Edited by

MARK L. HOWE
GAIL S. GOODMAN &
DANTE CICCHETTI

STRESS, TRAUMA, AND CHILDREN'S MEMORY DEVELOPMENT

NEUROBIOLOGICAL, COGNITIVE, CLINICAL, & LEGAL PERSPECTIVES

Stress, Trauma, and Children's Memory Development

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OXFORD
UNIVERSITY PRESS
2008

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Published by Oxford University Press, Inc.
198 Madison Avenue, New York, New York 10016

www.oup.com

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Library of Congress Cataloging-in-Publication Data
Stress, trauma, and children's memory development : neurobiological, cognitive, clinical,
and legal perspectives / edited by Mark L. Howe, Gail S. Goodman, and Dante Cicchetti.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-19-530845-7
1. Memory disorders in children—Etiology. 2. Post-traumatic stress disorder in
children—Complications. 3. Psychic trauma in children—Complications.
4. Abused children—Mental health. 5. Memory in children.
I. Howe, Mark L. II. Goodman, Gail S. III. Cicchetti, Dante.
[DNLM: 1. Stress Disorders, Post-Traumatic. 2. Child Abuse.
3. Child. 4. Memory. 5. Repression.
WM 170 S9155 2008]

RJ506.M36S87 2008

618.92'8521—dc22 2007036868

9 8 7 6 5 4 3 2 1

Printed in the United States of America
on acid-free paper

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Contributors

Jennifer K. Ackil, Department of Psychology, Gustavus Adolphus College
Else-Marie Augusti, Department of Psychology, University of California, Davis
Patricia J. Bauer, Department of Psychology, Emory University
Alisa Miller Beyer, Department of Psychology, University of Kansas
Stephanie D. Block, Department of Psychology, University of California, Davis
Charles J. Brainerd, Cornell University
J. Douglas Bremner, Department of Psychiatry and Behavioral Sciences, Department of Radiology, Emory University School of Medicine
Deirdre Brown, Department of Psychology, Lancaster University
Sarah L. Bunnell, Department of Psychology, University of Kansas
Melissa M. Burch, School of Cognitive Science, Hampshire College
Dante Cicchetti, Institute of Child Development and Department of Psychiatry, University of Minnesota
Michelle Culver, Department of Psychology, University of California, Davis
Jennifer S. Curtis, Department of Psychology, University of Kansas
W. John Curtis, Mt. Hope Family Center, University of Rochester
Elizabeth L. Davis, Department of Psychology and Social Behavior, University of California, Irvine
Gail S. Goodman, Department of Psychology, University of California, Davis
Andrea F. Greenhoot, Department of Psychology, University of Kansas
LaTonya S. Harris, Department of Psychology, University of California, Davis

Mark L. Howe, Department of Psychology, Lancaster University
Michael E. Lamb, Department of Social and Developmental Psychology, Cambridge University
Linda J. Levine, Department of Psychology and Social Behavior, University of California, Irvine
Carryl P. Navalta, Developmental Biopsychiatry Research Program, McLean Hospital, Harvard Medical School
Christin M. Ogle, Department of Psychology, University of California, Davis
Yael Orbach, National Institute of Child Health and Human Development
Margaret-Ellen Pipe, Department of Psychology, Brooklyn College, City University of New York
Jodi A. Quas, Department of Psychology and Social Behavior, University of California, Irvine
Valerie F. Reyna, Cornell University
Martin H. Teicher, Developmental Biopsychiatry Research Program, McLean Hospital, Harvard Medical School
Susan Timmer, Department of Psychology, University of California, Davis
Akemi Tomoda, Developmental Biopsychiatry Research Program, McLean Hospital, Harvard Medical School
Sheree L. Toth, Mt. Hope Family Center, University of Rochester
Anthony Urquiza, Department of Psychology, University of California, Davis
Kristin Valentino, Mt. Hope Family Center, University of Rochester
Dana L. Van Abbema, Department of Psychology, St. Mary's College of Maryland

Prologue

Turning Science into Practice

MARK L. HOWE, GAIL S. GOODMAN,
AND DANTE CICCHETTI

Memory for emotional events captivates writers, scholars, citizens, and scientists. From theories, historic and recent, concerning the unconscious preservation of traumatic memories to those suggesting that traumatic experiences are well preserved in our conscious mind, theorists have tried to unravel the mysteries of emotion and memory. Across the centuries, the most popular belief has been that records of our experiences, particularly emotional and traumatic ones, are preserved with reasonable accuracy in our memory system. Even as recently as the early twentieth century, writers were suggesting that every experience, even the very earliest, "leaves its mark.... Nothing of good or evil is ever lost" (Thorndike, 1905, pp. 330–331). Further, it is thought that the earlier these experiences occur in childhood, the more formative they are, and the more likely they are to remain in memory, exerting their influence throughout our lives regardless of whether we can bring these experiences to consciousness (see Howe & Courage, 2004). Such ideas were pivotal in Freudian theory as well as in many other conceptions of social, emotional, and personality development (e.g., Ainsworth & Bowlby, 1991). Adverse early experience

is thought to be at the root of later aberrant adult outcomes regardless of whether these experiences can be remembered (for reviews of these ideas, see Howe, in press; Kagan, 1996).

Recently, we have seen a steep rise in scientific research concerning the role of stress and trauma in memories for childhood experiences. Psychological science is now, more than ever, grappling with questions about whether traumatic childhood experiences are remembered differently than nontraumatic experiences. Does the fact that one has experienced trauma during childhood affect subsequent memory processing? Can children who have been maltreated remember and report those experiences accurately? Indeed, we are concerned not just with memory for traumatic and stressful events themselves but also with the long-term effects of these experiences on the course of "normal" memory development.

Few questions in developmental psychology have received as much international attention as have those concerning the impact of childhood trauma on memory. Until recently, the lack of scientific research to constrain theory has fueled controversy about such questions as "Does childhood trauma lead to deficits in memory, including a greater propensity for errors of commission (e.g., 'false memory') or errors of omission (e.g., 'lost memory')?" and "Are the neurohormonal changes that are linked to childhood trauma and stress associated with changes in children's basic memory processing abilities?" Scientists have also struggled with how to conceptualize and measure distress and other negative emotions—for instance, in terms of discrete emotions (fear, anger, sadness), physiological responsivity (e.g., through cortisol production; functional magnetic resonance imaging), or observer ratings.

To begin to answer these and other questions, the authors of the chapters in this book have focused on neurobiological, cognitive, clinical, and legal areas as they relate specifically to stress, trauma, and memory development. These areas were selected in order to (a) focus attention on the impact of stress and trauma on memory development by showcasing the most recent and innovative work and theories, (b) highlight the consequences of early traumatic experiences for subsequent memory performance, and (c) capture relations of early trauma to other measures of cognitive and clinical functioning in childhood, as well as to the longevity of trauma memories formed early in life.

In approaching these questions, we sought a translational approach, one in which science and practice converge. First, we wanted to provide

a framework in which basic research on memory development can be expanded into the study of childhood trauma and maltreatment (for an overview, see Howe, Cicchetti, & Toth, 2006). Here, authors were asked to examine links between "normal" patterns of memory development and those observed when children had experienced stress and trauma. Second, we wanted to know what science tells us about the cognitive and neurophysiological underpinnings of memory development, trauma, and stress, to inform practice in the clinical and forensic realms. Of course, these latter areas, in turn, provide many of the questions to which basic science needs to attend to fully understand the complexities of stress, trauma, and memory development.

Neurobiological Perspectives

In the first part, "Neurobiological Perspectives," the authors present state-of-the-art research on the consequences for memory and memory development of the neurobiological changes that accompany childhood stress, trauma, and maltreatment. Specifically, in the first chapter, Bremner examines the interaction between brain development, trauma onset, memory, and the neurobiological consequences of trauma. He proposes a model of how stress-induced changes in brain systems involved in stress and memory mediate changes in traumatic memories in patients with childhood abuse–related mental disorders. The second chapter in this section is by Navalta, Tomoda, and Teicher. These authors take on the challenge of reviewing what is known about the clinical neuroscience of child abuse and providing new findings on the neuroanatomical effects of child abuse and how they are related to changes in memory processes. They conclude that there exists a growing body of evidence suggesting that memory deficits do exist for individuals with abuse histories and that these deficiencies are related to neuroanatomical anomalies. Our third chapter in this section, by Cicchetti and Curtis, uses event-related potentials (ERPs) to study memory functioning in infants and children in normal populations and in children who have experienced maltreatment. The authors suggest how future research using ERPs and memory in samples of maltreated and nonmaltreated infants and children can inform the design and implementation of randomized prevention and intervention trials with children who have experienced maltreatment. Together, the three chapters in this part provide the reader with an up-to-date picture of the neurobiological consequences of stress and trauma and their impact

on the development of children's memory. As well, these chapters alert us to the many complexities of studying changes in neurobiological functioning as a consequence of stress, particularly in populations in which many of the relevant neural structures and systems are still developing. Despite these complexities, there is an emerging consensus concerning the changes that occur due to stress and maltreatment on memory-related neurobiological systems.

Cognitive Perspectives

In the second part, "Cognitive Perspectives," the authors examine memory for traumatic experiences and whether those experiences result in fundamental changes in children's memory development. In Chapter 4, Greenhoot, Bunnell, Curtis, and Beyer examine autobiographical memory for family violence using longitudinal data. These authors examine what is known about changes in autobiographical memory development and memory functioning that may be brought about by chronic exposure to stressful events such as abuse. Following this review, Greenhoot and colleagues present findings from their own research on these issues, integrating findings from their longitudinal study of children exposed to various forms of domestic violence and using these data to disentangle competing explanations concerning the mechanisms underlying these memory dysfunctions.

Chapter 5, by Ogle, Block, Harris, Culver, Augusti, Timmer, Urquiza, and Goodman, examines the claim that childhood trauma leads to a specific type of autobiographical memory functioning, namely "overgeneral memory." The authors provide a comprehensive review of scientific theory and research on autobiographical memory development, memory for trauma-related and nontrauma-related information in traumatized individuals, and autobiographical memory in nontraumatized and traumatized adolescents and adults. Finally, they present preliminary findings from an ongoing study that examines autobiographical memory development in documented child sexual abuse victims versus matched comparisons with participants who have no known history of child sexual abuse. Contrary to the overgeneral memory hypothesis, the authors conclude that individuals with child maltreatment histories, especially those with post-traumatic stress disorder (PTSD), may overfocus on trauma in their lives and in their pasts, and this focus may make their

autobiographical memories particularly accurate, especially for trauma-related information.

Chapter 6, by Bauer, Burch, Van Abbema, and Ackil, examines children's memory for a naturally occurring disaster (a tornado). Specifically, these authors tackle the deeply rooted assumption that highly stressful and traumatic events are remembered differently relative to events that are more affectively neutral or positive. The authors evaluate this assumption using data from a study of children's reports of the experience of a tornado that devastated the town of St. Peter, Minnesota, in March of 1998. The evaluation is multidimensional, including analyses of the amount children remembered, the type of information remembered, and the extent to which their reports were affected by their conversational partners, namely their mothers. The authors conclude that although there are some differences between children's reports of traumatic and nontraumatic events (e.g., conversations about the tornado were longer and had greater breadth than those about the nontraumatic events), there are some very important similarities (e.g., the level of detail provided about the traumatic and nontraumatic events did not differ).

Chapter 7, by Davis, Quas, and Levine, looks at the role of discrete emotions and children's memory for stressful experiences. The argument here is that if we are to understand children's memory for stressful events, we need to look beyond "distress" as a unitary construct and begin to evaluate children's understanding or appraisals of stressful events as well as children's discrete emotional experiences and emotion regulation techniques. The argument continues that with development, children appraise situations and regulate their emotions in increasingly complex ways. Younger children, with similar but simpler appraisal processes than adults and limited emotion regulation strategies, are likely to have a more narrow focus.

Together these chapters provide an up-to-date exegesis of the study of children's memory for traumatic experiences and the consequences of stress, trauma, and maltreatment on subsequent memory development. Although in many circumstances traumatic experiences are remembered better than nontraumatic experiences, the two kinds of memories exhibit many similarities, including, but not limited to, susceptibility to interference, suggestion, forgetting, and false recollection. These chapters also alert us to the need to refocus some of our research efforts by focusing on the impact of events on the children who experience them, including the types of appraisals children make about these events as well as

whether there are emotional sequelae associated with these experiences. Like those in the first part, these chapters remind us that a truly comprehensive understanding of stress, trauma, and memory development requires a multifaceted approach to research, one that benefits from interdisciplinary collaborations.

Clinical and Legal Perspectives

In our third and final part, "Clinical and Legal Perspectives," science is beautifully translated into practice in three unique chapters: one on forensic interviewing; one on the law and false memory; and our final chapter, on translating findings on memory development, stress, and maltreatment into good clinical technique. Chapter 8, by Brown, Lamb, Pipe, and Orbach, examines the problem of how best to question children in a forensic context. In this extensive review, the authors discuss how the quantity and quality of information elicited in forensic interviews with children reflects the behavior and capacities of both the child witness and the adult interviewers. They outline how even quite young children are capable of providing reliable testimony about abusive experiences when questioned appropriately. At the same time, because children need help retrieving, structuring, and reporting their experiences, there is a clear need to provide that support without degrading the quality of children's accounts. Guidelines for doing so are elaborated on in this chapter.

Chapter 9, by Brainerd and Reyna, provides an exhaustive review of children's spontaneous false memories and what these errors mean for the law. Research on developmental patterns in spontaneous false recollections (e.g., increases with age) is reviewed and the findings are linked to cases of child sexual abuse and the ensuing legal complications. The authors conclude by suggesting ways in which we might avoid eliciting false recollections, especially in cases where abuse has occurred.

In Chapter 10, Toth and Valentino use the literature on trauma and memory, particularly child maltreatment and memory, as the foundation for examining the clinical and social-policy implications of this research for children who have been victimized by abuse and neglect. Based on this review, the authors note that more research is still needed before the efficacy of trauma-specific versus more symptom-focused interventions for children who have been maltreated can be properly evaluated. That is, although for adults attention to trauma has been shown to increase the

effectiveness of the intervention, there is considerably less research favoring this approach with maltreated children. Future investigations will require careful attention to the age at which the trauma occurred, the time between the trauma and the provision of treatment, and the developmental period during which the intervention is initiated.

Together, these chapters provide a state-of-the-art snapshot of how the findings from neuroscience and the cognitive and developmental sciences of stress, trauma, and children's memory development can be effectively translated into legal, clinical, and social policy. Documents containing specific prescriptions for investigating child maltreatment, questioning child witnesses, and treating children who have been maltreated continue to be drafted and continue to be informed by science. Thanks to a translational focus, science has been put into practice and practice has informed science about some of the problems still in need of rigorous inquiry.

Conclusion

So, what have we learned about the two very broad questions posed at the beginning of this prologue? First, can children remember traumatic experiences? The answer is yes, especially if they occur after the period known as infantile amnesia (Howe, in press) and care is taken with the manner in which children attempt to recollect this information (including the manner in which others pose questions). However, memories for these experiences are not immune to processes that affect nontraumatic memories, namely suggestion, false memories, interference, and normal forgetting.

Second, can stress, trauma, and maltreatment affect the course of normal memory development? The growing consensus is yes. In particular, evidence from the neurobiological chapters suggests this might be so, as do the chapters in the cognitive and clinical and legal sections. Although far from over, the story that is emerging is one in which maltreated children may be more hypersensitive to emotional stimuli, possibly due in part to heightened amygdala reactivity following high-intensity trauma exposure. These effects can have far-reaching consequences for memory functioning, including how information is encoded, stored, and consolidated, and even how it is retrieved (also see LaBar, 2007).

Although children who have been maltreated may not have less specific autobiographical memories than children who have not been maltreated, maltreated children may nevertheless experience greater memory errors.

However, as the chapters in this book attest, such memory errors are by no means commonplace or typical of much of maltreated children's remembering. Indeed, when seen, these effects depend jointly on individual difference factors such as neuroendocrine regulation, trauma symptoms, and dissociative experiences (also see Cicchetti, Rogosch, Howe, & Toth, 2007; Eisen, Goodman, Qin, Davis, & Crayton, 2007; Howe, Toth, & Cicchetti, 2006).

Overall, then, stress, trauma, and maltreatment can affect memory development as well as memory for the traumatic experience(s). The interactions are often complex and depend on a whole host of factors, all of which have been documented in the chapters here. The diversity of topics, viewpoints, and approaches presented in this book underline the intricacy of the problem we are dealing with when studying the effects of stress and trauma on children's memory development and then trying to translate these findings into practice. We hope the readers appreciate this complexity as well as the scientific and practical advances made by the writers of these superb chapters.

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Part I
Neurobiological Perspectives

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1

The Neurobiology of Trauma and Memory in Children

J. DOUGLAS BREMNER

Goals of the Chapter

This chapter will outline the relation between stress and memory in children. The chapter will highlight the interactions among brain development, epoch of trauma onset, memory, and neurobiological consequences of trauma. This chapter will propose a model for how stress-induced changes in brain regions and systems involved in stress and memory mediate alterations in traumatic memories in patients with childhood abuse–related mental disorders. The chapter will also comment on the relevance of the model to current controversies about delayed recall of childhood abuse.

Childhood Trauma

Childhood trauma is an important public health problem in America affecting as many as one out of five children (MacMillan et al., 1997; McCauley et al., 1997). Childhood trauma can lead to post-traumatic stress disorder (PTSD), which affects about 8% of Americans at some time in their lives (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), as well as depression (Franklin & Zimmerman, 2001; Prigerson, Maciejewski, &

Rosenheck, 2001), substance abuse (Bremner, Southwick, Darnell, & Charney, 1996d; Kessler et al., 1995), dissociation (Putnam, Guroff, Silberman, Barban, & Post, 1986), personality disorders (Battle et al., 2004; Yen et al., 2002), and health problems (Dube, Felitti, Dong, Giles, & Anda, 2003). For many abuse victims, PTSD can be a lifelong problem (Kendall-Tackett, 2005; Saigh & Bremner, 1999). This chapter reviews the relation between trauma and memory in children in the context of the neurobiology of trauma, brain development, and memory. The thesis of this chapter is that alterations in brain regions and neurochemical systems involved in memory and the stress response in patients with abuse-related PTSD lead to alterations in memory function.

Normal Development of Cognition and the Brain

Cognition and the brain undergo changes across the lifespan from early childhood to late life (Bremner, 2005a). Understanding these normal developmental changes is critical for determining the difference between normal development and pathology, as well as how they interact.

Normal memory formation involves encoding, consolidation, and retrieval. Encoding refers to the laying down of the memory trace, consolidation is the process by which the memory goes from short-term to long-term storage, and retrieval is the process by which long-term memories are retrieved from storage (Schacter, 1996). Memories can be divided into explicit (also known as declarative), or available for conscious recall, and implicit (also known as procedural). Explicit memory includes recall of facts or lists, while implicit memory includes memory that is not accessed by conscious recall, such as procedural memories like riding a bike, as well as conditioned responses.

Children do not develop the capacity for long-term autobiographical memory until 2 to 3 years of age (Bruce et al., 2005; Eacott & Crawley, 1998; Howe & Courage, 1993, 1997; Usher & Neisser, 1993). This coincides with the development of the ability to place events in the context of the who, what, and where of the self. Children do have memories before the age of 2, as measured by a variety of laboratory tasks, although explicit memories are not retrieved before this time period in later life (Eacott & Crawley, 1998).

Although the bulk of brain development occurs in utero, the brain continues to develop after birth (Giedd, Shaw, Wallace, Gogtay, &

Lenroot, 2006). In the first 5 years of life there is an overall expansion of brain volume related to development of both gray matter and white matter structures; however, from 7 to 17 years of age there is a progressive increase in white matter (felt to be related to ongoing myelination) and decrease in gray matter (felt to be related to neuronal pruning), while overall brain size stays the same (Casey, Giedd, & Thomas, 2000; Durston et al., 2001; Giedd et al., 1999b; Paus et al., 1999). Gray matter areas that undergo the greatest increases throughout the 7-to-17-years period of development include frontal cortex and parietal cortex (Rapoport et al., 1999; Sowell et al., 1999). Basal ganglia decrease in size, while corpus callosum (Giedd, Blumenthal, & Jeffries, 1999a; Thompson et al., 2000), hippocampus, and amygdala (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Giedd et al., 1996b; Pfefferbaum et al., 1994) increase in size during early childhood, although there may be developmental-sex-laterality effects for some of these structures (Giedd et al., 1996a).

Stress and Memory

Stress at the time of memory encoding, consolidation, and retrieval can influence memory function. After President Kennedy's assassination, many people were able to remember where they were and what they were doing at the time (more than they could remember, say, what they ate for breakfast on that same date). This phenomenon came to be called "flashbulb memories" and became a subject of investigation (Brown & Kulik, 1977).

In the aftermath of the assassination attempt on President Reagan, stronger emotional reactions to hearing the news were associated with greater consistency of recall of the details of personal circumstances at the time of hearing the news from 1 to 7 months after the event (Pillemer, 1984). Some studies of the January 28, 1986, *Challenger* space shuttle explosion (Bohannon, 1988; Bohannon & Symons, 1992)—but not others (Neisser & Harsch, 1992)—showed a relation between emotional upset at the time the news was received and ability to recall personal circumstances several months after the explosion. Furthermore, a relation has been found between high emotionality and surprise and vividness of memories related to personal events (as opposed to national events) (Rubin & Kozin, 1984).

Experimental paradigms have also been used to assess the effects of stress on memory. Subjects exposed to a shocking film in which a young boy is shot in the face had impaired recall of details that preceded the violent act in the film (Loftus & Burns, 1982) and of words associated with the face (Christianson & Nilsson, 1984) relative to subjects who viewed a neutral film. In another study, subjects who viewed traumatic slides in which someone had been injured had better recall of central details and worse recall of peripheral details in comparison to those who viewed neutral slides (Christianson & Loftus, 1987, 1991). Subjects shown pictures of a crime scene focused on a gun or a knife to the exclusion of other details such as the faces in the picture, even after controlling for eye fixation on the central details of the scene (Christianson, Loftus, Hoffman, & Loftus, 1991). These studies showed that stress and emotion can enhance some aspects of memories and diminish others.

Stress and Memory in Children

Studies have also examined the effects of stress on memory in children. Three- to 4-year-old children interviewed after Hurricane Andrew were assessed for memory of the storm (Bahrick, Parker, Fivush, & Levitt, 1998). The authors found an inverted U curve, with best memory at intermediate levels of storm damage and a decrease in memory at the highest levels of storm damage.

Studies of healthy children 4 to 6 years of age who went to the doctor and had blood draws, injections, and genital and anal exams showed that children have reliable memories of the events and are resistant to suggestion (Goodman, Hirschman, Hepps, & Rudy, 1991; Saywitz, Goodman, Nicholas, & Moan, 1991). With decreases in age children became more susceptible to suggestion and had a decrease in reliability; they were also more susceptible to suggestion when interviewed by an adult than by a child, suggesting an eagerness to please authority (Ceci & Bruck, 1993; Ceci, Ross, & Toglia, 1987). Children have been shown to be resistant to abuse-related suggestions, such as "He took your clothes off, didn't he?"(Goodman & Aman, 1990; Rudy & Goodman, 1991). Reliability about genital exams was actually higher than for other parts of the physical exam (Saywitz et al., 1991). Children did not report the genital exam unless asked directly (Ceci et al., 1987). Children age 3 to 13 asked about a voiding cystourethrogram fluoroscopy they received at 2 to 6 years of age were less likely to recall

information if the procedure had been stressful, and were less likely to recall information the younger they were at the time of the procedure (Quas et al., 1999). In another study children ages 3 to 18 with leukemia who underwent a painful lumbar puncture were assessed 1 week after the procedure (Chen, Zeltzer, Craske, & Katz, 2000). Children of all ages showed a high accuracy of recall, and accuracy increased with age.

Children with a history of abuse have also been shown to be accurate in remembering details of doctor's genital and anal exams. In a study of 189 3- to 17-year-olds, all children showed >70% accuracy in recalling details of the exam (Eisen, Qin, Goodman, & Davis, 2002). There were no differences in accuracy of recall between abused and nonabused children, and there was no relation with dissociative tendencies or other measures of psychopathology. Older age was the only factor that predicted accuracy of recall.

In summary, the empirical literature suggests that children can have accurate recall of stressful events. These studies, however, have primarily been conducted in normal children. We cannot assume that studies in normal children can be generalized to all children, including abused children. The few studies that were conducted on abused children did not specifically look at those with PTSD or other stress-related mental disorders. Since, as reviewed below, memory and stress responsive systems are altered in patients with stress-related mental disorders, extrapolation of findings from healthy subjects to abuse victims with mental disorders, which is the group of primary interest in the debate about delayed recall of childhood abuse, has limitations.

Long-Term Recall of Childhood Abuse

The relation between trauma and memory in children has been fraught with controversy (Bremner, 1999; Freyd & DePrince, 2001; Howe, Cicchetti, & Toth, 2006; Howe, Cicchetti, Toth, & Cerrito, 2004; Howe, Toth, & Cicchetti, 2006; Kihlstrom, 1995; Schacter, Coyle, Fischbach, Mesulam, & Sullivan, 1995; Williams & Banyard, 1999). At issue is whether delayed recall of childhood abuse can exist, whether these memories are implanted by therapists, and whether lost memories of abuse are related to altered memory function in abused individuals or are due to ordinary forgetting. We first review research studies related to memory and forgetting abuse, then the experimental literature on memory distortion and the controversy that has ensued in the literature on delayed recall of abuse,

and finally findings from the neurobiology of trauma that are proposed as models for memory distortion in abused patients with mental disorders.

Several studies have shown varying degrees of lack of recall of childhood abuse events in later life. Williams studied 129 women with documented histories of sexual victimization in childhood (Williams, 1994). Thirty-eight percent reported no memory of the abuse. Factors associated with lack of recall included younger age and molestation by someone the women knew.

Widom and Morris (Widom & Morris, 1997) studied 1,196 victims of abuse or neglect 20 years after their initial assessments in childhood. Only 63% of individuals with documented sexual abuse in childhood reported this abuse in adulthood. Only 16% of men (compared to 64% of women) with documented sexual abuse reported childhood sexual abuse as adults. The authors concluded that there was "substantial under-reporting of childhood sexual abuse" that could be related to loss of memory, denial, or embarrassment about reporting abuse details. They also concluded that cultural or other social factors might explain why fewer men than women reported sexual abuse.

Alexander and colleagues (Alexander et al., 2005) studied 103 children involved in legal cases related to childhood abuse 10 to 16 years later. The authors found a 72% accuracy of remembering abuse. However, this was only in 94 of the subjects. Of the original 103, 3 said that they had never been abused even though they originally divulged abuse, and 2 said that the charges were false. Severity of PTSD was correlated with accuracy, and individuals who rated the abuse as their most traumatic life event had accurate memories of abuse regardless of PTSD severity. The authors concluded that memories of abuse were in general accurate.

Goodman et al. (2003) studied 175 individuals with documented childhood sexual abuse from age 4 to 17 at 13 years after the reported abuse. Of the subjects, 81% reported the documented abuse. Older age at the time when the abuse ended, maternal support, and more severe abuse were associated with a higher likelihood of disclosure.

Memory Distortion

Several studies in normal subjects have shown that memory is susceptible to distortions and deletions. For instance, in one study, subjects viewed a film of an automobile accident. When researchers used the

verb "smashed" as opposed to the verb "hit" in relation to the film, subjects gave higher estimates of the speed of the automobiles, and more subjects incorrectly endorsed the statement that broken glass was associated with the accident (Loftus & Palmer, 1974). When subjects were shown a series of slides that told a story involving a stop sign followed by a narrative that misleadingly described a yield sign, they were more likely to falsely recall that the slides included a yield sign than subjects not given the misleading information (Loftus, Miller, & Burns, 1978). In another example known as the "Deese/Roediger-McDermott paradigm," after its originators, words that are highly associated with a "critical lure," when presented in a list, will be associated with a "false" recall of the absent "lure." So, for example, if a subject is presented with the words thread, pin, eye, etc., the subject may include the "critical lure" needle, even though it was not part of the original list (Roediger & McDermott, 1995).

Memory can also be distorted to fit with subjects' expectations. Children told a story about the Six Million Dollar Man being unable to carry a can of paint, when tested 3 weeks later, were more likely to change their recall to fit with their pretesting knowledge (Ceci, Caves, & Howe, 1981).

In another study, the parents of college students provided surveys of their children's childhood events, and the students were asked to recall the events in a series of interviews. In addition to the true events, students were asked to recall the details of a fictitious episode, such as knocking over a punch bowl at a wedding (Hyman, Husband, & Billings, 1995). By the third interview, 25% of students falsely recalled the punch bowl; in addition, they tended to elaborate more on their own true events with each interview. Based on a series of studies, Oakes and Hyman (2001) outlined factors involved in the creation of false childhood memories. First, the event must be plausible, or something the individual thinks could have happened. The subject must then create an image with a narrative. Finally, the individual forgets the source of the image and narrative and incorrectly attributes it to the self.

Pezdek and colleagues (Pezdek, Finger, & Hodge, 1997) used a similar paradigm involving both plausible (lost in the mall as a child) and implausible (received a painful rectal enema as a child) stories. Consistent with the model of Oates and Hyman, only the "lost in the mall" anecdote was falsely recalled. No subjects falsely recalled the painful enema event.

These studies highlight the fact that amnesia for the source of the information plays a critical role in many of these experimental paradigms of "false memory." For instance, studies have shown that if subjects are cued to pay attention to the source of the information they receive, the false-recall effect associated with misleading information is lost (Lindsay, 1990; Lindsay & Johnson, 1989).

A clinically relevant question is whether memories can be forgotten and still be potentially accessible at a later time, or whether these memories no longer exist as memory traces in the brain. Adherents to the latter view hold that delayed recall of abuse memories are secondary to "implanting" of abuse memories by overzealous therapists (Loftus et al., 1978). They claim that authentic memories can be "overwritten" by memories that are implanted or introduced through suggestion or other means. One study addressed the question of whether memories could be overwritten. Subjects who saw slides that included a hammer were then given the misleading information that a screwdriver had been among the slides. The subjects were then forced to recall whether they had seen a hammer or a screwdriver. Subjects did not falsely recall the screwdriver more than expected by chance (McCloskey & Zaragoza, 1985). The authors concluded that if the misleading information could overwrite the original memory, then the subjects would have falsely recalled the screwdriver more often. The authors concluded that there was not evidence that memories could be "overwritten."

The past two decades of research on false memory have generated as much heat as light on this topic, with the evolution of two different languages to describe the topic. In response to the original study by Williams (Williams, 1994), Loftus, Garry, and Feldman (1994) argued that a loss of memory about abuse is related to normal forgetting. They dichotomized normal "forgetting" and "repression," and argued that there is no evidence for repression.

The choice of language, however, can often shape the conception of an issue. Loftus and colleagues chose to frame the debate about false memories of abuse by using a term derived from psychoanalysis that refers to memories that are banished from consciousness because of the existence of a painful conflict. For a variety of reasons, psychoanalysis has been resistant to empirically based research; in fact, only very recently has a published, controlled trial of psychoanalysis been performed (Milrod et al., 2007). The concept of repression is a difficult one to test empirically, which has contributed to the heated rhetoric surrounding this issue.

For instance, Pezdek and Lam (2007) reviewed the last decade of research on memory for abuse and concluded that only 13% of the articles claiming to study false memory actually used the word as originally intended (De Prince and colleagues similarly found that 70% did not use true false memory paradigms; De Prince, Allard, Oh, & Freyd, 2004). Pezdek and Lam found that most studies used the Deese/Roediger-McDermott paradigm (false recall of a critical lure after being read a list of words highly associated to the critical lure) (Roediger & McDermott, 1995) or the introduction of misinformation. As the authors pointed out, however, the Deese/Roediger-McDermott paradigm is not a true false memory paradigm—that is, the implanting of previously nonexistent information. Pezdek and Lam concluded that false memories and flawed memories should not be conflated, and that the term *false memory* should not be indiscriminately applied to experimental studies on memory, since the public generally extrapolated the findings to abused patients.

Predictably, following publication of this article, the rhetoric erupted once again. Wade and colleagues (2007) disputed the need to apply a narrow definition of false memory to experimental paradigms in the literature. Pezdek later wrote that the main effect of the article was "[to] obfuscate rather than clarify the discussion of false memory" (Pezdek, 2007). These articles show that we are no closer to consensus regarding the topic of false memory than we were a decade ago.

Memory in Patients with Abuse-Related PTSD

Empirical studies do show, however, that patients with early abuse and the diagnosis of PTSD or other stress-related mental disorders have a variety of memory problems (Buckley, Blanchard, & Neill, 2000; Elzinga & Bremner, 2002). Adults with early childhood abuse (Bremner et al., 1995) were found to have deficits in verbal declarative memory function based on neuropsychological testing (Wechsler Memory Scale and Selective Reminding Test); similar findings were found in traumatized children (Moradi, Doost, Taghavi, Yule, & Dalgleish, 1999). One study in adult women with a history of childhood sexual abuse–related PTSD (Bremner, Vermetten, Nafzal, & Vythilingam, 2004) showed that verbal declarative memories are specifically associated with PTSD and are not a nonspecific effect of trauma exposure. Another study of women with early childhood sexual abuse in which some, but not all, of the patients had PTSD showed

no difference between abused and nonabused women (Stein, Hanna, Vaerum, & Koverola, 1999). Children with PTSD related to mixed causes had deficits in verbal IQ compared to controls (Saigh, Yasik, Oberfield, Halamandaris, & Bremner, 2006). Another study in Lebanese youth with war-related PTSD showed deficits in scholastic performance compared to traumatized non-PTSD and nontraumatized youth (Saigh, Mroweh, & Bremner, 1997). Other types of memory disturbances studies in PTSD include gaps in memory for everyday events (dissociative amnesia) (Bremner, Steinberg, Southwick, Johnson, & Charney, 1993) and an attentional bias for trauma-related material (Moradi, Taghavi, Neshat-Doost, Yule, & Dalgleish, 2000). These studies suggest that traumas such as early abuse with associated PTSD result in deficits in verbal declarative memory.

In the 1994 comment by Loftus and colleagues on the report of Williams about 38% forgetting childhood abuse, the authors, after dismissing "repression," took on "amnesia," which they described as "trying to puff up [forgetting] with a scientific name to make it appear exotic . . . an example of psychological 'spin-doctoring,' the merging of science and politics."

However, spin doctors were not responsible for the description of the diagnosis of dissociative amnesia, which is an official disorder of the *Diagnostic and Statistical Manual of Mental Disorders*. This is the most common dissociative presentation of patients with PTSD, involving patients who have gaps in memory that are not due to normal forgetting and which can go from minutes to hours to days (Bremner et al., 1993). These symptoms of dissociative amnesia can include a lack of memory for episodes of childhood abuse. Some have argued that dissociative amnesia cannot be empirically verified; however, the same argument could be made for hallucinations in schizophrenics. The gold standard for psychiatric diagnosis continues to be self-reporting of symptoms.

Two studies have specifically looked at false memory paradigms in women with a history of childhood sexual abuse. Clancy, Schacter, McNally, and Pitman (2000) found that women with a history of delayed recall of childhood sexual abuse had an increase in false recall of the critical lure in the Deese/Roediger-McDermott paradigm. Bremner, Shobe, & Kihlstrom (2000) found that women with early childhood sexual abuse–related PTSD had higher rates of false recall on the Deese/Roediger- McDermott paradigm compared to abused non-PTSD women, nonabused non-PTSD women, and normal men. Given the range of

memory problems in PTSD patients, one interpretation of these findings is that there is a tendency to "fill in" facts when concrete declarative memory fails, as seen in patients with, for instance, hepatic encephalopathy, who will confabulate when presented with a false start to an autobiographical story.

Neurobiology of PTSD: Relevance to Memory Recall of Abuse

PTSD is associated with long-term changes in the function and structure of brain regions and neurochemical systems involved in the stress response (Bremner, 2002; Bremner, 2005b; Pitman, 2001; Vermetten & Bremner, 2002a, 2002b) (Fig. 1.1). Brain regions that are felt to play an important role in PTSD include hippocampus, amygdala, and medial prefrontal cortex. Cortisol and norepinephrine are two neurochemical systems that are critical in the stress response (Fig. 1.1). The neurobiology of PTSD is reviewed below as a background to the development of a model by which

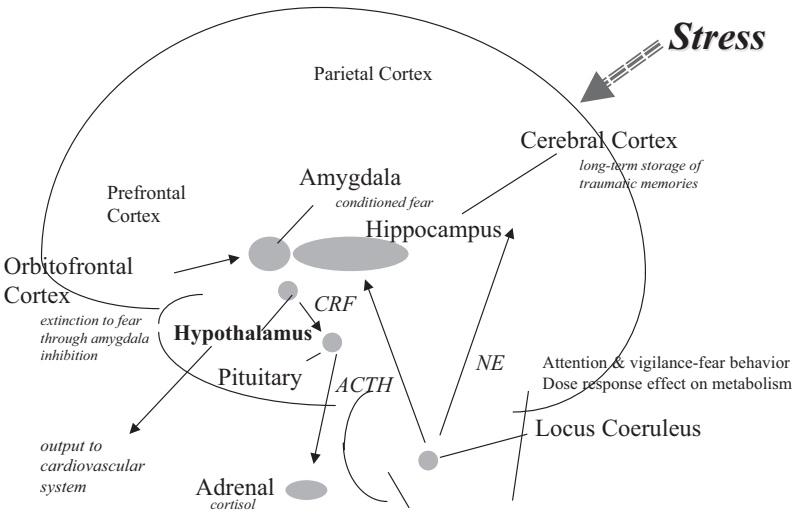

FIGURE 1.1. Functional neuroanatomy of traumatic stress. Lasting effects of trauma on the brain, showing long-term dysregulation of norepinephrine and cortisol systems and vulnerable areas of hippocampus, amygdala, and medial prefrontal cortex that are affected by trauma. ACTH: adrenocorticotropic hormone; CRF: corticotropin-releasing factor; NE: norepinephrine.

early abuse affects circuits and systems involved in memory, potentially leading to alterations in memory of early abuse.

The corticotropin-releasing factor (CRF)/hypothalamic-pituitary-adrenal (HPA) axis system plays an important role in the stress response. CRF is released from the hypothalamus, with stimulation of adrenocorticotropin hormone (ACTH) release from the pituitary, resulting in glucocorticoid (cortisol in humans) release from the adrenal, which in turn has a negative feedback effect on the axis at the level of the pituitary as well as central brain sites including hypothalamus and hippocampus. Cortisol has a number of effects that facilitate survival. In addition to its role in triggering the HPA axis, CRF acts centrally to mediate fear-related behaviors (Arborelius, Owens, Plotsky, & Nemeroff, 1999) and triggers other neurochemical responses to stress such as the noradrenergic system via the brainstem locus coeruleus (Melia & Duman, 1991). Stress also results in activation of the noradrenergic system, centered in the locus coeruleus. Noradrenergic neurons release a transmitter throughout the brain that is associated with an increase in alerting and vigilance behaviors, critical for coping with acute threat (Abercrombie & Jacobs, 1987; Bremner, Krystal, Southwick, & Charney, 1996b, 1996c).

There is increasing interest in the relation between trauma and memory (Elzinga & Bremner, 2002). Patients with trauma-related disorders such as PTSD demonstrate a wide range of deficits in memory. Brain areas, including hippocampus, amygdala, and medial prefrontal cortex, may mediate these alterations in memory (Bremner, 2003a) (Fig. 1.2). The hippocampus, a brain area involved in verbal declarative memory, is very sensitive to the effects of stress. Stress in animals was associated with damage to neurons in the CA3 region of the hippocampus (which may be mediated by hypercortisolemia, decreased brain-derived neurotrophic factor, and/or elevated glutamate levels) and inhibition of neurogenesis (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998; Magarinos, McEwen, Flugge, & Fluchs, 1996; McEwen et al., 1992; Nibuya, Morinobu, & Duman, 1995; Sapolsky, 1996; Sapolsky, Uno, Rebert, & Finch, 1990). High levels of glucocorticoids seen with stress were also associated with deficits in new learning (Diamond, Fleshner, Ingersoll, & Rose, 1996; Luine, Villages, Martinex, & McEwen, 1994). However, whether physiological levels of cortisol are actually toxic to the hippocampus continues to be debated (de Kloet, Oitzl, & Joels, 1999).

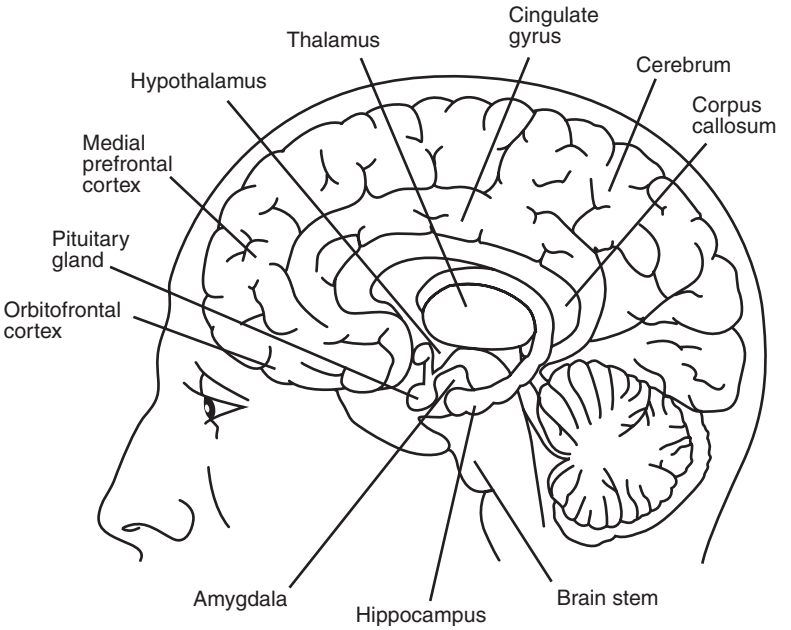

FIGURE 1.2. Brain areas involved in memory and the stress response. Brain areas that mediate memory, including the hippocampus, amygdala, and anterior cingulate, have been shown in brain imaging studies to be altered in patients with early-abuse-related PTSD. *Source:* Bremner, J. D. *Does Stress Damage the Brain?* Fig. 2.2, p. 44.

Antidepressant treatments were shown to block the effects of stress and/or promote neurogenesis (Czeh et al., 2001; Lucassen, Fuchs, & Czeh, 2004; Malberg, Eisch, Nestler, & Duman, 2000; Nibuya et al., 1995; Santarelli et al., 2003a). It has also been found that phenytoin blocks the effects of stress on the hippocampus, probably through modulation of excitatory amino acid–induced neurotoxicity (Watanabe, Gould, Cameron, Daniels, & McEwen, 1992). Other agents, including tianeptine, dihydroepiandosterone (DHEA), and fluoxetine, have similar effects (Czeh et al., 2001; D'Sa & Duman, 2002; Duman, 2004; Duman, Heninger, & Nestler, 1997; Duman, Malberg, & Nakagawa, 2001; Garcia, 2002; Lucassen et al., 2004; Malberg et al., 2000; McEwen & Chattarji, 2004). There is new evidence that neurogenesis is necessary for the behavioral effects of antidepressants (Santarelli et al., 2003b; Watanabe, Gould, Daniels, Cameron, & McEwen, 1992), although this continues to be a source of debate (Duman, 2004; Henn & Vollmayr, 2004).

The hippocampus demonstrates an unusual capacity for neuronal plasticity and regeneration. In addition to findings noted above related to the negative effects of stress on neurogenesis, it has recently been demonstrated that changes in the environment—for example, social enrichment or learning—can modulate neurogenesis in the dentate gyrus of the hippocampus and slow the normal age-related decline in neurogenesis (Gould, Beylin, Tanapat, Reeves, & Shors, 1999; Kempermann, Kuhn, & Gage, 1998). Rat pups that were handled frequently within the first few weeks of life (i.e., were picked up and then returned to their mother) had increased Type II glucocorticoid receptor binding that persisted throughout life, with increased feedback sensitivity to glucocorticoids and reduced glucocorticoid-mediated hippocampal damage in later life (Meaney, Aitken, van Berkel, Bhatnager, & Sapolsky, 1988). These effects appear to be due to a type of "stress inoculation" from the mothers' repeated licking of the handled pups (Liu, Diorio, Day, Francis, & Meaney, 2000). Considered together, these findings suggest that early in the postnatal period there is a naturally occurring brain plasticity in key neural systems that may "program" an organism's biological response to stressful stimuli. These findings may have implications for victims of childhood abuse.

The few studies of the effects of early stress on neurobiology conducted in clinical populations of traumatized children have generally been consistent with findings from animal studies (Cicchetti & Rogosch, 2001; Cicchetti & Walker, 2001; Gunnar & Vazquez, 2006; Hart, Gunnar, & Cicchetti, 1996). Research in traumatized children has been complicated by issues related to psychiatric diagnosis and assessment of trauma (Cicchetti & Walker, 2001). Some studies have not specifically examined psychiatric diagnosis, while others have focused on children with trauma and depression, and others on children with trauma and PTSD. Sexually abused girls (in which effects of specific psychiatric diagnoses was not examined) had normal baseline cortisol and blunted ACTH response to CRF (De Bellis et al., 1994), while women with childhood abuse–related PTSD had hypercortisolemia (Lemieux & Coe, 1995). Another study of traumatized children in which the diagnosis of PTSD was established showed increased levels of cortisol measured in 24-hour urine samples (De Bellis et al., 1999a). Emotionally neglected children from a Romanian orphanage had elevated cortisol levels over a diurnal period

compared to controls (Gunnar, Morison, Chisolm, & Schuder, 2001). Maltreated school-aged children with clinical-level internalizing problems had elevated cortisol compared to controls (Cicchetti & Rogosch, 2001). Depressed preschool children showed increased cortisol response to separation stress (Luby et al., 2003). Adult women with a history of childhood abuse showed increased suppression of cortisol with low-dose (0.5 mg) dexamethasone (Stein, Yehuda, Koverola, & Hanna, 1997). Women with PTSD related to early childhood sexual abuse showed decreased baseline cortisol based on 24-hour diurnal assessments of plasma cortisol, increased cortisol pulsatility (Bremner, Vermetten, & Kelley, in press), and exaggerated cortisol response to stressors (traumatic stressors [Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, in press] more than neutral cognitive stressors) (Bremner et al., 2002). We also found that patients with PTSD had less of an inhibition of memory function with synthetic cortisol (dexamethasone) than normal subjects (Bremner, Vythilingam, Vermetten, Newcomer, & Charney, 2005b). In a study of ACTH response to CRF challenge in children with depression with and without a history of childhood abuse, children with depression and abuse had an increased ACTH response to CRF challenge compared to children with depression without abuse. These children were in a chaotic environment at the time of the study, indicating that the ongoing stressors may have played a role in the potentiation of the ACTH response to CRF (Kaufman et al., 1997). Adult women with depression and a history of early childhood abuse had an increased cortisol response to a stressful cognitive challenge relative to controls (Heim et al., 2000) and a blunted ACTH response to CRF challenge (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001). These studies suggest that early abuse is associated with long-term changes in the HPA axis.

Studies have also shown changes in the brain in patients with a history of early stress and PTSD as well as other mental disorders. A 12% reduction in left hippocampal volume in 17 patients with childhood abuse–related PTSD compared to 17 case-matched controls was found that was significant after controlling for confounding factors (Bremner et al., 1997) (Fig. 1.3) (also see color insert). In a recent meta-analysis, we pooled data from all of the relevant published studies and found smaller hippocampal volume for both the left and the right sides, equally in adult men and women with chronic PTSD (Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005).

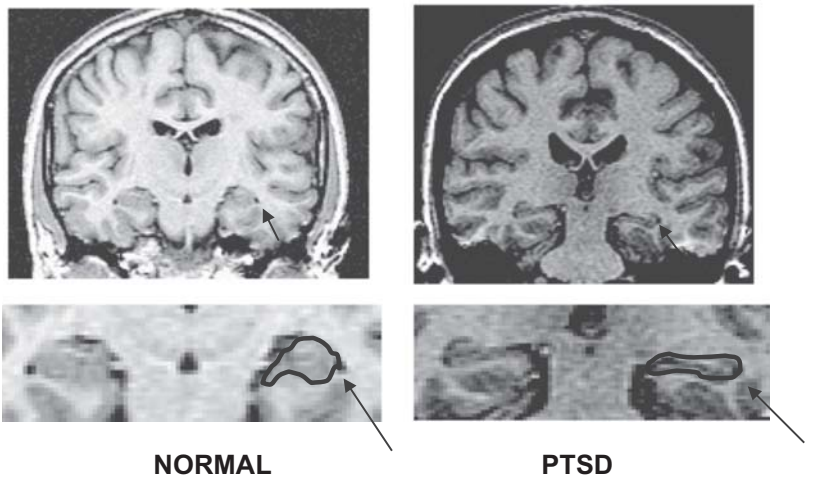

FIGURE 1.3. Hippocampal volume reduction in PTSD on magnetic resonance imaging (MRI). There is smaller hippocampal volume in this patient with PTSD (right) compared to a control (left). *Source*: Bremner, J. D. Brain Imaging Handbook. Fig. 6.3, p. 101.

We hypothesize that stress-induced hippocampal dysfunction may mediate many of the symptoms of abuse-related PTSD that are related to memory dysregulation, including both explicit memory deficits as well as fragmentation of memory in abuse survivors.

We have also found smaller hippocampal volume in patients with other abuse-related mental disorders. Both women with early abuse and dissociative identity disorder (DID) (Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006) and women with early abuse and borderline personality disorder (BPD) (Schmahl, Vermetten, Elzinga, & Bremner, 2003b) had smaller hippocampal volume than controls.

In addition to the hippocampus, other brain structures, including the amygdala and prefrontal cortex, have been implicated in a neural circuitry of stress. The amygdala is involved in memory for the emotional valence of events and plays a critical role in the acquisition of fear responses. The medial prefrontal cortex includes the anterior cingulate gyrus (Brodmann's area 32) and subcallosal gyrus (area 25), as well as orbitofrontal cortex. Lesion studies demonstrated that the medial prefrontal cortex modulates emotional responsiveness through inhibition of amygdala function (Morgan & LeDoux, 1995). Conditioned fear responses are extinguished

following repeated exposure to the conditioned stimulus in the absence of the unconditioned (aversive, e.g., electric shock) stimulus. This inhibition appears to be mediated by medial prefrontal cortical inhibition of amygdala responsiveness (Quirk, Garcia, & Gonzalez-Lima, 2006).

Animal studies also show that early stress is associated with a decrease in the branching of neurons in the medial prefrontal cortex (Radley et al., 2004). Women with PTSD related to childhood sexual abuse had smaller anterior cingulate volumes based on MRI measurements (Kitayama et al., 2005).

Based on findings related to the effects of antidepressants on neurogenesis, we assessed the effects of the selective serotonin reuptake inhibitor (SSRI) paroxetine on outcomes related to function of the hippocampus. We studied 28 patients with PTSD and treated them for up to a year with variable doses of paroxetine. Twenty-three patients completed the course of treatment, and MRI post-treatment was obtained in 20 patients. Neuropsychological testing was used to assess hippocampal-based declarative memory function and MRI was used to assess hippocampal volume before and after treatment. Treatment resulted in significant improvements in verbal declarative memory and a 4.6% increase in mean hippocampal volume. These findings suggested that long-term treatment with paroxetine is associated with improvement of verbal declarative memory deficits and an increase in hippocampal volume in PTSD (Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003).

Functional neuroimaging studies have been performed to map out the neural circuitry of PTSD related to early abuse (Bremner, 2003b; Bremner, 2005b; Bremner & Vermetten, 2001). These studies are consistent with dysfunction in a network of related brain areas including amygdala, medial prefrontal cortex, and hippocampus. We measured brain blood flow with positron emission tomography (PET) and $[^{15}O]H_2O$ during exposure to personalized scripts of childhood sexual abuse. Twenty-two women with a history of childhood sexual abuse underwent injection of $H_2[^{15}O]$ followed by PET imaging of the brain while listening to neutral and traumatic (personalized childhood sexual abuse events) scripts. Brain blood flow during exposure to traumatic versus neutral scripts was compared between sexually abused women with and without PTSD. Memories of childhood sexual abuse were associated with greater increases in blood flow in portions of anterior prefrontal cortex (superior and middle frontal gyri-Areas 6 and 9), posterior cingulate (Area 31), and motor cortex

in sexually abused women with PTSD compared to sexually abused women without PTSD. Abuse memories were associated with alterations in blood flow in medial prefrontal cortex, with decreased blood flow in subcallosal gyrus-Area 25, and a failure of activation in anterior cingulate-Area 32. There was also decreased blood flow in right hippocampus, fusiform/inferior temporal gyrus, supramarginal gyrus, and visual association cortex in PTSD relative to non-PTSD women (Bremner et al., 1999a). This study replicated findings of decreased function in medial prefrontal cortex and increased function in posterior cingulate in subjects with combat-related PTSD during exposure to combat-related slides and sounds (Bremner et al., 1999b).

In another study by Shin et al. (1999), 8 women with childhood sexual abuse and PTSD were compared to 8 women with abuse without PTSD using PET during exposure to script-driven imagery of childhood abuse. The authors found increases in orbitofrontal cortex and anterior temporal pole in both groups of subjects, with greater increases in these areas in the PTSD group. PTSD patients showed a relative failure of anterior cingulate/medial prefrontal cortex activation compared to controls. The PTSD patients (but not controls) showed decreased blood flow in anteromedial portions of prefrontal cortex and left inferior frontal gyrus.

These studies have relied on specific traumatic cues to activate personalized traumatic memories and PTSD symptoms in patients with PTSD. Another method to probe neural circuits in PTSD is to assess neural correlates of retrieval of emotionally valenced declarative memory. In this type of paradigm, instead of using a traditional declarative memory task, such as retrieval of word pairs like "gold-west," which has been the standard of memory research for several decades, words with emotional valence, such as "stench-fear," are utilized (Bremner et al., 2001). We used PET in the examination of neural correlates of retrieval of emotionally valenced declarative memory in 10 women with a history of childhood sexual abuse and the diagnosis of PTSD and 11 women without abuse or PTSD. We hypothesized that retrieval of emotionally valenced words would result in an altered pattern of brain activation in patients with PTSD similar to that seen in prior studies of exposure to cues of personalized traumatic memories. PTSD patients during retrieval of emotionally valenced word pairs showed greater decreases in blood flow in an extensive area that included orbitofrontal cortex, anterior cingulate, and medial prefrontal cortex (Brodmann's Areas 25, 32, 9), left hippocampus,

and fusiform gyrus/inferior temporal gyrus, with increased activation in posterior cingulate, left inferior parietal cortex, left middle frontal gyrus, and visual association and motor cortex (Fig. 1.4) (also see color insert). There were no differences in patterns of brain activation during retrieval of neutral word pairs between patients and controls.

Another study examined neural correlates of the Stroop task in sexually abused women with PTSD. The Stroop task involves color-naming semantically incongruent words (e.g., the word "green" is printed in the color red, and subjects are asked to name the color of the word). The Stroop task has consistently been found to be associated with activation of the anterior cingulate in normal subjects, an effect attributed to the divided attention or inhibition of responses involved in the task. Emotional Stroop tasks (e.g., where a trauma-specific word like "rape" is printed in a certain color, and the subject is asked to name the color) in abused women with PTSD have also been shown to be associated with a delay in color naming(Foa, Feske, Murdock, Kozak, & McCarthy, 1991). Women with early childhood sexual abuse–related PTSD (n = 12) and women with abuse but without PTSD (n = 9) underwent PET measurement of

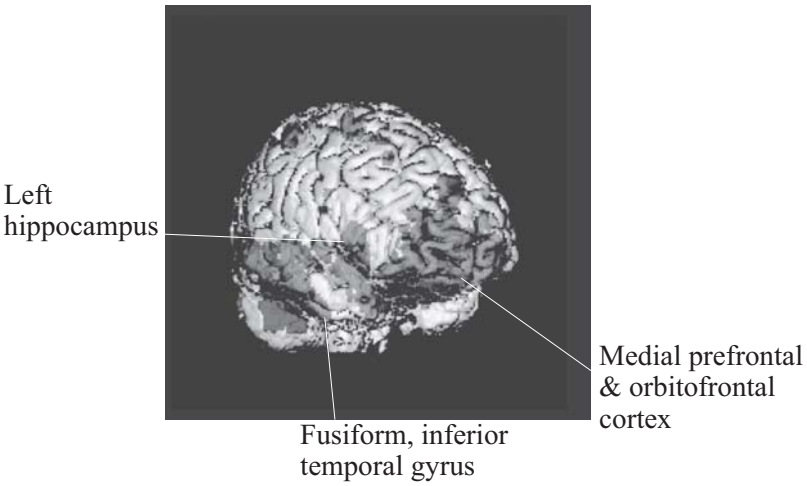

FIGURE 1.4. Decreased medial prefrontal function with exposure to emotionally valenced words like "rape-mutilate." There was a decrease in medial prefrontal and hippocampal blood flow with exposure to trauma-related words in women with a history of early-childhood-abuse-related PTSD compared to controls. *Source:* Bremner et al., 2004.

cerebral blood flow during exposure to control, color Stroop, and emotional Stroop conditions. Women with abuse with PTSD (but not abused non-PTSD women) had a relative decrease in anterior cingulate blood flow during exposure to the emotional (but not color) classic Stroop task. During the color Stroop there were also relatively greater increases in blood flow in non-PTSD compared with PTSD women in right visual association cortex, cuneus, and right inferior parietal lobule. These findings were consistent with dysfunction of the anterior cingulate/medial prefrontal cortex in women with early abuse–related PTSD (Bremner et al., 2003a).

We compared hippocampal function and structure in 33 women with and without early childhood sexual abuse and PTSD. Women with abuse with and without PTSD were studied during encoding of a verbal memory paragraph compared to a control task in conjunction with measurement of brain blood flow with PET. There were significantly greater increases in blood flow during verbal memory encoding in the hippocampus in non-PTSD abused women relative to PTSD women. PTSD women also had smaller left hippocampal volume on MRI volumetrics compared to abused women without PTSD and non-abused, non-PTSD women. Differences in hippocampal activation were statistically significant after covarying for left hippocampal volume, suggesting that failure of activation was not secondary to smaller hippocampal volume in patients with PTSD (Bremner et al., 2003b).

We have extended functional imaging studies to patients with abuse-related mental disorders other than PTSD. In a study of women with early trauma and BPD, exposure to scripts of an abandonment situation were associated with decreased medial prefrontal and hippocampal blood flow (Schmahl et al., 2003a). Decreased medial prefrontal/anterior cingulate was seen in BPD women with early abuse during exposure to a script of their early trauma (Schmahl, Vermetten, Elzinga, & Bremner, 2004).

Although some studies have demonstrated increased amygdala function in PTSD, the experience to date suggests that increased amygdala involvement is not necessarily seen in all of the study paradigms applied to PTSD. It is more likely that specific tasks are required to show increased amygdala function in PTSD. For instance, we found increased amygdala activation during acquisition of fear in a classical fear conditioning paradigm in women with early childhood sexual abuse–related PTSD (Bremner et al., 2005a) (Fig. 1.5) (also see color insert).

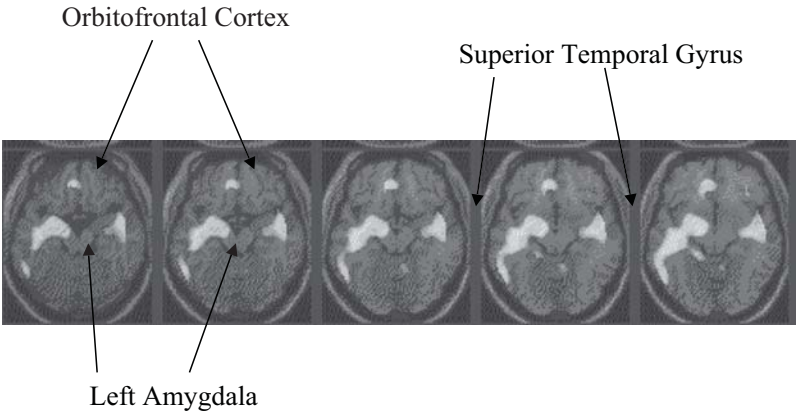

FIGURE 1.5. Increased amygdala function during acquisition of conditioned fear responses in women with early childhood abuse and PTSD. Lighter areas represent bilateral amygdala activation. There was greater amygdala activation with acquisition of fear responses (pairing of conditioned stimulus and unconditioned stimulus) in women with PTSD compared to controls; $z > 3.09$, $p < 0.001$. *Source:* Bremner et al., 2005.

Fewer brain-imaging studies have been performed in children with PTSD. Several studies have shown alterations in electroencephalogram (EEG) measures of brain activity in children with a variety of traumas who were not selected for diagnosis compared to healthy children. About half of the children in these studies had a psychiatric diagnosis. Abnormalities were located in the anterior frontal cortex and temporal lobe and were localized to the left hemisphere (Ito et al., 1993; Schiffer, Teicher, & Papanicolaou, 1995). Two studies have found reductions in brain volume in children with trauma and PTSD symptoms (Carrion et al., 2001; De Bellis et al., 1999b). One group did not find reductions in hippocampal volume either at baseline or over a longitudinal period (De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; De Bellis et al., 1999b) while another group found an 8.5% reduction in hippocampal volume that was not significant after controlling for smaller brain volumes in the PTSD group (Carrion et al., 2001). One study used single-voxel proton magnetic resonance spectroscopy (proton MRS) to measure relative concentration of N-acetylaspartate and creatinine (a marker of neuronal viability) in the anterior cingulate of 11 children with maltreatment-related PTSD and 11 controls. The authors found a reduction in the ratio of N-acetylaspartate to creatinine in PTSD patients relative to controls (De Bellis, Keshavan,

Spencer, & Hall, 2000). Studies have also found smaller size of the corpus callosum in children with abuse and PTSD relative to controls (De Bellis et al., 1999b), as well as larger volume of the superior temporal gyrus (De Bellis et al., 2002). In a study of abused children in whom diagnosis was not specified, there was an increase in T2 relaxation time in the cerebellar vermis, suggesting dysfunction in this brain region (Anderson, Teicher, Polcari, & Renshaw, 2002).

In summary, adults with early-abuse-related mental disorders show evidence of decreased medial prefrontal and hippocampal function and structure, as well as increased amygdala function. Although changes in medial prefrontal and corpus callosum structure were found in children with PTSD, changes in hippocampal volume were not. This is explainable by findings in animals showing that early stress does not manifest as changes in hippocampal structure until adulthood (Brunson, Eghbal-Ahmadi, Bender, Chen, & Baram, 2001; Brunson et al., 2005).

These findings have implications for understanding alterations in memories of abuse in patients with abuse-related PTSD (Bremner, 1999; Bremner, 2001; Bremner, Krystal, Charney, & Southwick, 1996a). This hippocampus plays a role in the integration of the individual elements of memory in the context of space and time (Zola-Morgan & Squire, 1990). Dysfunction of the hippocampus in patients with abuse-related PTSD may lead to an inability to effectively retrieve memories of early abuse.

Dissociation is defined as a breakdown in memory, consciousness, and the sense of self. Dissociation at the time of trauma is often seen in trauma victims, and three studies have now found a correlation between smaller hippocampal volume and dissociative symptom severity (Bremner et al., 2003b; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Vermetten et al., 2006). We have hypothesized that dissociation at the time of trauma represents a behavioral correlate of stress-induced hippocampal damage (Bremner et al., 1996a). If so, hippocampally mediated dissociative amnesia may represent a mechanism of altered recall of early abuse.

Neurohormonal Modulation of Memory

Hormones released during stress, including catecholamines and cortisol, modulate the encoding and retrieval of memory (McGaugh, 2000).

Administration of epinephrine (which is released from the adrenal) affects memory retention with an inverted U-shaped curve. Memory improves up to a point and decreases with high doses (Gold & van Buskirk, 1975; Liang, Juler, & McGaugh, 1986). Lower doses of norepinephrine injected into the amygdala promote memory for an inhibitory-avoidance task, while higher doses inhibit memory (Liang, McGaugh, & Yao, 1990). In humans, noradrenergic beta-blocker medications blocked the formation of emotional memories (Cahill, Prins, Weber, & McGaugh, 1994), while enhanced norepinephrine release was associated with enhanced encoding of emotional memories (Southwick et al., 2002). Vasopressin and oxytocin have been shown to modulate memory formation in both animals (McGaugh, 2000) and human subjects (including those with PTSD) (Pitman, Orr, & Lasko, 1993).

Glucocorticoids also affect learning and memory. Elevations of glucocorticoids within the physiological range result in reversible deficits in memory function in animals (Bodnoff et al., 1995; Oitzl & de Kloet, 1992) as well as human subjects (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Lupien, Gillin, & Hauger, 1999; Lupien et al., 1997; Lupien et al., 2002; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Newcomer et al., 1999; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001). Glucocorticoids released during stress, possibly acting through the hippocampus, may explain in part the acutely reversible as well as chronic effects that stress has on declarative memory (de Kloet et al., 1999; Kirschbaum et al., 1996; Porter & Landfield, 1998; Wolf, 2003). Greater deficits are seen in younger subjects in comparison to older subjects, hypothesized to be secondary to age-related decreases in glucocorticoid receptor density (Newcomer, Selke, Kelly, Paras, & Craft, 1995). Impairment of working memory by glucocorticoids may require noradrenergic stimulation to have its effect (Elzinga & Roelofs, 2005). We used a protocol of 1 mg of dexamethasone, followed by 2 mg one day later, and found an impairment in declarative memory function (percent retention of a paragraph after a delay) in healthy subjects but not in patients with depression (Bremner, Vythilingam, Vermetten, Newcomer, & Charney, 2004) or PTSD (Bremner et al., 2005b). We hypothesized that this might be due to disease-related decreases in glucocorticoid receptor function. This is consistent with the idea of PTSD as an "accelerated aging" (Bremner & Narayan, 1998) related to common theories of

progressive hippocampal atrophy and dysfunction in both processes. We have also shown that endogenous cortisol release stimulated by a cognitive stress challenge in healthy subjects impaired delayed recall of words and a spatial memory task (Elzinga, Bakker, & Bremner, 2005). Some studies have shown, however, that endogenous cortisol levels in healthy subjects who became upset during a social speech task were correlated with enhanced delayed memory recall of unpleasant pictures (Abercrombie, Speck, & Monticelli, 2005). These discrepant findings may be related to different effects of endogenous cortisol on recall of verbal versus visual materials.

Stress-related release of neurohormones can influence recall of childhood abuse memories. As noted above, the stress hormones catecholamines and cortisol influence the encoding and retrieval of memory. These neurohormones can be released at varying levels at the time of stress, thus influencing the encoding of traumatic memory. Also, they can be released at varying concentrations in an unpredictable manner at the time of memory retrieval. In addition, as reviewed above, release of these stress hormones is altered in patients with stress-induced mental disorders, which may lead to different outcomes than in healthy subjects.

Conclusions

This chapter has reviewed the neurobiology of stress and memory as it applies to traumatized children and questions related to delayed recall of childhood abuse. Studies of the effects of memory have shown that stressful events are remembered differently than normal events. For instance, evidence from "flashbulb" memory studies showed that emotional events are remembered better than neutral events. Other studies showed that the central features of emotional events are remembered better than peripheral details. Studies in normal children have shown that stressful memories in general are remembered accurately and are typically more resistant to suggestion.

Results from studies of abuse victims related to their ability to remember their abuse events have been varied. Due to the complex nature of abuse, underreporting, and the difficulties of verification, research in this area has been very difficult.

Studies have shown that memory is subject to distortion. However, implausible memories are more difficult to "implant" than plausible

memories, making it less likely that individuals can have memories of traumatic memories "implanted." On the other hand, abuse-related patients with mental disorders have greater memory impairment, making it more likely that they may have "source memory" errors. Consistent with this are studies showing that abused PTSD patients are more susceptible to suggestion on the Deese/Roediger-McDermott paradigm. For these reasons, therapists should proceed with caution in discussions of early abuse and not provide suggestions about abuse that the patient is not aware of.

Neurobiological studies have implications for the recall of abuse. Patients with abuse-related mental disorders have a wide range of memory impairments. At its most extreme, patients with early abuse and DID have a complete breakdown of autobiographical memory, making the accurate recall of personal life experiences more difficult. Patients with abuse-related mental disorders also have smaller hippocampal volume, which we hypothesize is stress related. Altered hippocampal function can be associated with an impairment of memory recall, or the accurate integration of individual elements of memory.

Abuse-related PTSD is also associated with increased amygdala function and decreased function of the medial prefrontal cortex/anterior cingulate. Increased amygdala function is associated with enhanced fear responses, while a failure of medial prefrontal function is associated with a failure of extinction, or inability to turn off the fear response. Deficits in medial prefrontal function are also seen in women with early abuse and BPD. Given the enhanced brain responsiveness to reminders of the trauma, it is anticipated that patients with early-abuse-related psychopathology will avoid reminders of the abuse, which may lead to the development of amnesia.

Changes in stress-responsive hormonal systems may also have an effect on memory in patients with abuse-related mental disorders. Traumatic memories can be both enhanced and impaired depending on release of stress hormones such as cortisol and norepinephrine, as well as the effects of stress on brain areas involved in memory and emotion such as the hippocampus, amygdala, and prefrontal cortex.

Understanding how stress affects memory and the brain will have important implications for the treatment of traumatized children throughout their lives. This area also has implications for public health and for promoting the health of children.

Future studies should examine normal and stress-related memory in children and adults with early childhood abuse–related mental disorders.