



Adult separation anxiety disorder in *DSM-5*

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HIGHLIGHTS

- Adult separation anxiety disorder has been under-diagnosed, as it was placed under “childhood onset” disorders in *DSM-IV*.
- Separation anxiety disorder in adulthood is prevalent, often comorbid and debilitating.
- A substantial portion of adults report first onset separation anxiety disorder in adulthood.
- Research on the epidemiology, etiology, and treatment of adult separation anxiety disorder, using *DSM-5* criteria, is needed.
- Prospective-longitudinal studies on trajectories of separation anxiety disorder from childhood to adulthood are important.

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ABSTRACT

Unlike other *DSM-IV* anxiety disorders, separation anxiety disorder (SAD) has been considered a disorder that typically begins in childhood, and could be diagnosed only in adults “if onset is before 18.” Moreover, SAD is the only *DSM-IV* anxiety disorder placed under “Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence” whereas most anxiety disorders typically start – and are diagnosed – in childhood. Therefore, adult SAD may have been under-recognized and under-diagnosed. A literature review was carried out on behalf of the Anxiety, Obsessive–Compulsive Spectrum, Posttraumatic, and Dissociative Disorders *DSM-5* workgroup to explore the evidence for SAD in adulthood, focusing on potentially relevant clinical characteristics and risk factors. The review revealed that SAD in adulthood is prevalent, often comorbid and debilitating. The *DSM-IV* age-of-onset criterion was not supported as a substantial portion of adults report first onset in adulthood. Research on putative risk factors is limited to childhood SAD: SAD runs in families, albeit patterns of familial aggregation and heritability estimates indicate low specificity. Tentative evidence for biomarkers and biased cognitive processes exists, again pointing to moderate SAD-specificity only. Further research on the epidemiology, etiology, and treatment of ASAD, using *DSM-5* criteria, is needed, and particularly prospective-longitudinal studies to understand the developmental trajectories of separation anxiety disorder from childhood to adulthood.

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1. Separation anxiety disorder in adults

This review evaluates issues relevant to adult separation anxiety disorder (ASAD) for DSM-5. Separation anxiety disorder (SAD) is classified in the DSM-IV under “Disorders Usually First Diagnosed in Infancy, Childhood or Adolescence.” The apparent effect of this placement is that separation anxiety disorder is not considered – and therefore likely is underdiagnosed – in adults. Also, because of its classification under childhood-onset disorders, it is separated from all other anxiety disorders, most of which have childhood onset just as commonly as SAD (Beesdo, Knappe, & Pine, 2009; Gallagher, Cartwright-Hatton, Bögels, & Schneider, submitted for publication). DSM-IV TR does mention ASAD in the text: “Adults with the disorder are typically overconcerned about their offspring and spouses and experience marked discomfort when separated from them” (p. 123), indicating that its diagnosis in adulthood is not precluded, although it has generally been overlooked.

2. Statement of the issue

This review explores the evidence for separation anxiety disorder as a diagnosis in adulthood, using the validators provided by the DSM-5 Task Force. The following questions are addressed: 1) What is the prevalence of ASAD, and its effect on psychosocial functioning? 2) Should ASAD require a childhood onset, as in DSM-IV? 3) What is the continuity of ASAD across the lifespan, and is this continuity specific to ASAD? 4) What is the pattern of comorbidity in adults? 5) Is there familial aggregation of ASAD and, if so, is it specific or shared with other disorders? 6) Are there biomarkers or neural substrates underlying ASAD and, if so, are they unique to ASAD or shared with other disorders? 7) Are there temperamental/personality antecedents or concomitants of ASAD and, if so, are they specific to ASAD? 8) Are there information/emotional processing characteristics that are antecedents or correlate with ASAD? If so, are these specific for ASAD? 9) Are there genetic risk factors for ASAD and, if so, are they specific to ASAD? 10) Are there environmental risk factors for ASAD and, if so, are they specific to ASAD? 11) What are the differential-diagnostic issues for ASAD in adults? 12) What treatments work for ASAD, and are these treatments specific to ASAD?

3. Search methods

ASAD research published since the release of DSM-IV (i.e., 1994 through 2011) was searched using PsycINFO and PubMed searches for English language articles and books. Search terms included (combinations of) (*adult*) *separation anxiety (disorder)*, *family* or *parental (history)*, *concordance*, *twins*, *genetics* for studies on the familial aggregation and putative biomarkers for (*adult*) *separation anxiety (disorder)*. These terms were crossed with *information processing (bias)*, *memory*, *attention*, and *cognition*, as well as with *personality*, *personality disorder (PD)*, and *temperament* to examine cognitive distortions and personality factors, respectively, as antecedents and concomitants of the disorder. The reference lists of the identified key manuscripts also were reviewed. Finally, the DSM-IV Sourcebook, the DSM-IV Options Book, and proceedings

and monographs of the preparatory research planning conference series for DSM-5 also were consulted.

4. Definitions

The literature focuses primarily on adult separation anxiety disorder (ASAD), generally measured using semi-structured interviews based on DSM criteria. Adult-onset ASAD refers to an adult separation anxiety disorder diagnosis without a documented history of childhood separation anxiety disorder, whereas childhood-onset ASAD refers to an adult separation anxiety disorder diagnosis in individuals who have also met the criteria of separation anxiety disorder in childhood. We also reviewed relevant studies measuring adult separation anxiety *on a symptom level*, using self-report questionnaires, for which we use the term adult separation anxiety without abbreviation. Similarly, we use the term childhood separation anxiety disorder (CSAD) referring to a DSM-based separation anxiety disorder diagnosis during childhood, and childhood separation anxiety (again without abbreviation) reviewing studies measuring childhood separation anxiety on a symptom level.

5. Prevalence, gender differences, cultural variation, and effects on psychosocial functioning

The National Comorbidity Survey Replication (NCS-R), a study of 5692 adults (Shear, Jin, Ruscio, Walters, & Kessler, 2006) found ASAD to be common in the U.S.: The lifetime prevalence rate of ASAD was 6.6%. Diagnosis was based on retrospective assessment using a criterion set parallel to that of the DSM-IV, “making age-appropriate modifications to the criterion A symptom questions” (p. 1075). The large majority (77.5%) of those diagnosed with ASAD reported onset in adulthood, more than half of sufferers had a history of mood disorders (53%), and the majority (75%) had received or were in treatment for emotional problems. In a clinical study (Pini et al., 2010), 42.4% of the anxiety and mood disorder outpatients studied also met the criteria for ASAD, 20.7% childhood- and 21.7% adult-onset types. Other clinical studies have suggested that separation anxiety (disorder) predates the onset of other anxiety disorders, and is the primary disorder (Manicavasagar, Silove, & Curtis, 1997; Manicavasagar et al., 2000).

Childhood SAD is more common in girls (odds ratio [OR] = 2.2), but gender differences are less strong in ASAD, and males are more likely to report first onset in adulthood (Shear et al., 2006; Silove, Marnane, Wagner, Manicavasagar, & Rees, 2010). Studies comparing outpatients with and without ASAD found higher female/male ratios in those with than those without ASAD (Pini et al., 2010), and in a study of ASAD patients' early separation anxiety symptoms, only females had elevated scores (Silove, Marnane, et al., 2010).

Separation anxiety is likely to vary across cultures. Strong interdependence is more common in collectivistic than individualistic cultures (Heinrichs et al., 2006), and may affect separation anxiety (disorder) prevalence. Most studies on maternal separation anxiety are conducted in Western societies, that is, in individualistic cultures. Because (a) separation anxiety is correlated with less

differentiation of self (Lutz & Hock, 1995), and (b) in collectivistic cultures interdependence is more important than in individualistic cultures, which focus more on independence (Heinrichs et al., 2006), it could be speculated that levels of separation anxiety symptoms may be higher in collectivistic cultures, whereas diagnoses of (A) SAD may be higher in individualistic cultures, given that the anxiety must be excessive relative to cultural norms. A study on the association of maternal separation anxiety and mothers' differentiation of self with their children's separation anxiety in Eastern-collectivistic Druze families (Peleg, Halaby, & Whaby, 2006) nevertheless showed that mothers' separation anxiety and less differentiated self were correlated with higher separation anxiety in their children, supporting the universality of the importance of differentiation of self and the balance of autonomy and connection in parent–child interactions. In addition, separation anxiety may be influenced by actual threats that heighten the chance of losing a loved one, such as war, poverty, or living in a dangerous neighborhood, and therefore may be more common in cultures with higher exposure to such circumstances.

ASAD may affect functioning seriously in various areas of life. Outpatients referred to an anxiety disorder treatment clinic because of anxiety disorder(s) were reassigned into those with ($n = 207$) and without ($n = 313$) ASAD based on an algorithm derived from their Adult Separation Anxiety Symptom Questionnaire score (Silove, Marnane, et al., 2010). Patients with ASAD were found to be more severely disabled in all areas of the Work and Social Adjustment Scale (WSAS): work, home management, social leisure activities, private leisure activities, and close relationships (Silove, Marnane, et al., 2010). Similarly, in a sample of 508 anxiety and mood disorder outpatients, those with ASAD had higher impairment, as measured with the Sheehan Disability Scale, in work and study performance and in interpersonal relationships, as well as showing trend-level greater impairment in family life/activities, compared to patients without either ASAD or CSAD (Pini et al., 2010). Further, patients with CSAD only and with both CSAD and ASAD were, in level of disability, in between patients with adult-onset ASAD and patients without ASAD. Although it is unknown whether the increased impairment can be attributed to adult-onset ASAD per se or simply to the greater comorbidity in these studies' patients, the NCS-R study showed that adult-onset ASAD can be a debilitating condition in its own right: 63% of non-comorbid cases showed impairment in one or more social roles (e.g., work, interpersonal relations) and 30% were severely impaired.

Further, adults with ASAD were found in the NCS-R to be more often unmarried or divorced, and ASAD, but not CSAD, was related to lower education, unemployment and being disabled for work, compared to healthy subjects (Shear et al., 2006). However, in a clinical study (Pini et al., 2010), no differences were found in marital status, employment status, or education between outpatients with and without ASAD.

The observed associations of ASAD with lower level of functioning are cross-sectional and thus are indeterminate regarding causality, but suggest that fears of losing one's parents, partner, and/or children interfere with relationships, work, and family functioning. Findings of impaired functioning are most pronounced on assessments of qualitative levels of functioning, and less clear on objective biographic data (e.g., employment and marital status).

How ASAD affects parenting, and whether it contributes to separation anxiety and/or other anxiety disorders in offspring, has not been studied. Thus, we only can hypothesize that ASAD directed towards losing one's child(ren) drives overprotective parenting, which is the most studied aspect of parenting that is associated with childhood anxiety disorders.

A case example of an adult patient meeting criteria for ASAD is given below. Note that this patient's complaints had been diagnosed earlier as generalized anxiety disorder. This may be the result of the diagnostic interview used (SCID-I; First, Spitzer, Gibbon, & Williams, 1996), which does not include separation anxiety disorder in adults, and/or of differential-diagnostic considerations, which we address in the section on differential diagnosis (question 11).

John: A case of adult separation anxiety disorder

Mary is a 14-year-old girl who was referred for treatment of anxiety disorders (social and generalized anxiety disorder, and specific phobias) at a child community mental health service. She had not attended school on a regular basis for the last 2 years (since she entered junior high school). She was randomized for treatment to a family CBT protocol. Therefore, the therapist involved both parents and her (older) brother and sister during treatment, and assessed their anxiety disorders as well. Mary's father, John, had been treated for generalized anxiety disorder (GAD) several years earlier at an adult community mental health center, following a CBT protocol for GAD. Because the semi-structured diagnostic interview that had been used with him did not assess ASAD, that diagnosis had not been considered. According to John, that treatment had not been successful, and as a result he was not very optimistic about the treatment of his daughter. During the family treatment, John came across as a warm, highly involved, but overprotective father and spouse, who was suffering from fears that something bad would happen to his children and his wife, and that he would lose them as a result. For example, when his wife, who was afraid to drive a car on her own in an unknown environment, was given the exposure assignment to drive in an unfamiliar environment, together with Mary, John was in a total panic that they would get in an accident, and kept telling them to be careful. Also, his oldest daughter (age 20), who already lived on her own, related that when she visited the family and was even 5 min late, John would jump in the car and drive around in a panic looking for her. On Mary's exposure hierarchy, the item "biking alone to school" was terrifying to John, as he again was afraid that she would get into an accident. Another example of John's fears was that when his 18-year-old son wanted to go by train to another city for a date, but was afraid to take the train on his own, John proposed that the whole family goes with him, because of his own fear that if his son traveled alone, something bad might happen to him. Finally, John did not want his wife to work outside of the home, because he would worry constantly that something bad would happen to her. John remembered that his father had been the same with him and his brothers and sisters, and John recognized the fears of his children. It is however unknown whether John had separation anxiety disorder as a child.

6. Adult-onset separation anxiety disorder

Unlike other DSM-IV anxiety diagnoses, DSM-IV separation anxiety disorder can be diagnosed in adults "Only if onset is before 18," albeit the reason for this criterion is unclear. Moreover, evidence suggests that separation anxiety may only reach the level of a disorder for the first time in young adulthood, for example when moving out of the parents' house, in relation to a first serious romantic relationship (i.e., fear of losing the partner) or after having children (i.e., fear of losing a child). For example, in a prospective-longitudinal community study of adolescents and young adults up to age 20, age-of-onset curves revealed that in the majority of cases, the disorder (threshold/subthreshold SAD) began in middle childhood, but the reported age of onset ranged from 2 to 20 (Brückl et al., 2006).

In the NCS-R (Shear et al., 2006), 77.5% of the adults diagnosed with lifetime ASAD and 75.2% of those with 12-months ASAD, had first onset in adulthood. Pini et al.'s (2010) clinical study identified almost as many ASAD patients without CSAD as those whose ASAD was preceded by CSAD. Two other clinical studies in which CSAD and ASAD were derived from questionnaire scores, one-third (Manicavasagar et al., 1997) to one-fourth (Silove, Marnane, et al., 2010) reported probable first-onset ASAD. In a sample selected for early fears about going to school ($N = 72$), 16 were identified with ASAD (Silove, Manicavasagar, & Drobny, 2002). Not only those with CSAD were eight times more likely

to develop ASAD, but also four patients with ASAD (25%) without CSAD were identified.

Among clinic patients who presented with ASAD, Pini et al. (2010) reported average ages of onset of 23.1 (± 11.5) and 8.3 years (± 8.1), respectively, for ASAD patients without and with CSAD. Similarly, Shear et al. (2006) reported that the majority of adult-onset ASAD cases began in the late teens or early twenties, whereas the childhood-onset ASAD cases began in early or middle childhood.

In conclusion, there is ample evidence for ASAD with first onset in adulthood, ranging from 25 to 50% of identified ASAD cases in clinical studies, and 75% of those identified in a community study. As discussed later, ASAD likely is preceded by heightened levels of separation anxiety in childhood, but not necessarily the full syndrome. Unfortunately, to date, all investigations of ASAD have relied on retrospective recall of CSAD, which may be subject to memory and reporting biases.

7. Course/continuity across the lifespan

Because ASAD generally has not been included as a possible adult “outcome” of CSAD, prospective longitudinal data are not yet available as to whether CSAD typically continues into adulthood. Rather, we have to rely on retrospective reports of adults with ASAD about their childhood separation fears. Although retrospectively recalled CSAD is more prevalent in adult patients with two or more (vs. only one) anxiety disorders, it is unknown whether this finding represents a recall bias, or whether CSAD is a risk factor for multiple anxiety disorders in adulthood (Lipsitz et al., 1994). Shear et al. (2006) found that 36% of adults classified retrospectively as CSAD had ASAD. Similarly, Manicavasagar et al. (2000) examined ASAD in a clinical sample of patients with panic disorder and GAD, and found that those with ASAD on the basis of a structured interview had higher scores on the Separation Anxiety Symptom Inventory (SASI; Silove et al., 1993), with the severity of their childhood separation anxiety symptoms accounting for 33% of the variance in their adult scores. Moreover, these symptoms appeared to predate their other anxiety symptoms. Further, Silove et al. (2002) examined ASAD in addition to the “standard” DSM adult anxiety disorders, and not only found that ASAD was strongly associated with retrospectively measured CSAD, but that this relation was strengthened by taking into account comorbidity; specifically, almost all cases of adult PTSD, GAD, and panic disorder with agoraphobia, who had histories of CSAD, also had ASAD.

Longitudinal prospective data are available concerning the association between CSAD and other (anxiety) disorders into adulthood. Klein (1993) observed that adults with panic disorder often reported histories of childhood separation anxiety, suggesting that CSAD and adult panic disorder/agoraphobia are associated and may reflect alternative manifestations of the same underlying pathophysiologic process. However, prospective longitudinal data, summarized in Craske et al.'s (2010) review, do not support this hypothesis. For example, in a large community longitudinal study, Brückl et al. (2006) found that SAD in adolescents and young adults (ages 14–22) was associated 4 years later with panic disorder or agoraphobia (hazard ratio [HR] = 18), but also with specific phobia (HR = 2.7), GAD (HR = 9.4), OCD (HR = 10.7), bipolar disorder (HR = 7.7), pain disorder (HR = 3.5), and alcohol dependence (HR = 4.7), so they concluded that, although their results reveal a strong association between ASAD and panic or agoraphobia, the results argue against a specific ASAD–panic with agoraphobia relation. Further, neither panic nor agoraphobia was either a specific outcome or a complete mediator of ASAD. In another study of this research group (Brückl, Zimmerman, Wittchen, & Lieb, submitted for publication), CSAD was found to predict a range of mental disorders in females but not in males, to have the highest persistence of any anxiety disorder, and to have the highest number of comorbid disorders among females. Craske et al. (2010) concluded in their review that although consistent observations of longitudinal associations between CSAD and adult/parental panic disorders do emerge, these associations are not sufficiently specific

to justify a view of separation anxiety disorder and panic disorder as alternative manifestations of the same process.

As far as we could determine, only Wijeratne and Manicavasagar (2003) have reported on ASAD in elderly adults. They interviewed 86 primary medical-care patients for lifetime mood and anxiety disorders, and patients also completed a battery of self-report measures. Older adult separation anxiety scores were moderately strongly correlated (r s ranged from .52 to .66) with childhood separation anxiety scores, as well as with both trait anxiety and state anxiety. Higher scores also were associated with greater lifetime history of both mood and other anxiety disorders. Because all data were retrospective, however, the degree to which reporting was biased by current anxiety is unknown.

8. Comorbidity with other psychopathology and personality disorders

Comorbidity is the rule rather than the exception in mental disorders, commonly as high as 50–60%. By investigating the pattern of comorbidities of ASAD with other disorders, more insight can be obtained into whether manifestations of ASAD are unique and autonomous or whether they are multiform and heterogeneous to other disorders (Klein & Riso, 1993). As ASAD symptoms may not be distinguished easily from dependent PD, and share features with panic disorder and agoraphobia, we specifically address the overlap with these disorders. We also specifically investigate possible differences in comorbidity patterns between ASAD with and without childhood onset. For example, adult ASAD without childhood onset may result from traumatic loss of loved ones in adulthood, and therefore the comorbidity with complicated grief and PTSD is of particular importance. See also section 15 on *Differential diagnosis* for a discussion of differential-diagnostic issues.

Using NSC-R data, Shear et al. (2006) found that comorbid anxiety disorders (OR = 4.9) and mood disorders (OR = 4.3) are common in cases identified with either CSAD (retrospectively) or ASAD, and there were no differences in the co-morbidity patterns between CSAD and ASAD cases. Odds ratios were 4.3 for specific phobia, 4.2 for PTSD, 3.9 for panic, 3.7 for GAD, 3.6 for social anxiety disorder, 2.9 for agoraphobia, and 2.4 for OCD. The overlap with personality disorders was not investigated.

In a controlled family study (Nestadt et al., 2003), including 80 case and 73 control probands, as well as 343 case and 300 control 1st-degree relatives, comorbidity was examined among 10 disorders selected because of their established associations with OCD, which was the focus of the study: Obsessive–compulsive PD (OCPD), tic disorder (TD), panic disorder or agoraphobia (Panic/AG), GAD, separation anxiety disorder, recurrent major depressive disorder (MDD), hypochondriasis or body dysmorphic disorder (SOM), pathologic skin picking or nail biting (PSP/NB), and eating disorder (ED; anorexia nervosa or bulimia nervosa). Significant odds ratios with lifetime separation anxiety disorder were found, in decreasing order, for six disorders: SOM (10.7), Panic/AG (7.4), OCD (6.2), NB/PSP (4.2), GAD (3.7), and MDD (2.6). However, assessment was for lifetime disorders and presumably used DSM-IV criteria (i.e., requiring onset before age 18), so it is unknown how many cases of SAD were limited to childhood only versus childhood onset but persistent into adulthood.

Silove, Marnane, et al. (2010), reassigned the primary anxiety disorder of 520 adult patients after including the ASAD diagnosis. Patients had completed an adult self-report questionnaire for separation anxiety symptoms, the Adult Separation Anxiety Symptom Questionnaire-27 (ASA-27; Manicavasagar, Silove, Wagner, & Drobny, 2003). The ASA-27 shows excellent concordance with the ASAD semi-structured interview based on the SCID (First et al., 1996). The ASAD diagnosis was based on an algorithm derived from DSM-IV-TR symptom criteria for separation anxiety disorder, excluding the childhood-onset criterion (Silove et al., 2007). Twenty-three percent of the anxiety-disordered patients received an ASAD diagnosis using this standard. The primary anxiety diagnoses before and after including the ASAD as a possible anxiety diagnosis were: Panic (23%, 12%), Panic-AG (31%, 11%), GAD (26%, 21%), and social

anxiety disorder (20%, 14%). A significantly higher proportion of Panic–AG primary diagnosis patients was reassigned to ASAD compared to patients with other primary anxiety diagnoses (GAD and social anxiety disorder). Note that OCD and PTSD were not included in this study as their base rates were too low. Moreover, specific phobia was not mentioned as a primary anxiety diagnosis, so presumably it was not considered as such in this clinical sample. The results should be interpreted with caution, because ASAD was measured via self-report, whereas the other anxiety diagnoses were made using clinical judgment and a diagnostic interview. Moreover, the standard procedure to decide on a primary diagnosis (i.e., which diagnosis is most debilitating and needs treatment first) was not followed for ASAD. Therefore, the percentage of primary ASAD may be overestimated. Nonetheless, this study does provide information about comorbidity with other anxiety disorders, suggesting the greatest comorbidity with Panic–AG.

Similarly, using a *DSM*-based interview, 508 patients with anxiety and mood disorders were reassessed for ASAD with or without CSAD by history (Pini et al., 2010). Panic disorder, but no other anxiety disorder, was more frequent among ASAD patients with a history of CSAD compared to patients without either ASAD or CSAD. Agoraphobia was not assessed separately.

Complicated grief may be linked to ASAD, as traumatic losses may be the precipitating event also in ASAD. To illustrate, Wijeratne and Manicavasagar (2003) describe three cases of ASAD in elderly patients, of which two developed after the loss of a child. Adult separation anxiety symptoms also were found to be a mediating factor in the relation between CSAD and complicated grief in adults (Shear et al., 2011), such that individuals whose CSAD continued into adulthood were at the highest risk for complicated grief. This finding suggests that loss of a loved one may trigger earlier separation fears, with complicated grief and ASAD as the result. In a study of war-affected Bosnian refugees, almost all persons with ASAD were found to have a comorbid PTSD, whereas only half those with PTSD had comorbid ASAD (Silove, Momartin, Marnane, Steel, & Manicavasagar, 2010).

With respect to the comorbidity with affective disorders, panic disorder patients with versus without comorbid bipolar disorder had more severe adult separation anxiety symptoms (Pini, Abelli et al., 2005), and patients with depressive disorder with versus without comorbid ASAD (and CSAD by history) had a greater number of depressive episodes (Pini et al., 2010).

The comorbidity of ASAD with dependent PD was examined in a large patient sample ($N = 708$) with alcohol or drug addictive disorders or eating disorder (anorexia or bulimia nervosa) compared to non-patient controls ($N = 784$) (Loas et al., 2002). Current and lifetime prevalence of (A)SAD according to *DSM-IV* criteria (i.e., requiring onset before age 18), in the control participants was 2% and 5%, respectively. Current and lifetime prevalence of (A)SAD in the patients was significantly higher, ranging from 6 to 16% (current) and 15 to 31% (lifetime). In both cases, those with alcohol addictions had the lowest prevalence of (A)SAD and those with bulimia the highest. However, the percentage of those with lifetime but not current separation anxiety disorder, that is, whose disorder desisted in childhood versus persisted into adulthood was not reported. The association between dependent PD and ASAD was strongest in the control group for both current ($OR = 12.03$) and lifetime ($OR = 9.85$) ASAD, as well as significant in all patient groups for current ASAD (OR range = 2.4–5.4) and for the substance-addicted patients for lifetime SAD ($Mdn OR = 2.7$). However, whether this association is specific to dependent PD or shared with other PD diagnoses was not addressed.

In a sample of 136 outpatients with anxiety disorders and 176 controls (Osone & Takahashi, 2006), separation anxiety symptoms, based on SASI scores, were examined and, as expected, outpatients had significantly higher scores. Further, when the clinical sample was divided into those with and without one or more PDs, those with PD had earlier onsets of their anxiety disorder, higher SASI scores, and poorer recovery of global functioning. SASI scores were higher in women and younger patients, but the strongest correlate was the number of PDs.

In contrast, in a small ($N = 44$) clinical sample, Manicavasagar et al. (1997) found only 17% overlap between ASAD and dependent PD. In adults referred to an anxiety clinic, the same research group (Manicavasagar et al., 2000) found similar PD rates in those with ASAD versus other anxiety disorders. Interestingly, Silove, Marnane, et al. (2010) found that ASAD patients with a childhood onset had more comorbid PDs (clusters B and C) than those with adult onset.

In sum, although early evidence suggested that ASAD was specifically comorbid with panic disorder or agoraphobia, recent research has revealed a broader range of comorbidities, with the largest overlap with complicated grief and PTSD. Further, mixed results have been found regarding comorbidity with PDs, but ASAD does not appear to be specifically linked to dependent PD, despite clear similarities in diagnostic criteria. Finally, CSAD appears to be a risk factor for ASAD and several other disorders with which it is frequently comorbid, such as complicated grief, PD, and bipolar disorder, as well as for severity (e.g., number of depressive episodes, number of PDs).

9. Familial aggregation

There are virtually no data on familial aggregation of ASAD per se, so in this section we review primarily literature on CSAD. According to *bottom-up* studies, separation anxiety disorder seems to run in families. Elevated rates of separation anxiety disorder were found in 1st and 2nd degree relatives of children with separation anxiety disorder (Last, Hersen, Kazdin, Orvaschel, & Perrin, 1991). Also, children with higher separation anxiety symptom scores were more likely to have either a sibling or child with school refusal (Silove & Manicavasagar, 1993). Conversely, *top-down* studies have documented familial aggregation among parental panic disorder (Biederman et al., 2001), maternal trait anxiety and personality styles (Motlagh, Jazayeri, Mazaheri, Khoshabi, & Karimlo, 2008) and offspring SAD. Maternal separation anxiety (Peleg et al., 2006) or, more generally, phobic anxiety (Bernstein, Laynea, Egana, & Nelson, 2005) was significantly associated with higher levels of separation anxiety in offspring.

Manicavasagar, Silove, Rapee, Waters, and Momartin (2001) may have conducted the only study of this type that actually assessed ASAD, and found that 63% of $n = 54$ children diagnosed with CSAD had at least one parent who suffered from the putative adult variant of the disorder, as compared with 47% and 42% in offspring with other parental anxiety disorders (panic, social anxiety disorder, OCD) or depressive disorder, respectively. This is one of the very few studies providing preliminary evidence for specificity of the family clustering of (A)SAD, because offspring SAD was not associated with other parental anxiety disorders. Familial concordance appeared to be particularly strong for mothers and daughters, which is concordant with findings from twin studies (see below), suggesting either a stronger genetic loading for separation anxiety or perhaps an environmental “modeling” effect in females more than in males (Manicavasagar et al., 2010). Conversely, Kearney, Sims, Pursell, and Tillotson (2003) found that parents reported greater depression, obsessive–compulsive behavior, phobic anxiety, and general distress when their offspring had SAD compared to those with subclinical or no SAD. However, these samples consisted of only 54 (Manicavasagar et al., 2001) and 44 (Kearney et al., 2003) children and their parents, and were clinically referred, limiting firm conclusions.

Further information on familial aggregation also can be drawn from two case–control and three twin studies to date. However, the studies were limited to childhood-onset ASAD, and may not generalize to adult-onset cases. In the first case–control study (Nestadt et al., 2001), higher rates of ASAD, GAD, panic disorder, agoraphobia, and recurrent major depression were found in individuals diagnosed with OCD than in unaffected (non-OCD) control relatives. A second case–control study (Strober, Freeman, Lampert, & Diamond, 2007) observed an association between anorexia nervosa and anxiety disorders among 574 first-degree relatives of 152 probands with anorexia nervosa, compared to

rates observed among 647 first-degree relatives of 181 never-ill control probands. After adjusting for comorbidity of the same illness in the proband, relatives of probands with anorexia nervosa had a significantly higher prevalence of not only ASAD, but also of other anxiety (GAD, OCD, social anxiety disorder, panic disorder), compared to relatives of never-ill control probands. The findings of these two studies indicate non-specificity of the familial aggregation of separation anxiety disorder. However, because comorbidity among the anxiety disorders and with other disorders (e.g., depressive disorders) was not taken into account, conclusions on the specificity of parent-to-offspring transmission of (A) SAD are still limited.

Overall, there is some, albeit not definitive, evidence for the familial aggregation of CSAD, and virtually no data on ASAD. Based on the majority of studies reporting cross-disorder associations between parental psychopathology and offspring SAD (and vice versa), we tentatively suggest non-specificity of parent-to-offspring transmission. Hence, not only ASAD, but also other parental anxiety disorders likely confer risk to offspring for SAD. Given the lack of prospective longitudinal family studies including ASAD, however, conclusions on the familial aggregation of SAD remain indefinite and those for ASAD even more so.

10. Underlying biomarkers

Similar to other anxiety disorders, there is little knowledge on underlying specific biomarkers that may argue for or against validity of the SAD diagnosis in either children or adults. For ASAD, most studies come from Pini's group, favoring the role of a particular peripheral-type benzodiazepine receptor binding. Chelli et al. (2008) suggested reduction of 18 kDa translocator protein (TSPO) density related specifically to the presence of ASAD in a sample of 40 adult outpatients with *DSM-IV* diagnosis of MDD with or without separation anxiety symptoms, and 20 healthy controls, indicating that TSPO expression may be a useful biological marker of ASAD. However, lower density of TSPO also was observed in patients with panic disorder (Pini, Martini, et al., 2005), and in a subgroup of bipolar patients who also met *DSM-IV* ASAD criteria (Abelli et al., 2010). Platelet expression of the 18-kDa translocator protein expression may therefore be a useful, albeit non-specific, biological marker of ASAD, co-occurring with other anxiety and mood disorders as well.

Another ASAD biomarker may be carbon dioxide hypersensitivity, because children of adults with panic disorder experience elevated rates of separation anxiety disorder (Capps, Sigman, Sena, Henke, & Whalen, 1996; Warner, Mufson, & Weissman, 1995), and because CSAD can lead into adult panic disorder. Support for this hypothesis comes from a study in which 104 children (aged 9–17 years), of whom 57 had an anxiety disorder, underwent 5% CO₂ inhalation (Pine et al., 2000). CO₂ hypersensitivity as indicated by enhanced respiratory rate response during CO₂ breathing, elevated minute ventilation, and lower end-tidal CO₂ during room-air breathing was clearly present for separation anxiety disorder and – albeit to a much lesser degree – for GAD, and absent in social anxiety disorder. Both children with SAD and adults with panic disorder display particularly enhanced sensitivity to respiratory stimulation; also see Pine et al. (1998) for findings from a previous study in a subsample. Similarly, in a study of 212 offspring from 135 families, abnormal respiratory physiology in response to CO₂ exposure was found in offspring with both SAD and parental panic disorder relative to offspring with either of these features alone (Roberson-Nay et al., 2010). Taken together, and given the common physiological perturbations of panic and separation anxiety disorder (i.e. physiological abnormalities, particularly respiratory dysregulation, and reaction to inhaled carbon dioxide), the findings argue for non-specificity of the various biomarkers suggested for ASAD.

11. Temperamental and personality antecedents or concomitants

The literature on antecedents of ASAD is almost non-existent, so we review briefly the larger body of literature on putative antecedents of

separation anxiety symptoms, which largely focuses on maternal separation anxiety towards the offspring, typically defined as an unpleasant emotional state evidenced by expressions of worry, sadness or guilt when a mother has to leave her child(ren).

Maternal separation anxiety on a symptom level typically is measured using the Maternal Separation Anxiety scale (Hock, McBride, & Gnezda, 1989), which assesses mothers' level of sadness and guilt when separated from her child(ren), mothers' beliefs about their child(ren)'s ability to adapt to – and benefit from – non-maternal care, and mothers' attitude about balancing maternal and employment roles. Maternal separation anxiety is a relatively stable characteristic (Hock, DeMeijs, & McBride, 1988), and has been linked to a less mature sense of self (as may occur in adolescent mothers) (Blunk & Williams, 1999), negative self-representations (Hock & Schirtzinger, 1992), lower self-esteem (McBride & Belsky, 1988), to memories of mothers' own upbringing as being rejected and discouraged in their independence from their parents, and to insecure attachment representations (Lutz & Hock, 1995). In turn, mothers with high levels of maternal separation anxiety are more likely to have insecurely attached infants (McBride & Belsky, 1988) and to demonstrate more intrusive and less autonomy-encouraging behavior towards their infants (Aber, 1987; cited in Heinrichs et al., 2006). As these findings are cross-sectional, it remains to be investigated to what extent maternal separation anxiety drives insecure attachment and overprotective parenting, or (also) results from child separation fears.

In a rare longitudinal study, Wilhelm, Boyce, and Brownhill (2004) examined relations between the Interpersonal Sensitivity Measure (IPSM), which has a separation anxiety scale, and diagnoses of depression and anxiety, in a cohort of 156 adults who were first assessed when they were young adults. Unfortunately, interpersonal sensitivity was not collected until waves 3 and 4, 10 and 15 years after wave 1. At wave 4, separation anxiety scores were associated with agoraphobia, panic disorder, GAD, and a history of recurrent major depressive episodes, but not with social anxiety disorder or specific phobias. However, this pattern of associations was not specific to separation anxiety (i.e., two other IPSM scales had a similar correlational pattern). Similarly, the authors reported a moderately strong correlation between neuroticism and separation anxiety, but again the relation was not specific, suggesting that separation anxiety may be part of a broader domain of interpersonal dysfunction. On the other hand, relations with various subscales assessing perceived parental environment, which had been measured at baseline, varied across the IPSM scales: For two scales, no significant relations were found, for separation anxiety, relations ranged from small to non-significant ($Mdn = .17$; range = $|.10|$ to $|.21|$), whereas for “fragile inner self,” all correlations were small but significant ($Mdn = .27$; range = $|.19|$ to $|.33|$).

Although prospective studies from childhood are lacking, a few studies have examined concurrent correlations of ASAD with several personality-relevant variables. For example, Silove, Marnane, et al. (2010) reported that patients with ASAD had higher neuroticism scores than patients with other anxiety disorders. Studying adult attachment styles in patients with panic disorder with and without ASAD, Manicavisingar, Silove, Marnane, and Wagner (2009) found that patients with, versus those without, ASAD scored higher on the Adult Attachment Questionnaire subscales of Need for Approval and Preoccupation with Relationships, suggesting that ASAD may be linked specifically to a preoccupied insecure attachment style in adult relationships.

To summarize briefly, the literature on antecedents of ASAD is almost non-existent, but the larger body of literature on separation anxiety symptoms shows them to be relatively stable and even more strongly linked concurrently with neuroticism and its correlates (e.g., low self-esteem, insecure attachment) than are other anxiety disorders. Adults with ASAD tend to have a preoccupied insecure attachment style in adult relationships, and mothers with symptoms of separation anxiety to have insecurely attached infants and, although prospective studies are lacking, they may be perpetuating the overprotective parental behaviors that they recall from their own childhoods. Studies on the important

issue of the relationship between ASAD and parent–child attachment are lacking.

12. Information processing bias in (A)SAD

Cognitive processes reflect relations between experienced events and subsequent emotional responses, so biases occurring in these processes are crucial for the development and maintenance of anxiety disorders (Beck, Emery, & Greenberg, 1985; Foa & Kozak, 1986). Cognitive biases in information processing in anxiety disordered individuals include biased or selective attention, biased judgment, and biased memory (Vasey & MacLeod, 2001), and have been shown to trigger negative interpretations of ambiguous stimuli. However, we did not identify studies reporting on information-processing biases in ASAD; therefore, we briefly summarize findings on selective attention, biased judgment, and biased memory in CSAD, and outline some assumptions about cognitive processes in ASAD.

Studies consistently report processing biases in children with SAD: Compared to non-anxious children, they make more threat interpretations (Bögels & Zigterman, 2000; Cannon & Weems, 2010; Lu, Daleiden, & Lu, 2007) and more avoiding-action plans relevant to ambiguous scenarios (Barrett, Rapee, Dadds, & Ryan, 1996; Chorpita, Albano, & Barlow, 1996), and feel less competent to cope with danger (Bögels & Zigterman, 2000). In contrast, Alfano, Beidel, and Turner's (2002) review concluded that negative cognitions are not consistently associated with clinically anxious children. Moreover, Eley et al. (2008) found that correlations of children's interpretation of ambiguous situations were stronger with depression than anxiety symptoms, when controlling for the other.

Attention selectively facilitates the early processing of threat, thereby initiating a chain of information-processing events, which may act reciprocally to maintain and magnify anxiety states (Vasey & Daleiden, 1996), and also may shape developing cognitive representations (Derryberry & Reed, 2002). Roy et al. (2008) examined attentional bias towards threat in pediatric GAD, social anxiety disorder, and CSAD compared to non-anxious controls. Children with any anxiety disorder displayed greater attention towards threat (vs. happy or neutral) faces compared to non-anxious controls, with no differences among disorders.

In-Albon, Dubi, Rapee, and Schneider (2009) examined interpretation bias using a forced-choice reaction-time paradigm with children diagnosed with CSAD or social anxiety disorder and non-disordered children. Children with CSAD rated ambiguous separation pictures as significantly more unpleasant and more arousing than non-anxious children, but there were no significant differences in reaction time or interpretation bias. In another study, In-Albon, Kossowsky, and Schneider (2010) used an eye-tracker paradigm to test whether children with CSAD have a similar attention bias for threatening information as anxiety-disordered adults. Children with CSAD gazed significantly more at separation (threatening) pictures than nonanxious children after a period of 1 s, but after 3 s the pattern reversed.

Bögels, Snieder, and Kindt (2003) examined whether interpretation bias in ambiguous stories describing separation or social situations or referring to generalized anxiety, and their related action plans was common across separation, social, and generalized anxiety disorders or whether the biases were content-specific in school-aged children who scored in the top 10% on a scale for separation, generalized, or social anxiety disorder, and not in the top 20% on the two other scales. Overall, high-anxious children displayed negative cognitive bias compared to control children, but did not differ from controls with respect to their action plans or avoidance. Further, children high on the separation and social anxiety disorder scales reported more negative thoughts and interpretations of separation themes compared to those high on GAD, indicating some support for content-specificity, but they were not different from each other, probably due to similarity in the stimulus material. Other studies also have not found convincing evidence for content-specificity of processing bias in SAD (Kindt, Bögels, & Morren, 2003;

Vasa et al., 2007; Waters, Craske, Bergman, & Treanor, 2008), suggesting that the information-processing bias may be a general vulnerability marker for anxiety disorders (Pine, Wasserman, & Workman, 1999).

Vasa et al. (2007) explored visual and verbal memory deficits in offspring of a parent with versus without a lifetime history of panic disorder or MDD, and found no differences between children with separation versus social or generalized anxiety disorder, or unaffected children. Offspring SAD marginally predicted visual memory ($p = 0.052$). On the other hand, Pine et al. (1999) found that verbal and visual memory deficits predicted future anxiety disorders (social, separation and overanxious disorder together) and symptoms.

A great deal of research has examined how and when biased cognitive mechanisms are triggered in CSAD, focusing on the role of family factors (Hudson & Rapee, 2002; Rachman, 1997), specifically, that cognitive bias might stem from relations between parent characteristics and childhood anxiety (e.g., anxious parents may model fearful behavior). Perez-Olivas, Stevenson, and Hadwin (2008) recently suggested that maternal overinvolvement increased a child's separation anxiety, finding that an attentional bias to angry faces was associated with an increased level of offspring's SAD, but only in older children (>10 years). In contrast, Bögels, van Dongen, and Muris (2003) did not find parents to maintain or enhance the interpretation bias of their anxious children. In adults, attentional bias towards threat is one of the most robust findings in experimental anxiety research (Cisler & Koster, 2010; Ouimet, Gawronski, & Dozois, 2009), but consideration of factors contributing to the maintenance and development of cognitive bias is rare.

Based on these findings, we may conclude that children do not yet possess elaborated fear networks, and that these networks are not chronically activated (Foa & Kozak, 1986), and thus do not reside in working memory, as they do in disordered adults who constantly dread the next panic attack or separation situation. This may help to explain the diversity of child findings. With increasing age, non-anxious children may learn to inhibit threat processing, whereas high anxious children do not, even into adulthood (Kindt et al., 2003). Hence, biases are found only in older children, and may be more robust in adults. Note that according to Last, Perrin, Hersen, and Kazdin (1996), CSAD has a very high recovery rate (96%), albeit symptoms may wax and wane across time and persist into adulthood, which also may explain the inconsistent findings.

Notably, it remains unclear whether content-specificity of information-processing bias exists in SAD, let alone in ASAD. For children, the evidence is weak, and given the high comorbidity among anxiety disorders, as well as the overlap of worries and fears across them, domain-specificity of bias seems unlikely. If cognitive distortions in memory, attention, or interpretation of ambiguous material exist, they may reflect dysfunction in the medial temporal lobe (Preston & Gabrieli, 2002; Vasa et al., 2007). Hence, identifying memory deficits in CSAD may highlight involved brain regions that also may be relevant in ASAD.

In sum, due to the observed diversity of findings in children, and the clear lack of studies in adult separation anxiety, inferences to biased cognitive processes in ASAD can hardly be drawn, thereby stressing the importance of further research on anxiety-related information processing in children and adults, because identification of specific sets of cognitive distortions may have implication for the treatment (CBT) of the disorder.

13. Genetic risk factors

13.1. Behavior genetics

We did not locate any twin or adoption studies of ASAD specifically, but the data are relatively consistent, with a higher prevalence of lifetime SAD in MZ compared to DZ twins (e.g., Ehringer, Rhee, Young, Corley, & Hewitt, 2006), and a higher concordance on SAD for MZ than for DZ twins, especially in girls (e.g., Bolton et al., 2006; Ogiari et al., 2010;

Silove, Manicavasagar, O'Connell, & Morris-Yates, 1995) although Ehringer et al. (2006) found this only for 12-month, not lifetime diagnosis, and results varied depending on the rating source (i.e., self vs. parental; Eaves et al., 1997; Topolski et al., 1997). Also generally found is a large *non-shared* environment contribution which, of course, includes non-systematic (i.e., error) variance.

In contrast, heritability of separation anxiety symptoms appears to be more modest, and *shared* environmental influences play a significant role (Eley, Rijdsdijk, Perrin, O'Connor, & Bolton, 2008; Feigon, Waldman, Levy, & Hay, 2001; Hallett, Ronald, Rijdsdijk, & Eley, 2009; Topolski et al., 1997). Importantly, in some studies, comorbidity among SAD and both specific phobia and social anxiety disorder syndromes (i.e., minus impairment criteria) was influenced by shared environment, whereas only the comorbidity between SAD and social anxiety disorder was under genetic influence, suggesting that (1) the genetic influence may act more generally on or through interpersonal relations, (2) the shared environment component may have been overestimated due to data from maternal-informant diagnostic interviews, which concomitantly (3) would underestimate the heritability estimates.

Similar results were obtained in a child and adolescent female twin sample (Silberg, Rutter, & Eaves, 2001), with aspects of the shared environment that influenced symptoms of depression also contributed to symptoms of separation anxiety, specific phobias (only in children), and overanxious disorder (only in adolescents). Hence, there is tentative evidence for significant influence of both additive genetic and shared environmental influences on separation anxiety during middle childhood and adolescence, but these influences do not appear to be specific to separation anxiety.

The search for genetic, albeit non-specific, factors in separation anxiety is further supported by associations between *neuroticism* and separation anxiety disorder. Neuroticism has been shown to be a heritable vulnerability for a mood and anxiety disorders, including separation anxiety (Lahey, 2009). Eaves et al. (1997) did report a substantial genetic contribution to separation anxiety that was distinct from neuroticism but only in females.

In addition to direct genetic influences, most studies of CSAD have found environmental influences to play an important *moderating* role in development of the disorder (for reviews, see Eley, 1999; Feigon et al., 2001). In particular, genetic effects on separation anxiety symptoms in childhood and adolescent panic symptoms appear to increase across independent negative life events. For example, Lau, Gregory, Goldwin, Pine, and Eley (2007) reported on heritability rates for childhood (28–38%) and adolescent (41–48%) SAD in two longitudinal twin studies. Heritability estimates for separation anxiety and panic symptoms did not differ with age, but were consistently larger among individuals who reported versus did not report negative life events, indicating environmental moderation of genetic effects. The question remains, however, whether similar findings can be observed for ASAD and, if so, whether the effects are independent of other comorbid, especially anxiety disorders.

13.2. Biological genetic studies

Although important progress has been made, understanding the genetic background of separation anxiety and other anxiety disorders and identifying links with specific genes has been slow, most likely because multiple genes of small effect size influence anxiety with varying degrees of specificity (Gregory & Eley, 2007). Moreover, research on ASAD is limited largely to studies on the genetic background of CO₂ hypersensitivity in small patient samples; therefore, the findings we review are primarily based on CSAD.

Genetic (e.g., linkage, association) studies on SAD are rare, and most focus on the overlap between CSAD and adult panic disorder (see Silove, Manicavasagar, Curtis, & Blaszczyński's, 2004 review), based on Klein's (1993) longstanding separation anxiety–panic disorder hypothesis, according to which there is a common genetically determined neurophysiological vulnerability underlying these two conditions. In a multivariate

Norwegian twin sample ($N = 712$, mean age 30.9 years; Battaglia et al., 2009), determinants shared between retrospectively assessed CSAD and lifetime panic explained 89% of the genetic variance and thus may be the primary underlying cause of both disorders' association with heightened CO₂ sensitivity (e.g., Roberson-Nay et al., 2010), and the developmental continuity of CSAD and adult panic disorder, as well as ASAD.

Subpopulations of adult patients with panic (Pini, Martini, et al., 2005) and depressive disorder (Chelli et al., 2008) were found to have lower levels of peripheral-type benzodiazepine receptors, but only in the presence of comorbid ASAD. These findings argue for common underlying genetic factors predisposing for a dysregulation of the biological underpinnings of a putative attachment system (i.e., controlling individuals' response to separation from major attachment figures), and thus for a specific link between CSAD and adult panic disorder. This predisposition may be manifested in heightened sensitivity to inhaled CO₂ (Fiese, Winter, Wamboldt, Anbar, & Wamboldt, 2010), in dysregulation in oxytocin, and/or vulnerability (again, hyperreactivity) to environmental stress, such as loss of a caregiver (Lau et al., 2007; Silberg, Rutter, Neale, & Eaves, 2001).

The dysregulation of *oxytocin* as a putative mechanism underlying social attachment has been examined widely in animal studies, and recently has become of interest in human studies. Costa et al. (2009a) found Ala147Thr substitution in translocator protein to be associated with adult separation anxiety in patients with depression. Further, diagnostic specificity of genes influencing the biological system(s) that modulate(s) the search for – and maintenance of proximity to – significant attachment figures (Costa et al., 2009b) was considered in depressed patients with and without ASAD, and controls, revealing no mutations in promoter and coding regions of the oxytocin preprohormone. Albeit certain polymorphisms were evidenced in 21% to 39% of the three groups, comparison of genotype distributions yielded no significant differences among them, suggesting non-specificity. Similarly, alterations of oxytocin levels were found in adult patients with depression, autism, and obsessive–compulsive disorder (Costa et al., 2009a, 2009b). Although diverse polymorphisms in untranslated regions of the human oxytocin gene have been found, neither association nor functional studies have been carried out.

With respect to the specificity of genetic effects, it is unclear whether those for separation anxiety disorder are selectively linked to panic disorder or are more general anxiety-related risk factors. For example, higher prevalence of not only separation anxiety, but also of specific phobia and GAD, was reported in 109 children with Williams Syndrome (a genetic disorder caused by a deletion on chromosome 7q11.23), relative to the general population and other genetic disorders associated with intellectual disability (Leyfer, Woodruff-Borden, & Mervis, 2009). The comorbidity suggests a connection between not only this deletion and separation anxiety, but also with anxiety more generally, not just with panic disorder. Because most studies lack comparisons with healthy controls, however, specificity of the familial aggregation and genetic findings cannot be evaluated.

In sum, findings indicate moderate heritability of separation anxiety symptoms and stronger influence for SAD, especially in females. We cannot yet estimate the degree of heritability of SAD. Its underlying causal factors and mechanisms likely include genetic and environmental components that are strongly correlated with those of other anxiety disorders. The question of which genes or polymorphisms may be involved in the etiology of separation anxiety, beyond the association between ASAD and oxytocin peptide and receptor polymorphisms, is still unknown. Further analyses, allowing also for the effects of age on the expression of genetic and environmental factors, are needed.

14. Environmental risk factors

Behavior-genetics research on CSAD shows unique environmental risk factors to be strong, especially in boys, but such research has not been carried out for ASAD. Research on the comorbidity of ASAD (see

Comorbidity with other psychopathology and personality disorders section), however, provides some insight into possible environmental risk factors for ASAD. The large overlap between ASAD and PTSD suggests that trauma, and related fear for personal safety, is a risk factor for ASAD, whereas the strong association between ASAD and complicated grief suggests that loss of a loved one, through death, divorce, or change of caregiver, is another. Moreover, a gene–environment interaction is suggested by the finding that ASAD mediated the relation between CSAD and complicated grief (Vanderwerken, Jacobs, Parkes, & Prigerson, 2006). Parental death and divorce also have been found to be related to panic with agoraphobia (Tweed, Schoenbach, George, & Blazer, 2008). Although ASAD was not included in this study, given other observed relations between panic and ASAD, it could be hypothesized that after experiencing one's parent's death, individuals may develop either a fear of dying themselves (i.e., panic disorder), a fear of other loved ones dying (i.e., ASAD), or both.

Parenting may be another environmental risk factor for ASAD. In general, parenting shows small correlations with child anxiety (McLeod, Wood, & Weisz, 2007; van der Bruggen, Stams, & Bögels, 2008; Wood, 2007), and those with parental anxiety are even smaller (van der Bruggen et al., 2008). A few studies have examined associations between parenting and separation anxiety specifically. In adults, ASAD, but not panic disorder, was associated with retrospective reports of maternal overprotection (Manicavasagar, Silove, Wagner, & Hadzi-Pavlovic, 1999), but other aspects of interpersonal sensitivity also have shown this association (Wilhelm et al., 2004). In children, Wood (2007) found parental intrusiveness to be related to CSAD, but not to other childhood disorders. Similarly, maternal overinvolvement has been associated with SAD (Perez-Olivas et al., 2008).

Herein, In-Albon, and Schneider (2006) investigated cognitions in parents of children with SAD or social anxiety disorder, and control children. Mothers of children with SAD versus with social anxiety showed lower parenting self-efficacy and, similarly, lower parenting self-efficacy and satisfaction compared to mothers of the control children. The results were unaffected by parental anxiety, and suggest that parenting self-efficacy may be an environmental factor for maintenance of SAD, although the direction of the relation is yet unknown: Parenting a child with separation anxiety disorder may undermine parental self-efficacy, or low parental self-efficacy may cause or maintain child separation anxiety.

Environmental risk factors for ASAD may be linked to certain developmental periods including prenatal cocaine exposure (e.g., Morrow et al., 2009). For example, Hock, Eberly, Bartle-Haring, Ellwanger, and Widamann (2001) developed an adult separation anxiety scale to assess the separation-related fears of parents of adolescents. Anxiety about separation was modulated by the adolescents' age and the attachment security of the parent–adolescent relationship, from the perspective of both parents and adolescents. Thus, children becoming independent may be an environmental risk factor for ASAD, depending on the quality of the attachment relationship.

15. Differential diagnosis

What differential-diagnostic issues will arise now that ASAD is systematically considered as an adult anxiety diagnosis in *DSM-5*? Initially, the disorder closest to ASAD would seem to be the *DSM-IV-TR* diagnosis of panic disorder with agoraphobia (Silove, Marnane, et al., 2010), with the difference being that fear of having a panic attack does not drive separation anxiety as it does to agoraphobia. Patients with ASAD may develop panic attacks in the face of separation from loved ones, but the primary fear is of the separation, not a panic attack.

Given that the diagnostic category of agoraphobia can be diagnosed separately from panic disorder in *DSM-5* (Wittchen, Gloster, Beesdo-Baum, Fava, & Craske, 2010), it also is important to consider the overlap between ASAD and agoraphobia alone. Agoraphobic situations are defined as confined places and situations (crowds, shops, restaurants,

transportation) or similar places or situations from which escape might be difficult (e.g., open spaces) or in which help might not be available in the event of panic-like, incapacitating, or embarrassing symptoms; thus, agoraphobic patients often seek company to ensure that help would be available. The demarcation from primary separation anxiety is the different situations that trigger the fear, as well as the reason for fearing being alone (the unavailability of help in agoraphobia vs. something happening to loved ones in ASAD).

The differential diagnosis between GAD and ASAD is also an important issue. Worrying about something happening to loved ones can be a fear theme in GAD, as it is in ASAD. This differential-diagnostic issue is present already in CSAD versus GAD. That is, half of the children and adolescents with GAD do worry about harm befalling their parents when not with them (Masi, Mucci, Favilla, Romano, & Poli, 1999), and the vast majority of children diagnosed with SAD have comorbid GAD (Verduin & Kendall, 2003). Comparing the criteria, the difference between the disorders appears to be that fear/worry of losing loved ones is one of many possible themes in GAD, within an adult who excessively worries about a variety of events and situations (i.e., everyday matters such as health issues, money, death, family problems, friendship problems, interpersonal relationship problems, or work difficulties), whereas fear/worry of losing a limited array of significant attachment figures is the central characteristic of those with (A)SAD.

The differential diagnosis between ASAD and dependent PD is another important issue. In dependent PD the underlying fear is to be unable to care for oneself physically or to cope emotionally on one's own, whereas in ASAD the fear of losing, for example, a child is unrelated to the former and may be unrelated to the latter as well. Also, dependent PD is characterized by a pervasive and indiscriminate tendency to rely excessively on others, for example, for decision-making, due to a general lack of self-confidence, whereas in ASAD there is a more limited array of concerns about the proximity and safety of attachment figures (Pini et al., 2010). However, if the primary attachment figure in ASAD and/or dependent PD is the spouse or the partner, there may be considerable overlap in the basis for the extreme wish for his or her constant presence.

In addition, fear of losing a primary attachment figure, especially one's partner, may take the form of morbid jealousy in ASAD. An excessive and unrealistic fear that the partner may commit adultery and eventually leave is not described in the *DSM*, but is a not uncommon clinical problem that responds well to cognitive-behavior therapy (CBT; Leahy & Tirsch, 2008). Note that “recurrent suspicions, without justification, regarding fidelity of spouse or sexual partner” also is a criterion for *DSM-IV-TR* paranoid PD. Thus, the fears in ASAD may have an obsessive, and/or paranoid/jealous quality to them, instead of – or in addition to – the more typical self-concern-based distress. Note also that “frantic efforts to avoid real or imagined abandonment” is a criterion for *DSM-IV-TR* borderline PD, which reflects well the desperate fear of losing a loved one seen in ASAD. However, we could find no research investigating the distribution of these different “facets” of separation anxiety in adults and it is unlikely that clearly distinct subtypes exist. Rather, it is more plausible that a wide variety of cognitive contents share a common underlying dimension of severity of distress and that it will be more fruitful to assess the degree of anxiety/distress and then characterize the nature of the distress on a clinical-case basis.

16. Treatment

ASAD has been found to be a debilitating condition, and 75% of those with ASAD in the NCS-R community sample had received treatment for emotional problems, although ASAD had not been a focus of treatment in most (68%). Moreover, we could find no studies in which ASAD was the specific target of treatment other than case studies (e.g., Butcher, 1983). It is unknown, however, whether this is because clinicians think of separation anxiety as a childhood disorder and so do not inquire about it in adults, because there are no specific treatments, or some other reason. Therefore, the question remains whether ASAD should be

a specific focus of treatment. CSAD has been treated successfully in the context of CBT for child anxiety disorders in general (e.g. [Bodden et al., 2008](#)), as well as disorder-specific CBT ([Schneider et al., 2011](#)), the latter showing that 76.2% of the children no longer met the criteria for CSAD, compared to 13.6% of the waitlist control children.

Two studies examined the effect of adult separation anxiety on outcome of CBT for anxiety disorders, not directed to separation anxiety. [Kirsten, Greyner, Wagner, and Manicavasagar \(2008\)](#) found that adult separation anxiety negatively influenced outcome of the treatment target in patients with social anxiety disorder, panic disorder, or GAD. Similarly, [Aaronson et al. \(2008\)](#) found that patients with panic disorder and comorbid ASAD were four times more likely to have a poor outcome with CBT than those without comorbid ASAD, and this effect remained after controlling for other prognostic factors, such as severity of anxiety symptoms and agoraphobia, number of comorbid anxiety disorders, duration of illness, and socio-economic status. Case studies further revealed that traditional CBT focused on other anxiety disorders does not reduce adult separation anxiety ([Manicavasagar & Silove, 1997](#)). Thus, we can hypothesize that treatments such as CBT that specifically focus on ASAD, either on its own or with other anxiety disorders, would reduce separation anxiety and produce better outcomes but, of course, ASAD needs to be assessed in adults referred with anxiety disorders before this can be tested. Inclusion of ASAD in *DSM-5* is expected to encourage this assessment in clinical and research settings.

Lacking treatment studies of ASAD, we briefly discuss the treatment outcome literature for CSAD. Most studies on the treatment of child anxiety disorder test a general CBT designed for treating several anxiety disorders, and have not specifically tested how children with CSAD respond to treatment relative to children with other anxiety disorders. A few studies focused specifically on CSAD, and found promising results for parent–child interaction training, “summer camp” CBT ([Ehrenreich, Santucci, & Weiner, 2008](#)). With respect to psychopharmacological treatment, SSRIs (e.g., fluoxetine) have proven effective in treating child anxiety disorders, but again have not been tested specifically for CSAD ([Ehrenreich et al., 2008](#)). Thus, in the child literature as well, there is little information as to whether children with separation anxiety disorder need different treatment approaches. It should be noted that as (1) separation anxiety in children, unlike in adults, is a well recognized problem, and (2) CBT for child anxiety disorders is designed to cover several anxiety disorders within one treatment protocol, including separation anxiety disorder, CBT for (separation) anxiety disorder in children does not inform us about whether treatment of separation anxiety disorder can be differentiated from other treatment of other anxiety disorders in children, let alone in adulthood.

Finally, the literature on the treatment of dependent PD may be informative. Psychodynamic treatment, CBT, schema-focused therapy, group psychotherapy, marital and family therapy, and pharmacotherapy have been described ([Faith, 2008](#)); however few controlled outcome studies have been completed. In particular, marital and family therapy – approaches that make sense because these patients tend to be dependent on their spouses and family (as patients with ASAD) – has not been examined as stand-alone treatments.

17. Discussion and preliminary recommendations for *DSM-5*

This review focused on the evidence for an adult form of separation anxiety disorder (ASAD). Although *DSM-IV-TR* does allow for a diagnosis of ASAD, this anxiety category generally has been overlooked as it was placed in the “begins in childhood” section. However, studies from three independent research groups in Australia, Italy and the U.S., respectively, provide evidence for the existence of an adult form of this disorder. The U.S. study is the only large community sample to date, whereas large clinical-sample studies were conducted in Australia and Italy. All three studies show that ASAD is an identifiable diagnostic entity, is prevalent, is as or more debilitating than most anxiety disorders, appears to precede the onset of other anxiety disorders and depression,

and has comorbidity patterns with other anxiety disorders and depression that are similar to those found in other anxiety disorders. As ASAD has not been measured in longitudinal and family studies, we can only rely on retrospective assessments of adults with separation anxiety disorder, but those studies do suggest continuity of separation anxiety across the life span, as well as family aggregation. Some biomarkers have been identified for ASAD, but nonspecific to ASAD, similar to what is found with other anxiety disorders. The heritability of CSAD has been found to be moderately strong, but no behavior genetic studies on ASAD exist. Trauma and loss appear to be environmental risk factors. Moreover, ASAD may be, more than other anxiety disorders, related to parental overprotection and intrusiveness, which are the most frequently investigated parenting styles related to the intergenerational (i.e., parent to child) environmental transmission of anxiety disorders (e.g., [van der Bruggen et al., 2008](#)). The little existing research on treatment suggests that adult separation anxiety negatively affects treatment outcome of other anxiety disorders, and this finding tentatively suggests that identifying ASAD systematically, and tailoring treatment to the specific needs of these patients, could improve outcomes.

Allowing a more explicit ASAD diagnosis in *DSM-5* will enhance the developmental sensitivity of the *DSM* to assess disorders across the life span, and stimulate research into the developmental continuity, family aggregation, etiology, and treatment response of separation anxiety. Importantly, it also will eliminate an imbalance in the categorization of anxiety, in which separation anxiety is the only disorder that appears in the “childhood onset” category and thus is not explicitly applicable to adults as well as children, which has resulted in its being inconsistently used by clinicians and ignored in epidemiological research.

The *DSM-IV* criterion “onset before age 18” is not supported by the literature, showing that a substantial portion of adults with separation anxiety disorder has first onset in adulthood, although symptoms of separation anxiety may have been present during childhood, but without the person retrospectively meeting full disorder criteria. Thus, it has been removed in *DSM-5*, so we look forward to increasing research into ASAD in the future.

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