Recall of Emotional States in Posttraumatic Stress Disorder: An fMRI Investigation

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Background: *The goal of this study was to examine the neuronal circuitry underlying different emotional states (neutral, sad, anxious, and traumatic) in posttraumatic stress disorder (PTSD) in traumatized subjects versus traumatized subjects without PTSD.*

Methods: *Traumatized subjects with (*n *= 10) and without (*n *= 10) PTSD were studied using the script-driven symptom provocation paradigm adapted to functional magnetic resonance imaging (fMRI) at a 4 Tesla field strength.*

Results: *Compared to the trauma-exposed comparison group, PTSD subjects showed significantly less activation of the thalamus and the anterior cingulate gyrus (area 32) in all three emotional states (sad, anxious, and traumatic).*

Conclusions: *These findings suggest thalamic and anterior cingulate dysfunction in the recollection of traumatic as well as other negative events. Thalamic and anterior cingulate dysfunction may underlie emotion dysregulation often observed clinically in PTSD.* Biol Psychiatry 2003; 53:204–210 © *2003 Society of Biological Psychiatry*

Key Words: Posttraumatic stress disorder, functional magnetic resonance imaging, thalamus, anterior cingulate, script-driven imagery, emotion regulation

Introduction

Several neuroimaging studies have examined the anatomical and functional neural correlates of human emotions, including happiness, sadness, anxiety, and disgust (Gemar et al 1996; George et al 1995; Kimbrell et al 1999; Lane et al 1997; Liotti et al 2000; Mayberg et al 1995, 1999; Paradiso et al 1997; Pardo et al 1993; Partiot et al 1995; Reiman et al 1997; Schneider et al 1995). Reiman and colleagues (1997) investigated functional neuronal substrates of normal human emotion and their relationship to whether the emotion was internally or externally generated. Both film- and recall-generated emotions were associated with significantly increased activity in the medial prefrontal cortex and thalamus, suggesting that these regions participate in aspects of emotion that do not depend on the source of the emotional stimulus. Moreover, the medial prefrontal cortex and thalamus were activated in different emotional states (happiness, sadness, and disgust), suggesting that activation of these regions is not specific to one emotion, but rather occurs across different emotional states. In a subsequent paper, this group (Lane et al 1998) reported positive correlations between scores on the Levels of Emotional Awareness Scale and cerebral blood flow in area 24 of the anterior cingulate gyrus during film- and recall-induced emotion. This finding suggests a role for the anterior cingulate cortex in the experiential aspects of emotion (Lane et al 1998). Indeed, an extensive animal literature also supports the contention that the anterior cingulate gyrus plays a role in monitoring and regulating emotional states and responses (e.g., Vogt et al 1993; Devinsky et al 1995).

Posttraumatic stress disorder (PTSD) neuroimaging studies have implicated limbic and paralimbic structures in the pathophysiology of PTSD (Bremner et al 1999a, 1999b; Liberzon et al 1999; Shin et al 1997, 1999). A recent functional magnetic resonance imaging (fMRI) study examined amygdala responses to masked facial stimuli in Vietnam veterans with and without PTSD. The results demonstrated that patients with PTSD showed exaggerated amygdala responses to masked-fearful versus masked-happy faces (Rauch et al 2000). Studies employing script-driven imagery have generally not found increased activation of the amygdala in PTSD subjects as compared to comparison subjects (Bremner et al 1999a, 1999b; Shin et al 1999), although Shin et al (1997) found greater activation in the right amygdala for internally generated versus externally perceived traumatic stimuli in PTSD subjects but not comparison subjects. Paralimbic

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structures thought to underlie PTSD symptomatology include the orbitofrontal cortex and anterior cingulate gyrus (including Brodmann's areas [BA] 24, 32, and 25; for review, see [Hamner 1999]). Studies using trauma-specific reminders have consistently implicated paralimbic regions, but they have less consistently found activation or failure of activation in specific structures (Bremner et al 1999a, 1999b; Liberzon et al 1999; Shin et al 1997, 1999). Prefrontal structures implicated in neuroimaging studies include the left inferior prefrontal cortex and Broca's area (Bremner et al 1999a, 1999b; Liberzon et al 1999; Shin et al 1997, 1999).

Our group (Lanius et al 2001) has recently examined the neural correlates of PTSD using script-driven imagery adapted to fMRI. Our findings suggest that, compared to control subjects, during internally generated remembrances of traumatic experiences, PTSD subjects showed significantly less activation of the thalamus, anterior cingulate gyrus (BA 32), and medial frontal gyrus (BA 10/11).

To our knowledge, this is the first neuroimaging study to investigate differential patterns of activation between PTSD and comparison subjects with trauma exposure but no history of PTSD across three negatively valenced emotional remembrances. Previous PTSD neuroimaging studies have not compared recall of a traumatic memory to other emotional states (Bremner et al 1999a, 1999b; Liberzon et al 1999; Shin et al 1997, 1999). Based on clinical observations of generalized affect dysregulation in PTSD patients (van der Kolk et al 1996) and prior neuroimaging findings in normal and PTSD subjects, particularly our findings with script-driven imagery and fMRI (Lanius et al 2001), we hypothesized that, compared to control subjects, PTSD patients would show less activation in the anterior cingulate gyrus and the thalamus across traumatic and nontraumatic emotional states.

Methods and Materials

Subjects

Ten subjects who had developed PTSD as a result of sexual abuse/assault ($n = 7$) during childhood or motor vehicle accidents during adulthood (MVAs) ($n = 3$) were studied. Comparison subjects were 10 subjects who met criterion A for PTSD (as a result of sexual abuse/assault [$n = 6$] or MVAs [$n = 4$] during adulthood) for PTSD but who did not meet DSM-IV criteria. Written consent was obtained from all subjects. Subjects were diagnosed using the Structured Clinical Interview for DSM-IV (SCID; First et al 1997) and the Clinician Administered PTSD Scale (CAPS) (PTSD mean 75 [SD 5.2]; control mean 4.6 [SD 2.17]) (Blake et al 1995). Comorbidity in the PTSD group included major depression ($n = 2$), dysthymia ($n = 4$), and panic disorder ($n = 3$), lifetime history of drug abuse and dependence (multisubstance abuse and dependence over several years) ($n = 2$), lifetime history of alcohol abuse and dependence ($n = 4$), and current nicotine abuse ($n = 4$). The comorbid major depression, dysthymia, and panic disorder appeared after the trauma exposure. The comparison subjects were of similar age (35 [SD 12.3] for PTSD group and 39 [SD 11.03] for comparison group), gender, and race. None of the subjects in the comparison group met criteria for any psychiatric disorders. All subjects were right handed. Patients had undergone a supervised drug washout for at least 2 weeks before scanning. All patients with a history of psychosis, bipolar disorder, and substance use disorder in remission for less than 6 months were excluded from the study, as were patients with any significant medical conditions, neurologic illness, or a history of head injury. The study was approved by the Office of Research Ethics at the University of Western Ontario.

fMRI Procedures

Magnetic resonance imaging studies were performed on a 4 Tesla, whole-body Varian (Palo Alto, CA)/Siemens (Erlangen, Germany) imaging system with a 90-cm diameter horizontal bore and a whole-body, 68-cm diameter gradient set with a maximum strength of 40 mT/m and a slew rate of 120 mT/mins. A whole-head hybrid birdcage radio frequency (RF) coil was used for transmission and detection of signal. Before imaging, a global shimming procedure, using first- and second-order shims, was performed to optimize the magnetic field over the imaging volume of interest.

The RF coil was placed around the subject's head. Each functional brain volume was acquired using a navigator echo-corrected, interleaved multi-shot (4 shots) echo planar imaging pulse sequence with a 64×64 matrix size and a total volume acquisition time of 5 sec (echo time = 15 msec, flip angle = 45 degrees, field of view = 24.0 cm). The volume acquired covered the whole brain and consisted of 12 transverse slices, 6 mm thick (voxel size = $1.87 \times 1.87 \times 6$ mm).

With regards to a ceiling effect, in which a very high degree of activation could produce a smaller degree of uncoupling between cerebral blood flow change and CMRO2, it is highly unlikely that this occurred in the present study. Sensory stimuli typically result in the largest changes seen and usually account for 5% of the fractional signal change during a task. At these levels fMRI has been shown to still be linear with neural activity (Boynton et al 1996; Friston et al 1994). Higher-order cognitive tasks such as the one used in the present study do not reach these levels of signal changes. The signal changes in the present experiment were approximately 3%. It is therefore unlikely that a ceiling effect occurred in this study.

SPM99 Analysis

Functional maps of the activated pixels were constructed by comparing, on a pixel-by-pixel basis, the signal intensity in the baseline and task-related images, using Statistical Parametric Mapping (SPM99, Wellcome Department of Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm). Basis functions representing epochs of interest were entered into SPM99. Variability in

Table 1. Regions of Activation during Memory Recall Versus Implicit Baseline Where the Comparison Group (n = 10) Shows Greater Activation than the Posttraumatic Stress Disorder Group (n = 10)

Condition	Talairach	R/L	Effect Lobe	Effect Gyrus	Brodmann's Area	P Voxel	T Voxel
Trauma	12, −12, 2	R	Sub-lobar	Thalamus		8.05E-14	8.8207
	−4, −8, 6	L	Sub-lobar	Thalamus		4.96E-07	6.6513
	−4, −14, 18	L	Sub-lobar	Thalamus		7.31E-07	6.5884
	0, 36, −12	R&L	Limbic lobe	Anterior cingulate	BA 32	8.86E-05	5.7497
	−6, 7, 25	L	Limbic lobe	Anterior cingulate	BA 24	6.12E-06	6.2316
	−8, 64, 6	L	Frontal lobe	Superior frontal gyrus	BA 10	5.20E-04	5.4052
	44, 30, −12	R	Frontal lobe	Inferior frontal gyrus	BA 47, 11	3.55E-06	6.325
	−20, 26, −8	L	Frontal lobe	Inferior frontal gyrus	BA 47	7.64E-05	5.7776
	24, −84, 42	R	Parietal lobe	Precuneus	BA 19	7.25E-05	5.7875
Sad							
	12, −8, 10	R	Sub-lobar	Thalamus		9.35E-11	7.8913
	−6, −16, 14	L	Sub-lobar	Thalamus		1.86E-07	6.7808
	−4, −6, 10	L	Sub-lobar	Thalamus		5.44E-06	6.2228
	10, 14, 26	R	Limbic lobe	Anterior cingulate	BA 32, 24	1.00E-03	5.19
	−12, 18, 36	L	Limbic lobe	Anterior cingulate	BA 32	2.29E-05	5.9686
	−2, −26, 44	L	Limbic lobe	Cingulate gyrus	BA 31	2.34E-05	5.9641
	20, −30, −2	R	Limbic lobe	Parahippocampal gyrus	BA 27, 30	1.18E-05	6.0875
	18, −28, −10	R	Limbic lobe	Parahippocampal gyrus	BA 28	6.29E-04	5.3323
	16, −48, −2	R	Limbic lobe	Parahippocampal gyrus	BA 19, 30	4.44E-05	5.8471
	−28, −94, 24	L	Occipital lobe	Middle occipital gyrus	BA 19	1.29E-06	6.4669
	−14, −94, 22	L	Occipital lobe	Cuneus	BA 19	3.51E-11	8.0233
Anxious							
	−6, −18, 18	L	Sub-lobar	Thalamus		2.22E-16	10.093
	−16, −26, 16	L	Sub-lobar	Thalamus		1.35E-05	6.1105
	−8, 32, 4	L	Limbic lobe	Anterior cingulate	BA 24	1.25E-08	7.236
	−4, −2, 32	L	Limbic lobe	Anterior cingulate	BA 24	8.04E-07	6.5896
	−2, −28, 24	L	Limbic lobe	Cingulate gyrus	BA 23	1.28E-06	6.5134
	−20, 32, 30	L	Frontal lobe	Medial frontal gyrus	BA 9	4.70E-12	8.3233
	−38, 34, 14	L	Frontal lobe	Inferior frontal gyrus	BA 46	1.79E-14	9.0155
	−34, 32, −2	L	Frontal lobe	Inferior frontal gyrus	BA 47	1.10E-06	6.5387
	−6, 4, −10	L	Frontal lobe	Subcallosal gyrus	BA 34	9.19E-06	6.1786
	16, −100, 18	R	Occipital lobe	Cuneus	BA 18	2.06E-08	7.1614

Control > posttraumatic stress disorder; k > 10; df = 1648. R, right; L, left.

scans attributed to each basis function relative to SPM99's implicit baseline were revealed using contrasts. Fixed-effects analyses were performed by modeling each group's evoked BOLD response using hemodynamically convolved boxcar basis functions. The regions of interest (ROIs) were defined on the basis of T1-weighted images and Talairach coordinates (Talairach and Tournoux 1988).

Script-Driven Imagery

The script-driven imagery procedure was adapted to fMRI according to previously published methods (George et al 1996; Lanius et al 2001; Rauch et al 1996; Shin et al 1997).

Scanning of the neutral, sad (unrelated to the traumatic memory), anxious (unrelated to the traumatic memory), and traumatic memory conditions were repeated three times. A fixed order (neutral scripts followed by sad, anxious, and traumatic scripts) was used for all subjects to prevent anxiety elicited by the anxious and traumatic scripts from persisting into the neutral and sad scripts as previously described by (Bremner et al 1999a). Each scan proceeded as follows: 1) Each subject was instructed to lie still, breathe through his/her nose, and allow himself/herself to begin focusing on the neutral, sad, anxious, or traumatic script as soon as the script was read. Reading of the script lasted 30 sec. As soon as the subject heard the script, he/she was encouraged to remember all sensations that were associated with the neutral, sad, anxious, or traumatic event for 60 sec. Measurement of heart rate occurred during that time. One hundred and twenty seconds were allowed to pass until the script was repeated. Baseline brain activation was calculated based on average activation patterns 60 sec before each recollection of the neutral, sad, anxious, or traumatic event. Brain activation during the recall of the neutral, sad, anxious, or the traumatic event was calculated based on average activation patterns during the final 30 sec of the recall of the sad, anxious, or traumatic event.

Results

Table 1 shows regions of activation during the traumatic, sad, or anxious memory recall versus implicit baseline where the comparison group (n = 10) shows greater

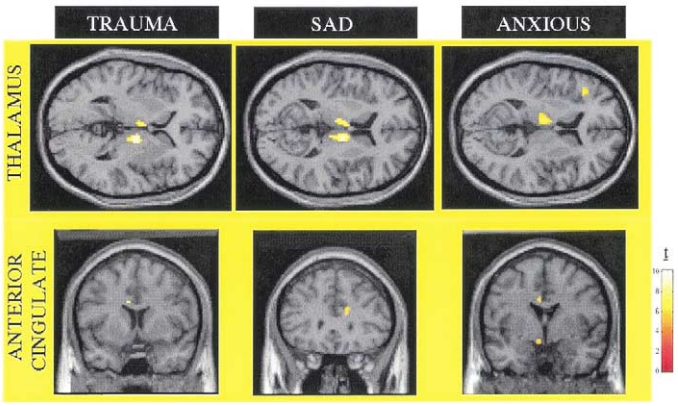

Figure 1. Regions of activation during memory recall versus implicit baseline where the comparison group ($n = 10$) shows greater activation than the posttraumatic stress disorder group ($n = 10$), k > 10.

activation than the PTSD group. For all three of the emotional states (traumatic, sad, and anxious), the comparison group showed greater activation than the PTSD group in the thalamus and the anterior cingulate gyrus.

Recalling of the neutral memory resulted in activation of the right anterior cingulate gyrus (BA 32), the middle and inferior frontal gyri (BA 10), the left parietal lobe (BA 40, 7), and the occipital lobe (BA 18) in both PTSD and comparison groups. Comparison subjects showed significantly ($p < .001$) more activation in only two clusters (occipital lobe [BA 18] and the parietal lobe [BA 7]) during the recall of neutral memory as compared to the PTSD group (data not shown).

Brain activation during the first 30 sec of recall showed patterns similar to the final 30 sec of recall. In addition, time courses of activation showed that brain activation returned to baseline during rest periods in all brain areas studied for both PTSD and comparison groups. These time courses indicate that 60 sec was sufficient time for subjects to recover from the traumatic, sad, and anxious script-driven remembrances. Baseline brain activation *did not* differ between PTSD patients and comparison subjects (data not shown).

Figure 1 shows regions of activation during the traumatic, sad, and anxious memory recall versus implicit baseline where the comparison group ($n = 10$) showed greater activation than the PTSD group ($n = 10$). Note the similarity of activation patterns in the thalamus and anterior cingulate gyrus across all three emotional states (traumatic, sad, and anxious). Similar brain activation patterns were seen in PTSD subjects with comorbid major depression.

Ratings of the emotional analog scales during the traumatic script-driven imagery showed the following results: 1) anger: PTSD: mean 3.1 (scale 0–7), SD 2.51; comparison group: mean 1.6, SD 1.35 [$p > .05$ (t test, one-tailed), $t(13.8) = 1.66$]; 2) fear: PTSD: mean 4.7, SD 1.42; comparison group: mean 1.6, SD 1.50 [$p = .0003$ (t test, one-tailed), $t(17.93) = 4.74$]; 3) disgust: PTSD: mean 2.7, SD 2.54; comparison group: mean 1.3, SD 1.70 [$p > .05$ (t test, one-tailed), $t(15.7) = 1.45$]; 4) sadness: PTSD: mean 3.6, SD 2.46; comparison group: mean 0.9, SD 0.88 [$p = .03$ (t test, one-tailed); $t(11.2) = 3.27$]; 5) guilt: PTSD: mean 2.5, SD 2.27; comparison group: mean 0.7, SD 1.57 [$p > .05$ (t test, one-tailed); $t(15.98) = 2.06$]; 6) shame: PTSD: mean 2.1, SD 2.02; comparison group: mean 0.8, SD 1.61 [$p > .05$ (t test, one-tailed; $t(17.17) = 1.59$]. The degrees of freedom were based on unequal variances. The sad and anxious memories were reviewed to ensure that they were not mixed with other emotions (e.g., anger, guilt, disgust).

Discussion

Our results show less activation in the anterior cingulate gyrus and the thalamus across the traumatic and nontraumatic (sad and anxious) emotional states studied. Previous PTSD neuroimaging studies did not compare recall of the traumatic memory to other emotional states (Bremner et al 1999a, 1999b; Liberzon et al 1999; Shin et al 1997, 1999). The current data suggest that previously reported PTSD neuroimaging findings were not necessarily specific to conditions involving the recollection of traumatic events in PTSD, but may also be observed in conditions involving the recollection of other negative events. This may be important, given the generalized affect dysregulation often observed clinically in PTSD patients (van der Kolk et al 1996).

As reported in our previous article (Lanius et al 2001), during traumatic script-driven imagery, PTSD subjects, compared to comparison subjects, exhibited less activation in the anterior cingulate gyrus (BA 32), medial frontal

cortex (BA 10/11), and thalamus. The findings for anterior cingulate gyrus and medial prefrontal cortex are consistent with previous positron emission tomography (PET) studies using script-driven imagery with sexual abuse- and combat-related PTSD (Bremner et al 1999a; Liberzon et al 1999; Shin et al 1999). Aside from our own work, studies to date have not reported changes in thalamic activation in subjects with PTSD. One explanation for this discrepancy may be the differences in methodology used (PET vs. fMRI); subcortical structures such as the thalamus are more accessible at a 4 Tesla field strength. With regard to the sad and anxious emotions, activation of the frontal (BA 9), parietal (BA 7), and temporal (BA 37, 41, and 42) lobes and insula during recall of script-driven sad emotion is consistent with previous findings (George et al 1996; Liotti et al 2000; Pardo et al 1993; Reiman et al 1997). Similarly, activation of the anterior temporal lobe and insula during recall of script-driven anxious emotion is consistent with a previous PET study examining recall of anxious memories (Liotti et al 2000).

It is interesting to note that the thalamus and anterior cingulate gyrus show greater levels of activation in the comparison subjects as compared to the PTSD subjects across all three emotional states (sad, anxious, and traumatic). The anterior cingulate gyrus is a complex structure with multiple functions (Vogt et al 1992). The anterior cingulate cortex has been shown to play a key role in emotion. Positive correlations between scores on the Levels of Emotional Awareness Scale and cerebral blood flow in area 24 of the anterior cingulate gyrus during film- and recall-induced emotion were reported in a PET study, suggesting a role for the anterior cingulate cortex in the experiential aspects of emotion (Lane et al 1998). The anterior cingulate gyrus has also been shown in animal experiments to have extensive connections with multiple brain structures, including the amygdala, hypothalamus, nucleus accumbens, ventral tegmental area, substantia nigra, raphe, locus coeruleus, periaqueductal gray, and brain stem autonomic nuclei (Carmichael and Price 1995; Frysztak et al 1994; Neafsey et al 1993; Sesack and Pickel 1992; Sesack et al 1989). As a result, the anterior cingulate cortex has a role in orchestrating the autonomic, neuroendocrine, and behavioral expression of emotion and is thought to play a key role in the visceral aspects of emotion (Vogt and Gabriel 1993). Given the key involvement of the anterior cingulate gyrus in the experiential and/or expressive aspects of emotion, a disruption in its functioning may contribute to the dysregulation of emotion, including difficulty modulating anger, chronic self-destructive and suicidal behaviors, difficulty modulating sexual involvement, and impulsive risk-taking behaviors, often observed in PTSD.

Alterations in thalamic activation may be attributable to high levels of arousal that can arise from the recall of emotional material. The thalamus is involved in the relay of sensory information from external sources to different parts of the cerebral cortex where sensory information can then be further integrated. High levels of arousal during emotional experiences have been hypothesized to lead to altered thalamic sensory processing (Krystal et al 1995), which in turn results in a disruption of transmission of sensory information to the frontal cortex, anterior cingulate gyrus, amygdala, and hippocampus. Abnormal functioning of the thalamus could therefore have significant effects on emotional behavior through its connections with the anterior cingulate gyrus and amydala. The thalamus, specifically the mediodorsal and paraventricular nuclei, is an important relay station for visceral information traveling from the nucleus of the solitary tract and parabrachial nucleus to the ventral anterior cingulate gyrus (Vogt and Gabriel 1993). Disruptions in thalamic functioning may therefore also play a role in the dysregulation of emotion commonly observed in PTSD.

A fear conditioning model of PTSD implicating an anterior cingulate–amygdala circuit has been proposed through empirical findings (e.g., Shin et al 1997) and theoretical work (Hamner et al 1999). This model draws on several lines of evidence, in both animals and humans, for anterior cingulate involvement in inhibition of conditioned fear responses; however, consistent with the findings of the present study, neuroimaging studies comparing PTSD to control subjects have more consistently implicated the anterior cingulate than the amygdala component of this proposed circuit. For example, in two studies, Bremner et al (1999a, 1999b) did not find greater amygdala activation in PTSD than comparison subjects when comparing responses to script-driven traumatic versus neutral memories. Bremner et al (1999b) speculated that the amygdala is activated during external perception and encoding but not internal imagery and retrieval, which is consistent with subsequent PTSD neuroimaging findings (Liberzon et al 1999). Shin et al's comparison (Shin et al 1997) of responses to script-driven traumatic versus neutral memories indicated greater activation of the anterior cingulate but not the amygdala in PTSD versus comparison subjects (this difference was not found for perception of traumatic vs. neutral stimuli); however, Shin et al (1997) also found that, compared to control subjects, PTSD subjects had greater amygdala activation in the traumatic imagery than in the traumatic perception condition. A fear-conditioning model of PTSD that emphasizes amygdala equally with anterior cingulate is therefore inconsistent with published neuroimaging evidence.

There are several limitations of this study. The relatively small numbers of study participants ($n = 10$ in each

group) did not allow for the performance of a random effects analysis. Studies using larger sample sizes are currently in progress. In addition, the comorbidity of the PTSD subjects, especially major depression, may be a confounding factor in the study. Furthermore, the current study used subjects who had experienced a mixture of traumas (sexual/physical abuse and motor vehicle accidents). Future studies will need to address potential variations among different traumas.

In conclusion, our results have shown less activation in the anterior cingulate gyrus and thalamus across traumatic and nontraumatic (sad and anxious) emotional states in patients with PTSD as compared to control subjects. Given the role of the anterior cingulate gyrus and thalamus in the awareness and autonomic/arousal regulation aspects of emotion, dysfunction of these areas as observed in PTSD may provide a neural basis of emotion dysregulation, including extremes of reexperiencing and avoiding emotionally distressing memories, as well as generalized problems with physiologic hyperarousal and emotional numbing in this disorder.

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