MANIPAL
ACADEMY of HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

DY Patil PG Lecture Series
Date: Nov 7, 2024

Pharmacotherapy of Borderline Personality Disorder

Dr. Samir Kumar Praharaj, DPM, MD

KMC Manipal

Disclosure & Acknowledgment

- None to declare

- Thank Dr Rashmin Cholera
- Not an expert in BPD!

Objective

1. Variations in clinical presentations
2. Neurobiological understanding of symptom clusters
3. Pharmacotherapy of symptom clusters

This presentation **does not cover concepts, etiological models, crisis intervention, psychotherapies**

National Library of Medicine
National Center for Biotechnology Information

Log in

PubMed®

"borderline personality disorder"

Search

Advanced Create alert Create RSS

User Guide

Save Email Send to

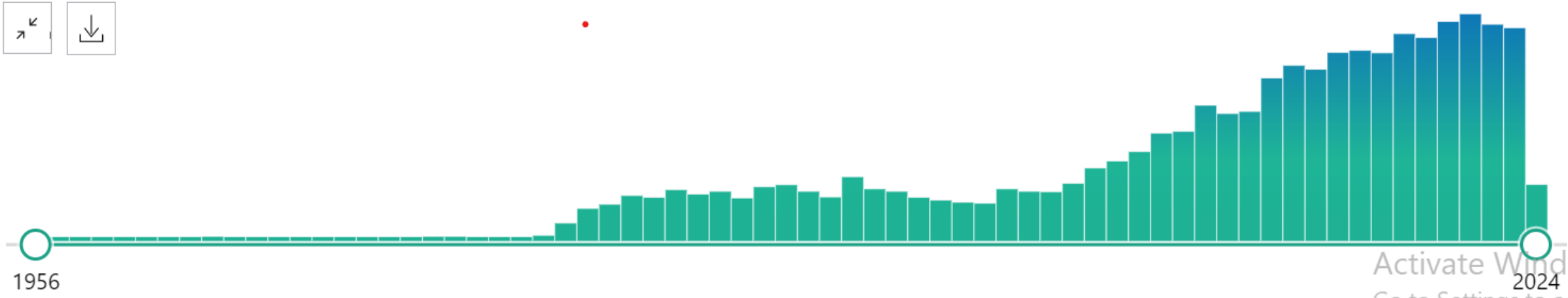
Sort by: Most recent

Display options

RESULTS BY YEAR

10,494 results

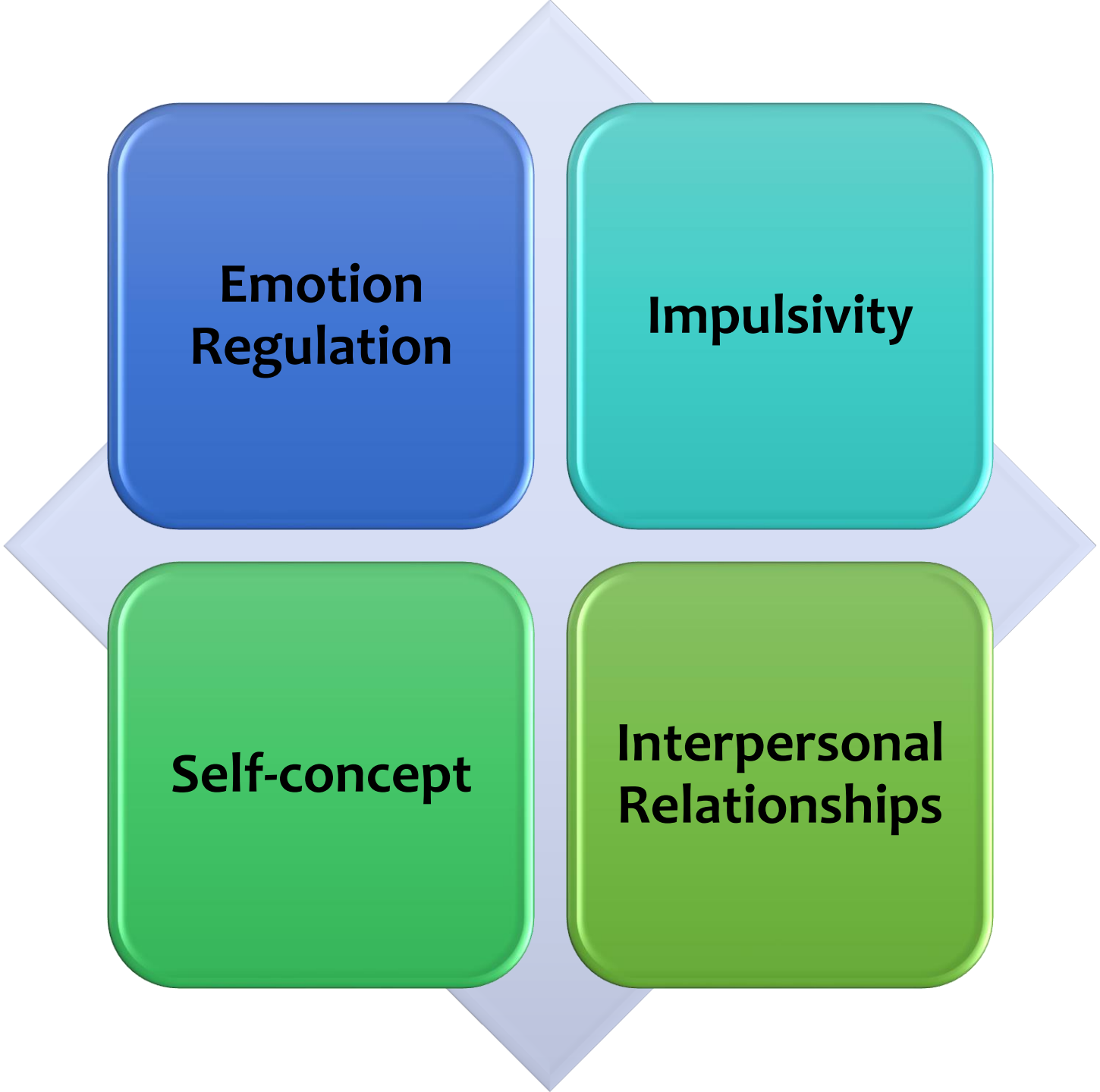
Page 1 of 1,050



Borderline symptoms

Fear of **abandonment** (real or imagined)
Unstable **interpersonal relationships** (idealization and devaluation)
Identity disturbance (unstable self-image or sense of self)
High **risk behaviors** (sexual, driving, substance use, binge eating)
Self-harm (suicide attempts, self-mutilation)
Emotional instability (dysphoria)
Chronic feelings of **emptiness**
Difficulty controlling **anger** (shouting, breaking things, physical fights)
Transient **dissociative symptoms**

BPD Core features



Atypical presentations

- Persistent depressive symptoms
- Prominent dissociative symptoms
- Somatic symptom disorder
- Erratic patterns of substance use, polysubstance
- Persistent psychotic-like symptoms
- Less impulsivity and suicidality in older individuals, more depression and chronic emptiness

Cultural differences

- Less impulsivity in some cultures
- Self-poisoning more in eastern countries (minor self-harm behaviors less well studied)
- Taboo of sexual behavior
- Availability of illicit substances

Genetic

- Family, twin, adoption studies - BPD traits are heritable
- Candidate-gene association studies
  - Serotonergic, dopaminergic, noradrenergic systems
  - BDNF, Vasopressin receptor 1A, Sodium channel (voltage-gated, type IX, alpha subunit)
- Gene based analysis
  - Dihydropyrimidine dehydrogenase (DPYD) on chromosome 1
  - Plakophilin-4 (PKP4) on chromosome 2
  - Serine incorporator 5 (SERINC5) gene on chromosome 9

- Overlap with schizophrenia, BD, MDD, smaller sample

Epigenetic changes

- Increased methylation of glucocorticoid receptor gene (NR3C1)
- Increased methylation of BDNF gene
- Reduced expression of oxytocin receptor gene (OXTR)

- Correlates with **adverse childhood experiences (ACEs)**
- **Intergenerational transmission** (**epigenetic trail of negative experiences**)

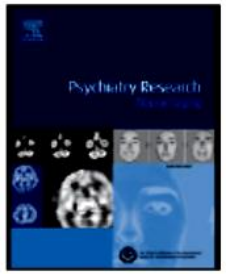
Structural brain changes

Psychiatry Research: Neuroimaging 201 (2012) 245–252

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

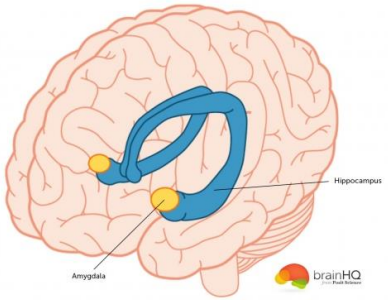
journal homepage: www.elsevier.com/locate/psychresns



Review article

Amygdala and hippocampal volume reductions as candidate endophenotypes for borderline personality disorder: A meta-analysis of magnetic resonance imaging studies

Anthony C. Ruocco [a,b,*], Sathya Amirthavasagam [a], Konstantine K. Zakzanis [a]



Volume reductions bilaterally in the amygdala (13%) and hippocampus (11%) (Cohen's *d* moderate)

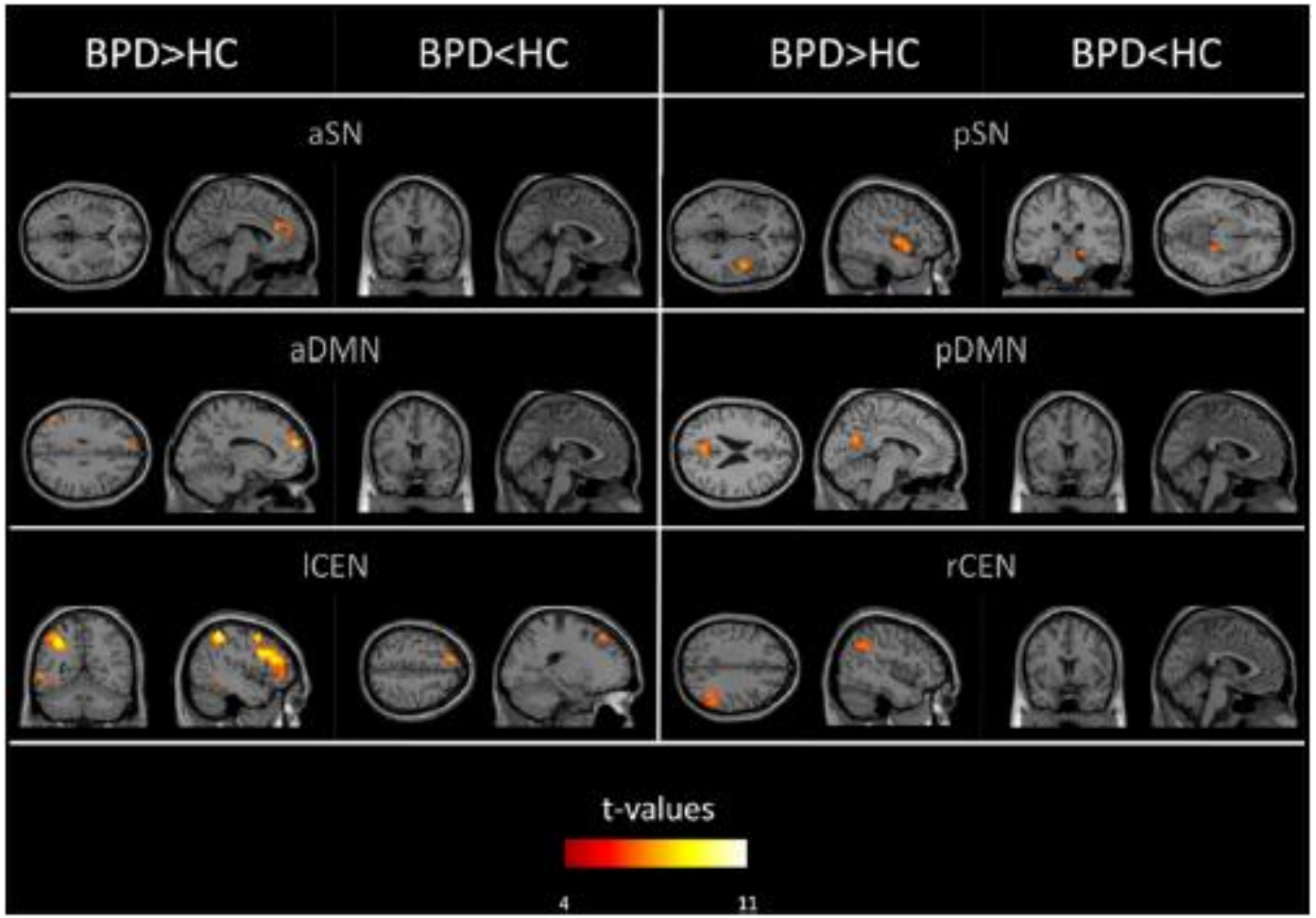
Volumetric MR Imaging Summary

- **Smaller volumes** of the **frontal lobes**
- Smaller **amygdala, hippocampus**, and frontal cortex volumes
- More gray matter volume in the **right basolateral nucleus of the amygdala**
- Less gray matter in the **cingulate cortex** and **medial PFC**
- Lower volumes in the **orbitofrontal cortex** and **ventromedial PFC**
- Smaller **parietal cortex** (including **precuneus**)

- **Greater volume** in the **right supplementary motor area**, **right cerebellum** (lobules IV/V), and **right middle frontal gyrus**, including **dorsolateral PFC**

Ruocco & Carcone 2016

Abnormal **Intrinsic Connectivity Networks** at Resting State

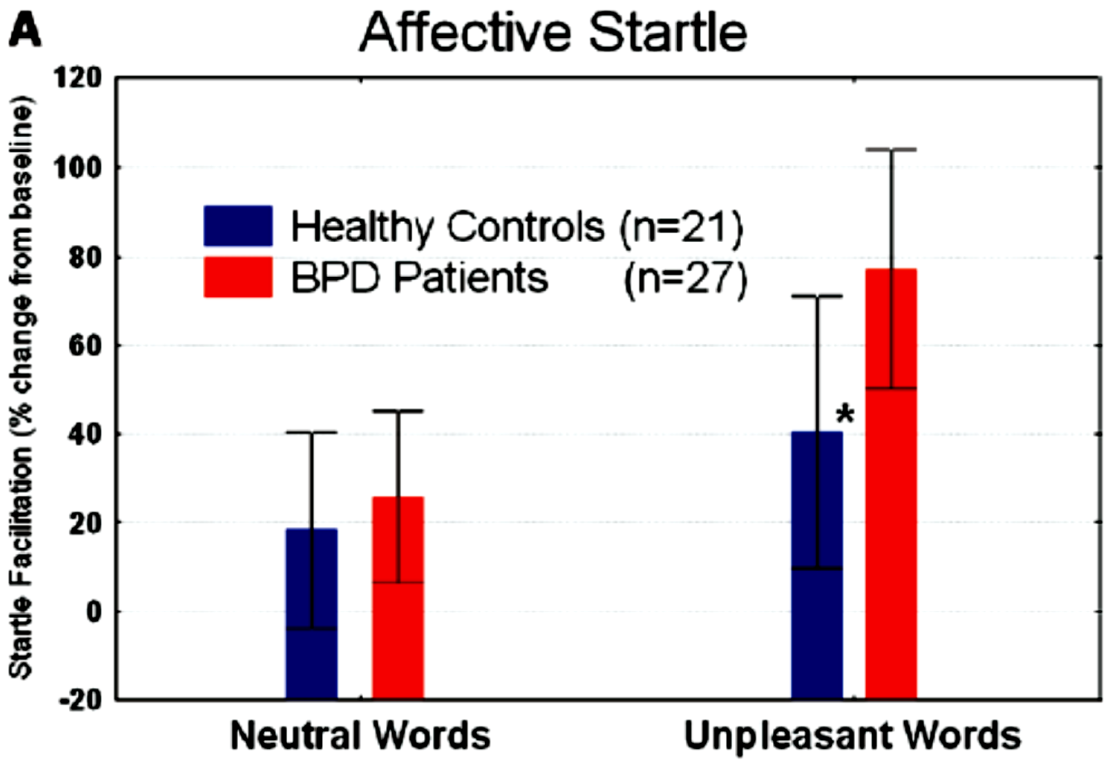


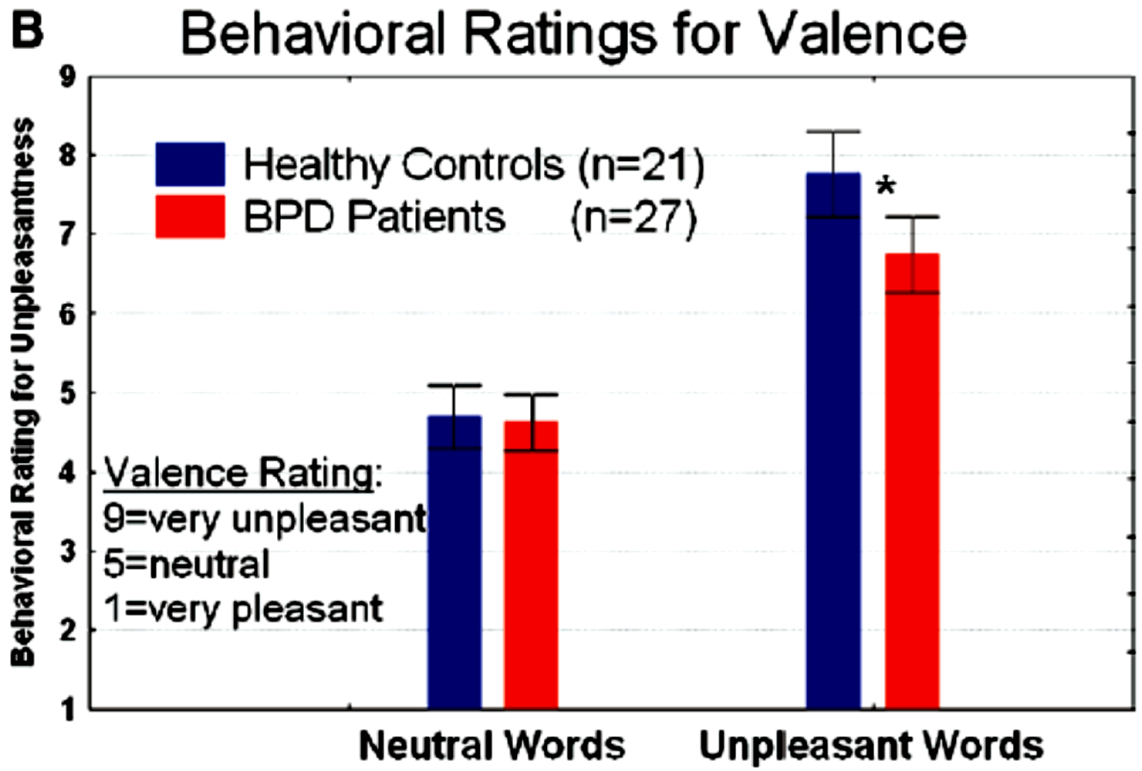
- **Salience Network**
- **Default Mode Network**
- **Central Executive Network**
- Increased iFC in frontal, parietal cingulate cortices, PFC, parietal lobe, insula
- Decreased iFC in rt hippocampus, lt DLPFC

Doll et al. Front Hum Neurosci 2013

Emotion Processing and Emotion Regulation

Hyperresponsive to **unpleasant** emotional probes

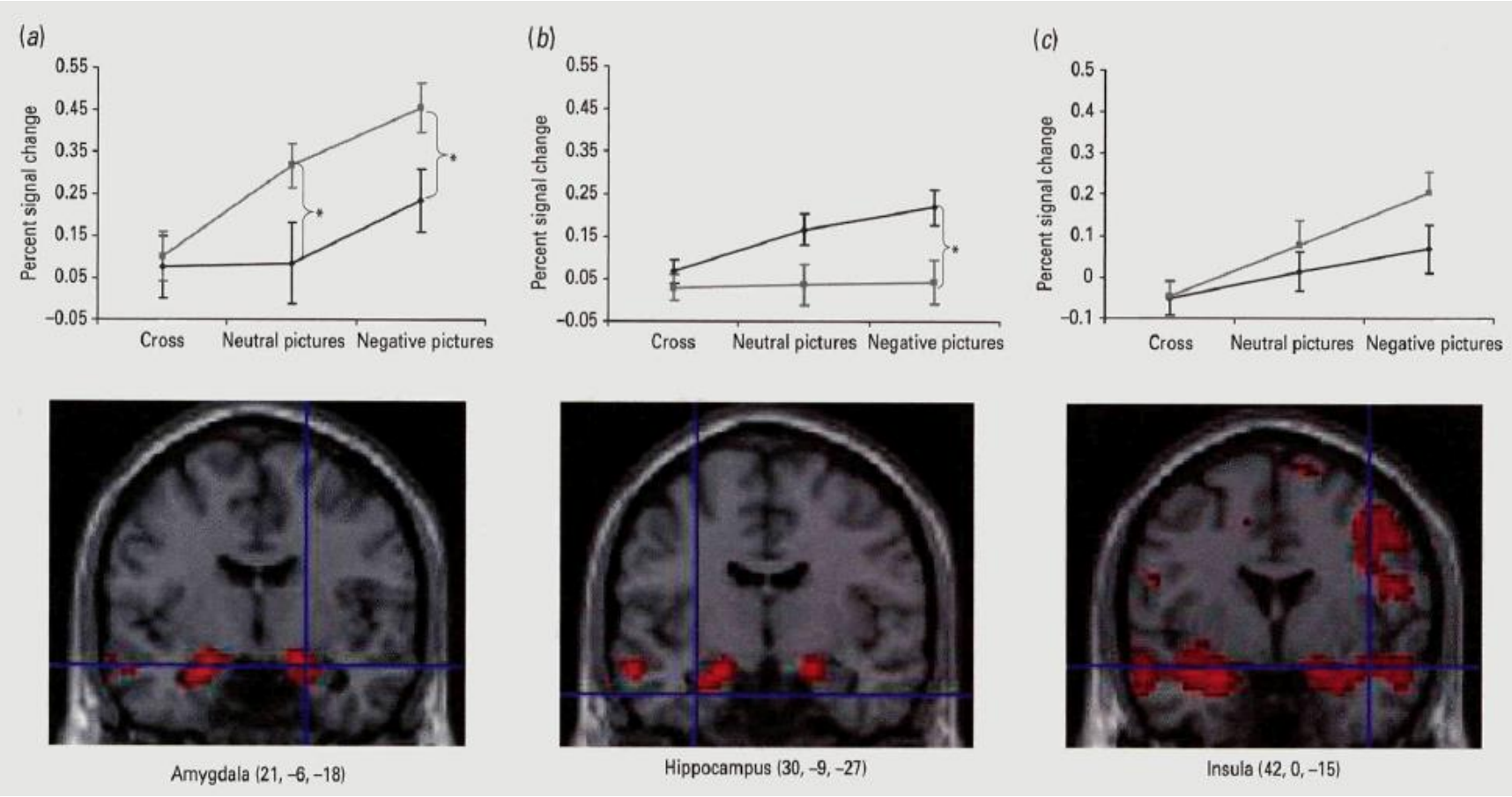




BPD subjects rated unpleasant words as **less unpleasant**

Hazlett et al. Biol Psychiatry 2007

Activation of amygdala to negative emotional stimuli

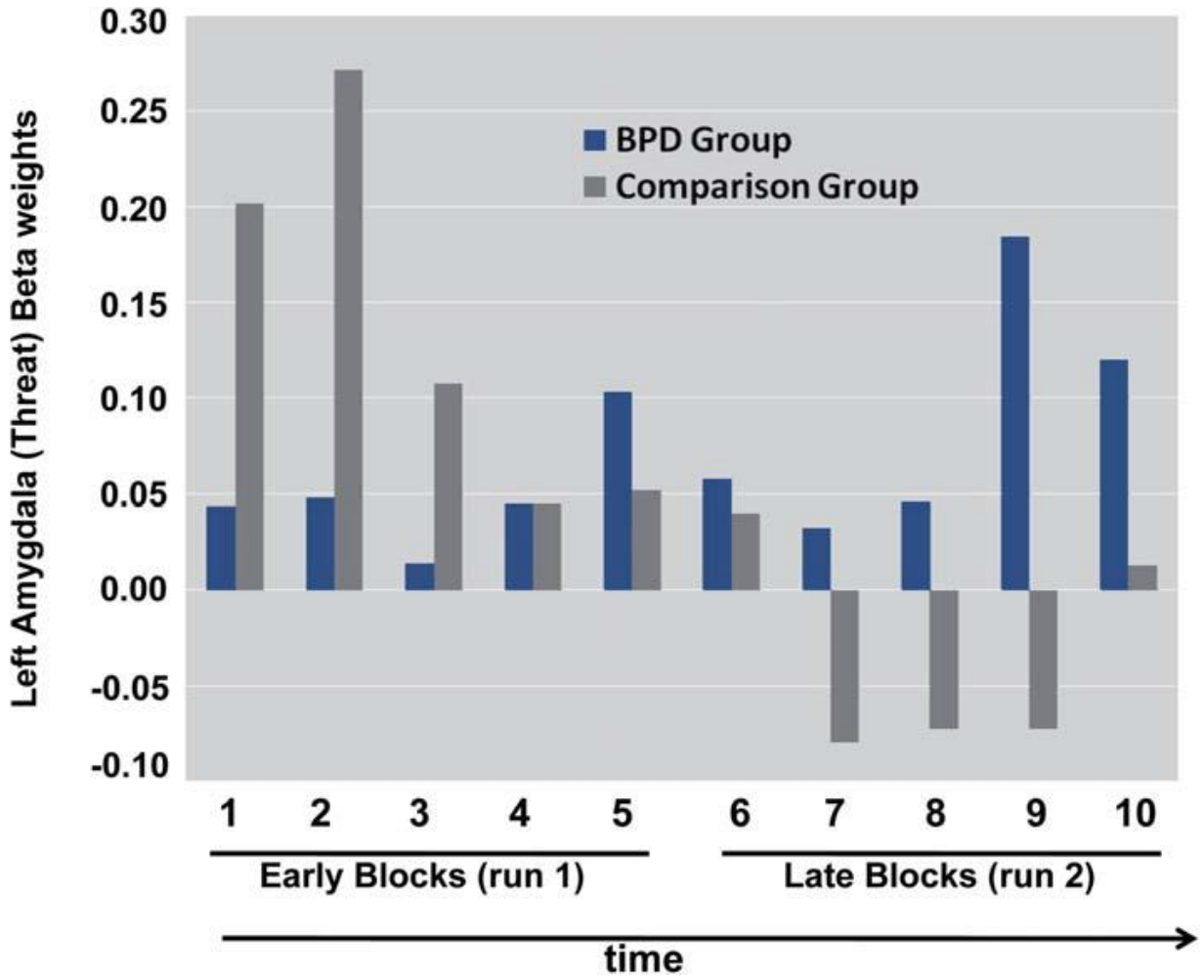


Higher activation of **limbic structures** (amygdala, hippocampus, insula)

Krause-Utz et al. Psychol Med 2012

Prolonged hyperactivity of amygdala after **threat related stimuli**

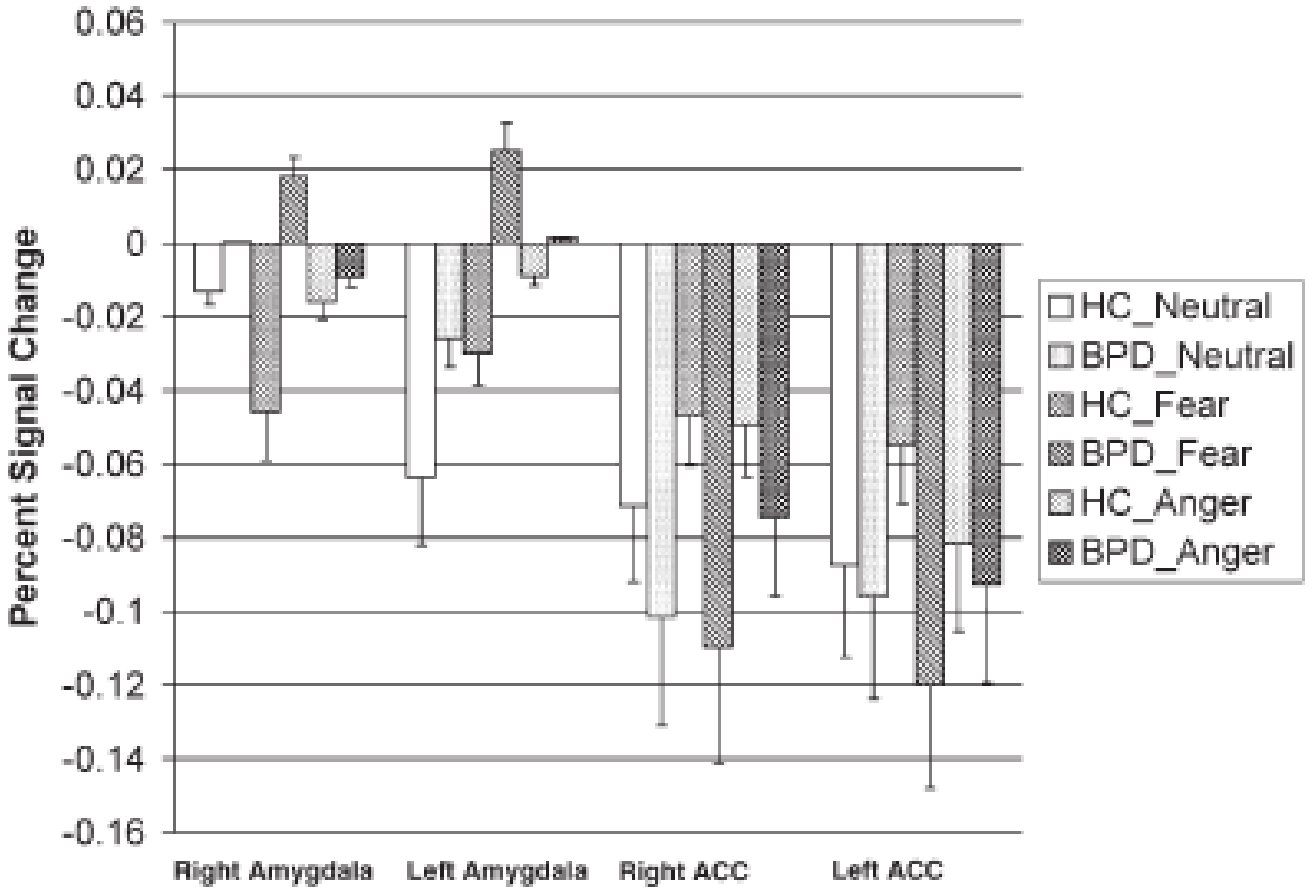
- **No decrease of amygdala activity** in BPD patients over time
- **Increased connectivity of the amygdala with vmPFC**



Kamphausen et al. World Biol Psychiatry 2013

Hypoactivation of frontal regions with negative emotional stimuli

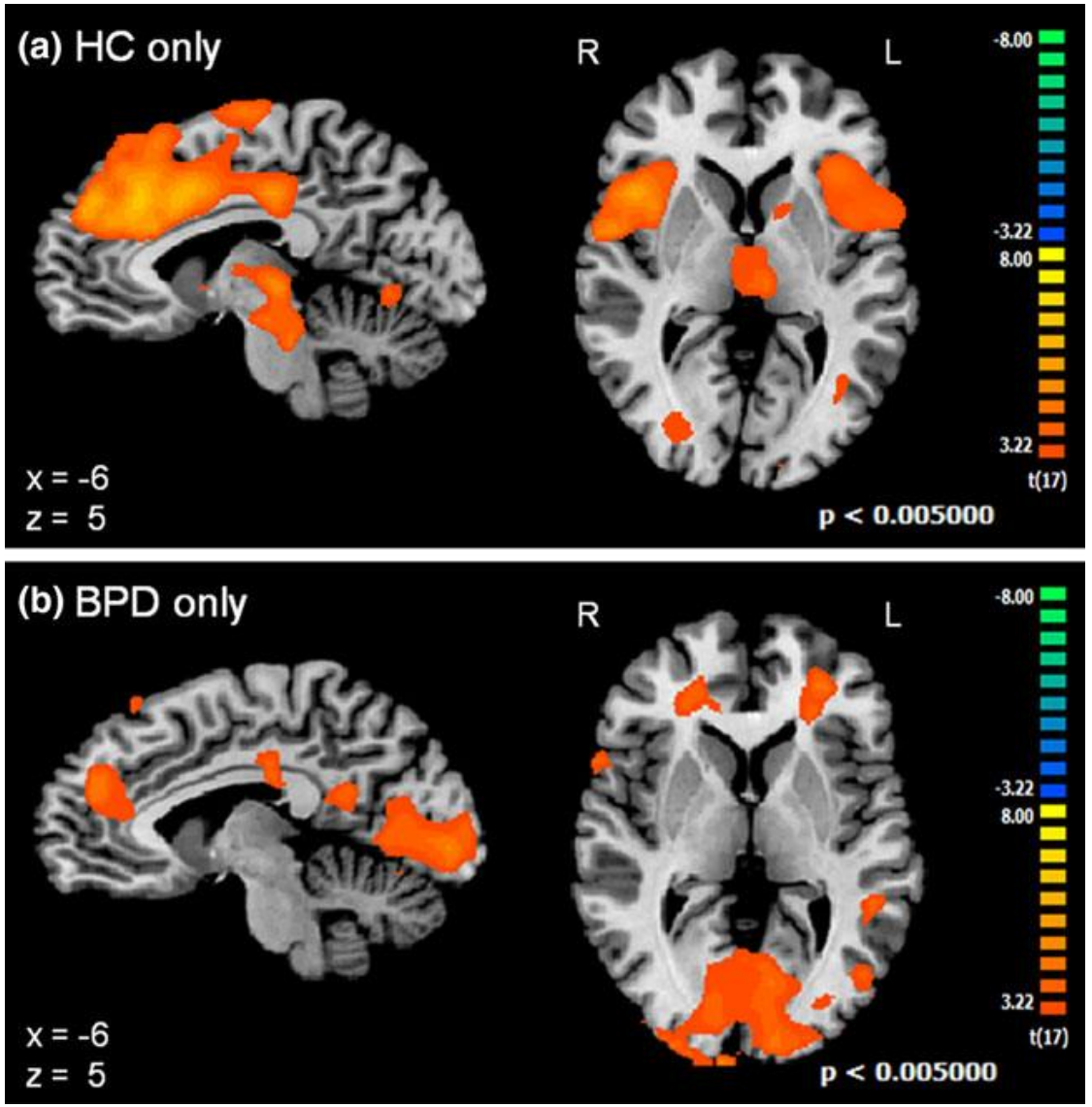
- Greater activation in **right amygdala**
- Less activation of **bilateral rostral/ subgenual ACC**



Minzenberg et al. Psychiatry Res 2007

Abnormal activation patterns in the anticipation of emotional stimuli

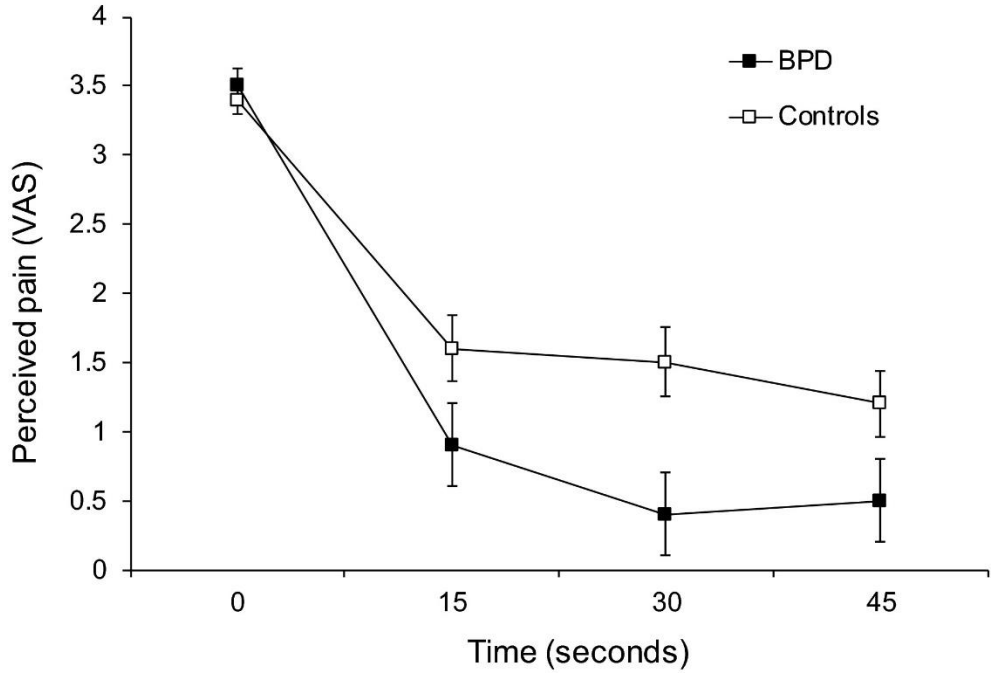
- **Less signal change** in left dorsal anterior cingulate cortex (dACC) and left middle cingulate cortex (MCC)
- **Enhanced activations** in left pregenual ACC, left posterior cingulate cortex (PCC), left visual cortical areas

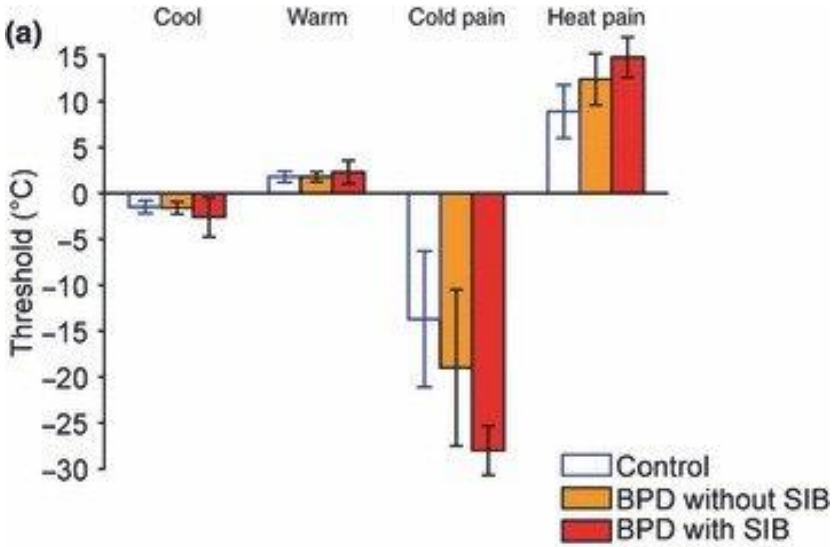


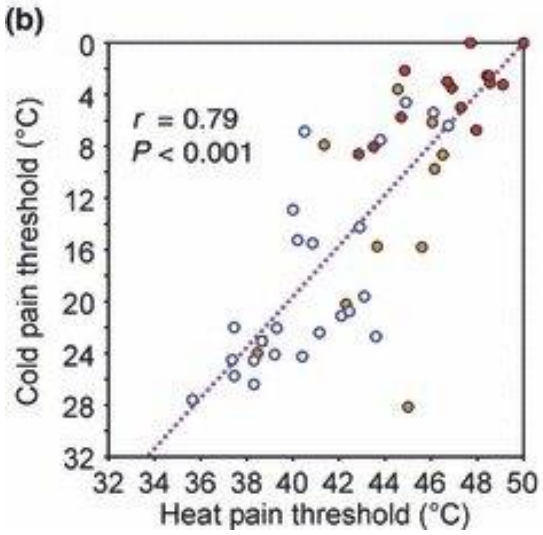
Scherpiet et al. Eur Arch Psychiatry Clin Neurosci 2014

Self-Injury and Altered Pain Processing

Heightened pain threshold in BPD

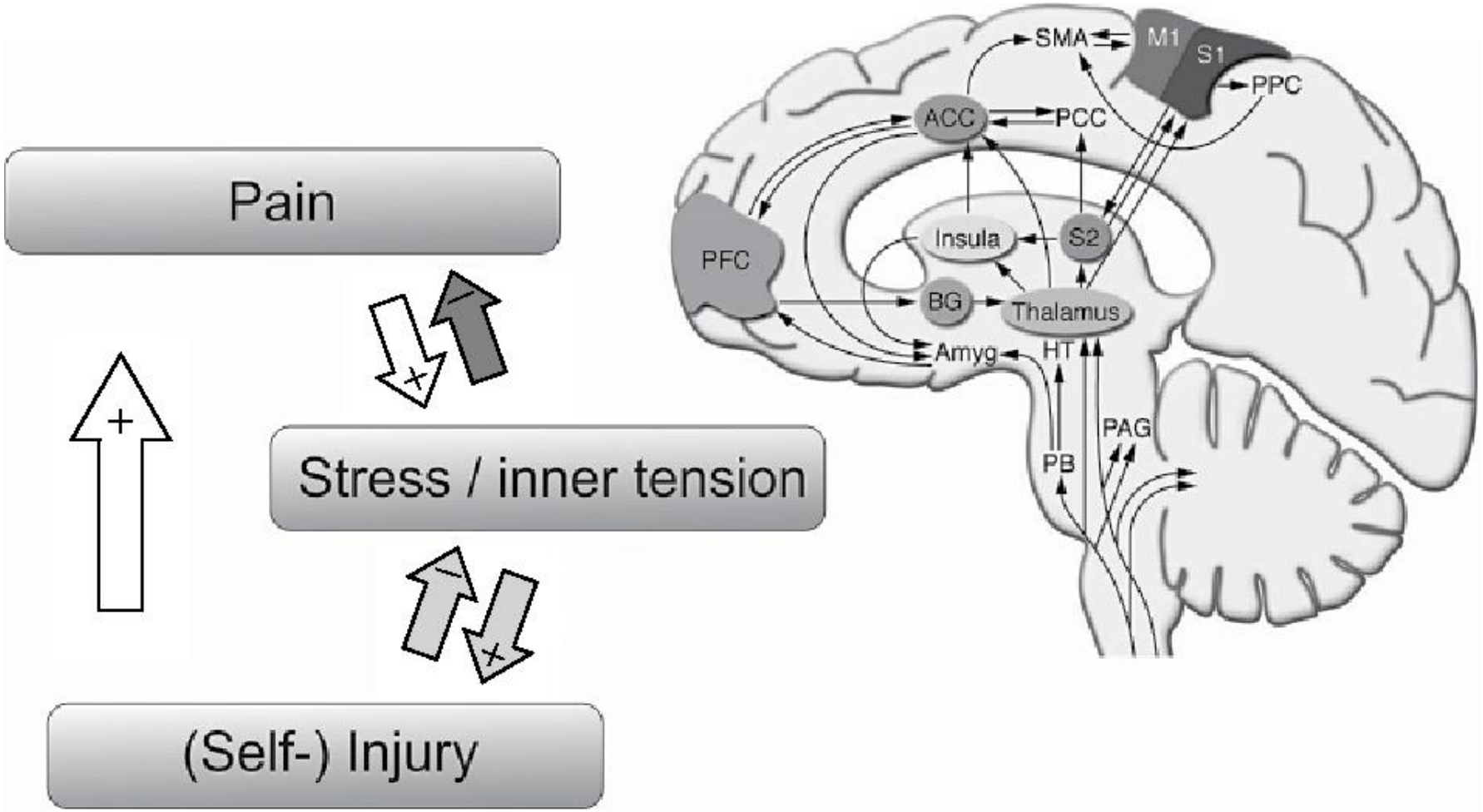




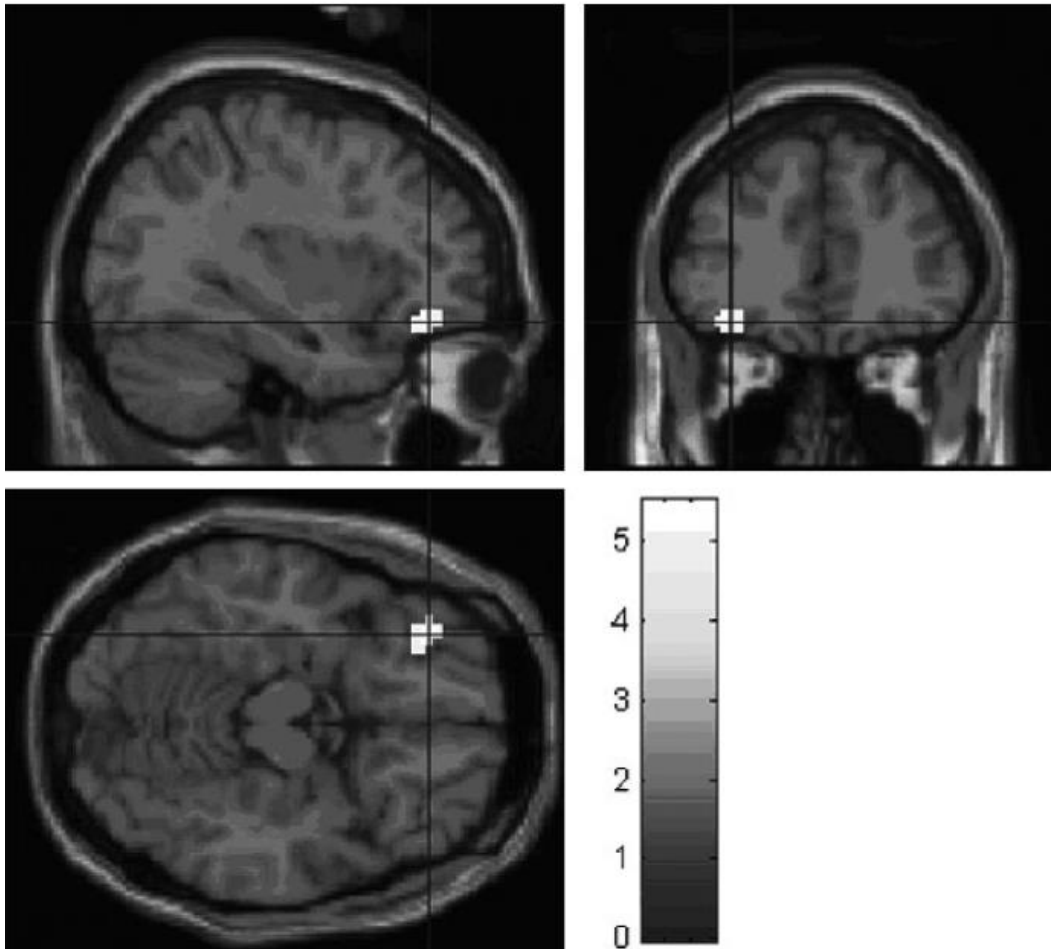


- Less experience of pain
- Normal pain mechanism

Interaction of stress/inner tension, injury, and pain



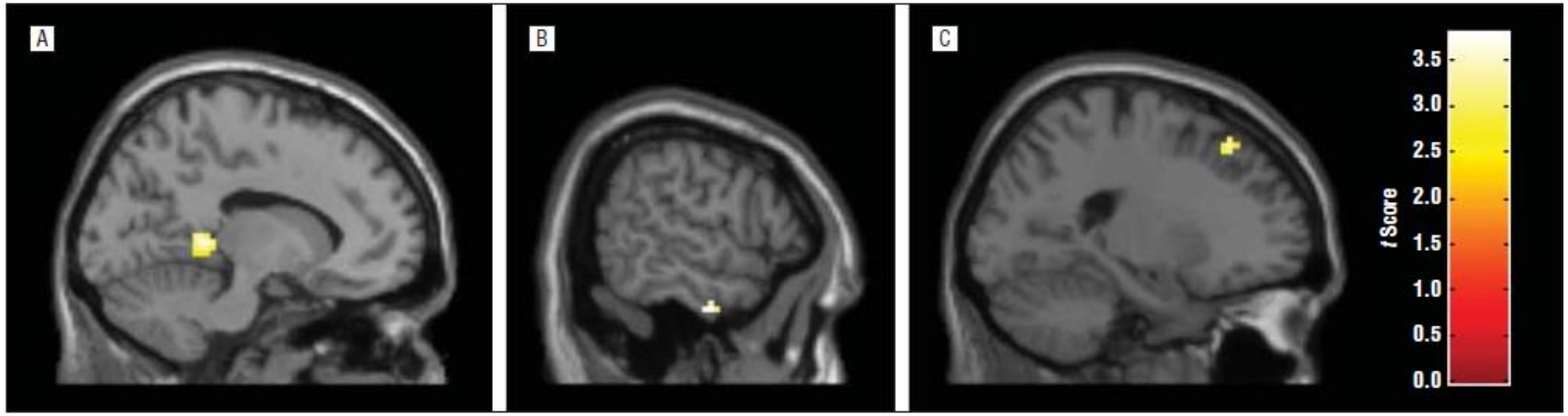
Script driven imagery of SIB (fMRI study)



- Listening to the situation triggering NSSI – **reduced activation in the OFC** and **increased activation in the DLPFC**

Kraus et al. Acta Psychiatr Scand 2010

Alterations in Default Mode Network Connectivity During Pain Processing



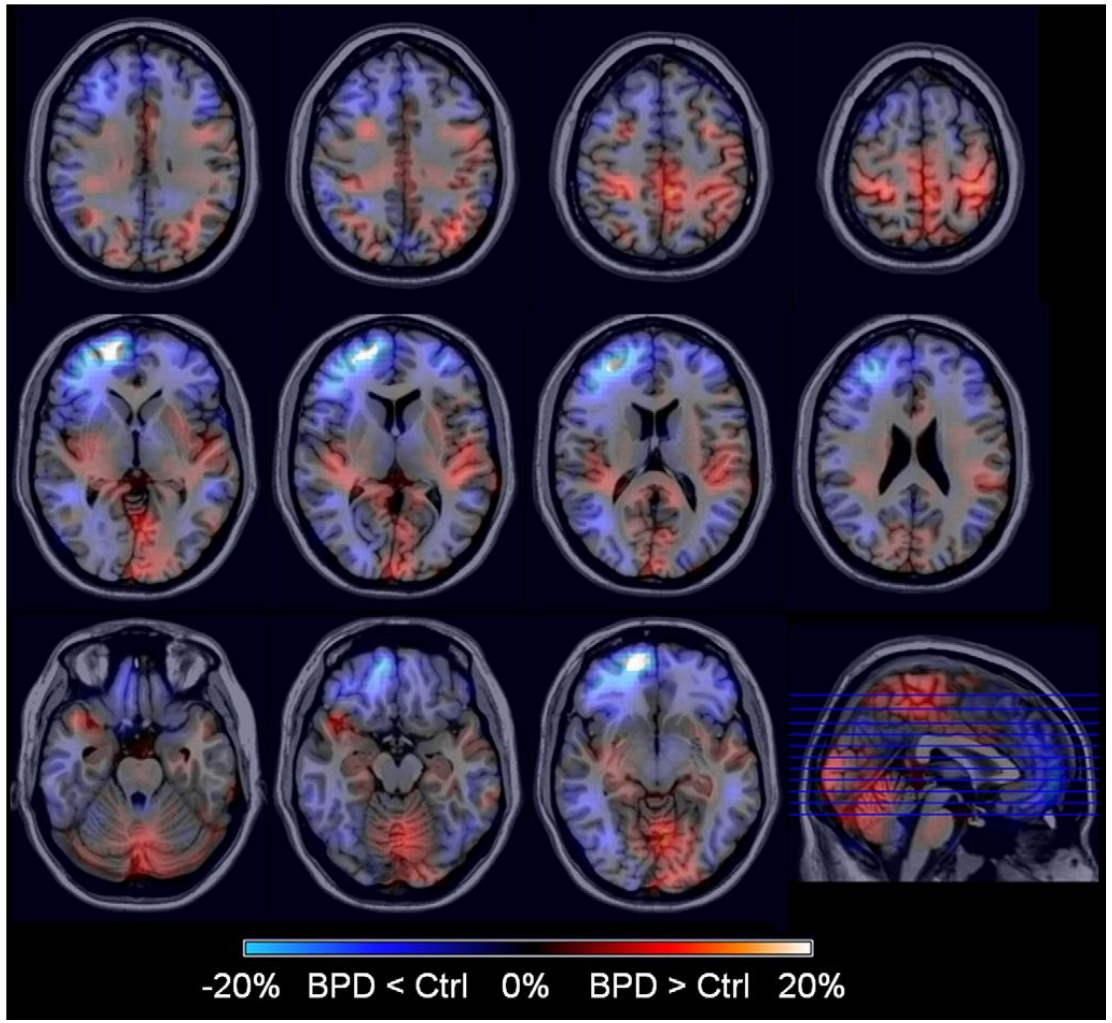
During pain vs neutral, patients with BPD exhibited **less posterior cingulate cortex** seed region connectivity with the **left dorsolateral prefrontal cortex**

Kluetsch et al. Arch Gen Psychiatry 2012

Behavioral Dysregulation and Impulsivity

Fronto-limbic dysfunction

- **Hypometabolism in frontal lobe**
- **Hypermetabolism** in motor cortex, medial and anterior cingulus, occipital lobe, temporal pole, left superior parietal gyrus and right superior frontal gyrus



Salavert et al. J Affect Disord 2011

Journal of Psychiatric Research 44 (2010) 1075–1081

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Tryptophan-hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls

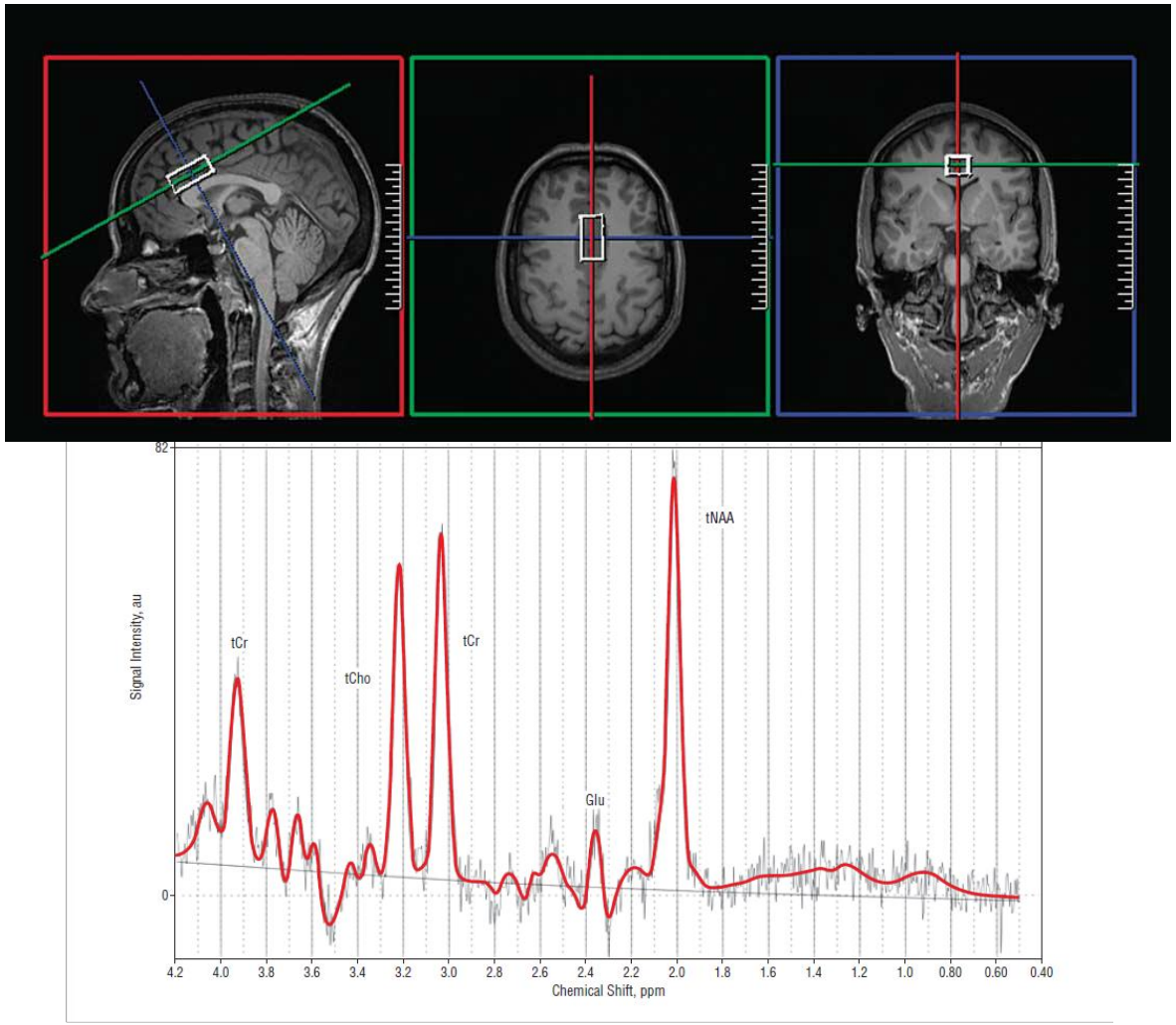
M. Mercedes Perez-Rodriguez [a], Shauna Weinstein [a,b], Antonia S. New [a,b], Laura Bevilacqua [c], Qiaoping Yuan [c], Zhifeng Zhou [c], Colin Hodgkinson [c], Marianne Goodman [a,b], Harold W. Koenigsberg [a,b], David Goldman [c], Larry J. Siever [a,b,*]

[a] *Department of Psychiatry, Mount Sinai School of Medicine, Psychiatry Box # 1230, One Gustave L. Levy Place, New York, NY 10029, USA*
[b] *The Mental Health Patient Care Center, James J. Peters Veterans Affairs Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468, USA*
[c] *Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, 5625 Fishers Lane, Room 3S-32: MSC 9412, Bethesda, MD 20892-9412, USA*

Deficient serotonergic function associated with impulsive-aggressive behavior and deficient inhibitory control

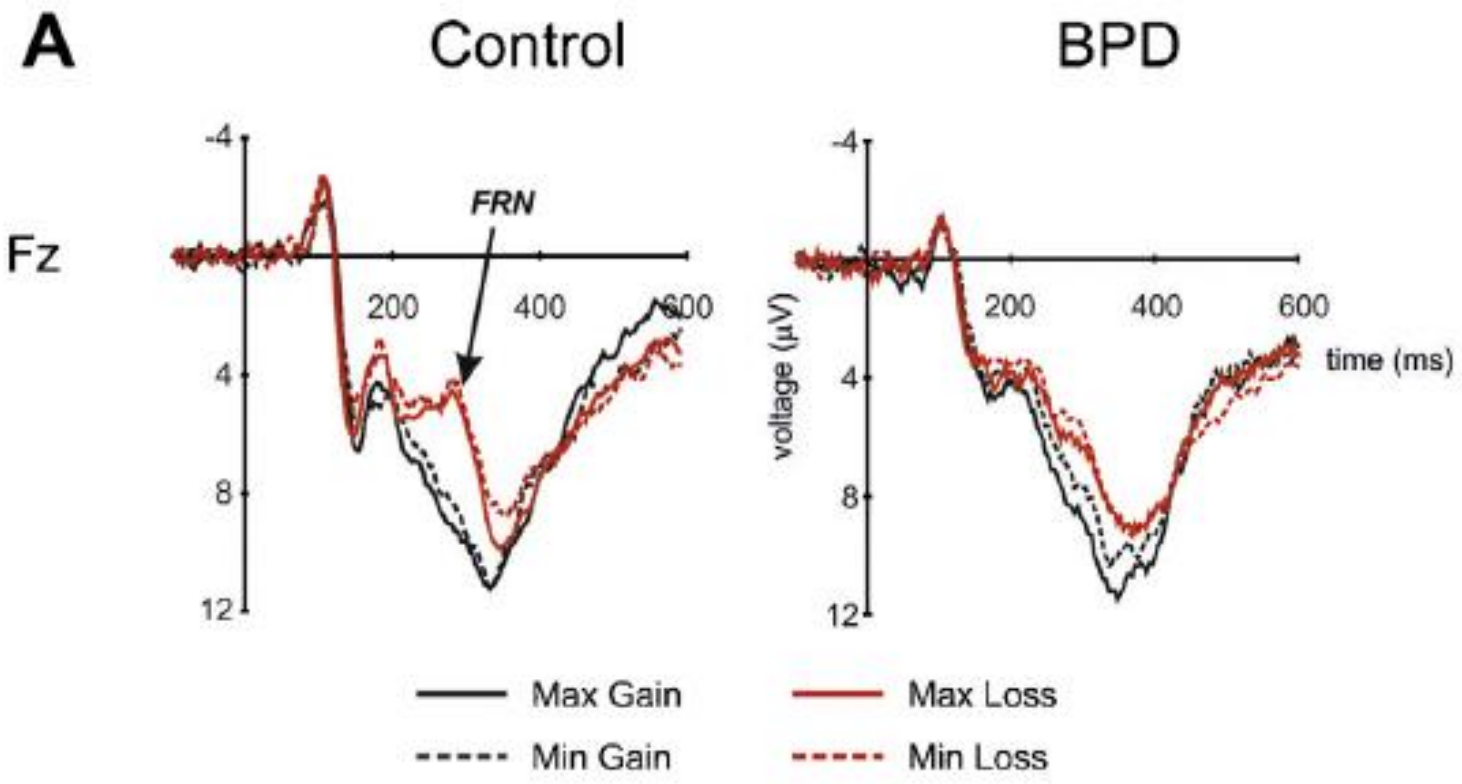
Glutamate levels in ACC – MRS study

- **Increased ACC Glutamate levels**
- ACC Glutamate levels **correlated with impulsivity**



Hoerst et al. Arch Gen Psychiatry 2010

Feedback related negativity (FRN)

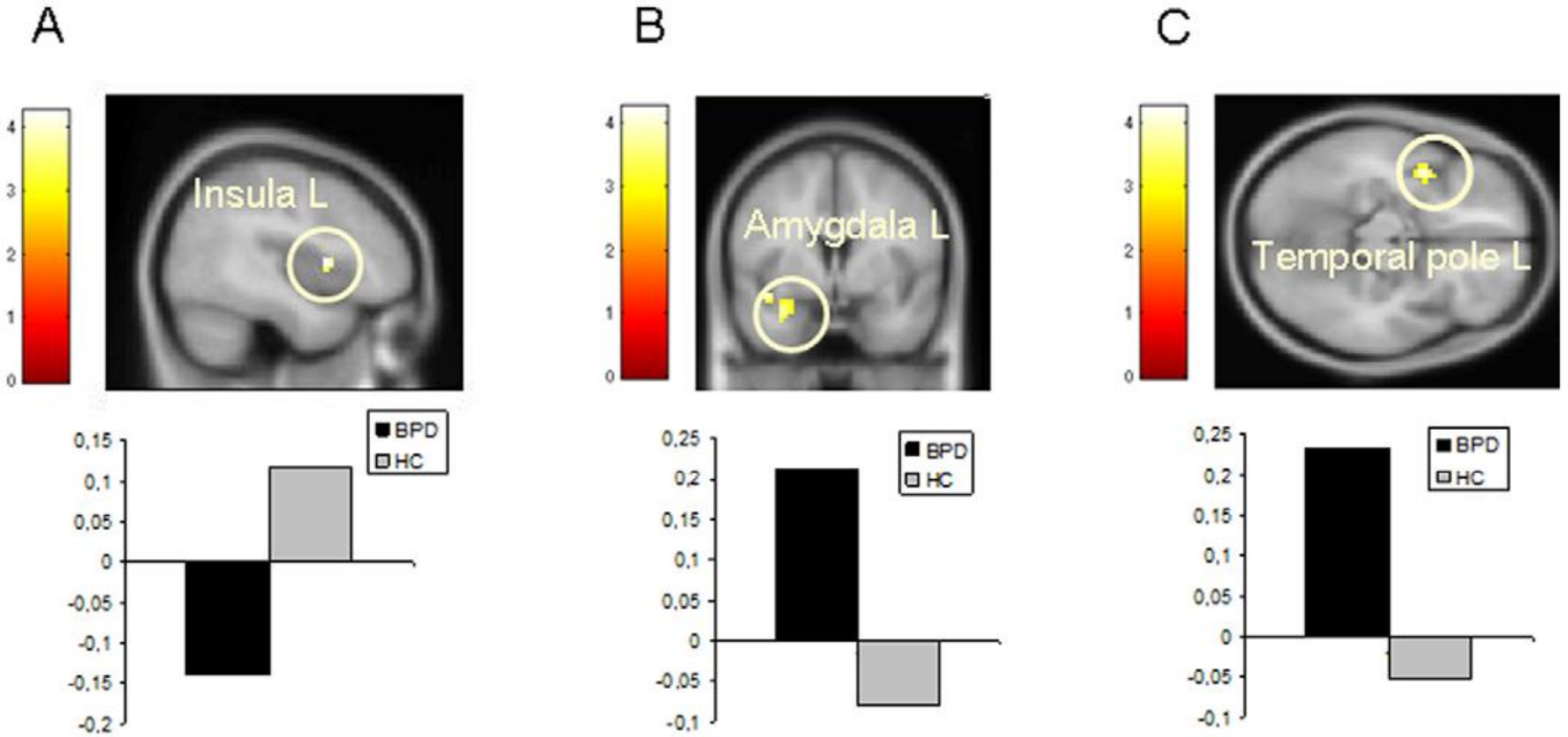


- 250–300 ms after **feedback after monetary loss** or **incorrect action**
- Possible **teaching signal** concerning **worse than expected consequences** of actions

Vega et al. Biol Psychol 2013

Interpersonal Disturbances

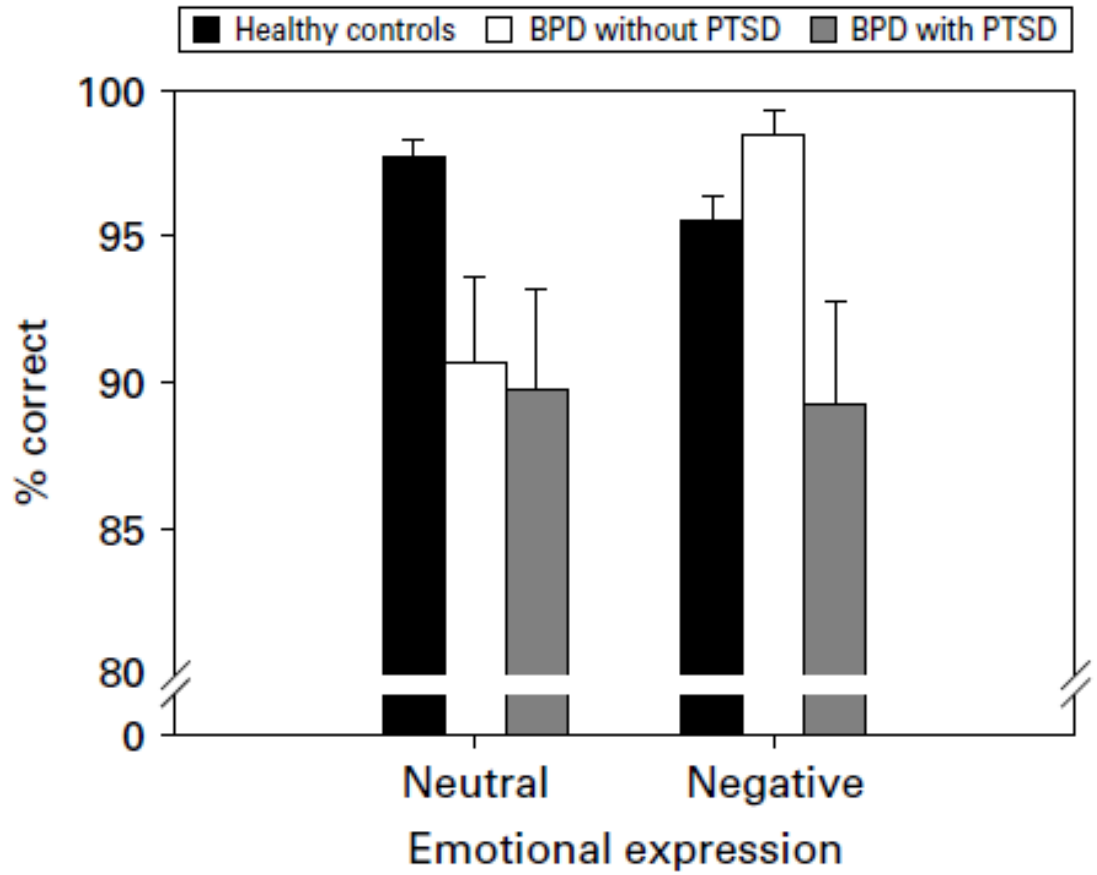
Highly vigilant of social stimuli - Limbic hyperactivity



Hyperreactivity of amygdala and other limbic regions

Frick et al. PLoS One 2012

Negative bias in fast emotion discrimination

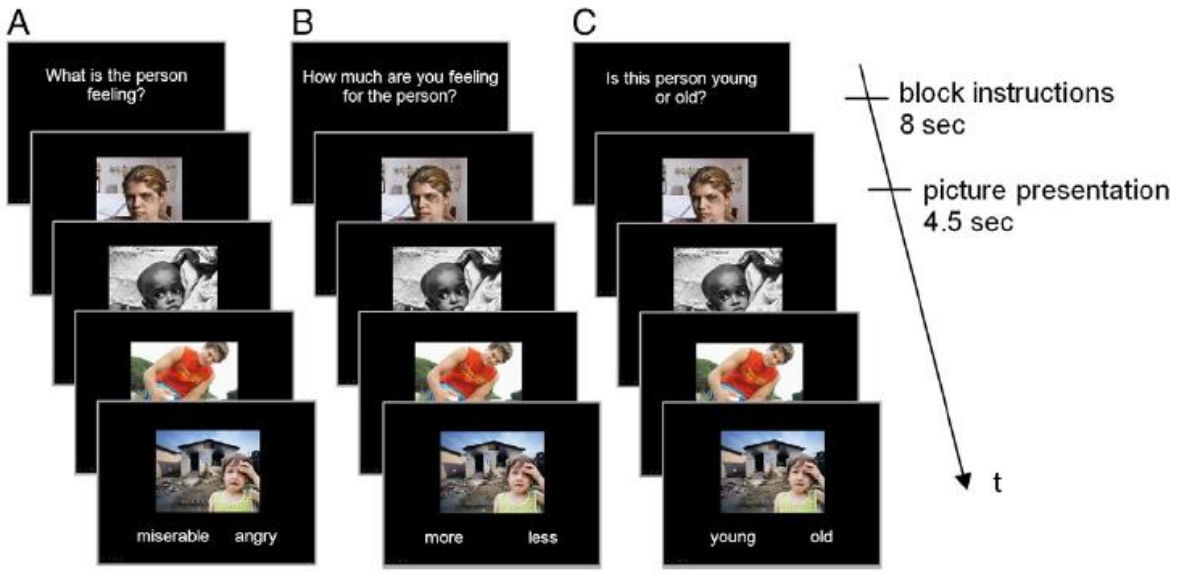


- Selective deficit in **rapid and direct discrimination** of negative and neutral emotional expressions
- Tendency to **misinterpret neutral facial expressions** as angry or hostile

Dyck et al. Psychol Med 2009

Altered empathy and social cognition

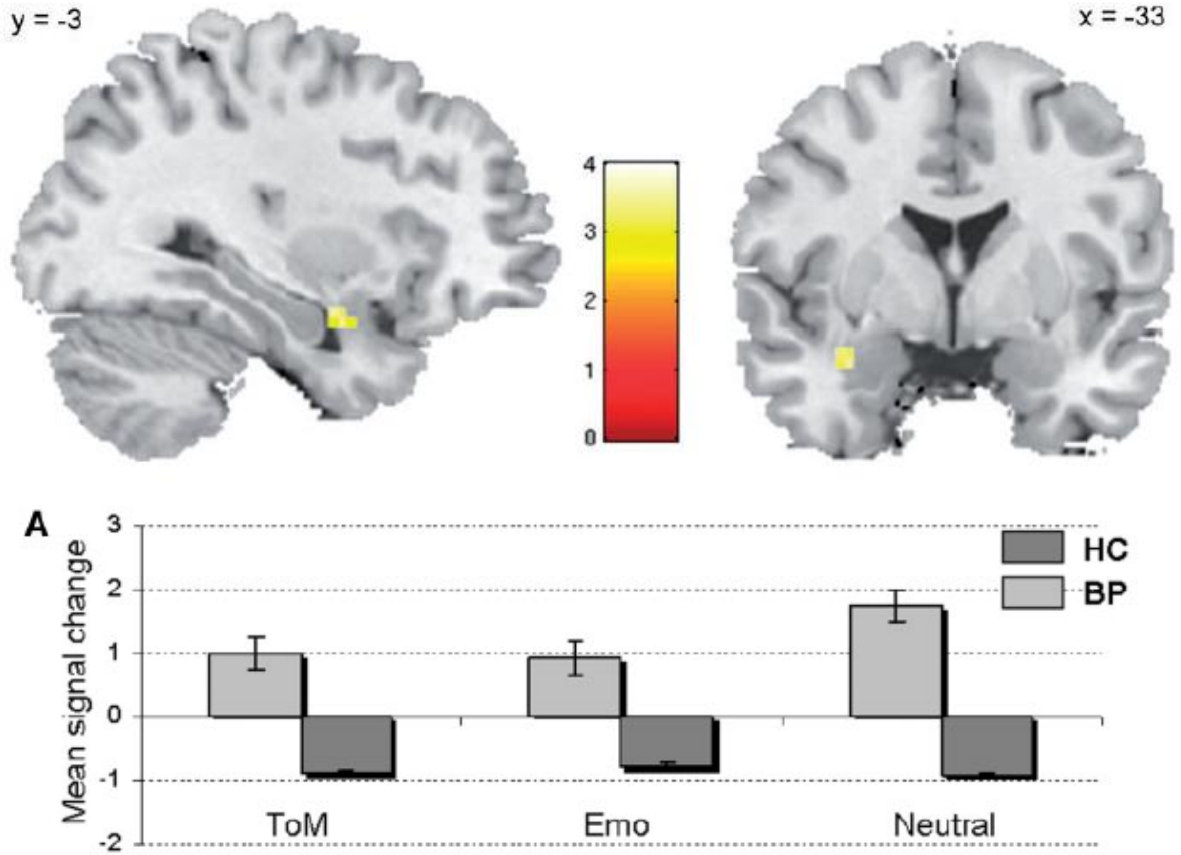
- Impairment in both cognitive and emotional empathy
- **Less activation in STS/STG** region during **cognitive empathy**
- **Greater activation in middle insula** region during **emotional empathy**



Dziobek et al. NeuroImage 2011

Abnormal activation with social cognition tasks

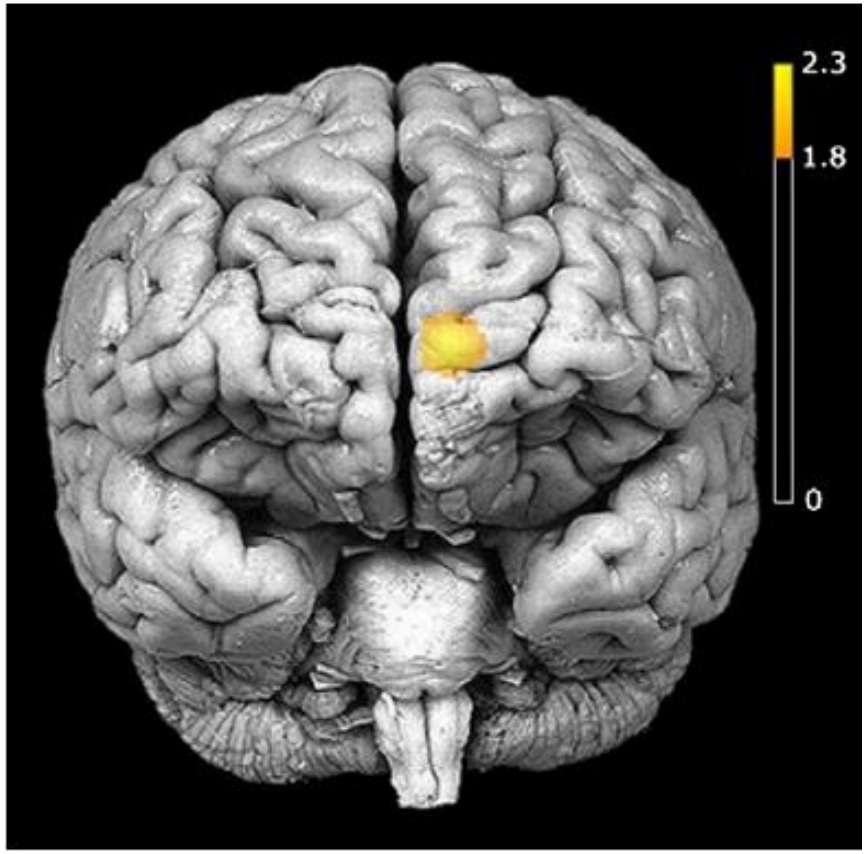
- **Hypoactivation of MNS** (superior temporal sulcus & BA44)
- **Hyperactivation of amygdala** independent of task complexity
- Exhibit **stronger emotional involvement while processing social stimuli**, which might hinder social-cognitive processing



Mier et al. SCAN 2013

Social exclusion paradigm (fNIRS study)

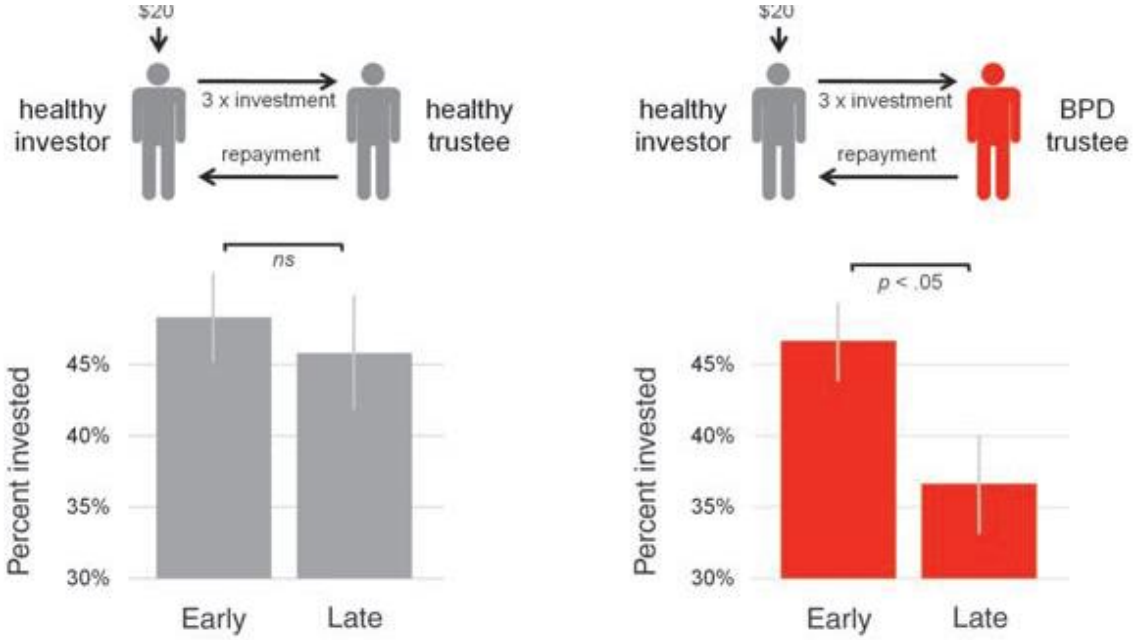
- **Increased activation** in **medial prefrontal cortex**
- Medial prefrontal activation was correlated with **rejection sensitivity** and **fear of abandonment**



Ruocco et al. Psychiatry Res 2010

Expectation of unfairness and cooperative behavior during social exchange

- Cooperation tended to **decrease over time**
- **Differential activation in insula** in healthy control subjects depending on the **fairness of the transaction** – whereas **insula activity in BPD patients was elevated throughout**



King-Casas et al. Science 2008

Pharmacotherapy of BPD

BPD was considered as…

- Atypical form of **schizophrenia** (Brinkley et al. 1979) – low-dose antipsychotics
- Atypical forms of **depression** (Akiskal 1981, Klein 1975, 1977, Stone 1979) – antidepressant

Initial observations

- **Antipsychotics** were as effective in diminishing **depression** as were antidepressants (Cowdry and Gardner 1988; Soloff et al. 1989)
- **Dramatic effects** of first few weeks of hospitalization (Siever and Davis 1991; Soloff et al. 1989)
- Borderline **patients' judgments** about the benefits of a medication could differ dramatically from judgments made by professionals
- Although many types of medications could be helpful, no type proved **consistently** beneficial

Medications in BPD

- Even in the 1980s, only ~ 10% of psychiatrists treated BPD without medications (Cole et al. 1984)

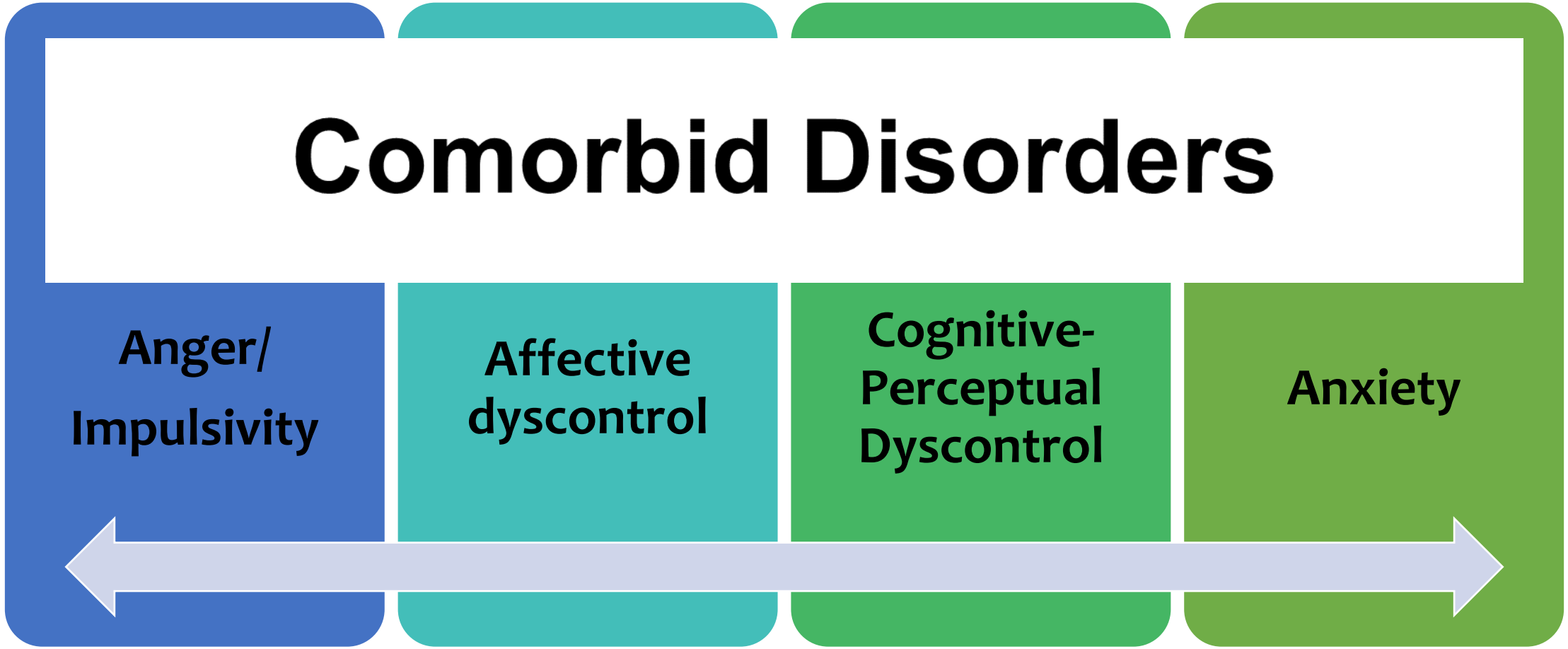
- **90%** of the borderline patients received **psychotropic medications** - significantly higher than major depression (Bender et al. 2001)

- **Polypharmacy** is very common in BPD (Zanarini et al. 2004) - **40%** taking **≥3 medications**, **20% ≥ 4**, and **10% ≥ 5**

Complexity of medication effects

- Many of the symptoms that are the targets of medications are very **dependent on context**
- Medications are used as **vehicles for projection**
- Medications are **rarely dramatic** in their effectiveness, their effect is almost always **partial and modest**

Symptom cluster (chasing)



Antidepressants

- **MAOI** (Tranylcypromine, Phenelzine) – depression, anxiety, rejection sensitivity
- **SSRI** (4RCTs Fluoxetine 20-60, 1 RCT Fluvoxamine 150-200) – anger, depression (caveat – comorbidity)
- **TCA** (Amitryptyline 150) – anxiety/hostility, not better than haloperidol for depression
- Mianserin – not effective

Emotional numbness with SSRIs

Typical Antipsychotics

- Haloperidol (2 RCTs, 5 mg) – anxiety/hostility, depression, cognitive/ perceptual
- Thiothixene low dose – cognitive/ perceptual
- Loxapine 15 mg, Chlorpromazine 100 mg
- Flupenthixol decanoate 20 mg – suicide attempts lower

Lithium

- 1 RCT - anger, suicidality
- Less mood instability
- Less premature treatment discontinuations

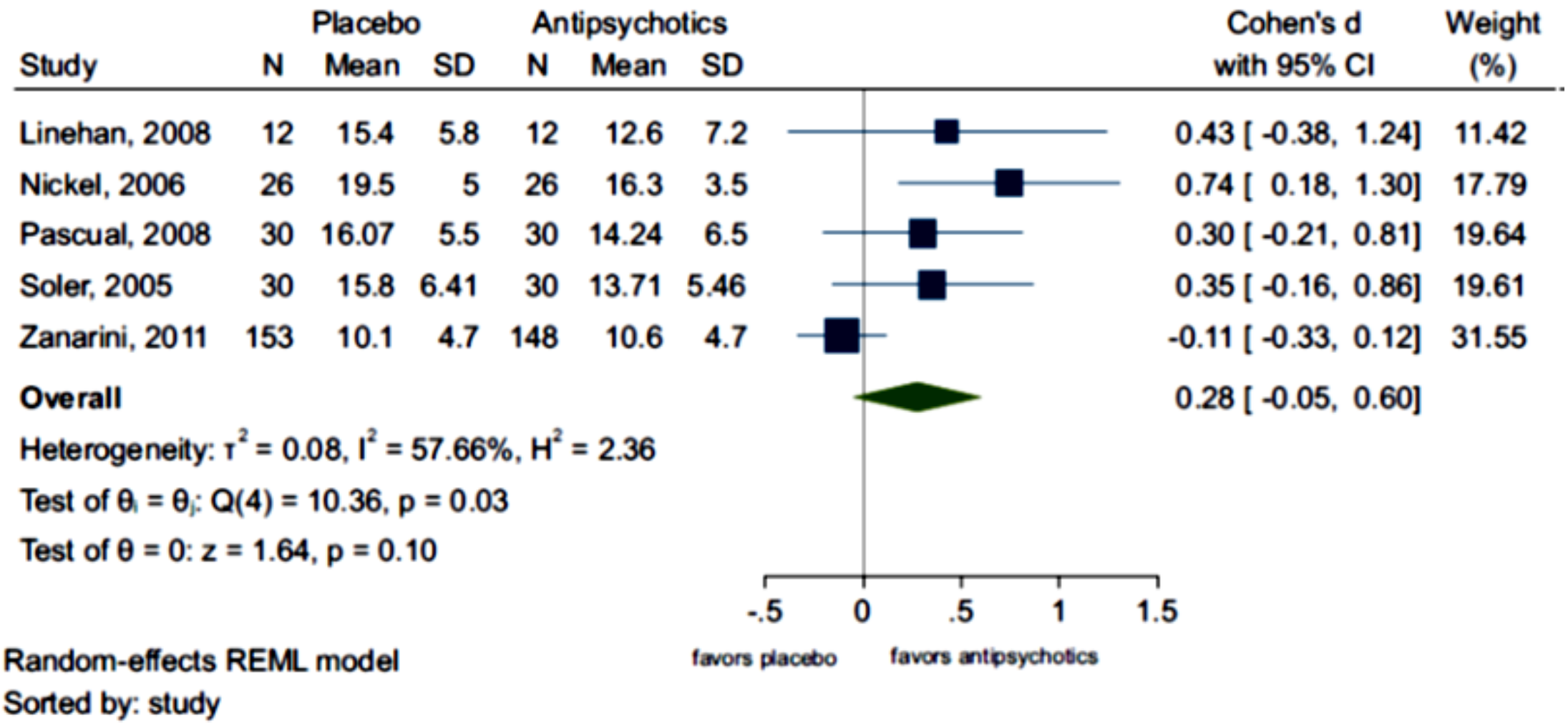
Anticonvulsants

- Valproate (53RCTs, 80 µg/ml) – interpersonal sensitivity, anger/hostility, impulsive aggression
- Carbamazepine – behavioral dyscontrol, anxiety, anger, euphoria, impulsivity, suicidality
- Topiramate (3 RCTs, 50-250 mg) – anger, irritability
- Lamotrigine (2 RCTs, 50-200 mg) – aggression, anger

Atypical antipsychotics

- Olanzapine (5-10 mg) – anxiety, paranoia, anger/hostility, interpersonal sensitivity (6 RCTs, Weight gain is limitation)
- Olanzapine-Fluoxetine Combination (OFC) superior to Fluoxetine alone (1 RCT)
- Aripiprazole (1 RCT, 15 mg) – depression, anger, paranoia
- Quetiapine ER (1 RCT, 150-300 mg) – depression, impulsivity, aggression, self-harm
- Ziprasidone (1 RCT, 80 mg) – no effect

Atypical antipsychotics for depressive symptoms



Misc.

- Omega-3 fatty acids (2 RCTs) – aggression, depression
- Intranasal oxytocin - normalizes some aspects of interpersonal dysfunction, increase emotional empathy, reduces social withdrawal and stress levels
- Naloxone IV (1 RCT) – No effect
- Alprazolam – increased behavioral dyscontrol, suicidality

Medication	Anger/Impulsivity
Mood stabilizers	
Carbamazepine	++
Valproate	++
Topiramate	++
Lamotrigine	+
Antidepressants	
Selective serotonin reuptake inhibitors	++
Tricyclics	–
Monoamine oxidase inhibitors	+
Dual-action	?
Antipsychotics	
Typical and atypical	+
Benzodiazepines	–

Lithium

Medication	Affective dyscontrol/ depression
Mood stabilizers	
Carbamazepine	+/−
Valproate	+/−
Topiramate	+/−
Lamotrigine	+
Antidepressants	
Selective serotonin reuptake inhibitors	++
Tricyclics	+/−
Monoamine oxidase inhibitors	+
Dual-action	+
Antipsychotics	
Typical and atypical	+
Benzodiazepines	+/−

Medication	Cognitive-perceptual dyscontrol
Mood stabilizers	
Carbamazepine	?
Valproate	?
Topiramate	?
Lamotrigine	?
Antidepressants	
Selective serotonin reuptake inhibitors	?
Tricyclics	?
Monoamine oxidase inhibitors	?
Dual-action	?
Antipsychotics	
Typical and atypical	++
Benzodiazepines	?

Medication	Anxiety
Mood stabilizers	
Carbamazepine	?
Valproate	?
Topiramate	?
Lamotrigine	?
Antidepressants	
Selective serotonin reuptake inhibitors	+
Tricyclics	+/–
Monoamine oxidase inhibitors	+ (somatic)
Dual-action	?
Antipsychotics	
Typical and atypical	+
Benzodiazepines	
Long-acting	+ (psychic)

Pharmacotherapy summary

Medication class	BPD-associated symptoms
Anticonvulsants	Affective dysregulation (e.g., mood lability, temper outbursts, suicidal thoughts and behavior, rejection sensitivity), impulse behavioral dyscontrol (e.g., aggression, anger, hostility, impulsiveness, self-injury)
Antidepressants	Affective dysregulation (e.g., depression, anxiety, mood lability, suicidal thoughts and behavior), impulse behavioral dyscontrol (e.g., aggression, anger, hostility, impulsiveness, self-injury)
Antipsychotics	Affective dysregulation (e.g., anger, mood lability, suicidal thoughts and behavior), cognitive-perceptual disturbance (e.g., illusion, paranoid ideation, ideas of reference), impulse behavioral dyscontrol (e.g., aggression, impulsiveness, hostility, self-injury), psychoticism
Benzodiazepines	Anxiety, agitation, impulsiveness
Melatonin	Sleep disturbance
Opioid-agonists/antagonists	Self-injurious behaviors
Sedative-hypnotic medications	Sleep disturbance

What do guidelines say?

- **NICE** – No drug therapy except for **comorbidities**
- **APA**
  - **Antidepressants** for affective dysregulation and impulsive behavioural dyscontrol, **antipsychotics** for cognitive-perceptual symptoms (First line)
  - Mood stabilizers and second generation antipsychotics for affective instability and impulsive behaviours (Second line)
- **WFSBP** – Off-label use of psychotropic agents improve **affective symptoms** and **impulsivity**

Changing trends…

- Shift in prescription from antidepressants to **anticonvulsants** and **antipsychotics**
- Cochrane review
  - **Mood stabilizers**, **second generation antipsychotics**, and **omega-3 fatty acids** may be effective for treating specific BPD symptoms
  - Antidepressants only in patients with concomitant major depression

Recommendations for medications in BPD

1. Medications can be helpful, but their overall **role is adjunctive**. No effect on core symptoms.
2. They should **not be expected to be curative**
3. Convey **cautious optimism** about expectable benefits
4. Patient's **collaboration in identifying target symptoms** that medications might reasonably benefit (e.g. stabilizing affects, undesirable behaviors, distorted perceptions)
5. Choose an **outcome that would reflect** the desired response (e.g. amount of decrease in the undesirable symptoms)

Recommendations for medications in BPD

6. Outline the **expectable time course** by which benefits might occur
7. Inform about the **possible adverse side effects** and about alternative medications
8. Before prescribing the medication, **evaluate** the patient for symptoms that might possibly be side effects of the proposed medication
9. Encourage the patient to **read about** whatever medications are prescribed
10. Stress that effects are difficult to evaluate, enlist the **patient as an ally** in this process
11. Because noncompliance is common, stress the necessity for **meticulous and responsible use** to evaluate effectiveness

samir.kp@manipal.edu