Response inhibition deficit as a transdiagnostic risk factor for posttraumatic neuropsychiatric sequelae

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Response inhibition

The ability to suppress irrelevant or inappropriate actions in response to novel information

>> Cognitive control

Stevens et al AJP 2021

Powers et al EJPT in press
Response inhibition

Right inferior frontal gyrus (rIFG)
- Attentional monitoring
- Expectancy violation

Reduced activation in e.g., PTSD\(^1\), ADHD\(^2\)

\(^1\)van Rooij et al (2014) JPN
\(^2\)van Rooij & Jovanovic (2019) Progress in NPP & BPS
Fear inhibition

The ability to regulate the fear response in a *safe* environment

In van Rooij et al 2021; Adapted from Milad et al 2009
Fear inhibition

- **vmPFC**
  - Inhibition of behavior and emotions, fear response

- **Hippocampus**
  - Contextual learning/memory modulating responses based on contextual cues
Inhibition as mechanism for cross-domain psychopathology

Psychopathology (P) factor → “A single dimension is able to measure and maybe even explain a person’s liability to mental disorder, comorbidity among disorders, persistence of disorders over time, and severity of symptoms”\(^1\)

One hypothesis: response inhibition is core mechanism
- Poor impulse control over emotions
- Impulsive speech and action in response to experienced emotions
- Cognitive impulsiveness (rumination) about distress
- Impulsive overgeneralization from negative events

\(^1\)Caspi & Moffitt, 2019 AJP
Inhibition as mechanism for post-trauma risk vs resilience

Hypothesis PTSD: Enhanced ability to use contextual information to regulate emotions and behavior may enhance resilience and protect against the development of PTSD
Response inhibition related to **chronic** PTSD vs resilience

Chronically traumatized women of the Grady Trauma Project
Clinical outcomes: PTSD symptom scale (PSS), trait resilience (CD-RISC)

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

van Rooij, Stevens ... Jovanovic., 2016, *Front Psych*
Response inhibition predictive of future PTSD

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

1 month post-trauma scan
3+6 months post-trauma PSS

van Rooij, Stevens.. Jovanovic (2018) Biological Psychiatry
Contextual response inhibition related to future PTSD

**Reactive inhibition**
- Go trial
- Stop trial

**Proactive inhibition**
- Stop Signal Probability level
  - 0%
  - 22%
  - 33%

A. Right inferior frontal gyrus (rIFG)
- rIFG contrast estimate

B. Ventromedial prefrontal cortex (vmPFC)
- vmPFC contrast estimate

PTSD symptoms (PSS) at 6 months

Powers, Hinojosa .... van Rooij (in press) Eur J Psychotraum
Contextual fear inhibition related to future PTSD vs resilience

**Fear conditioning**

- **CS+ > CS-**

**Effect of context during extinction**

- **B. ROI analysis resilience**
  - CS+ old context > CS+ new context

- **B. ROI analysis 3 mo PTSD symptoms**
  - Standardized residuals for PTSD symptoms at 3 months (PSS total) corrected for baseline PTSD symptoms, age, gender

van Rooij, Ravi.. Stevens (2021) *Behav Brain Res*
Discussion (1)

- Small studies, but consistent findings
  - Greater hippocampal activation during inhibition related to lower levels of PTSD and greater levels of resilience
  - Some evidence for lower levels of vmPFC and rIFG during response inhibition in PTSD

Next step: larger studies
AURORA ED study

Intensive assessment of APNS throughout key early development period

In-person evaluation of subset of study participants during the early posttraumatic period (n=800)

In-person evaluation of subset of study participants after the development of APNS (n=800). Additional follow-up blood draw group (n=2,200)

Legend:
- web-based neurocognitive assessment;
- flash surveys of cognition and symptoms;
- wrist device evaluating circadian and physiologic characteristics;
- saliva collection;
- blood product collection;
- continuous smartphone app data collection;
- self-report questionnaires
Response inhibition hippocampus PTSD risk factor for men

Lower posterior hippocampal activation was related to greater 6mo PTSD symptoms in men (sex*posthipp, p=0.003)
Response inhibition vmPFC risk for PTSD and other adverse neuropsychiatric sequelae (APNS) in impulsivity domain

Lower vmPFC activation was related to greater PTSD symptoms, but also greater **impulsivity** and sleep impairment.
• Hippocampus findings 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 factor across domains
Resilience factor

Following the rationale of the p-factor

1. Can we create unbiased cross-domain resilience factors in the early aftermath of trauma?

2. Can we identify neurobiological correlates of the r-factor?
Month 6: Clinical outcomes

Flash surveys for posttraumatic neuropsychiatric sequelae (APNS)

- PTSD - PCL-5
- Depression - PROMIS
- Anxiety - PROMIS
- Sleep - PROMIS
- Alcohol, Marijuana use (# of days)
- Impulsive Behavior - SUPPS-P
R-factor analyses

**Item-level data (46 items)** for PTSD, depression, anxiety, sleep, alcohol/marijuana use and impulsivity at 6 months used to create **unbiased resilience factors** across domains

- Principal Component Analyses (PCA)
- N=2062 from **AURORA study** with 6-month item-level data
  - N=1827 with complete data

### Total Variance Explained

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<tr>
<th>Component</th>
<th>Initial Eigenvalues</th>
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### R-factor analyses - correlations with items

(greater r = greater resilience against item)

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R-factor analyses

1. Global stress resilience
   • Resilient to: depression, anxiety, PTSD
   • No sex differences, but non-significant greater r-factor scores for men

2. Trauma reminder resilience
   • Resilient to: avoiding and reexperiencing of trauma
   • Lower scores in women (mean=-0.10) than men (mean=0.18), p<0.001

3. Impulsivity resilience
   • Resilient to impulsivity, risk taking (sleep, jumpy, irritable)
   • Correlation with age, r=0.121, p<0.001 (older, less impulsive)
Neuroimaging data

- **Functional MRI**
  - Inhibition - GNG task (N=215)
  - Whole brain analyses, corrected for site
    - Primary threshold, $p<0.001$
    - Cluster-level corrected threshold, $p<0.05$ + Bonferroni correction for multiple testing (3 factors), $p<0.016$
Whole brain r-factor analyses

BOLD response Go/NoGo

Whole brain correlation

R-factor continuous score

p<0.001, cluster level p<0.016
R-factor: global stress and trauma reminders

No whole brain findings that survived correction for multiple testing
- global stress resilience
- trauma reminders resilience
R-factor: impulsivity resilience

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<th>state</th>
<th>F-statistic</th>
<th>p-value</th>
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*Right middle frontal gyrus*
*Right inferior frontal gyrus*
*Right middle temporal gyrus*
*Left precuneus*
*Right middle temporal gyrus*

**R Middle/Inferior frontal gyrus**

**Impulsivity resilience**

**R Middle/Inferior frontal gyrus**

**L precuneus**

**R middle temporal gyrus**

**Negative association, p<0.001**

Cluster-level correction + Bonferroni multiple testing, p<0.016

**Inhibition, positive, p<0.001**

P<0.001, cluster-level + Bonferroni correction, p<0.016
Discussion

No significant correlations with general stress resilience

→ whole brain correlations with threat and reward (incl rIFG)

More impulsive resilience
More right **Middle/Inferior Frontal Gyrus**
- Attentional monitoring
- Expectancy violation

Less right **Middle Temporal Gyrus, left precuneus**
- Reflections upon self
Future directions and implications

Resilience is NOT merely the absence of psychopathology or PTSD after stress/trauma

* Definition: The set of complex and dynamic processes that allow individuals to maintain psychological well-being in the face of adversity\(^1\)

Next steps:
Dynamic resilience - capacity to recover to a state of well-being within a few weeks to months of a major stressful life event
→ Analyze symptom change from baseline

\(^1\)Roeckner, Oliver... Stevens, Translational Psychiatry, 2021
Thank you for your attention!

Jennifer Stevens  
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Barbara Rothbaum  
Kerry Ressler  
Tanja Jovanovic  
GTP volunteers and staff

Sam McLean  
Karestan Koenen  
Ron Kessler  
Nathaniel Harnett  
Lauren Lebois  
Vishu Murthy  
AURORA study team

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R-factor: Global stress resilience

Threat: negative
Reward: positive, negative

Primary threshold, $p<0.001$
+ cluster-level Bonferroni correction, $p<0.016$