, p.02)
  - TCI: Fear of uncertainty (HA2): inversely with ANC (-0.57,p.035)

- **Males only (n=15): Correlations**
  - HamD: inversely with HIP (-0.62,p.014), LOF (-0.62, p.014), MFC (-0.70, p.003), OCC (-0.67, p.006)....unexpected direction... but...
  - HamD directly with BIS (+0.77, p.001), Lifetime number of suicide attempts (+0.51, p.04)
- **Males only (n=15): Regressions**
  - In Regression models with group, age, and personality variables as independents, ROIs as dependents:
  - LHA contributes to variance of OCC (p.04) [and HIP (p.056)];
  - Fatigability (HA4) to LOF (p.04) [and MFC (p.059)];
  - Harm Avoidance to ANC (p.009);
  - BDHI-verbal to OCC (p.023).
- **Healthy Controls**
  - N = 10 Male, 11 Female subjects,
  - Age range: 18-46 yrs. (mean, s.d. = 25.4 (8.6) yrs., 15 subjects ≤ 25 years old),
  - No group diffs by Age, HamD (mean, s.d. = 0.71 (1.3)), BIS, BDHI, TCI (NS,RD,P).
  - For Harm Avoidance (HA), male> female (p.005)
  - For LHA, male> female (p.001)
- **Healthy Controls (n=21)**
  - BP values for Male > Female subjects in: HIP (p.009), LOF (p.014), THL (p.024), with trends in MFC, SUG, OCC (all p.057),(Mann-Whitney U test)
    - Analyses restricted to these 6 ROIs.
  - ANOVA with age co-varied: significant gender effects remain in HIP,LOF,THL, with trends (p.<.1) in MFC, SUG, OCC.

- **[18F] Altanserin Binding in Healthy Female (11) and Male (10) Control Subjects**



Logan BP values in with atrophy correction
Mann-Whitney U Test, 2 tailed

- ***Healthy Controls (n=21): Correlations***
  - In total sample, BIS,LHA, HamD have no significant correlations with BP values in any ROI.
    - but for males only, LHA inversely related to MFC (-0.63, p.05), SUG (-0.68,p.03), THL (-0.66, p.04)
  - In total sample, BDHI-negativism is directly related to HIP (0.47, p.034)
    - but for females only (0.72, p.012)

- **Healthy Controls (n=21): Correlations**
  - Novelty Seeking is directly related to: LOF (0.47,p.035), MFC (0.48, p.032), SUG (0.46, p.04), THL (0.46, p.04), OCC (0.55, p.01)
    - NS and OCC, female only (0.68, p.03)
  - Harm Avoidance to: LOF (0.51,p.02), SUG (0.47, p.04), THL (0.47, p.035), HIP (0.60, p.005),
    - HA and HIP: female only (0.65, p.04)
    - HA and OCC: male only (-0.77, p.009)

- **Healthy Controls (n=21): Correlations**
  - Reward Dependence to: SUG (0.47, p.038), HIP (0.51, p.022),
    - RD and HIP, female only (0.64, p.046)
    - RD and SUG, female only (0.68, p.031)
  - No gender differences in the relationship between TCI scales and BP values in LOF, THL, MFC

- **Healthy Controls (n=21): Regression**
  - Regression model: Gender, age, psychological variables as independents, BP values in ROIs as dependents.
    - [BDHI-neg contributes to HIP (p.056)]
    - [Fatigability (HA4) to SUG (p.053)]
  - Contribution of psychological variables to BP values is not significant when gender, age are covaried.

- **Discussion**
  - Results were unexpected:
    - In healthy subjects, most 5HT2A binding is in frontal and prefrontal cortex, less in HIP or AMY (Adams et.al.2004).
    - diff. between female BPD and controls in LOF was of trend significance only.
  - Marked gender differences were found in both BPD and Controls (BP increased in BPD females in HIP, decreased in BPD males in ANC,HIP,LOF,MFC,OCC)
  - Male BPD sample still too small for conclusions.

- **Discussion**
  - Structural MRI studies: loss of volume in HIP and AMY assoc. with hx of childhood abuse (Lyoo 2005, review).
  - Functional imaging studies: a). (FDG) PET: One study showed decreased uptake in HIP in BPD ***(Juengling et.al.2003)***.
  - b.) [150] water-PET: Decreased rCBF in HIP (rt.) and AMY in BPD with "abandonment scripts" ***(Schmahl et.al.2003)***;

- **Discussion (cont.)**
  - Functional significance of increased 5HT2A binding in HIP in female BPD unclear. (Relationship to BIS,LHA,BDHI,TCI not significant).
  - A. Decreased serotonergic agonism in HIP is associated with:
    - low self-esteem, hopelessness, pessimism (Deakin 2003), "dysfunctional attitudes" (Meyer et.al. 2003), ...predisposing to affective instability

- **Discussion**
  - B. HIP is also involved in:
    - updating associative memory,
    - monitoring and reconciling internal emotional states and external stimuli,
    - responding to current and anticipated threat.
  - C.HIP has extensive reciprocal connections to the orbital and ventral medial PFC, involved with modulation of affective and behavioral responses to external stimuli. (Wall and Messier,2001).

- **Discussion (cont.)**
  - Aberrations in HIP-PFC connectivity or function may contribute to affective instability and dysfunctional attitudes associated with BPD.
  - Gender differences in neurobiology may contribute to differences in affective and impulsive behavior in men and women with BPD, ...perhaps also in healthy suibjects.

BORDERLINE PERSONALITY DISORDER: ISN'T IT TIME FOR A NEW NAME?

ANTONIA S. NEW, M.D

MOUNT SINAI SCHOOL OF MEDICINE &
BRONX VA MEDICAL CENTER

Bio

Dr. New is Associate Professor of Psychiatry at Mount Sinai. She is involved in research, clinical work, and teaching at the Mount Sinai School of Medicine. Her research focus is on emotion dysregulation resulting in symptoms such as impulsive aggression and borderline personality disorder. In addition, Dr. New explores individual differences in response to stress and trauma, focusing on how this relates to emotion regulation. She uses brain imaging techniques, genetic studies, and laboratory assessment of behavior to explore mechanisms of treatment and to develop novel treatments for emotion dysregulation. Dr. New is the Principal Investigator of grants from the National Institutes of Health and from the Veterans Affairs Research Division, and completed a Career Development Award from the Veterans Administration. Dr. New has won several awards for teaching and scholarship. She completed her residency in psychiatry at New York Hospital/ Payne Whitney Clinic and a postdoctoral research fellowship at Mount Sinai. She received her medical degree from Cornell University School of Medicine.

Objectives

To review the history of the disorder and its name
To review the effect of stigma on misunderstanding how this disorder is treated
To present evidence of a neurobiological model of BPD as a disorder of affect regulation

Abstract

Borderline personality disorder (BPD) is a prevalent and disabling condition and yet the empirical research into its nature and treatment have not been commensurate with the seriousness of the illness. One reason for this may be the high level of stigma associated with the diagnosis. Mental illnesses in general are stigmatized compared to other medical illnesses, but BPD has been among the most severely stigmatized of all. While there are undoubtedly many factors contributing to the stigma attached to this diagnosis, we believe that an important component is that its name so poorly describes the nature of the disease. We argue here for the renaming of this disorder and its placement on Axis I. Our proposed new name is "**Interpersonal Dysregulation Disorder**". In this talk, I will address three fundamental misconceptions about BPD that I believe have contributed to misunderstanding of the disease, and are at least in part related to its name. I will then review what is known from empirical evidence about the etiology, phenomenology and course of this disorder, and finally will propose a model for the illness utilizing what is known to date about its clinical features, natural history, causes and neurobiology.

Why is it important to study this disorder?

- Borderline personality disorder (BPD) is a prevalent and disabling illness with high morbidity and mortality
- Paucity of effective treatments
- Important public health consequences
- Seriously stigmatized even among mental illnesses

Reasons for stigma

- 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
- Name so poorly describes the nature of the disease.

Consequences of Stigma

- The level of stigma often precludes a frank discussion with the patient and family about the diagnosis.
- This deprives patients of information about their illness, prognosis and information about proper treatment.

History of the disorder

- The term "borderline" coined in 1938 by Adolph Stern: individuals on the border between neuroses and psychoses
- In 1941, Zilboorg described a disorder "a mild version of schizophrenia", now called schizotypal.
- In 1942, Deutsch: patients lacking a consistent sense of identity, she called "as-if personalities", since patients over-identified with those upon whom they depended.
- In 1959, Schmideberg first described borderline disorder as a disorder of character.

- Grinker first to describe borderline personality through systematic empirical investigation. Original *Diagnostic and Statistical Manual of Mental Disorders (DSM-I)*: emotionally unstable personality.
- In 1975, Kernberg conceptualized borderline personality disorder (BPD) as a diagnosis in a group of patients with primitive defense mechanisms and pathologic object relations, focusing on the interpersonal.
- In 1981, first structured diagnostic tool for BPD: Diagnostic Interview for BPD (Gunderson, et al,1981). Five domains of functioning: social adaptation, impulse/action patterns, affects, psychosis, and interpersonal relations, led to the diagnosis in the DSM-III (1980).

➢ What is a personality disorder?

The DSM-IV –TR

- "an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time and leads to distress or impairment".

This definition, separating Axis I from Axis II, is problematic:

- Many Axis I disorders meet these criteria. e.g., .schizophrenia, with enduring pervasive patterns of behavior, and often inflexible. Chronic illness onset in adolescence.
- BPD may be chronic compared to Major Depressive Disorder, even MDD, the prototype of an episodic disorder, is often associated with chronic symptoms that interfere with function.
- Personality disorders have been traditionally viewed as the result of environmental factors, while Axis I disorders have been viewed as having a "biological basis", but MDE is more common in those losing a parent before the age of 11, and PTSD clearly is in some part the consequence of environmental factors.

➢ 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

➢ Prevalence of BPD

- BPD is present in approximately 1-4% of the general population, making it as prevalent as schizophrenia and bipolar I disorder (Torgersen, Kringlen et al. 2001; Moran, Coffey et al. 2006).
- Borderline patients are heavily represented in clinical populations (Zimmerman, Rothschild et al. 2005) and are disproportionate users of mental health services at all levels of care (Comtois, Russo et al. 2003; Bender, Skodol et al. 2006)

➢ 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)

(Sanislow et al, 2000, 2002)

➢ Support from Factor Analyses for Single Construct

- Subsequent analyses: confirmed factors but showed factors (disturbed relatedness, behavioral dysregulation and affective dysregulation) were highly correlated with one another (r = .90, .94, and .99)
- Subsequent study also supported unified construct and showed
  - "frantic efforts to avoid abandonment", although uncommon even in BPD, was virtually absent in *the non-borderline group*
  - Affective instability was also highly informative for BPD diagnosis

➢ Co morbidity with BPD

- Axis I: PTSD & substance abuse (Skodol et al, 1999)
- High rate MDD (79% lifetime) in BPD, but also OPDs (66-82%) (Skodol et al, 1999)

- Axis II: ASPD & Dependent PD (McGlashan et al, 2000)
- Recent data show moderate increase rate bipolar I and II (19.4% in BPD, 7.9% in OPD(Gunderson et al, 2006)
- But,
- BPD does not run in families with bipolar disorder(Kelsoe et al, 2003; Silverman et al, 1991)
- Treatment with antidepressants improves mood stability in PDs, not bipolar disorder

(Coccaro et al, 1997; Kavoussi et al, 1994)

➢ Findings of Specificity

Our data suggest that it is specifically the feature of affective instability (ALS), and most robustly, the anger subscale of that distinguishes Borderline Personality disorder patients from non-Cluster B personality disorder controls

➢ BPD and MDE

	Borderline	MDE	Bipolar
Age onset	childhood	Any time in life	Late adolescence
Sex ratio	F>M	F>M	F=M
Common familiality	With MDD, not bipolar	Not studied with borderline	Not with borderline
Anger	++++ chronic	±	++++ in episodes
Mood Instability	++++ chronic	±	++++ episodes
Co-morbidity	Increased with MDE	Somewhat with Bipolar	By definition with MDE
Response to SSRIS	++ mood stabilizing	+++ antidepressant	Worsens mood instability

➢ 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

➢ Empirical Evidence about BPD: Course and Prognosis

- The completed suicide rate in BPD approaches 10%; with 75% attempting suicide at least once ***(Black, Blum et al. 2004).***

- BPD is associated with elevated risk of: physical illnesses, cigarette smoking, medical emergency room visits, motor vehicle accidents, violence towards others and generalized occupational and psychosocial dysfunction ***(Frankenburg et al, 2004;Dumais et al, 2005:Porcerelli et al, 2004;Skodol et a; 2002)***.

- A naturalistic large longitudinal study showed that 88% BPD patients achieve remission over 10 years, with about 1/3 of those remitting in the first two years ***(Zanarini et al, 2006)***

- Good prognostic indicators: younger age, absence of childhood sexual abuse, no family history of substance use disorder, good vocational record, absence of Cluster C PD, low neuroticism, and high agreeableness.

- Remission was defined in this study as no longer meeting criteria for BPD, but may have remaining symptoms.

➢ Childhood Trauma in BPD

- High rates of childhood physical and sexual abuse have been reported in BPD populations by many researcher gathered by patient self report.
- Presence of some type of childhood abusive experience almost ubiquitous ***(Zanarini, 2000)***
- In BPD, it appears, especially high rates of verbal abuse and perhaps sexual abuse reported
- This has led to consideration of BPD as a form of PTSD.

➢ However…

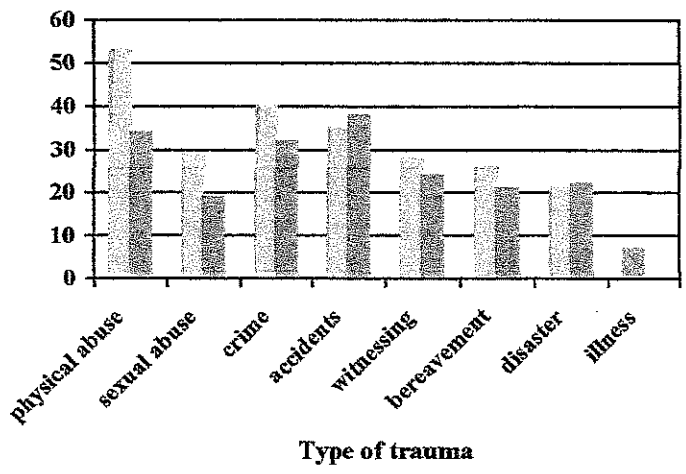
- Most studies were conducted in hospitalized individuals. Community samples are less consistent.
- Meta-analysis of 21 studies looking at BPD and CSA with over 2000 subjects ***(Fossati et al, 1999)*** yielded a pooled effect size of only $r = .28$ ***(Fossati et al, 1999)***
- Childhood abuse in BPD, while common is NOT universal. Of patients with BPD, 20-40% do not have history of childhood abuse.
- Conversely, 80% individuals with history of childhood abuse have no demonstrated personality pathology.

➢ Abuse in BPD and PTSD

- Trauma histories were gathered in 180 individuals with PDs.
- Total sample had 17.8% rate of PTSD, individuals with BPD had higher rates of PTSD than non-BPD.
- Childhood trauma was a predictor for PTSD, however BPD diagnosis made no difference in likelihood of having PTSD.

(Golier et al, 2003)

➢ Prevalence of trauma in childhood and/or adolescence in BPD subjects and subjects with other personality disorders



Borderline pd (n=72)

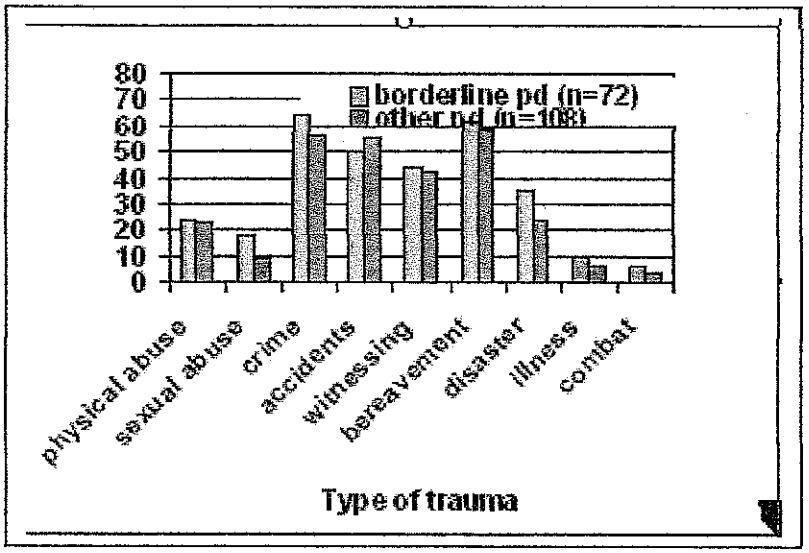
Other pd (n=108)

Childhood physical and sexual abuse common in personality disorder subjects

Of all types of trauma, only physical abuse was significantly more common in borderline subjects (53% vs. 34%; log. regression controlling for gender x2=5.4, p=0.02

(Golier et al, 2003)

➢ Prevalence of trauma in adulthood in BPD subjects and subjects with other personality disorders



Subjects with borderline personality disorder do not have higher rates of physical or sexual assault or other types of trauma in adulthood than subjects with other types of personality disorders

(Golier et al, 2003)

➢ Sequelae of Childhood Sexual Trauma

- A primary care sample of 506 women were screened for CST. 31% met criteria.
- 100 interviewed, 24% had no disorder.
- BPD was particularly associated with threats of violence and mother injuring father.

	Prevalence
BPD	29.3%
MDE	21.8%
Panic	31.3%
Agoraphobia	12.2%
PTSD	32%
Bulimia	7.7%
Substance abuse	53.3%
Suicide attempts	47.3%

Katerndahl et al, 2005

➢ 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

- **Family Studies**
  - Borderline personality disorder runs in families: first degree family members of borderline patients are more likely than other psychiatric patients to have borderline personality disorder.
  - Impulsivity or affective instability appeared in relatives of BPD, but independently.
  - This does not separate nature from nurture.

- **Heritability**
  - Twin studies: monozygotic are more likely to share dimensions of borderline personality disorder than dyzygotic twins. A Norwegian study showed heritability of .69 for BPD.
  - An additional 10% of the variance may come from common environmental factors

- **Twin Studies in Borderline Personality Disorder**
  - An early small study showed high heritability for dimensions of BPD, especially for direct assaultiveness
  - Recent studies show high heritability (0.65-0.79) for borderline personality disorder itself

- Like many other mental illnesses, these data suggest a model of Gene-Environment Interactions, or stress diathesis model

(eg. *Caspi et al, 2002*)

- **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

- **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
  - Maybe we have the wrong outcome measures, we miss the interpersonal in traditional pharmacologic trial outcomes
    - Event contingent recording
    - Informant information for treatment response

- **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

- **Biological Markers**

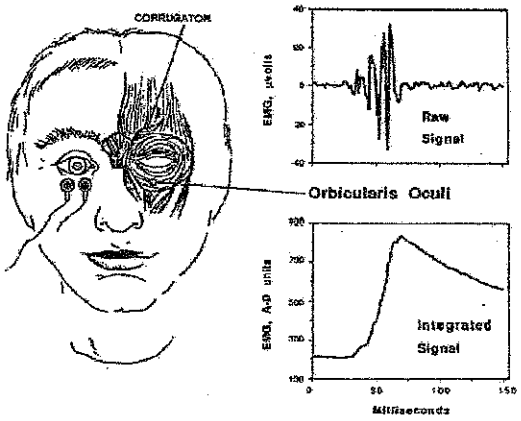
  You have heard about some of these already and will hear more…areas of PFC are under active, perhaps limiting "top down" control of emotion.

- **Startle Eyeblink Modification: an objective measure of affect responsiveness**

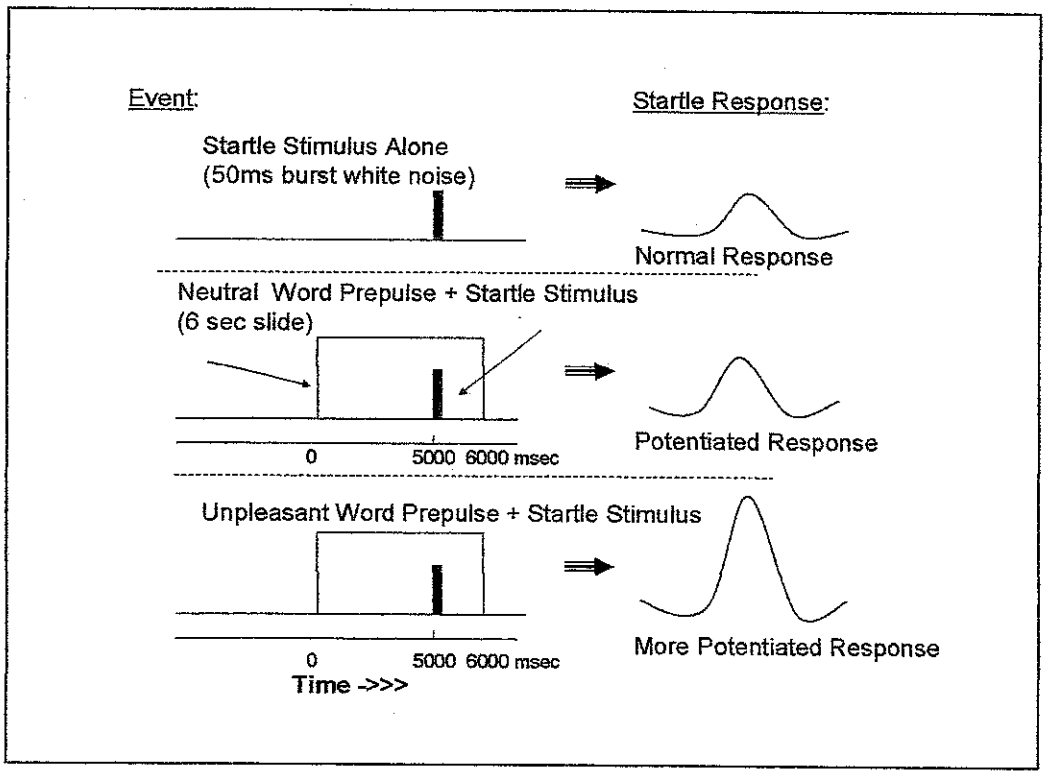
- **Startle Eye Blink Modification**
  - Measurement of intensity of blink via contraction of orbicularis oculi in response to sound burst
  - Emotion can influence this intensity: negative emotion in healthy controls enhances intensity

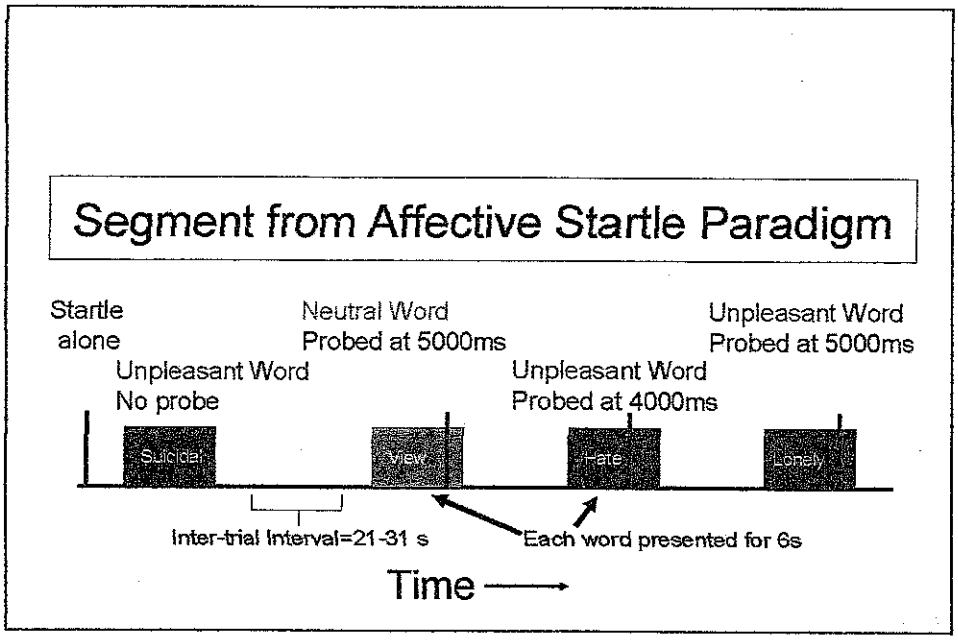
- **BPD startle**
  - Herpertz et al. (1999) found no differences between females with BPD and healthy controls in affective modulation of startle with emotional slides from IAPS.
  - IAPS emotional slides were high on disgust (mutilation etc) not most likely to differentiate BPD from Controls.

- **Startle Eye-blink Measurement**

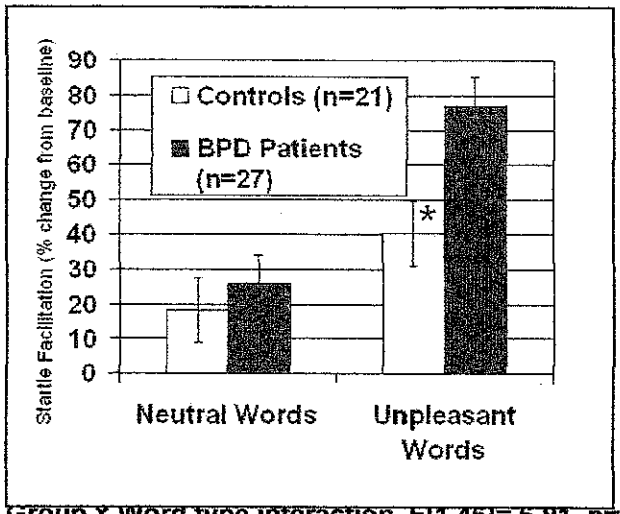


- **Affective Startle Modulation**

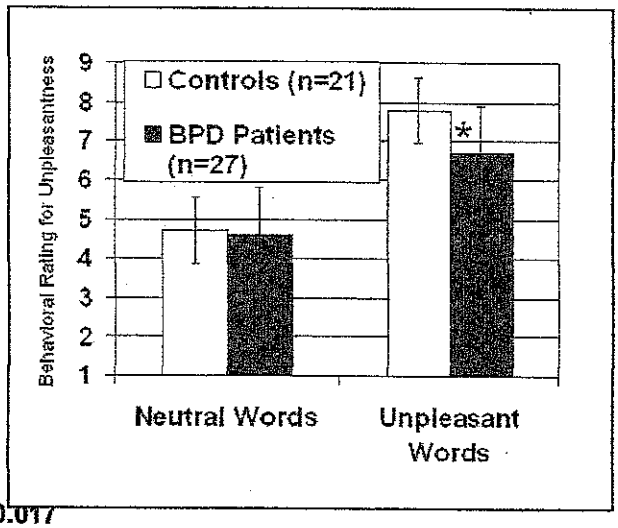




- **Affective Startle Modulation**



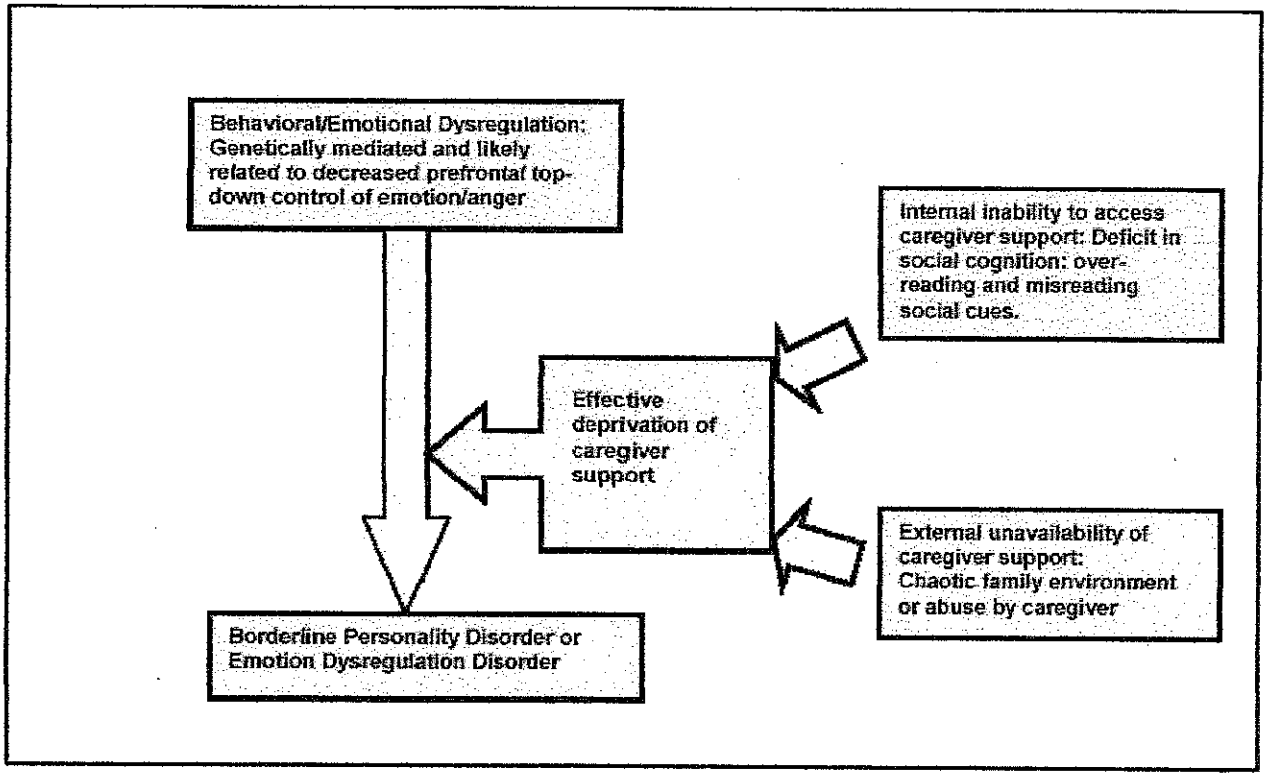
Behavioral Response to Pictures



Group × Word type interaction, F[1,46]= 6.91, p=0.017

- **Social Cognition: an over-reading of emotion**
  - BPD women identified fear and anger, more accurately than controls, but also misread neutral faces over-reading anger ***(Wagner et al, 1999).***
  - Multimorph Facial Affect Recognition Task: BPD correctly identified facial affect at an earlier stage than did healthy controls, showing heightened sensitivity to emotional expressions regardless of valence ***(Lynch et al, 2006).***
  - fMRI showed over-activation of amygdala in BPD to faces (fear <u>and</u> neutral) and saw neutral faces as threatening ***(Donegan et al, 2003)***
  - fMRI showed over-activation of right amygdala in BPD to fearful compared to neutral faces in

A New Model for BPD



Suggestion of Renaming

- Shall we rename this disorder and place it on Axis I?
- One proposed new name is "Interpersonal Emotion Regulation Disorder" (IEDD). This captures the element of emotion dysregulation as the core diathesis and the interpersonal disruptions that leave the individual vulnerable to the other sequelae comprising full blown borderline personality disorder.

Collaborators

- Marije Aan Het Rot
- Monte Buchsbaum
- Dennis Charney
- Janine Flory
- Marianne Goodman
- Erin A. Hazlett
- Emily Hart
- Lisa Iskander
- Harold Koenigsberg
- Sophie Lazarus
- David Meyerson
- Michael Minzenberg
- Vivian Mitropoulou
- Randall Newmark
- Larry J. Siever
- Joseph Triebwasser

IMPULSIVE AGGRESSION & BORDERLINE PERSONALITY: PHENOMENOLOGY, BIOLOGY, & IMAGING

EMIL F. COCCARO, MDD

ELLEN C. MANNING PROFESSOR & CHAIR
DEPARTMENT OF PSYCHIATRY
THE UNIVERSITY OF CHICAGO

Bio

Dr. Emil F. Coccaro is currently the Ellen C. Manning Professor and Chairman of the Department of Psychiatry at The Pritzker School of Medicine, The University of Chicago. He received his undergraduate B.S. degree in Biology from Fordham University, where he graduated *Magna Cum Laude* in 1975. Dr. Coccaro continued his studies at the New York University School of Medicine, completing his M.D. degree in 1979. After a medical internship at the University of Cincinnati Medical Center and a psychiatric residency at the Mount Sinai Medical Center in New York City, Dr. Coccaro joined the faculty of the Department of Psychiatry at the Mount Sinai School of Medicine in 1983. In 1989, Dr. Coccaro moved to Philadelphia to found and direct the Clinical Neuroscience Research Unit at the MCP Hahnemann School of Medicine. Dr. Coccaro moved to the Pritzker School of Medicine as the Director of the Clinical Neuroscience & Psychopharmacology Research Unit in September 1999. He became Chairman of the Department in November 2004. Dr. Coccaro is a Distinguished Fellow of the American Psychiatric Association (APA) and a Fellow of the American College of Neuropsychopharmacology (ACNP).

Dr. Coccaro has been the recipient of various awards, including the A.E. Bennett Award for Outstanding Research (1989) and the National Alliance for the Mentally Ill's Exemplary Psychiatrist Award (1992). He also serves on the editorial boards of several journals, among them *International Clinical Psychopharmacology, Journal of Personality Disorders, and Aggression and Violent Behavior.* In addition, he is the Impulse Control and Personality Disorders Section Editor for *Current Psychiatry Reports.* Dr. Coccaro has been the recipient of a number of research grants from the National Institute of Mental Health, the American Foundation for Suicide Prevention, the Borderline Personality Disorder Research Foundation, and the Harry Frank Guggenheim Foundation. Dr. Coccaro is the author or co-author of over 100 peer-reviewed journal articles, as well as 30 book chapters. He has edited or co-edited three books, most recently, *Aggression: Psychiatric Assessment and Treatment*, published by Marcel Dekker. He lectures widely on topics such as mood and personality disorders and the neuroscience, neuropsychopharmacology, genetics, and treatment of impulsive aggressive behavior.

Abstract

Research into the neurobiology and treatment of aggression in Personality Disorder (BPD) *include data related to familial/genetic, neurotransmitter based,* and *neuroimaging* characteristics of patients with PD. Familial and genetic studies strongly suggest that impulsive aggression is transmitted in families and are under substantial genetic influence. Neurobiologically, impulsive aggression is correlated inversely with central serotonin (5-HT) function and correlated directly with other (e.g, vasopressin, catecholamines) facilitory neurotransmitters. From a clinical neuroscience perspective, imaging studies suggest dysfunction of frontal-limbic circuits. This presentation will review the current state of the field regarding the neurobiological aspects of impulsive aggression in PD. This includes reviewing data from family, genetic, neurochemical, neuroendocrine, and neuroimaging studies of BPD. Data from clinical psychopharmacological trials will also be presented to highlight the relevance of biology in the etiology and treatment of impulsive aggression in PD.

References

Coccaro EF, Siever LJ. Neurobiology; In JM Oldham, AE Skodol, DS Bender (Eds), Textbook of Personality Disorders, pp. 155-169, American Psychiatric Press, Arlington, VA, 2005.

Coccaro EF, McCloskey MS, Fitzgerald DA, Phan KL. Amygdala and orbitofrontal Reactivity to social threat in individuals with impulsive aggression. Biological Psychiatry (E-Pub. On January 6, 2007).

Disclosure Information for
Emil Coccaro, MD

- *Consultant*
  - Abbott Labs, Eli Lilly
- *Research Grants*
  - Abbott Labs, Eli Lilly
- *Speakers' Bureau*
  - Abbott Labs, GSK, Forest Labs, Eli Lilly
- *Other Remuneration*
  - Abbott Labs, Forest Labs, GSK, Eli Lilly, Ortho-McNeal

- **Core Features of BPD**
  - Impulsive Aggression
  - Affective Lability
  - Self-Damaging Acts

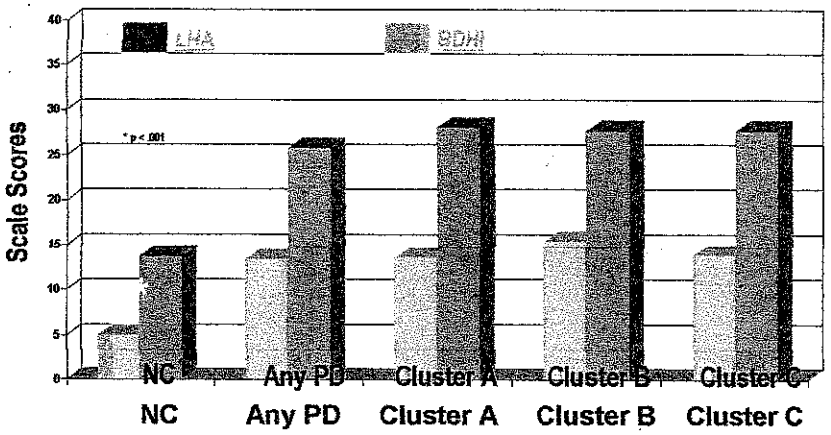
- **Aggression**

  Behavior by one individual directed at another person or object in which either verbal force or physical force is used to injure / coerce or to express anger

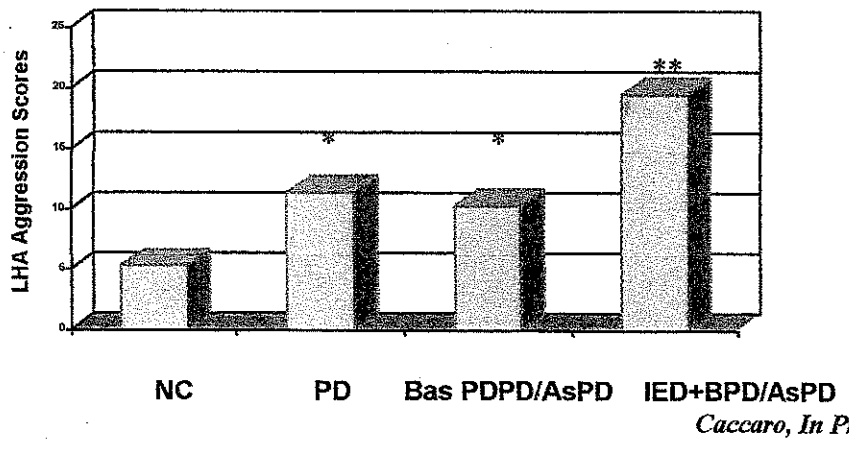
- **Aggression: Part of a Complex Triad of Behavior, Emotion, Cognition**

  Aggression = Behavior
  Anger = Emotion
  Hostility = Cognition

- **Aggression is Higher in PDs than Controls**

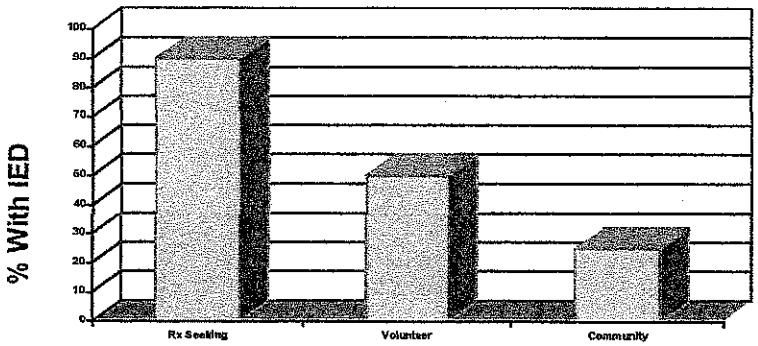


- **Aggression as Function of PD / BPD / AsPD Status**



Caccaro, In Prep

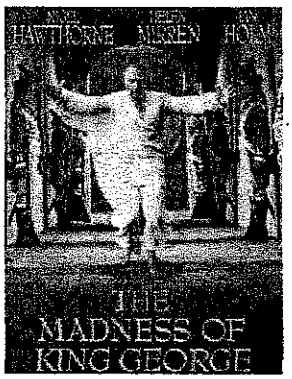
➢ How Many BPD / AsPD Have IED?



Coccaro et al., 2004; Coccaro & Kessler, In Prep.

➢ Types of Aggression

Socially Sanctioned
(WW II Soldier)



Medically Related
(e.g., Porphyria)

➢ Types of Aggression

Premeditated
(Psychopath)

Impulsive
(Your Neighbor?)

Premeditated
& Impulsive
Aggression
(Mob Boss)

- **Types of Aggression**

Premeditated:
Goal Directed
Aggression

Impulsive:
Frustration / Threat
Induced Aggression

- **Primary Aggression =**

  Intermittent Explosive Disorder

- **Diagnosis Before the DSM-III Era**

  - DSM-I (1956) "Passive-Aggressive Personality" (Aggressive Type)
  - Persistent reaction to frustration with irritability/temper
  - DSM-II (1968) "Explosive Personality"
  - "Gross outbursts of rage… strikingly different from usual behavior"
  - "Patients are excitable, aggressive, and over-responsive to environmental pressures"

➢ DSM-III IED Criteria

A. Several discrete episodes of loss of control of aggressive impulses resulting in serious assault or destruction of property
B. Behavior that is grossly out of proportion to any precipitating psychosocial stressor
C. *Absence of signs of generalized impulsivity or aggressiveness between episodes*
D. Not due to Schizophrenia, Antisocial Personality Disorder, or Conduct Disorder *(not during the course of psychotic disorder, Organic Personality Syndrome, Antisocial/Borderline Personality Disorder, Conduct Disorder, or intoxication with a psychoactive substance: Revision of "D" in DSM-IIIR).*

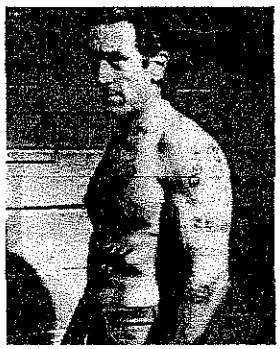
➢ DSM-IV IED Criteria

- Several discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property.
- The degree of aggressiveness expressed is grossly out of proportion to any precipitating psychosocial stressors.
- The aggressive behavior is not better accounted for by another mental disorder and are not due to the direct physiological effects of a substance or a general medical condition

➢ Problems with DSM-IV IED Criteria for IED

- What constitutes a "serious assaultive act" or destruction of property?
- How many aggressive acts and in what time frame?
- What is the nature of the aggressive act?

➢ Aggression is the Cardinal Feature of Intermittent Explosive Disorder But... What Type of Aggression?



Premeditated:
Goal Directed Aggression

Impulsive:
Frustration / Threat Induced Aggression

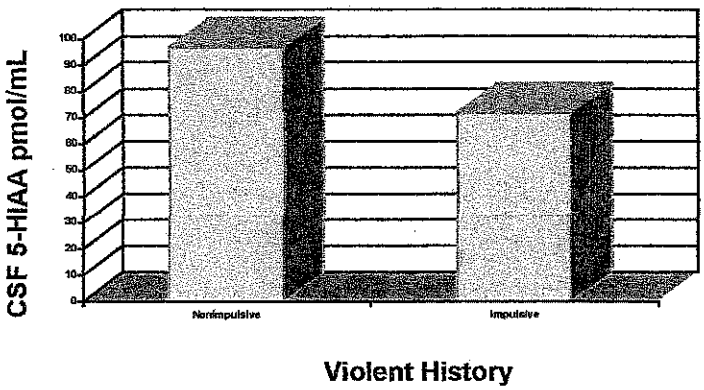
- **Why Impulsive Aggression?**

  1. "Premeditated" Aggression more relevant to Criminal Justice rather than Mental Health Systems.

  2. "Explosivity" suggests "Impulsivity".

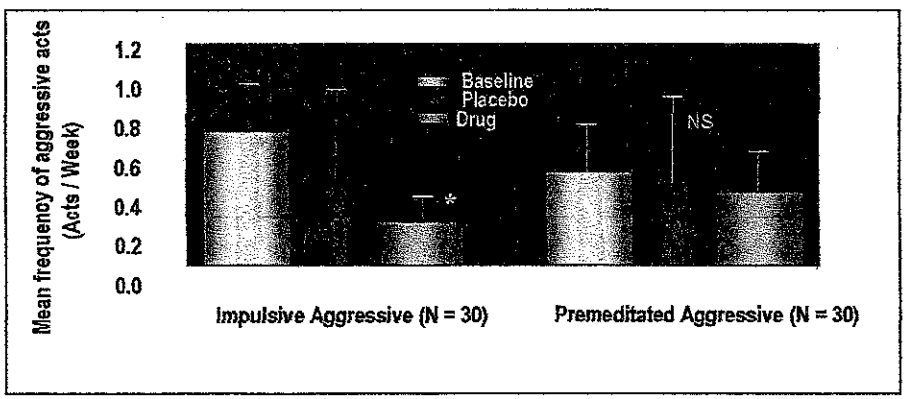
  3. 3. "Impulsive Forms" of Aggression have clear psychobiological relevance.

- **CSF 5-HIAA: History of Impulsive vs Non-Impulsive Violence in Violent Offenders**



Linnoila et al, 1983

- **Effect of Phenytoin on Impulsive & Premeditated Aggression in Prison Inmates (Mean Frequency)**



Barratt, et al. 1997.

- **Research Criteria for IED**

  Allows for:

  Frequent, though low intensity, aggressive acts

  as well as

  Infrequent, but high intensity, aggressive acts

  Requires:

  Aggressive acts to be impulsive in nature

  Distress / impairment due to aggressive acts

- **Research Criteria for IED**

  A1. Verbal or physical aggression toward other people, animals or property, occurring twice weekly on average for one month

  OR

  A2. At least three episodes of physical assault against other people or episodes involving destruction of property over a one-year period

  B. The degree of aggressiveness expressed is grossly out of proportion to the provocation or any precipitating psychosocial stressors

- **Research Criteria for IED**

  C. The aggressive behavior is generally impulsive and is not committed in order to achieve some tangible objective (e.g., money, power, intimidation, etc.)

  D. The aggressive behavior causes either marked distress in the individual or impairment in occupational or interpersonal function

  E. Not better accounted for by another mental disorder (e.g., major depression/mania/ psychosis; ADHD), general medical condition (e.g., head trauma, Alzheimer's disease); or to the direct physiological effects of a substance

- **DSM-IV IED Criteria**

  A. Several discrete episodes of *failure to resist aggressive* impulses that result in **serious assaultive acts or destruction of property**.

  B. Grossly out of proportion to any precipitating psychosocial stressors.

  C. Not better accounted for by another mental disorder / direct physiological effects of a substance or a general medical condition.

IED-IR Criteria

A. Verbal / physical aggression twice weekly on average for one month

or

Three or more episodes of physical assault / destruction of property over a one-year period

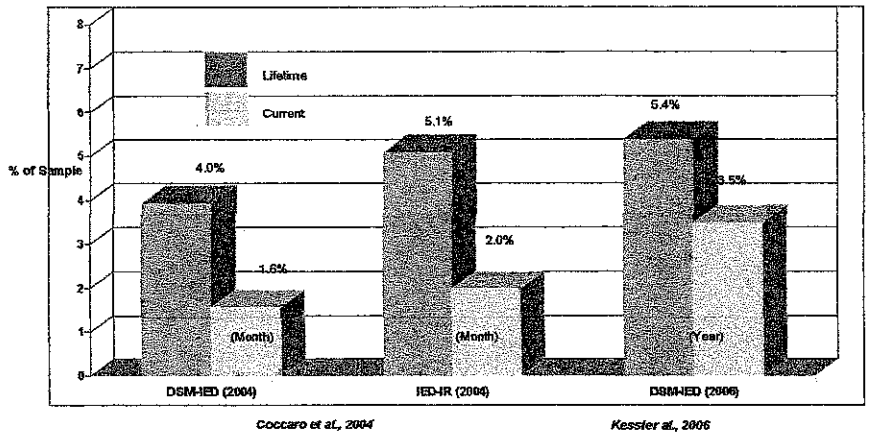
B. Grossly out of proportion to provocation

C. Aggression is generally impulsive

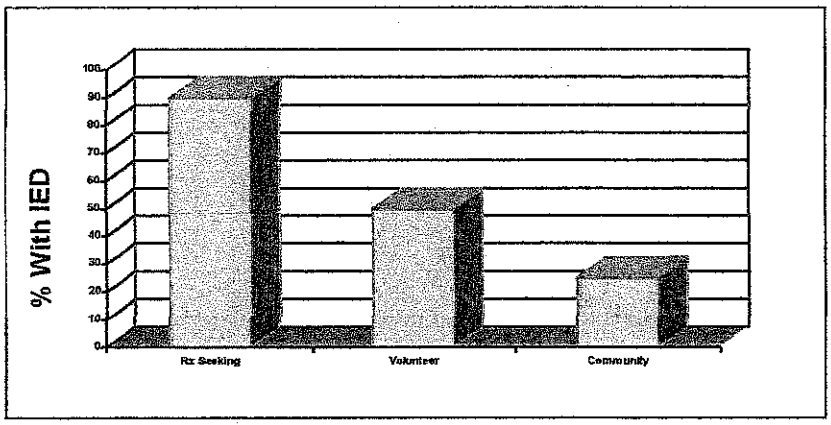
D. Causes distress or impairment

E. Not better accounted for...

- How Much IED is "Out There"?
- How Much IED is there in the General Community?

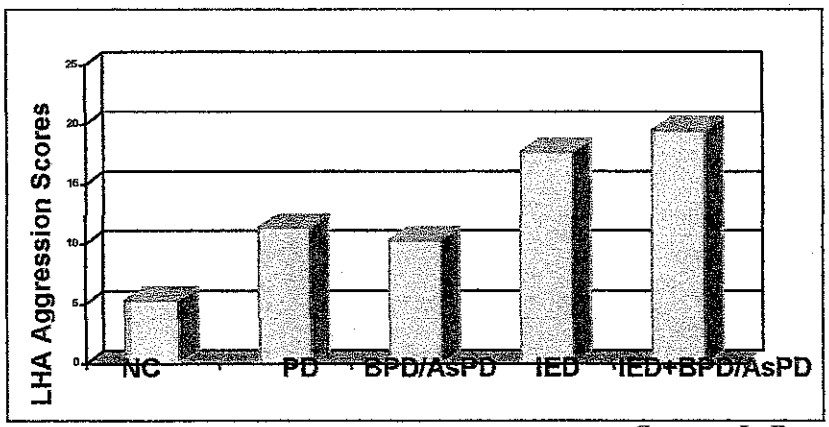


- How Many BPD/AsPD Have IED?



Coccaro et al., 2004; Coccaro & Kessler, In Prep.

- Aggression as Function of PD/IED Status

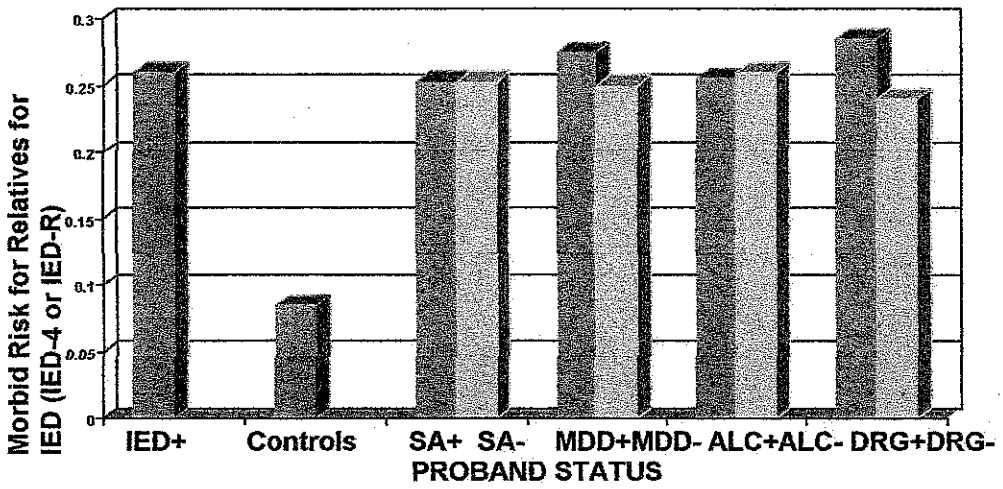


Coccaro, In Prep.

- **Underpinnings of Aggression**
  - **Familial**
    (transmission in families)
  - **Genetic**
    (heritability)
  - **Environmental**
    (experience of / witnessed aggression)
  - **Biological**
    (neurotransmitter / pathway dysfunction, etc)

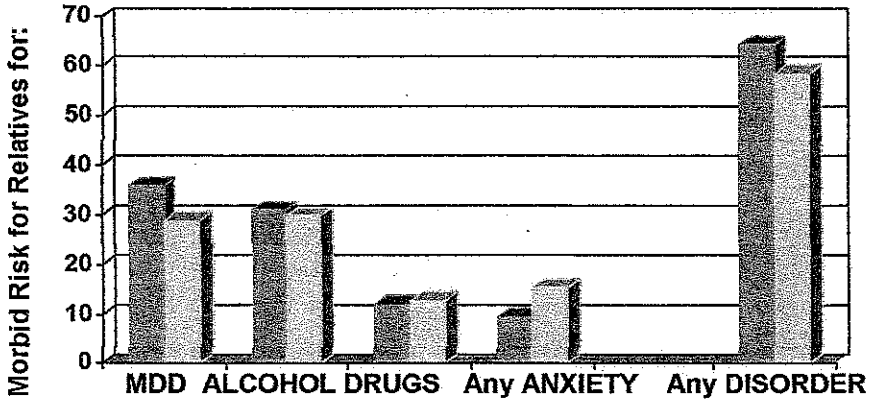
- **Familiality of IED**

- **Morbid Risk of IED in Relatives of IED Probands:**
  Function of Axis I Comorbidity in Proband



Coccaro et al., 2001

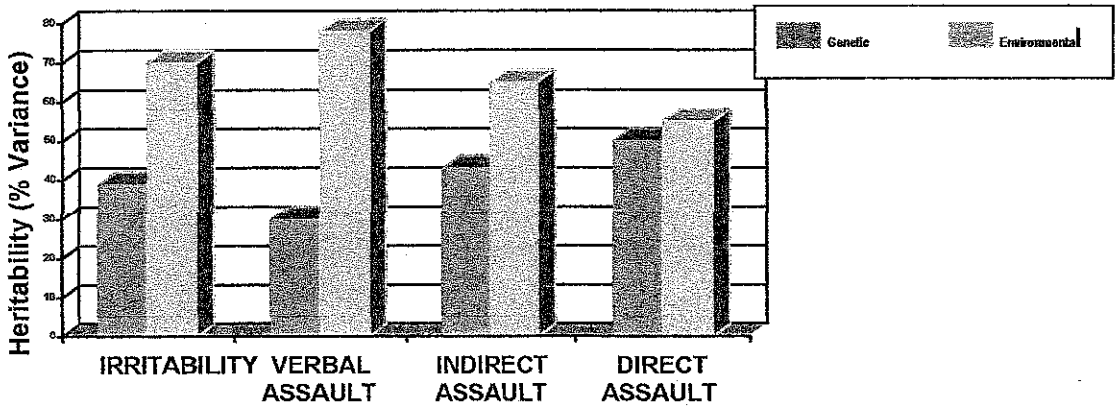
- **Morbid Risk of Co-Morbid Disorders in Relatives of IED Probands as a Function of IED Status**



Coccaro et al., 2001

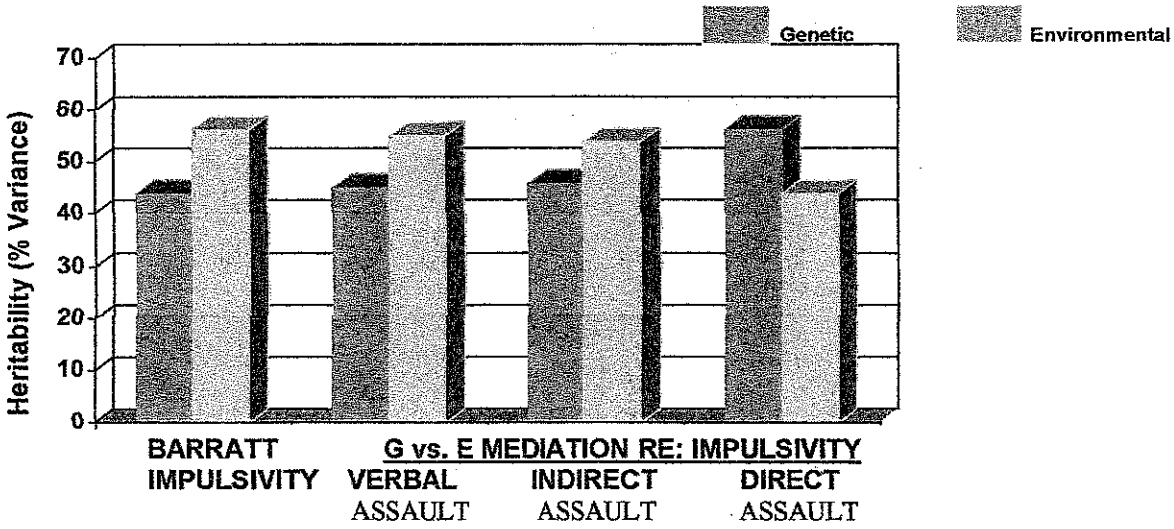
- **Genetic Factors**

- **Heritability of Buss-Durkee Aggression Scales in Men**



Coccaro, et al. 1997

- **Heritability of Impulsiveness and its Relationship with Aggression in Men**



Seroczynski, et al. 1999

- **Environmental Factors**

  Experience of aggression as a child

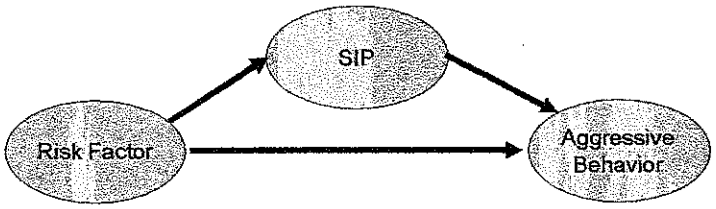
  Witnessing aggression as a child

  Parental dysfunction

- **Effect of "Environment" Mediated by Deficits in Social Information Processing**

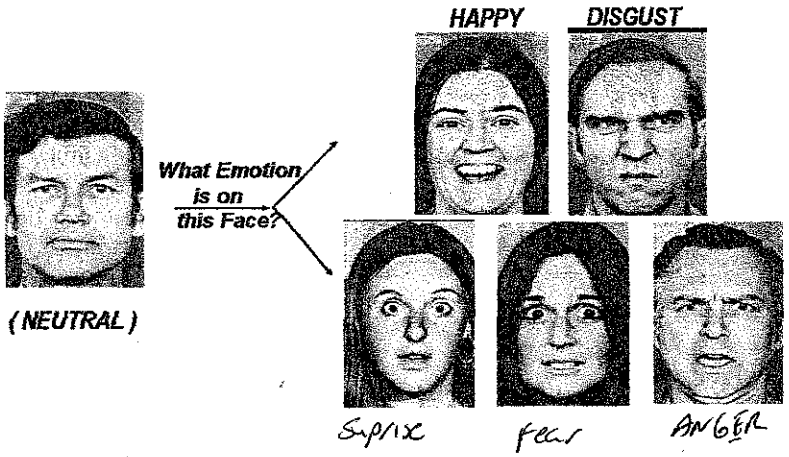
Aggression in Childhood Associated with Deficits in SIP:

a. Reduced Encoding of Relevant Social Information
b. Increased Tendency for Hostile Attributions

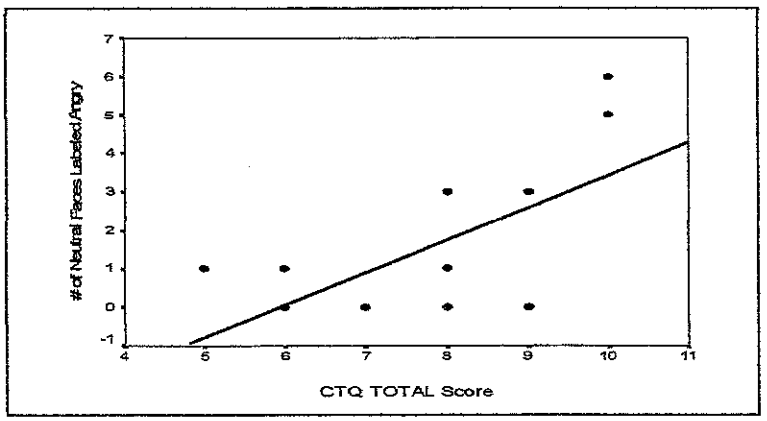


Aggression in Childhood, etc

- **Assessment of Attributional Tendencies in the "Lab"**



- **Relationship Between Hx of Childhood Trauma & HA in Adult IED Subjects**

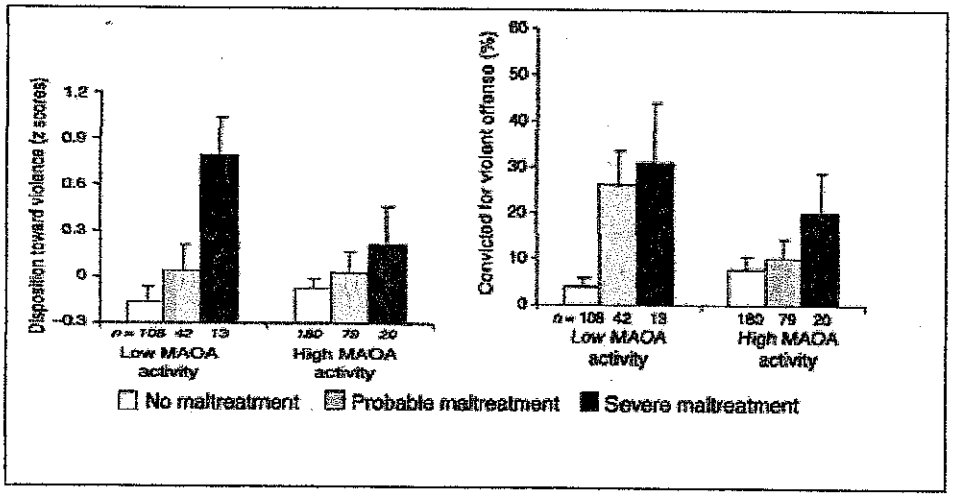


Coccaro et al., 2003

- **Are Effects of Environmental Factors Mediated by Bio-Genetic Factors?**

Probably!

- ***Interaction Between MAO-A Genotype and Violent Behavior in Male Children***



Caspi et al., 2002

- **Neuro-Biological Factors**

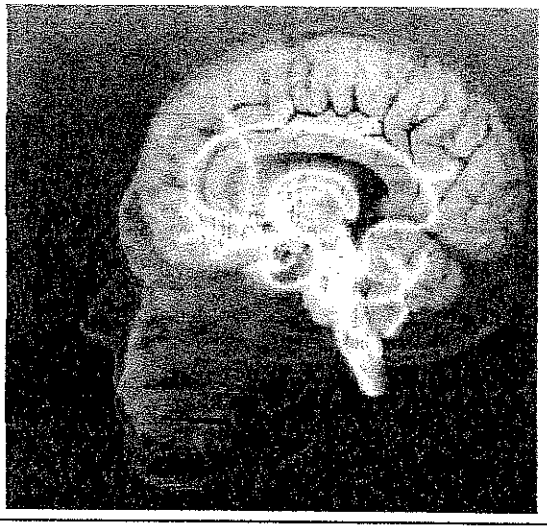
  Dysfunction of Central Serotonin

  Dysfunction of other Central Systems

  Social-Emotional Information Processing

- **Serotonin System**

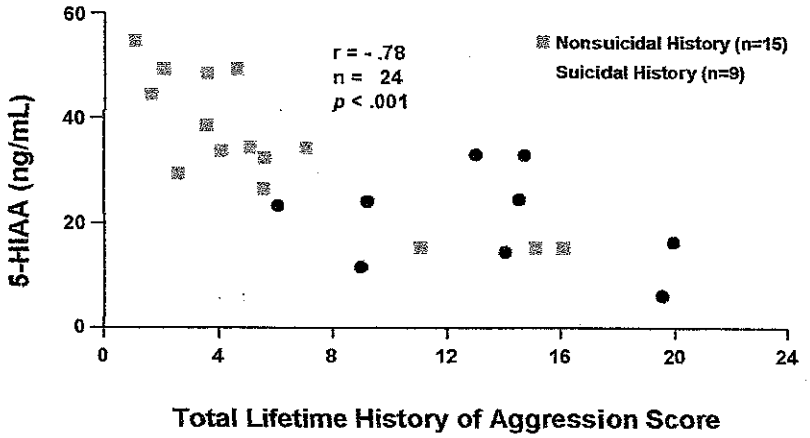
  Serotonergic neurons in the raphe nuclei project to diverse areas of the brain, including the cerebral cortex, hypothalamus, thalamus, basal ganglia, septum, and hippocampus



- **Impulsive Aggression as Example of Translational Research**

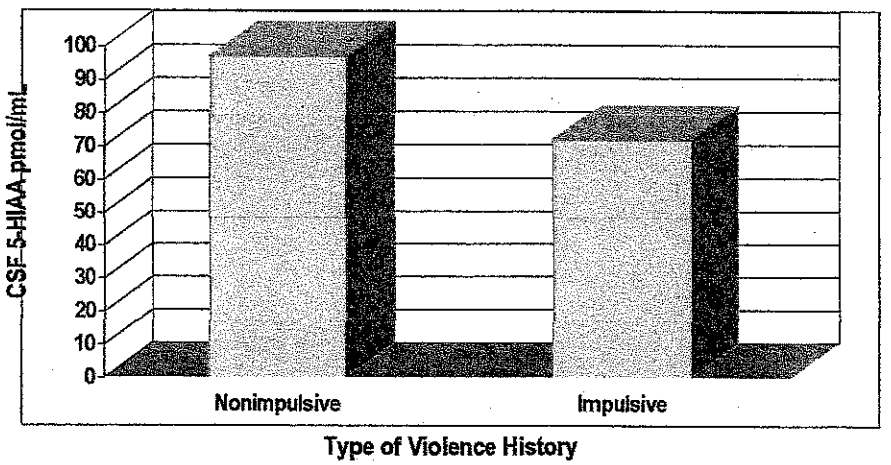
1970's.....
Animal studies reveal inverse relationship between brain serotonin (5-HT) levels and "aggressive responding"
(Low 5-HT → High Aggression)

- **Impulsive Aggression as Example of Translational Research**



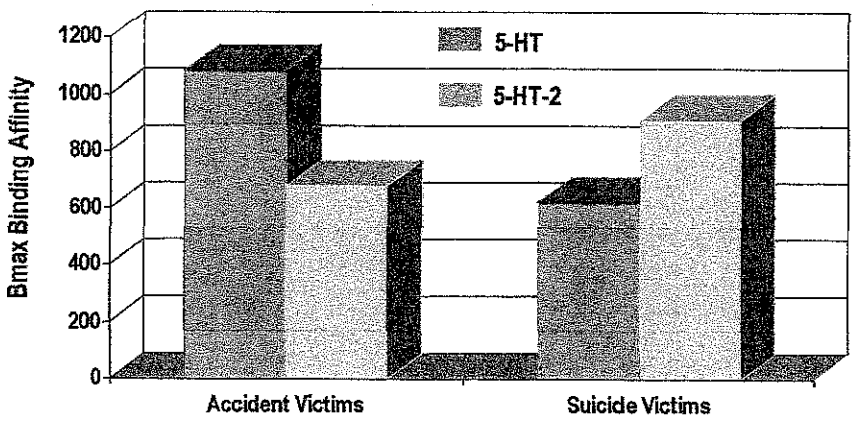
Brown et al., 1979

- **Impulsive Aggression as Example of Translational Research**



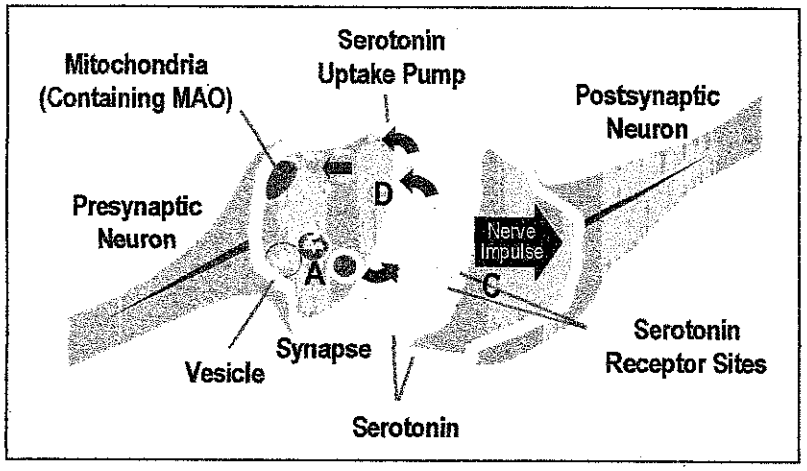
Linnoila et al, 1983

- **Frontal Cortex 5-HTT and 5-HT-2 Receptor Binding Sites in Suicide Victims vs. Accident Controls**

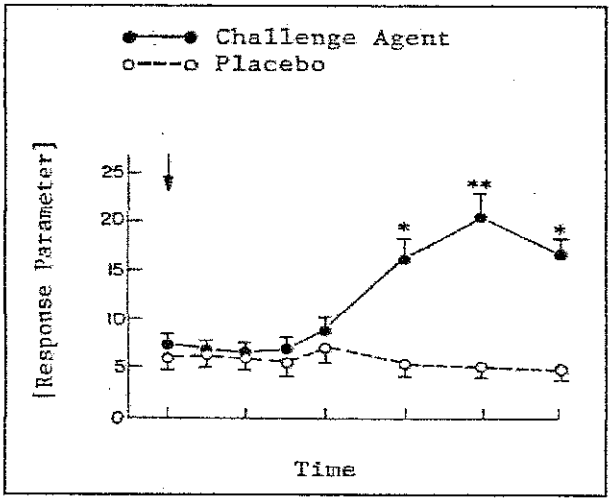


Stanley et al., Stanley & Mann 1982

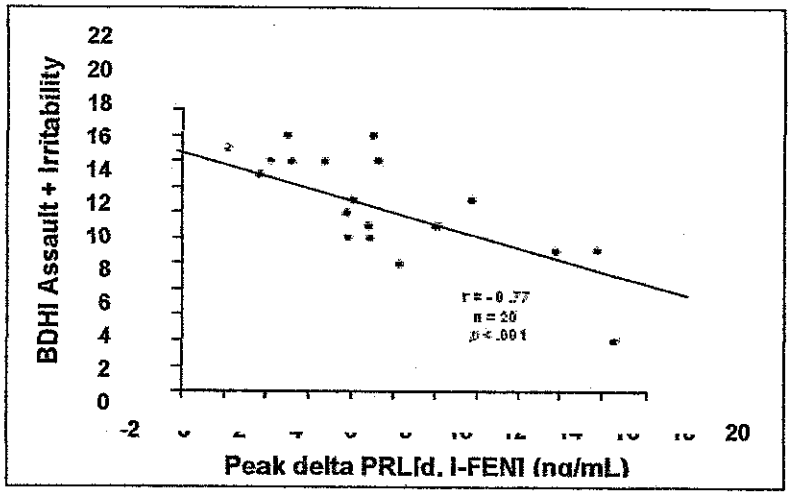
- **Serotonergic Neurotransmission**



- **The Neuropsychopharmocologic Challenge**

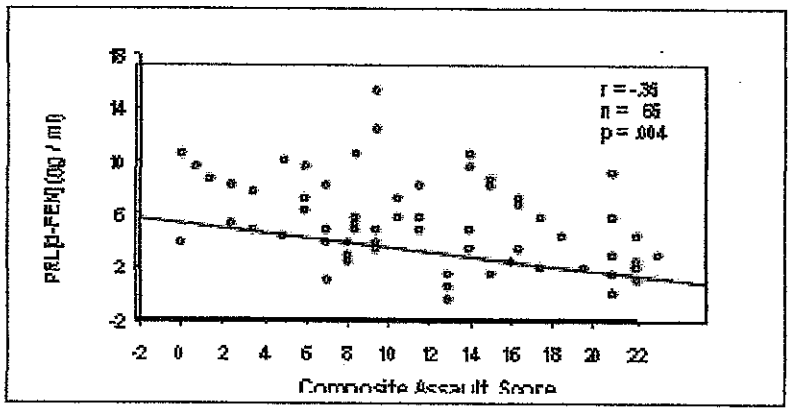


- **Peak Delta PRL[d,l-FEN] Correlates Inversely With Assault/Irritability in Male PD Subjects**



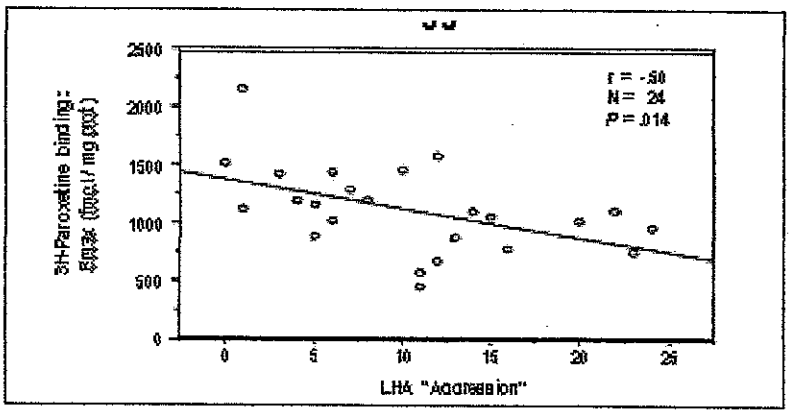
Coccaro et al., 1989

- **PRL[d-FEN] & Assault in Male PDs**



Coccaro, et al. 2003

- **Platelet 5-HT Transporter As a Function of Aggression**

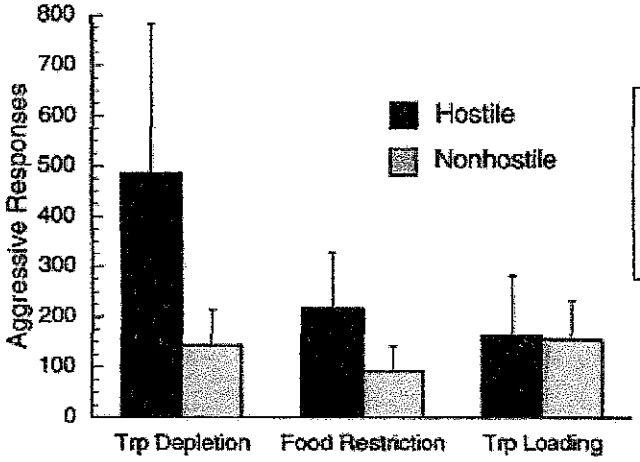


Coccaro, et al. 1996.

- **Serotonin & Aggression**

Low Serotonin = High Aggression

- **Acute Tryptophan Depletion Increases Aggressive *Responding but only in "Hostile" Subjects***



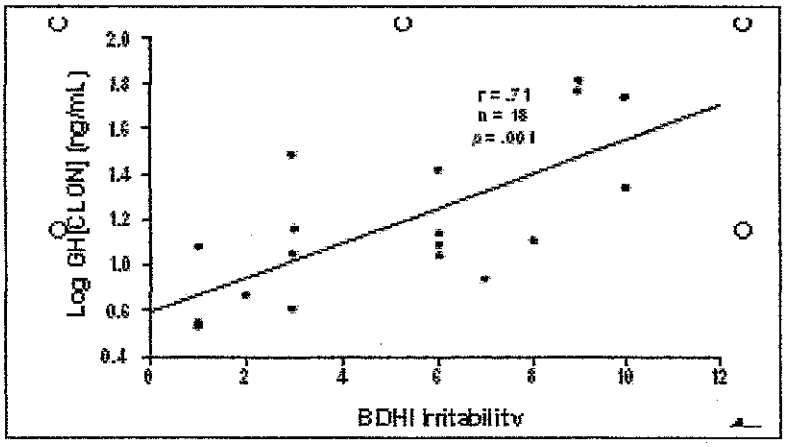
LHA Scores of Groups:	
Aggressive	= 21.0 ± 6.9
Non-Aggr.	= 12.0 ± 1.4

Dougherty et al., 1999

- **Other Neurotransmitter Dysfunction**

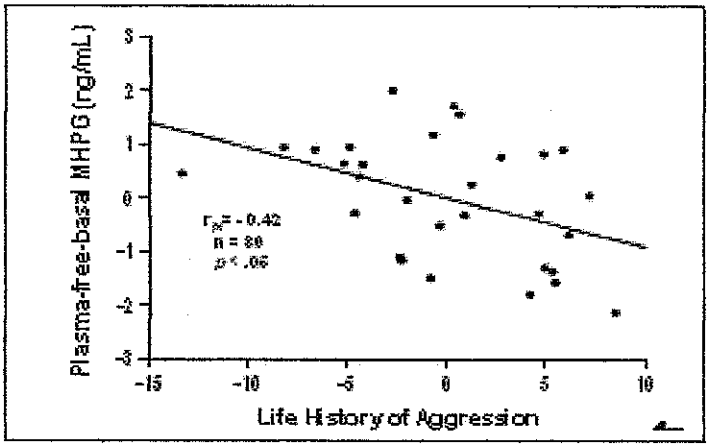
Catecholamines
Vasopressin
Oxytocin

- **GH[CLON] Response Correlates With Irritability in Male PD/NC Subjects**



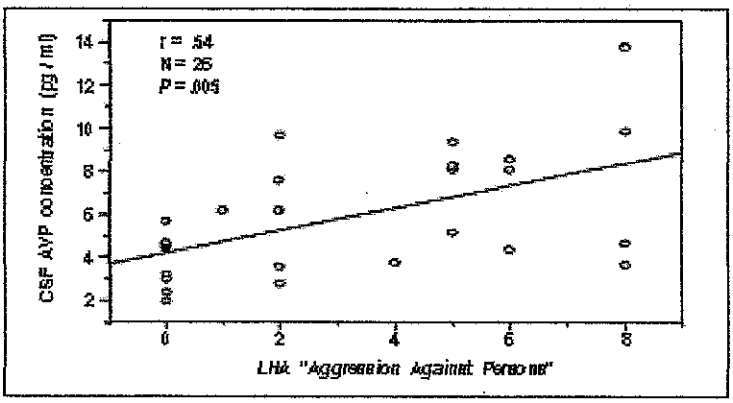
Coccaro et al. 1991

- **Free pMHPG Correlates Inversely With Life History of Aggression in Male PDs**



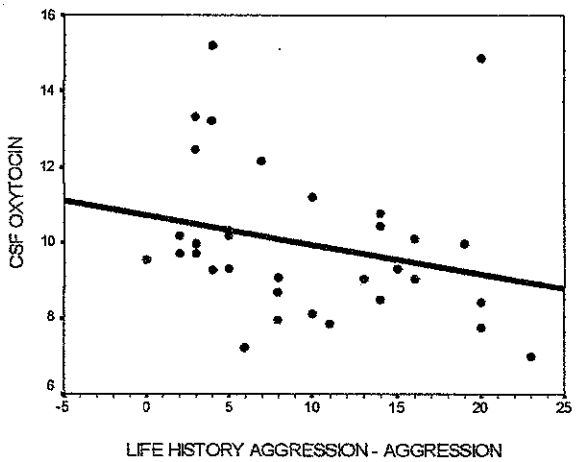
Coccaro et al. 2003

- **CSF Vasopressin & Aggression in PD**



Coccaro, et al. 1998.

- **CSF Oxytocin & Aggression in PD**

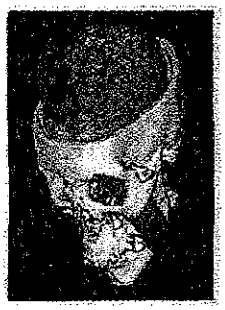


Coccaro et al., In Preparation

- **OTHER NEUROMODULATOR DYSFUNCTION**

Testosterone
ACTH
Cholesterol
Fatty Acids

- **Where in the Brain Are the Abnormalities?**



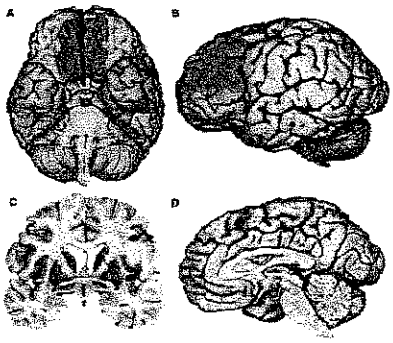
The Case of Phineas Gage

"Normal" Personality until tamping iron bore through skull and brain. Physically recovered but later became irreverent & impulsive with poor display of judgment.

Reconstuction of "lesion" from examination of skull suggests damage to Ventro-Medial and Orbito- Pre-Frontal Cortex.

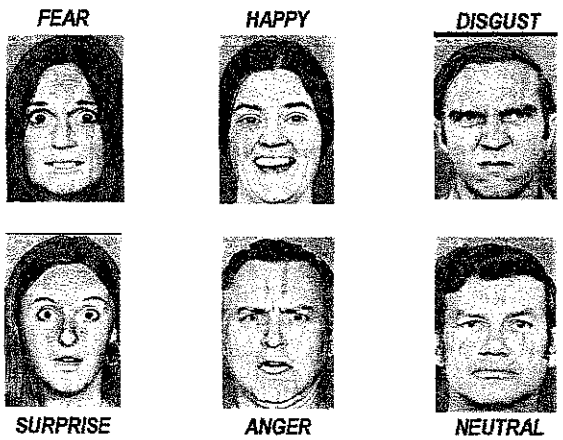
Damasio et al., 1994

- **Areas Relevant to Emotional Regulation / Impulsive Aggression**



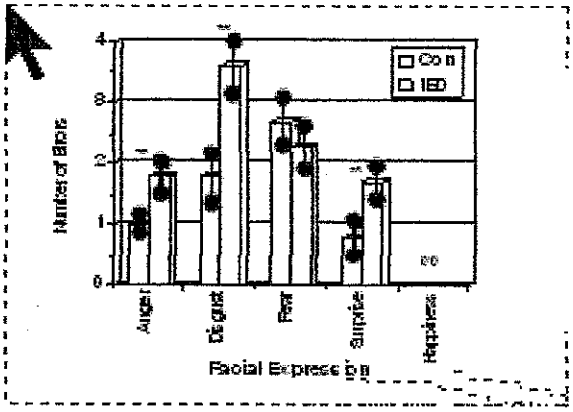
Green = Orbital PFC
Red = Ventromedial PFC
Blue = Dorsolateral PFC

Orange = Amygdala
Yellow = Anterior Cingulate

- 

- **Test of Facial Expressions**

Number of Errors Made by Each Group for 5 Facial Expressions

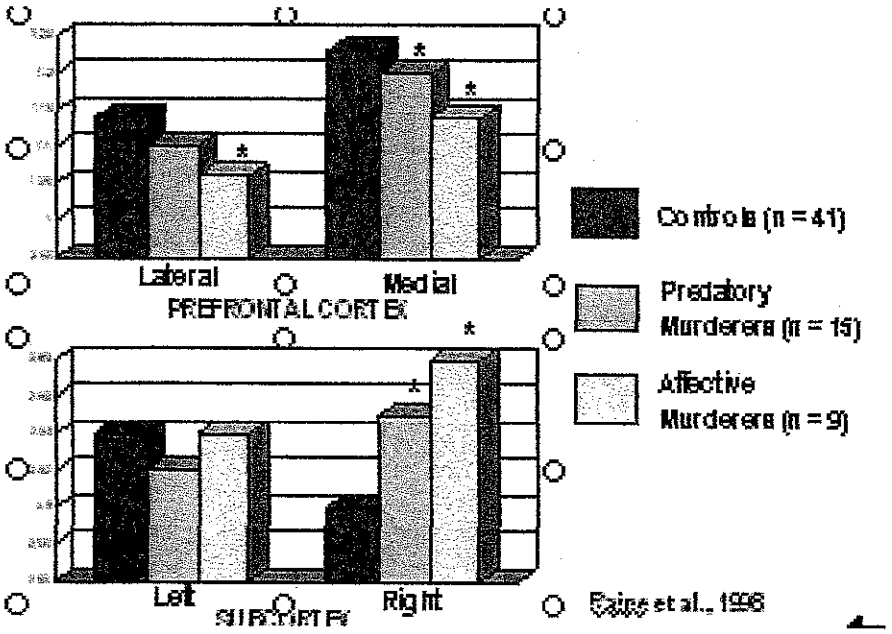


- IED subjects made significantly more errors for anger, disgust and surprise

- **Where in the Brain are the Abnormalities?**

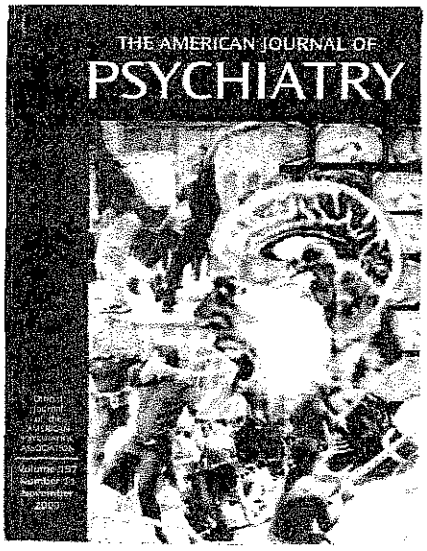
Functional Imaging:
PET Studies

- **FDG-PET in Controls and Predatory & Affective Murderers**



Raine et al., 1998

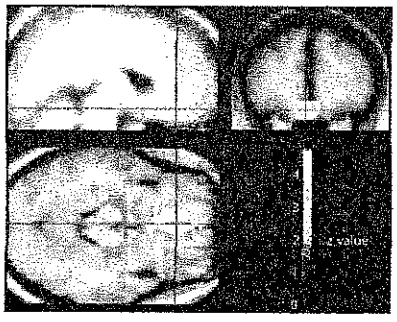
➢



PET Study of Aggressive Imagery in Normal Subjects

Pietrini et al., 2000

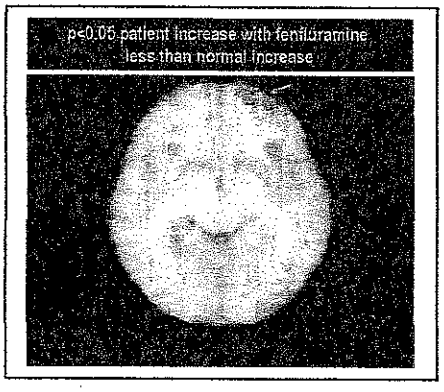
➢ **Decreases in rCBF in Response to an Imagined Scenario Involving Unrestrained Aggression Compared With an Imagined Scenario Involving Emotionally Neutral Behavior in 15 Healthy Subjects**



Peak *deactivation* in left medial frontal gyrus (Brodmann's Area 11)

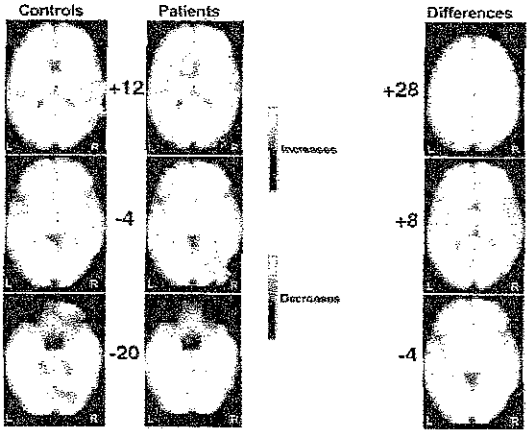
Pietrini et al., 2000

➢ **FDG Pet in Patients with IED/BPD (N = 6) vs. NC (N = 6)**



Siever et al, 1999

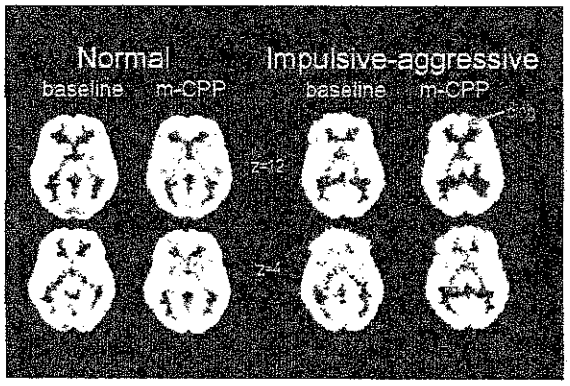
- **FDG (d,l-FEN) PET in BPD and CONTROL SUBJECTS**

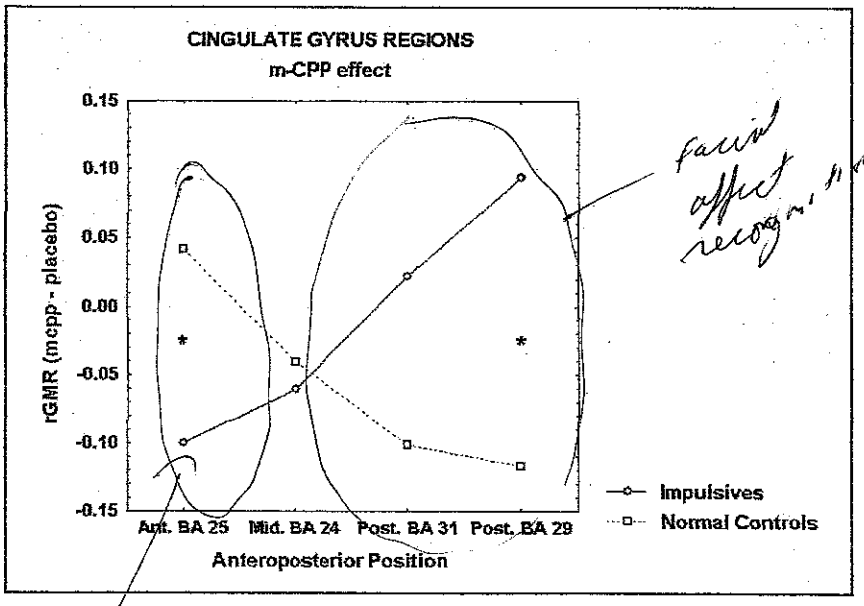


FDG Uptake
BPD < Controls

1. Medial/Orbital Right PFC
2. Left Middle/Superior Temproal Gyri
3. Left Parietal Lobe
4. Left Caudate Body

Soloff et al., 2000

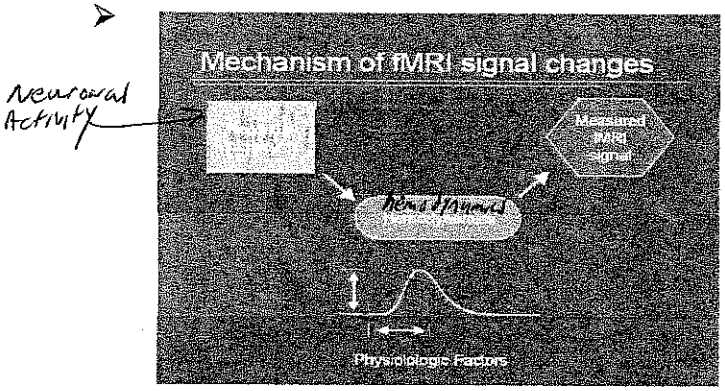
- 

- 

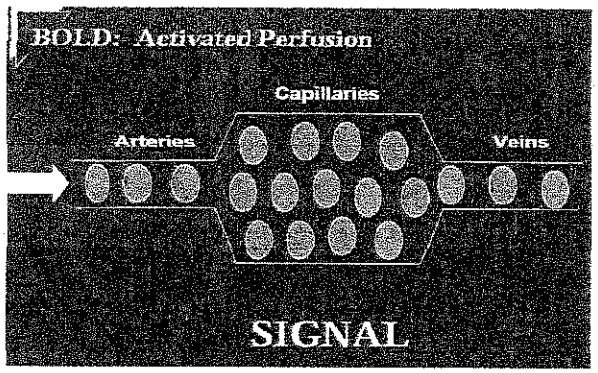
- **Where in the Brain are the Abnormalities?**

  Functional Imaging:

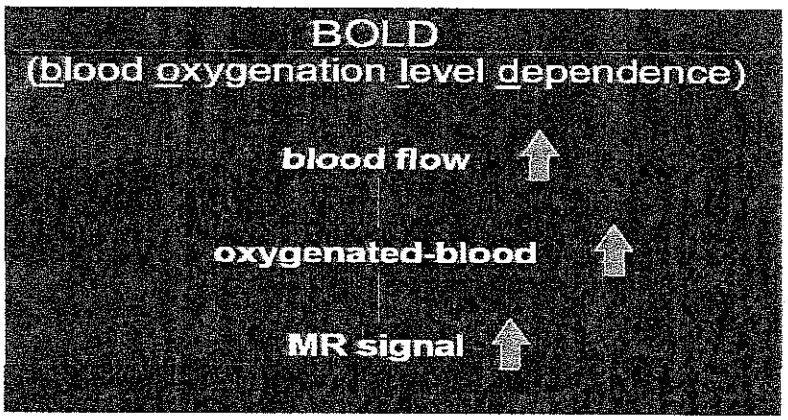
  fMRI Studies

- 

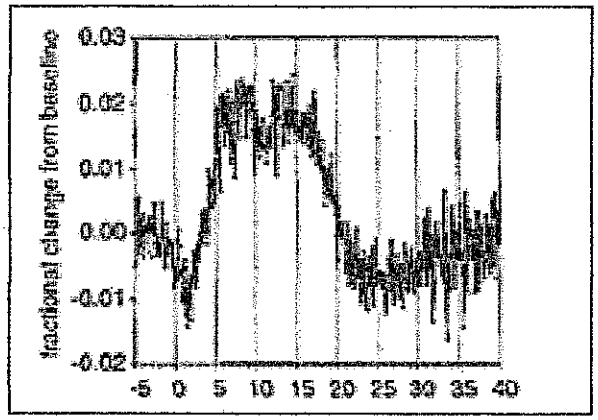
- **The BOLD Signal**



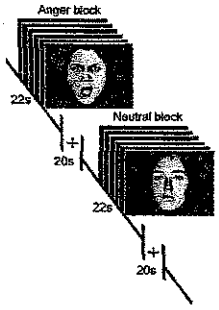
- **The BOLD Signal**



- **BOLD: Information in Time Evolution?**



- **Cortico-Limbic Responses to Harsh Faces in IED Subjects**



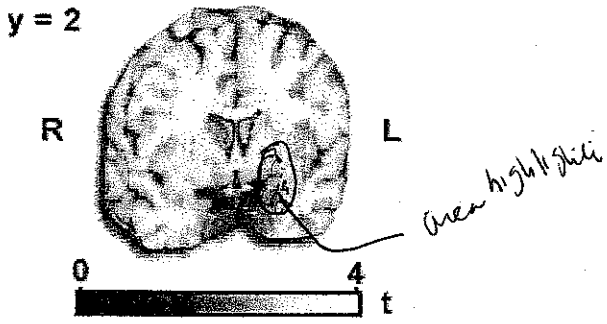
- 5 minute runs
- 6 runs per scan
- expression order counter- balanced across runs

Subjects: 10 patients with IED, 10 healthy controls.
Imaging: BOLD-sensitive whole-brain fMRI at 3T (reverse spiral, 2s TR, 25ms TE)
Paradigm:

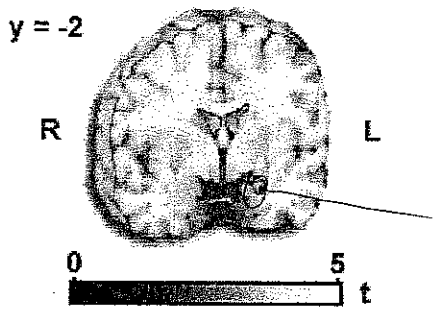
- Block design using the Ekman and Friesen Pictures of Facial Affect.
- Blocks each contained one expression type (*Anger, Fear, Disgust, Happy, Sad, Surprise, Neutral*), a crosshair was used as baseline.
- Subjects were asked to identify gender only.

Analysis: Preprocessing and general linear model applied using SPM2, standard 2-sample t-test (random effects) used to look at differences between groups.

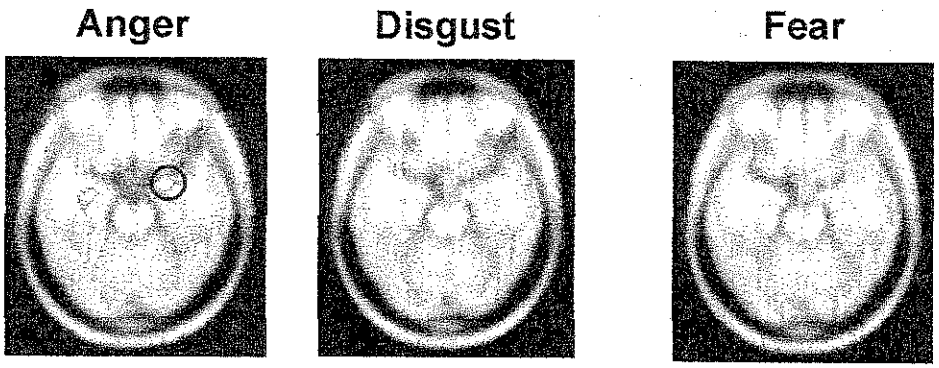
- **Amygdala Activation to Harsh (Anger, Disgust, Fear) vs. Rest: Greater in IED than Healthy Volunteers**



- **Amygdala Activation to Anger vs. Rest: Greater in IED than Healthy Volunteers**

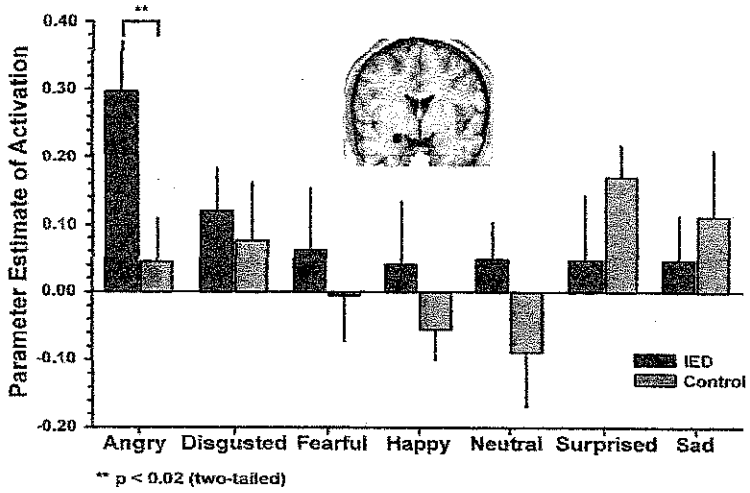


- **Amygdala Overactivation to Harsh Faces Driven by Response to "Anger" Faces in IED Individuals**

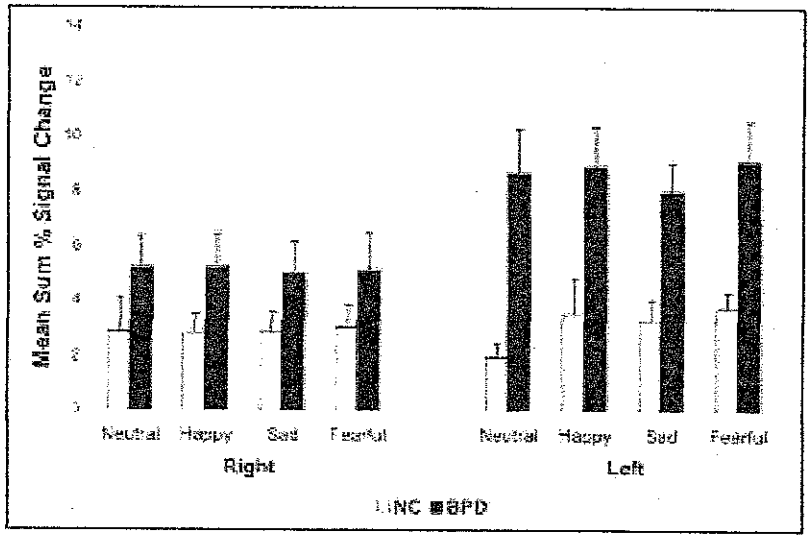


Coccaro, McCloskey, Phan et al., 2005

- **Parameter Extracts of Emotion vs. Baseline (Spherical ROI Centered on Left Amygdala)**

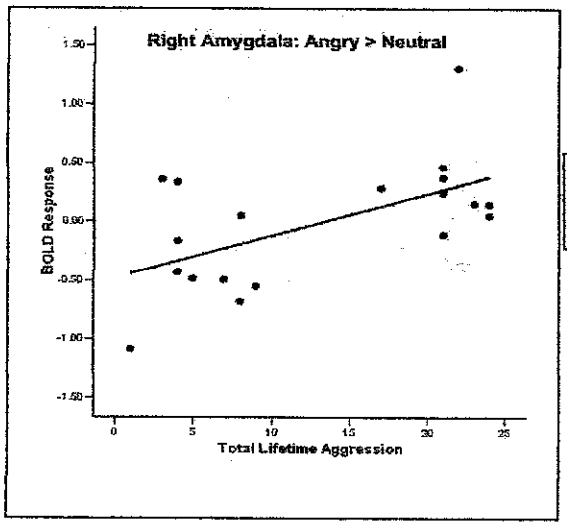


- **Amygdala Response to Emotional Faces: BPD vs. NC**



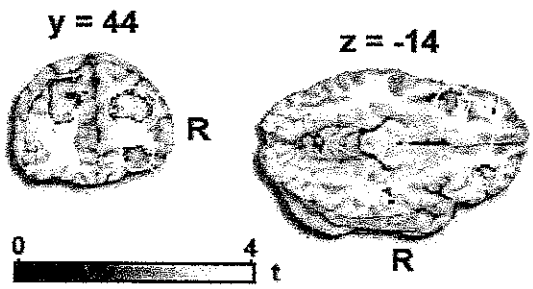
Donegan et al., 2004

- **Correlation Between LHA Aggression and Right Amygdala Responses to Anger Faces**

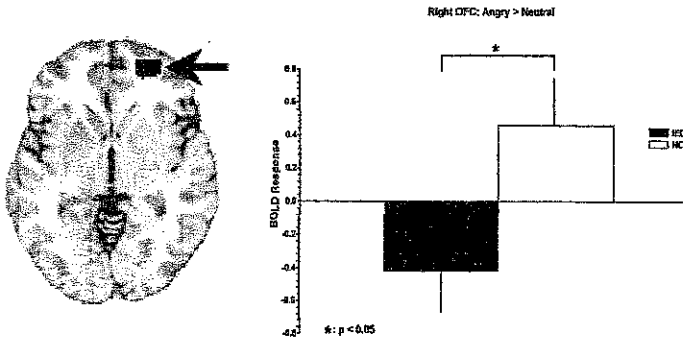


r = 0.59
p = 0.006

- **OFC/DLPFC Activation to Harsh (Anger, Disgust, Fear) vs. Rest: Greater in Healthy Volunteers than IED**

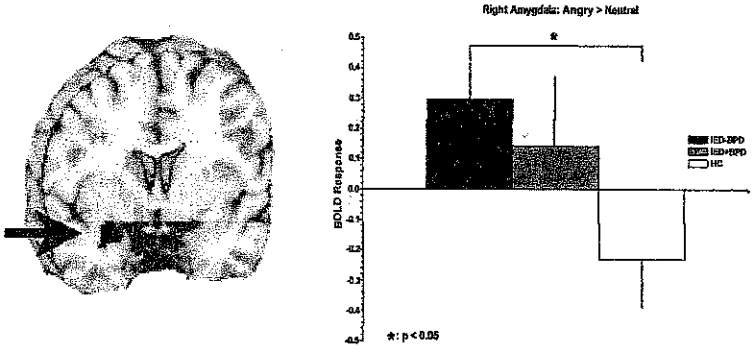


- **Activity of OMPFC in IED vs. Controls**
  BOLD Responses to Anger Faces (Implicit EIP)



Foci from whole-brain analysis (see arrows) and extracted BOLD response of OMPFC hypo-activity in IED (black bars) compared to HC (white bars) subjects

- **Activity of Amygdala in IED vs. Controls**
  BOLD Responses to Anger Faces (Explicit EIP)



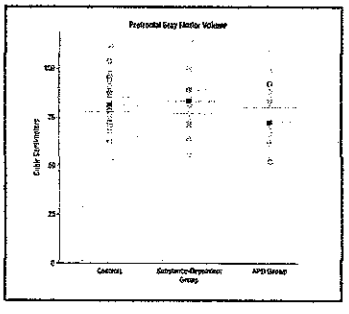
Foci from whole-brain analysis (see arrow, left panel) and extracted BOLD response of right amygdala hyper-activity in IED-BPD (black bars, right panel) compared to HC (white bars) subjects; IED+BPD (gray bars).

- **Where in the Brain are the Abnormalities?**

  Structural Imaging:

  Volumetric Studies

- **Prefrontal Gray Matter Reduced in AsPD Subjects**



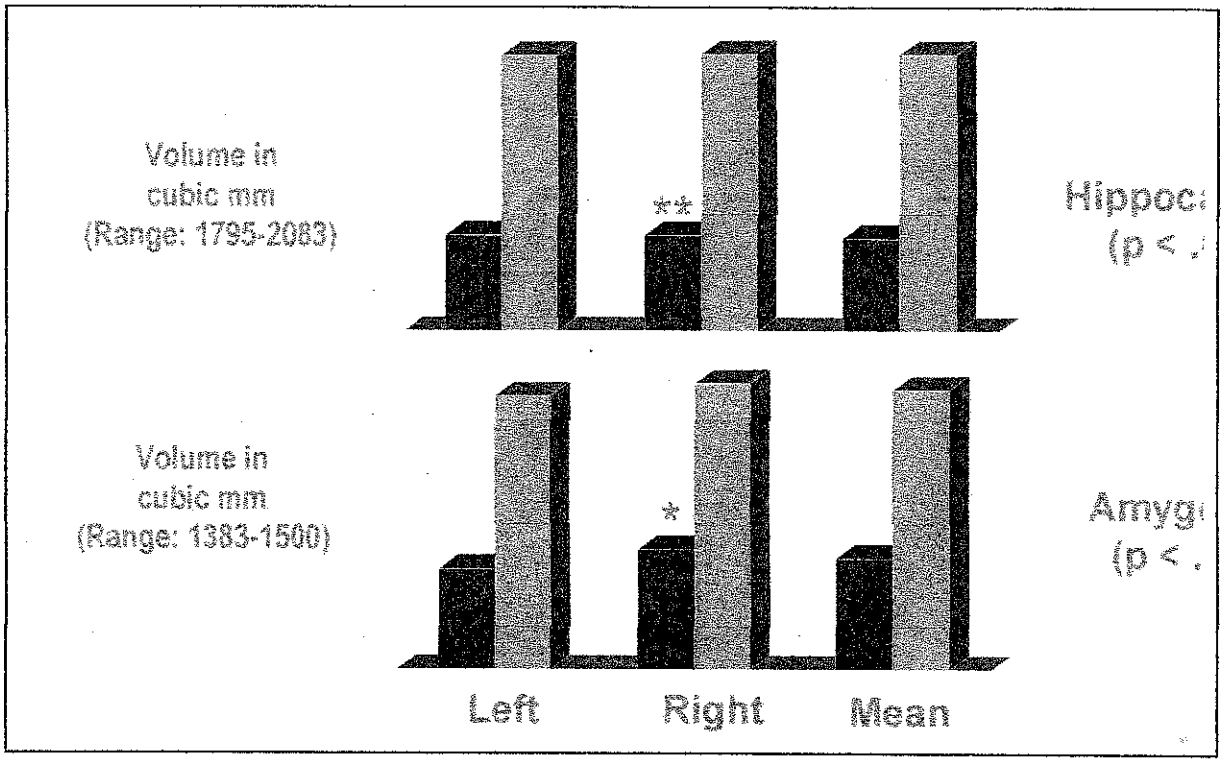
Raine et al., 2000

- **Where in the Brain are the Abnormalities?**

  Structural Imaging:

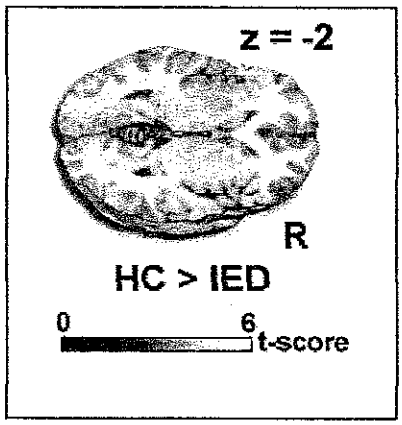
  VBM Studies

- **BPD Females: Lower Volume in Hippocampus & Amygdala**



Drissen et al., 2000

- **Voxel-Based Morphometry (VBM) in IED**



HC (n=40) vs. IED (n=40), Unmedicated

Reduced medial OFC grey matter concentration (max foci at [7, 46, -2], cluster = 189 voxels, $t = 4.63$, $Z = 4.34$). No significant differences in amygdala grey matter concentration.

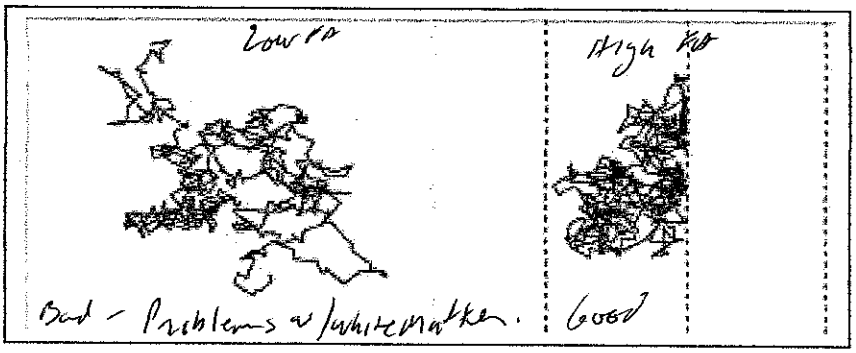
Optimized VBM procedure (Good et al., 2001): 1) whole-brain map shown at $p < 0.0001$ uncorrected at voxel-level ($t > 3.90$), $p < 0.05$ corrected at cluster level (cluster > 20 voxels); 2) group differences after accounting for global brain volume

- **Where in the Brain are the Abnormalities?**

  Structural Imaging:

  DTI Studies

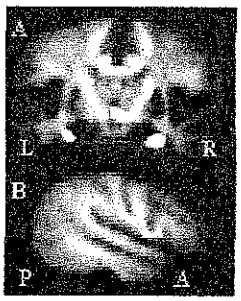
- **Diffusion Tensor Imaging: Anisotropy**



Free Diffusion of Water
Low Anisotropy

Constrained iffusion of Water
High Anisotropy

- **Reduced FA Values in White Matter in Brains of IED vs. Controls**



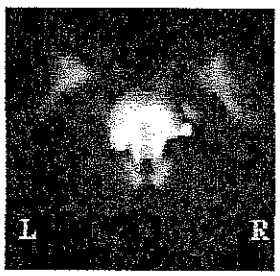
Reduced FA in WM:

A. Adjacent to Amygdala (Bilaterally)

B. Superior Longitudinal Fasciculus (Bilaterally)

Coccaro, Phan, Arfanakis et al., 2006)

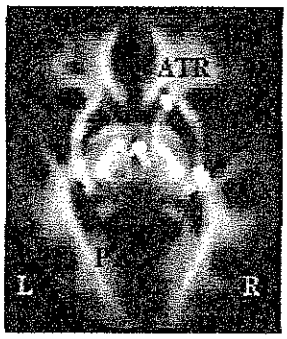
- **Reduced FA Values in White Matter in Brains of IED vs. Controls**



Reduced FA in WM in Brain Stem.

(Coccaro, Phan, Arfanakis et al., 2006)

- **Reduced FA Values in White Matter in Brains of IED vs. Controls**

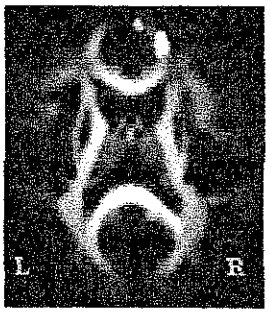


Reduced FA in WM in:

- Bilateral Posterior Thalamic Radiations (PTR)
- Right Anterior Thalamic Radiations (ATR)

(Coccaro, Phan, Arfanakis et al., 2006)

- **Reduced FA Values in White Matter in Brains of IED vs. Controls**

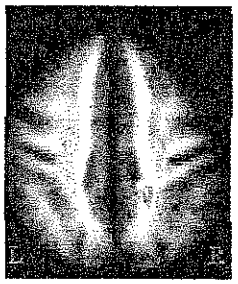


Reduced FA in WM in:

Forceps Minor where ATR, U-fibers that connect left and right frontal lobes, and Cortico-Pontine fibers are located.

(Coccaro, Phan, Arfanakis et al., 2006)

- **Reduced FA Values in White Matter in Brains of IED vs. Controls**

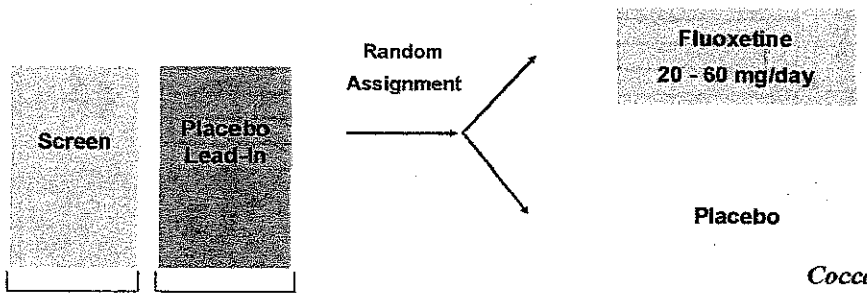


Reduced FA in WM in:

Posterior Cingulate Gyrus which includes PTR, Cortico-Pontine fibers, and fibers of Corpus Callosum connecting left and right Posterior Cingulate Gyri

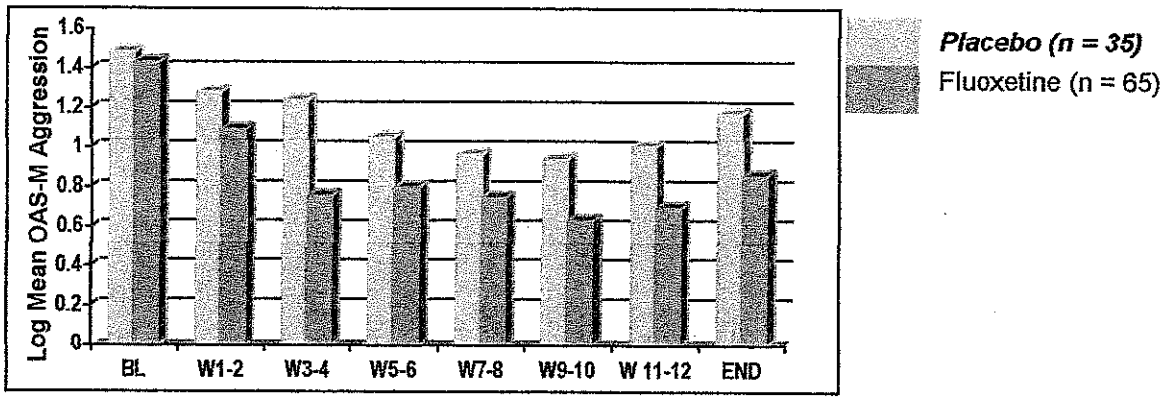
(Coccaro, Phan, Arfanakis et al., 2006)

- **Treatment Studies**
- **Fluoxetine Treatment of IED Flexible-Dose Study**



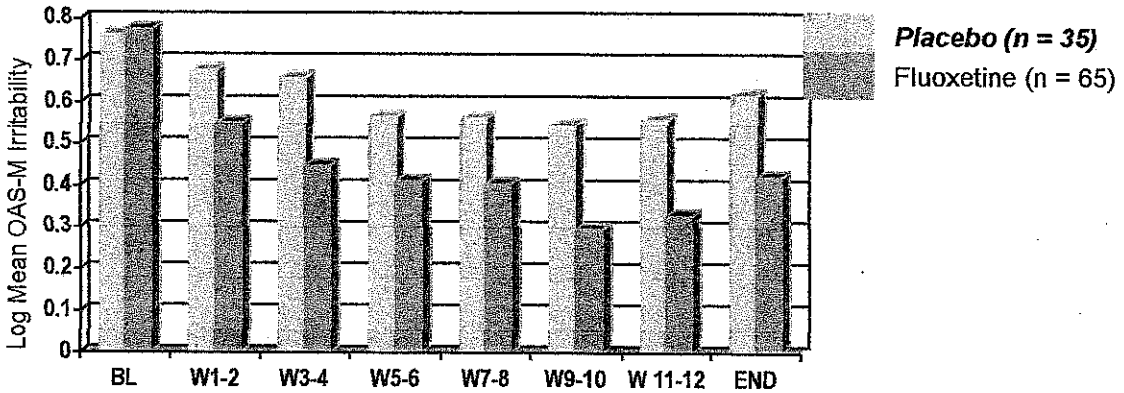
Coccaro & Kavoussi, 1997

- **Fluoxetine vs. Placebo in IED: OAS-M Aggression Scores**



+ p < .10; * p < .05, **, p < .01 *Coccaro, et al. 2006*

- **Fluoxetine vs. Placebo in IED: OAS-M Irritability Scores**

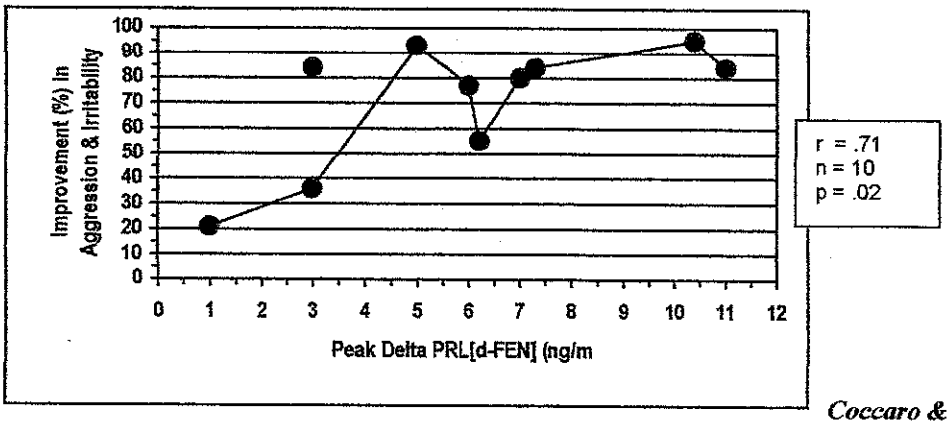


**p <.05; **p <.01, ***, p <.001* *Coccaro, et al. 2006*

- **Fluoxetine Treatment of IED**

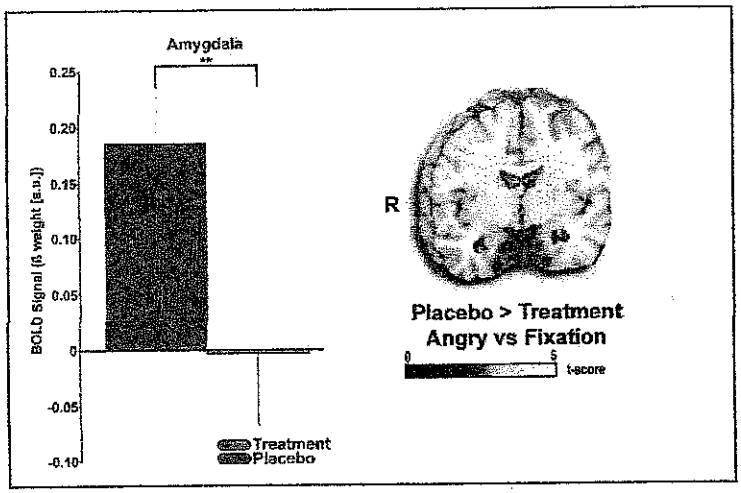
  For SSRIs to work may require relatively intact central 5-HT receptor function

- **PRL[d-FEN] and Anti-Aggressive Response to Fluoxetine**

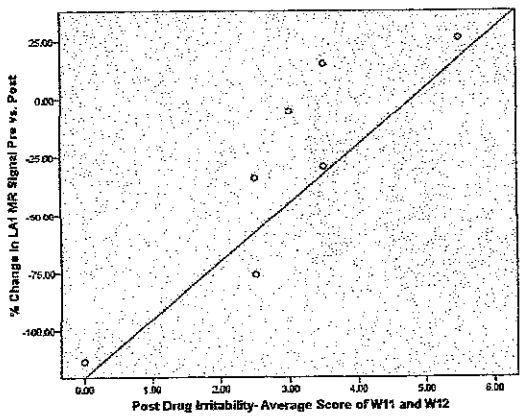


Coccaro & Kavoussi, 1997

- **Effect of Pharma Rx on Amygdala BOLD Responses To Anger Faces in IED**



- **Reduction in BOLD Response to Anger Faces in Amygdala Correlates with Post-Rx OAS-M Irritability**



- **Collaborators**

CNPRU (Chicago): Royce Lee, M.D., K. Luan Phan, M.D., Michael McCloskey, Ph.D., Kristen Jacobson, Ph.D. Konstantinos Arfanakis, Ph.D.

CNSRU (Philadelphia): Richard Kavoussi, M.D., Scott Bunce, Ph.D.

New York: Larry Siever, M.D., Antonia New, M.D.

Other Outside Collaborators: Richard Hauger, M.D., John Csernansky, M.D., Craig Ferris, Ph.D., Luke Van de Kar, Ph.D., C.S. Bergeman, Ph.D., Gerald Nestadt, M.D., Nicki Crick, Ph.D., Tom Cooper, M.A.