Disregolazione emotiva, instabilità umorale (ciclotimia) e reattività agli eventi: basi neurobiologiche ed implicazioni terapeutiche

Giulio Perugi - giulio.perugi@med.unipi.it

Institute of Behavioural Sciences “G. De Lisio”
Department of Psychiatry University of Pisa
Diagnosis of Emotional Dysregulation (Cyclothymia)

- More challenging than classic presentations (BP-I, -II)
- Treatment-seeking behavior most linked to the consequences than to cyclothymia per se
- Unless being on the lookout for bipolarity or using systematic assessment of BP spectrum, diagnosis often focused on apparent complaints
  - Depression
  - Anxiety disorder
  - Personality disorder (Borderline)
  - **Eating disorder (bulimia, BE)**
  - Addictive behavior
  - Self-injurious behaviors…
Review

Cyclothymia reloaded: A reappraisal of the most misconceived affective disorder

Giulio Perugi a,b,*, Elie Hantouche c, Giulia Vannucchi a, Olavo Pinto d

a Department of Clinical and Experimental Medicine, University of Pisa, Italy
b Institute of Behavioural Science "G. De Lisio", Pisa, Italy
c Centre des Troubles Anxieux et de l’Humeur, Cliniques Universitaires, Geneva, Switzerland
d International Mood Clinic, Rio de Janeiro, Brazil

What we need?

• Specific (operational) criteria
• Prevalence in clinical population
• Distinct phenomenology (within the BP domain)
• Related risks (comorbidity, suicide... )
• Validating robust factors (age of onset, family history, course of illness, drug reactivity, genetic...)
• Clinical utility-Treatment implication
Definition of Emotional Dysregulation (Cyclothymia)

• Operational criteria
  – Excessive emotional reactivity and sensitivity since adolescence or before
  – Rapid shifts in energy, thought and/or mood
  – Ups and Downs (mood, thought, behaviour…etc.)
  – Persistent circularity (continuous cycling)
  – Psychological faults
  – Impulsivity and behavioural problems
  – Negative psychosocial consequences (school, work, love, family…)
Dimensions of (Emotional) Reactivity

- Emotion Intensity
- Emotion Persistence
- Excessive Emotion Sensitivity

M'Nock, Behav Therapy, 2008
Linear correlations between Cyclothymic Temperament, Affective Lability, Interpersonal Sensitivity and Separation Anxiety in Atypical Depressive patients

Affective Lability (ALS) → Interpersonal Sensitivity (ISSI)
- \( r = 0.35, F = 9.7, p = 0.001 \)

Cyclothymic Temperament → Interpersonal Sensitivity (ISSI)
- \( r = 0.39, F = 10.7, p < 0.0001 \)

Interpersonal Sensitivity (ISSI) → Separation Anxiety (ASAD)
- \( r = 0.69, F = 19.8, p < 0.0001 \)

Separation Anxiety (ASAD) → Affective Lability (ALS)
- \( r = 0.29, F = 7.8, p = 0.006 \)

Cyclothymic Temperament → Affective Lability (ALS)
- \( r = 0.45, F = 11.7, p = 0.001 \)

Perugi G. et al., World Psychiatry, 2012
Psychological faults

- Sensitivity to rejection, judgment, criticism
- Sensitivity to separation and affective dependency
- Pathological Jealousy
- Excessive need to please others
- Compulsive need for compliments and emotional rewards
- To believe not to be loved enough or to be misunderstood
- Novelty-seeking mixed with harm-avoidance
- Compulsive and impulsive behaviors
- Shaky self-esteem, from low self-confidence to overconfidence
Behavioural consequences

- Hostility towards significant others, unstable and intense interpersonal relationships
- Efforts to avoid real or imagined abandonments, dramatic reaction to real or dreaded abandonment, pathological attachment
- Interpersonal “cannibalism”
- Submissiveness, pathological altruism, dependence
- Attention seeking, seductive or provocative behavior, physical appearance to draw attention, pseudo-hypersexuality
- Compulsive and impulsive thoughts
- Tendency to test and exceed limits in interpersonal relationships
- Conflicting behavior, need for psychological explanations and treatments
- Substance use and behavioral addictions (gambling, compulsive buying, compulsive sexuality, etc.)
- Romantic, geographical and work instability

Conceptualizing Emotional Dysregulation (Cyclothymia)

• **Subtype of Mood Disorder**
  - chronic presentation with low-grade depressive and hypomanic episodes

• **Temperament Style**
  - risk factor for psychopathology, particularly Bipolar Spectrum (increased risk of developing BP-I or BP-II)

• **Neurodevelopmental Disorder**
  - Desincronization in the maturative process of limbic system (e.g., amygdala and hippocampus) and neocortex (especially the prefrontal cortex)
Features of borderline personality disorder (DSM from -III to -5)

(1) Efforts to avoid real or imagined abandonment  
(2) Unstable and intense interpersonal relationships  
(3) Identity disturbance  
(4) Impulsiveness  
(5) Recurrent suicidal, or self-mutilating behavior  
(6) Affective instability, marked reactivity of mood  
(7) Chronic feelings of emptiness  
(8) Anger, hostility  
(9) Transient, stress-related paranoid ideation or severe dissociative symptoms

APA Diagnostic and Statistical Manual of Mental Disorders, 1994
Cyclothymia well-suited to neurodevelopmental disorder

Genetic factors

Neurobiologic Factors

Cyclothymic Temperament

Emotional Dysregulation

- Emotional Reactivity
- Affect Instability
- Basic Insecurity (SA)
- Interpersonal Hypersensitivity

Psychological vulnerability

“Borderline-like”
Studies supporting Trauma in the etiology of BPD

- BPD+ adults more likely than BPD- to report early physical and sexual abuse and witnessing domestic violence

- Adult BPD predicted by sexual abuse and/or emotional denial by male caretakers, and inconsistent treatment by female caretakers

- Childhood sexual abuse, separation from parents, and unfavourable parental rearing styles predicted adult BPD

- Association of BPD with childhood abuse and neglect more than MDD or schizotypal, avoidant, OC personality disorders

Battle C.L. et al., *Childhood maltreatment associated with adult personality disorders: Finding from the Collaborative Longitudinal Personality Disorders Study.* J. Personal Disord 18: p. 193-211
Studies non-supporting Trauma in the etiology of BPD (2)

- Meta-analysis of 21 studies yielded a small pooled effect size for BPD/Child abuse association ($r = .28$)
- In community samples of personality disorders, childhood physical and sexual abuse did not predict BPD

20%-40% BPD patients have no history of sexual abuse

80% of sexually abused patients have no personality pathology

Longitudinal follow-up of children with documented abuse shows a high rate of resilience

BPD and BD spectrum disorders are heterogeneous conditions

The BPD and BD controversy could not be resolved only on clinical description.

Similarities in brain changes among several conditions characterized by emotional dysregulation (BD, BPD and ADHD, Tourette, ASD)
  - alterations in the limbic system (e.g., amygdala and hippocampus) and neocortex (especially the prefrontal cortex).

Some of these disorders can be conceptualized as neurodevelopmentally related conditions
Overlapping Neurodevelopmental Disorders

- Tic disorders/Tourette's disorder\(^1\)
- ADHD\(^1\)
- Pervasive developmental disorder\(^1\)
- Autism spectrum disorder\(^1\)
- Intellectual Disability\(^1\)
- Emotional/mood disregulation (cyclothymia)\(^1,2\)

Childhood Psychiatric Disorders as Anomalies in Neurodevelopmental Trajectories

Philip Shaw,* Nitin Gogtay, and Judith Rapoport

Child Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland

ADHD

Figure 1. How developmental trajectories can go awry. In all examples hypothetical data representing the change in cortical thickness of a cerebral point is given. (A) The pathological trajectory has the same form as the typical trajectory but is displaced upward along the age axis and so key characteristics such as peak thickness, shown in the bold arrows, is moved later. (B) The pathological trajectory has the same form, but changes at a higher velocity. (C) The pathological trajectory loses the form of a typical trajectory.
Trajectory disturbances and neuropsychiatric disorders

Age (yrs)

Cortical dimensions (volume/thickness)

Autism

Typically developing children

ADHD
In età evolutiva nell’ADHD si osserva un ritardo di sviluppo delle aree corticali prefrontali, parietali e temporali. Si stima che lo sviluppo di queste aree nell’ADHD, in termini di crescita di spessore corticale e successivo “pruning”, avvenga con un **ritardo di 2-3 anni rispetto al neuro-sviluppo tipico.**

ADHD e regolazione emotiva

Shaw et al. 2014
Orbitofrontal cortex

Amygdala

Caudate

Putamen

Right Inferior Gyrus

Middle and Superior Frontal Gyri

Cognitive control

Temporal Information processing

Reward processing
Rispetto alle sue “comorbidità” la disregolazione emotiva è qualcosa che corre parallelamente rispetto all’evoluzione del disturbo o dei disturbi diagnosticabili insieme a esso.
Treatment and Management Perspective

“Should Cyclothymia be considered as a Specific and Distinct Bipolar Disorder?”

Emotional dysregulation - Cyclothymia: reasons for difficulties

- Complex clinical picture
- “Dark” hypomania (impulsivity, irritability)
- Lack of clear-cut episodes
- Rich co-morbidity (anxiety, impulse control disorders, drug abuse)
- Young age of onset
- Multitude of psychological dysfunctions
- Overlap with cluster B and C personality features
- Complicated patient-doctor relationships
- Less response to conventional approaches
- Frequent exposure to antidepressants and sedatives

# Treatment strategy for cyclothymia

<table>
<thead>
<tr>
<th></th>
<th>Acute 0-8 weeks</th>
<th>Continuation 1-6 months</th>
<th>Maintenance Indefinite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychoeducation</strong></td>
<td></td>
<td>Cognitive reorganization, emotional coaching, changes in behavioral systems, and so on.</td>
<td>Psycho-re-education Coping with psychological faults</td>
</tr>
<tr>
<td><strong>Mood-stabilizers (MS) +</strong></td>
<td>Antidepressant, Antipsychotic “Go slow, Stay low”</td>
<td>Mood-stabilizers (MS) Tapering adjunctive drugs</td>
<td>Long-term MS (which should “stay low”); anticipate hypomania and depression</td>
</tr>
<tr>
<td>Depressive, Mixed or Hypomanic states</td>
<td>Symptomatic Recovery</td>
<td>Psychosocial maladjustment Functional Recovery</td>
<td>Stability Optimizing adaptation <strong>Goodness of fit</strong></td>
</tr>
</tbody>
</table>
Cyclothymia: Need for a Specific Psycho-Education

Cyclothymia is a distinct form of BP
- Patients do not match with BP-I psycho-education group
- Patients want to share their own experiences with same others
- Need for psychotherapeutic expertise in the domain of Soft Bipolarity
- Need for an appropriate “format” of Psycho-Education (based on an adapted “model”?)

Drug Treatment of Cyclothymia

- Better difficult bipolar than borderline
- Be cautious with Antidepressants and BDZ
  - Lithium prevents suicide...but side effects and abrupt discontinuation
  - best combination “lamotrigine + lithium” (mood instability)
  - Divalproex (mixed depression, anxiety)
  - SG Antipsychotics, small doses, (severe impulsivity)
  - Lamotrigine (compulsive eating behavior, obesity)
  - Gabapentin (social anxiety, panic attacks)
  - Memantine: highly promising in refractory cases and cognitive deterioration

Concluding remarks

**Emotional Disregulation-Cyclothymia** as a complex neurodevelopmental form of emotional/mood disregulation

- Early onset
- Mood reactivity/instability
- Multiple comorbidity

**Emotional Disregulation-Cyclothymia** and **(cluster B an C PD)** are strongly related

- Affective lability
- Separation anxiety
- Interpersonal Sensitivity
- Trauma and Emotional Neglect

**Future research**

- Relationships with other neurodevelopmental disorder
- the role of Antidepressant Exposure
- mood stabilizers and specific psychoeducation from the beginning?
...thank you!

Perché una realtà non ci fu data e non c'è; ma dobbiamo farcela noi, .....; e non sarà mai una per sempre, ma di continuo e infinitamente mutabile...

A truth was not given us and doesn't exist per se, but we must create it by ourselves, ......; and it will never be a truth for ever, an eternal truth, but continuously, and infinitely transformable.

Luigi Pirandello

“Uno, Nessuno, Centomila”