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Separation Anxiety Disorder in Childhood as a Risk Factor for Future Mental Illness

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Abstract

Objective—To ascertain the extent to which childhood separation anxiety disorder (SAD) confers risk for the development of psychopathology during young adulthood (ages 19–30).

Method—A subset of the participants of the Oregon adolescent depression project (n = 816) was used. Subjects provided retrospective reports of lifetime mental illness (including SAD) and concurrent reports of current mental illness at age 16, and were then followed prospectively until age 30. Diagnostic assessments were conducted twice during adolescence, and again at ages 24 and 30. Based on diagnosis during childhood/adolescence, the subjects were partitioned into four orthogonal groups: SAD (*n* = 42), other anxiety disorders (*n* = 88), a heterogeneous psychiatric disorders control group (*n* = 389), and a not mentally ill control group (*n* = 297). Adjusting for demographic variables that were significantly associated with group status and for comorbid disorders prior to age 19, the results were analyzed with hierarchical multiple logistic regression.

Results—SAD was a strong (78.6%) risk factor for the development of mental disorders during young adulthood. The major vulnerabilities were for panic disorder and depression.

Conclusions—Because SAD creates a major vulnerability for mental disorders during young adulthood, clinicians should be sensitive to the presence of SAD, and children and adolescents with SAD should be provided with treatment. Future research should evaluate whether successful treatment for SAD and/or the provision of a preventative intervention during childhood/adolescence reduce the risk for future psychopathology.

Keywords

separation anxiety; risk factor; psychopathology

Introduction

Separation anxiety disorder (SAD) has been recognized as a disorder of childhood since the DSM-III.[1] The central phenomenology of SAD focuses on a child's reluctance to be separated from major attachment figures because of his/her fear that something awful might happen to the attachment figure. Although there have been several recent reviews of SAD,[2-5] relatively little is known about SAD's long-term course and its potential to predispose individuals to

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future psychopathology (with the exception of panic disorder, reviewed later). It has been estimated that 33%–40% of children with SAD develop at least one adult psychiatric disorder.[6,7] The purpose of this study is to contribute to the understanding of the course of SAD and to identify specific subsequent mental illnesses associated with SAD. Such an understanding may help mental health professionals develop preventative programs for children/adolescents with SAD.

Childhood SAD Predicting Subsequent Anxiety Disorders

Multiple lines of evidence suggest that childhood SAD may confer an increased risk for developing subsequent anxiety disorders. For instance, retrospective reports indicate elevated rates of anxiety disorders[8] such as social phobia, panic disorder (PD) or panic disorder-agoraphobia (PD-Ag) among those with a childhood history of SAD, [9] and prospective studies indicate elevated rates of specific phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and acute stress disorder among individuals who had SAD during childhood.[10] The findings reported by Orvaschel et al's[11] prospective study suggest many disorders “breed true” (ie, individuals who are diagnosed with two disorders at different points of time are more likely to be diagnosed with two disorders from the same general diagnostic category than diagnosed with two disorders from separate diagnostic categories). Thus, we hypothesized that an individual with SAD would be more likely subsequently to develop a second anxiety disorder.

Childhood SAD Predicting Subsequent Nonanxious Disorders

Several studies have examined the specific link between childhood SAD and subsequent MDD. Aschenbrand et al[10] and Hayward et al[12] presented evidence from prospective studies suggesting MDD often appears later in life among individuals who had SAD as a child, especially among those with persistent childhood SAD.[2] These findings are consistent with those reported by Orvaschel et al.[11] Therefore, we predicted an increased incidence for depression among individuals with a history of childhood SAD.

Few researchers have examined the link between childhood SAD and subsequent externalizing disorders or substance misuse. At least one research group[13] reported that SAD retrospectively assessed at age 11 did not predict substance use or abuse prospectively assessed at age 14; however, others have linked childhood anxiety disorders in general to subsequent substance use problems in prospective studies.[14] Based on the results reported by Orvaschel et al.[11] suggesting that that most disorders “breed true” and the results of King et al.[13], we predicted that compared to controls, the children/adolescents with SAD would not show an increased incidence of alcoholism and drug abuse. Childhood SAD Predicting Subsequent Panic Disorder

Decades ago, Gittelman and Klein[15-17] suggested the intriguing hypothesis that SAD in childhood may serve as a specific risk factor for adult panic disorder. Since that time, many researchers have observed a link between retrospectively reported childhood SAD and prospective adolescent panic attacks[18] or retrospectively reported childhood SAD and adult PD/PD-Ag.[19-24] The estimated percentage of adults with PD/PD-Ag who experienced juvenile SAD have ranged from 18%[25] to 50%.[26] Although a multitude of research groups have detected a link between juvenile SAD and subsequent PD/PD-Ag, others have failed to replicate this relationship in prospective studies.[10,12,27] Still other researchers have detected a relationship between childhood SAD and adult PD/PD-Ag *in retrospective studies*, but stress this relationship is *not* unique.[9,28]

Some researchers have suggested the mixed findings may be a result of the heterogeneity of symptom profiles among children with SAD. For instance, Manicavasagar et al[29] demonstrated that adults who retrospectively reported high levels of childhood SAD symptoms were much

more likely than those with low levels of SAD symptoms to develop PD/PD-Ag as adults. Other researchers have provided evidence that the SAD and PD/PD-Ag link may be stronger in females than in males.[30] Additional reasons for the equivocal nature of the link between childhood SAD and subsequent PD/PD-Ag include differential symptom assessment (ie, participant versus parent report), study design (ie, prospective versus retrospective), and the concurrent presence of other mental disorders. A recent review by Silove et al[27] concludes the link between SAD and PD/PD-Ag is far from conclusive.

The Effects of Comorbidity

Most previous researchers have examined whether childhood SAD confers an increased risk for subsequent mental illness *without* consideration for the potential impact of diagnoses that co-occur with childhood SAD. Given the high degree of comorbidity between anxiety disorders and between anxiety disorders and other mental disorders,[31-34] it is plausible that links between childhood SAD and future psychopathology are attributable, completely or partially, to the presence of the comorbid condition(s).

The Current Study

In this study, we examine the hypothesis that childhood SAD confers an increased risk for the development of *internalizing* disorders in young adulthood (anxiety but especially panic disorder as well as depression) and a decreased risk for externalizing disorders (ie, alcoholism and substance abuse) in a community sample. We also conducted exploratory analyses examining the potential links between age of SAD onset, SAD duration, and severity of SAD symptomatology and the likelihood of developing subsequent psychopathology.

Additionally, we assessed the extent to which SAD increases risk for mental disorders during early adulthood (ages 19 to 30—ie, specifically of the link between SAD and future psychopathology) compared with other childhood/adolescent disorders. Our hypothesis is that even when controlling for the occurrence of other psychological disorders through age 19, SAD will contribute a unique degree of increased risk for the occurrence of subsequent mental disorders between 19 and 30. As indicated earlier, we predicted that children with SAD will be more likely to develop anxiety and depression disorders, but not alcoholism or drug abuse, by age 30, than those without SAD. We also expected to replicate the childhood SAD to subsequent panic disorder link reported by previous research groups.

Method

Participants and Procedures

Participants for the Oregon Adolescent Depression Project (OADP) were randomly selected from nine high schools that were representative of rural and urban communities in western Oregon, as previously described.[34] The cohort was assessed at four time points: Time 1 (T1) during adolescence (*M age = 16.1*), Time 2 (T2) approximately 1 year later (*M age = 17.2*), Time 3 (T3) at the average age of 24 (*M age = 24.2*), and Time 4 (T4) at the average age of 30 (*M age = 30.1*). At each time point, participants provided information about current episodes of mental disorders and retrospective information about any disorder that had occurred between the previous data collection time point (or birth, in the case of T1) and the current data collection time point. At T1 and T2, there were 1,709 and 1,507 participants in the sample, respectively. All adolescents with a history of MDD ($n = 351$) or nonmood disorders ($n = 293$) and a random sample of participants with no history of psychopathology ($n = 457$) by T2 were invited to participate in T3 data collection. All nonwhite participants were retained for the T3 sample to maximize ethnic and racial diversity. Of the 1,101 participants asked to participate in T3 data collection, 941 (85%) completed the T3 mailer questionnaire and diagnostic interview. As participants reached their 30th birthday, they were asked to participate in the T4 data collection

procedure. Of the 941 participants in the T3 sample, 816 (87%) completed the T4 assessment. It is important to note that by design the proportion of participants with a history of a mental disorder during childhood/adolescence is overrepresented in the sample used in the present study.

Diagnostic Interview

At T1 and T2, participants were interviewed with a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) that combined features of the epidemiologic version (K-SADS-E)[35] and the present episode version (K-SADS-P), and included additional items so that DSM-III diagnoses could be derived. Both versions of the K-SADS have been shown to possess adequate psychometric properties.[36] Coefficient alpha for the K-SADS items was acceptable ($\alpha = .75$). At T3, the interview was expanded to assess DSM-IV[37] disorders in addition to DSM-III-R disorders. At T4, the Structured Clinical Interview for DSM-IV, nonpatient version, was administered.[38]

T1 assessments asked participants to report all episodes of mental illness that had occurred during their lifetime (ie, retrospective reports of mental illness going back from T1 and reports of current [at T1] psychopathology were collected). Thus, participants provided retrospective data at T1, and then were followed prospectively until T4 (age 30).

At T2, T3, and T4, participants were interviewed using the Longitudinal Interval Follow-Up Evaluation,[39] revised to probe for continuing or new psychiatric episodes (ie, participants reported not only disorders they were currently experiencing, but also disorders they had experienced between the previous data collection time point and the present data collection time point). T3 and T4 interviews were conducted over the phone, which generally produces similar results as face-to-face interviews.[40,41]

Diagnostic interviewers were highly trained (most had an advanced degree and completed a 70-hour course in diagnostic interviewing). All interviewers were required to demonstrate a kappa of at least .80 across all symptoms for three interviews and one videotaped interview prior to conducting participant interviews. Interrater reliability was acceptable (ie, κ for mood disorders, at T1 = .82, at T2 = 1.00, at T3 = .86, and at T4 = .81; κ for anxiety disorders, at T1 = .76, at T2 = .80, at T3 = .87, and at T4 = .76).

SAD Diagnosis

At T1 and T2, diagnostic data were scored using DSM-III-R criteria. A DSM-IV SAD diagnosis, requiring 4 rather than 2 weeks of symptom duration, was derived from available data and preliminary analysis identified no differences between the DSM-III-R and DSM-IV diagnostic groups on outcomes of interest (all p's > .05). For this paper, the DSM-III-R SAD group was used to maintain the historical integrity of the data and maximize statistical power.

Diagnostic Groups

At T1, 66 participants (3.9% of the sample) met full SAD criteria. The mean symptom count for T1 participants meeting full SAD criteria was 4.3 (*SD* = 1.2; Range = 3–8). The average age of onset in months was 85.7 (*SD* = 37.3; Range = 24–181) and average episode duration in weeks was 158.7 (*SD* = 136.9; Range = 2–710). Due to our interest in SAD predicting psychopathology through age 30, the final sample of interest (T4 SAD) included all participants who completed a diagnostic interview at the T4 assessment ($n = 816$). Of the 816 T4 participants, 42 (5.1%) *had* met full DSM-III-R SAD criteria at the T1 assessment.

Since we were interested in the development of new episodes of disorder in young adulthood, we defined future psychopathology as total incidence (first incidence or recurrence of a

disorder) from age 19 to 30. Thus, we obtained the age of onset of each mental disorder from the original T1 and T2 diagnostic data, and determined which disorder(s) each participant had experienced prior to the age of 19. That is, the T1, T2, and T3 data that was retrospectively reported through age 19 was used to determine all diagnoses before the age of 19. The disorder (s) each participant had experienced from the age of 19 to 30 were determined on the basis of the T3 and T4 diagnostic information. It is important to note that while the link between SAD and subsequent mental disorder may be said to be *prospective*, the determination of all mental disorders that occurred during the duration of the study (except for those that existed at the time of the assessment) is *retrospective*.

Participants in a current episode of the disorder of interest at age 19 were excluded from relevant analyses to ensure that we were only assessing new onset of cases that occurred from the 19^{th} birthday forward (ie, we did not want to use cases that had initially begun before the age of 19 and were simply continuing in an episode on their 19^{th} birthday). Thus, the analyzed sample varied based on the dependent variable of interest. For any disorder, 151 cases (18.5%) were excluded. For depression, panic, anxiety, and substance use, 27 (3.3%), 6 (0.7%), 34 (4.2%), and 91 (11.2%) cases were excluded, respectively, because they were in a current substance episode at the time of their 19^{th} birthday.

Attrition analyses were conducted to explore demographic and T1 diagnostic differences between those who comprised the T4 SAD diagnostic group ($n = 42$; i.e., those who completed all 4 assessments) and the T1 participants with a SAD diagnosis lost to follow-up between T1 and T4 ($n = 24$; those who failed to complete all four assessments). No significant differences between the two groups were identified for T1 demographics, major diagnostic categories at T1, or for SAD characteristics such as number of SAD symptoms, age of first onset, or duration (all p's > .05). The completion rate from T1 to T4 of individuals with SAD (63%) was not statistically different than the study's overall completion rate (74%; $\Pi^2 = .76$, $df = 1$, p = ns).

In the analyses described later, 42 participants comprise the diagnostic group of interest (the SAD group tracked from T1 to T4). For purposes of comparison, three additional orthogonal groups were identified based on diagnostic history at T1:1) an anxiety disorder group (ANX) including all participants who met criteria for an anxiety disorder other than SAD ($n = 88$), 2) a psychopathology control group (PC) that includes all participants who met full diagnostic criteria for any disorder other than anxiety ($n = 389$), and 3) a no disorder group (NMI) made up of individuals who had not met diagnostic criteria for any disorder by age 19 ($n = 297$). See Table 1 for a breakdown of the specific ANX and PC DSM diagnoses.

T1 demographic characteristics (age, % female, % White, % living with two biological parents, and % one or both parents had a college degree) of the four diagnostic groups were compared. The groups were similar across all categories with two exceptions: All three diagnostic groups (SAD, ANX, and PC) contained a significantly greater proportion of females than the NMI group, and the SAD and ANX groups contained a greater proportion of females when compared to the PC group. A significantly greater proportion of individuals in the NMI group lived with both biological parents at the T1 assessment compared to the three diagnostic groups. Participant sex and T1 household composition were included in subsequent models due to the lack of group equivalence on these variables. The main effect of T1 household composition was nonsignificant in all adjusted models controlling for participant sex and group status. Group by demographic and group by future psychopathology interactions were tested via a forward step method for each block. All were nonsignificant.

Analytic Strategy

Subsequent analyses were adjusted for demographic variables that were significantly associated with group status. Group differences in the total incidence rates of psychiatric

disorders between ages 19 and 30 (ie, in those who were not in a current episode for a specific disorder at age 19) were evaluated using hierarchical multiple logistic regression. Demographic variables, four dichotomous diagnostic variables for substance, panic, anxiety, or depressive disorders present prior to age 19, diagnostic status, and three planned contrasts comparing the SAD group to the three comparison groups were entered as the first block, and interactions between group status and demographic variables were tested in the second block. Forced entry of the first block was followed by a forward stepwise entry procedure for the second block to test whether each interaction term contributed to the model based on the significance level of the score statistic.

Results

Effects of T1 Demographic Variables on Future Psychopathology

After adjusting for diagnostic group status in the hierarchical logistic regression models, the main effect of participant sex was still a significant predictor of psychopathology between ages 19 and 30. Being female increased the likelihood of developing a future panic (OR = 7.34, 95% CI = 4.08-13.21) or depressive disorder (OR = 2.45, 95% CI = 1.81-3.34). Conversely, being female reduced the likelihood (OR = 2.16, 95% CI = 1.54-3.03) of developing a substance use disorder between ages 19 and 30. The interaction term of T1 SAD diagnosis × gender was nonsignificant.

Effects of SAD Characteristics on Future Psychopathology

There were no significant correlations between SAD onset age or SAD episode duration and each of the dependent variables (any disorder, anxiety, panic, depression, and substance use disorder: all p's > .05, despite .80 power to detect a large effect size). SAD severity (as indicated by the total number of separation anxiety symptoms) was only significantly correlated with future substance use disorders ($r = .31$, $p < .05$). However, when Type I error is appropriately controlled for, this correlation became nonsignificant.

Future Psychopathology as a Function of Diagnostic Group Status

Table 2 describes the frequency of psychiatric disorders from ages 19 to 30 as a function of diagnostic status through age 18. Three planned contrasts were specified to compare the SAD group to the three control groups: 1) SAD versus ANX, 2) SAD versus PC, and 3) SAD versus NMI. Table 3 reports effect sizes, ORs, and CIs for the specified group contrasts of the logistic models after adjusting for participant sex and T1 household composition (block 1) and psychopathology by age 18. The reported effects for the adjusted models indicate the risk associated with group membership above and beyond the contribution of the T1 demographic variables and comorbid psychopathology through age 18.

After controlling for demographics and comorbid psychopathology before age 19, participants with a SAD diagnosis were more likely to develop a subsequent panic disorder compared to the other three groups. Adolescents with a SAD diagnosis had an increased probability of developing a depressive disorder as compared to the PC and NMI groups, as well.

Epidemiological Findings and Comorbidity Rates

Because our study is one of the few studies to examine SAD based on DSM criteria in a community sample, we report a number of epidemiological findings that may be of interest to the field. For the total sample (N = 1,709), 3.9% met criteria for SAD before age 19; 76% of these had experienced another mental disorder. Among the latter, over 80% developed SAD before the other mental disorder. As indicated earlier, SAD has an early onset age of approximately 7 years and a duration of approximately 3 years. Most children's SAD symptoms

remitted by late adolescence, as only 6% of the children with a SAD diagnosis before T1 still had SAD at the T2 assessment point.

Of the 42 participants with a SAD diagnosis by age 19 (*i.e., during childhood*), 32 (76%) had a comorbid diagnosis. Six (14.3%) had a phobic disorder, 3 (7.1%) had a comorbid diagnosis of posttraumatic stress disorder, 2 (4.8%) had a panic disorder, 2 (4.8%) had an obsessive-compulsive diagnosis, 22 (52.4%) had an affective disorder, 11 (26.2%) had a substance use disorder, 6 (14.3%) had an adjustment disorder, 4 (9.5%) had a disruptive disorder, and 1 (2.4%) had an eating disorder.

Discussion

In this study, we examined the hypothesis that childhood SAD confers an increased risk for the development of *internalizing* disorders in young adulthood and a decreased risk for externalizing disorders (ie, alcoholism and substance abuse) in a community sample. Additionally, we assessed the extent to which SAD increases risk for mental disorders during early adulthood compared with other childhood/adolescent disorders. Our results were consistent with our hypothesis that even when controlling for the occurrence of other psychological disorders through age 19, SAD contributed a unique degree of increased risk for the occurrence of certain subsequent mental disorders between 19 and 30. Specifically, children with SAD were more likely to develop panic disorder and depressive disorders, but not other anxiety disorders or substance use disorders by age 30, than those without SAD. This study improves upon many previous SAD studies in that it initially (at T1) obtained retrospective reports of child psychopathology, but then followed participants prospectively through the age of 30. Furthermore, its diagnoses were based on structured diagnostic interviews and DSM criteria.

Having experienced an episode of SAD emerged as a major risk for future psychopathology, as 73.5% of the SADs (almost all of whom had recovered from the SAD by age 19) developed an episode of psychopathology during young adulthood. Previous researchers have debated whether childhood SAD is uniquely related to the development of panic disorder in adulthood, and as indicated earlier, there have been conflicting findings reported in the literature. Our results supported those of Biederman et al.[22-24] and Gittleman and Klein[15], suggesting that childhood SAD is linked to subsequent panic disorder. Our results also suggested that childhood SAD confers a vulnerability for subsequent depression, with 75% of the subjects with childhood SAD experiencing an episode of depression during young adulthood. This is consistent with the findings reported by Orvaschel et al.[11] Similarly, Warner et al[42] also argued that anxiety symptoms are the earliest manifestations of psychiatric disorders and that early anxiety symptoms increase the risk for subsequent MDD. Other findings in the literature also indicate that anxiety disorders usually precede depressive disorders.[43]

Given the preponderance of evidence that SAD creates a substantially elevated risk for future mental disorder, a child who develops SAD should not only receive treatment for the SAD but also be a candidate for preventive efforts aimed to minimize the chances of future psychopathology—especially depression and panic disorder. It remains for future research to ascertain whether successful treatment for SAD during childhood/adolescence and provision of preventative interventions reduce the likelihood of future psychopathology. The self-limiting nature of SAD may make it difficult for parents (and children) to accept treatment for SAD, but the long duration of SAD episodes and increased likelihood of subsequent panic disorder and/or depressive disorders should help to persuade parents and children of the importance of SAD treatment.

Despite the fact that our data suggest an association between SAD and future pathology, they do not allow for comments about causality. Although it is possible that SAD is a causal agent for subsequent psychopathology, it is also possible that childhood SAD and adult depressive and panic pathology may be caused by a common, underlying vulnerability. If the latter is true, it may also be that SAD is a marker for severity of the underlying vulnerability.

This study should be evaluated in light of its strengths and weaknesses. A strength of our study is that the presence of the symptoms of SAD were obtained during adolescence, ie, in relatively close temporal proximity to the SAD episode. The majority of previous studies examining the relationship between childhood SAD and subsequent psychopathology have relied upon retrospective reports of childhood SAD obtained during adulthood, and concerns about the accuracy of long-term retrospective self-reporting can be raised. Another strength of our study is that our data were collected from a large community sample. Thus, our conclusions may be more generalizable to the population at large but perhaps not to clinical samples.

A limitation of our study is that we were unable to examine whether childhood SAD predicted the development of future Axis II disorders. It is reasonable that individuals affected early in life by SAD might be at an increased risk for the development of certain personality disorders like dependent personality disorder. This possibility seems plausible given the similarity between certain symptoms (eg, feeling intensely fearful with the thought of being left alone without a primary caretaker).[44] Relatedly, we were unable to examine whether SAD predicts an increased future occurrence of certain Axis I disorders, including eating disorders and psychotic disorders, due to the small number of individuals in our sample who developed these disorders.

An additional concern with our data is that they were solely based on participant self-report. Previous researchers have raised important questions about the degree to which one can rely on child reports for information about SAD diagnosis.[45] In this regard, it is fortunate that mother's report of children's SAD symptoms were collected in a subset of the participants in this study but only fair concordance rates were observed (ICC[3,1] = .46).[46] Because maternal reports were only available for a subset of participants, and because the ICC was low, we relied solely upon adolescent reports of SAD symptoms. However, the study would have been strengthened by the inclusion of maternal and paternal interviews regarding childhood SAD symptoms in the entire sample. An additional limitation is that because parental psychopathology was not assessed in this sample, and given that both pure SAD and comorbid SAD have been found to be associated with parental anxiety disorder, it is unclear whether the association between SAD and panic and depression are affected by parental psychopathology.

Finally, we did not collect data on the presence of adult SAD as proposed by Manicavasagar et al.[47,48] These investigators have suggested a possible continuity between child SAD and adult SAD. If future researchers are able to assess this question in a prospective design that assessed SAD symptoms beyond adolescence, our understanding of Manicavasagar and colleagues' proposal would be enhanced.

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References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. 3rd. Washington, DC: American Psychiatric Association; 1980.

2. Foley DL, Pickles A, Maes HM, Silberg JL, Eaves LJ. Course and short-term outcomes of separation anxiety disorder in a community sample of twins. J Am Acad Child Adolesc Psychiatry 2004;43:1107–1114. [PubMed: 15322414]
3. Barlow, DH.; Pincus, DB.; Heinrichs, N.; Choate, ML. Anxiety disorders. In: Stricker, G.; Widiger, TA.; Weiner, IB., editors. Handbook of Psychology: Clinical Psychology. Vol. 8. Hoboken, NJ: John Wiley & Sons; 2003. p. 119-147.
4. Perwien, AR.; Bernstein, GA. Separation anxiety disorder. In: Ollendick, TH., editor. Phobic and Anxiety Disorders in Children and Adolescents: A Clinician's Guide to Effective Psychosocial and Pharmacological Interventions. New York: Oxford University Press; 2004. p. 272-305.
5. Silverman, WK.; Dick-Niederhauser, A. Separation anxiety disorder. In: March, JS.; Morris, TL., editors. Anxiety Disorders in Children and Adolescents. Vol. 2nd. New York, NY: Guilford; 2004. p. 164-188.
6. Flakierska N, Lindstrom M, Gillberg C. School refusal: A 15–20 year follow-up study of 35 Swedish urban children. Br J Psychiatry 1988;152:834–837. [PubMed: 3167471]
7. Berg I, Jackson A. Teenage school refusers grow up: A follow-up study of 168 subjects, ten years on average after in-patient treatment. Br J Psychiatry 1985;147:366–370. [PubMed: 4075023]
8. Lipsitz JD, Martin LY, Mannuzza S, Chapman TF, Liebowitz MR, Klein DF, et al. Childhood separation anxiety disorder in patients with adult anxiety disorders. Am J Psychiatry 1994;151:927–929. [PubMed: 8185008]
9. Otto MW, Pollack MH, Maki KM, Gould RA, Worthington JJ III, Smoller JW, et al. Childhood history of anxiety disorders among adults with social phobia: Rates, correlates, and comparisons with patients with panic disorder. Depress Anxiety 2001;14:209–213. [PubMed: 11754127]
10. Aschenbrand SG, Kendall PC, Webb A, Safford SM, Flannery-Schroeder E. Is childhood separation anxiety disorder a predictor of adult panic disorder and agoraphobia? A seven-year longitudinal study. J Am Acad Child Adolesc Psychiatry 2003;42:1478–1485. [PubMed: 14627883]
11. Orvaschel H, Lewinsohn PM, Seeley JR. Continuity of psychopathology in a community sample of adolescents. J Am Acad Child Adolesc Psychiatry 1995;34:1525–1535. [PubMed: 8543521]
12. Hayward C, Killen JD, Kraemer HC, Taylor CB. Predictors of panic attacks in adolescents. J Am Acad Child Adolesc Psychiatry 2000;39:207–214. [PubMed: 10673832]
13. King SM, Iacono WG, McGue M. Childhood externalizing and internalizing psychopathology in the prediction of early substance use. Addiction 2004;99:1548–1559. [PubMed: 15585046]
14. Chassin L, Pitts SC, DeLucia C, Todd M. A longitudinal study of children of alcoholics: Predicting young adult substance use disorders, anxiety, and depression. J Abnorm Psychol 1999;108:106–119. [PubMed: 10066997]
15. Gittelman R, Klein DF. Relationship between separation anxiety and panic and agoraphobic disorders. Psychopathology 1984;17(Suppl 1):56–65. [PubMed: 6369368]
16. Klein D. Delineation of two drug-responsive anxiety syndromes. Psychopharmacologia 1964;5:397–408. [PubMed: 14194683]
17. Klein D. Anxiety reconceptualized: Early experience with imipramine and anxiety. Compr Psychiatry 1980;21:411–427. [PubMed: 7428347]
18. Hayward C, Wilson KA, Lagle K, Killen JD, Taylor CB. Parent-reported predictors of adolescent panic attacks. J Am Acad Child Adolesc Psychiatry 2004;43:613–620. [PubMed: 15100568]
19. Ayuso JL, Alfonso S, Rivera A. Childhood separation anxiety and panic disorder: A comparative study. Prog Neuropsychopharmacol Biol Psychiatry 1989;12:665–671. [PubMed: 2781038]
20. Laraia MT, Stuart GW, Frye LH, Lydiard RB, Ballenger JC. Childhood environment of women having panic disorder with agoraphobia. J Anxiety Disord 1994;8:1–17.
21. Silove D, Harris M, Morgan A, et al. Is early separation anxiety a specific precursor of panic disorder-agoraphobia? A community study. Psychol Med 1995;25:405–411. [PubMed: 7675927]
22. Biederman J, Petty C, Faraone SV, Hirshfeld-Becker DR, Henin A, Rauf A, et al. Childhood antecedents to panic disorder in referred and nonreferred adults. J Child Adol Psychop 2005;15:549–562.
23. Biederman J, Petty CR, Faraone SV, Hirshfeld-Becker DR, Henin A, Brauer L, et al. Antecedents to panic disorder in nonreferred adults. J Clin Psychiatry 2006;67:1179–1186. [PubMed: 16965194]

24. Biederman J, Petty CR, Hirshfeld-Becker DR, Henin A, Faraone SV, Fraire M, et al. Developmental trajectories of anxiety disorders in offspring at high risk for panic disorder and major depression. Psychiat Res 2007;153:245–252.
25. Breier A, Charney D, Heninger G. Agoraphobia with panic attacks. Arch Gen Psychiatry 1986;43:1029–1036. [PubMed: 3767595]
26. Klein D, Zitrin CM, Woerner MG, Ross DC. Treatment of phobias II: Behavior therapy and supportive psychotherapy: Are there any specific ingredients? Arch Gen Psychiatry 1983;40:139–145. [PubMed: 6130751]
27. Silove D, Manicavasagar V, Curtis J, Blaszczynski A. Is early separation anxiety a risk factor to adult panic disorder? A critical review. Compr Psychiatry 1996;37:1–14.
28. Biederman J, Petty C, Faraone SV, Hirshfeld-Becker DR, Hennin A, Pollack MH, et al. Patterns of comorbidity in panic disorder and major depression: Findings from a nonreferred sample. Depress Anxiety 2005;21:55–60. [PubMed: 15816058]
29. Manicavasagar V, Silove D, Hidzi-Pavlovic D. Subpopulations of early separation anxiety: Relevance to risk of adult anxiety disorders. J Affective Disord 1998;48:181–190.
30. Balon R, Yeragani V, Pohl R. Higher frequency of separation anxiety in panic disorder patients. Am J Psychiatry 1989;146:1351. [PubMed: 2782484]
31. Lewinsohn PM, Zinbarg R, Seeley JR, Lewinsohn M, Sack WH. Lifetime comorbidity among anxiety disorders and between anxiety disorders and other mental disorders in adolescents. J Anxiety Disord 1997;11:377–394. [PubMed: 9276783]
32. Verduin TL, Kendall PC. Differential occurrence of comorbidity within childhood anxiety disorders. J Clin Child Adolesc Psychol 2003;32:290–295. [PubMed: 12679288]
33. Gregory AM, Caspi A, Moffitt TE, Koenen K, Eley TC, Poulton R. Juvenile mental health histories of adults with anxiety disorders. Am J Psychiatry 2007;164:301–308. [PubMed: 17267794]
34. Rohde P, Lewinsohn PM, Seeley JR, Klein DN, Andrews JA, Small JW. Psychosocial functioning of adults who experienced substance use disorders as adolescents. Psychol Addict Behav 2007;21:155–164. [PubMed: 17563135]
35. Orvaschel H, Puig-Antich JC, Tabrizi MA, Johnson R. Retrospective assessment of prepubertal major depression with the Kiddie-SADS-E. J Am Acad Child Adolesc Psychiatry 1982;21:392–397.
36. Ambrosini PJ. Historical development and present status of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). J Am Acad Child Adolesc Psychiatry 2000;29:49–58. [PubMed: 10638067]2000
37. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. 4th. Washington, DC: American Psychiatric Association; 1994.
38. Spitzer, RL.; Williams, JBW.; Gibbon, M.; First, MB. User's Guide for the Structured Clinical Interview for DSM-III-R; SCID. Washington, DC: American Psychiatric Association; 1990.
39. Keller MB, Lavori PW, Friedman B, Neilsen E, Endicott J, McDonald-Scott PA. The Longitudinal Interval Follow-Up Evaluation: A comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987;44:540–548. [PubMed: 3579500]
40. Rohde P, Lewinsohn PM, Seeley JR. Comparability of telephone and face-to-face interviews in assessing Axis I and II disorders. Am J Psychiatry 1997;154:1593–1598. [PubMed: 9356570]
41. Sobin C, Weissman MM, Goldstein RB, et al. Diagnostic interviewing for family studies: Comparing telephone and face-to-face methods for the diagnosis of lifetime psychiatric disorders. Psychiatr Genet 1993;3:227–233.
42. Warner V, Weissman MM, Mufson L, Wickramaratne PJ. Grandparents, parents, and grandchildren at high risk for depression: A three-generation study. J Am Acad Child Adolesc Psychiatry 1999;38:289–296. [PubMed: 10087690]
43. Kessler, RC. The prevalence of psychiatric comorbidity. In: Wetzler, S.; Sanderson, WC., editors. Treatment Strategies for Patients with Psychiatric Comorbidity. New York, NY: Wiley; 1997. p. 23-48.
44. Silove, D.; Manicavasagar, V. Early separation anxiety and its relationship to adult anxiety disorders. In: Vasey, MW.; Dadds, MR., editors. The Developmental Psychopathology of Anxiety. New York, NY: Oxford University Press; 2001. p. 459-480.

45. Foley D, Rutter M, Pickles A, Angold A, Maes H, Silberg J, et al. Informant disagreement for separation anxiety disorder. J Am Acad Child Adolesc Psychiatry 2004;43:452–460. [PubMed: 15187805]

46. Cantwell DP, Lewinsohn PM, Rohde P, Seeley JR. Correspondence between adolescent report and parent report of psychiatric diagnostic data. J Am Acad Child Adolesc Psychiatry 1997;36:610–619. [PubMed: 9136495]

47. Manicavasagar V, Silove D, Curtis J, Wagner R. Continuities of separation anxiety from early life into adulthood. J Anxiety Disord 2000;14:1–18. [PubMed: 10770232]

48. Manicavasagar V, Silove D, Wagner R, Drobny J. A self-report questionnaire for measuring separation anxiety in adulthood. Compr Psychiatry 2003;44:146–153. [PubMed: 12658624]

Table 1

Breakdown of anxiety disorders diagnostic group and psychopathology control group by DSM diagnosis at T1

Disorder by group	*N* (%)
Anxiety disorder group (*n* = 88)	
Phobia	41 (46.6)
Agoraphobia	3 (3.4)
Social phobia	19 (21.6)
Simple/Specific phobia	22 (53.7)
Panic	15 (17.0)
Panic disorder with agoraphobia	6 (6.8)
Panic disorder without agoraphobia	9 (10.2)
Overanxious disorder	12 (13.6)
Obsessive-Compulsive disorder	4 (4.5)
Post traumatic stress disorder	32 (36.4)
Psychopathology control group (*n* = 389)	
Affective disorder	
MDD	211 (54.2)
Dysthymia	19 (4.9)
Bipolar	12 (3.1)
Non-affective disorder	
Substance abuse/dependence	153 (39.3)
Eating disorder	14 (3.6)
Disruptive disorder	68 (17.5)
Personality disorder	11 (2.8)
Somatization disorder	1 (0.3)
Psychotic disorder	
Schizophrenia	1 (0.3)
Brief psychotic disorder	1 (0.3)
Adjustment disorder	81 (20.3)

Table 2

Frequency of diagnosis in young adulthood (19–30) by adolescent diagnostic group

	Adolescent Diagnostic Group			
Period Incidence 19–30	**SAD (%)**	**ANX (%)**	**PC (%)**	**NMI (%)**
Any disorder	73.5	85.1	71.1	54.2
Anxiety	18.9	20.3	11.1	4.7
Panic	25.0	10.7	3.6	2.4
Depression	75.0	58.5	47.6	32.0
Substance	28.2	39.0	38.8	24.2

Note: SAD = Separation anxiety disorder; ANX = Anxiety disorder other than SAD; PC = Psychiatric control, a disorder other than anxiety; NMI = Not mentally ill.

Table 3

Adjusted odds ratios for adolescent diagnostic group predicting diagnosis in young adulthood (19–30)

	Adjusted OR (95% CI)[a]		
Period Incidence 19–30	**SAD vs ANX**	**SAD vs PC**	**SAD vs NMI**
Any disorder	0.47 (0.09-2.45)	1.16 (0.49-2.74)	1.23 (0.51-2.96)
Anxiety	1.00 (0.23-4.42)	1.88 (0.75-4.75)	2.62 (0.86-8.01)
Panic	8.79** (2.00-38.64)	5.87*** (2.13-16.19)	4.76* (1.28-17.69)
Depression	3.09 (0.97-9.81)	2.91** (1.30-6.51)	3.12** (1.35-7.21)
Substance	1.19 (0.38-3.72)	0.53 (0.23-1.21)	0.79 (0.32-1.91)

Note: SAD = Separation anxiety disorder; ANX = Anxiety disorder other than SAD; PC = Psychiatric control, a disorder other than anxiety; NMI = Not mentally ill; Anxiety = Period incidence of any anxiety disorder other than panic developed between ages 19–30.

[a] Adjusted for gender, family structure, and adolescent comorbid disorders prior to age 19.

* $p < .05$.

** $p < .01$.

*** $p < .001$.