

THE WAR WITHIN

Neuroimaging studies in Posttraumatic Stress Disorder

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Introduction

Since World War II, the concept of war has changed considerably (see van Creveld (1991)). Modern forms of armed conflict are characterized by an increase in intra-national (as opposed to inter-national) conflicts. These conflicts are led by individual leaders (as opposed to governments) and are motivated by religious, nationalistic, or ethnic factors (as opposed to territorial expansion). International organizations, such as the United Nations, North Atlantic Treaty Organization, European Union, and the Organization for Security and Co-operation in Europe, have played an important role in observing, monitoring and resolving these armed conflicts. The Dutch Army has participated in a large number of these observational, peacekeeping and peace enforcement operations (see Klep and van Gils, 2005). Although the majority of soldiers adapt successfully to ‘ordinary life’ after deployment, some may experience medically unexplainable physical symptoms (10–20%). Some (3–5%; see Engelhard et al., 2007) may also develop posttraumatic stress disorder.

Psychiatrists using the DSM-IV may diagnose PTSD if the person has been exposed to a traumatic event in which “the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others **and** the person’s response involved intense fear, helplessness, or horror (APA,1994). Besides the presence of these criteria (the A1 and A2 criterion respectively), the person must re-experience the event and display persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma). Finally, symptoms of increased arousal should also be present. If all these criteria are met, symptoms persist for a period greater than one month and cause significant clinical distress, a person is given the diagnosis of PTSD.

Various methods are used to study the neurobiological mechanisms of PTSD. In the Military Mental Health Research Centre in Utrecht, the Netherlands, a number of different methods are employed. We perform research on personality, neuroimmunological and neuroendocrinological parameters, and

sleep. In addition, we have performed a number of neuroimaging studies in veterans with PTSD.

All studies performed, however, are only as good as the methods used. While neuroimaging methods are generally proven and tried, there are a lot of methodological issues in neuroimaging that need resolution. In addition, neuroimaging is an expensive tool. Neuroimaging tools, such as structural MRI, functional MRI, PET imaging, PET receptor imaging, EEG, magnetoencephalography, provide new promises and exciting prospects. However, in the case of complex psychiatric disorders or in the field of cognitive neuroscience, there is no reason to be pretentious. Ultimately, research culminates more research. Despite its limitations, however, neuroimaging is a valuable tool that enables us to take a look at the active brain in a relatively non-invasive manner. This provides us not only with new insights into the brain and neurobiological mechanisms, but also sheds light on the manifestation of psychiatric disorders in the brain.

Structural Neuroimaging in PTSD

The advance of neuroimaging techniques has resulted in a burgeoning of studies reporting abnormalities in brain structure and function in a number of neuropsychiatric disorders. Measurement of hippocampal volume has developed as a useful tool in the study of neuropsychiatric disorders. We have conducted an extensive review of hippocampal volumetric findings in neuropsychiatric disorders (Geuze, Vermetten, & Bremner, 2005b; Geuze, Vermetten, & Bremner, 2005a). Smaller hippocampal volumes have been found in epilepsy, Alzheimer's Disease, dementia, mild cognitive impairment, the aged, traumatic brain injury, cardiac arrest, Parkinson's disease, Huntington's disease, Cushing's disease, herpes simplex encephalitis, Turner's syndrome, Down's syndrome, survivors of low birth weight, schizophrenia, Major Depression, PTSD, chronic alcoholism, borderline personality disorder, obsessive-compulsive disorder, and anti-social personality disorder. The specificity of hippocampal deficits for any psychiatric disorder is thus very low.

Cortical Thickness

Structural neuroimaging studies in PTSD have focused primarily on structural alterations in the medial temporal lobe (Bremner et al., 1995a; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005), and only a few have examined gray matter reductions in the cortex. Advances in computational image analysis provide new opportunities to use semi-automatic techniques to determine cortical thickness, but these techniques have not yet been applied in PTSD. We have examined twenty-five male Dutch veterans

with deployment-related PTSD and twenty-five male veterans without PTSD matched for age, year and region of deployment with structural MRI. Individual cortical thickness maps were calculated from the MR images, and all the subjects' brains were aligned using cortex-based alignment in a region of interest based approach. Cortex-based alignment substantially improves statistical analysis by reducing anatomical variability. Regions of interest examined included the bilateral superior frontal gyri, bilateral middle frontal gyri, bilateral inferior frontal gyri, bilateral superior temporal gyri, and bilateral middle temporal gyri. Veterans with PTSD revealed reduced cortical thickness in the bilateral superior and middle frontal gyri, the left inferior frontal gyrus, and the left superior temporal gyrus. Cortical thinning in these regions may correspond to functional abnormalities (such as in executive functioning, working memory and failure of inhibition of fear) observed in these areas in patients with PTSD.

Functional Neuroimaging in PTSD

Memory

Over the last decades, several studies have reported deficits in learning and memory in patients with PTSD. Patients with PTSD display poorer performance on several tests of learning and memory including the Wechsler Memory Scale – Revised (WMS-R) (Golier et al., 2002; Bremner et al., 1993; Nixon, Nishith, & Resick, 2004), California Verbal Learning Test (CVLT) (Yehuda, Golier, Halligan, & Harvey, 2004; Yehuda, Golier, Tischler, Stavitsky, & Harvey, 2005; Stein, Kennedy, & Twamley, 2002; Stein, Hanna, Vaerum, & Koverola, 1999; Lindauer, Olf, Meijel, Carlier, & Gersons, 2005), Rey Auditory Verbal Learning Test (AVLT) (Uddo, Vasterling, Brailey, & Sutker, 1993; Vasterling et al., 2002; Brandes et al., 2002), Selective Reminding Test (Bremner et al., 1995b), and the Rivermead Behavioural Memory Test (Moradi, Doost, Taghavi, Yule, & Dalgleish, 1999; Koso & Hansen, 2005). The majority of these studies were performed in patients with PTSD related to combat experience, (Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Vythilingam et al., 2005; Neylan et al., 2004; Yehuda et al., 1995) whereas only some have examined cognitive performance in PTSD related to civilian trauma, (Bremner, Vermetten, Afzal, & Vythilingam, 2004; Pederson et al., 2004; Yehuda et al., 2005) or in children with PTSD (Moradi et al., 1999; Beers & De Bellis, 2002).

Although clinical experience and epidemiological studies indicate that PTSD has an impact on social and occupational functioning, few studies have examined functional impairments (Bleich & Solomon, 2004; Alonso et al., 2004). If objective memory performance serves as an accurate predictor

of social and occupational functioning, it may be considered as a target for psychopharmacological intervention in PTSD, as is currently proposed by the MATRICS program in patients with schizophrenia (Marder et al., 2004; Green et al., 2004). To date, no study has been published relating memory performance in patients with PTSD to occupational and social functioning. We examined fifty Dutch veterans (25 with deployment-related PTSD and 25 without PTSD matched for age, and year and country of deployment) were assessed with a comprehensive neuropsychological test battery consisting of four subtests of the WAIS III (Picture Arrangement, Block Patterns, Similarities, and Vocabulary), WMS-R Figural Memory, WMS-R Logical Memory, CVLT, and the AVLT. Veterans with PTSD were free of medication and substance abuse. Multivariate analysis of variance was used to assess group differences of memory performance. Veterans with PTSD had similar total IQ scores compared to veterans without PTSD, but displayed deficits of figural and logical memory. Veterans with PTSD also performed significantly lower on measures of learning and immediate and delayed verbal memory. Memory performance accurately predicted current social and occupational functioning (Geuze et al., in press).

Memory processing

Although patients with PTSD frequently report memory difficulties and empirical research provides support for a memory deficit in PTSD, few fMRI studies have adequately investigated neural correlates of learning and memory of neutral (i.e. not trauma related) material in patients with PTSD compared to controls. In studies with healthy subjects, memory processing has been investigated using various fMRI designs. These studies indicate that a fronto-temporal network (including the prefrontal cortex, endorhinal cortex, parahippocampal gyrus, and the hippocampus) constitute a neural substrate for the encoding and retrieval of memory (Eichenbaum, 2000; Taylor et al., 2000; Squire, Stark, & Clark, 2004). Previous research has also shown that paired associates learning is impaired in patients with PTSD (Gurvits et al., 1993; Golier et al., 2002; Golier, Harvey, Legge, & Yehuda, 2006).

We designed a study to investigate associative memory processing in PTSD with fMRI using the encoding and retrieval of 12 word-pair associates as a neurocognitive task in Dutch veterans with PTSD and without PTSD (Geuze, Vermetten, de Kloet, & Westenberg, 2007; Geuze, Vermetten, Ruf, de Kloet, & Westenberg, 2007). Twelve male veterans with PTSD, and twelve male veterans without PTSD, were recruited, and matched for age, region and year of deployment. Changes in the fMRI BOLD response to encoding and retrieval of non-emotional word pairs (reflecting deactivation and activation of brain areas involved in associative memory processing)

were assessed. Veterans with PTSD revealed underactivation of the frontal cortex, and overactivation of the temporal cortex during the encoding phase compared to control veterans without PTSD. Retrieval of the paired associates resulted in underactivation of right frontal cortex, bilateral middle temporal gyri, and the left hippocampus/parahippocampal gyrus in veterans with PTSD. These data support the long-held notion that altered activity in fronto-temporal circuits is related to deficits in memory performance in veterans with PTSD.

Pain processing

Clinical studies have reported that pain experience in persons with PTSD is significantly increased compared to controls, and that chronic pain is a commonly reported symptom of patients with PTSD (Smith, Egert, Winkel, & Jacobson, 2002) (Asmundson, Coons, Taylor, & Katz, 2002; Beckham et al., 1997). However, previous empirical research has also reported that patients with PTSD report a decrease in pain intensity ratings after being exposed to traumatic reminders (van der Kolk, Greenberg, Orr, & Pitman, 1989). This has been purported to be related to opioid mediated stress induced analgesia (Pitman, van der Kolk, Orr, & Greenberg, 1990). Activation of the μ -opioid receptor system by endogenous opioid peptides has indeed been associated with reductions in sensory and affective ratings of pain experience (Zubieta et al., 2003; Zubieta et al., 2001).

Recently we performed an fMRI study (in combination with painful tonic phasic heat stimuli) to compare the brain activity in patients with PTSD and controls (Geuze et al., 2007). Both fixed temperature heat stimuli which was the same for all subjects, and individual temperature heat stimuli which were adjusted for equal subjective pain in all subjects were used. We predicted that patients with PTSD would display altered activity in brain areas related to pain processing.

The experimental procedure consisted of a psychophysical assessment and neuroimaging with fMRI. Two conditions were assessed during fMRI in both experimental groups: one with administration of a fixed temperature of 43 °C (fixed temperature condition), and one condition with an individual temperature for each subject but with a similar affective label, equal to 40% of the subjective pain intensity (individual temperature condition). Twelve male veterans with PTSD, and twelve male veterans without PTSD, were recruited, and matched for age, region and year of deployment. Veterans with PTSD rated temperatures in the fixed temperature assessment as less painful compared to control veterans. In the fixed temperature condition, veterans with PTSD revealed increased activation in the left hippocampus, and decreased activation in the bilateral ventrolateral prefrontal cortex, and the right amygdala. In the individual temperature condition veterans with

PTSD showed increased activation in the right putamen, and bilateral insula, as well as decreased activity in right precentral gyrus, and the right amygdala. These data provide evidence for reduced pain sensitivity in PTSD. It has been proposed that opioid-mediated stress induced analgesia is the mechanism responsible for this phenomenon. The witnessed neural activation pattern was proposed to be related to altered pain processing in patients with PTSD.

Concluding Remarks

Very little is known about the biological basis of individual differences in stress response and vulnerability for stress-related mental disorders. The neuroimaging studies described in this paper have provided support for neurobiological alterations in Dutch veterans with deployment-related PTSD. One of the major strengths of all the empirical studies in this paper is the use of matched trauma controls. We had access to a unique population of Dutch veterans from the Veterans Institute in Doorn. This enabled us to match our veterans with deployment-related PTSD to control veterans without PTSD. The groups were carefully matched with respect to year of deployment, region or country of deployment, and age. This means that control veterans had very similar experiences during deployment compared to the patients. They were also approximately the same age at the time of deployment.

Traumatic stress affects nearly all veterans, but while the majority of veterans learn to live with their experiences, for some veterans traumatic stress seethes inside. These veterans (as many as 5–15% of all veterans) experience a ‘war within’. The war within experienced by a proportion of returning veterans after deployment is threefold in nature. For these veterans, (1) the war is not over, (2) they are at war with themselves, and (3) they experience a ‘neurobiological war within’.

Structural neuroimaging has identified a number of morphological changes including smaller hippocampal volume and thinner prefrontal cortex. Functional MRI showed that veterans with PTSD have decreased pain sensitivity and altered painprocessing. In addition, veterans with PTSD show altered prefrontal and temporal cortex activation during associative memory processing. Neuropsychological memory assessment confirmed a structural verbal and visual memory deficit which was related to current social and occupational functioning. These neurobiological alterations witnessed in veterans with PTSD provide some acknowledgement that the problems experienced by them are not just ‘figments of the imagination’ but very real neurobiological consequences of traumatic stress. It is this neurobiological ‘war within’ that we should learn to wage and win.

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