Chapter I

Structural and Functional Neuroimaging in PTSD: A Neurobiological Update

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Abstract

Advances in neuroimaging permit in vivo investigation of the structural and functional neurobiology of post-traumatic stress disorder (PTSD). Recent reviews of structural and functional neuroimaging in PTSD are discussed together with recent studies. The significance of the findings is limited by the disparate groupings of PTSD trauma exposures, making generalization difficult, and this, combined with the heterogeneity inherent in the existing diagnostic criteria, renders the often conflicting data confusing. There has been an emphasis on studies of cortical structures, without adequate consideration of neural circuit models implicating other brain structures. There has been a move towards investigating subsets of symptoms, such as hyperarousal and dissociation, particularly in functional imaging studies. Overall, neuroimaging research in PTSD faces challenges for the future. The key improvements lie in: the definition and classification of trauma exposures, as they are not all equivalent in nature or indeed comparable; the study of restricted phenotypic subsets of symptoms or endophenotypes, such as hyperarousal and dissociation which may have different neural substrates; adequate study designs for power and control of confounders; and more focused research based upon targeted investigation of neural networks putatively involved in the processing and re-experiencing of trauma.

Cotidie damnatur qui semper timet.
“The man who is in fear is constantly condemned.”
Publilius Syrus (c. 100 B.C.E.)
Introduction

This chapter aims to provide a critical update on the status of structural and functional neuroimaging studies of PTSD as a means of studying the in vivo neurobiology of the disorder. As such, we have focused upon studies from the last decade and we are summarizing from number of comprehensive reviews that have been published recently on structural [1,2] and functional imaging [3,4]. The overall impression in this field is that there is much of interest, but equally much more to be done, both theoretically and methodologically, to advance our understanding of the in vivo structural neurobiology of PTSD.

We begin with an introduction to some of the theoretical and methodological issues in neuroimaging of PTSD. The first section of the chapter summarizes the findings from structural (MRI) and functional magnetic resonance imaging (fMRI). The second section summarizes radioisotope functional neuroimaging, Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). Finally, we summarize our findings and draw conclusions.

Theoretical and Methodological Issues

Characterization of PTSD

A key issue in such correlative brain imaging studies is the selection of study groups, and in particular, diagnostic criteria. Most studies have accepted diagnoses for PTSD, as defined via the DSM-III-R or DSM-IV [5,6]. Surprisingly, within reviews of these studies, there has been little discussion of the diagnostic criteria and their suitability for characterizing the disorder from a neuropathologic and hence, in vivo neuroimaging viewpoint.

Whilst different types of stressors, exposures and impacts may result in different presentations, the field has apparently assumed that these processes drive the same neurobiological processes. In the main, exploration to date has focused upon the cerebral cortex, in what has been termed a cortico-centric model of cognition [7]. This differs from the understanding of cognitive processing as being segregated into multiple, parallel distributed networks. For example, visual components of experience, arguably including trauma, are processed via different circuitry than auditory and cognitive components being routed via different pathways through the basal ganglia [7]. However, recent structural and functional studies have begun to investigate networks of distributed cognition, particularly in relation to subsets of symptoms in PTSD.

Methodological Issues

The key methodological issues we have identified in this review are:
1. Insufficient characterization of the trauma exposure, which is significant and may partly explain conflicting results from non-equivalent exposures or reactions to those being compared;

2. Evolution of diagnostic criteria;

3. Impact of number of stressors and exposures;

4. Specificity of symptom constellations (such as hyperarousal and dissociation) within these criteria;

5. Severity of symptomatology;

6. Studies of inadequate statistical power to examine group differences;

7. Variation in imaging methodology, even within modality and technological innovation with the passage of time, compromising comparisons from different periods;

8. Lack of accounts of treatment effects;

9. Variation in candidate neuroanatomical structures and networks being studied.

The trauma exposures for criteria A1 and A2 of the accepted DSM-IV diagnostic criteria for PTSD remain controversial because of the inherent subjectivity of these experiences. That is, what is perceived as constituting actual or threatened death or serious injury (A1); and intense fear, horror or helplessness (A2); is subjective and difficult to standardize. In children, this assessment is even more problematic.

Finally, the issue of the nature of the threat: to life (e.g. serious assault) or integrity (e.g. sexual abuse), may vary in experience or meaning. Similarly, the evolution of the vague diagnostic criterion A from: “The person has experienced an event that is outside the range of usual human experience and that would be markedly distressing to almost anyone,” in DSM-III-R adds further complexity to neuroimaging studies; yet this variation in definition has received little comment in existing reviews.

Indeed, as is common in psychiatric research, the disorder is assumed to exist in some reified form based upon diagnostic criteria. For example, Karl et al. [1] structural MRI review includes: 6 studies on combat related trauma, 4 of childhood sexual abuse, with a variety of other exposures from domestic violence, experiences of police officers and cancer survivors to be considered among the 21 groups included in the meta-analysis. Can such diverse experiences be considered equivalent? In relation to neuroimaging studies, are they necessarily processed by the same neural circuitry? This would seem unlikely.

We have not been the only group to propose that grouping all PTSD subjects together is questionable. For example, Lanius et al., [3], has observed that doing so may interfere with our understanding of post-traumatic symptomatology. In raising this criticism, we accept existing cohorts have varied exposures and indeed have had to resort to combining subjects with different exposures to increase the power of such studies.

However, a more logical, parsimonious, approach would be to classify types of trauma exposure, document subsequent psychological sequelae and investigate structural correlates of the same. The logical comparison, which has laudably been adopted in most extant studies, is to compare those with the same exposure who developed PTSD with those who did not. One prism which could be used to focus such research may to investigate more restricted subsets of phenotypic symptomatology and behaviour, known as endophenotypes. Thus,
clusters of symptoms, such as dissociative phenomena, traumatic re-experiencing, and hyperarousal might usefully be investigated for their structural and functional correlates, rather than the whole ensemble of PTSD diagnostic criteria. In addition, then we might usefully investigate the correlation of the severity of symptomatology with structural and functional imaging.

When we examine studies purporting to identify structural or functional changes in the brain of persons suffering from PTSD, we find that the numbers of subjects in the studies are relatively small. We accept that enrolling subjects with specific traumatic experience is very difficult, and acknowledge the further challenge of finding those exposed to the same experience that did not develop PTSD. Nonetheless, studies of less than fifteen patients, by our calculations, would require a very large effect size to show significance and, perhaps, overestimate random effects as difference, especially if significance is set at $p<0.05$.

Whilst acknowledging the informative work of previous reviewers, we also question the utility of comparing research using different diagnostic criteria and different image modalities for meta-analysis. Depending on the segmentation methods used, there may be considerable variation in delineation of brain structures or identification of activity due to different MRI acquisition and SPECT/PET protocols. Each study can contribute a piece to solving the puzzle through how they fit together, but perhaps not all pieces are equally useful.

This brings us to a general problem of brain imaging, and that is of adequate hypotheses, for adequate designs, preceding acquisition of images. It seems to us there has been a dearth of coordinated approaches to examining the neural circuitry implicated in PTSD. By this, we mean specific investigations based upon some putative circuitry or functional neuroanatomy of PTSD [8]. Indeed Lanius et al. [3] has proposed decomposing the PTSD symptoms into two clusters which could be examined separately, from the perspective of different exposure at least, functional imaging: hyperarousal and dissociative patterns and endophenotypes, which may have different neural circuit substrates. These patterns were previously proposed by Bremner [9]. To this could be added traumatic re-experiencing, in the form of flashbacks, studied in recent functional imaging symptom-provocation studies. That is, focus should be upon endophenotypes of PTSD, such as dissociation, re-experiencing and hyperarousal, which may have their basis in particular brain circuitry. To this, we may add that memory disorders, such as re-experiencing may also occur. For example, some of the authors of this chapter have investigated the structure of the caudate in frontostriatal circuits postulated to be involved in re-experiencing of trauma-related experience [10].

Having raised these methodological issues, we now turn to the summaries of recent research, acknowledging and drawing upon previous reviews [1-4] for this update.

**Structural MRI Studies**

**Recent Reviews**

*Karl et al., [1] – Meta-analysis of Structural Brain Abnormalities in PTSD*

Karl et al., [1] reviewed 21 MRI studies from 1990 to 2005 via meta-analysis. Their inclusion criteria were relatively rigorous, so their review is a good base to build upon for an
update. Therefore, we have summarized directly from their review in this section. However, we add the reservations, noted above, that not all trauma exposures are equivalent, although symptoms resulting may be similar; and the variation in diagnostic criterion A from DSM-III-R to DSM-IV remains problematic for those classified as having PTSD. The issues addressed in inclusion criteria for the meta-analysis were: inclusion of DSM-III-R or DSM-IV PTSD compared to non-PTSD exposed or controls; sufficient methodological specification (sample, MRI methodology); and sufficient statistical testing.

However, the issue of endophenotypic characterization, in contrast to the use of the extant criteria was not discussed, nor was the issue of heterogeneity of trauma exposures explored. Thus, the studies summarize findings from disparate trauma exposures and populations, using a broad classification of PTSD which may obscure differences due to differential pathophysiology of the endophenotypes of hyperarousal, re-experiencing or dissociation.

**Hippocampal Volumetric Studies**

This was the most frequently investigated area. The meta-analysis found that PTSD subjects had smaller bilateral hippocampal volumes than healthy controls, whilst meta-analysis of exposed non-PTSD persons compared to those with PTSD was only significant for left hippocampal volume [1]. Interesting methodological factors were moderators: MRI acquisition protocols and delineation of hippocampal boundaries (mostly manual in these studies). Only the studies using high resolution MRI and correction for whole brain volume showed differences for non-PTSD exposed compared to those exposed with PTSD in the left hippocampus; whilst the findings for PTSD versus controls were robust even with low resolution and no brain volume correction. There were indications that studies using the alveus/fornix and superior colliculi/basilar artery to trace the hippocampus coronally found significantly smaller bilateral hippocampal volume in PTSD compared to controls, in contrast to studies using mamillary bodies/fornix as a boundary. Other significance moderators were age, severity and gender, as might be expected. Overall, the effect size for the hippocampal volume reductions in PTSD were generally between 0.0 and 0.5, with the percentage of reduction generally between 0-20%, which is quite a large reduction in volume. Examining the breakdown by trauma type, there seems a trend toward combat trauma resulting in larger changes, followed by childhood sexual abuse, accidents and interpersonal violence. Also, trauma severity may be proportional to the extent of the violence directed towards an individual.

**Amygdala**

Left amygdala volume was found to be smaller in PTSD subjects compared to healthy controls (n=320) and trauma-exposed non-PTSD subjects (n=213) with an effect size between 0.1-0.4. However, Karl et al., [1] noted there was a significant sample heterogeneity in all these groups.

**Corpus Callosum**

The corpus callosum (n=221) was primarily investigated in children and adolescents and was found to be smaller in those with PTSD, with an effect size circa 0.4.
Caudate
No significant group differences were found in caudate nucleus volumes in a heterogenous group of children, adolescents and adults (n=281).

Frontal Lobes
The tracing or delineation of the frontal lobes remains technically challenging due to variations in the morphology of these regions across individuals. In children and adolescents (n=223), the prefrontal cortex was significantly smaller in PTSD compared to healthy controls and non-PTSD exposed, albeit with a small effect size c. 0.3-0.4.

Cavum Septum Pellucidum
In a very small meta-analysis of a heterogenous grouping of adults and children (n=63), no significant differences were found across PTSD compared to healthy controls and non-PTSD exposed.

Jackowski et al., [2] – Pediatric Neurostructural Findings in PTSD
In a brief non-systematic review, Jackowski et al. [2] have summarized some of the relevant findings in pediatric populations. They proposed that the failure to find significant volumetric alterations in the hippocampus in children and adolescents with PTSD may represent neuro-maturational differences. That is, early life stresses may have an impact that is not evident until later development. Whilst they also emphasize the corpus callosum differences identified in the Karl et al. [1] meta-analysis, the authors of the pediatric review speculate these changes may be due to either developmental differences and/or selective vulnerability of callosal regions in critical periods of development to trauma. Generalized reduction in brain volume, reduced frontal lobe, prefrontal cortex, right temporal lobe, and white matter volumes has been found in pediatric populations with PTSD. In addition, bilateral ventricular enlargement and increased prefrontal CSF volume has been found. These finding appear isolated to children, and the authors suggested generalized atrophy or impaired brain development as mechanisms.

Recent Structural MRI Studies since the Karl et al. [1] Meta-analysis
There have been interesting developments, some of which have used new MRI acquisition and analysis methods.

Anterior Cingulate Cortex
Using diffusion-tensor analysis, Abe et al. [11] studied 9 victims of the Tokyo subway Sarin attack with PTSD compared with 16 controls, and found a significant increase in fractional anisotropy in the left anterior cingulum underlying the region in which the same group found a volumetric reduction in the left anterior cingulate grey matter. This structural finding supports the hypothesis of neural circuit dysfunction, with the suggestion that there is increased connectivity and thus, hyper-responsivity of the circuits traversing this region. Why this should result in volumetric reduction of the adjacent grey matter is more problematic. Researchers from the same group have used voxel-based morphometry and found that there were significant grey matter reductions in right hippocampal cortex, pregenual anterior
cingulate cortex and bilateral insular regions in combat-exposed twins with (n=18) and without PTSD (n=23) [12]. In another study on the same cohort, using manual segmentation of the cerebellum, no significant differences in the volume of the cerebellar vermis were found [13].

**Other Cortical Regions**

Two recent studies have found changes, albeit in opposite directions, in pediatric PTSD and in adults with PTSD. Geuze et al., [14] compared 25 male veterans with PTSD with 25 without PTSD, matched for age, year and region of deployment; using a cortical thickness algorithm to find that veterans with PTSD had reduced thickness in bilateral superior and middle temporal gyri, and left superior temporal and inferior frontal gyri. However, cortical thickness was not correlated with memory measures. The pediatric study of Carrion et al., [15] used semi-automated segmentation and voxel-based morphometry in 24 children with PTSD compared to 24 age and gender matched controls. The pediatric study found increased gray matter volume in the bilateral inferior and superior prefrontal cortex, with reduction in the pons and posterior cerebellar vermis. The VBM study showed increased gray matter density in ventral prefrontal cortex. Again, the pediatric studies are intriguing, with evidence of some possible developmental hypertrophic differences which may precede volume loss in adult life.

**Caudate Nucleus**

Looi et al. [10] assessed 36 subjects aged less than 65 recruited from transport workers in Stockholm who reported having been unintentionally responsible for a person-under-the-train accident or among employees having experienced an assault in their work (1999–2001) between 3 months and 6 years before MRI scanning. After adjustment for the covariates (age, sex, intracranial volume, years since trauma, and number of trauma episodes), there was a significant difference in raw right caudate nucleus volume between subjects with PTSD (n=19) compared with those without PTSD (n=17). Volume of the left caudate nucleus was not significantly different between the PTSD and no PTSD groups. The right caudate volume in the PTSD group was 9% greater compared with the no PTSD group, superimposed upon a baseline asymmetry, indicating possible involvement of frontostriatal circuitry in PTSD.

**Conclusion: Structural MRI Findings**

In general, structural MRI findings have been restricted to the ensemble of the entire PTSD criteria, rather than endophenotypic subsets, and this, together with trauma exposure heterogeneity, renders the findings somewhat questionable in their specificity for PTSD. In addition, there has been a focus upon the cortex as structural basis for PTSD, but it is not necessarily clear how specific the cortical changes are to PTSD. Indeed hippocampal volumetric loss has been reported in depression, dementia and schizophrenia, and may merely be a general stress response, rather than specific to PTSD. Similarly, the findings for the amygdala, corpus callosum and developmental abnormalities might represent some generalized, non-specific structural basis for vulnerability to stress. The more specific
findings relating to key structures in cortico-subcortical circuits relevant to processing trauma, such as the anterior cingulate and caudate, both components of frontostrriatal circuits potentially serving as a basis for endophenotypes, are step forward to more focused, parsimonious research.

**Functional MRI Studies**

We have synthesized findings here derived from the reviews of Lanius et al. [3] and Francati et al. [4], and followed this with an update of recent studies since these reviews.

The group led by Lanius has reported a number of fMRI findings in PTSD [3,4]. Using trauma scripts in PTSD subjects with sexual assault/abuse and motor vehicle accidents (n=9) paired with controls, decreased activation was found in the thalamus, anterior cingulate and medial frontal gyrus in PTSD subjects with hyperarousal and reliving/re-experiencing [16]. They subsequently presented findings with increased activation in the medial frontal gyrus and anterior cingulate gyrus, and activation in superior and middle temporal gyri, inferior frontal gyrus, parietal and occipital lobes in 7 subjects with dissociative PTSD responses compared to 9 controls [17]. There have been interesting findings supportive of circuit dysfunction, with enhanced patterns of right hemisphere connectivity in the posterior cingulate gyrus, parietal and occipital lobes and in the caudate nucleus [18]. Other clusters of symptoms may have different patterns, as the same group found activation in bodily state networks in PTSD subjects with dissociative symptoms such as the superior temporal gyrus, right middle frontal gyrus, right insula and cuneus, and left parietal lobe [19].

Other groups have investigated different stimuli [4]. Exposure to emotional face representations has been used in studies of PTSD in comparison with healthy controls. Rauch et al. [20] presented such images to combat veterans with PTSD, finding enhanced amygdala responsivity; whilst Shin et al. [21] also found enhanced amygdala responsivity with decreased medial prefrontal cortex activity in civilians with PTSD. Emotionally-valenced words have also been used as stimuli [4], with findings of amygdalar activation [22] and underactivity of rostral anterior cingulate [23].

**fMRI Findings since Lanius et al. [3] ; Francati et al. [4]**

Recent fMRI studies have explored either the dissociative or hyperarousal clusters of symptomatology, indicating more focussed and parsimonious approaches are being adopted to PTSD.

Another study from the Lanius [24] group compared 17 women with chronic early life trauma exposure or those who were adults when exposed to trauma with PTSD to 15 controls using fMRI. They demonstrated increased connectivity in healthy controls of the posterior cingulate/precuneus to the right amygdala, hippocampus and parahippocampal gyrus in comparison to those with PTSD. The authors concluded that the default process of
spontaneous self-reflection and monitoring was dysfunctional in PTSD and thus, may result in dissociative symptomatology.

Felmingham et al. [25] investigated the function of arousal networks in 11 subjects with PTSD and 11 matched controls on an oddball task that involved responding to non-trauma-related auditory target tones embedded in low frequency background tones and also measured skin conductance response. There was evidence of greater activity in PTSD subjects compared to controls on background tasks in greater dorsal anterior cingulate, supramarginal gyrus and hippocampus. However, when skin conductance responses were evident, showing arousal, the PTSD subjects showed reduced ventral anterior cingulate activity, which due to implication in fear-extinction processes, suggests faulty fear-extinction may occur in PTSD.

**Conclusion: Functional MRI Findings**

In general, functional MRI findings have shown more specific findings relating to key structures in circuits relevant to processing trauma, focusing on components of neural circuits potentially serving as a basis for endophenotypes, such as hyperarousal and dissociation. For example, dissociation may arise from faulty self-reflection and monitoring processes, whilst hyperarousal may result from faulty fear-extinction. In addition, memory disturbances, such as traumatic re-experiencing, which have been investigated in some functional imaging studies, may also serve as a useful endophenotype. Thus, hyperarousal, dissociation and re-experiencing may arise from dysfunction in different neural circuits, resulting in specific patterns.

**Functional Imaging: SPECT and PET**

Over the past decade, it has become increasingly clear that a number of specific brain structures play a key role in the generation of PTSD symptoms. These structures are involved in emotional, memory, linguistic, visuospatial and motor processing, all of which might be affected in PTSD. Proposed neural correlates of psychotherapy have also been investigated, revealing neurobiological effects on brain functions.

Functional studies by single photon emission computed tomography (SPECT) and positron emission tomography (PET) can now reliably detect changes in cerebral blood flow (CBF) and metabolism patterns, suggesting a specific role for each of the brain areas in various components of emotional processing.

Functional mapping of brain by PET is considered to be superior to SPECT due to: the applicability of positron-emitting “bioisotopes”, i.e. oxygen-15 and fluorine-18, allowing investigation of both brain CBF and metabolism; the relatively good spatial resolution (4-7 mm); and the ability to perform quantitative assessment [26]. Nevertheless, its availability is restricted by the heavy on-site capital investment required to build an in-house cyclotron facility, even if currently several centres perform the studies with commercially available positron emitters. Due to this, the number of PET cameras remains relatively small, as compared to the numerous SPECT facilities, making SPECT the most commonly used
technique especially in routine examinations. SPECT imaging allows measurements of CBF also reflecting neuronal activity. The maximum spatial resolution of present high-resolution SPECT cameras is of the order of 7-9 mm. SPECT is a qualitative method, reflecting the distribution of radiotracers, and whose results are usually expressed in semi-quantitative values. However, SPECT has the advantage compared to PET, allowing for experiments to be performed in ideal psychological conditions in quiet environments outside the camera gantry. In fact, due to the characteristics of SPECT, image acquisition can be commenced some hours after administration whilst still depicting the radiopharmaceutical brain distribution at the moment of injection.

Both SPECT and PET have shown in PTSD regional cerebral blood flow (rCBF) changes during trauma recall. In this respect symptom provocation paradigms are an extremely useful and powerful way of delineating the functional anatomy of traumatic memories that characterize PTSD. Alterations of local activations at specific tasks indicate dysfunctions of neural processing. Autobiographical trauma-script exposure [27-29] or audio and visual trauma-related stimuli [30,31] are a valid approach to elicit rCBF changes in PTSD and the improvements in both technical capabilities and methodology have made neuroimaging studies particularly suitable in investigating in vivo the neurobiology of emotions.

Following symptom provocation in PTSD patients, rCBF was found to be either increased [32-34], or decreased [33-35] within hippocampus, amygdala, medial pre-frontal cortex (mPFC), including orbito-frontal (OFC) and anterior cingulate (ACC) cortices, cerebellum, as well as temporal and posterior cingulate cortices. These initial findings resulted in the formulation of neurocircuitry models of PTSD that emphasize the functional relationship between a triad of brain structures: amygdala, ventro-medial prefrontal cortex (vmPFC) and hippocampus [32,36-41]. The findings from studies performed by some of our authors [42] suggest an involvement of these brain structures in PTSD, and are consistent with the results of previous functional neuroimaging studies based on symptom provocation paradigms investigating rCBF response to different stressors.

However, other structures have been shown to be involved in PTSD such as the thalamus [43-45], insula [41,46,47], Broca’s area [48-50], ACC [8,30,51,52] parietal lobes [53-56].

Pagani et al. [27] investigated 20 transport workers in Stockholm who reported having been unintentionally responsible for a person-under-the-train accident or among employees having experienced an assault in their work (1999-2001) between 3 months and 6 years before MRI scanning, symptomatic for PTSD and compared their CBF to a group of 27 drivers undergoing the same trauma without developing PTSD. Multivariate analysis identified the right hemisphere as the brain region showing statistical differences between the CBF in the two groups.

The right hemisphere integrates sensory modalities, processes nonverbal emotional communication and seems to be strongly connected with the amygdala, from which receives incoming stimuli of fear and hostility, and the relative regulation of autonomic and hormonal responses. It is also responsible for intrusive emotional memory component of PTSD and autobiographical memories [57].

The left hemisphere generates symbolic representations by categorizing stimuli and personal experiences into novel images and symbols and labels perceptions.
From the analysis of the regions involved in PTSD it appears that a large part of the limbic system (hippocampus, fusiform gyrus, amygdala and nucleus accumbens, lentiform nucleus, anterior cingulate and orbitofrontal cortex) plays a key role in the regulation of emotions and storage and retrieval of memories. The reported dysfunctions in governing cortices and medial prefrontal cortex are likely related to alterations in planning, execution, inhibition of responses and extinction of fear resulting in motor responses, and in effects on peripheral, sympathetic and cortisol systems. Furthermore in PTSD patients changes in prefrontal cortex, essential for encoding and retrieving verbal memories, might result in the difficulties in cognitively restructuring traumatic experiences.

Considering the key role of this structure in PTSD, it is worth noting the amygdala has been suggested to be mainly activated during recognition and induction of emotions by visual stimuli rather than during the reaction to recalled stimuli [58]. Furthermore due to the finest spatial resolution of PET and to the small dimensions of amygdala the detected functional blood flow and metabolism changes in this structure are reliably described only in PET studies.

In general, in PTSD patients, limbic hyperactivation is paralleled by higher cortical hypofunction [59] resulting in a lack of inhibition of reaction to fear from amygdala and lack of adequate attenuation of peripheral sympathetic and hormonal responses to stress. It has been proposed that such hyperperfusion and hyperactivity of limbic and paralimbic regions is related to stress-induced long-term potentiation between amygdala and periacquedural grey through N-methyl-D-aspartate (NMDA)-mediated pathway, once a sufficient amount of glutamate is released following stressing events [60]. In PTSD, psychological hyperactivation of an overlearned survival response with intrusive phenomena representing an active reworking of trauma memories at cognitive level has also been hypothesized by [61].

The critical involvement of limbic system has been postulated to be connected to the fear-related stimuli and to the emotional responsiveness to the retrieved traumatic experience elicited by symptom provocation. It is worth noting that chronic PTSD is often associated with long-term pharmacological treatment and/or alcohol and substance abuse further affecting brain structures and function and in case confounding the results of the investigations.

Following the predominance of PTSD studies performed in the past on veterans and abused women and children, there has been a recent focus on traumas more related to the daily life and to societal problems. In this respect, the choice of the control group is a critical step of the global analysis in neuroimaging. In PTSD subjects that were exposed to the same trauma as patients without suffering any symptom are likely the best ones to be compared to the study group since the CBF distribution differences found in group comparisons would be completely related to the disorder itself and not confounded by possible group and trauma discrepancies nor biased by other variables.

Lindauer et al. [28] studied a group of 30 traumatized police officers with and without PTSD that underwent SPECT scanning after neutral and trauma scripts. Within the PTSD group, rCBF was higher in reaction to the neutral scripts in comparison with the trauma scripts in the ventral part of the insula. The insula has an important role in body representation, pain experience and subjective emotional experience. Alterations in left insular activity (increased or decreased) have been found in healthy volunteers with induced
anxiety [62], subjects with a variety of anxiety disorders [32] and affective disorder patients with anxiety symptoms [63]. In a PET study, correlating regional cerebral perfusion with flashback intensity (a novel and interesting approach to severity of presentation) following an auditory script of their traumatic event [64], the investigators scanned a group of chronic PTSD subjects with a history of flashbacks. They detected the involvement of a number of brain areas, including bilateral insula and somatosensory regions, but no gradient of dysfunction based upon severity of symptoms.

As observed in a study performed on a group of civilian trauma survivors by Bonne and co-workers [65], rCBF distribution was higher in subjects with PTSD than in trauma-exposed healthy subjects in several brain regions, including a region extending from inferior parietal cortex (BA 40) to the post-central gyrus (BAs 1, 2, and 3).

Other neuroimaging studies highlighted the role of the parietal lobes, which are thought to be implicated in visuo-spatial information processing [53-55] as well as in temporal and spatial orientation [56].

A previous study by Liberonz et al. [56] with combat veterans who developed PTSD reported increased subcortical activity centred over the thalamus, as compared to cortical regions, while presenting combat sound stimuli. Conversely, a group of PTSD patients in resting state showed decreased rCBF in the right thalamus as compared to a group of healthy subjects [66]. Thalamus has been reported to play an important role in temporal binding, especially in the unity of perception [43-45] and in the generation of dissociative symptoms in PTSD, characterized by a significant alteration of the relative distribution of CBF between cortex and thalamus during flashbacks [67].

Posterior cingulate, parietal and motor cortices are functionally related to prefrontal cortex and mediate cognitive functions of the visuospatial processing, critical in extreme stress situations. The lentiform nucleus, consisting of the putamen and the globus pallidus, was found by Lindauer et al. [28] to show a decreased 99mTc-HMPAO uptake distribution possibly resulting in reduced motor activities and fewer active coping reactions [68].

The cerebellar involvement in PTSD has been described in two studies [65,69]. Cerebellum is involved in the autonomic regulation of both cardiovascular and skin responses and emotional behaviour as well as in motor conditioning response. Patients with cerebellar dysfunction have a diminished heart rate reduction upon fear conditioning [70] and an abnormal startle response in PTSD [71]. This might result in abnormal delay in habituation, increased heart rate variability, exaggerated startle response and sleep abnormalities [65]. Importantly, these findings suggest that the methodological use of cerebellum as reference region for data normalization in PTSD might be inappropriate. The involvement in PTSD of regions processing learning, preparation and execution of motor tasks results in an increased basal level of anxiety and arousal through a continuous preparatory motor activation [65].

Nucleus accumbens, also known as ventral striatum, was found to be activated in two studies [29,33]. It receives inputs from amygdala, prefrontal cortex and subiculum and projects to basal forebrain, diencephalon and rostral brainstem. Its functional-anatomic location makes it involved in creating appropriate emotional responses to incoming stimuli and sensitive to aversive incoming signals. In turn, it modulates the activity in downstream brain structures affecting in PTSD the motor aspect of adaptive responding resulting in
exaggerated reactions to incoming information (i.e. hyperirritability, hypersensitivity and hyperexcitability).

Among the four SPECT studies we are aware of in which the effect of therapy on PTSD has been investigated by neuroimaging (see Table 4) two dealt with eye movement desensitization and reprocessing [EMDR] [27,72]; one with selective serotonin reuptake inhibitor [SSRI] [73]; and one with cognitive restructuring therapy [74].

EMDR is an eclectic therapy method utilizing, among other techniques, relaxation exercises, safe place exercises, cognitive restructuring, future projections and imaging of the trauma combined with positive sensory stimulation. Cognitive restructuring was an exposure-based therapy consisting of an introductory session, an anamnesis session and three restructuring sessions. The SSRI citalopram was administered for 8 weeks at 20 mg/day (first two weeks) and 40 mg/day (last 6 weeks). The therapy delivered in three studies [27,73,74] lasted 8 weeks only and was a little longer in the Lansing et al. [72] study (on average about 10 weeks).

The traumatic events were very heterogeneous across the EMDR treatment studies, but the designs of the studies included an individual trauma script during SPECT in three out of four investigations [27,73,74]. As for the effect of therapies on CBF, both increases and decreases were reported. Probably due to the large variety of traumatic events and therapies the patients underwent to, the regional changes were distributed in almost all cortex. In general in PTSD and in anxiety disorders deactivations are considered to be related to symptom relief and to the normalization of reciprocal associative circuitry regulation and of hyperreactivity in emotional and memory disturbances. Activations were seen as an effect of therapies in improving negative symptoms as depression [27,72] or as a better inhibition of feed-back processes related to amygdala activity [74].

**Conclusion: Functional Imaging –SPECT and PET**

Overall, the findings for functional imaging with SPECT and PET demonstrate some interesting data, but there are limitations in common with structural MRI and to a lesser extent, functional MRI. The majority of the studies have used symptom-provocation models to elicit trauma-related responses to map regional cerebral blood flow changes. These studies show functional activation in hippocampus, amygdala and ventromedial prefrontal cortex to symptom provocation. Apart from such presumably direct activation, it has been observed there may also be relative hyperactivity of the limbic system, with cortical hypofunction. A number of other discrete brain regions have been implicated, both cortical and subcortical, including the cerebellum.

However, the emphasis on symptom provocation in SPECT and PET to date would appear to restrict these findings to the domain of hyperarousal PTSD symptomatology, in contrast to the fMRI findings for possible dissociative symptomatology noted above.

Treatment studies have been much more heterogenous in relation to exposures and the interpretation of increased or decreased activity in the context of symptomatic improvement remains problematic.
Overall Conclusion

In this brief update on the structural and functional imaging of PTSD we have summarized recent reviews and studies from the last few years, and conclude with some suggestions for future research. The increasing sophistication of studies is evident in: the extensive exploration of different symptom subsets that may constitute endophenotypes, such as hyperarousal, re-experiencing and dissociation; consideration of moderating factors; inclusion of larger numbers of subjects and controls; and, exploration of the role of both cortical and subcortical neural networks implicated in processing trauma.

More emphasis should be placed on classifying the trauma exposures into different subgroups, such as combat trauma, sexual abuse, physical abuse, domestic violence etc. These exposures are neither similar in nature, homogenous or functionally equivalent in their impact on persons, and thus should not be conflated. Perhaps separate studies of different types of trauma should be specifically designed, based upon the expected symptom profile from previous studies.

We suggest that rather than studying the entire cluster of symptoms as a whole, a more productive approach to investigation of PTSD may be to concentrate on subsets of clinical features that may serve as endophenotypes, predicated upon disturbances in neural circuitry, such as hyperarousal, re-experiencing and dissociation. The rationale for this has been established in our summary of imaging, in that different brain structures are implicated in the neural circuitry of different trauma responses, and such studies need to include subcortical as well as cortical structures. This will also help avoid the problem of evolving diagnostic criteria, and perhaps specific symptom cluster-related diagnostic criteria should be developed for researchers.

Further improvements will result from grouping homogeneous trauma exposures (by appropriate selection) and recruiting larger numbers of subjects, to permit studies with greater power to demonstrate differences. Controls exposed to the same trauma, but without persistent symptoms, are necessary to act as satisfactory controls, and it is even more preferable to have healthy controls without trauma exposure for further comparison.

Combinations of structural and functional imaging methods on larger, well-characterized samples will help advance understanding of structural-functional correlations. Longitudinal studies, involving follow-up of symptomatology and outcomes will add to our understanding of structural-functional correlations in the neuroimaging of PTSD.

Dulce bellum inexpertis.

“War is sweet to those who have not experienced it.”

Pindaros (c. 522-443 B.C.E.)

Author Contributions
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