Sex-specific effects for impaired hippocampal functioning as a PTSD risk factor

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Trauma exposure

About 70% of general population

6-8% develops PTSD
  - Majority is resilient

Trauma research:
Identify individuals at RISK and understand mechanisms of RESILIENCE
PTSD mechanism of interest

Inability to regulate the fear response in a safe environment

*Working hypothesis:* Enhanced ability to use contextual information to regulate emotions and behavior may enhance resilience and protect against the development of PTSD
Brain regions of interest (1): Hippocampus

• Contextual learning/memory modulating responses based on contextual cues
• In PTSD
  • Decreased volume$^1$
  • Reduced recruitment during fear inhibition$^{2,3}$ particularly related to contextual cues$^3$

Brain regions of interest (2): vmPFC

- Inhibition of behavior and emotions, fear response
- In PTSD
  - Reduced functional connectivity with the amygdala during threat\textsuperscript{1}

\textsuperscript{1}Stevens Jovanovic, ... Ressler 2013 J Psych Res

Mah et al 2015 Curr Opinion in Psychiatry
Inhibition paradigm

Go trials
- Press “1”
- Press “2”

NoGo trials
- Do not press
- Do not press

NoGo cue
- Response inhibition
- NoGo > Go trials

Investigating vmPFC and hippocampal functioning in PTSD using the Go/NoGo paradigm
Is vmPFC or hippocampal activation during response inhibition related to chronic PTSD or resilience?

Chronically traumatized women of the Grady Trauma Project

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Jovanovic, Ely, ... Ressler, 2013, Cortex

van Rooij, Stevens ... Jovanovic., 2016, Front Psych
Is vmPFC or hippocampal activation during response inhibition predictive of future PTSD?

Recently traumatized civilians (N=58) in the GTP Emergency Department study

van Rooij, Stevens.. Jovanovic (2018) Biological Psychiatry
Is vmPFC or hippocampal activation during contextual fear inhibition related to future PTSD or resilience?

### Fear conditioning

- **CS+ > CS-**

### Effect of context during extinction

- **CS+ old context > CS+ new context**

van Rooij, Ravi.. Stevens (2021) Behav Brain Res
Is vmPFC or hippocampal activation during contextual response inhibition related to future PTSD?

Powers, Hinojosa .... van Rooij (in press) Eur J Psychotraum
Discussion

• Small studies, but consistent findings
  • Greater hippocampal activation during response inhibition related to lower levels of PTSD and greater levels of resilience
  • Some evidence for lower levels of vmPFC during response inhibition in chronic PTSD
    • More studies on vmPFC in other task paradigms

• Underpowered for assessment of effect of sex
AURORA ED study

Large multisite Emergence Department Study

AURORA, N=2611 (included here)

Gender assigned at birth

PTSD symptoms at 6 months (PCL-5)
- Men: 20.8
- Women: 25.3

$p < 0.001$
Sex-specific effects for hippocampal activation as a PTSD risk factor?

Lower posterior hippocampal activation was related to greater PTSD symptoms in men (sex*posthipp, $p=0.003$)
vmPFC as risk factor for PTSD and other adverse neuropsychiatric sequelae (APNS)?

Lower vmPFC hippocampal activation was related to greater PTSD symptoms, but also greater impulsivity and sleep impairment.

No sex differences
Conclusion (1)

• Hippocampus specific to PTSD in men
  • Potential risk pathway for men
  • Possibly related to its role in spatial recognition and the hypothesis that impaired hippocampal functioning represents reduced context processing
  • More research into sex differences needed

• vmPFC related to transdiagnostic APNS in inhibitory domain
  • next step: create one risk vs resilience: R-factor
R-factor analyses

- Principal Component Analyses (PCA)
- N=2062 from AURORA study with 6-month item-level data
- Main component: R-factor
  - Low scores on: PTSD, depression, anxiety, sleep impairment, impulsivity
  - No sex differences, but non-significant greater r-factor scores for men

- N=215 with usable neuroimaging data
  - Whole brain analyses
  - Corrected for: age, sex, site
Go/NoGo whole brain R-factor

vmPFC

right IFG
Conclusion (2)

• More activation in inhibitory control regions related to resilience
• Potential transdiagnostic mechanism for early interventions?

• Additional analyses:
  • R-factor analyses for fearful faces, reward tasks
  • R-factor analyses relating to neuropsychological measures

• Future directions: early interventions targeting these regions
Thank you for your attention!

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