

Brain rhythm hypersynchrony in soldiers with PTSD

Dr. Benjamin T. Dunkley, Ph.D.

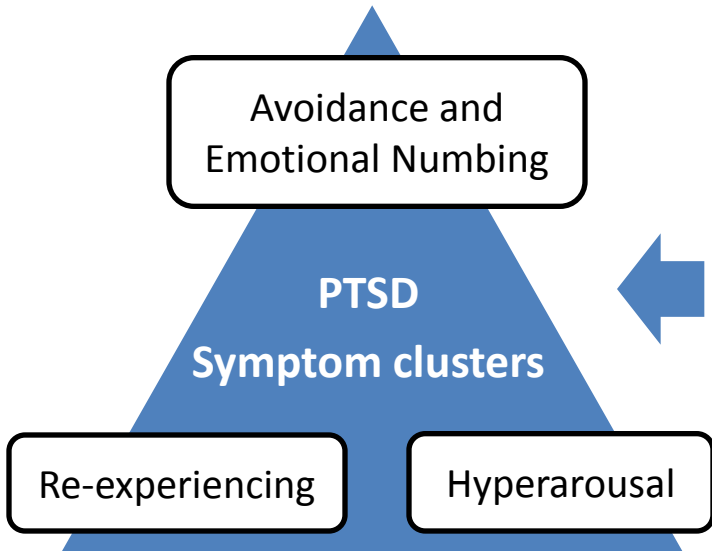
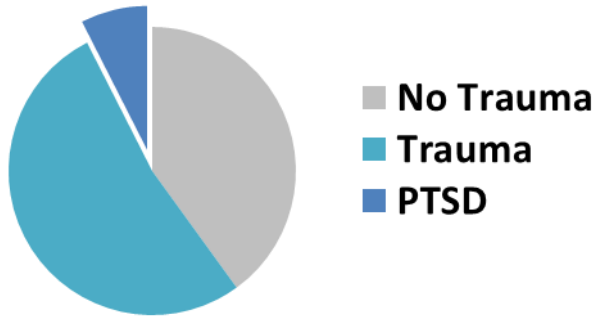
MEG Clinical Associate, Diagnostic Imaging, Neurosciences & Mental Health
Hospital for Sick Children

Assistant Professor, Medical Imaging
University of Toronto

Post-traumatic stress disorder

Incidence and symptoms

DSM-IV-TR: Anxiety and stressor-related disorders



Pre-existing cognitive risk factor



Trauma

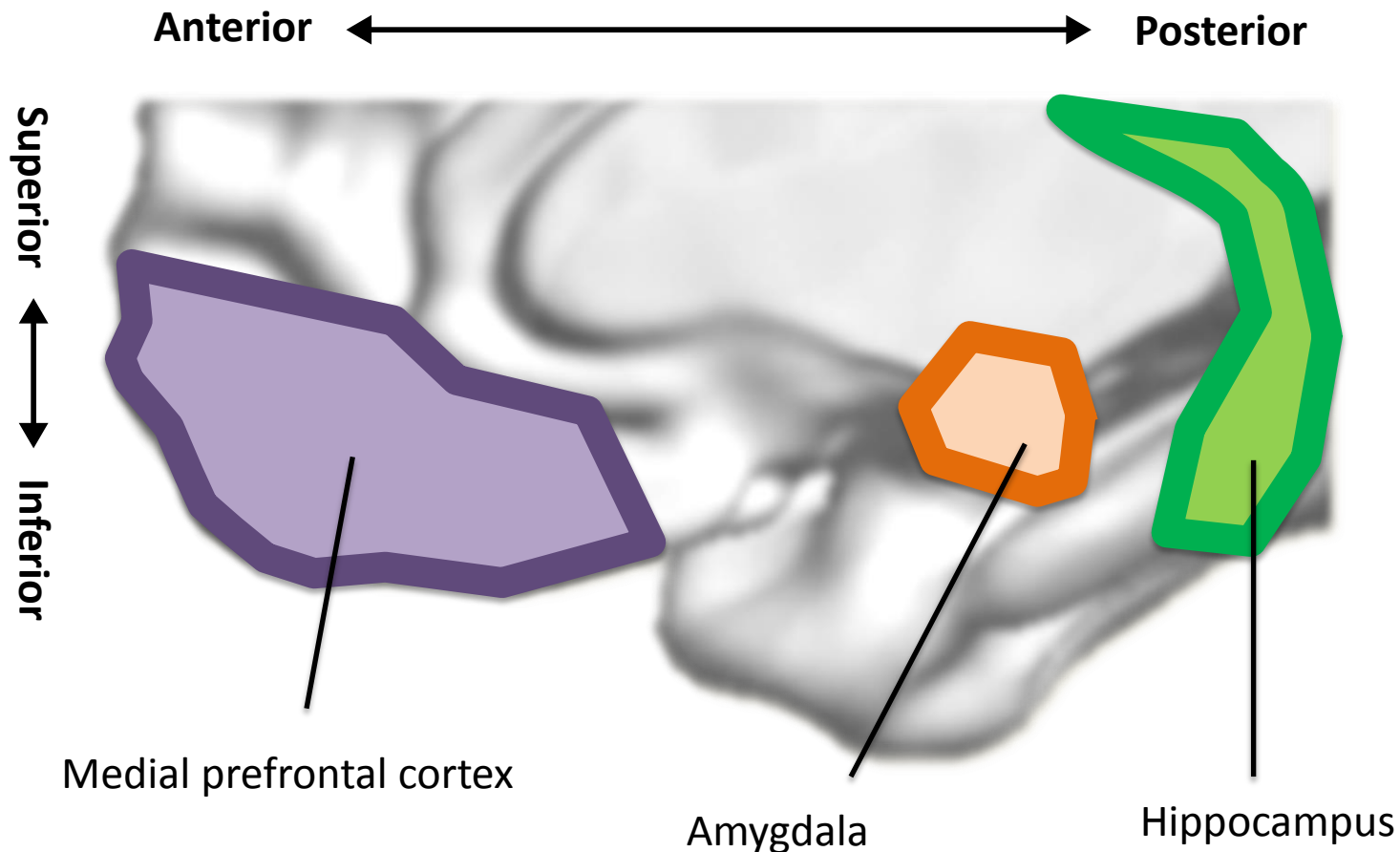


1. Learned association (conditioning) between trauma and stimuli
2. Unable to direct attention away from trauma reminders



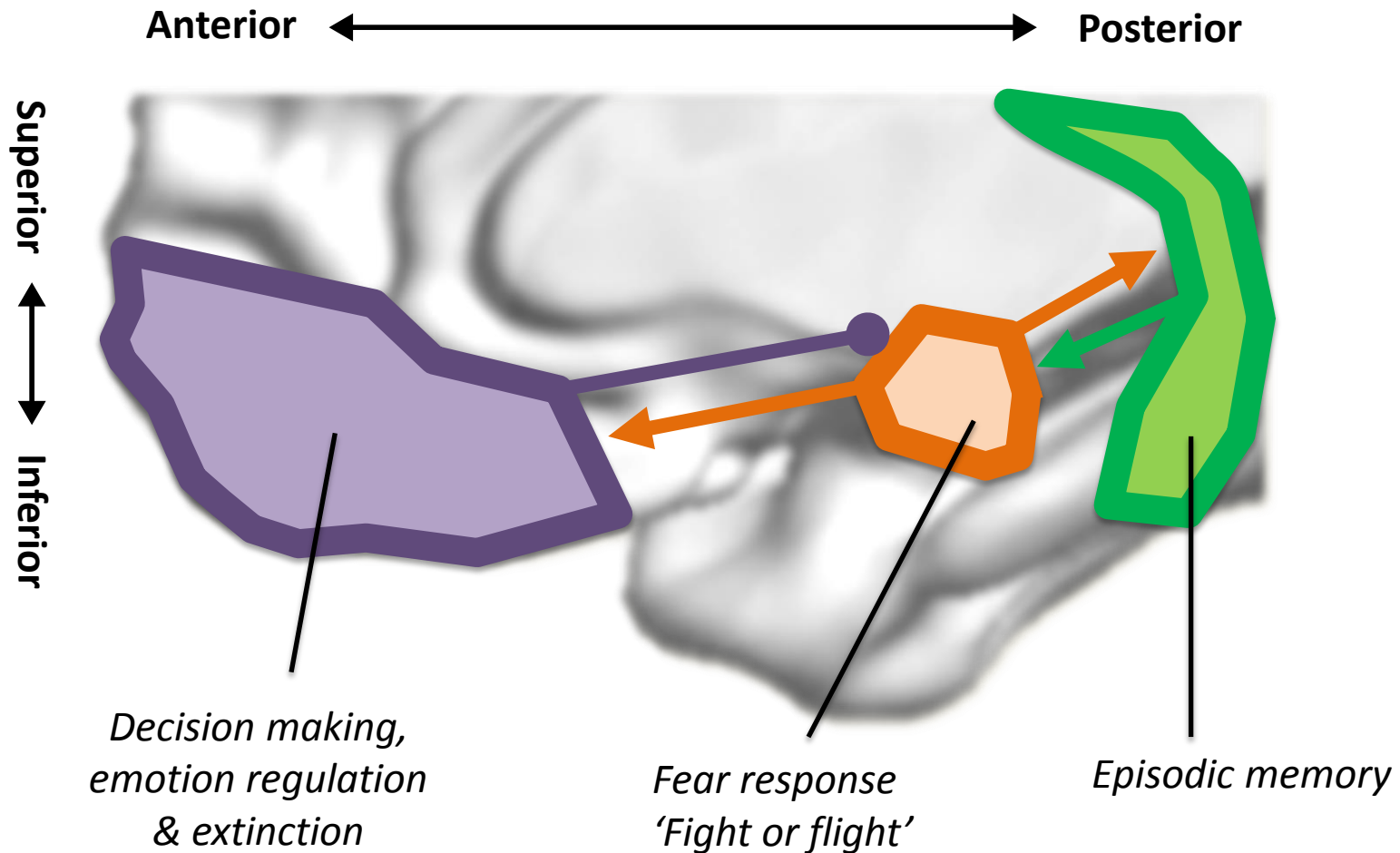
Neuronal circuitry model of PTSD

Animal models of PTSD have been informative regarding the (homologous) neurobiological structures involved in **fear, conditioning** and **memory**



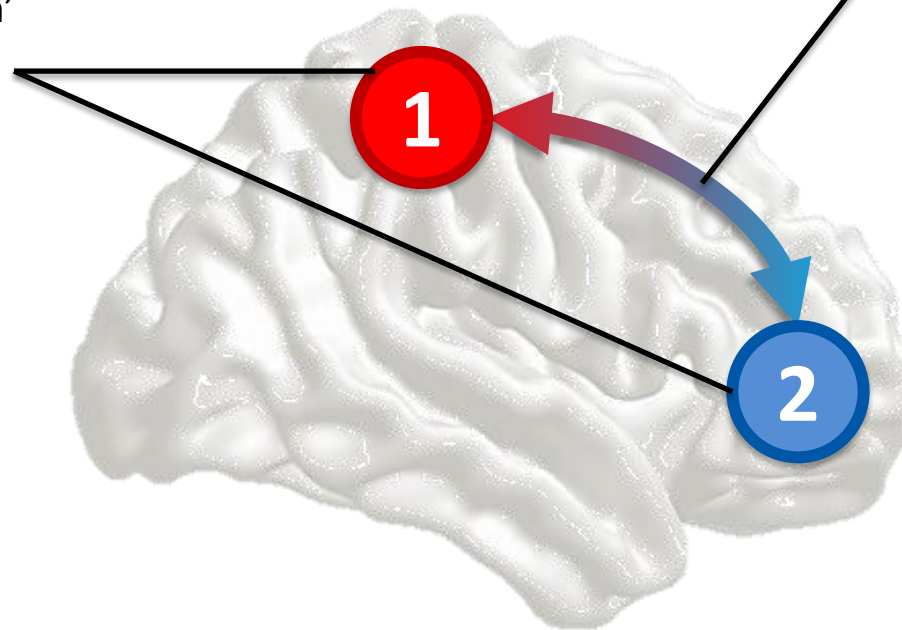
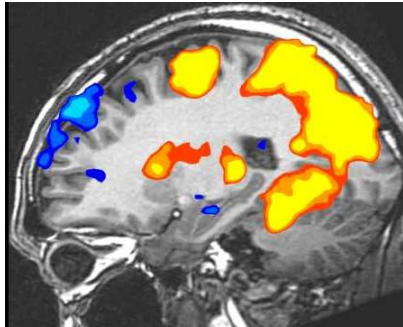
Neuronal circuitry model of PTSD

PTSD subserved not just by regional **atypical function**, but aberrated connectivity – a **disorder of circuits/networks & communication?**

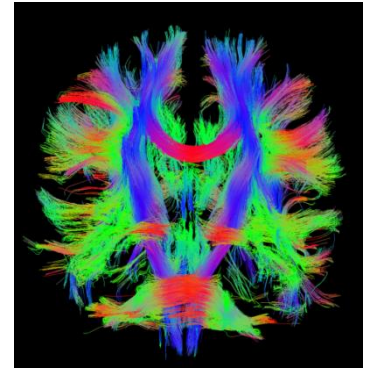


Brain connectivity and communication

'Functional specialisation'
of individual regions –
Measured via fMRI



Communicate via structural
pathways ('white matter') -
Measured using DTI



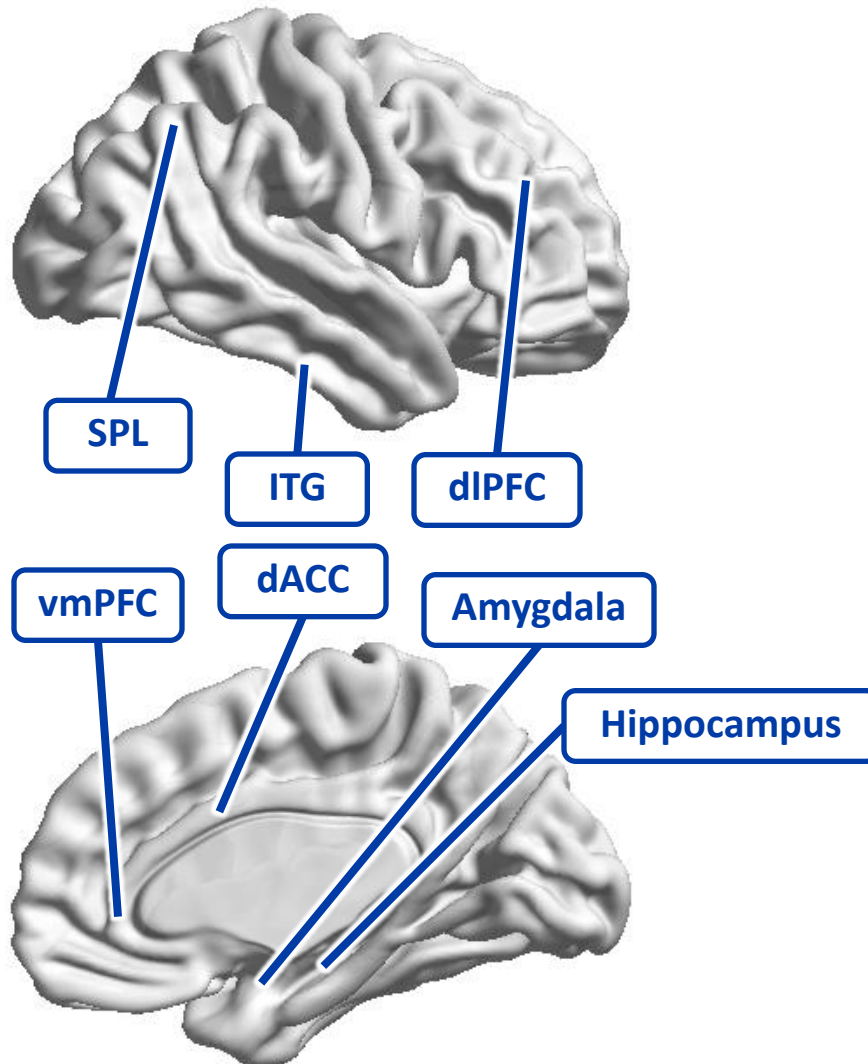
Functional connectivity – covariations/correlations in signal between regions

Structural connectivity – anatomical connections linking areas

Shift from reductionism to emergent properties: *Mental states arise from coordinated action of neuronal groups – or networks* (Yuste, 2015)

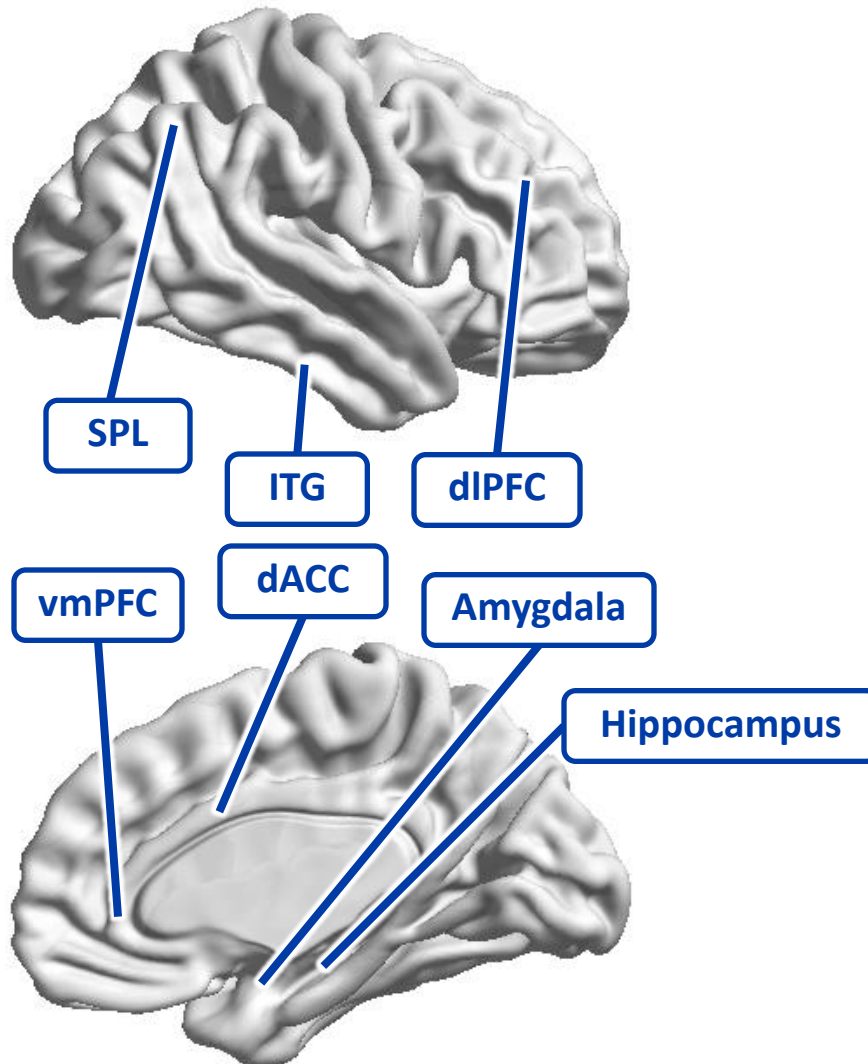
Human MRI imaging of PTSD

Structural and Functional MRI



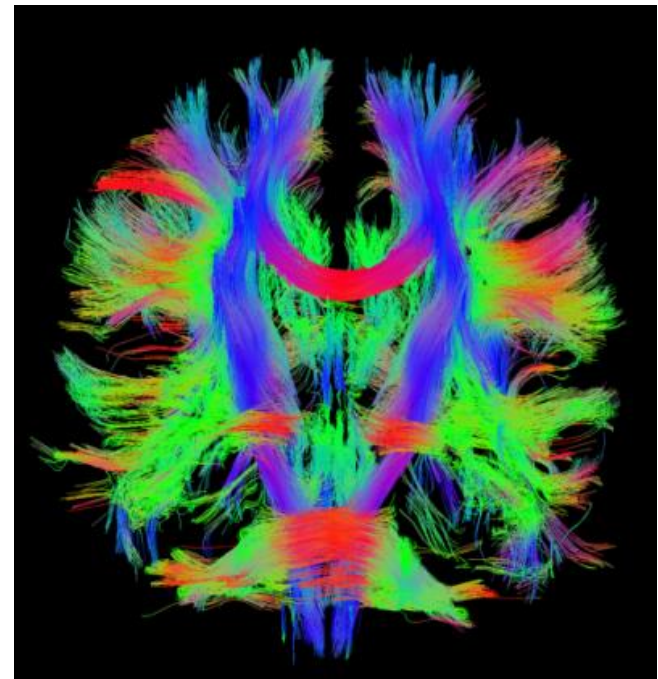
Human MRI imaging of PTSD

Structural and Functional MRI



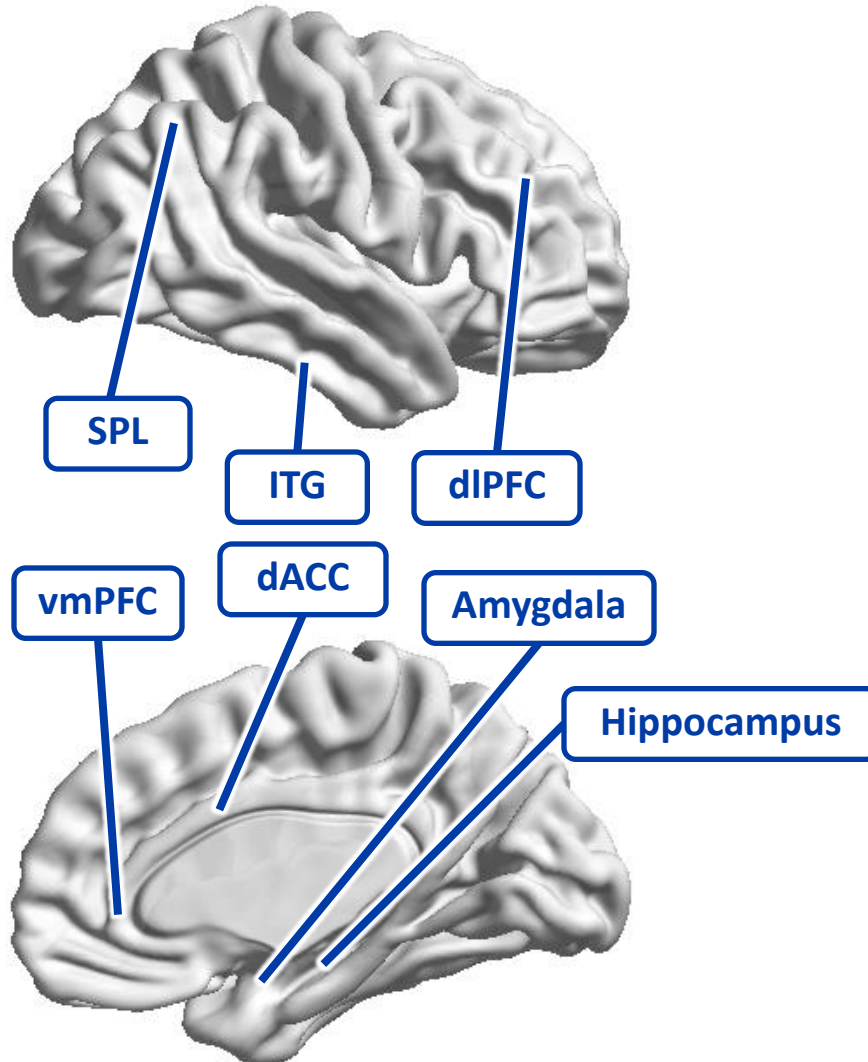
However there are limitations:

sMRI/DTI measures '**static**' circuits (circuits need to be **dynamic** for goal-directed, adaptable behaviour).



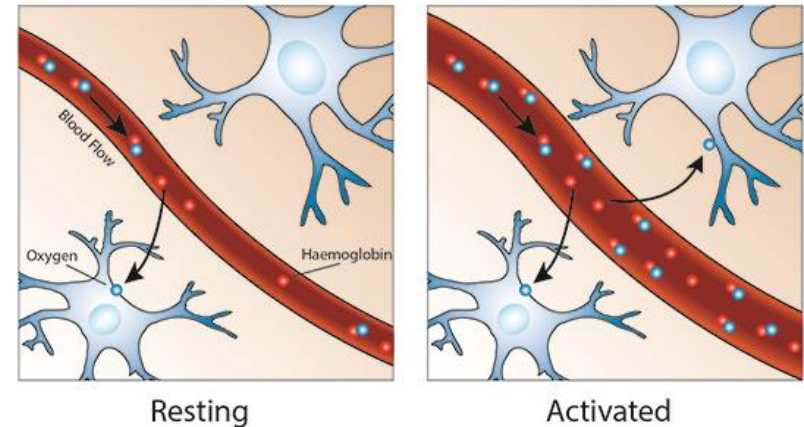
Human MRI imaging of PTSD

Structural and Functional MRI



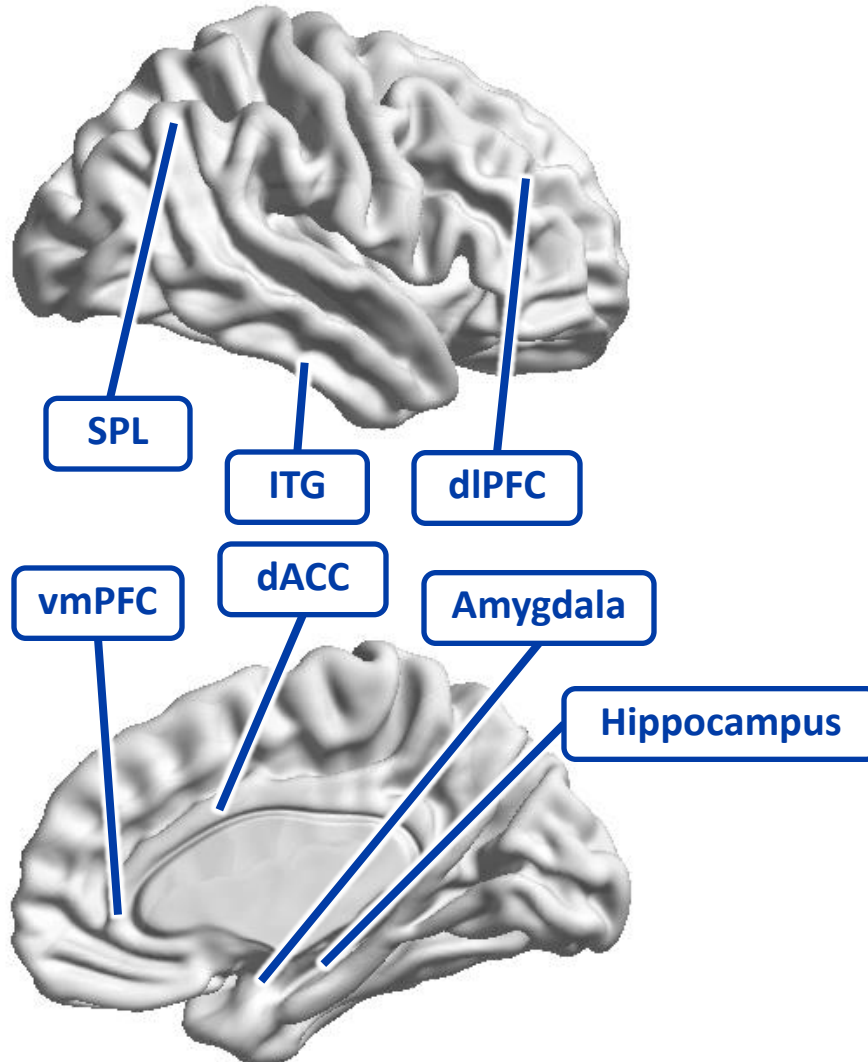
However there are limitations:

fMRI only measures **haemodynamics** (not associated neural activity).



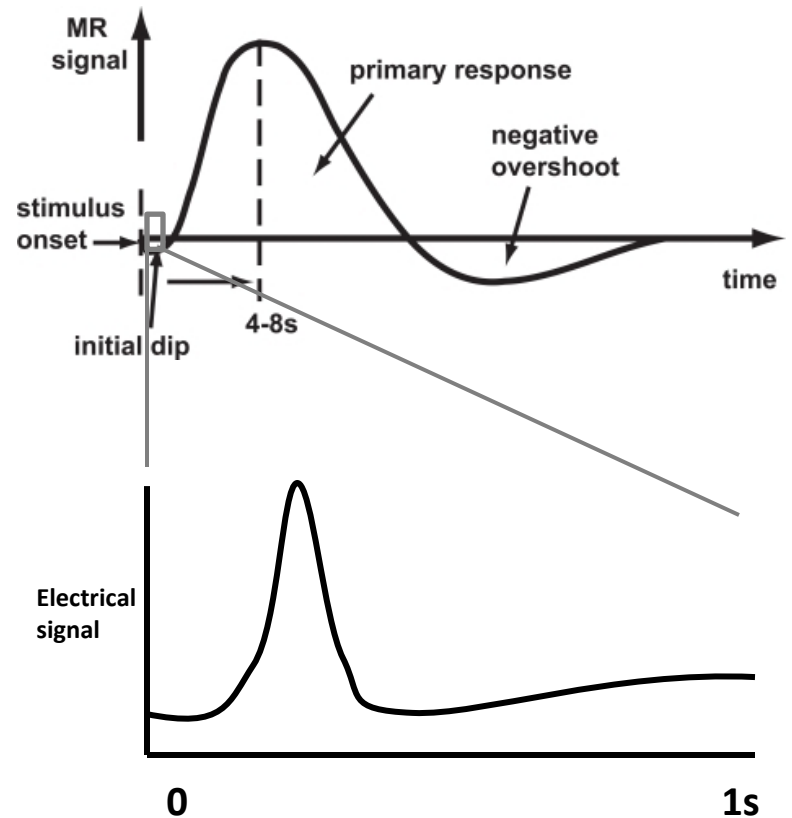
Human MRI imaging of PTSD

Structural and Functional MRI



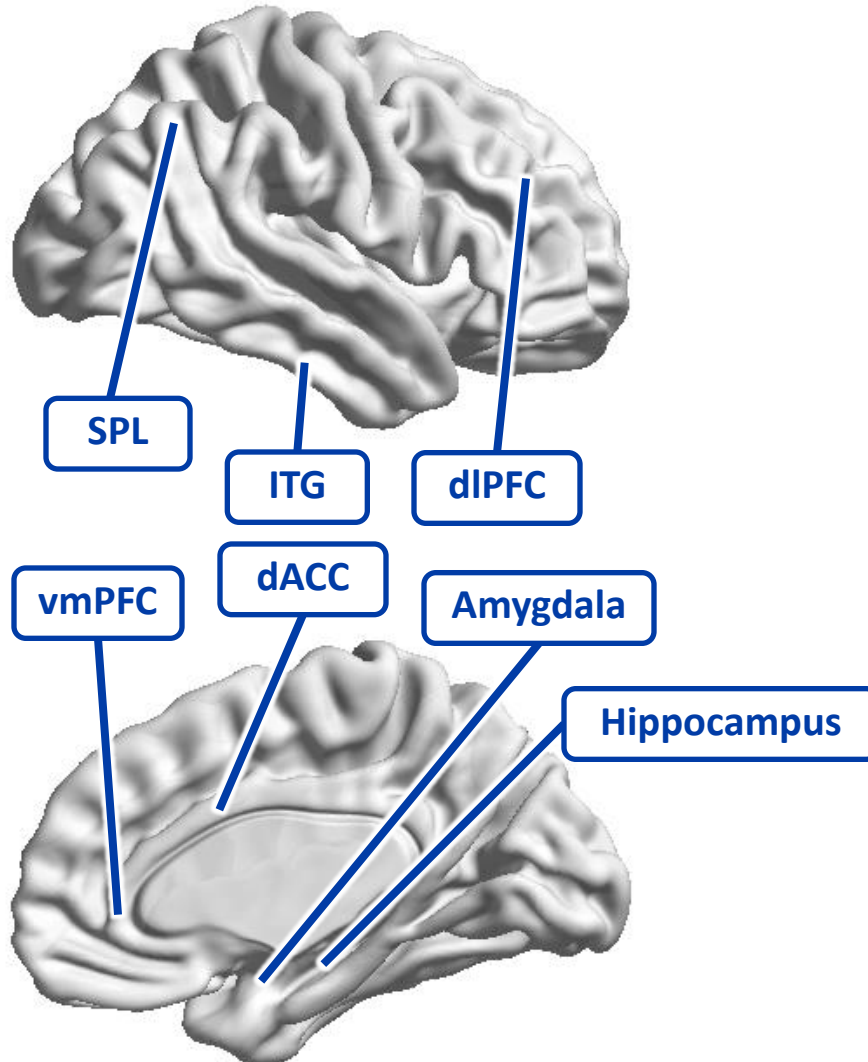
However there are limitations:

fMRI is very **slow** (neuronal activity is on time scales **orders of magnitude** faster).



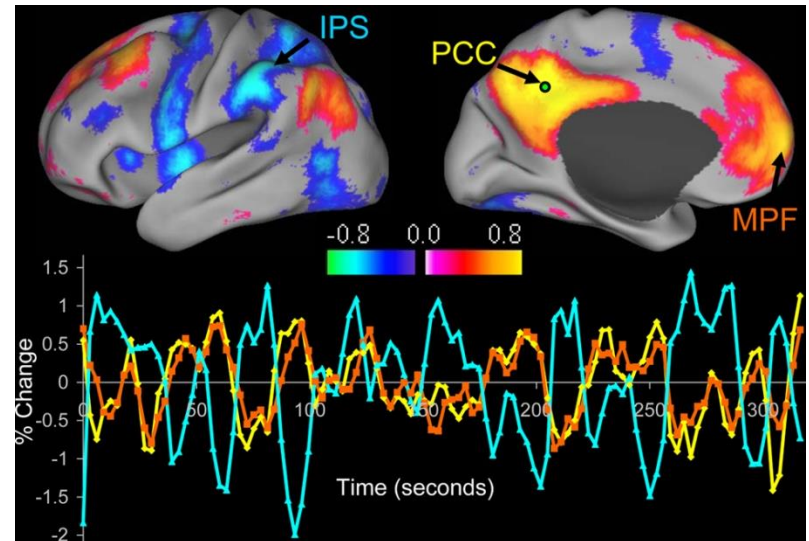
Human MRI imaging of PTSD

Structural and Functional MRI



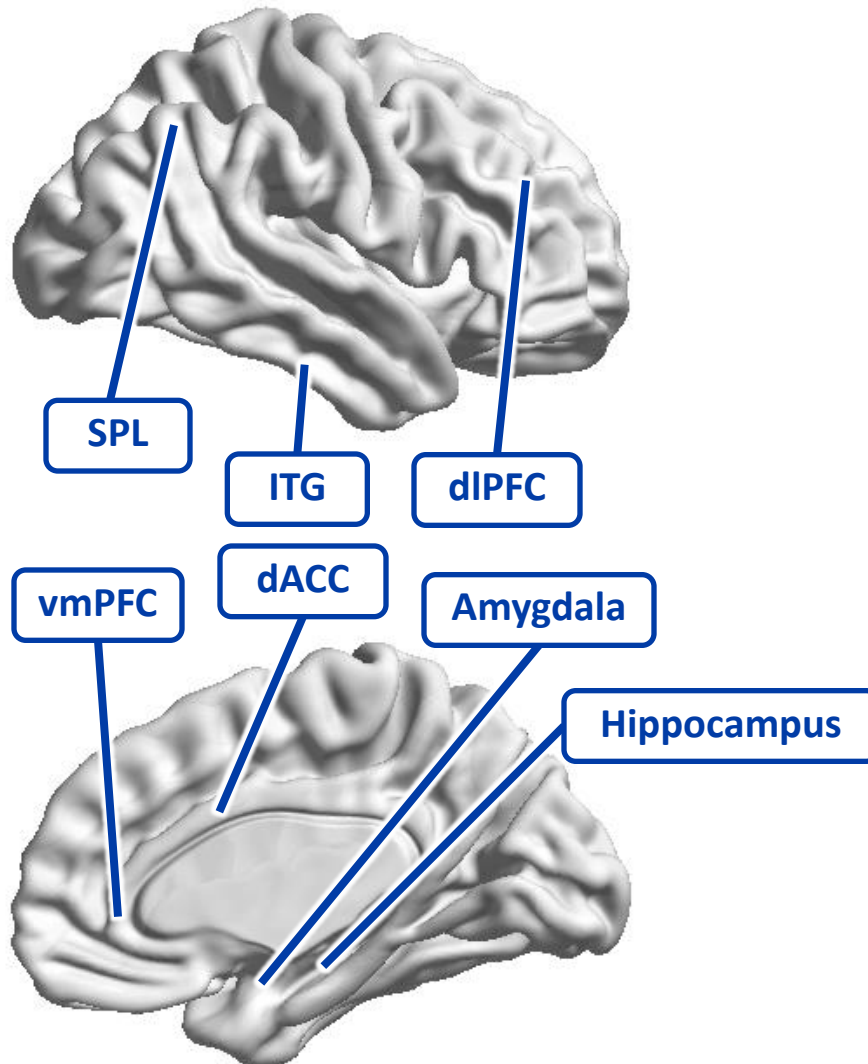
However there are limitations:

Temporal covariations/coupling in BOLD not really *how* areas communicate.



Human MRI imaging of PTSD

Structural and Functional MRI



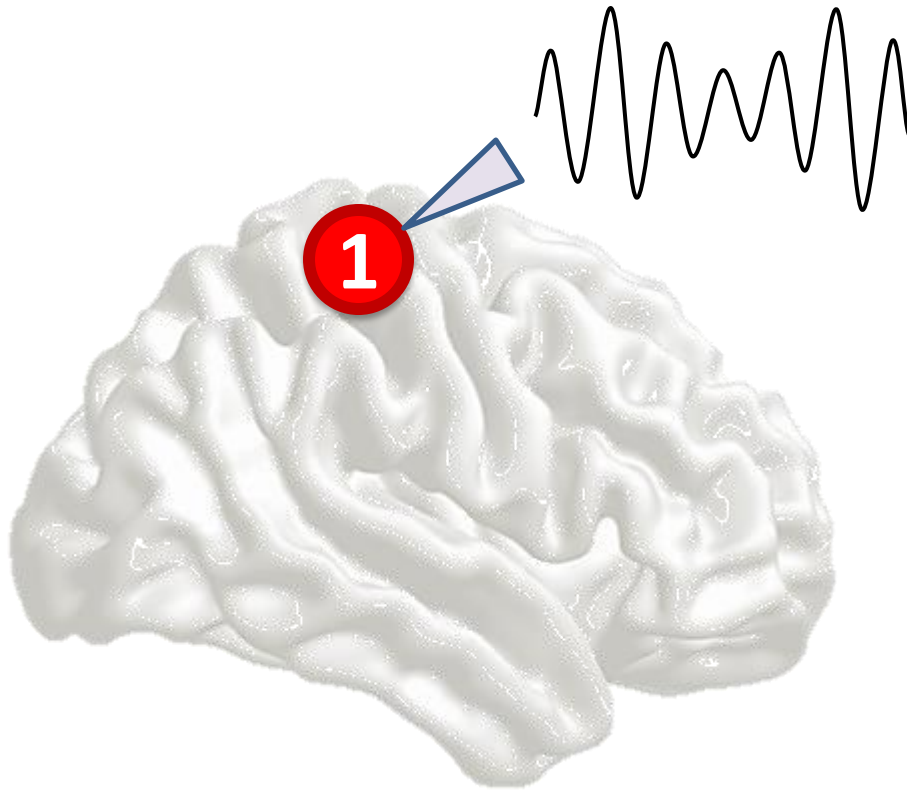
However there are limitations:

Of course, invasive recording (ie. direct) of neuronal activity in humans is very difficult...

Therefore, unknown how neurophysiological interregional communication is affected in PTSD

How do areas of the brain communicate?

One mechanism – brain ‘waves’ or oscillations

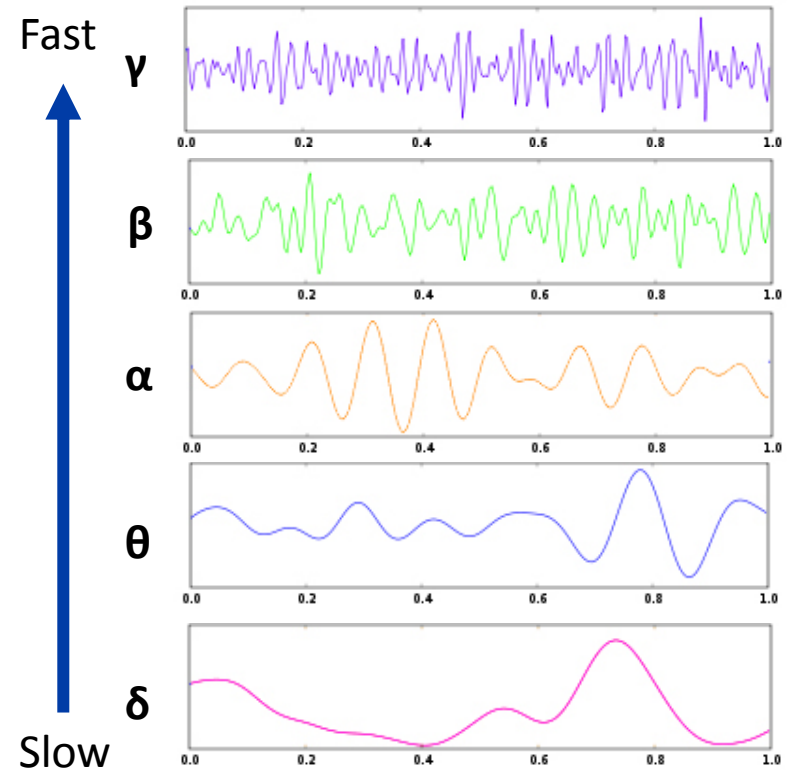


Different frequencies support different functions

- Gamma (30-80 Hz):** local processing & activity
- Beta (15-25 Hz):** somatosensory & motor control
- Alpha (8-14 Hz):** visual perception & attention
- Theta (3-7 Hz):** learning and memory
- Delta (1-3 Hz):** sleep processes

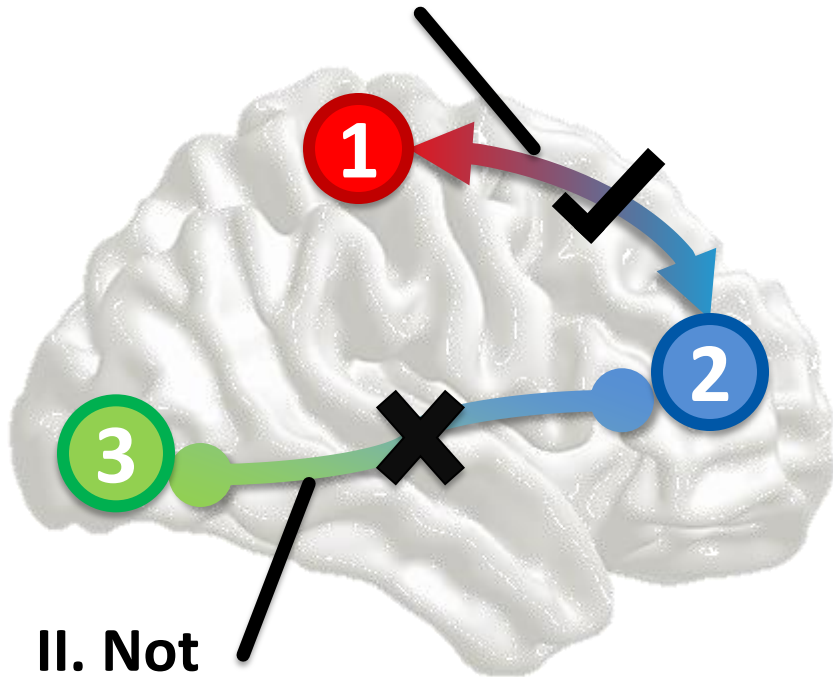
Groups of neurons rhythmically oscillate together at different frequencies - **a fundamental mode of action**

Reflects periodic changes in excitability and micro-circuit activity in the cortex



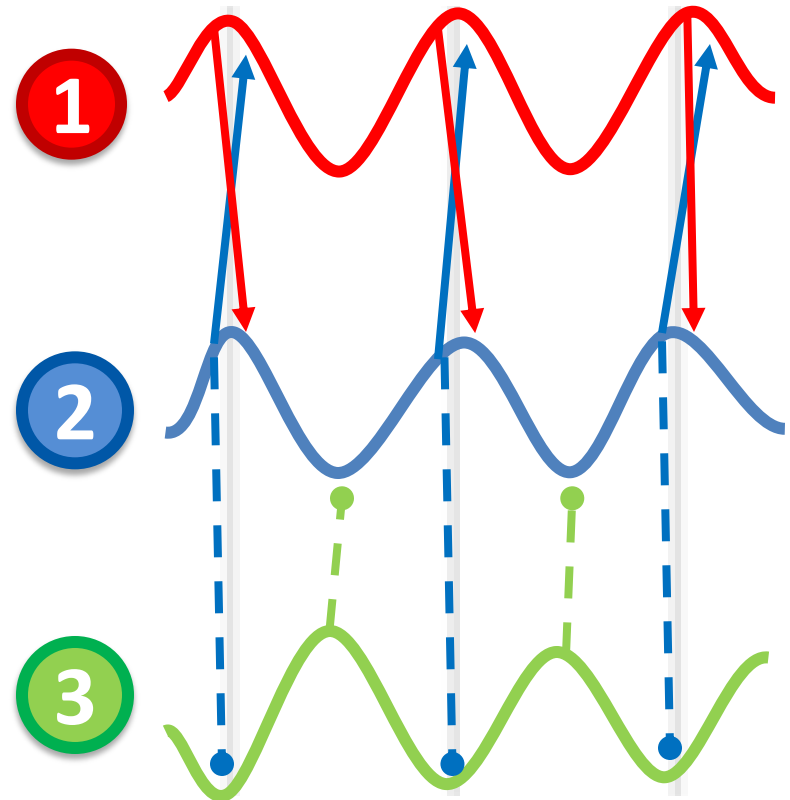
Communication via 'brain waves'

I. Communicating



II. Not communicating

'Communication-through-coherence' hypothesis (Fries, 2005)



Oscillations/synchrony/'waves' dynamically reconfigure networks - spatially and temporally organise information (**open** and **close** circuits), supporting brain communication (Engel et al., 2013)

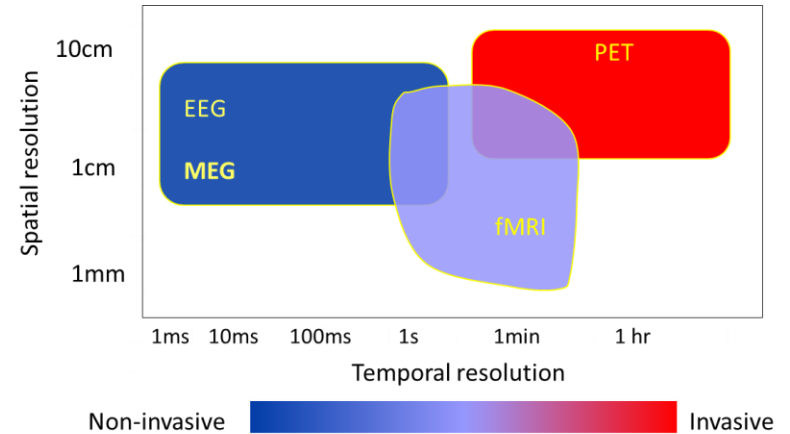
Aberrant synchrony observed in many different neuropsychiatric/clinical populations

How do we measure synchrony in humans?

Magnetoencephalography



SickKids Research MEG

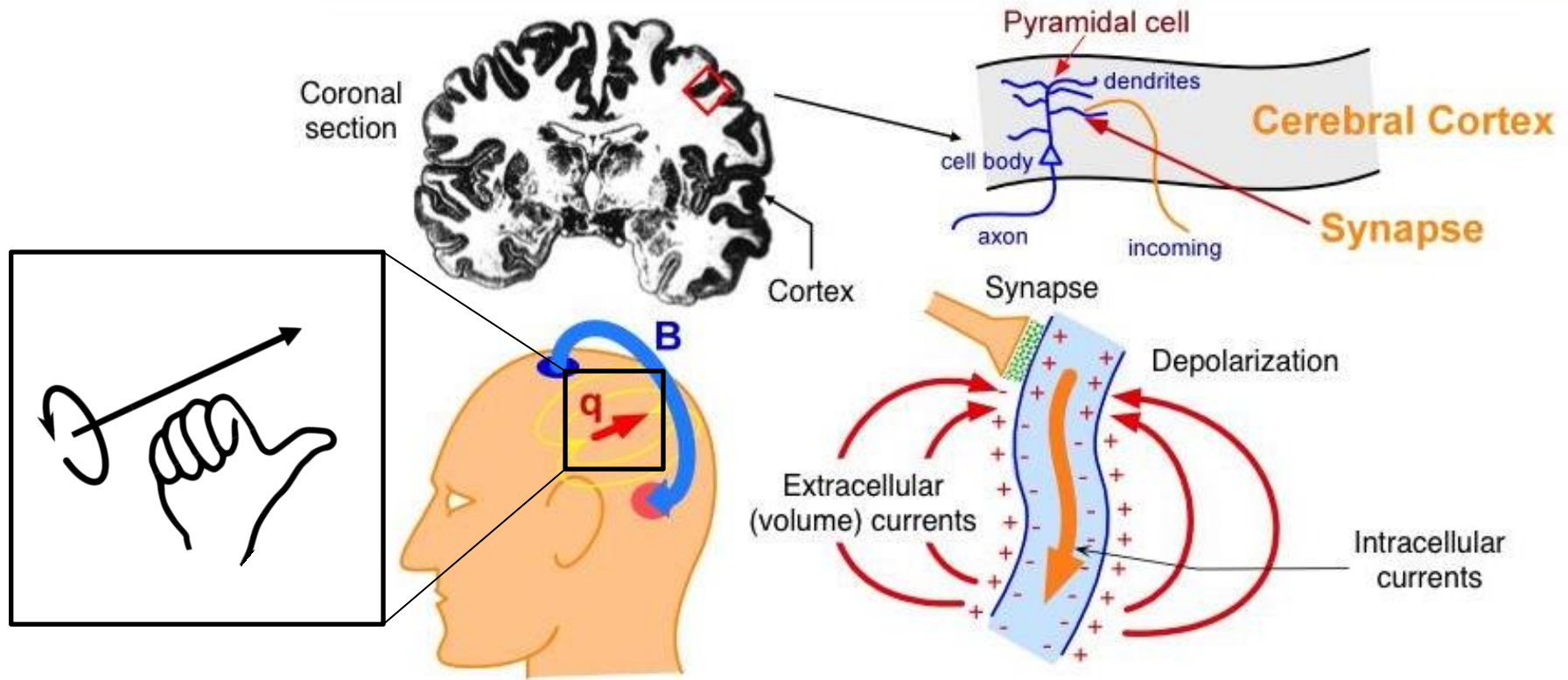


- Excellent temporal resolution
- Good spatial resolution (using 'virtual sensors')
- Fully quiet
- Completely passive (i.e. totally non-invasive)
- Non-claustrophobic
- Direct measure of neural activity from primary currents

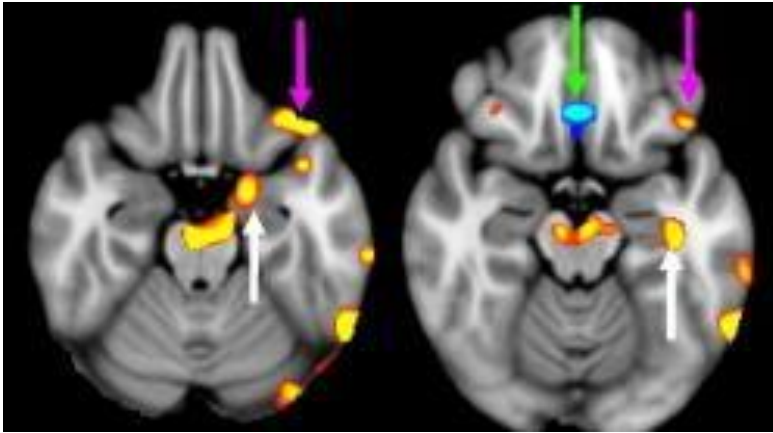
Neural generators of the MEG signal

Magneto-Encephalo-Graphy

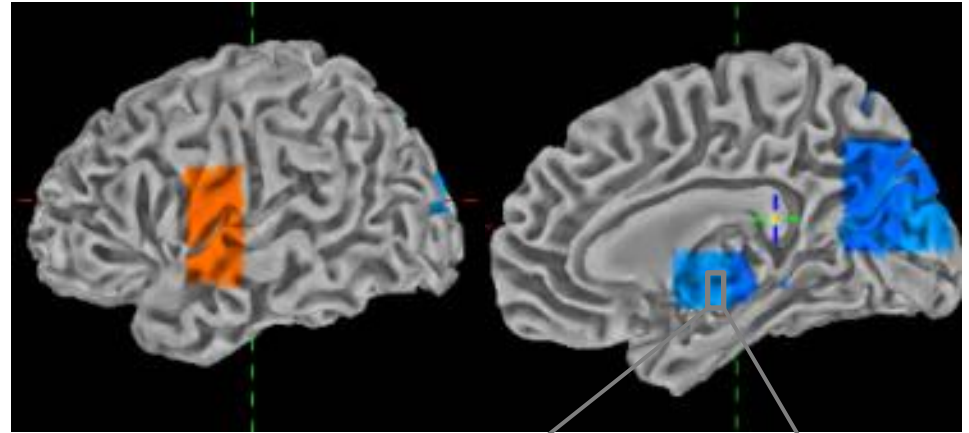
A measure of the extracranial magnetic fields generated by postsynaptic intracellular currents



MEG studies of brain waves in PTSD



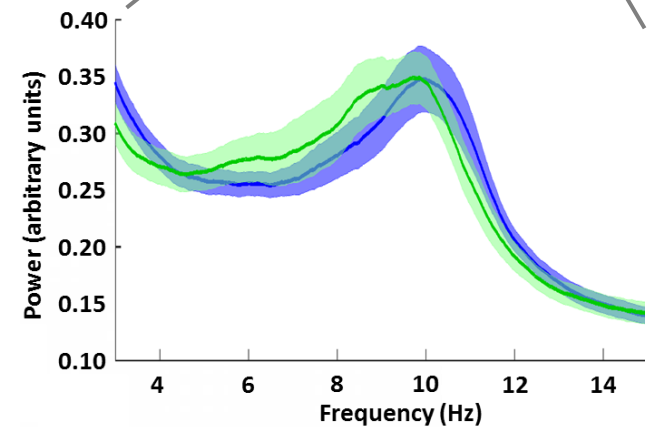
(Huang et al., 2014)



(Kolassa et al., 2007)

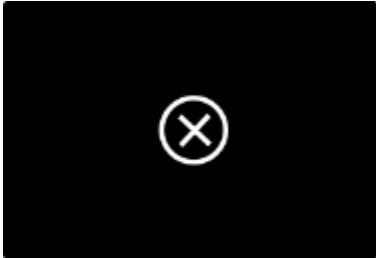
Previous MEG studies on PTSD have examined power spectrum density (**magnitude** of frequency-specific brain waves) in isolation

Interregional communication has not been considered



Study protocol – MEG for the objective assessment of PTSD

Pre-triggering resting state



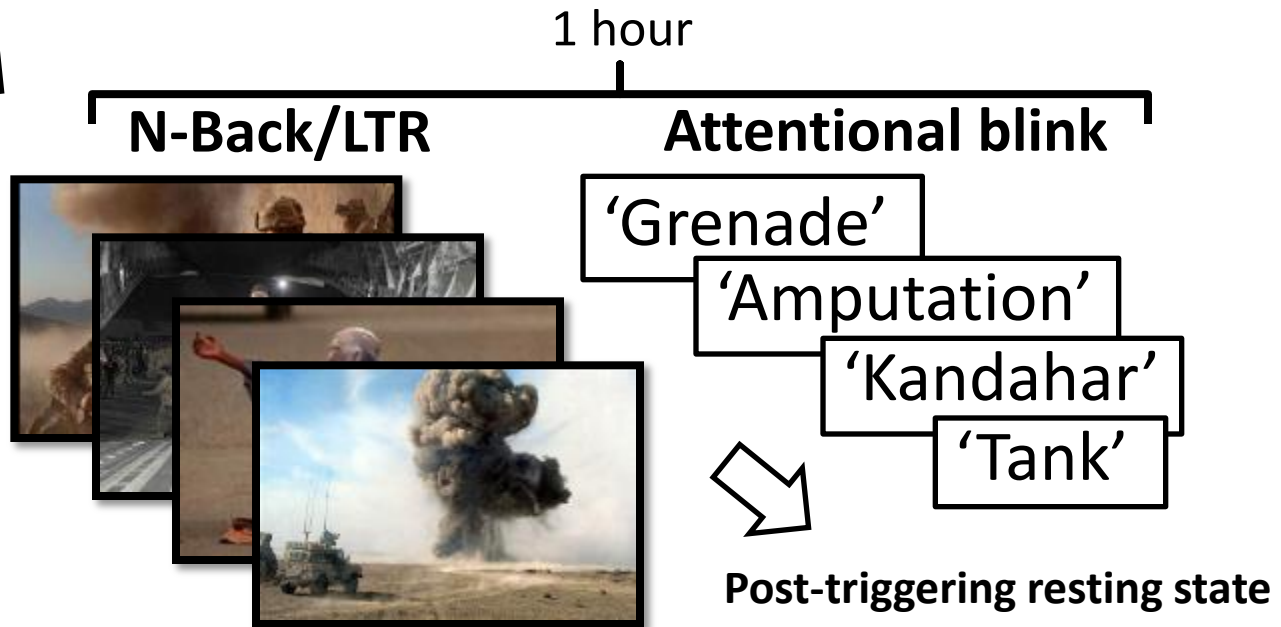
300 s @ 600 Hz on
151 channel CTF system

Eyes open, fixate X, relaxed state of wakefulness
Examine intrinsic, spontaneous functional connectivity
Translatable, high repeatability, easy to perform



Cognitive tasks comprised of emotionally-salient stimuli intermixed with neutral stimuli:

- Mental flexibility
- Working memory
- Attention
- Emotional processing
- Delayed recognition



Participants & criteria

PTSD

25 soldiers with combat-related PTSD (all male, mean age = 37.4, SD = 6.8)

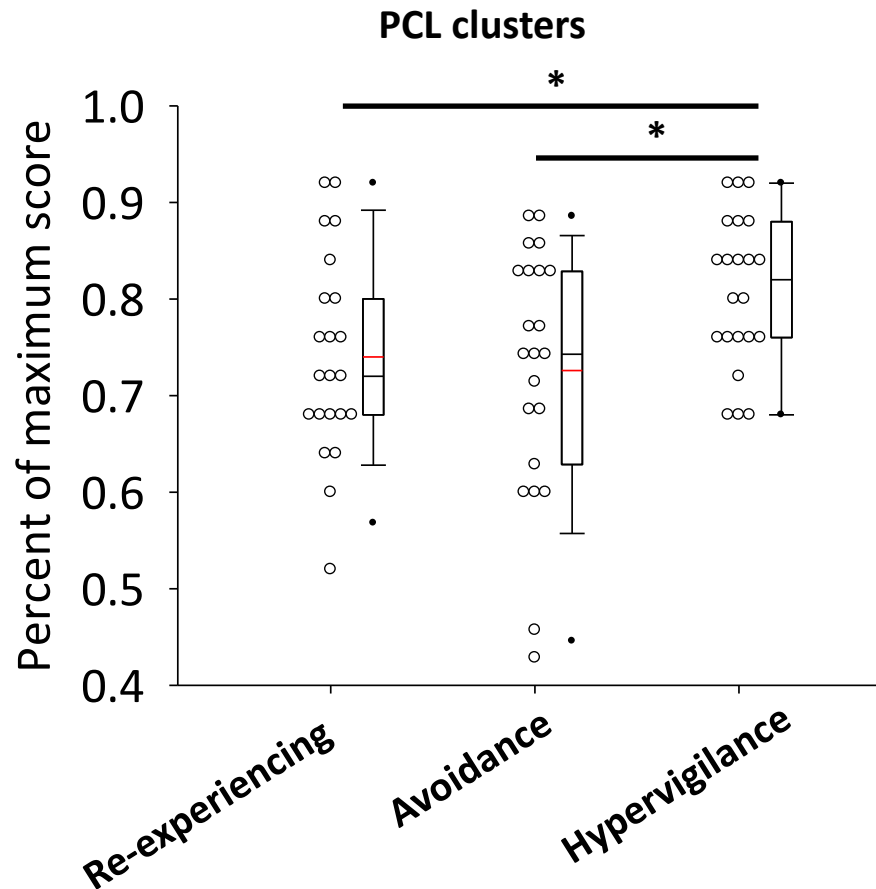
28 combat-exposed control soldiers (all male, mean age = 33.05, SD = 5.26)

- matched on age, rank, education level, handedness and military experience

PTSD severity – hypervigilance

PTSD soldiers assessed using **PTSD Check List (PCL)** (m = 63.9, SD = 7.6)

- Determines nature and extent of symptoms
- One of the inclusion criteria for PTSD group

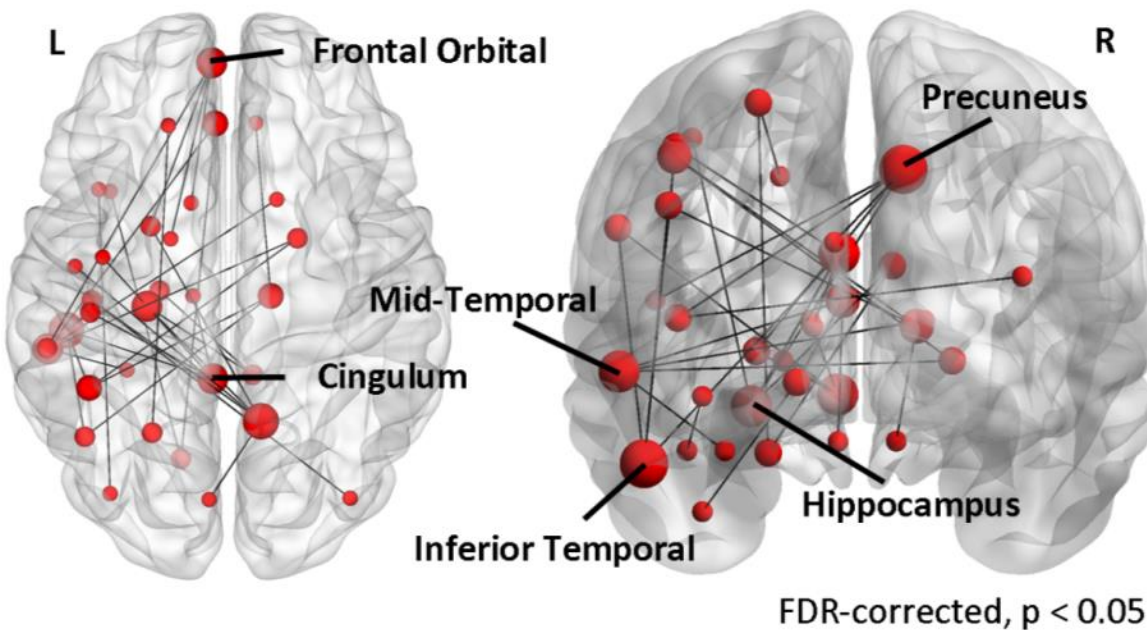


High-frequency phase synchrony in PTSD

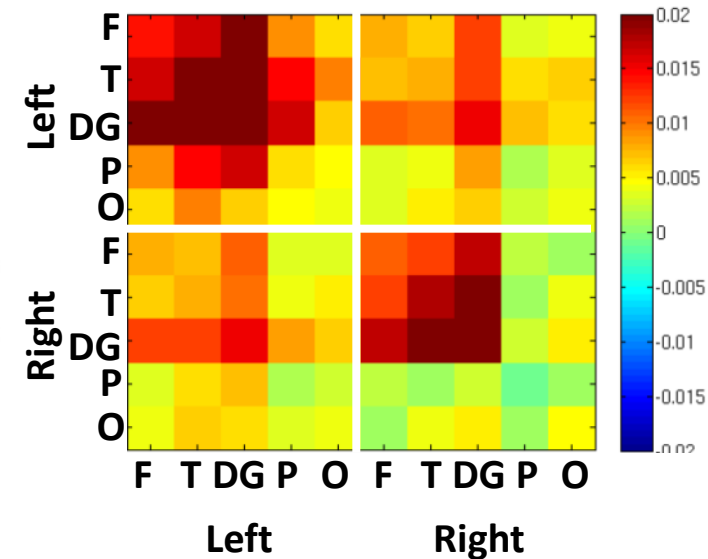
Pre-triggering resting-state networks

High-gamma (80-150 Hz)

● Node radius scaled by degree, labels $k \geq 3$

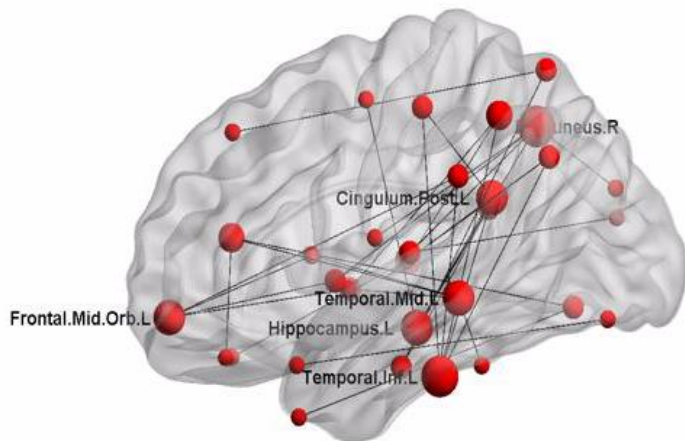


Intra- and inter-hemispheric lobe-lobe interactions
Mean WPLI PTSD - Control

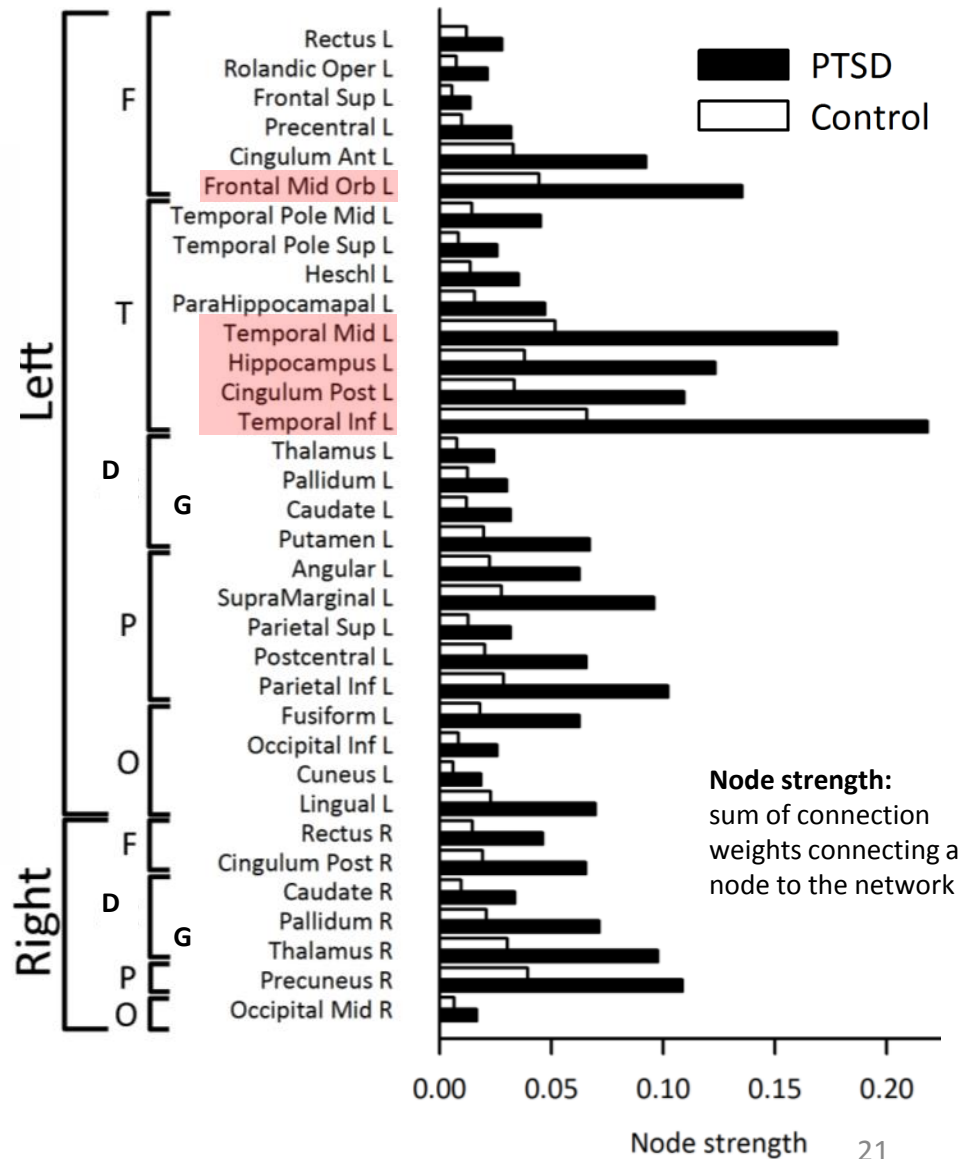


(Dunkley et al., 2014, *NeuroImage: Clinical*)

High-frequency phase synchrony in PTSD

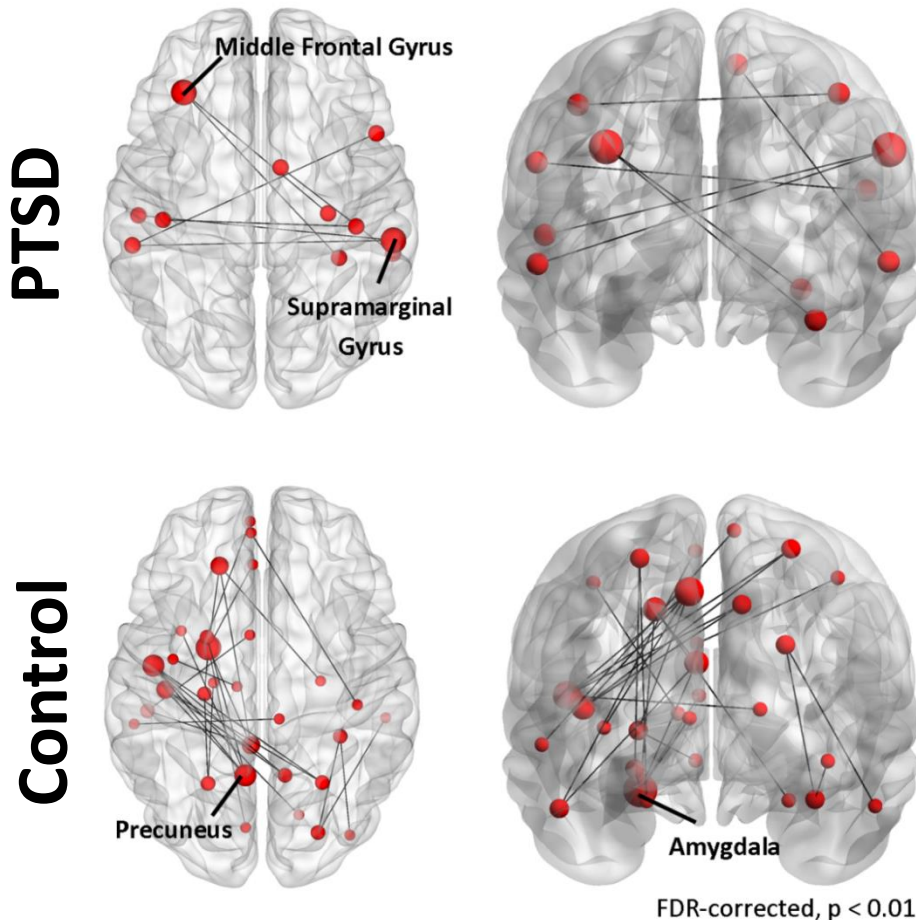


● Node radius scaled by degree, labels $k \geq 3$



'Triggering' in soldiers without PTSD

Post versus pre-triggering resting-state networks



Greater increase in network synchrony in *control soldiers*

– Post-trigger network topography in control soldiers is **similar** to initial PTSD hyperconnectivity

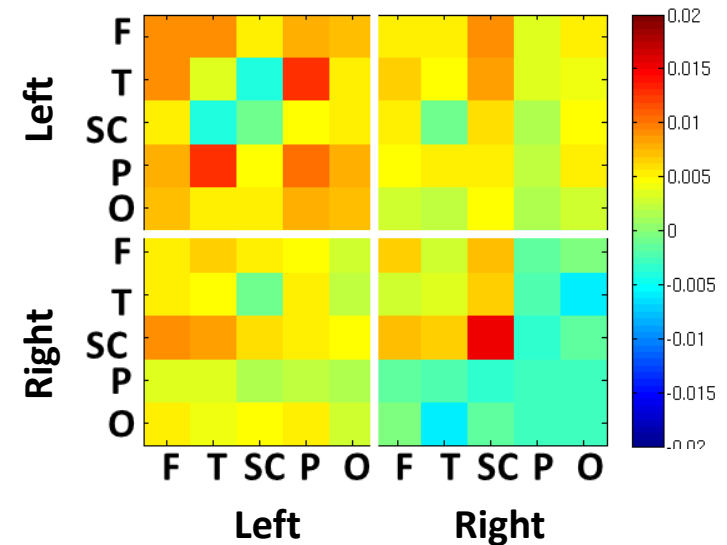
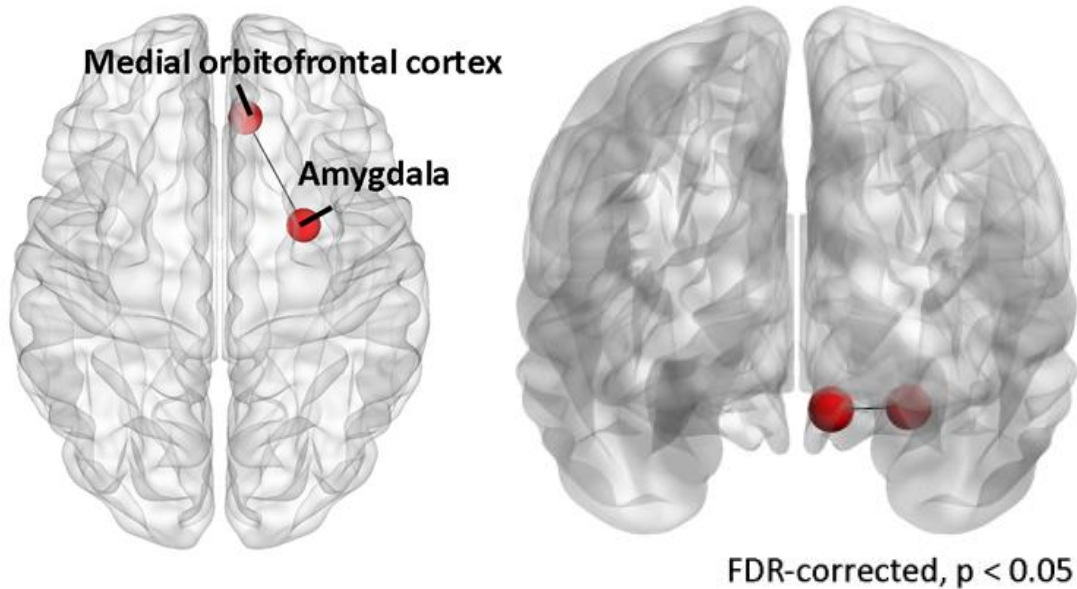
● Node radius scaled by degree

'Triggering' in soldiers without PTSD

Post-triggering resting-state networks

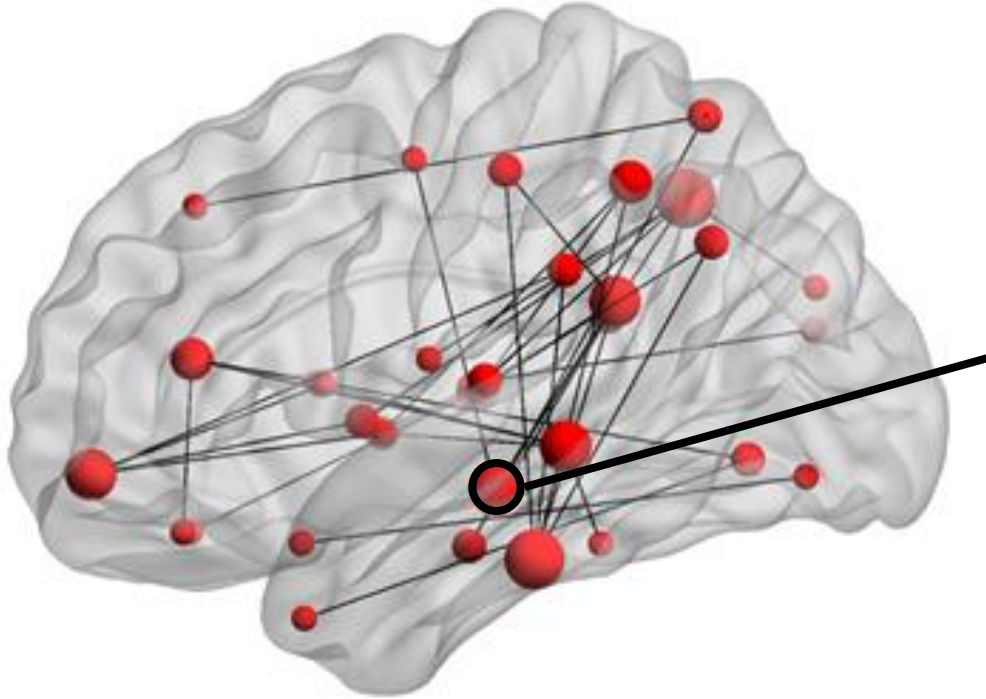


PTSD > Control

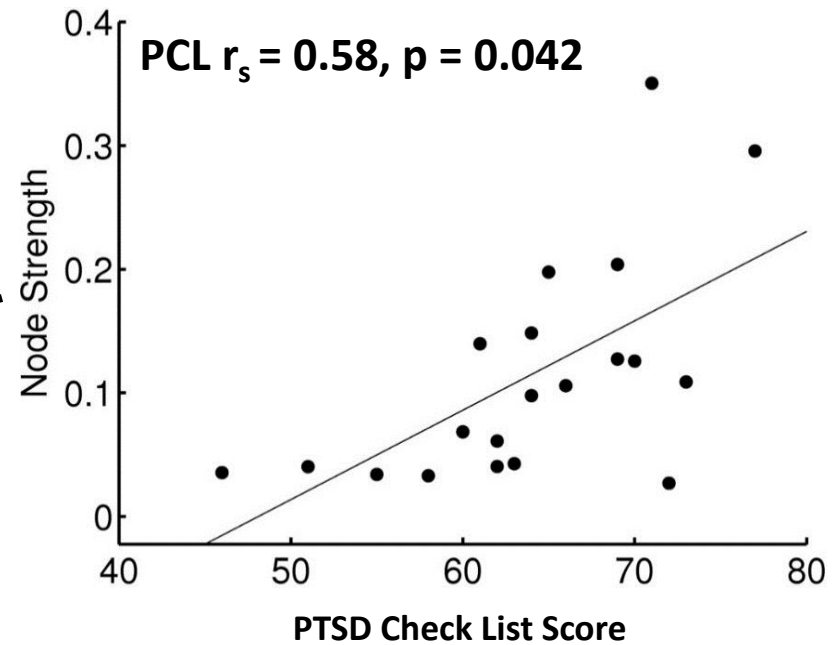


Hippocampal synchrony correlates with symptoms

Pre-triggering resting-state



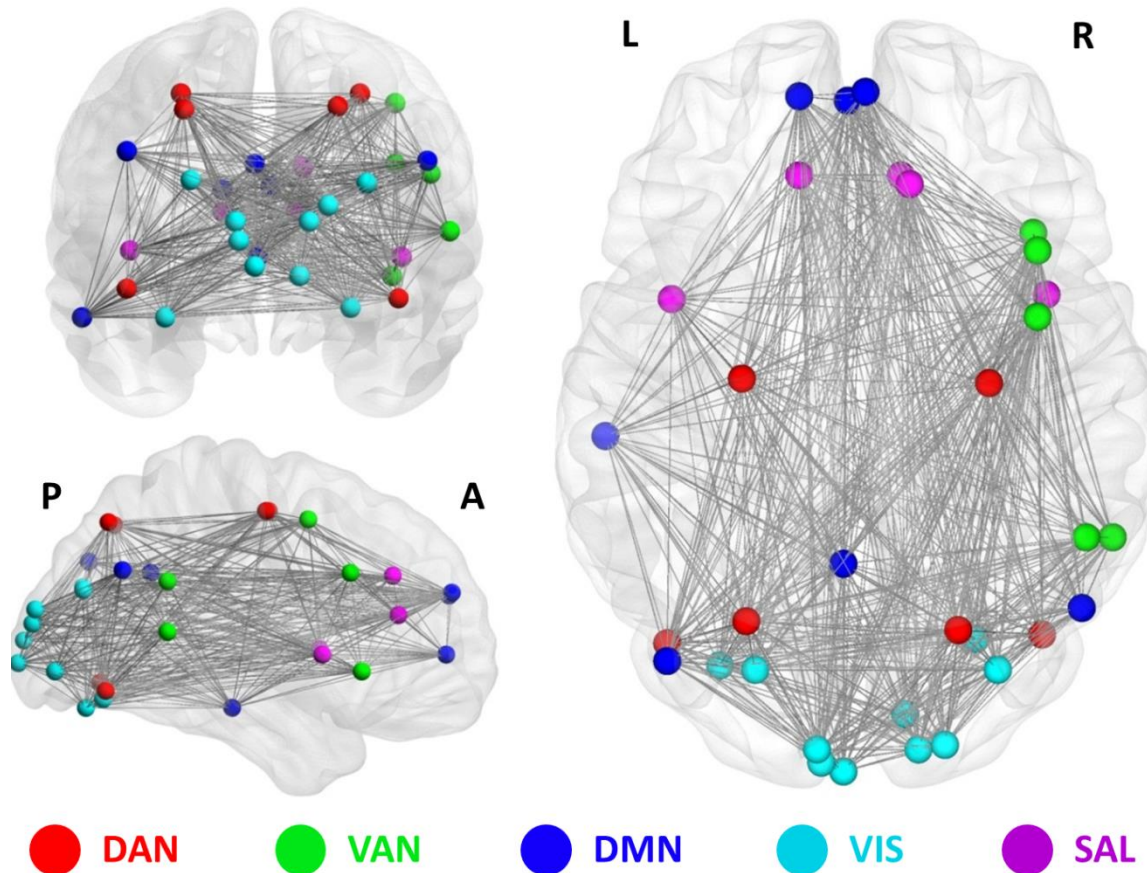
Hippocampus L



Previous research shows that high-frequency brain waves in temporal regions directly involved in memory formation, recollection and arousal states (Canolty et al., 2006)

Re-experiencing of traumatic memories and hypervigilance in PTSD

Follow-up analyses: Intrinsic communication networks in PTSD



Default mode network:
centre of network dynamics
and implicated in introspection

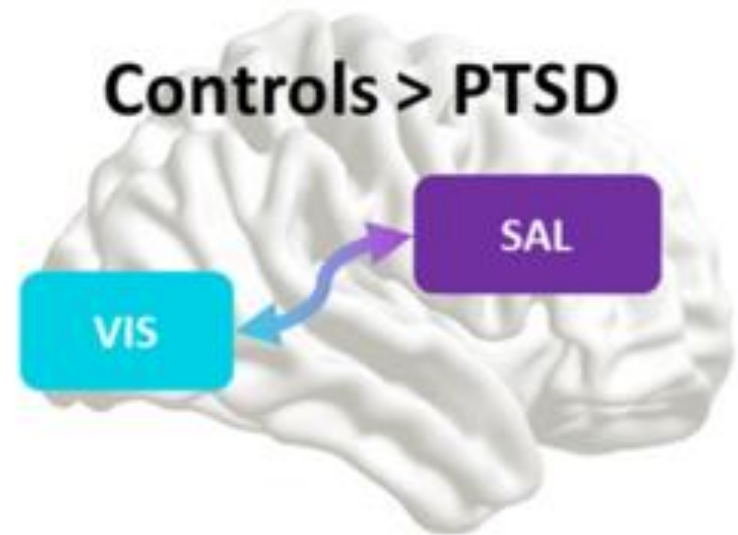
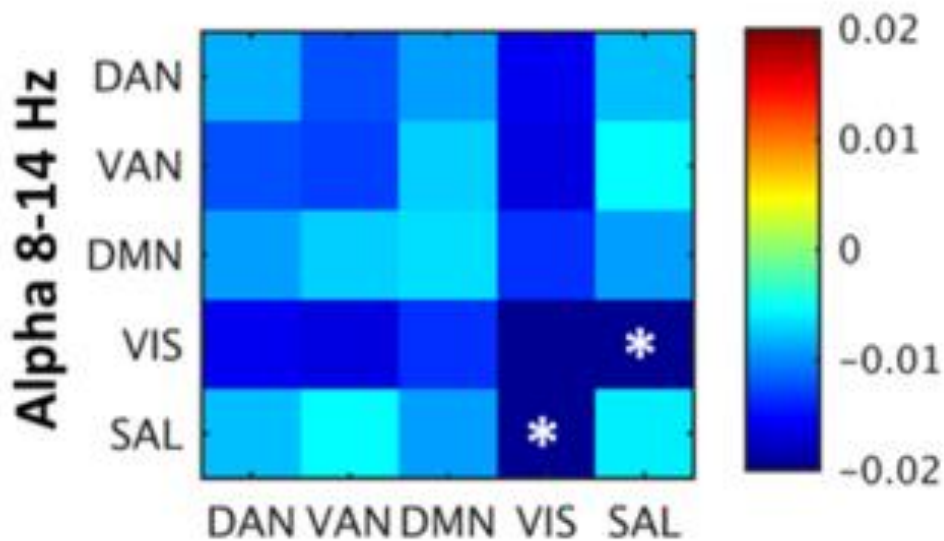
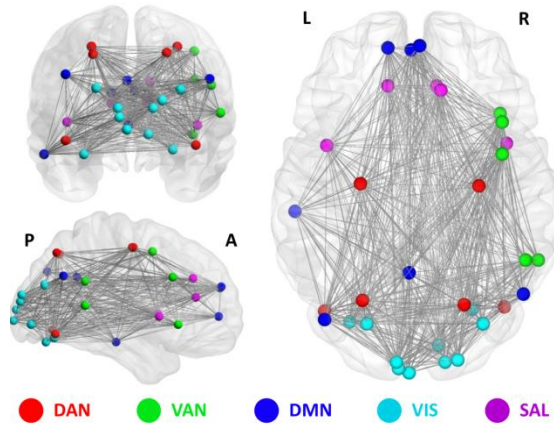
Salience network:
goal-directed action and the
pertinence of an item

Visual network:
visual processing

Dorsal and ventral attention :
part of the central executive
and involved in attention

NOI (Network of interest) approach, rather than data-driven

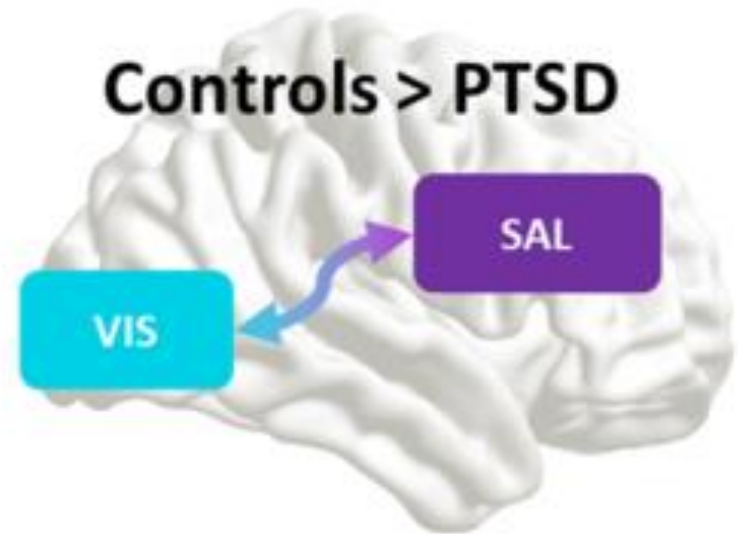
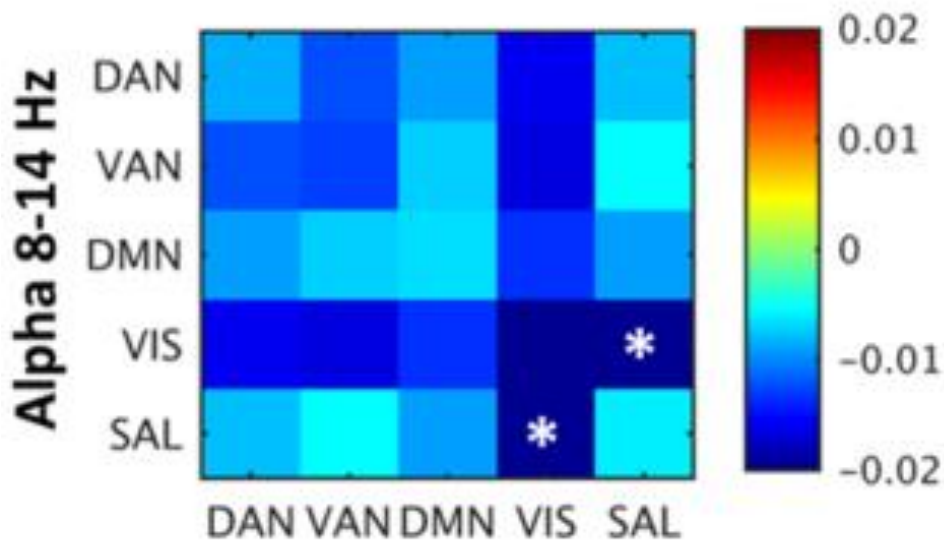
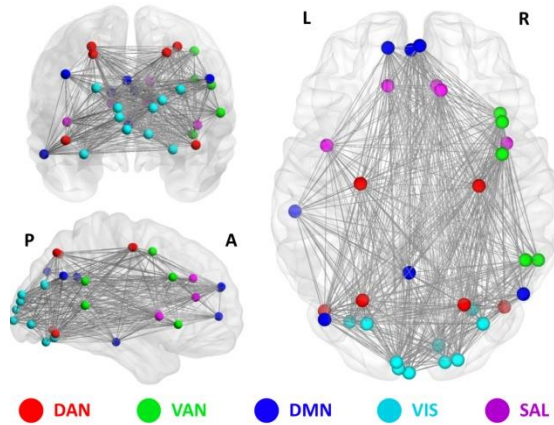
Reduced alpha networks in PTSD



* $p_{\text{corr}} < 0.05$; ** $p_{\text{corr}} < 0.01$

(Dunkley et al., 2015, *Psychiatry Research: Neuroimaging*)

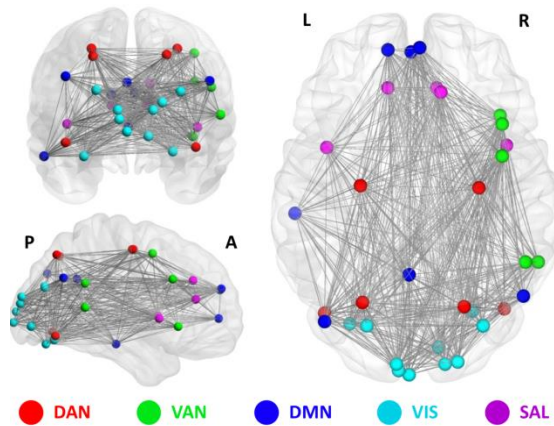
Reduced alpha networks in PTSD



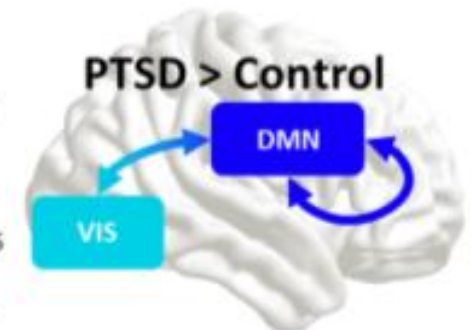
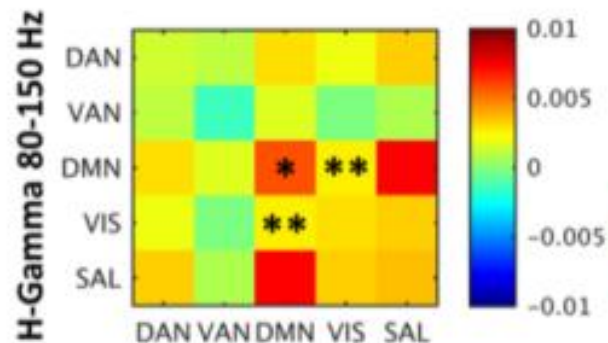
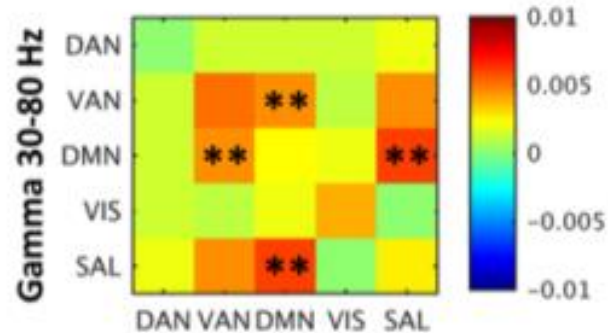
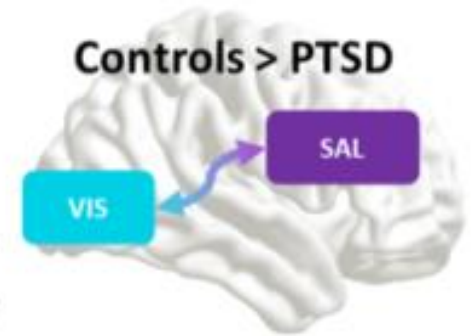
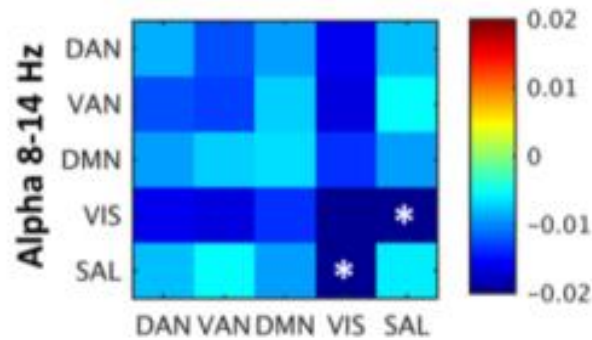
* $p_{\text{corr}} < 0.05$; ** $p_{\text{corr}} < 0.01$

(Dunkley et al., 2015, *Psychiatry Research: Neuroimaging*)

Increased gamma networks in PTSD

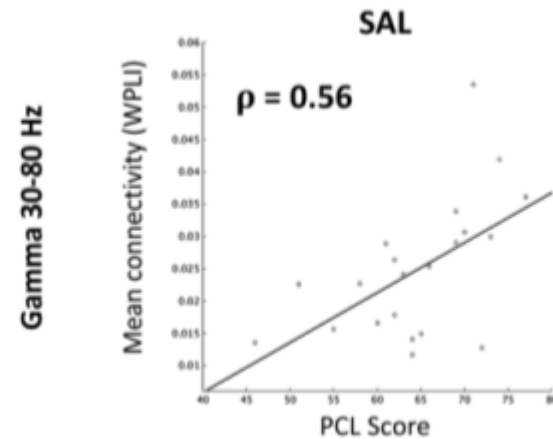
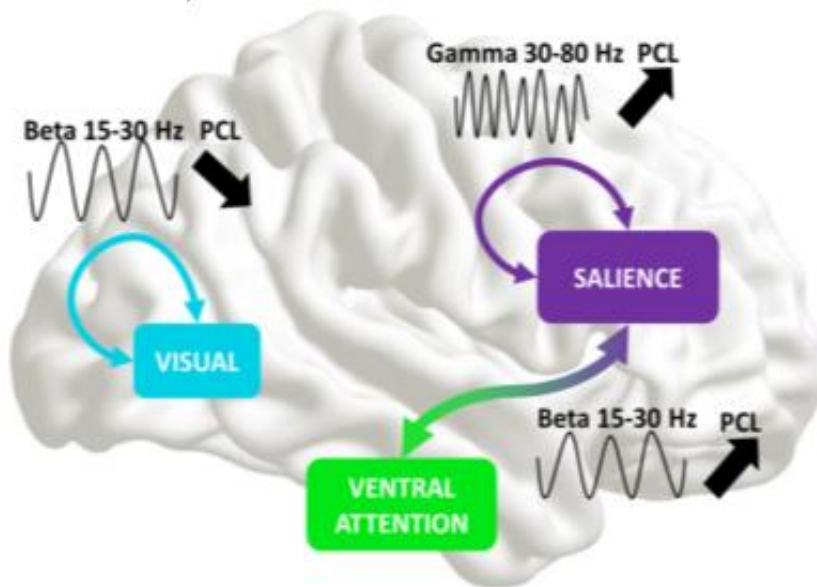
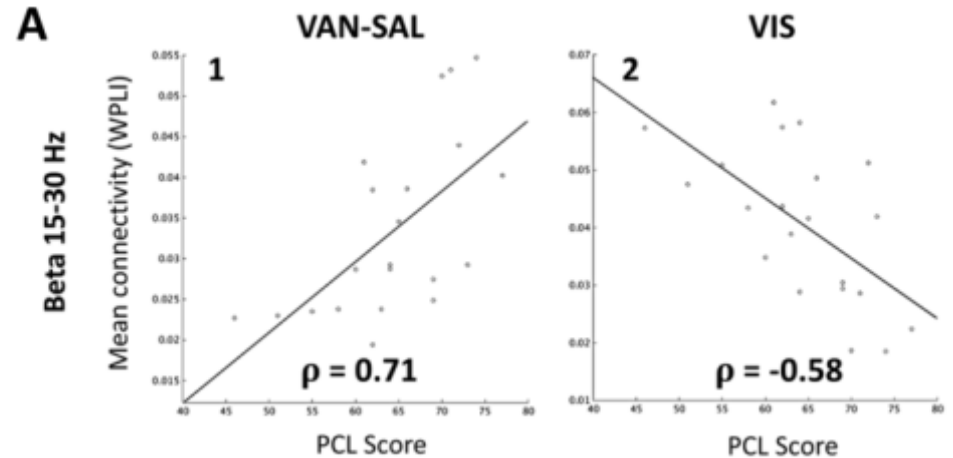
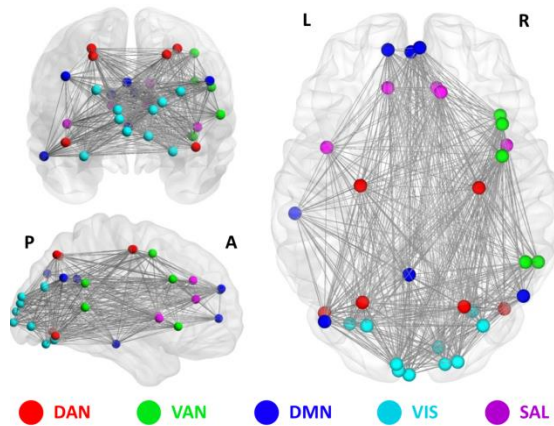


Multi-scale (both frequency and network) alterations in PTSD



* $p_{\text{corr}} < 0.05$; ** $p_{\text{corr}} < 0.01$

Multi-scale synchrony correlates with PTSD severity



(Dunkley et al., 2015, *Psychiatry Research: Neuroimaging*)

Summary & conclusions

Observation	<ol style="list-style-type: none">1. Increased high-frequency synchrony <i>even at rest</i> in PTSD2. ‘Triggering’ induces synchrony in trauma-exposed soldiers3. Symptoms associated with network interactions
Aetiology	Related to intrinsic brain function and ongoing mental state – pre-existing factor or chronic stressor/episode-induced?
Significance	<ol style="list-style-type: none">1. Quantitatively and phenomenologically-distinct mechanism that underlies brain communication – first observance in PTSD2. Supports the integration of cognitive contents (memories & emotional linkages) between areas/within networks3. PTSD a brain network/circuitry disorder

Translation and applications

- **Diagnostics**

- Machine learning/'big data' – utility validated in mTBI (Vakorin et al., 2016)
- Pre-post deployment scans
- 'Return to deployment' – objective + subjective assessment

- **Intervention**

- Precision/personalised therapy
- Brain stimulation (e.g. rTMS, TACS) targets in *space and frequency*
- Neurofeedback/neuromodulation – target frequencies and locations (due to connectivity) unobtainable in EEG

Acknowledgements

Hospital for Sick Children:

Margot J. Taylor

Elizabeth W. Pang

Sam M. Doesburg

Marc Lalancette

Amanda Robertson

Canadian Armed Forces:

Rakesh Jetly

Pang N. Shek

Paul A. Sedge

Richard J. Grodecki



UNIVERSITY OF
TORONTO



Financial support: Defence Research and Development Canada & Canadian Forces Health Services (W7719-135182/001/TOR), Canada Foundation for Innovation (CFI), and Canadian Institutes of Health Research (CIHR)