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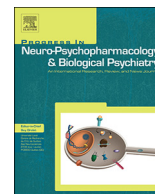
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Neuroimaging research in posttraumatic stress disorder – Focus on amygdala, hippocampus and prefrontal cortex

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ABSTRACT

Neuroimaging research reflects the complexity of post-traumatic stress disorder and shares some common difficulties of post-traumatic stress disorder research, such as the different classifications of the disorder over time, changes in diagnostic criteria, and extensive comorbidities, as well as precisely delineated and prevailing genetic and environmental determinants in the development of the disorder and its clinical manifestations. Synthesis of neuroimaging findings in an effort to clarify causes, clinical manifestations, and consequences of the disorder is complicated by a variety of applied technical approaches in different brain regions, differences in symptom dimensions in a study population, and typically small sample sizes, with the interplay of all of these consequently bringing about divergent results. Furthermore, combinations of the aforementioned issues serve to weaken any comprehensive meta-analytic approach.

In this review, we focus on recent neuroimaging studies and those performed on larger samples, with particular emphasis on research concerning the amygdala, hippocampus, and prefrontal cortex, as these are the brain regions postulated by the core research to play a prominent role in the pathophysiology of post-traumatic stress disorder. Additionally, we review the guidelines for future research and list a number of new intersectional and cross-sectional approaches in the area of neuroimaging. We conclude that future neuroimaging research in post-traumatic stress disorder will certainly benefit from a higher integration with genetic research, better profiling of control groups, and a greater involvement of the neuroimaging genetics approach and from larger collaborative studies.

1. Introduction

Neuroimaging is believed to be an effective tool in providing novel insights into the pathophysiological processes underlying clinical manifestations of post-traumatic stress disorder (PTSD) (Bremner, 2007). Difficulties in the generalization of neuroimaging research are numerous, and a portion of them is common to all PTSD research (Hull, 2002, Shin et al., 2006, Huges and Shin, 2011). Even precise definition of the clinical entity under study a key element of any research intended to result in meaningful and generalizable conclusions is in PTSD more difficult than in other areas of psychiatric research. In most cases, PTSD does not appear as a single diagnosis, for example, leading to some research indicating that more than three-quarters of Vietnam veterans meet the criteria for additional diagnosis (Blanchard and Hickling, 1997). Furthermore, unmet full diagnostic criteria for a comorbid disorder at the time of a subject's inclusion in a study does not necessarily

mean that some symptoms of the future comorbid disorder were not already present. This uncertainty is significant in neuroimaging research, as studies have revealed opposite changes in the same brain region under study in different clinical entities.

In addition, neuroimaging studies are inevitably performed with reference to smaller sample sizes, most frequently due to financial constraints related to the expensive technologies used in such studies. When drawing on a smaller sample, the essential prerequisite to obtaining plausible results is to minimize between- and within-sample variabilities. While within-sample variabilities, if analyzed, mostly rely on the maintenance of targeted conditions between samplings and on technical precision in respect of measurements and analytical skills, there is considerable difficulty, in the definition of the control group, in minimizing between-samples variability. In other research, stratification by demographic characteristics will often suffice for the formation of a "healthy controls" group, but this type of selection would hardly

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suffice in studies of PTSD, as the exposure to a traumatic event is elementary for diagnosis. Few prior neuroimaging studies have used a control group who were exposed to a traumatic event, and, even with the presence of a traumatic event, in its general terms, such an anamnesis of a control group could hardly suffice, at least for trauma types in which symptom dimensions are dependent on the specific type of the traumatic event (Henigsberg et al., 2001). Insufficiently delineated samples may lead to the large variabilities seen in the majority of studies, even when only the coefficient of variability of the primary variable is analyzed. Given such large variabilities and small sample sizes, only a few previously published studies have been sufficiently powered to accept a null hypothesis. Consequently, the issue that researchers are confronting now with regard to PTSD is common to that faced by all neuroimaging research in all areas of psychiatry, but to a larger extent, and that is a scatter of positives dispersed irregularly around the brain. Thus, neuroimaging genetics has arisen as a promising approach with which to maximize the analytic potential of small-scale trials.

There is continuous and ongoing improvement in the area of neuroimaging methods, with neuroimaging techniques becoming more refined and more specific, and, even more importantly and related to the aforementioned sampling issue, they are becoming increasingly accessible to researchers. Of specific interest here are functional neuroimaging methods, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). These techniques produce different dependent measures, such as blood oxygenation level-dependent signals in fMRI and regional cerebral blood flow or regional cerebral metabolic rate for glucose (or any other ligand) in PET and SPECT analysis. Neurophysiological processes can then be assessed at the level of the brain structures that are known to be involved in the neurobiology of the disorder, with the amygdala, hippocampus, and prefrontal cortex being among the more frequently cited regions (Rauch et al., 2006).

2. Amygdala

Animal models of fear learning have led to the supposition that dysfunction in amygdala activity, the key structure in the regulation of fear and stress (Simmons and Matthews, 2012), is common to various anxiety disorders. Correspondingly, negative emotional processing has been registered among PTSD patients (Shin et al., 2004, 2005; Williams et al., 2006), and the results of some prior research point to increased amygdala activity (Etkin and Wager, 2007; Morey et al., 2009; Murrough et al., 2011) among PTSD patients. However, others have observed no difference between a group of subjects with PTSD and control groups consisting of subjects without the disorder (Clark et al., 2002; Ganzel et al., 2008; Shin et al., 2001).

Furthermore, contemporary research into amygdala activation levels indicates that activation is not equally present among all PTSD patients. In a study of 16 Vietnam veterans with PTSD, 15 Vietnam veterans without PTSD (control group 1), and 14 healthy male subjects (control group 2), by applying PET scanning, Britton et al. (2005) found that, during the exposure of subjects to emotional aversive stimulus, there was no increased amygdala activation among the PTSD patients compared to the control groups. Additionally, the control group made up of Vietnam veterans without PTSD showed increased left amygdala activation in response to aversive stimuli.

Etkin and Wager (2007) posited that experience itself affects differences in the functioning of neural assemblies for emotional processing in PTSD, social anxiety, and specific phobia. This meta-analysis (using PET and fMRI) showed an increased amygdala activity in the PTSD and control groups. However, the amygdalae activation was smaller than in the social anxiety and specific phobia cases. The level of activity was found to relate to the severity of the symptoms, with different and more complex emotional dysregulation observed in individuals with PTSD. Subsequently, fMRI results obtained by St.

Jacques et al. (2011) indicate that PTSD patients have higher amygdala activation (in the right amygdala) during the construction of negatively intense autobiographical memory, when compared to that of a control group.

The amygdala function is further investigated in the work of Stevens et al. (2018), which examined associations between data-driven symptom dimensions and episodic memory formation. Symptom dimensions were defined by applying principal component analysis (in respect of a sample of 3881 trauma-exposed African American women). The amygdala function was additionally investigated in an fMRI study of episodic memory formation in relation to a smaller group composed of 54 women. The subjects viewed scenes featuring neutral, negative, and positive content during an fMRI scan and completed a delayed cued recall task. PCA analysis elicited five symptom dimensions interpreted as reflecting negative affect, somatic symptoms, re-experiencing, hyperarousal, and numbing. Re-experiencing was the only symptom type associated with amygdala function, predicting increased amygdala activation. In contrast, the negative affect component predicted lower amygdala activation for subsequently recalled scenes (Stevens et al., 2018).

The role of the amygdala in the pathophysiology of PTSD has still not been completely resolved, although recent brain neuroimaging studies have identified increased amygdala activation among people with PTSD following exposure to traumatic memory recalls. Furthermore, in prior research, participants being presented with emotional facial expressions that are not directly connected with traumatic experience has elicited an increased amygdala response (Shin et al., 2006). Also, within studies of correlations between the occurrence of PTSD and other parameters, a high correlation has been found between increased amygdala activity and certain personality traits (several dimensions of neuroticism and psychopathology, especially anxiety traits), as well as the human serotonin transporter gene (SLC6A4) (Hariri et al., 2002).

Neuroimaging used in PTSD studies has identified an increased activation of amygdala presented in personalized traumatic narratives (Shin et al., 2004), combat sounds (Pisioti et al., 2002), and during the acquisition of fear conditioning in abuse survivors (Bremner et al., 2005). While it has been shown that activation of the amygdala positively correlates with symptoms of PTSD (Shin et al., 2004), though, a few studies have not found amygdala activation during symptomatic conditions in PTSD, possibly owing to issues associated with using a smaller sample (Bremner et al., 1999; Lanius et al., 2001). It is important to emphasize too that hyperactivity of amygdala is also associated with other anxiety disorders (Etkin and Wager, 2007).

2.1. Amygdala volume in PTSD

A relatively small number of studies dealt with the research of amygdala volume in relation to certain external or internal factors. Experimental studies on mice have shown changes in amygdala morphology in relation to chronic stress, or unique features of structural plasticity in the amygdala. These results may be important for further research among people with mood disorders and post-traumatic stress disorder (Roosendaal et al., 2009).

The research conducted by Popoli et al. (2011) showed that traumatic stress causes trophic changes and synaptogenesis in the amygdala. In the studies conducted both on mice and humans, Yang et al. (2008) pointed out a relationship between smaller amygdala volume, increased levels of fear conditioning and excessive glucocorticoid stress response. The meta-analysis on a sample composed of 11 relevant studies pointed out to a decreased volume within the left amygdala among adults with PTSD, as opposed to healthy adult control groups (Karl et al., 2006).

The research conducted by Morey et al. (2012) conform to some previous research (Yang et al., 2008; Gianaros et al., 2008) which showed a relationship between smaller amygdala volume, stronger fear

conditioning and stress response. The research is also consistent with a general theoretical model according to which smaller amygdala volume imposes a risk for the development of PTSD, and does not result from the disease itself (Yang et al. 2008). This studies also showed that elevated corticosterone levels lead to increased amygdala volume.

Kuo et al. (2012) in their sample consisting of veterans with PTSD, showed increased total amygdala volumes compared to the control group consisting of veterans without PTSD, contrary to the research that displayed decreased left amygdala volume in PTSD (Starcevic et al., 2014). Relating to the severity of PTSD symptoms and amygdala volume, in a cross-sectional study Akiki et al. (2017) applied a high-resolution MRI and showed that participants with more severe PTSD symptoms showed an indentation in the dorsal region of the right amygdala (corresponding to the centromedial amygdala). Other studies including one meta-analysis failed to identify amygdala volumetric abnormalities associated with PTSD (Fennema-Notestine et al., 2002; Herringa et al., 2012; Sui et al., 2010). This was also confirmed by Woon and Hedges (2009) through the analysis of nine studies comparing amygdala volumes among adults with PTSD and control groups consisting of people without PTSD, in which no significant difference in amygdala volume between these two groups were found.

3. Hippocampus

Post-traumatic stress disorder (PTSD) is one of the most complex psychiatric disorders which may suddenly arise as a result of exposure or witnessing to events considered dangerous for life, or posing a threat which may result in severe physical and/or psychological self injuries or injuries of other people. The hippocampal structure has a key role in the control of stress response, declarative memory and fear conditioning (Jovanović et al., 2009, Milad et al., 2009), and hippocampus is one of the most investigated structures regarding PTSD effects on the brain (Fuchs and Gould, 2000). Trauma and stress induce synaptic degeneration, and neuronal atrophy in the hippocampus (Popoli et al., 2011) and numerous studies have shown decreased hippocampal volume in PTSD (Kühn and Gallinat, 2013; Morey et al., 2012; Pavić et al., 2007; Sussman et al., 2016). However, results are not consistent across the studies (Golier et al., 2005; Pederson et al., 2004).

Prolonged exposure to stressful conditions and increased level of glucocorticoids (or increased sensitivity to glucocorticoids) result in hippocampal damage (reduction in the number of dendrites, loss of dendritic spines and damages in neurogenesis) (Conrad, 2008). In this context the study by Jatzko et al. (2006) was the first MRI study to investigate the volume of the hippocampus using two different evaluation methods. They included a sample of 15 subjects with chronic PTSD traumatized at the air show plane crash in 1988 in Germany and 15 healthy persons (control group). Results of the voxel-based morphometry showed no difference among patients and controls in total hippocampal volume, neither in the left nor the right hippocampal regions. Post hoc analysis of Bonne et al. (2008) established no difference in the volumes of anterior hippocampus or subiculum.

It cannot be claimed with certainty whether decreased hippocampal volume constitutes a risk factor for PTSD or it is a result of PTSD (Heim and Nemeroff, 2009). In a comparative study of people with chronic PTSD, acute PTSD and symptoms of acute depression, Apfel et al. (2011) identified, on average, smaller hippocampal volumes among the subjects with chronic PTSD, as opposed to other two subgroups. By these results, the authors pose an investigative question whether a decreased hippocampus constitutes a risk factor for the inability of PTSD recovery or if reduced hippocampal volume constitutes a reversible process after the withdrawal of PTSD symptoms.

In hippocampal activation, deficits occur while solving the tasks relating to verbal declarative memory (Bremner et al., 2003; Sherin and Nemeroff, 2011). Stevens et al. (2018) investigated a relationship between hippocampal activation and symptoms of reliving, and came to the result that such activation is increased. Reliving was the only

symptom related to hippocampal function, predicting an increased activation associated with memory encoding in the hippocampus and amygdala. Symptom dimensions were not associated with hippocampal volume. The results of fMRI on the sample of 44 people who had survived a traffic accident, showed a correlation between lower hippocampal volumes assessed in post-seizure weeks, and increased risk for PTSD development (Xie et al., 2017).

The scientific working group “ENIGMA - Enhancing Neuroimaging Genetics through Meta-Analysis” working in the field of PTSD, compared hippocampal structural volumes between PTSD patients and control subjects in the largest PTSD neuroimaging study up to the present time. The study included data from 1868 subjects from 16 cohorts and showed the connection between PTSD and lowered hippocampal volume (Logue et al., 2018).

The biggest criticism of such research is the fact that it is still not possible to claim with certainty whether decreased hippocampal volume can be considered a cause or result of PTSD. A smaller hippocampus may constitute a sign that a person is at higher risk after a traumatic event. There is always a possibility that both notions are correct, so diminished hippocampus presents an increased risk for PTSD, whereas diminished hippocampus could also be a consequence of trauma exposure.

Conflicting results even in are with most homogenous findings emphasize the need for more complex pathology models related to trauma.

4. Anterior cingulum

Two well-designed studies that compared of the anterior cingulate cortex (ACC) in PTSD group versus the group exposed to a traumatic event, but without PTSD, indicate decreased activation of ACC in PTSD. In his PET study, Bremner et al. (1999) showed that, as opposed to childhood sexual abuse survivors without PTSD, those with PTSD failed to activate the rostral anterior cingulate cortex (rACC) in response to traumatic versus neutral scripts. The research conducted by Hou et al. (2007) in people participating in a mining accident with severe acute PTSD and among men participating in a mining accident but without PTSD, reported decreased ACC activation in response to trauma-related versus neutral pictures. Research results point out to the fact that neurophysiological changes, as well as memory deficit, occur among people with severe acute PTSD.

Number of the neuroimaging studies involving energetic brain metabolism is considerably low (Bonne et al., 2003; Molina et al., 2007). A study authors Shin et al. conducted among veterans with PTSD and their twins showed significantly higher resting cerebral metabolic rate for glucose (rCMRglu) in dorsal anterior cingulate/mid cingulate cortex (dACC/MCC). Increased dACC activation may constitute a family risk factor for PTSD (Shin et al., 2009). PTSD symptoms correlate with activation in the ventromedial prefrontal cortex (vmPFC) (Hopper et al., 2007; Kemp et al., 2007; Shin et al., 2005; Williams et al., 2006).

5. Medial prefrontal cortex

Some neuroimaging studies reported smaller activations and deactivation in vmPFC regions during the exposure to traumatic script-driven imagery. In a case-study, Shin et al. (2004) observed less activation in medial frontal gyrus on a sample consisting of male Vietnam veterans and female nurse veterans with PTSD relative to those without. Furthermore, by applying SPECT in their work, Lindauer et al. (2004) observed lower activation in the medial frontal gyrus in response to traumatic versus neutral scripts among police officers with PTSD exposed to trauma, compared to those without PTSD. Lanius and colleagues (Lanius et al., 2001) found decreased rACC and medial frontal gyrus activation in a traumatic and baseline imagery condition in PTSD compared with traumatized individuals without PTSD. Several morphometric MRI studies have reported decreased volumes of frontal

Table 1

Major findings from key PTSD neuroimaging studies related to amygdala, hippocampus and PFC (2000–2012).

Brain Regions	Findings	Neuroimaging methods and reference
Amygdala	Increased amygdala activations	fMRI: Rauch et al. (2000); Pissiota et al. (2002) fMRI, PET: Etkin and Wager (2007) PET: Bryant et al. (2005)
Hippocampus	Smaller amygdala volume Smaller hippocampal volume No consistent results	MRI: Kuo et al. (2012); Morey et al. (2012) MRI: Villarreal et al. (2002); Hedges et al. (2003); Kitayama et al. (2005); Pavić et al. (2007); Morey et al. (2012) MRI: Schuff et al. (2001); Pederson et al. (2004); Jatzko et al. (2006) fMRI: Fennema-Notestine et al. (2002)
PFC	Less activation in vmPFC Decreased volumes of frontal cortex	fMRI: Rauch et al. (2006); fMRI, SPECT and PET: Huges and Shin, 2011 fMRI: Carrion et al. (2001); Fennema-Notestine et al. (2002)

cortex in PTSD (Carrion et al., 2001; Fennema-Notestine et al., 2002). Anterior cingulate volumes appear to be smaller in PTSD compared to trauma-exposed control groups (Woodward et al., 2006).

In research of Bremner et al. (1999) women who were sexually abused in childhood, were applied the PET analysis during exposure to neutral and traumatic scripts. Memories of sexual abuse were associated with greater increased blood flow in portions of anterior prefrontal cortex in sexually abused women with PTSD than in sexually abused women without PTSD.

The vmPFC's hypoactive response is the most common finding in the researches attributed to emotional dysregulation (Etkin and Wager, 2007; Shin et al., 2006). It is not known whether this hypoactivity of vmPFC is caused by a disorder or it is a secondary effect. The study by Koenigs et al. suggests a more complex role of vmPFC in persons with PTSD (Koenigs et al., 2008). They found that the damage of vmPFC protected person from PTSD symptoms respectively that this regions actively contributes to the regulation of emotional re-experience in PTSD (Koenigs and Grafman, 2009).

To sum up, the research studies indicate structural and functional abnormalities in prefrontal cortex in PTSD patients. Neuroimaging studies of PFC are lower in number, but most frequently share an observation of lower prefrontal cortex activity (Shin et al., 2006).

6. Conclusions

Development of new brain imaging techniques contributed to numerous findings relating to the structure, function and neuroanatomic abnormality in PTSD patients, especially of the amygdala, hippocampus and prefrontal cortex. Underlying neurobiological mechanisms of PTSD are not entirely clear, and further researches have to contribute to the better understanding of basic pathophysiology, which could result in the development of more effective therapies.

This review took into account only a portion of performed neuroimaging studies. We did not have pre-planned selection criteria for inclusion of studies, and this is a certain limitation of this review. We have included only studies performed on larger samples, especially those that were break-through in the field when published, those with a high-quality control group and that well argument conflicting results. The list of some researches according brain regions, research finding, method of neuroimaging and authors references are presented in Table 1.

Most uniform results are present in neuroimaging studies of amygdala and hippocampus (Logue et al., 2018). Current research indicates an increased level of amygdala activation during a traumatic affective experience. Such findings can also be observed in other anxiety disorders, including specific phobias (Etkin and Wager, 2007). Also, the symptoms of PTSD are positively associated with amygdala activity. It can be concluded that PTSD involves different and more complex emotional dysregulation. Also, a large number of studies are congruent in a finding of decreased hippocampal volume (Morey et al., 2012). Amygdala and hippocampus are two highly interconnected regions that have a common influence on the effect on emotional memory.

Furthermore, the studies above provide evidence of functional connectivity - increased amygdala activity induces a reaction of reducing medial prefrontal cortex activity.

Researchers found more regularly that the medial prefrontal cortex was smaller and hyper-reactive during symptomatic conditions.

Small sample sizes, diagnostic criteria evolving, a variety of trauma types analyzed, different periods elapsed from trauma to analysis and frequently unclear approach to comorbidities are confounding interpretation of majority of neuroimaging studies.

The common question asked in the research was whether changes in the structure of these brain parts are the cause or consequence of PTSD. Through the future researches, it will be important to explore the relationship between volumetric and functional changes in these brain structures, as well as a comparison of PTSD patients with and without comorbid disorders, and the introduction of better profiled control groups. Current findings of differences in PTSD compared to other anxiety disorders are very scarce. Also, future research should put more focus on the integration of genetic determinants of exposure and conditional risks to an overall model.

Finally, it should be emphasized that neuroimaging is relatively new and fast evolving research area. Given the complexity of diagnosis and objectively existing difficulties relating to the PTSD research in general, neuroimaging is among more promising methods. A multimodal approach that would include research of functional connectivities and higher involvement of neurogenetic approach will certainly contribute to overall quality of research.

Collaborative research and integration of neuroimaging observations from past will represent a considerable step forward in neuroimaging research. That approach could not only aid to better interpretation of already performed research and to the identification of research gaps to be covered but would also contribute to the better visibility of neuroimaging research in general and especially in the area of PTSD.

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