TECHNICAL COMMENTARY

fMRI, PET, SPECT

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POST-TRAUMATIC STRESS DISORDER LIBRARY

Introduction

Functional magnetic resonance imaging (fMRI) measures blood flow to determine activation and deactivation of the specific brain regions at rest and when associated with particular tasks. Positron emission tomography (PET) is a nuclear based imaging technique that utilises a radioactive tracer to visualise functional brain activity. The radioisotope tracers are coupled with a biological molecule such as glucose, which is used during cellular metabolism and can be used to highlight areas with changes in metabolic activity. Single-photon emission computed tomography (SPECT) offers more limited spatial and temporal resolution than PET but is less expensive as it does not require a cyclotron in close proximity.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with PTSD. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. When multiple copies of reviews assessing the same topic were found, only the most recent and/or comprehensive was included. We prioritised reviews with pooled data for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found three systematic reviews that met our inclusion criteria[3-5].

- Compared to non-trauma-exposed controls, moderate to high quality evidence found the following regions showed clusters of increased activation in PTSD during resting state or task processing (various): bilateral anterior insula, left amygdala, left putamen, left precuneus, right hippocampus, right middle frontal gyrus fusiform gyrus, and right postcentral gyrus. The following regions showed clusters of decreased activation: bilateral precentral gyrus, left angular gyrus, left supramarginal gyrus, left middle frontal gyrus, right posterior cingulate cortex, right medial prefrontal cortex, and right caudate nucleus.
- Compared to trauma-exposed controls, people with PTSD showed increased activation during resting state or task processing (various) in the left fusiform gyrus, right precuneus, right thalamus, dorsal anterior cingulate cortex, and lateral

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medial temporal lobe. People with PTSD showed decreased activation in the left thalamus, left parahippocampal gyrus, right medial prefrontal cortex, right orbitofrontal cortex, right precentral gyrus, left frontal pole, bilateral inferior frontal gyrus, bilateral middle frontal gyrus, and dorsal anterior cingulate cortex.

- During trauma-related autobiographical memory tasks, moderate quality evidence found increased activation in PTSD in clusters in the left posterior cingulate extending into the precuneus and the mid-cingulate cortex, right parahippocampal gyrus, and the right dorsal anterior cingulate cortex. There was decreased activation in PTSD in clusters in the right ventromedial prefrontal cortex extending into the orbitofrontal and the perigenual anterior cingulate, and the left midline nucleus of the thalamus extending into the medial and the lateral dorsal nuclei and the left angular gyrus.
- Increased PTSD symptom severity in patients was associated with increased activation during trauma-related autobiographical memory tasks in clusters in the left insula extending into the lentiform nuclei, the putamen, the hippocampus, and the amygdala, right caudate nucleus extending into the thalamic anterior nucleus, right middle frontal gyrus, and bilateral ventromedial prefrontal gyrus extending into the perigenual anterior cingulate.
- Compared to borderline personality disorder, moderate to low quality evidence found more activation in the PTSD group during negative affect processing in the left inferior frontal gyrus (triangular), left middle temporal gyrus, right striatum, bilateral middle frontal gyrus (including parts of the left superior frontal gyrus, dorsolateral), ventral premotor cortex, and right posterior parietal cortex.
- Compared to major depressive disorder, there was more activation in the PTSD group during negative affect processing in the left inferior frontal gyrus (including ventrolateral prefrontal cortex), bilateral amygdala and hippocampus, left superior frontal gyrus, dorsolateral prefrontal gyrus, and right middle frontal gyrus.
- Overlapping regions of abnormal brain activation in PTSD, major depression and borderline personality disorder during negative affect processing were; hyperactivation of the right median cingulate gyrus and hypoactivation of the right middle frontal gyrus and the right middle occipital gyrus.

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Patel R, Spreng RN, Shin LM, Girard TA

Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies

Neuroscience and Biobehavioral Reviews 36: 2130-42

View review abstract online

Comparison	**Functional activity during resting state or task processing (various) in people with PTSD vs. non-trauma-exposed and trauma-exposed controls.**
Summary of evidence	**Compared to non-trauma-exposed controls, moderate to high quality evidence (large samples, reliable, direct) found the following regions showed clusters of increased activation in PTSD; bilateral anterior insula, left amygdala, left putamen, left precuneus, right hippocampus, right middle frontal gyrus fusiform gyrus, and right postcentral gyrus. The following regions showed clusters of decreased activation; bilateral precentral gyrus, left angular gyrus, left supramarginal gyrus, left middle frontal gyrus, right posterior cingulate cortex, right medial prefrontal cortex, and right caudate nucleus.** **Compared to trauma-exposed controls, people with PTSD showed increased activation in the left fusiform gyrus, right precuneus, right thalamus, dorsal anterior cingulate cortex, and lateral medial temporal lobe. People with PTSD showed decreased activation in the left thalamus, left parahippocampal gyrus, right medial prefrontal cortex, right orbitofrontal cortex, right precentral gyrus, left frontal pole, bilateral inferior frontal gyrus, bilateral middle frontal gyrus, and dorsal anterior cingulate cortex.**

Functional activation

Resting state or task associated

20 studies, N = 595 vs. non-trauma-exposed controls

Clusters in the following regions showed increased activation in PTSD vs. non-trauma-exposed controls;

Left amygdala

Right hippocampus

Bilateral anterior insula

Left putamen

Left precuneus

Right middle frontal gyrus Right fusiform gyrus Right postcentral gyrus *Clusters in the following regions showed <u>decreased activation in PTSD</u> vs. non-trauma-exposed controls;* Left angular gyrus Right posterior cingulate cortex Right medial prefrontal cortex Left supramarginal gyrus Left middle frontal gyrus Bilateral precentral gyrus Right caudate nucleus 19 studies, N = 429 vs. trauma-exposed controls *Clusters in the following regions showed <u>increased activation in PTSD</u> vs. trauma-exposed controls;* Dorsal anterior cingulate cortex Right precuneus Lateral medial temporal lobe Right thalamus Left fusiform gyrus *Clusters in the following regions showed <u>decreased activation in PTSD</u> vs. trauma-exposed controls;* Right medial prefrontal cortex Left parahippocampal gyrus Bilateral inferior frontal gyrus Bilateral middle frontal gyrus Left frontal pole Dorsal anterior cingulate cortex Right orbitofrontal cortex Right precentral gyrus Left thalamus	
Consistency in results‡	Heterogeneity is not reported, but authors report results are reliable.
Precision in results§	Unable to assess; no measure of precision is reported.
Directness of results‖	Direct

Schulze L, Schulze A, Renneberg B, Schmahl C, Niedtfeld I

Neural Correlates of Affective Disturbances: A Comparative Meta-analysis of Negative Affect Processing in Borderline Personality Disorder, Major Depressive Disorder, and Post-Traumatic Stress Disorder

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2019; 4: 220-32

View review abstract online

Comparison	**Functional activity during negative affect processing compared to neutral stimuli in people with PTSD, borderline personality disorder, or major depression (all diagnoses vs. controls).**
Summary of evidence	**Compared to borderline personality disorder, moderate to low quality evidence (large sample, indirect) found more activity in the PTSD group during negative affect processing in the left inferior frontal gyrus (triangular), left middle temporal gyrus, right striatum, bilateral middle frontal gyrus (including parts of the left superior frontal gyrus, dorsolateral), ventral premotor cortex, and right posterior parietal cortex.** **Compared to major depressive disorder, there was more activity in the PTSD group in the left inferior frontal gyrus (including ventrolateral prefrontal cortex), bilateral amygdala and hippocampus, left superior frontal gyrus, dorsolateral prefrontal gyrus, and right middle frontal gyrus.** **Overlapping regions of abnormal brain activation were hyperactivation of the right median cingulate gyrus (MNI coordinates 8, 216, 40) and hypoactivation of the right middle frontal gyrus (MNI coordinates: 42, 4, 52) and the right middle occipital gyrus (MNI coordinates: 38, 276, 2).**

Functional activation

Negative affect processing

70 studies, N = 3,081

Clusters in the following regions showed increased activation in the PTSD group vs. controls than in the borderline personality disorder group vs. controls;

Left inferior frontal gyrus (triangular)

Left middle temporal gyrus

Right striatum

Bilateral middle frontal gyrus, including parts of the left superior frontal gyrus, dorsolateral

Ventral premotor cortex Right posterior parietal cortex *Clusters in the following regions showed increased activation in the PTSD group vs. controls than in the major depression group vs. controls;* Left inferior frontal gyrus, including ventrolateral prefrontal cortex Bilateral amygdala and hippocampus Left superior frontal gyrus Dorsolateral prefrontal gyrus Right middle frontal gyrus Overlapping regions of abnormal brain activation were; hyperactivation of the right median cingulate gyrus (MNI coordinates 8, 216, 40) and hypoactivation of the right middle frontal gyrus (MNI coordinates: 42, 4, 52) and the right middle occipital gyrus (MNI coordinates: 38, 276, 2). There were no consistent moderating effects of age, sex, or medication status.

Consistency in results	Heterogeneity is not reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Indirect comparisons between PTSD and other diagnoses (all via controls analyses).

Thome J, Terpou BA, McKinnon MC, Lanius RA

The neural correlates of trauma-related autobiographical memory in posttraumatic stress disorder: A meta-analysis

Depression and Anxiety 2020; 37: 321-45

View review abstract online

Comparison	**Functional activation during trauma-related autobiographical memory in people with PTSD, vs. mostly trauma-exposed controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct) found decreased activation in PTSD during trauma-related autobiographical memory in clusters in the right ventromedial prefrontal cortex extending into the orbitofrontal and the perigenual anterior cingulate, and the left midline nucleus of the thalamus extending into the medial and the lateral dorsal nuclei and the left angular gyrus.** **There was increased activation in PTSD in clusters in the left posterior cingulate extending into the precuneus and the**

	mid-cingulate cortex, right parahippocampal gyrus, and the right dorsal anterior cingulate cortex. **Increased PTSD symptom severity in patients was associated with increased activation in clusters in the left insula extending into the lentiform nuclei, the putamen, the hippocampus, and the amygdala, right caudate nucleus extending into the thalamic anterior nucleus, right middle frontal gyrus, and bilateral ventromedial prefrontal gyrus extending into the perigenual anterior cingulate.**
Functional activation **Trauma-related autobiographical memory**	
28 studies, N = 710 *Clusters in the following regions showed decreased activation in PTSD compared to controls;* Right ventromedial prefrontal cortex extending into the orbitofrontal and the perigenual anterior cingulate Left midline nucleus of the thalamus extending into the medial and the lateral dorsal nuclei and the left angular gyrus *In retrieval autobiographical memory tasks, clusters in the following regions showed decreased activation in PTSD compared to controls;* Left middle temporal gyrus Right medial orbitofrontal cortex extending into the perigenual anterior cingulate cortex *In re-experiencing autobiographical memory tasks, clusters in the following regions showed decreased activation in PTSD compared to controls;* Right ventromedial prefrontal cortex extending into the dorsomedial prefrontal and the perigenual anterior cingulate cortex Left midline nucleus of the thalamus extending into the medial and the lateral dorsal nuclei, the right inferior frontal gyrus Right precuneus Dorsal anterior cingulate *Clusters in the following regions showed increased activation in PTSD compared to controls;* Left posterior cingulate extending into the precuneus and the mid-cingulate cortex Right parahippocampal gyrus Right dorsal anterior cingulate cortex *In retrieval autobiographical memory tasks, clusters in the following regions showed increased activation in PTSD compared to controls;* Left posterior cingulate extending into the precuneus and the mid-cingulate gyrus Right parahippocampal gyrus	

Left precentral gyrus *In re-experiencing autobiographical memory tasks, clusters in the following regions showed <u>increased activation in PTSD</u> compared to controls;* Right caudate nucleus Left posterior cingulate cortex extending into the precuneus Right dorsal anterior cingulate cortex Right ventromedial prefrontal cortex Right middle temporal gyrus *Increased PTSD symptom severity in patients was associated with <u>increased activation</u> in clusters;* Left insula extending into the lentiform nuclei, the putamen, the hippocampus, and the amygdala Right caudate nucleus extending into the thalamic anterior nucleus Right middle frontal gyrus Bilateral ventromedial prefrontal gyrus extending into the perigenual anterior cingulate Overall, the results did not change after excluding studies with non-trauma-exposed controls.	
Consistency in results	Heterogeneity is not reported, authors report some findings were not reliable.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

MDI = Montreal Neurological Institute, N = number of participants, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[6].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[6].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[6];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[8].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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