Comparing Thalamic Nuclei Volumes Between PTSD Subjects and Controls in the Psychiatry Genetics Consortium (PGC)-PTSD Dataset

A. Research Question, Goal, or Specific Aims

Provide a brief description (e.g., 1 paragraph) describing the aims of the proposal and the research questions to be addressed.

Post-traumatic stress disorder (PTSD) is an illness that has a lifetime prevalence of 6.8% among adult Americans (1). PTSD is present in 4-10 % of OEF/OIF veterans (2) and poses significant burden to society and the health system (2, 3). The neurobiology of PTSD involves (1) abnormal fear learning model, which encompasses altered fear conditioning, fear extinction and fear generalization hypotheses; (2)exaggerated threat detection model which postulates altered attention, anticipation, or "alarm" functions; and (3) a diminished emotional regulation/executive function (EF) model which postulates deficient regulatory capacity of cognitive/executive function regions over emotion generating limbic structures (4).

The thalamus is a subcortical structure situated between the cerebral cortex and midbrain, in the dorsal part of the diencephalon(5). In addition to regulating consciousness and sleep(5, 6), its primary function is to relay sensory and motor information to relevant cortical areas from other subcortical structures(6, 7). It also mediates cognition(8) and pain perception(9).

Role of thalamus in PTSD - Translating from animal studies (10, 11), the thalamus plays a role in fear conditioning in conjunction with the basolateral complex of the amygdala. This has also been shown in human fMRI studies of context based conditioning in virtual reality environments, showing involvement of left medial dorsal thalamus (12), medial thalamic nuclei (13). Its role in fear conditioning has also been shown using MEG (14) and PET imaging(15). Thalamic involvement is also present in fear generalization (16). Resting state functional connectivity studies show altered frontothalamic connectivity in PTSD subjects compared to controls (17).

A meta – analyses of fMRI studies in PTSD showed increased activation of anterior thalamus during fear conditioning, increased activation of thalamus during extinction learning and increased activation of posterior thalamus during extinction recall in trauma exposed healthy controls compared to PTSD subjects(18). Resting state functional connectivity between left thalamus and bilateral dorsal anterior cingulate was also seen to be reduced in subjects with higher early life stress (ELS) scores (19).

Previous studies have used distinct white matter cortical and subcortical connectivity to parcellate thalamic nuclei in vivo (20, 21). Using a more recent segmentation atlas based on histological data, the thalamus has been divided into 26 nuclei (22). The nuclei groups include anterior (anteroventral), lateral (laterodorsal, lateral posterior), ventral (ventral anterior, VA magnocellular, ventral lateral anterior, ventral lateral posterior, ventral posterolateral, ventromedial), intralaminar (central medial, central lateral, paracentral, centromedian, parafascicular, reuniens, mediodorsal medial magnocellular, mediodorsal lateral parvocellular), posterior (lateral geniculate, medial geniculate, suprageniculate, pulvinar anterior, pulvinar medial, pulvinar inferior). A previous study comparing thalamic volumes between PTSD subjects and controls in the PGC dataset showed reduced whole thalamic volumes in PTSD subjects compared to controls(23). However this difference was not significant(23). Hence in this analyses,

we propose to compare volumes of distinct thalamic nuclei between PTSD subjects and controls from the PGC dataset.

The neurobiology of PTSD involves sensory hyperactivity and impaired threat perception(24, 25). For this reason we plan to focus on the following nuclei in our analyses: - somatosensory relay (VPL), vision (LGN, PA, PI, PM) and auditory processing (MGN)

B. Analyses Plan

Using data from the PTSD Psychiatric Genetics Consortium (PGC-PTSD) neuroimaging project, we will extract thalamic volumes from subjects across 29 different sites. We have two groups of subjects – controls (trauma exposed or healthy) and subjects with PTSD. Possible covariates for the data include age, gender, childhood trauma score, alcohol use and comorbid MDD.

Primary aims

1. To compare volumes of thalamic nuclei between subjects with PTSD versus controls (including trauma exposed and healthy) in the PGC-PTSD dataset.
2. To explore association between PTSD severity scores and thalamic nuclei volumes in PTSD subjects

Primary hypotheses

1. We hypothesize that thalamic nuclei involved in somatosensory relay (VPL), vision (LGN, PA, PI, PM) and auditory processing (MGN) will show greater volume differences between PTSD subjects and controls.
2. We also hypothesize a significant association between PTSD symptom severity on CAPS and these nuclei volumes.

Variables to be used in the analysis (the main predictor and outcome variables, and potential covariates must be identified)

Main predictor

- Diagnosis (PTSD vs healthy controls)

Outcome variables

- Volume of subnuclei of the thalamus (see below)
- Total thalamic volume

Covariates

Age

Age^2

PTSD x Age

Childhood Trauma (number of categories from CTQ)

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PTSD x Childhood Trauma

Gender

ICV

Comorbidity (depression and alcohol use disorder)

Some of the thalamic nuclei defined by Iglesias and colleagues are very small. To minimize floor effects and segmentation failures, we recombine these subnuclei to five larger groups of thalamic subnuclei per hemisphere (see table below).

Nucleus group	Nucleus (in Iglesias et al)	Definition
Anterior	Anteroventral	Well defined nucleus, starting rostrally. Continued by the LD. Small/medium sized neurons. We include the anterior medial and anterior dorsal nuclei into the AV.
Lateral	Laterodorsal	Made up of small cells, pale and homogeneously distributed.
	Lateral posterior	Group of loosely arranged small and medium neurons. It continues as the ventral lateral nucleus and its posterior part (VLP) caudally, as far as the PuA.
Ventral	Ventral anterior	Located at the anterior pole of the thalamus, and formed by medium size neurons crossed by bundles of fibres.
	Ventral anterior magnocellular	Formed by big and dark neurons, loosely arranged.
	Ventral lateral anterior	Formed by small neurons in clusters, in the dorsolateral part of the nucleus.
	Ventral lateral posterior	Made up of large neurons, loose appearance.
	Ventral posterolateral	Formed by small and medium sized neurons from the ventral part of the VLP to the PuI and PuL. The medial portion (ventral posteromedial nucleus) is included in our definition of VPL.
	Ventromedial	The neurons are similar to VA neurons, but without bundles of crossing fibres. It lies ventral to VA.
Intralaminar/ medial	Central medial	Formed by a compact group of dark neurons, located close to MV-Re and PV.
	Central lateral	Made up of big neurons, arranged in clusters. It lies dorsal to the MD, lateral to the MDl and underneath the AV and LD.
	Paracentral	Lateral to MDl. Medial to VLP. Small and connected islands, loose.
	Centromedian	Formed by small, condensed neurons. Fibres of the internal medullary lamina surround it.
	Parafascicular	Formed by small and compact neurons. It lies ventral and medial to the CM.
	Paratenial	Rostro-caudally oriented group of small neurons along the stria medullaris.
	Reuniens (medial ventral)	Rostrally situated, it consists of a mix of large and small neurons. Fused with the other side through the adhesion interthalamica. Anteroventral to CM and medial to VA.
	Mediodorsal medial magnocellular	Made up of big and darkly stained neurons, sometimes in irregular groups at the ventral part.
	Mediodorsal lateral parvocellular	Smaller neurons, which form, varied forms of groupings. Bordered by the Pc, CL and Pf ventrally.
Pulvinar	Pulvinar anterior	Group of neurons located ventromedially to the LP.
	Pulvinar medial	Formed by small and pale neurons of uniform appearance and distribution. It lies at the posterior end of the thalamus.
	Pulvinar lateral	Large in size, it occupies most of the lateral part of the caudal thalamus. Many fibres cross it.
	Pulvinar inferior	Located ventrally and laterally to the PuM, and formed by small and medium neurons.

Adapted from Iglesias et al. (2018)

C. Investigative Team

1. Gopalkumar Rakesh
2. Delin Sun

3. Emily Clarke
4. Courtney Haswell
5. Rajendra Morey
6. Paul Thompson
7. Neda Jahanshad
8. Eugenio Iglesias
9. Odile van den Heuvel
10. Chris Vriend
11. ENIGMA-PTSD Workgroup
12. PGC-PTSD Neuroimaging Workgroup

D. Resources Needed

Describe the resources needed to achieve the aims of the analysis, including variables needed, analysis support, and any other issues that may affect the feasibility of the plan.
We will process T1 weighted structural MRI images of all subjects using Freesurfer 7 to segment the thalamus. After this, the add-on thalamic segmentation pipeline (Iglesias et al) (22) will subsegment thalamus into (25 X2) different sub nuclei.

E. Timeline

6 months

F. Collaboration

The following is the standard PGC policy about secondary analyses. Any deviation from this policy needs to be described and justified, and could negatively impact the proposal.
PGC investigators who are not named on this proposal but who wish to substantively contribute to the analysis and manuscript may contact the proposing group to discuss joining the proposal.

G. Authorship

We will follow the authorship policy of the PGC-PTSD which can be found at https://pgc-ptsd.com/wp-content/uploads/2017/06/Authorship-Guidelines-PGC-PTSD.pdf

(a) are you following the authorship policies of the groups involved? ***YES see https://pgc-ptsd.com/wp-content/uploads/2017/06/Authorship-Guidelines-PGC-PTSD.pdf***

(b) will there be a writing group and if so, who will be included? ***The writing group will be comprised of the investigative team (#1 - #5) listed above.***

(c) what groups or individuals will be listed as authors? ***Authors will include the writing group plus individual and group contributors of data and analysis from each site (generally 2-3 co-authors from each site).***

(d) will PGC members not listed as named authors be listed at the end of the manuscript? ***All individuals who meet the criteria established in the PGC-PTSD authorship policy will be co-authors. Other PGC members will not be listed at the end of the manuscript.***

(e) will PGC members or groups be listed as "collaborators" on the PubMed abstract page? ***All individuals and groups who meet the authorship criteria of the PGC-PTSD authorship policy will***

be listed as collaborators on the PubMed abstract page. No other individuals or groups will be listed.

(f) *how will funding sources be handled or acknowledged?* ***All funding sources that supported data collection and analysis will be listed in the manuscript.***

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