EMORY UNIVERSITY SCHOOL OF MEDICINE

GRADY trauma PROJECT

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

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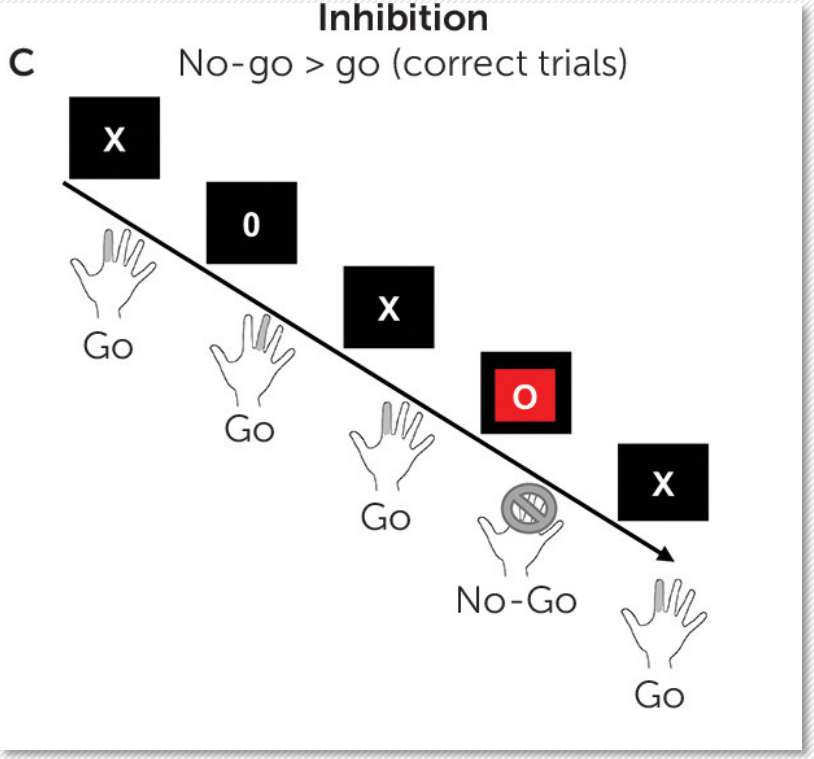
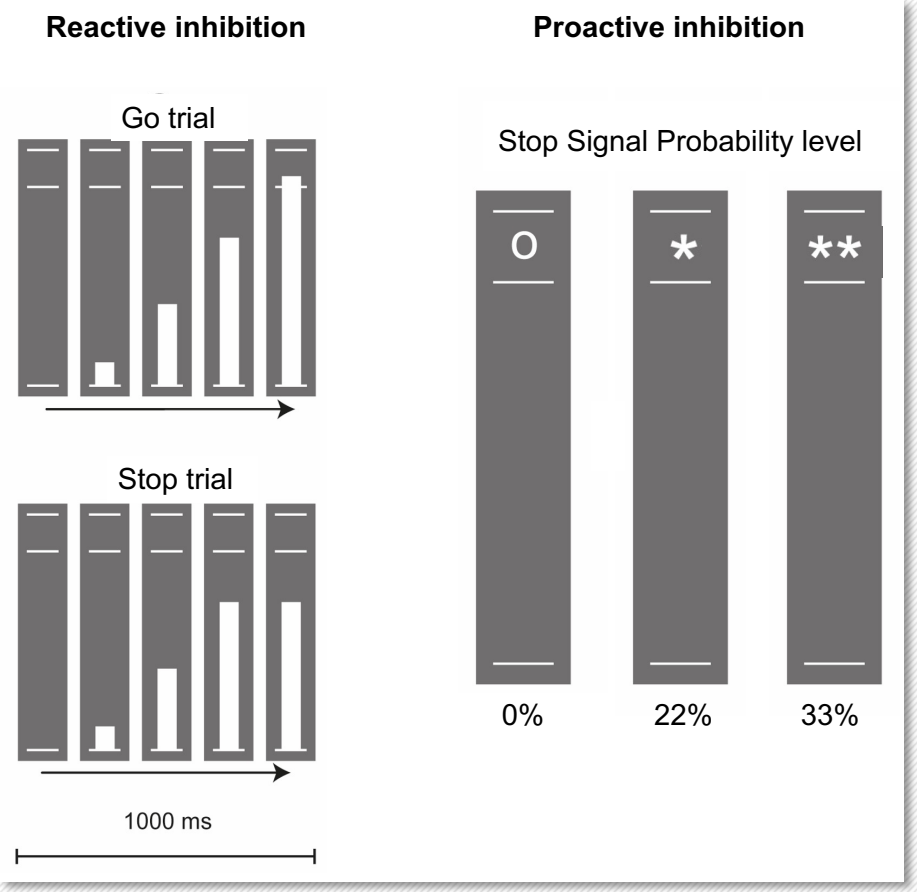
Response inhibition

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

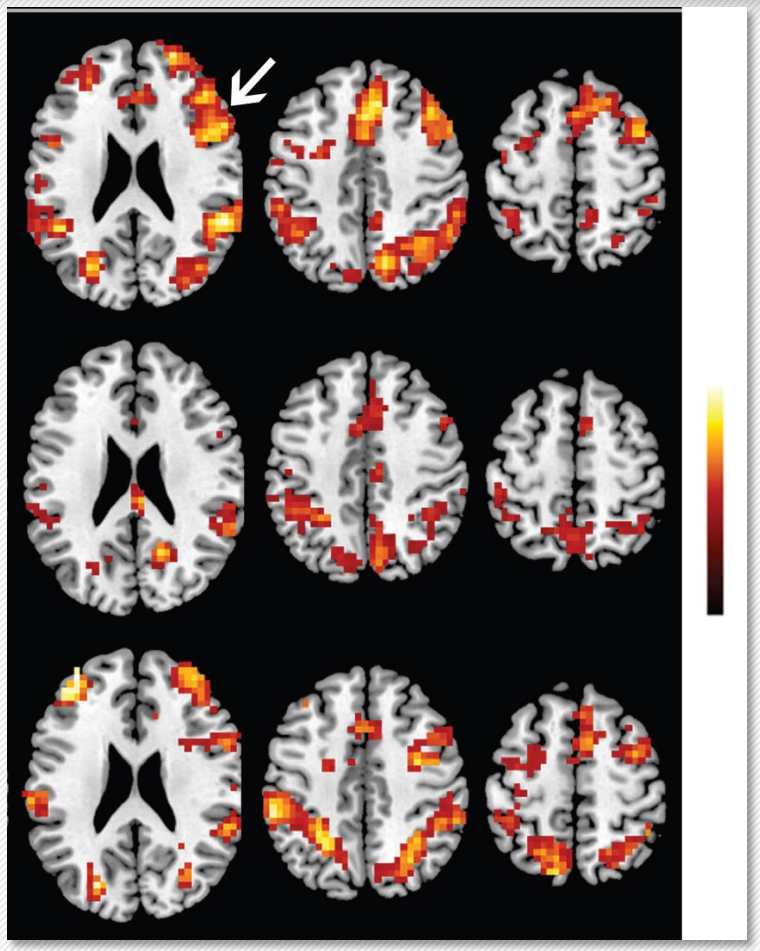
Response inhibition

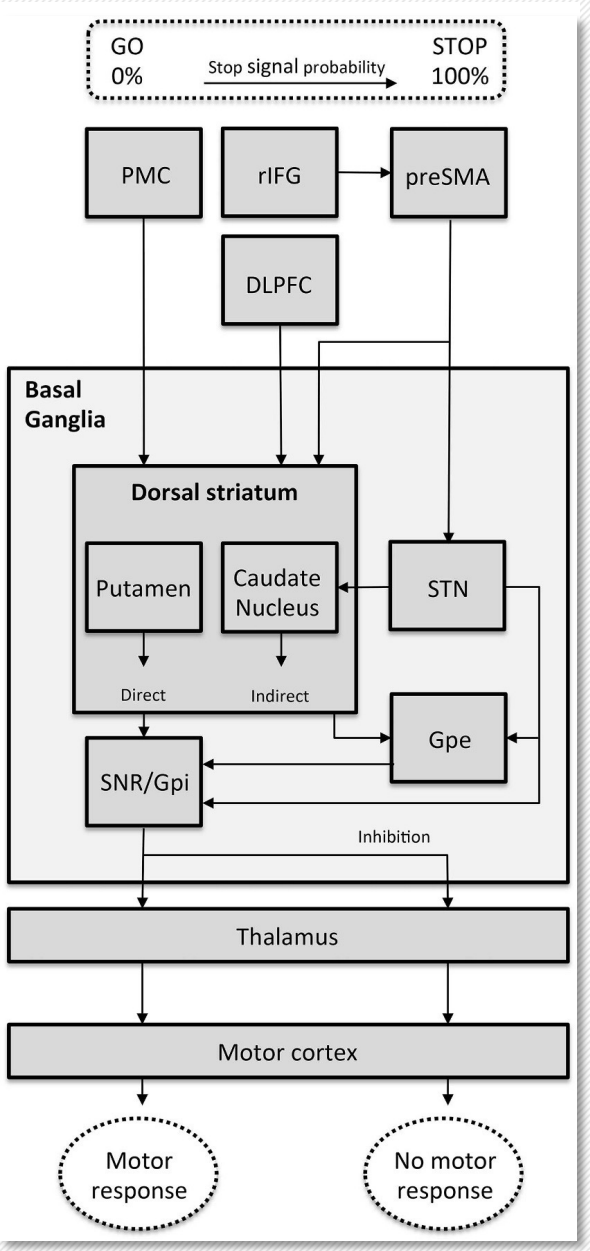
Right inferior frontal gyrus (rIFG)

- Attentional monitoring
- Expectancy violation

Reduced activation

in e.g., PTSD[1], ADHD[2]



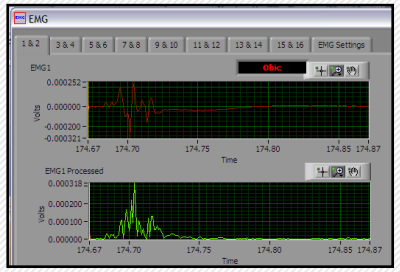


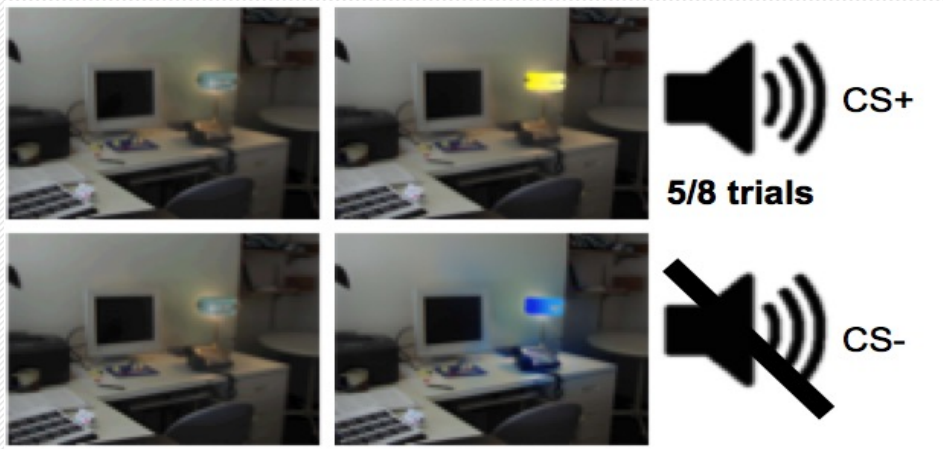
[1]van Rooij *et al* (2014) *JPN*

van Rooij & Jovanovic (2019) *Progress in NPP & BPS*

Fear inhibition

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

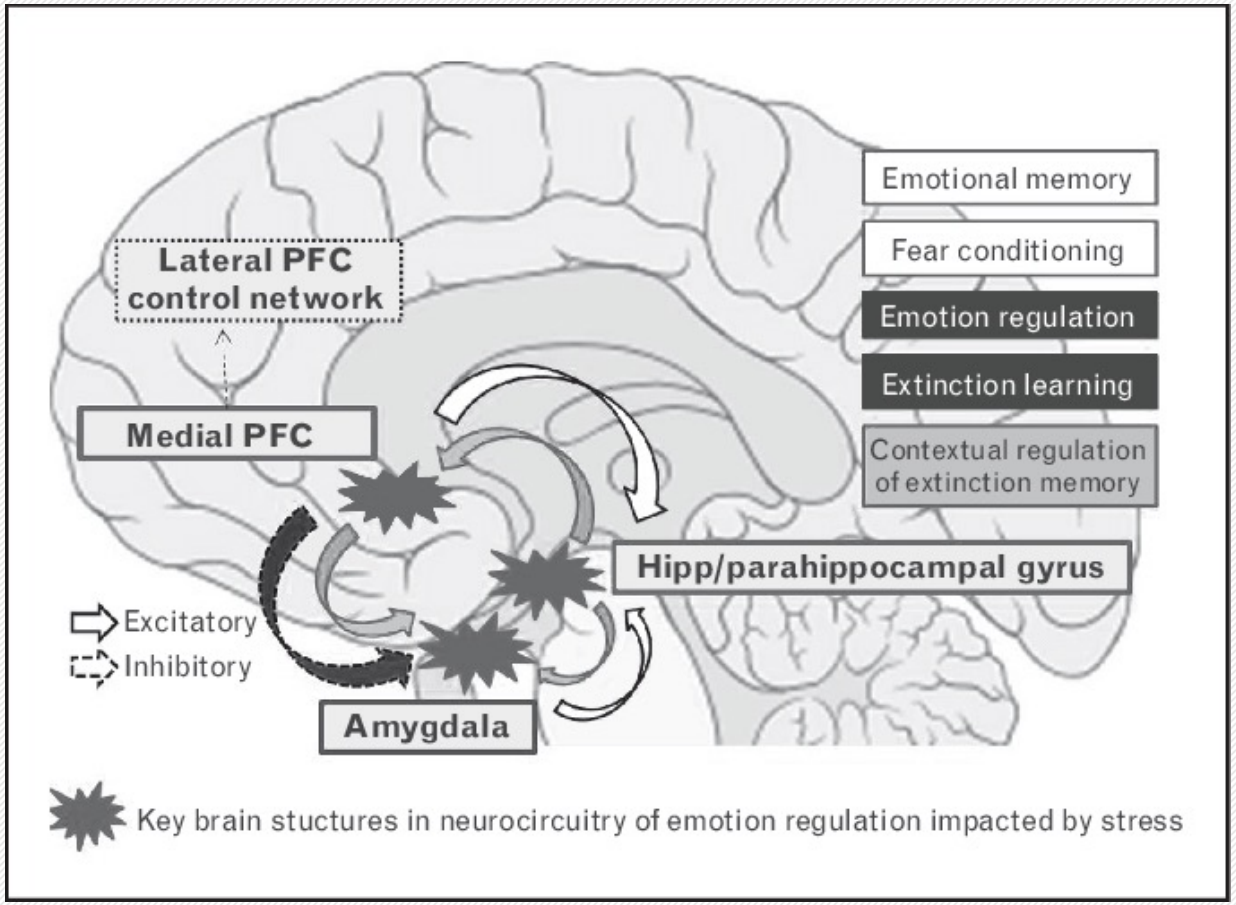




CS+ > CS-

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

Fear inhibition



Mah et al 2015 Curr Opinion in Psychiatry

- 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: <u>response inhibition is core mechanism</u>

- 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*

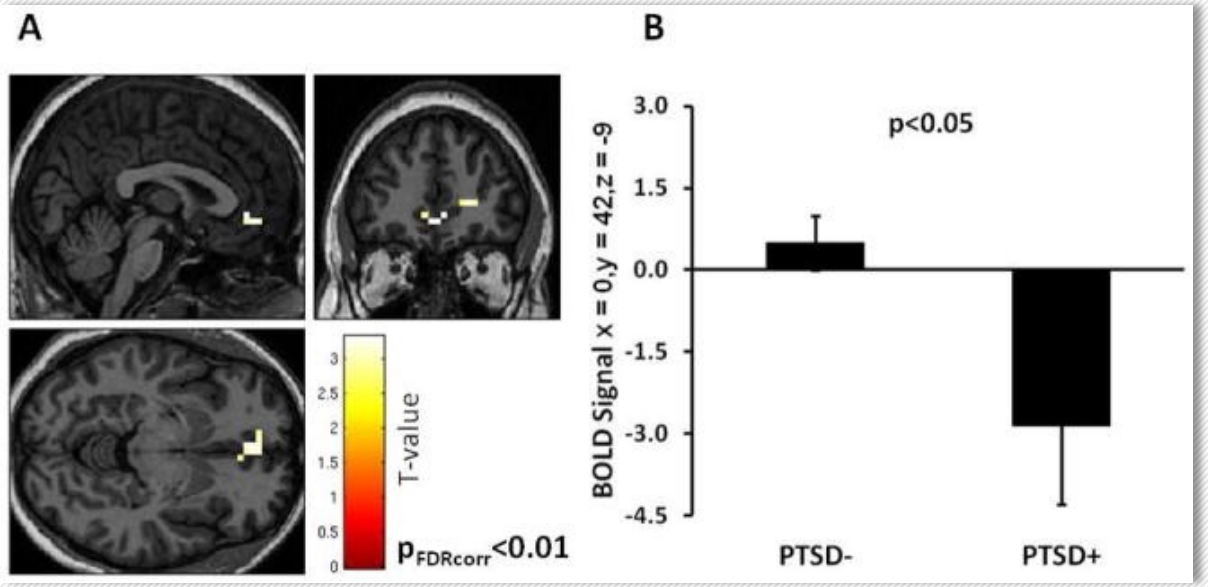
Inhibition as mechanism for **post-trauma** risk *vs* resilience

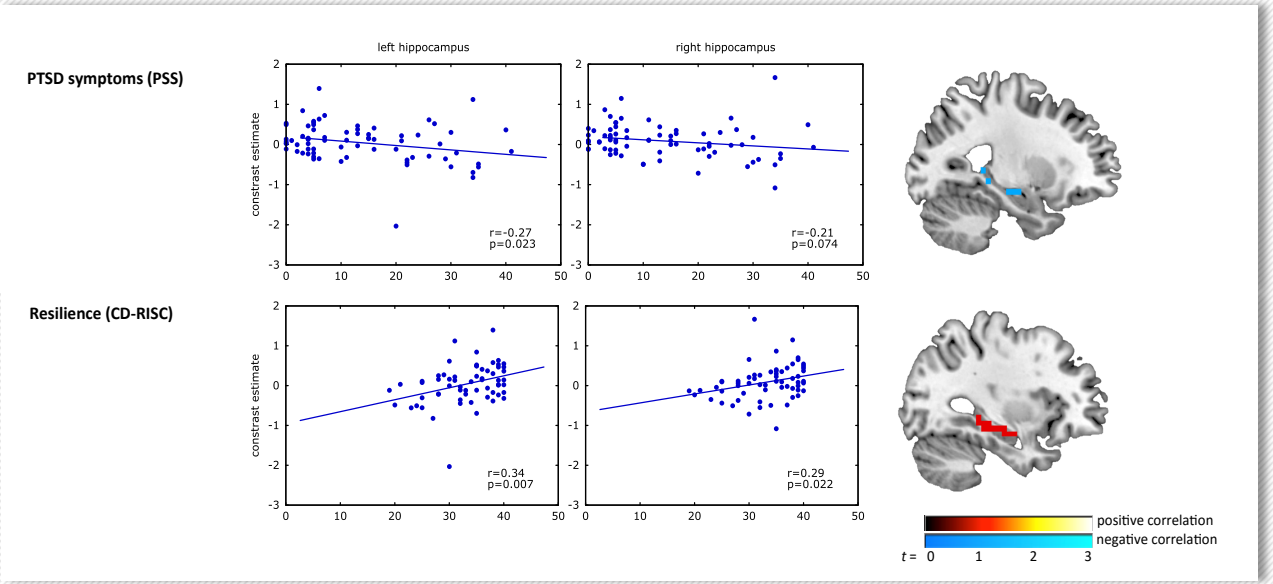
Hypothesis PTSD: Enhanced ability to use contextual information to regulate emotions and behavior may enhance resilience and protect against the development of PTSD

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*

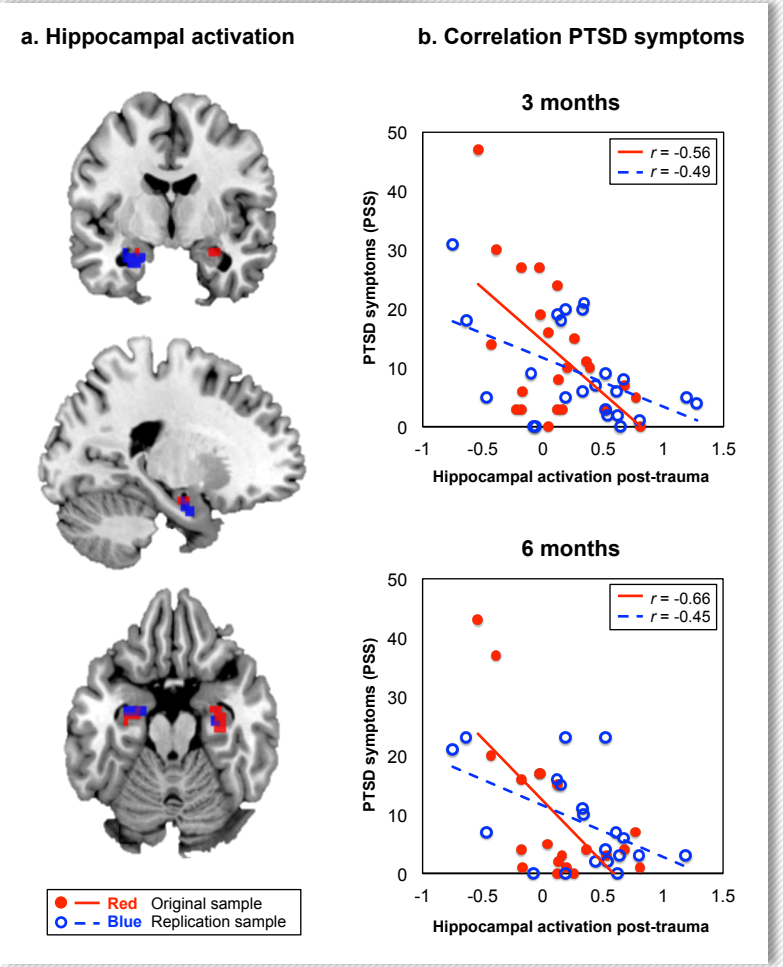
Response inhibition predictive of future PTSD

Recently traumatized civilians (N=58)

in the GTP Emergency Department study

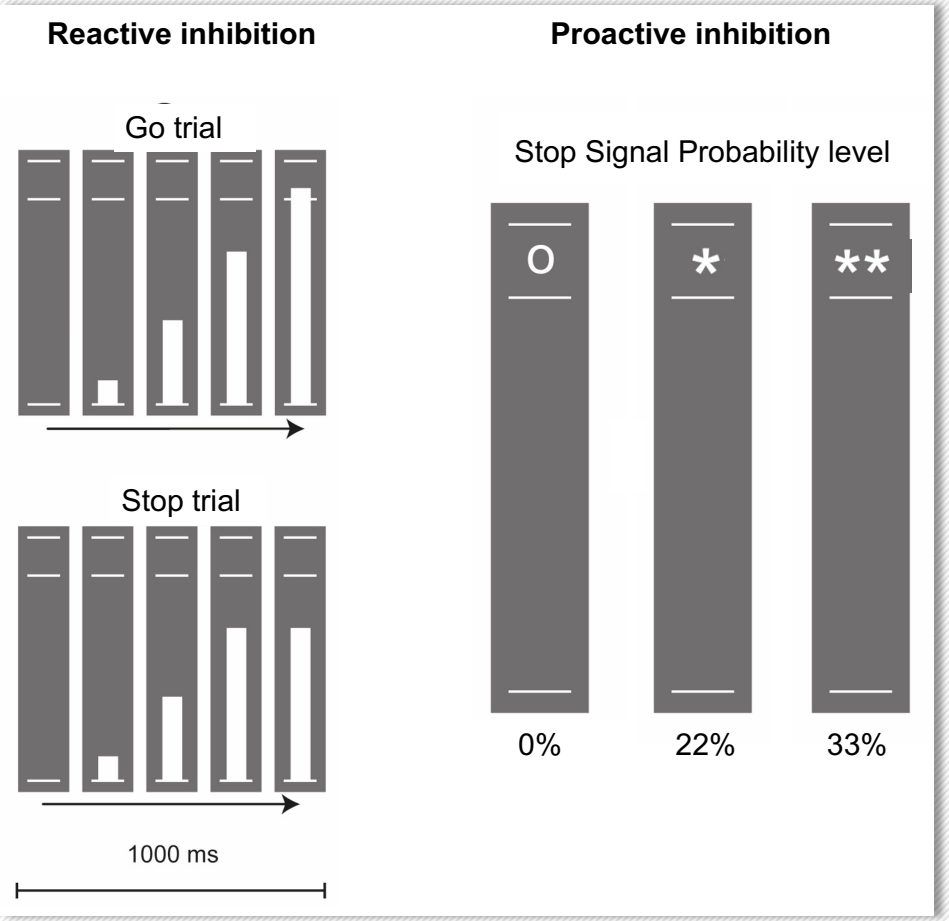
1 month post-trauma scan

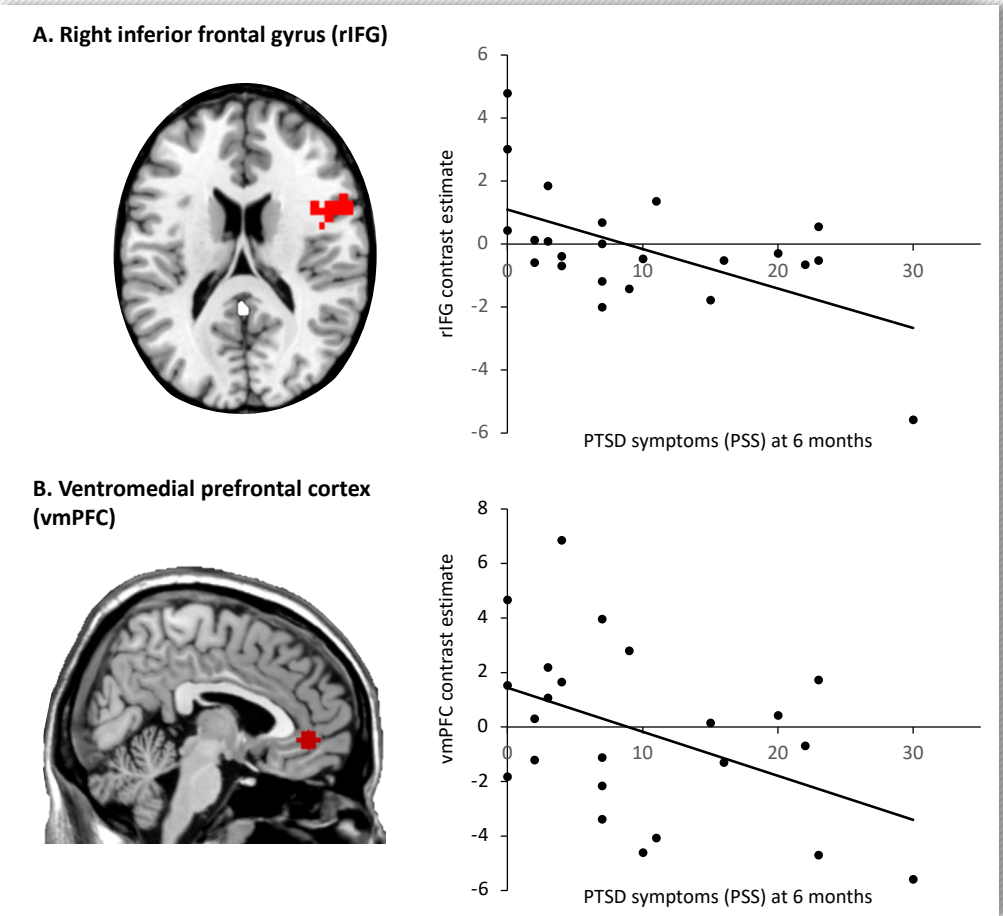
3+6 months post-trauma PSS



van Rooij, Stevens.. Jovanovic (2018) *Biological Psychiatry*

Contextual response inhibition related to future PTSD

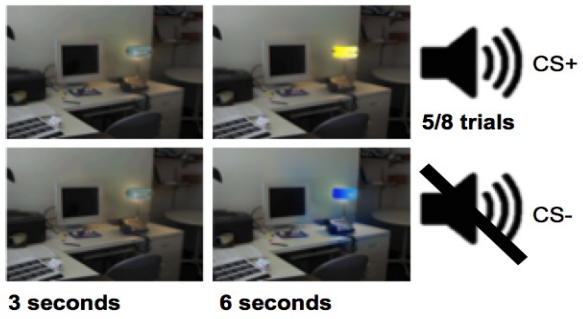




Powers, Hinojosa …. van Rooij (in press) *Eur J Psychotraum*

Contextual fear inhibition related to future PTSD vs resilience

Fear conditioning



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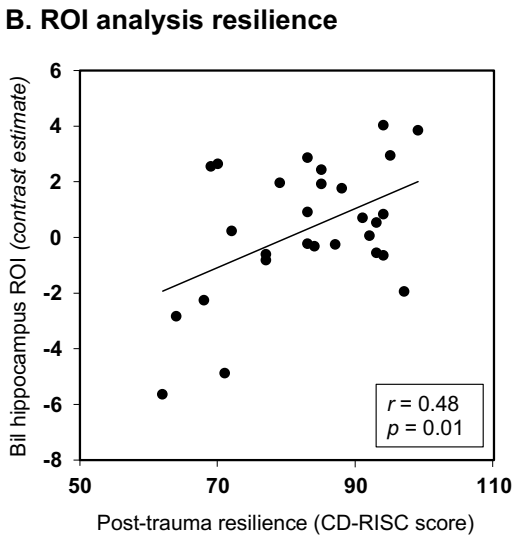
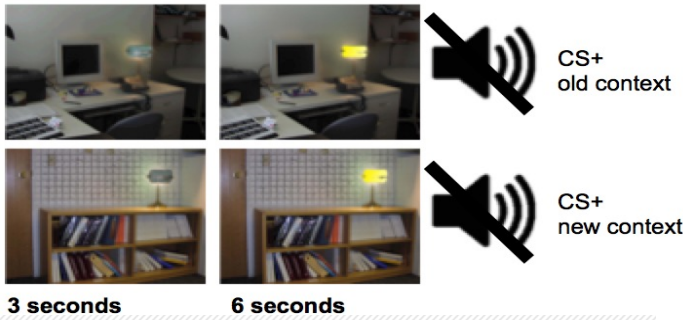
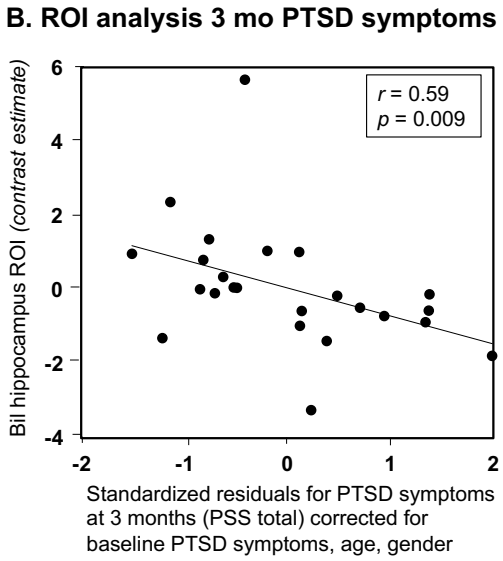


Effect of context during extinction



CS+ old context >
CS+ new context



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

AURORA

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)

Saliva collection n=2000: weeks 1 - 4
Flash surveys daily: week 1

Wrist device worn continuously: weeks 1 - 12
Flash surveys every other day: weeks 2 - 12

Wrist device worn variable intervals: weeks 13 - 52
Flash surveys once per week: weeks 13 - 52

Traumatic Event

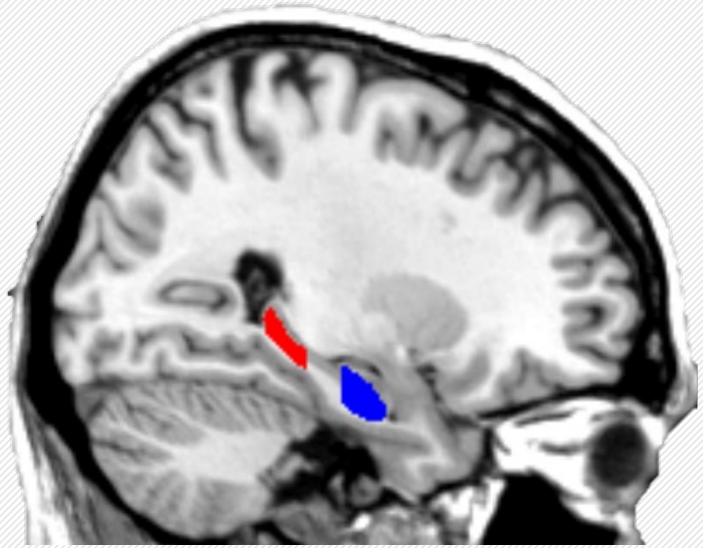
ED

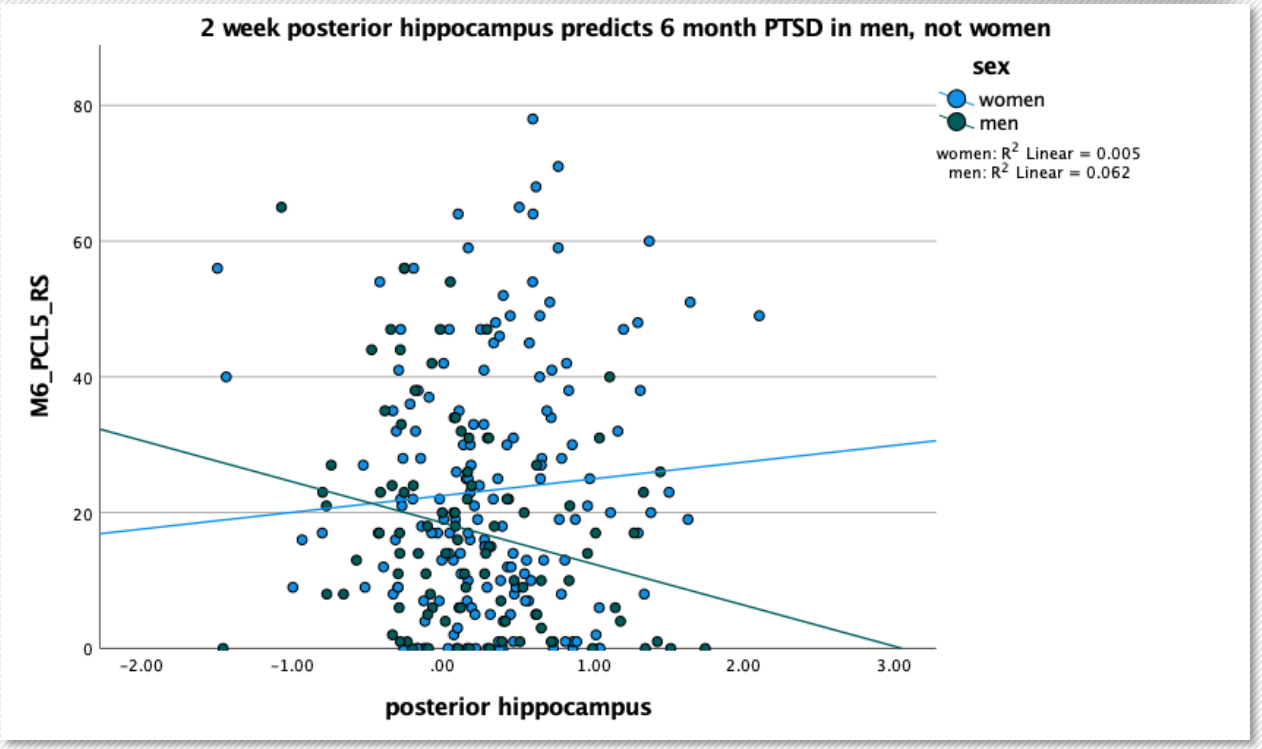
Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | Wk 7 | Wk 8 | Wk 9 | Wk 10 | Wk 11 | Wk 12 | Month 3 | Month 6 | Month 9 | Month 12

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

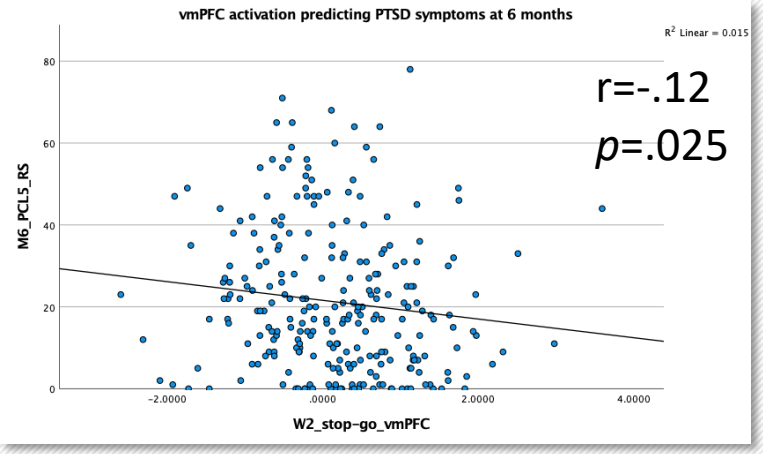
Response inhibition hippocampus PTSD risk factor for men

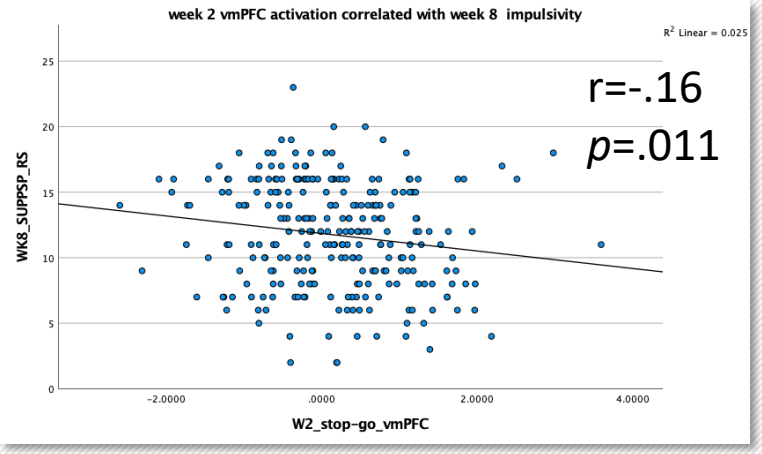


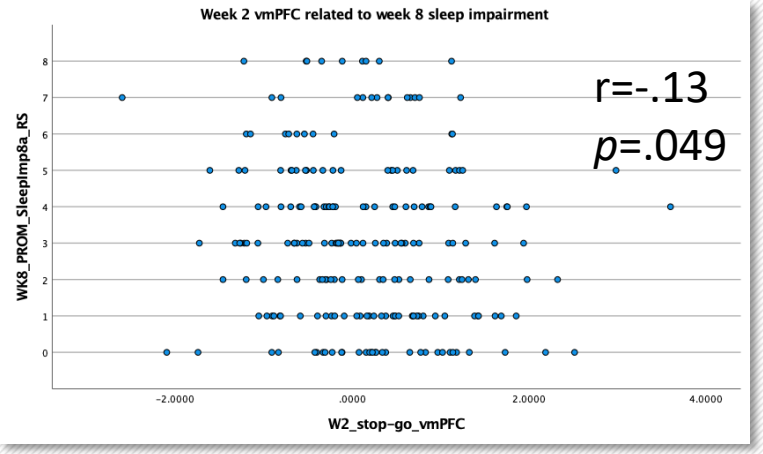


Lower posterior hippocampal activation was related to greater 6mo PTSD symptoms in men (sex*posthipp, *p*=0.003)

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.**

Conclusion (1)

- 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

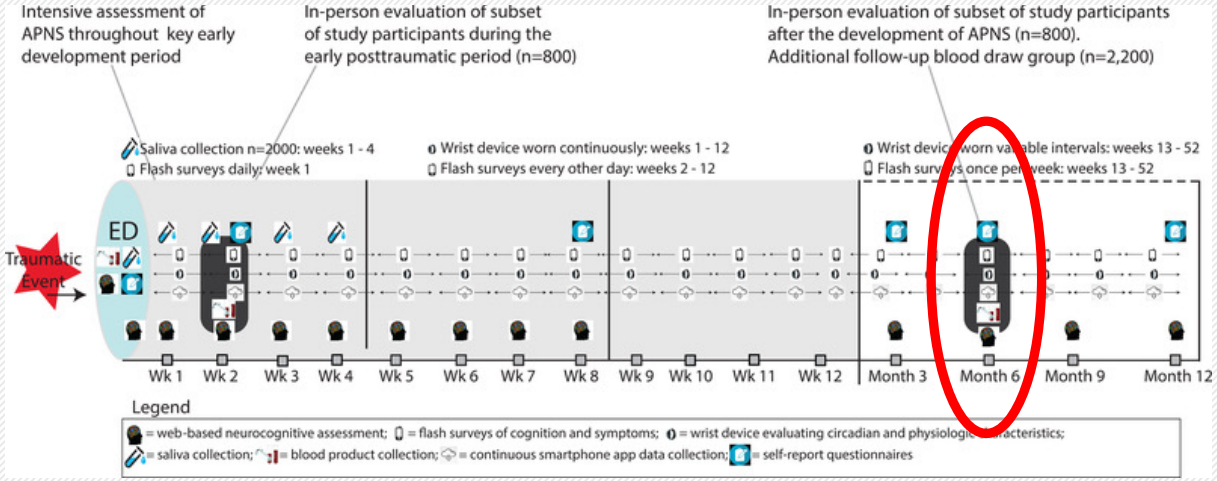
1. Can we create unbiased cross-domain **resilience factors** in the early aftermath of trauma?

2. Can we identify neurobiological correlates of the r-factor?

Month 6: Clinical outcomes

Flash surveys for posttraumatic neuropsychiatric sequalae (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

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	23.872	51.895	51.895	23.872	51.895	51.895	12.187	26.493	26.493
2	2.410	5.239	57.134	2.410	5.239	57.134	9.162	19.917	46.410
3	2.198	4.779	61.913	2.198	4.779	61.913	3.973	8.636	55.046

R-factor analyses – correlations with items

(greater r = greater resilience against item)

Clinical domain	item	1	2	3
Anxiety	Anxious	0.64	0.38	0.11
Anxiety	Tense	0.64	0.39	0.09
Anxiety	TroubleRelax	0.64	0.37	0.08
Anxiety	WorryAboutThings	0.64	0.36	n.s
Depression	Depressed	0.79	0.28	0.16
Depression	Failure	0.81	0.26	0.25
Depression	Helpless	0.79	0.29	0.25
Depression	Hopeless	0.81	0.26	0.25
Depression	NothingInterest	0.70	0.35	0.24
Depression	NothingToLookForward	0.82	0.23	0.26
Depression	Sad	0.77	0.31	0.13
Depression	Unhappy	0.79	0.27	0.15
Depression	Worthless	0.81	0.26	0.29
Impulsivity	ActWithoutThinkExcited	0.25	0.22	0.78
Impulsivity	ActWithoutThinkUpset	0.34	0.23	0.67
Impulsivity	FeelingRejected	0.34	0.23	0.68
Impulsivity	LoseControl	0.29	0.24	0.76
Impulsivity	SeeThingsThrough	n.s	0.06	n.s
Impulsivity	ThinkCarefully	0.07	0.13	0.10
Impulsivity	ThinkThingsOver	0.18	0.16	0.22
Impulsivity	UnfinishedTasks	0.39	0.21	0.29
Pain	Pain	0.22	0.44	0.13
PTSD	AvoidReminders	0.30	0.78	0.16
PTSD	AvoidStressExperience	0.32	0.79	0.16
PTSD	BadDreams	0.34	0.72	0.17
PTSD	BlamingSelf	0.51	0.60	0.20
PTSD	DifficultyConcentrate	0.52	0.43	0.24
PTSD	DisturbingMemories	0.34	0.77	0.12
PTSD	FeelingCutOff	0.69	0.42	0.19
PTSD	FeelingFear	0.58	0.58	0.19
PTSD	FeelingIrritable	0.56	0.46	0.28
PTSD	FeelingJumpy	0.32	0.58	0.26
PTSD	FeelingUpset	0.35	0.78	0.10
PTSD	LackPositiveEmotions	0.70	0.44	0.27
PTSD	LossOfInterest	0.65	0.47	0.20
PTSD	NoOneCanBeTrusted	0.63	0.51	0.24
PTSD	RelivingEvent	0.28	0.77	0.23
PTSD	SleepProblems	0.39	0.40	0.11
PTSD	StrongPhysicalReactions	0.33	0.78	0.17
PTSD	Superalert	0.22	0.58	0.18
PTSD	TakingRisks	0.30	0.30	0.57
PTSD	TroubleRemember	0.34	0.57	0.26
Sleep	DiffStayAwakeInDay	0.22	0.18	0.14
Sleep	SleepProbDiffGetThingsDone	0.29	0.23	0.28
Substance	MarijuanaNumDays	0.07	n.s	n.s
Substance	NumDaysAlcohol	0.06	n.s	0.15

R-factor analyses

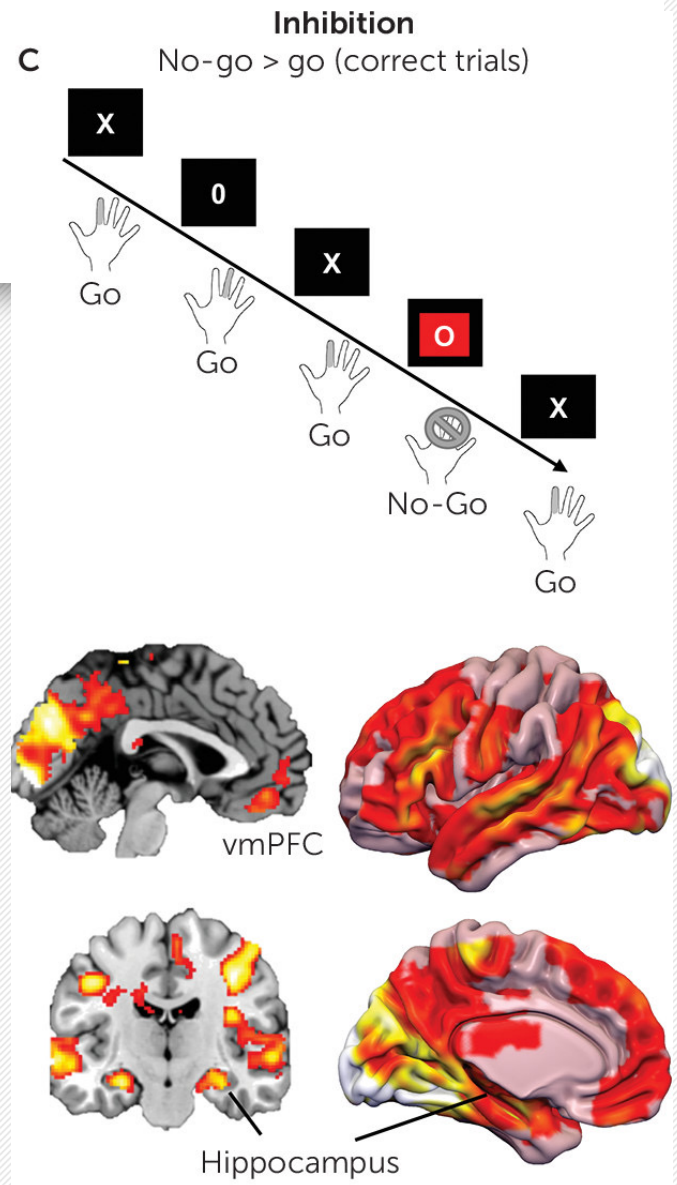
1. **Global stress resilience**
   - Resilient to: depression, anxiety, PTSD
   - No sex differences, but non-significant greater r-factor scores for men

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)

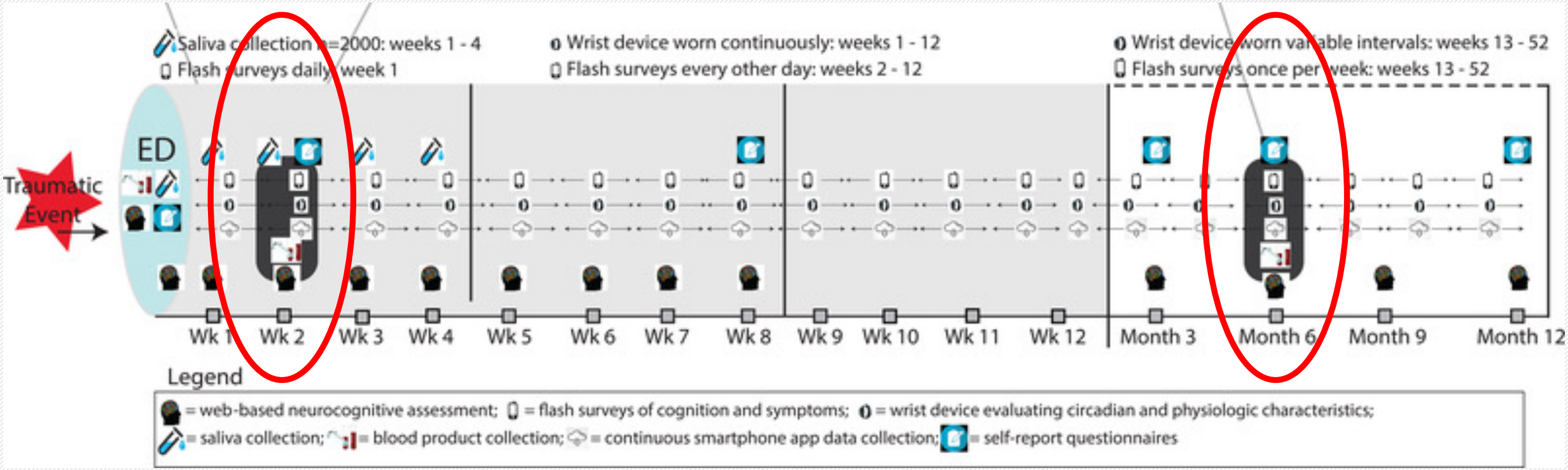
Neuroimaging data

- *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**



Stevens et al, 2021, *AJP*

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

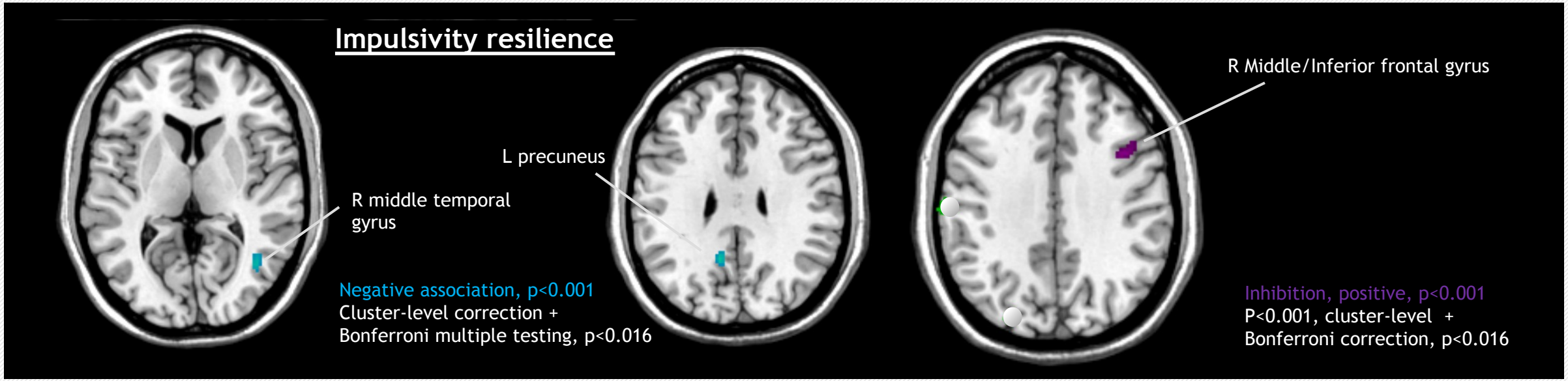
R middle/inferior frontal gyrus

R-factor: impulsivity resilience

*

Inhibition	positive	**52**	**0.006**	**4.11**	**40**	**12**	**38**	**right middle frontal gyrus**
		27	0.037	3.74	46	24	22	right inferior frontal gyrus
Inhibition	negative	**59**	**0.004**	**3.94**	**40**	**-64**	**6**	**right middle temporal gyrus**
		57	**0.004**	**4.10**	**-10**	**-56**	**32**	**left precuneus**
		24	0.048	3.77	68	-28	-2	right middle temporal gyrus

BOLD - Primary threshold, 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)

<u>More impulsive resilience</u>

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

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Barbara Rothbaum
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R-factor: Global stress resilience