Cumulative Life Stress and Hippocampal Activation During Recognition Memory in Major Depressive Disorder and Borderline Personality Disorder

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Factors That Cause And Maintain BPD

- **Environmental**
  - Childhood trauma/maltreatment, but causal link unclear

- **Genetic-Biological**
  - Heritability .65-.75
  - Epigenetic changes linked to childhood maltreatment
Cumulative Stress and Memory Systems

- Stress has a detrimental impact on mammalian memory ability.
  - Rodents (Green & McComick, 2013) and humans (Shields et al., 2017) exhibit episodic memory impairment following exposure to stressors.
  - Traumatic stress (Isaac et al., 2005; Zlomuzica, 2018), early life adversity (Lambert et al., 2017; Molett et al., 2016), and cumulative stress (Ohman et al., 2007; VonDras et al., 2010) have each been associated with disruptions in episodic memory ability.

- The hypothalamic-pituitary-adrenocortical (HPA) axis coordinates the release of the stress hormone cortisol.

- The hippocampus acts to downregulate the release of cortisol as part of a negative feedback loop.
Stress and Psychopathology

- “Cumulative Stress Hypothesis”
  - Largely attributed to McEwen, 2003’s *Mood disorders and allostatic load*
  - Suggests that the likelihood of developing psychopathology is related to the experience of past stressors:
    - Traumatic events (Barzilay et al., 2019; Glover et al., 2006)
    - Poverty (Wadsworth et al., 2016)
    - Childhood adversity (MacMillan, 2001)
Multiple Neurocognitive Domains are Affected in BPD

- Attention: Cohen's d = -0.59
- Processing Speed: Cohen's d = -0.68
- Verbal Memory: Cohen's d = -0.45
- Visual Memory: Cohen's d = -1.59
- Visual Spatial: Cohen's d = -0.59
- Cognitive Flexibility: Cohen's d = -0.29
- Planning: Cohen's d = -1.43

266 patients with BPD
255 healthy controls

Neurocognitive Deficits Are Associated with Trauma in BPD

Childrenhood physical abuse was associated with more severe deficits in verbal comprehension. Additionally, patients with PTSD performed worse in verbal comprehension, visual episodic memory, and perceptual reasoning.

Hippocampal activity was not significantly correlated with recognition memory performance in the BPD group. The strength of this correlation—but not the overall magnitude of hippocampal activation—was significantly different between the groups.

Cumulative Lifetime Stress and Hippocampal Structure

- T2- weighted high-resolution MRI scan of the medial-temporal lobe.
- Lower bilateral hippocampal volume is associated with greater lifetime stress.

$N=50$ (30 with a depressive disorder, including 15 with BPD, and 20 controls)

Goals of the Present Study

1. Investigate how cumulative stress is related to functional neural correlates of episodic memory.

2. Explore how stress may mediate established relationships between personality psychopathology and neural activation.
Participants

- Participant Groups:
  - BPD+MDD ($n=20$) *(expected moderate-severe stress)*
  - MDD only ($n=22$) *(expected mild-moderate stress)*
  - Controls with neither BPD/MDD ($n=22$) *(expected minimal stress)*

- Inclusion criteria: ages 18-55 and right-handed

- Exclusion criteria: current/lifetime DSM-5 psychotic disorder, current moderate or severe substance use disorder, neurodevelopmental disorder, neurological illness, serious physical illness, and moderate-to-severe traumatic brain injury
Measures

- Cumulative lifetime stress was assessed using the *Stress and Adversity Inventory (STRAIN)*
  - Computer-administered adaptive questionnaire; assesses 12 domains of stressful life experience, including housing, education, death, and life-threatening situations, among others.
  - Provides a count of the total number of stressors experienced, and an estimate of the cumulative severity of these stressors.

- Global Personality Psychopathology Severity
  - *Personality Inventory for ICD-11* (PiCD; Oltmanns & Widiger, 2018)

- Other symptom severity measures included the Hamilton Depression Rating Scale and Zanarini BPD Rating Scale.
Levels of Reported Cumulative Stress ($N=56$)

Shapiro-Wilk $p = .048$. Assumption of normality not violated.
Scanner Memory Task

- Memory Task: 3 runs of the following:
  - Encoding Blocks (x4)
  - High Frequency Foil Blocks (x4)
  - High Frequency Target Blocks (x4)
  - Math Baseline (x4)
Encoding Blocks

8 novel scenes presented
Indoor/outdoor button press

3sec + ~1500ms + 3sec + ~1500ms
Foil Blocks

6 novel scenes presented, 2 scenes from previous encoding block
New/old button press

3sec ~1500ms 3sec ~1500ms
Target Blocks

2 novel scenes presented, 6 scenes from previous encoding block
New/old button press

3sec + ~1500ms + 3sec + ~1500ms
Math (Baseline) Blocks

8 single-digit add or subtract operations
Odd/even button press

3 + 6

+ 9 + 2

3 sec ~1500 ms 3 sec ~1500 ms
Results

- Cumulative stress was significantly correlated with global personality psychopathology, $r = .708$, $p < .001$, and general psychological distress, $r = .644$, $p < .001$. 
Hippocampal Activation During Visual Episodic Memory Encoding

There were no significant differences in hippocampal activation between participant groups, $F(51)=1.97, p=.15$

Bilateral Hippocampal Activation During Target > Foil Blocks
Hippocampal Activation and Associations with Symptom Severity

- Hippocampal activation was not significantly associated with MDD or BPD severity, or global personality psychopathology (all $|r|'s<.24$, $p's>.08$).
Mediation of Personality Psychopathology by Stress on Hippocampal Activation

Global Personality Psychopathology (PICD)  
Cumulative Stress (STRAIN)  
Bilateral Hippocampal Activation (% Signal Change)

Direct Effect $B = .149 \ (p=.348)$

Indirect Effect $B = -0.212 \ [-.406, -.014] \ *$

Raw correlation $= -.0.64 \ (p=.245)$

Cumulative Stress (STRAIN)  
Cumulative Stress (STRAIN)

$B = .541 \ (p<.001)$

$B = -.392 \ (p=.015) \ *$

$B = -.392 \ (p=.015) \ *$
Conclusions

- Cumulative stress shows an inverse correlation with bilateral hippocampal activity during visual recognition memory.

- Cumulative stress is a significant mediator between global personality psychopathology and hippocampal activation.
  - Personality psychopathology acts indirectly on hippocampal activation through their mutual association with cumulative stress.
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