Length of Time Between Onset of Childhood Sexual Abuse and Emergence of Depression in a Young Adult Sample: A Retrospective Clinical Report

Martin H. Teicher, M.D., Ph.D.; Jacqueline A. Samson, Ph.D.; Ann Polcari, R.N., C.S., Ph.D.; and Susan L. Andersen, Ph.D.

Objective: Depression is the most common adult outcome of exposure to childhood sexual abuse (CSA). In this study, we retrospectively assessed the length of time from initial abuse exposure to onset of a major depressive episode.

Method: A community-based survey of childhood experiences in 564 young adults aged 18 to 22 years, conducted between 1997 and 2001, identified 29 right-handed female subjects with CSA but no other exposure to trauma. Subjects were interviewed for lifetime history and age at onset of Axis I disorders using the Structured Clinical Interview for DSM-IV Axis I Disorders.

Results: Sixty-two percent (N = 18) of the sexual abuse sample met full lifetime criteria for major depressive disorder. Episodes of depression emerged a mean ± SD of 9.2 ± 3.6 years after onset of exposure to sexual abuse. Mean survival time from onset of abuse to onset of depression for the entire sample was 11.47 years (95% CI = 9.80 to 13.13 years). There was a surge in new cases between 12 and 15 years of age. Mean ± SD time to onset of posttraumatic stress disorder was 8.0 ± 3.9 years.

Conclusions: Exposure to CSA appears to sensitize women to the development of depression and to shift age at onset to early adolescence. Findings from this formative study suggest that clinicians should not interpret the absence of symptoms at the time of CSA as a sign of resilience. Continued monitoring of victims of CSA as they pass through puberty is recommended. Reasons for the time lag between CSA and depression are proposed along with potential strategies for early intervention.

J Clin Psychiatry 2009;70(5):684–691

Received March 22, 2008; accepted July 14, 2008. From the Department of Psychiatry, Harvard Medical School, and the Developmental Biopsychiatry Research Program, McLean Hospital, Belmont, Mass.

This research was supported by RO1 grants to Dr. Teicher from the National Institute of Mental Health (MH-53636) and National Institute on Drug Abuse (DA-017846), along with donor support from NARSAD and the John W. Alden Trust.

Drs. Teicher, Samson, Polcari, and Andersen report no additional financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Martin H. Teicher, M.D., Ph.D., Developmental Biopsychiatry Research Program, McLean Hospital, 115 Mill St., Belmont, MA 02478 (e-mail: martin_teicher@hms.harvard.edu).

Childhood exposure to trauma in general, and sexual abuse in particular, has been linked to a host of adverse consequences. Recent epidemiologic studies suggest that exposure to trauma and household dysfunction accounts for about 50% of the population-attributable risk for major depression and suicide.[1,2] Specific associations between exposure to childhood sexual abuse (CSA) and subsequent development of depressive disorders have been observed in large samples of adults[3–5] as well as in adolescents.[6,7] Depression is the most extensively documented outcome of exposure to CSA in adults,[8] but in children, the most discernible manifestations are sexualized behaviors rather than depression or posttraumatic stress disorder (PTSD).[8]

Despite the numerous studies demonstrating an association between exposure to CSA and emergence of depression, we are not aware of any studies that have specifically reported on the length of time between exposure to CSA and development of major depression. There are several possibilities. One is that depression follows rapidly on the heels of exposure to CSA. Another possibility is that depression emerges after exposure or risk of exposure to CSA has abated.

A third possibility is that CSA does not directly lead to depression but that it sensitizes the individual, enhancing his or her risk of developing depression as he or she passes through adolescence into middle age as part of a neuromaturational process.[9] Major depression can emerge at any age, but the greatest surge in newly emergent cases occurs between 15 and 18 years of age in females.[10] Recent studies indicate that the average age at onset for

major depression is 32 years. Females outnumber males 2:1,[11] with gender differences in prevalence emerging between 11 and 15 years of age.[12] Hence, depression may emerge with an unusually high frequency in CSA-exposed individuals during the 15- to 18-year-old adolescent surge or later in adulthood, as part of the natural course of the disorder. A fourth possibility is that CSA could both sensitize and accelerate the process leading to an earlier age at onset, as has been reported to occur in patients with bipolar[13] or substance abuse[14] disorders. Finally, episodes of major depression may emerge in sensitized individuals only if they are exposed to new losses or traumas, resulting in a very variable onset time between individuals.

Determining the temporal relationship between CSA and onset of depression is difficult, as CSA usually occurs in individuals who have been, or will be, exposed to multiple other forms of trauma.[15,16] However, delineating the time course is a fundamental prerequisite for designing intervention strategies to prevent or minimize the long-term sequelae of abuse and for interrupting the cycle of violence.

To begin to address this issue we retrospectively examined the temporal relationship between CSA and depression in a group of subjects participating in our ongoing studies of trauma[16] who were exposed to CSA but to no other forms of trauma or severe early stress. We now report that there was a mean lag of 9.2 years between onset of CSA and onset of depression and that most of the subjects exposed to early abuse who developed major depression had their first depressive episode between 12 and 15 years of age.

METHOD

Detailed ratings of symptoms and history of exposure to emotional abuse and trauma were collected and analyzed from 564 young adults 18 to 22 years of age (mean ± SD age, 19.8 ± 1.4 years; 385 female and 179 male) who responded to community advertisements requesting either healthy, normal controls or individuals with a history of an unhappy childhood as part of a larger study of childhood abuse.[16] Because a primary goal of the larger study was to examine the relationship between trauma and brain development,[17] subjects were also required to be right-handed, unmedicated, and free of any significant history of fetal, neonatal, or childhood disorders that could adversely affect brain development. The study was approved by the McLean Hospital Institutional Review Board. All subjects gave written informed consent prior to completion of questionnaires and again prior to interview and assessment. The study was conducted between 1997 and 2001.

History of exposure to CSA was obtained in a 2-step process. The first step was self-report, followed by detailed assessment using the semistructured Traumatic Antecedents Interview (TAI).[18] Individuals with CSA were initially identified if they responded in the affirmative to this question: "Have you ever been forced into doing more sexually than you wanted to do or were too young to understand? (By *sexually* we mean being forced against your will into contact with the sexual part of your body or of his/her body)." They were also asked to provide information on their relationship to this individual, number of times they were forced, age at first and last abuse, and whether or not they felt terrified or had their life or another person's life threatened.[16]

Respondents reporting CSA were further evaluated using the TAI, which is a 100-item semistructured interview designed to elicit and evaluate reports of physical abuse, sexual abuse, witnessing violence, physical neglect, emotional neglect, significant separations, losses, verbal abuse, and parental discord.[18] The reliability of TAI variables range from acceptable to excellent (median intraclass R = 0.73).[18]

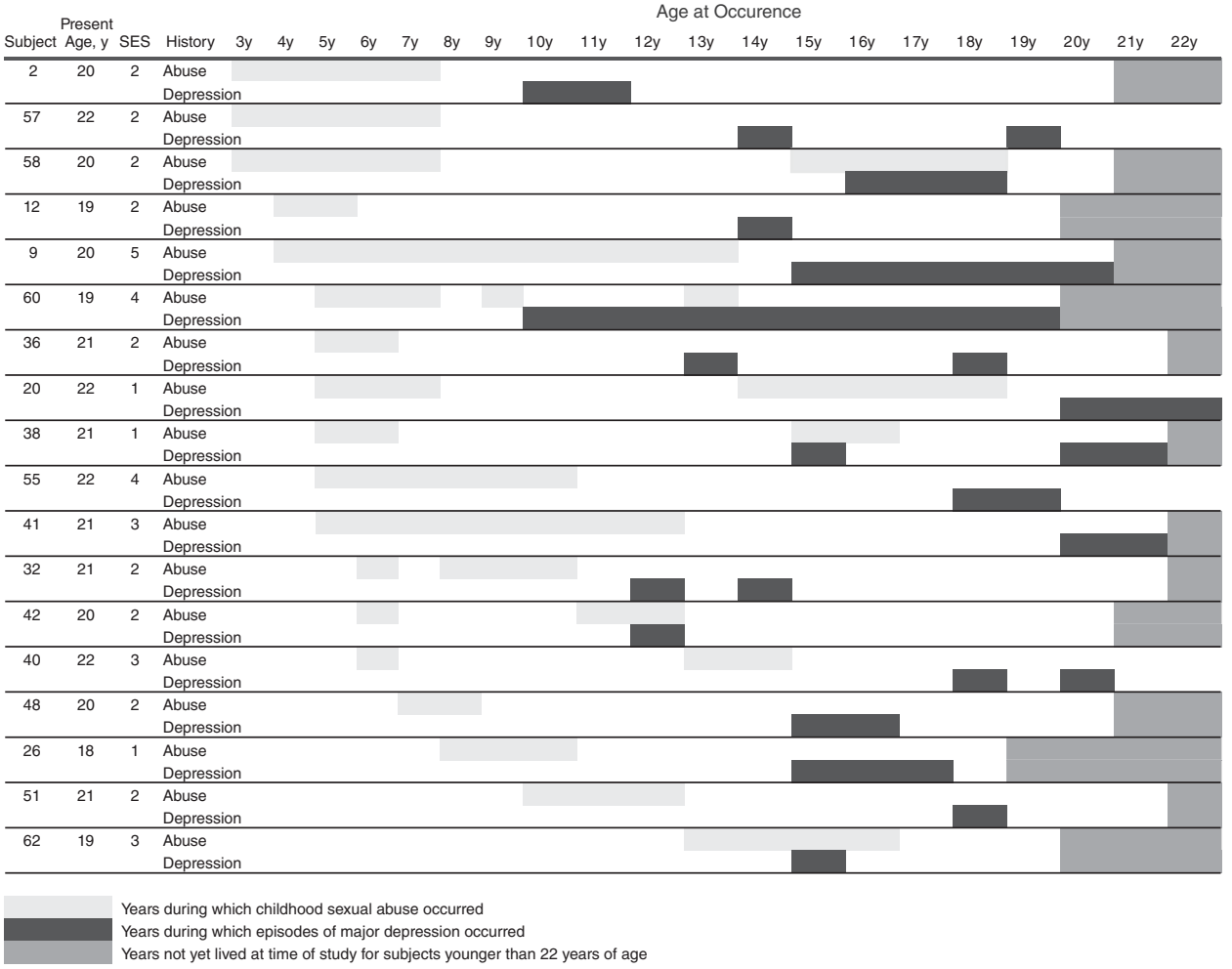
For this formative study, we selected only respondents who indicated, on both self-report and TAI interview, that they experienced 3 or more episodes of forced-contact CSA accompanied by fear or terror. Further, they had not experienced any other types of childhood abuse or other severe stressors (e.g., gang violence, motor vehicle accidents, near-drowning, natural disasters, animal attacks). We required a history of 3 or more exposures on the basis of the assumption that CSA is typically a repeated event and that a major factor affecting brain development may be persistent fear of recurrence. Using these criteria, 29 female and 3 male respondents were identified for study. Results are limited to women due to known gender differences in prevalence rates for depression and the small size of our male sample.

Psychiatric history was assessed by certified mental health clinicians (clinical nurse specialists or Ph.D. psychologists) using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D),[19] and the Diagnostic Interview for Borderline Patients (DIB).[20] Age at onset, assessed as a part of this interview, can be reliably determined through this form of assessment.[21,22]

Kaplan-Meier analysis (SPSS, version 11.0; SPSS, Inc.; Chicago, Ill.) provided mean survival time (± 95% confidence interval [CI]) for onset of CSA and from onset of CSA to emergence of depression. Additional analyses were conducted to examine time between exposure to CSA and onset of PTSD as it became clear that a substantial number of subjects met criteria for this diagnosis.

The resulting sample consisted of 29 women with a mean ± SD age of 20.0 ± 1.3 years. All were in college, and 90% came from a middle-class or higher socioeconomic-status family (mean ± SD socioeconomic status

Figure 1. Relationship Between Age at Experience of Childhood Sexual Abuse and Onset of Depression



Abbreviation: SES = socioeconomic status.

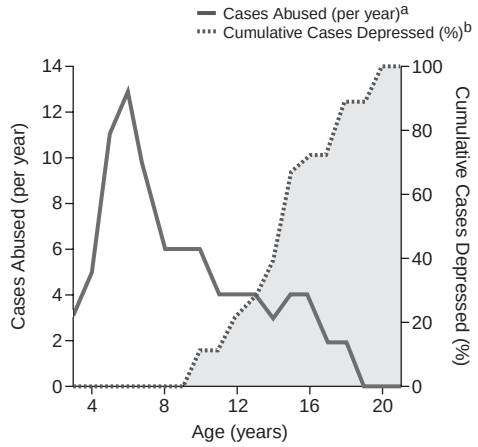
(SES) = 2.3 ± 1.0). The SES score was assigned using the Hollingshead Two-Factor Index of Social Position,[23] which combines level of formal education and level of occupation status into a single score. Lower scores indicate higher socioeconomic status. Reported perpetrators were part of the extended family and/or members of the community, with only 3 perpetrators being stepparents. None of the subjects in this sample reported experiencing CSA by their biologic parents.

RESULTS

As illustrated in Figure 1, subjects who developed major depressive disorder (N = 18) had onset of CSA between 3 and 13 years of age (mean survival to CSA, 6 years; 95% CI = 5 to 7 years) and onset of depression between 10 and 20 years of age (mean survival, 15.0 years; 95% CI = 13.6 to 16.4 years). Eighty-three percent (N = 15) of these subjects experienced significant suicidal ideation during their index episode of major depression. The mean ± SD time from onset of CSA to onset of major depression, in those who developed depression, was 9.2 ± 3.6 years. Mean survival time from onset of CSA to onset of depression for the entire sample was 11.47 years (95% CI = 9.80 to 13.13 years). Mean survival from offset of CSA (first episode if there were multiple perpetrators) was 9.55 years (95% CI = 7.45 to 11.65 years). Figure 2 illustrates the number of cases with a history of depression who experienced CSA in a given year and the cumulative prevalence of depression. Note that many of the subjects who went on to develop major depressive disorder experienced CSA at ages 5 and 6 and that 56% of depressive episodes began between 12 and 15 years of age.

Subjects who met criteria for PTSD (N = 8) had onset of abuse between 3 and 15 years of age (mean survival,

Figure 2. Age at Abuse and Cumulative Incidence of Depression for 18 Childhood Sexual Abuse Subjects Developing Depression



[a]Solid line and left axis indicate number of subjects exposed to childhood sexual abuse at each age.
[b]Dashed line, shaded area, and right axis indicate the percentage of subjects who had an episode of major depression prior to or during each year of age.

7 years; 95% CI = 4 to 9 years) and onset of PTSD between 10 and 19 years of age (mean, 14 years; 95% CI = 12 to 17 years) (Figure 3). The mean survival time from onset of abuse to onset of PTSD was 8 years (95% CI = 5 to 11 years). Five of these subjects had a comorbid history of major depression. In 3 cases, depression and PTSD developed within a year of each other. In 1 case, PTSD preceded depression by 8 years, and, in the other, depression preceded PTSD by 7 years.

Eight CSA-exposed subjects (27.5%) have not so far met diagnostic criteria for major depressive disorder or PTSD. These subjects experienced abuse between 3 and 13 years of age (mean survival, 7 years; 95% CI = 5 to 10 years) (Figure 4). A mean ± SD of 12.3 ± 4.4 years (range, 5–17 years) have elapsed between onset of CSA and age at the time of diagnostic assessment. Mean ± SD duration of abuse exposure in this group was 2.9 ± 2.0 years. Subjects who developed PTSD or depression had a mean ± SD duration of abuse exposure of 4.7 ± 2.5 years ($F = 3.23$, $df = 1,27$; $p = .08$). Eighteen percent of subjects who have not developed depression (2 of 11) had parents with a definite history of depression versus 11% (2 of 18) of the sample who developed depression (Fisher exact test, $p > .6$).

Of interest, 7 of the subjects who developed depression subsequent to exposure to childhood sexual abuse reported a second (or third) sequence of abuse occurring either before or after the onset of depression. We examined this "multiple exposure" subgroup to determine if the time to onset of depression was related to number of sequences of abuse. There was a mean ± SD gap of 4.1 ± 2.3 years between sequences, and depression emerged 2.6 ± 2.4 years after the start of the second sequence. However, while depression tended to occur soon after the second exposure to abuse, there was no statistically significant difference between this group and those with a single abuse sequence in time to onset of depression following onset or offset of the first sequence of abuse. Depression emerged a mean ± SD of 9.1 ± 3.5 years after initial exposure in subjects with a single sequence of CSA and 9.4 ± 4.2 years in subjects with multiple sequences ($F = 0.04$, $df = 1,16$; $p > .8$). Two of 8 subjects developing PTSD and 2 of 8 subjects with neither PTSD nor depression reported multiple sequences. Hence, within this limited sample there was no evidence to suggest that multiple exposure sequences increased the likelihood or hastened the onset of depression or PTSD.

In addition to depression and PTSD, 3 subjects had lifetime diagnoses of dissociative disorders, 2 had obsessive-compulsive disorder, 2 had separation anxiety disorder, 2 had substantial cannabis use, 1 had generalized anxiety disorder, 1 had bulimia nervosa, and 1 had an adjustment disorder. None met criteria for borderline personality disorder.

DISCUSSION

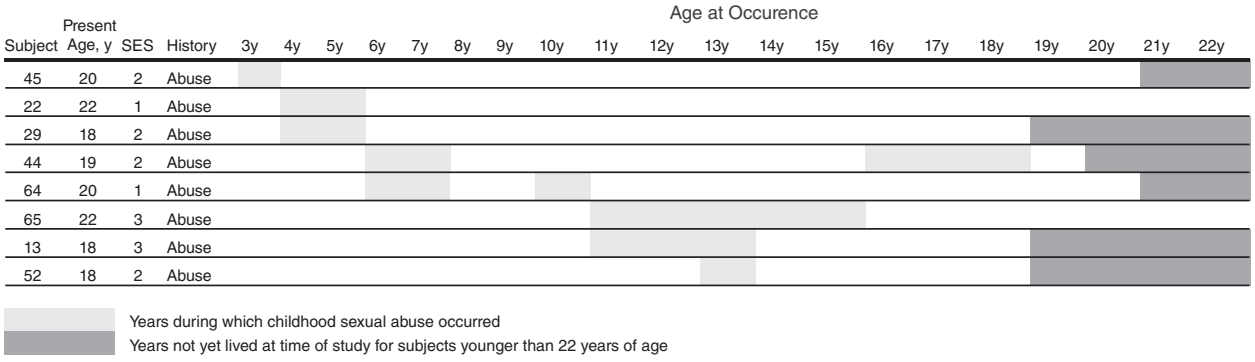
A full 62% (N = 18) of our sample of young adult women with history of exposure to CSA met diagnostic criteria for major depressive disorder, and 45% (N = 13) of the sample met criteria by age 16. The expected prevalence rate for any depressive disorder in females by age 16 is 11.7%,[24] and lifetime prevalence rate for major depression in women in the population at large is about 20%.[12] The elevated rate reported by these CSA subjects is remarkable for many reasons. First, this was a nonclinical sample selected without regard to psychopathology. Second, the entry criteria excluded subjects currently receiving medications or with a history of drug or alcohol abuse. Third, subjects were exposed to only one form of trauma, which is relatively rare (33% of CSA subjects in the original sample), and, finally, at the time of the study, they were younger than the mean age at onset expected for major depressive disorder.

One possibility is that our advertisements seeking individuals with histories of abuse or unhappy childhood could bias recruitment to include a preponderance of individuals with depression. Of interest, 8 of the 29 subjects reported in this article answered the advertisement for normal controls. There were no significant differences between CSA subjects responding to the advertisement targeting normal controls or targeting individuals with unhappy childhood in rates of present or past depression or PTSD, no significant differences in ages at onset or offset of abuse, and no significant differences in the time lag

Figure 3. Relationship Between Age at Experience of Childhood Sexual Abuse and Onset of Posttraumatic Stress Disorder (PTSD)

Abbreviation: SES = socioeconomic status.

Figure 4. Age at Experience of Childhood Sexual Abuse in Subjects Without History of Depression or Posttraumatic Stress Disorder



Abbreviation: SES = socioeconomic status.

between age at abuse and onset of Axis I pathology. The high rate of occurrence of major depression in this sample is consonant with the epidemiologic finding of Kendler et al.[5] that CSA involving intercourse was associated with a 3.14-fold increase in lifetime prevalence of major depression. We did not require CSA subjects to have experienced intercourse but required at least 3 episodes of forced sexual contact accompanied by fear or terror, which probably also ensured that the experience was highly traumatic.

The high rate of occurrence of depression in young adult women with a history of CSA was not, however, the major point of the study. High prevalence rates for major depression have been reported in large epidemiologic samples of older adults with CSA.[3–5] The key finding of this formative study is that episodes of major depression or PTSD did not immediately occur following exposure to CSA but took several years to emerge. Further, the onset of depression did not directly coincide with the abatement of CSA. Rather, there was typically a long delay between exposure to CSA and onset of depression, with a surge in new cases occurring between 12 and 15 years of age. This is somewhat earlier than the peak surge of newly emergent cases reported to occur between 15 and 18 years of age in a prospective longitudinal study of a contemporary birth cohort.[10] Overall, these findings are most compatible with the hypothesis that CSA sensitizes the individual to later emergence of depression during adolescence and that it shifts the peak period of risk from midadolescence to early adolescence. This finding is consistent with a

previous report of earlier age at onset of depression in women with histories of childhood abuse.[25]

Clinically, this is important information as it shows that there may be substantial time available in which to potentially intervene to minimize the most common major psychiatric consequences of CSA. Moreover, these findings warn against the fallacy of assuming that a child who experienced CSA is out of danger if she did not develop depression or PTSD during, or within months of, her period of exposure. Finally, these findings also suggest a need for extra vigilance when working with children with a history of CSA as they pass through puberty into early adolescence.

These are important caveats as some therapists maintain that it is inappropriate to treat children for sexual abuse per se and that treatment needs to be directed toward specific presenting conditions.[26] Some therapists argue that half of all cases of CSA appear asymptomatic[27] and that, in such cases of extrafamilial abuse, treatment can be short-term and problem-focused, assisting parents to provide the psychological and social support their child needs.[26] This perspective may be shortsighted. What we recognize as common disorders in adult medicine and psychiatry may be the result of what we failed to recognize or treat in childhood.[15]

This sample of young adult subjects exposed to repeated bouts of CSA had high lifetime prevalence rates for major depressive disorder and PTSD, yet none met criteria for borderline personality disorder. This may seem surprising as CSA is frequently considered a major risk factor for developing borderline personality disorder.[28] There are several possible reasons why we failed to find an association. First, age at onset for borderline personality disorder is typically between 19 and 34 years of age, so our subjects were just entering the age of risk. Second, they were in college, which can provide a significant degree of external structure and opportunity for less demanding relationships. Third, research by Heffernan and Cloitre[29] suggests that the development of borderline personality disorder in women exposed to CSA is associated with co-occurrence of maternal physical or verbal abuse. We excluded individuals from the study who had these, or any other, multiple abusive experiences. Fourth, none of the subjects in this study indicated that the perpetrator was a biologic parent, and only 3 subjects reported abuse by a stepparent. The predominantly extrafamilial nature of the abuse may have spared these individuals from some of the more pathologic psychosocial consequences of CSA.[16]

Given the high risk for major depression that appears to be associated with CSA, might there be effective intervention strategies that can provide prophylaxis? Answers to this question will most likely depend on (1) the mechanisms mediating or moderating this risk and (2) the constellation of factors responsible for the emergence of depression in adolescence or adulthood in sensitized individuals.

The first consideration is the potential ways that exposure to early stress can exert a sensitizing affect on brain development or later behavior. Theoretically, this can occur through epigenetic modifications[30,31] that program stress response systems[32] and through establishment of set points for neurotransmitter function or neurotrophic factors.[33]

Of particular relevance is the finding by Caspi et al.[34] on the role of the serotonin transporter in moderating the influence of stressful life events on susceptibility to major depression. Briefly, these investigators found in a prospective, longitudinal study that the short-allele functional polymorphism in the serotonin transporter gene linked promoter region (5-HTTLPR), associated with reduced transcriptional efficiency, markedly increased risk for developing depression in individuals exposed to childhood maltreatment. However, this polymorphism did not increase risk for developing depression in the absence of early stress.[34] Since the serotonin transporter is largely responsible for inactivation of released serotonin, one interpretation of this finding is that risk for depression stems from overactivation of the serotonin system during development. This may seem counterintuitive given the role of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression. However, this hypothesis fits with preclinical observation that certain enduring effects of early experience are mediated through transient alterations in serotonin release[35] and that exposure to drugs that enhance serotonin neurotransmission during early life result in depressive symptoms during adulthood.[36,37]

If overactivation of serotonin neurotransmission during development is a moderating or mediating factor responsible for sensitization, then certain therapeutic hypotheses follow. First, drugs that diminish firing rate of serotonin neurons, such as the anxiolytic drug buspirone,[38] may have prophylactic properties if administered acutely. Second, SSRIs administered early may paradoxically increase risk, particularly in individuals with the protective polymorphism associated with higher transcriptional efficiency of the serotonin transporter.

Delayed onset of symptoms may have some relationship to the overproduction and pruning of dendrites, axons, synapses, and receptors that occur during postnatal development. We have previously reported that exposure to early stress in rats is associated with a significant reduction in hippocampal synaptic density. This reduction occurs as a consequence of diminished synaptic overproduction and is not apparent until after puberty.[39] This may help to explain why 5 studies[40–44] reported reduced hippocampal volume in adults with histories of childhood physical or sexual abuse, whereas 3 studies[45–47] failed to find hippocampal volume reduction in abused children.

Volumetric magnetic resonance imaging scans were obtained on 26 (90%) of the subjects included in this study, and results have been published elsewhere.[17] Briefly, we found evidence for reduced hippocampal volume bilaterally in these young adult women, particularly in those who experienced CSA between 3 and 5 years of age or between 11 and 13 years of age. Corpus callosal area was reduced in individuals with CSA between 9 and 10 years of age, and frontal cortex gray matter volume was reduced in individuals with CSA between 14 and 16 years of age.[17] It may be the case that CSA during early sensitive periods exerts delayed affects on the hippocampus that become manifest after puberty along with symptoms of major depression.

The delay in symptom onset provides a window of opportunity for treatment,[33] and preclinical studies suggest a variety of strategies that may be beneficial. First, exposure to early stress can exert enduring deleterious effects on brain and behavior of rodents by producing an epigenetic modification (methylation) of the glucocorticoid receptor promoter site regulating the expression of receptors for corticosteroids, such as cortisol. However, environmental experiences such as increased maternal care can reverse (i.e., unmethylate) the epigenetic modification by inducing an early-response gene (*NGFI-A*, also known as *egr-1* and *zif-286*).[31] Hence, it is conceivable that certain forms of psychosocial contact (e.g., nurturing contacts) may reverse epigenetic programming of the glucocorticoid systems to overreact. This may then prevent or curtail the deleterious effects of stress hormones on the hippocampus.[48] Kaufman et al.[49] found that the presence of positive social supports helped to protect children with the short allele of 5-HTTLPR from developing depression following exposure to childhood abuse.

Second, hippocampal neurogenesis and synaptogenesis are persistently reduced by exposure to early stress, which may consequently lead to the development of depression.[50] Vigorous exercise, environmental enrichment, or exposure to certain types of cognitive tasks[51–53] may stimulate these processes and, thus, may constitute possible routes for preventive interventions geared toward preserving hippocampal neurogenesis. Whether these findings can be extrapolated to humans is an open question, but they provide a theoretical rationale for developing novel intervention strategies to protect against a major adverse consequence of exposure to CSA. Pereira et al.[54] recently reported the possibility of tracking changes in neurogenesis/angiogenesis in the human hippocampus using imaging techniques.

To our knowledge, this is the first study to analyze the time delay between exposure to CSA and emergence of major depression and to indicate the importance of this temporal relationship for development of rational intervention strategies. This study is limited by use of retrospective assessment methods, the small sample size, and the uniqueness of the participants, who were exposed to CSA but to no other form of childhood traumatic stress. The latter, however, was an important prerequisite for the analysis, and a large sample of subjects were carefully screened to recruit this special population. Moreover, given that our population was not selected from a clinical setting and that respondents to our community solicitations were primarily college students, we suspect that our subjects represent the higher-functioning group of individuals exposed to CSA and perhaps represent individuals who might be labeled as "resilient" in other studies. Rates of psychopathology may have been even greater if our sample had included subjects who reported multiple forms of abuse throughout childhood.[16] However, if we are correct in that adolescence is a critical age for the emergence of depression, then these individuals would have shown a similar onset pattern.

It is quite likely that other investigators have data sets that can be analyzed in a similar manner to support or refute these findings. Understanding the maturational events that intervene between CSA and adverse outcomes such as depression, PTSD, or substance abuse may provide the necessary insights to establish an integrative science of preventive psychiatry.

REFERENCES

1. Chapman DP, Whitfield CL, Felitti VJ, et al. Adverse childhood experiences and the risk of depressive disorders in adulthood. J Affect Disord 2004;82:217–225
2. Dube SR, Anda RF, Felitti VJ, et al. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. JAMA 2001;286:3089–3096
3. Wise LA, Zierler S, Krieger N, et al. Adult onset of major depressive disorder in relation to early life violent victimisation: a case-control study. Lancet 2001;358:881–887
4. Fergusson DM, Swain-Campbell NR, Horwood LJ. Does sexual violence contribute to elevated rates of anxiety and depression in females? Psychol Med 2002;32:991–996
5. Kendler KS, Bulik CM, Silberg J, et al. Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and co-twin control analysis. Arch Gen Psychiatry 2000;57(10):953–959
6. Donald M, Dower J. Risk and protective factors for depressive symptomatology among a community sample of adolescents and young adults. Aust N Z J Public Health 2002;26:555–562
7. Kilpatrick DG, Ruggiero KJ, Acierno R, et al. Violence and risk of PTSD, major depression, substance abuse/dependence, and comorbidity: results from the National Survey of Adolescents. J Consult Clin Psychol 2003;71:692–700
8. Putnam FW. Ten-year research update review: child sexual abuse. J Am Acad Child Adolesc Psychiatry 2003;42(3):269–278
9. Andersen SL, Teicher MH. Stress, sensitive periods and maturational events in adolescent depression. Trends Neurosci 2008;31(4):183–191
10. Hankin BL, Abramson LY, Moffitt TE, et al. Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. J Abnorm Psychol 1998;107:128–140
11. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602
12. Kessler RC. Epidemiology of women and depression. J Affect Disord 2003;74:5–13
13. Post RM, Leverich GS, Xing G, et al. Developmental vulnerabilities to the onset and course of bipolar disorder. Dev Psychopathol 2001;13:581–598

14. Dube SR, Felitti VJ, Dong M, et al. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the Adverse Childhood Experiences Study. Pediatrics 2003;111:564–572
15. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998;14(4):245–258
16. Teicher MH, Samson JA, Polcari A, et al. Sticks, stones, and hurtful words: relative effects of various forms of childhood maltreatment. Am J Psychiatry 2006;163:993–1000
17. Andersen SL, Tomada A, Vincow ES, et al. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J Neuropsychiatry Clin Neurosci 2008;20(3):292–301
18. Roy CA, Perry JC. Instruments for the assessment of childhood trauma in adults. J Nerv Ment Dis 2004;192:343–351
19. Bremner JD, Steinberg M, Southwick SM, et al. Use of the Structured Clinical Interview for DSM-IV Dissociative Disorders for systematic assessment of dissociative symptoms in posttraumatic stress disorder. Am J Psychiatry 1993;150:1011–1014
20. Gunderson JG, Kolb JE, Austin V. The diagnostic interview for borderline patients. Am J Psychiatry 1981;138:896–903
21. Farrer LA, Florio LP, Bruce ML, et al. Reliability of self-reported age at onset of major depression. J Psychiatr Res 1989;23:35–47
22. Prusoff BA, Merikangas KR, Weissman MM. Lifetime prevalence and age of onset of psychiatric disorders: recall 4 years later. J Psychiatr Res 1988;22:107–117
23. Hollingshead AB, Redlich FC. Social Class and Mental Illness: A Community Study. New York, NY: John Wiley and Sons; 1958
24. Costello EJ, Mustillo S, Erkanli A, et al. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry 2003;60:837–844
25. Gladstone GL, Parker GB, Mitchell PB, et al. Implications of childhood trauma for depressed women: an analysis of pathways from childhood sexual abuse to deliberate self-harm and revictimization. Am J Psychiatry 2004;161:1417–1425
26. Wolf TL, Campbell TW. Effective treatments for children in cases of extra-familial sexual abuse. Issues in Child Abuse Accusations 1994;6: 207–213
27. Caffaro-Rouget A, Lang RA, van Santen V. The impact of child sexual abuse. Ann Sex Res 1989;2:29–47
28. Herman JL, Perry JC, van der Kolk BA. Childhood trauma in borderline personality disorder. Am J Psychiatry 1989;146:490–495
29. Heffernan K, Cloitre M. A comparison of posttraumatic stress disorder with and without borderline personality disorder among women with a history of childhood sexual abuse: etiological and clinical characteristics. J Nerv Ment Dis 2000;188:589–595
30. Meaney MJ, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. Dialogues Clin Neurosci 2005;7:103–123
31. Weaver IC, D'Alessio AC, Brown SE, et al. The transcription factor nerve growth factor-inducible protein a mediates epigenetic programming: altering epigenetic marks by immediate-early genes. J Neurosci 2007;27:1756–1768
32. Liu D, Diorio J, Tannenbaum B, et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science 1997;277:1659–1662
33. Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? Neurosci Biobehav Rev 2003;27:3–18
34. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386–389
35. Smythe JW, Rowe WB, Meaney MJ. Neonatal handling alters serotonin (5-HT) turnover and 5-HT2 receptor binding in selected brain regions: relationship to the handling effect on glucocorticoid receptor expression. Brain Res Dev Brain Res 1994 Jul 15;80(1–2):183–189
36. Vogel G, Neill D, Hagler M, et al. A new animal model of endogenous depression: a summary of present findings. Neurosci Biobehav Rev 1990;14:85–91
37. Andersen SL, Dumont NL, Teicher MH. Differences in behavior and monoamine laterality following neonatal clomipramine treatment. Dev Psychobiol 2002;41:50–57
38. Jann MW. Buspirone: an update on a unique anxiolytic agent. Pharmacotherapy 1988;8:100–116
39. Andersen SL, Teicher MH. Delayed effects of early stress on hippocampal development. Neuropsychopharmacology 2004;29:1988–1993
40. Bremner JD, Randall P, Vermetten E, et al. Magnetic resonance imaging–based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse: a preliminary report. Biol Psychiatry 1997;41:23–32
41. Stein MB. Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med 1997;27:951–959
42. Driessen M, Herrmann J, Stahl K, et al. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. Arch Gen Psychiatry 2000;57:1115–1122
43. Vythilingam M, Heim C, Newport J, et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry 2002;159:2072–2080
44. Vermetten E, Schmahl C, Lindner S, et al. Hippocampal and amygdalar volumes in dissociative identity disorder. Am J Psychiatry 2006;163: 630–636
45. Carrion VG, Weems CF, Eliez S, et al. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biol Psychiatry 2001;50: 943–951
46. De Bellis MD, Keshavan MS, Clark DB, et al. Developmental traumatology, pt 2: brain development. Biol Psychiatry 1999;45:1271–1284
47. De Bellis MD, Keshavan MS, Shifflett H, et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. Biol Psychiatry 2002;52: 1066–1078
48. McEwen BS. Effects of adverse experiences for brain structure and function. Biol Psychiatry 2000;48:721–731
49. Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Social supports and serotonin transporter gene moderate depression in maltreated children. Proc Natl Acad Sci U S A 2004;101:17316–17321
50. Malberg JE, Eisch AJ, Nestler EJ, et al. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000;20: 9104–9110
51. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 2002;25:295–301
52. Bredy TW, Zhang TY, Grant RJ, et al. Peripubertal environmental enrichment reverses the effects of maternal care on hippocampal development and glutamate receptor subunit expression. Eur J Neurosci 2004;20:1355–1362
53. Scaccianoce S, Del Bianco P, Caricasole A, et al. Relationship between learning, stress and hippocampal brain-derived neurotrophic factor. Neuroscience 2003;121:825–828
54. Pereira AC, Huddleston DE, Brickman AM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A 2007;104:5638–5643