

CASE STUDY

Posttraumatic Stress Disorder in a Patient With No Left Amygdala

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Existing biological models of posttraumatic stress disorder (PTSD) posit that the amygdala plays a critical role in the development and expression of this disorder. However, increasing data indicate that the amygdalae are not functionally identical, raising the possibility that the 2 amygdalae may make differential contributions to the expression of PTSD. The authors present a unique patient who developed PTSD following a traffic accident that occurred 2 years after she had undergone removal of her left amygdala to treat pharmacologically intractable epilepsy. The authors propose that the right amygdala is preferentially involved in several processes related to the expression of PTSD symptoms, such that the disorder can occur even in the absence of the left amygdala.

Keywords: emotion, epilepsy, anxiety disorders, lateralization, hemispheric asymmetries

Neurobiological models of posttraumatic stress disorder (PTSD) consistently highlight the role of the amygdala in the development and expression of this psychopathology (Rauch, Shin, & Phelps, 2006; Rauch, Shin, & Wright, 2003). Such models focus on the critical role of the amygdala in fear conditioning (see LeDoux, 2000; Maren, 2001, for reviews) and its involvement in modulating arousal and vigilance functions (Davis, Walker, & Lee, 1997). This structure also plays a key role in modulating memory for emotional context (Malin & McGaugh, 2006; Rudy, Huff, & Matus-Amat, 2004). Thus, the amygdala is in a position to directly mediate many of the symptoms of PTSD, such as the sustained elevations in arousal and startle sensitivity and the ability of contextual cues related to the trauma (e.g., places, activities, and people) to trigger emotional distress.

Existing amygdalocentric theories of PTSD do not differentiate between the roles of the left and right amygdalae. This is not surprising given that much of the early work of fear conditioning in animals used bilateral preparations, and patients with medial temporal lobe lesions in either hemisphere have shown reductions in acquisition of conditioned-fear responses (LaBar et al., 1995). However, recent research suggests that the amygdalae are both

structurally (Szabo, Xiong, Lancaster, Rainey, & Fox, 2001) and functionally asymmetrical (Baas, Aleman, & Kahn, 2004). For instance, Baker and Kim (2004) observed that in rats, posttraining lesions to the right amygdala lead to larger impairments in conditioned contextual fear responses than lesions to the left amygdala. In humans, temporal lobectomy patients show asymmetries in their recall of unpleasant autobiographical memories; patients with right temporal lobectomies show a decreased ability to recall unpleasant emotional events, whereas left temporal lobectomy patients show normal levels of recall (Buchanan, Tranel, & Adolphs, 2006). Damage to the right amygdala also has been observed to produce a more global deficit in electrodermal responses than damage to the left amygdala (Gläscher & Adolphs, 2003; Weike et al., 2005), perhaps reflecting an asymmetry in global autonomic control.

Neuroimaging data have also pointed to functional asymmetries in amygdalar function. Several studies suggest that the right amygdala responds more to experientially learned or conditioned fearful stimuli, whereas the left amygdala appears more active during the perception of innately fear-related items such as photographs of threatening stimuli or fearful faces (e.g., Büchel, Morris, Dolan, & Friston, 1998; Dolan & Morris, 2000; Morris et al., 1998). Similarly, Furmark, Fischer, Wik, Larsson, and Fredrikson (1997) noted that regional cerebral blood flow in the right, but not the left, amygdala correlated with autonomic responses to aversively conditioned photographs. Finally, experiences of intense fear or panic more commonly arise during seizures involving the right medial temporal region than the left temporal lobe, a ratio that has been estimated at greater than 5:1 in favor of the right hemisphere (Sazgar, Carlen, & Wennberg, 2003).

Taken together, these animal-lesion, neuropsychological, and neuroimaging data suggest that many of the cognitive processes and physiological responses that are symptomatic of PTSD are preferentially mediated by the right amygdala. This viewpoint is

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supported by the work of Shin et al. (2005) who reported that regional cerebral blood flow in the right amygdala, but not the left amygdala, positively correlated with PTSD symptom severity in veterans exposed to trauma scripts. Similarly, PTSD symptom severity has been found to correlate with right amygdala responses to masked facial expressions of fear (Armony, Corbo, Clement, & Brunet, 2005; Rauch et al., 2000). These findings suggest that there is an asymmetry in the importance of the right and left amygdala in the development of PTSD. Whereas both amygdalae may contribute to the expression of fear conditioning, the right amygdala would be predicted to play a more critical role in mediating the larger constellation of symptoms associated with PTSD. As such, the symptoms of PTSD may arise in full even in the absence of the left amygdala. Consistent with this possibility, we present data from a patient who developed PTSD after being hit by a car two years after having undergone a resection of her left amygdala and anterior hippocampus.

Patient Details

CD is a 50-year-old, right-handed female who underwent a unilateral selective amygdalohippocampectomy (SAH) to alleviate pharmacologically intractable medial temporal lobe epilepsy. CD's neurological history indicates that she had a prolonged febrile seizure at 7 months of age and likely began experiencing seizures at age 4. She was diagnosed with epilepsy in her early 20s. Her seizures were of the complex partial type with myoclonic jerking in the right hand. EEG data during this period indicated a left-temporal focus to her seizures. CD's seizure frequency peaked in 1996, during which she recorded 115 seizures. She subsequently underwent an evaluation for neurosurgery. An MRI indicated left hippocampal sclerosis and FGD-PET scanning detected hypometabolism in the left inferior mesial-temporal lobe. WADA testing revealed right lateralization of memory, whereas language showed the typical left lateralization.

CD underwent an SAH using the transcortical approach (Olivier, 2000) in 1999. As can be seen in Figure 1, her entire left amygdala has been removed, as has the anterior portion of her hippocampus to approximately 8 mm posterior to the posterior commissure. CD has been free of epileptiform activity since her surgery and is currently taking 1.5 mg of clonazepam per day.

Results of presurgical and postsurgical neuropsychological testing are presented in Table 1, with the postsurgery assessment occurring 6 years following her surgery. At both times, her non-verbal intellectual abilities were better than verbal intellectual abilities, with the difference becoming more accentuated postsurgery (her 22-point difference represents a statistically significant difference in performance). The 36-point difference between her low average Verbal Comprehension Index and her high average Perceptual Organizational Index following surgery was also highly significant, and is consistent with intact right- relative to left-hemisphere functioning. As was predicted by her initial WADA testing, CD's memory functioning was right lateralized, and removal of her left hippocampus does not appear to have produced additional memory impairment.

PTSD Symptoms

Two years following her neurosurgery, CD was struck by a red, Chevrolet Ventura van while walking down a sidewalk. The im-



Figure 1. T1-weighted MRI performed 6 years postsurgery. The entire amygdala and anterior half of the hippocampus are absent in the left hemisphere. Data were collected on a 3T Philips Intera Achieva scanner (Philips Electronics N.V., Eindhoven, the Netherlands) with a 3D turbo field-echo sequence, with 1 mm^3 voxels: field of view = $256 \times 256 \times 170$, flip = 5° , echo time = 3.7 ms, time to repetition = 8 ms.

patient resulted in broken ribs, a punctured lung, and permanent damage to her left leg. Although she hit her head upon impact with the ground, there is no specific evidence that she sustained a closed-head injury. Indeed, CD quickly regained consciousness after being hit and has vivid memories of the emergency responders that arrived at the scene of the accident.

The diagnosis of PTSD in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) includes three classes of symptoms: recurrent re-experiencing of the trauma, persistent symptoms of arousal, and avoidance of stimuli associated with the trauma. CD displays pronounced symptoms in each of these categories. She consistently experiences intense distress when exposed to situations and stimuli that are linked to the event. Paramount among these emotional reactions is the feeling of fear when exposed to motor vehicles that resembled the van that hit her. She remains apprehensive whenever cars approach a car she is riding in. She similarly experiences severe distress when seeing flashing EMS lights (e.g., as on ambulances or police cars) or hearing sirens that she associates with the emergency vehicles that arrived at the accident scene. The patient additionally reports recurrent intrusive, distressing recollections of the event, as well as nightmares related to the trauma. In all of these situations, she demonstrates marked physiological reactivity including perceived difficulty breathing, tachycardia, and sweating. On multiple occasions, these fear responses were observed by the authors, and the patient's self-reports indicate that they occur with substantial regularity.

Persistent symptoms of increased arousal were also evident. These included difficulty breathing, irritability, difficulty concentrating, hypervigilance, and an exaggerated startle response. There was no evidence of emotional detachment or a general numbing of responsiveness; if anything, her affect was more labile, rather than blunted, since the trauma. The patient indicated that this increased arousal represented a substantial change from her pretrauma state.

Symptoms of avoidance were also notable, as she avoided numerous activities that would require exposure to cars or stimuli associated with the accident. CD also demonstrates severe apprehension when crossing streets. Complete avoidance of these situations is not possible due to the necessity of traveling in cars to obtain medical care and the need to cross streets when walking. However, she demonstrates extreme caution while walking, and for a period of time wore a bright orange work vest with the words "LIVE PEDESTRIAN" written on it.

Table 1
Neuropsychological Results

Test	Presurgery		Postsurgery	
	Index score	Percentile	Index score	Percentile
IQ ^a	95	37		
Verbal IQ	107	68	88	21
Performance IQ			109	73
Verbal Comprehension			82	12
Perceptual Organizational			118	88
Working Memory Index			90	25
Perceptual Speed Index			91	27
Memory ^b	73	4		
Auditory Immediate	117	87	86	18
Auditory Delayed			86	18
Visual Immediate			115	84
Visual Delayed			106	66

^a Presurgery: Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981); postsurgery: Wechsler Adult Intelligence Scale—III (Wechsler, 1997a).

^b Presurgery: Wechsler Memory Scale—Revised (Wechsler, 1987); postsurgery: Wechsler Memory Scale—III (Wechsler, 1997b).

Whether or not she experiences a sense of foreshortened future, as described in the *DSM-IV* criteria, is not clear, but she indicated that she does not expect to be able to return to having a career and seemed doubtful about romantic possibilities. At the time of assessment she was receiving disability payments and did not plan on returning to work. Instead, she focuses on seeking treatment of her symptoms and on her PTSD-related artwork, an example of which is shown in Figure 2.

Quantitative assessment of CD's PTSD symptoms were performed using the Revised Civilian Mississippi Scales, a 30-item scale designed to measure PTSD symptoms (Norris & Perilla, 1996). CD scored 107 on this scale (mean item score = 3.56/5), which is substantially greater than scores for non-PTSD individuals (mean item score = 1.68) and is consistent with a severe level of PTSD symptoms.

To help us examine issues of comorbidity, CD completed the Structured Clinical Interview for *DSM-IV* Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1997). Since her neurosurgery, CD has not met criteria for any other Axis I disorders outside of PTSD. She noted some periods of depressed mood and hopelessness, but none approached a clinical level of severity. Prior to her neurosurgery, she had experienced a period of bereavement (after her sister was killed in a car crash) and subsyndromal claustrophobia (after having been trapped in an elevator), but both issues had resolved by the time she had surgery and have not reemerged. Thus, her psychiatric problems postsurgery appear limited to her PTSD symptoms.

Experimental Tasks

Observation of CD's behavior and her own self report suggest a high degree of attention and emotional reactivity to stimuli associated with her trauma. To empirically assess this reactivity, we asked CD and a group of 9 age- and education-matched controls ($M = 50.9, SD = 4.9$ years) to complete two experimental tasks that measure the level of attentional disruption caused by exposure to emotional stimuli.



Figure 2. A drawing by the patient expressing her anxiety symptoms. Reprinted with permission of the patient.

The emotional Stroop task provides an index of the degree to which emotion interferes with the ability to focus attention on specific characteristics of linguistic stimuli (Williams, Mathews, & MacLeod, 1996). Previous research has shown that emotionally arousing words slow participants' ability to state the color in which the word is printed. Research also indicates that PTSD patients show enhanced distraction when exposed to trauma-related material (McNally, 1998; McNeil, Tucker, Miranda, Lewin, & Nordgren, 1999; Beck, Freeman, Shipherd, Hamblen, & Lackner, 2001).

In the current study, CD and 6 of the control participants completed computerized emotional Stroop tasks involving either emotionally positive or negative words (data from 3 of the control participants were unfortunately not available for this task). Both the positive and negative emotional Stroop tasks consisted of eight blocks, each consisting of 16 experimental trials. Four of the blocks contained emotionally neutral words from the same general category (e.g., *evening*, *morning*), two blocks of highly arousing words (e.g., *pain*, *fear*), and two blocks of mildly arousing words (e.g., *lonely*, *gloom*); stimulus lists were identical to those listed by Compton et al. (2003). On each trial, participants were instructed to state the color in which the word was printed as quickly and as accurately as possible. The word remained on the screen until the participant responded verbally. Reaction times and accuracy data were recorded for each participant.

CD demonstrated an exaggerated response to highly arousing negative words, showing a dramatically slowed response (1,107.6 ms), which is 3.4 standard deviations higher than that showed by age and education matched controls ($M = 732.3$ ms, $SD = 110.5$). Her responses to highly arousing positive words were slower than those of controls, although to a much less extent than found for negative words (CD = 961.1 ms; controls = 838.7 ms, $SD = 122.6$ ms; 1 SD difference). In contrast, her reaction time for neutral stimuli was within normal limits (792.5 ms) relative to the controls ($M = 734.2$, $SD = 97.3$). Her responses to low arousing positive and negative words were not dramatically slowed compared to controls (both <1 SD slower). These results indicate that CD was particularly sensitive to negative emotional words; she explained this effect by stating that these words reminded her of the fact that she has PTSD.

CD and 9 healthy controls also completed an emotional-attentional-blink paradigm (Most, Chun, Widders, & Zald, 2005). In this task, participants viewed a series of 17 photographs presented in a rapid-serial-visual-presentation (RSVP) stream. Participants were instructed to detect a target image (a rotated photograph) in this RSVP stream and to indicate whether the image was rotated 90° to the left or to the right. It is critical to note that distracting emotional photographs can appear either 200 ms (Lag 2) or 800 ms (Lag 8) before the target; previous studies have shown that these distractors impair accuracy (correct detection of the target) at Lag 2, suggesting a transient, emotion-induced "blink" of attention.

We have recently shown that aversively conditioned photographs can also elicit an attentional blink (Smith, Most, Newsome, & Zald, 2006). In this study, photographs of either cars or birds were paired with a loud burst of white noise during a conditioning paradigm. Following these aversive exposures, participants completed an emotional-attentional-blink study in which the critical distractors were cars, birds, or landscapes (similar to the 16 other

items in the RSVP display). We found that the conditioned class of stimuli impaired target detection at Lag 2 relative to the unconditioned class of stimuli.

In the current study, we assumed that CD's PTSD would serve as conditioning for photographs of cars. We therefore had her complete the same experiment as mentioned above, without the conditioning phase. Our hypothesis was that her learned, intense reactions to cars would impair her performance in this task. Consistent with our predictions, CD's accuracy was dramatically impaired when cars served as the critical distractors. Her accuracy on these trials was 21% lower than on neutral trials; in contrast, controls were only 9.5% worse on car-related trials ($SD = 5.05$). CD was therefore more than 2 standard deviations below the norm, suggesting that she had an exaggerated sensitivity to these stimuli. Interestingly, CD's accuracy on trials in which car photographs were presented was nearly identical to the accuracy of undergraduates who performed this task after being conditioned to fear cars or birds (Smith et al., 2006). Taken together with her emotional Stroop results, these data indicate that CD shows a significant attentional bias for processing threat-related stimuli that generalizes across at least two distinct types of attentional tasks.

Discussion

The current case study demonstrates that PTSD can develop in the absence of a left amygdala. The patient displayed the cardinal triad of PTSD symptoms including reexperiencing of the trauma, persistent avoidance of stimuli associated with the trauma, and persistent symptoms of increased arousal. In addition to these classic symptoms, CD also shows attentional biases toward stimuli that are related to her PTSD. This case is consistent with the hypothesis that due to functional asymmetries in amygdalar functioning, the right amygdala plays a more critical role than the left amygdala in the expression of PTSD. Indeed, the present data suggest that the asymmetry may be great enough that the disorder can occur even in the absence of the left amygdala.

Several caveats must be considered regarding the generalizability of conclusions drawn from this case. First, CD's history of seizures may have influenced the functioning of both her healthy right temporal lobe and closely connected neural structures. Due to the presurgical dysfunction of her left amygdala, CD's right amygdala may have become exceptionally efficient at establishing or maintaining fear-related connections (i.e., the right amygdala was performing the functions of both amygdalae). This adaptation may have primed the right amygdala to respond to fear, thus making it more sensitive to fear learning and less sensitive to extinction processes than the amygdalae of healthy brains. Similarly, the history of seizures may have altered other closely connected areas, such as the ventromedial frontal regions, that typically play a role in extinction (Quirk, Garcia, & Gonzalez-Lima, 2006). Thus, it might be speculated that CD's continued hyperresponsivity to cars and sirens, despite years of reexposure, might reflect seizure-induced dysfunction of her extinction mechanisms. Subtle damage to the ventral frontal lobe as a consequence of hitting her head during the accident might also have impaired extinction mechanisms. However, any ventral frontal impairment is speculative, as there is no MRI evidence of structural damage.

Second, it is possible that the removal of the left amygdala actually accentuated right amygdalar processing through a release

of interhemispheric inhibition. According to this view, in a normal brain the left and right amygdalae achieve a functional balance, with each amygdala ensuring that the other amygdala does not become hyperresponsive. Damage to one amygdala would therefore release the other amygdala from this inhibition, thereby allowing its functions to be expressed to a greater degree than usual. In CD's case, this release would manifest itself as an enhanced propensity to develop learned fearful associations such as those experienced in PTSD. However, this explanation of CD's condition appears unlikely. The primate brain has very sparse connections between the left and right amygdalae and sends almost no cross-hemisphere projections to the other amygdala through the anterior commissure or corpus callosum, with the exception of some sparse labeling of the dorsal cortical nuclei (e.g., Demeter, Rosene, & Hoesen, 1990; Di Virgilio, Clarke, Pizzolato, & Schaffner, 1999). Given this dearth of direct connections, lesioning of the left amygdala would not be predicted to affect processes that are primarily dependent upon right-amygdala activity. Consistent with this interpretation is the fact that we know of no studies in which fear conditioning or memory for emotional context were enhanced following unilateral amygdala lesions.

A final issue that must be addressed is the possibility that events prior to CD's left amygdala resection predisposed her to suffer PTSD at a later date. During interviews, CD described being sexually abused at age 5. She also reported a history of physical abuse from her second husband. Both of these traumas occurred while she had both amygdalae (although in the latter instance her left amygdala would have likely been damaged by years of seizures). Although there is no evidence that she had PTSD associated with these events, it is possible that these traumatic events altered her amygdala sensitivity (Teicher et al., 2003) as well as her hippocampal functioning (Shin et al., 2004) in such a way as to make her more susceptible to developing PTSD symptoms. Consistent with this view, rates of combat-related PTSD are significantly higher in military personnel with childhood exposure to trauma (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993; Cabrera, Hoge, Bliese, Castro, & Messer, 2007).

The current research complements one other case in the literature involving a patient who showed signs of PTSD after a resection of the amygdala. In this case (Adami, Konig, Vetter, Hausmann, & Conca, 2006), a 19-year-old girl with a history of childhood abuse started showing symptoms of PTSD, as well as hysterical symptoms, two weeks following a left-amygdala resection for intractable epilepsy. This case differs from CD in that the PTSD-like symptoms were associated with a presurgical trauma (childhood abuse) rather than a postsurgical trauma (being hit by a car). Indeed, CD appears to be the first reported case of an individual developing PTSD for a traumatic event that occurred after one amygdala was removed.

CD's unique case makes clear that PTSD can develop in the absence of one amygdala, and the observed laterality appears consistent with the hypothesis that the right amygdala plays a greater role than the left amygdala in the development of PTSD. It must be noted, however, that the current study represents a single individual. Given possible individual differences in the lateralization of amygdalar function (see Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004; Canli, Sivers, Whitfield, Gotlib, & Gabrieli, 2002; Zald, 2003), we must be cautious in the degree to which we generalize conclusions regarding laterality to larger

populations. This is an unavoidable limitation: To study responses to trauma in lesion patients, one needs to have the conjunction of neurological patients with specific brain lesions and exposure to traumatic events. Given the infeasibility of recruiting large numbers of individuals with this conjunction of neuropathology and subsequent trauma, singular examples, such as the case of CD, provide the best available evidence of the effects of lateralized lesions on trauma-related disorders.

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