Childhood Separation Anxiety and the Pathogenesis and Treatment of Adult Anxiety

Barbara Milrod, M.D.

John C. Markowitz, M.D.

Andrew J. Gerber, M.D., Ph.D.

Jill Cyranowski, Ph.D.

Margaret Altemus, M.D.

Theodore Shapiro, M.D.

Myron Hofer, M.D.

Charles Glatt, M.D.

Clinically significant separation anxiety disorder in childhood leads to adult panic disorder and other anxiety disorders. The prevailing pathophysiological model of anxiety disorders, which emphasizes extinction deficits of fear-conditioned responses, does not fully consider the role of separation anxiety. Pathological early childhood attachments have far-reaching consequences for the later adult ability to experience and internalize positive relationships in order to develop mental capacities for self-soothing, anxiety tolerance, affect modulation, and individuation. Initially identified in attachment research, the phenomenon of separation anxiety is supported by animal model, neuroimaging, and genetic studies. A role of oxytocin is postulated. Adults, inured to their anxiety, often do not identify separation anxiety as problematic, but those who develop anxiety and mood disorders respond more poorly to both pharmacological and psychotherapeutic interventions. This poorer response may reflect patients' difficulty in forming and maintaining attachments, including therapeutic relationships. Psychotherapies that focus on relationships and separation anxiety may benefit patients with separation anxiety by using the dyadic therapist-patient relationship to recapture and better understand important elements of earlier pathological parent-child relationships.

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The fear extinction model of anxiety, a unifying construct in the Research Domain Criteria (RDoC) of the National Institute of Mental Health, focuses on biological underpinnings and plasticity of a critical behavioral response. Despite its many empirical strengths, it provides an incomplete model of anxiety (1, 2). Separation anxiety and attachment models hold promise for translational research, address aspects of anxiety complementary to fear conditioning, and may warrant consideration in working theoretical models of anxiety.

Anxiety induced by separation from close attachment figures is normal and adaptive in early childhood (3–5). Yet if this prominent emotional state persists into later childhood, adolescence, and adulthood, separation anxiety becomes linked to increasingly pathological self-perceptions and inadequate homeostatic regulation of internal object relations. An individual with separation anxiety feels unable to function in the absence of the mother or her surrogate (4, 5). Separation anxiety is often comorbid with mood, anxiety, and personality disorders (6). Its developmental role in panic disorder has long been considered formative (7–11). From the perspective of neural systems underlying fear and reward, separation anxiety may indicate excessive activation of fear circuits in response to separation and overactivation of reward circuits with reunion. However, it seems possible, even likely, that observed functional differences in fear and reward circuitry in individuals with separation anxiety do not cause but, rather, result from abnormalities or deficits in systems underlying social representation and cognition (12, 13). While the fear conditioning paradigm illuminates anxiety resulting from trauma, it sheds less light on the developmental pathway of chronic anxiety of more insidious onset. The following case illustrates this point.

"Lena," a 25-year-old graduate student, had multiple daily severe, terrifying panic attacks wherein she felt she could not breathe and was dying. She described severe agoraphobia, inability to travel anywhere alone (including to her doctor's office), terror of being any distance from her home, a new inability to drive because of panic, and frantic clinging to her girlfriend, "Jane," toward whom she had mixed feelings. She sought treatment after being forced to take leave from her graduate program because she could not drive alone in her car to commute to school. Her DSM-IV diagnoses on the Anxiety Disorders Interview Schedule for DSM-IV (14) at intake were panic disorder (with a score of 7 out of a possible 8, indicating severe symptoms), agoraphobia (7 of 8, severe), and generalized anxiety disorder (3 of 8, indicating trait-level symptoms not meeting the full DSM criteria). Lena's anxiety had increased to panic proportions several months before, when she began to contemplate breaking up with her previous girlfriend. Careful history revealed that anxiety had dominated Lena since earliest childhood.

Terrified and highly anxious throughout childhood, Lena experienced severe anxiety daily when her mother left for work. She reported crying throughout the day, even when her father or grandmother was present. Throughout childhood she could sleep only when sharing her mother's bed, a situation that contributed to her

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parents' divorce. At age 9, when her mother expelled her from her bed, Lena began sleeping with her younger sister. She remained frightened of being alone, especially at night. At college, she immediately began sharing her roommate's bed. When she sought treatment at age 25, she had never spent a single night alone in a bed, having frantically juggled family, friends, and lovers to avoid this terrifying experience, which she described as "being alone in the void."

Lena's parents had sent her repeatedly to psychiatrists and therapists through childhood and adolescence. Although she had sometimes found it helpful to discuss aspects of her life, she never mentioned her terror of separation to any therapist, knowing it was "definitely unusual and really embarrassing." She considered it an accepted, nearly imperceptible, if highly embarrassing backdrop to other aspects of her chaotic life.

Importance of Separation Anxiety Across Anxiety Disorders

Central attachment relationships form the core of human emotional development. The formation and qualities of the dyadic bond between the mother (primary caretaker) and infant create the nexus of an "internal working model" of the mind/brain (4, 5). Bowlby described this internal working model as the safe base from which the toddler can explore the surrounding world. This model in turn often affects patterns in future adult relationships. We describe this model as a separation-sensitive social schema.

The inherent dependency of the human infant makes anxiety normal for young children (like other mammals) when separated from caregivers. In contrast, separation anxiety disorder in childhood and adulthood describes a nonnormative, pervasive anxiety state accentuated by separations from close attachment figures at developmental junctures where the need for proximity to attachment figures is no longer adaptive. DSM-IV identified separation anxiety disorder solely as a childhood anxiety syndrome—indeed, as the only anxiety disorder listed under "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence" (15). DSM-5 groups it more broadly among the anxiety disorders. The National Comorbidity Survey Replication epidemiological survey documented a 6.6% lifetime prevalence of separation anxiety disorder in adults across a large national general population sample (16). Prevalence ranges between 12% and 40% in adult psychiatric clinic settings (17, 18). (The studies by Silove et al. [17] and Pini et al. [18] had two of the largest clinical samples used to investigate adult separation anxiety disorder. Silove et al. [17] found a consistently higher degree of symptom severity and impairment associated with separation anxiety than with other adult anxiety disorders. Pini et al. [18] found delineation between the onset ages for patients with childhood separation anxiety only and those who had the disorder in both childhood and adulthood.)

Separation anxiety has both heritable (genetic) and social (experiential/epigenetic) origins. Some patients presumably have an inborn anxious propensity (i.e., lower thresholds); others may be phenocopies due to anxious or anxiety-provoking caretaking (anxious children have anxious mothers [19]); still others may represent an interaction of genes and environment. Anxiety about separations in 1–3-year-olds is a normative sign of healthy relationships (19), but its pathological persistence impairs children's comfort in independent exploration and autonomy, and it complicates age-normative developmental tasks, such as sleeping without a parent or attending school, thus interfering with age and stage adaptation (10).

Patients with separation anxiety disorder have greater disability, more severe depression and anxiety symptoms, and larger stress responses than do other anxiety disorder patients routinely treated in anxiety disorder clinics (17). In cross-sectional findings, 75% of adults with anxiety disorders seeking treatment at anxiety disorders clinics report having had separation anxiety disorder in childhood (20). A recent longitudinal twin study suggests that a common genetic diathesis underlies childhood separation anxiety disorder and adult panic attacks (21). A meta-analysis of case-control, retrospective, and cohort studies associated childhood separation anxiety disorder with panic disorder and other anxiety disorders in adulthood (10). Nonetheless, the developmental perspective that informs such studies—specifically, links between separation anxiety and the course of other anxiety and mood disorders—has lacked sufficient articulation (20).

Table 1 contrasts summary findings on separation anxiety with findings on fear extinction in anxiety disorders.

Genetic and Epigenetic Animal Models of Separation Anxiety

Separation anxiety has deep evolutionary roots. The larger literature on primate and subprimate mammals is selectively sampled below.

As juveniles, rats bred for high levels of infant calling responses upon separation from mothers showed major changes in autonomic responses when isolated. These animals engaged in significantly less social play behavior than control rats. As adults, they emerged significantly more slowly from familiar enclosed spaces into open areas and showed the distinctively passive, "helpless" behavioral pattern in a swim test, validated for detecting vulnerability to depression and anxiety in laboratory rats (28, 29).

Mother bonnet macaques showed rejection behavior toward their infants (30) when exposed to a variable feeding delivery schedule, a laboratory-induced environmental stress (31). The stressed mothers' distant behavior toward their babies led to infants' fearfulness and clinging to their mothers, difficulties in both leaving mothers and interacting socially, and lifelong "timidity" accompanied by high stress responses. The investigators (32) identified a specific genetic-environmental interaction constituting a risk for developing this abnormal mother-infant relationship that produced chronic anxiety later in life.

TABLE 1. Comparison of Fear Extinction and Potential Separation/Attachment Models of Anxiety

Domain	Fear Extinction Model	Separation/Attachment Model
Paradigmatic disorder	Posttraumatic stress disorder	Panic with or without agoraphobia
Psychosocial treatment	Exposure	Psychodynamic or interpersonal therapy
Animal model	Fear conditioning	Disrupted maternal care producing greater hypothalamic/pituitary responsivity to stress
Neuroimaging findings	Heightened activity in the amygdala and dorsal anterior cingulate cortex (fear expression), diminished activity in the ventromedial prefrontal cortex	Circuitry underlying separation-sensitive social schemas and attachment: subcortical areas (amygdala, hippocampus, striatum) and cortical limbic areas (insula, cingulate); may imply predisposing endophenotypes from circuitry involved in attention, learning, and executive control (medial prefrontal cortex, superior temporal sulcus, and temporoparietal junction) (22)
Genetics	Potential systems: FK506-binding protein 5 (FKBP5, 6), brain-derived neurotrophic factor (BDNF, 23), serotonin transporter (24)	Potential systems: oxytocin receptor (25), vasopressin 1A receptor (26), D_2 dopamine receptor (DRD2, 27)

High levels of maternal "anxiety" or stress appeared to mediate these changes, impairing the mothers' ability to form normal attachments with their infants.

Diorio and Meaney (33) found that changes in rat postnatal maternal behavior in response to environmental stress during pregnancy yielded increased fear behaviors and adrenocortical responses in their adult offspring. The investigators traced these transgenerational effects to epigenetic changes in brain gene expression patterns throughout the offspring's development. While possibly adaptive in the setting of acute stressors in adulthood, under normal conditions these changes placed the offspring at risk for multiple pathologies and lifelong heightened stress responses. These early nurture differences generated long-term changes in gene expression levels throughout life (28, 34).

Adult Separation Anxiety: Prevalence in Anxiety and Mood Disorder Patients

The traits of separation sensitivity, excessive dependence on close attachment figures, and anxiety surrounding separations (the standard threshold is a score of 35 or higher on the Panic-Agoraphobic Spectrum Self-Report [35]) have been linked to development of complicated grief (36) following loss. A study comparing 53 subjects with complicated grief to 50 healthy bereaved comparison subjects found levels of adult separation anxiety significantly higher ($p<0.001$) in the group with complicated grief than in the comparison subjects. In both groups a higher level of separation anxiety was associated with higher depressive and manic symptom levels on the self-report version of the Structured Clinical Interview for Mood Spectrum (MOODS-SR) (37), and in both groups mood variations appeared dimensionally related to separation anxiety (38). Greater depressive, bipolar, and anxiety disorder comorbidity in the group with complicated grief, however, makes it difficult to interpret these observations. A separate study of 283 subjects (36) significantly associated childhood separation anxiety with development of complicated grief (odds ratio: 3.2, 95% confidence interval [CI]: 1.2–8.9).

High levels of anxiety generally (39), high levels of separation anxiety, and high rates of panic spectrum symptoms, which include measures of separation anxiety, are common among patients with bipolar I disorder (50% prevalence of high separation anxiety level in bipolar I disorder [40, 41]), complicating course and treatment response. Patients with bipolar disorder and high levels of panic spectrum symptoms report worse depression after short-term treatment, higher rates of suicidal ideation (49% in patients with high levels of panic spectrum symptoms versus 19% in those with low panic symptom levels), and a 6-month delay in response to short-term treatment relative to bipolar I patients with low panic symptom levels (44 weeks versus 17 weeks) (40). Childhood and adult separation anxiety are associated with mood instability and development of bipolar II disorder or cyclothymia in adulthood (42–44). Both childhood separation anxiety and adult separation anxiety disorder were common in patients with cluster B personality disorders (29% in patients with cluster B disorders versus 10% in those without cluster B disorders, $p<0.01$) and patients with cluster C disorders (55% in patients with cluster C disorders versus 26% in those without, $p<0.01$) in a study of 397 adult outpatients with primary anxiety disorders (45).

Negative Effect of Separation Anxiety on Treatment Outcome

Through still unknown mechanisms, separation anxiety is associated with poor response to treatments of adult anxiety and mood disorders, potentially through disruptions in the therapeutic relationship (40, 46–49). In adults, co-occurring separation anxiety, as well as anxiety generally (49), negatively moderates treatment response in major depression, worsening symptom chronicity and quality of life (46, 49). Among 226 treated patients with

major depression, separation anxiety accounted for 24% of the variance associated with impaired quality of life (46). High levels of panic spectrum symptoms inhibited the benefits of interpersonal psychotherapy (50), both alone and in combination with selective serotonin reuptake inhibitors (SSRIs). Panic-related symptoms decreased the rate of response to interpersonal therapy alone from 68.4% to 43.5% and prolonged the time to response after the addition of an SSRI to interpersonal therapy from 10.3 weeks to 18.1 weeks (47).

The only published study of which we are aware that investigated the moderating effect of adult separation anxiety on the response to cognitive-behavioral therapy (CBT) for patients with panic disorder similarly found that separation anxiety lessened CBT response. Among 256 patients with primary panic disorder with or without agoraphobia who were given 11 weeks of CBT, the overall response rate for the intent-to-treat group was 44.1% and the rate for completers was 65.6%; the odds ratio for nonresponse among patients with separation anxiety was 3.74 (95% CI, 1.8–7.8) (51). Separation anxiety predicted medication nonresponse in an open-label trial (SSRIs and tricyclic antidepressants, alone or combined, by algorithm) in 57 subjects with panic disorder with agoraphobia (p=0.001) (48).

Family Context

Childhood separation anxiety often arises in the context of anxious parenting (52–57). A parental sense of incompetence in facing children's anxiety (54, 58) can aggravate anxiety symptoms, even in the absence of parental anxiety disorders per se.

Because separation anxiety clusters in families, it may not emerge as a treatment focus in adults, who normalize living with profound, life-limiting restrictions that are consonant with family worries and accepted frameworks. Yet these predispositions may later erupt into overwhelming anxiety and mood disorders (7, 20). Children's anxiety surrounding separations can echo the often imperceptible, background-noise quality of separation anxiety in adults, so parents may not notice the children's separation anxiety; this situation offers a sense of typical patterns in such families (59, 60).

Bowlby's work on attachment, and the literature his findings have engendered, elucidate the centrality of the infant-caretaker relationship to subsequent lifelong patterns of attachment quality, quality of relationships, and mental health. Bowlby highlighted the developmental premise that small children's mothers buffer and externally modulate overwhelming external stimuli that the biologically immature infant cannot integrate. Bowlby contrasted normal development, in which anxiety levels do not limit the child's capacity to explore age-appropriate developmental challenges, with the development of anxiety-laden, insecure attachments that underlie separation anxiety and limit exploration of the environment and the child's sense of safety.

Normal, secure attachments arise from children's maturational ability to use their mothers as "a secure base from which to confidently explore the environment" (4, p. 13). When mothers reassure and encourage exploratory behavior within the child's mastery, children develop a secure sense of competence in their (social) environments. Anxious, ambivalent, depressed, withdrawn, or neglectful caretakers may foster insecure attachment, generating inhibition and anxious avoidance (5).

Toddlers manifest a range of attachment types as they develop the physical capacity for locomotion (61). Children's security in exploring the environment beyond the mother's or caretaker's presence relates inversely to the degree of separation anxiety. Secure attachment describes Mahler's separation-individuation paradigm: a toddler's comfort in exploring the environment, briefly checking back with the mother or caretaker for security ("refueling"), then setting out on new adventures away from the mother or caretaker (61). The mother's calm encouragement of the toddler's exploration fosters development of secure attachments. In insecure attachments, however, some toddlers become anxious and inhibited, manifesting fear and various stress response patterns, including freezing, becoming mute, weeping, or crumpling when separated from their mothers (19).

Although anxious, inhibited early attachment styles have been linked to development of childhood anxiety disorders (54), a meta-analysis connecting inhibited attachment with internalizing disorders (62) found this link "small" (Cohen's d=0.15). Nevertheless, many observations show that mother-child attachment relationships, which form the core of the separation-sensitive social schema, powerfully influence the development of anxiety disorders. Parenting style, the level of parental anxiety, especially surrounding separations, and parents' ability to tolerate their child's distress without urgently intervening all affect the onset of anxiety disorders in childhood, irrespective of whether the parents have anxiety disorders (54, 55, 63, 64). Humans, like other mammals (28, 30–32), display a complex relationship of genetic predisposition, early experiences (the first 3 years of human life), and development of anxiety in later life (65). Whatever the environmental contributions to this anxiety may be, developing insecure central attachments does not require trauma-level criteria, such as DSM posttraumatic stress disorder criterion A (e.g., child abuse). Attachment style likely depends on far more subtle parent-child interactions, responses to children's distress and anxiety, and the available capacity to moderate stimuli (52, 58).

Social Support

Secure attachment styles and supportive social relationships putatively buffer the negative emotional and physical

impacts of acute, overwhelming stress, protecting against PTSD and other disorders (53, 66, 67). Thus, separation anxiety emerged as a specific risk factor for PTSD in burned children (68). Degree of maternal stress as well as physical separation from mothers correlated directly with children's anxiety responses to Scud missile attacks (66). Anxious attachment style and high separation anxiety likely compromise the ability to modulate stress with social supports for several reasons: people with separation anxiety develop fewer social supports, they approach them more cautiously, and the social supports they have are more emotionally fraught, less "supportive" (66, 69).

Treatment Implications

Relative Ego-Syntonicity of Separation Anxiety

Patients with separation anxiety have profound sensitivity to transitions and losses, including those experienced in therapeutic relationships (7). Often normalized, so that patients and clinicians may hardly recognize its presence or potency, separation anxiety fuels chronic anxiety and a global sense of inadequacy and incompetence that can undermine psychiatric treatments of any modality (7). To enable change, the psychotherapist must consistently focus on separation anxiety and the distortions it evokes to facilitate its verbal articulation. It is interesting that contemporary communication devices (e.g., mobile phones) may cloak a pathological need for immediate contact, making careful clinical evaluation even more important.

Psychosocial Interventions

The dyadic nature of psychotherapy leads us to predict that attachment styles can affect psychotherapy effectiveness. Conversely, attachment styles can change: several studies have shown that psychotherapy can render attachment style more secure (70–72). Indeed, attachment can differ among various dyads for the same individual, although formative early dyadic models strongly influence later central attachments.

Key active ingredients of psychotherapy include the capacities to trust, to share, and to feel soothed by the therapist (71). Psychotherapies differ in their degree of focus on attachment and separation-sensitive social schemata. Behavioral therapies for anxiety tend to focus on the fear extinction paradigm (73) rather than attachment per se. In contrast, psychodynamic and interpersonal psychotherapies for anxiety focus on relationships and associated affects. These therapies actively address improving patients' capacity for reflection and helping them to recognize and tolerate emotional responses and perceived dangers surrounding attachment (69). Therapists attuned to patients' separation fears may detect them in the transference or in outside relationships and can use dynamic or interpersonal approaches to articulate and help patients to better understand them, thereby decreasing their intensity. This work presumably increases patients' reflective function (74). A putative mediator of affect-focused psychotherapies, reflective function measures emotional understanding of one's formative relationships and one's own and others' attachments and emotions (75). Reflective function studies may be useful in delineating mechanisms of change occurring in psychiatric symptoms through modulation of attachment and reflection (74–76).

Affect-Focused Psychotherapies Targeting Separation Anxiety

The negative impact of separation anxiety and panic spectrum symptoms on the outcomes of treatment for mood and anxiety disorders suggests that research should evaluate psychotherapy interventions targeting relationships, attachment, and associated affects. Indeed, the potency of separation anxiety argues for developing better-tailored treatments across disorders (49, 77). We highlight two small pilot psychotherapy trials in which some of us were involved.

Cyranowski et al. (77) treated 18 subjects with primary major depression and high levels of lifetime panic spectrum symptoms (35) in an open trial of interpersonal psychotherapy adapted to focus on depression, anxiety, and anxious avoidance. Fourteen (78%) subjects met remission criteria after 12 weeks, with improvements ($p<0.0001$) across all measured domains: depression, anxiety, and psychosocial functioning. A randomized trial comparing this treatment with supportive therapy is further evaluating this approach.

In another study, 49 adults with primary panic disorder with or without agoraphobia were randomly assigned to panic-focused psychodynamic psychotherapy (78) or to applied relaxation training (unpublished manual of J.A. Cerny et al., 1984), an efficacious non-separation-anxiety-focused intervention for panic disorder (79). The principles of panic-focused psychodynamic psychotherapy emphasize free association, centrality of the transference, and unconscious thoughts underlying physical sensations of panic and difficulty with separation and autonomy. The therapist focuses on these processes as they relate to panic symptoms. Common themes of difficulty with separations and unconscious rage inform interpretive interventions. Panic-focused psychodynamic psychotherapy, as an affect-focused psychotherapy, specifically targets separation anxiety as a core component of understanding panic; patients' high separation anxiety levels constitute a central organizing element in their self-view as incompetent and unable to manage developmentally normative tasks without the presence of their central attachment figures. The inevitable repetition of this dyadic pattern with the therapist within a time-limited 24-session, 12-week format heightens the opportunity to work with separation anxiety and permits the reexperiencing and better understanding in verbal form of this affectively charged paradigm (7, 78).

Eleven of 23 patients receiving applied relaxation training (48%) and 15 of 26 in panic-focused psychodynamic psychotherapy (58%) had high baseline levels of current separation anxiety and panic spectrum symptoms, i.e., a score of 35 or higher on the Panic-Agoraphobic Spectrum Self-Report (37). A significant interaction between treatment and baseline score predicted panic symptom improvement at treatment end ($b=-11.0$, $t=-3.68$, $df=44$, $p<0.001$), indicating that baseline severity of separation anxiety moderated the effect of panic-focused psychodynamic psychotherapy on panic symptoms. Panic-focused therapy had significantly greater efficacy than relaxation training among patients with high levels of separation anxiety. Thus, patients with primary panic disorder with higher baseline separation anxiety levels responded particularly robustly to panic-focused psychodynamic psychotherapy, but not to applied relaxation training.

When Lena began panic-focused psychodynamic psychotherapy, she needed a friend to accompany her from a distant suburb because of her terror of traveling alone. The therapist first explored Lena's worst panic attacks, which had occurred in cars when she was in the midst of deciding to break up with her last serious girlfriend. During panic attacks, she felt terrified and completely isolated, as if her car were a "tomb" and "as though I'll never see anyone I love again."

The therapist helped Lena to begin to trace an emotional line between her fury at her abusive ex-girlfriend and her plan to leave her, her subsequent physical sensations of overwhelming anxiety, her sense of loss of executive control as highlighted by her relatively new inability to drive, and her central fantasy of her car as a tomb, separating her forever from the people she loved, especially from her mother. In carefully delving into the complicated, ambivalent, yet intense and dependent relationships she tended to form, the therapist explored an emerging core fantasy Lena had about herself that fueled much of the intensity of her relationships: that she was incompetent and unable to manage situations that might arise (on the train to appointments with her therapist, for example).

Lena relinquished her travel companion and began traveling and attending sessions alone by session 5. She rapidly resumed driving and no longer felt so isolated in her car or as though she would panic. The therapist continued to pursue Lena's core fantasy that she was incompetent like a small child and terrified to be apart from her mother, as she had been when she was very young, and that therefore she was unable to handle matters that might arise at night if she were to sleep alone without her new girlfriend. After session 11, Lena slept alone for the first time in her life.

The therapist helped Lena to verbally articulate how her strength and newfound independence were associated with her relationship with the therapist, something she would have to relinquish soon because of the (24-session) study time limit. Lena actively mourned the loss of her therapist, experiencing "jumpy nerves" on the train when coming to see her, resisting a "pull" to "pick up women to make it better," and later expressing anger and sadness that the therapy could not continue. She said that she had never said goodbye as she was now in parting with the therapist, permitting herself to feel the sadness of the loss without becoming overwhelmingly anxious and frantic to replace the therapist with new "emergency" relationships. Despite tremendous anticipatory anxiety, Lena felt calmer and more comfortable: traveling, working, and attending school without anxiety at termination. She had ended her relationship with the new girlfriend after session 17 and despite feeling "lonely and unusual," had very uncharacteristically not rushed into a new relationship and was adopting a "wait and see" approach to dating. At termination, the Anxiety Disorders Interview Schedule for DSM-IV indicated a score of 3 out of 8 for panic disorder (subsyndromal), 3 out of 8 for agoraphobia, and a score of 0 for generalized anxiety disorder.

These two small adult studies demonstrate preliminary but promising outcomes of psychotherapies for patients with prominent separation anxiety symptoms amid different DSM disorders. Better tracking of separation anxiety throughout treatment course and the development of interventions to relieve its global effects might help in specifically targeting interventions for individual patients.

Separation Anxiety as a Research Model for Developing and Treating Anxiety Disorders

Neuroendocrine Markers

Close relationships can profoundly reassure patients with anxiety disorders and depression. Biological mechanisms and neural circuitry underlie this phenomenon. We note two interrelated systems that might serve as potential biomarkers of anxiety surrounding separation and attachment: respiratory sinus arrhythmia, a marker for parasympathetic nervous system activation, and oxytocin. Lower resting respiratory sinus arrhythmia levels are associated with impairment of adaptive reactivity to stressors (80, 81). Reductions have been noted across anxiety disorders (82), depression (83), and borderline personality disorder (84). Low respiratory sinus arrhythmia correlates with ineffective, inflexible coping responses and insecure attachment (85, 86). Important hypotheses to test are whether low respiratory sinus arrhythmia is associated with separation anxiety and whether improving separation anxiety increases respiratory sinus arrhythmia.

Oxytocin is a hypothalamic neuropeptide that across species suppresses endocrine and behavioral stress responses, relieves pain, and facilitates prosocial behaviors, including maternal behavior and affiliative contact seeking (87). For individuals with an anxious attachment style (88) or borderline personality disorder, intranasal oxytocin aggravates negative reactions to social stimuli (89). Resting plasma oxytocin levels bear a complex, still sketchily mapped relationship to interpersonal empathy, closeness, and trust (25, 90, 91) and to anxiety (25, 92), interpersonal difficulties, and romantic attachment anxiety and distress (93, 94). Higher plasma oxytocin levels

are associated with greater anxiety and relationship dissatisfaction in separation anxiety disorder (95). Growing evidence supports peripheral oxytocin levels and the oxytocin receptor polymorphism rs53576 as potential biomarkers of social responsivity and capacity for attachment (25, 96).

Neuroimaging

Neuroimaging research has focused on brain regions and circuits whose activity appears abnormal at a single time point in individuals with anxiety and separation anxiety from close attachments. Biomarkers of underlying vulnerability related to attentional and memory systems that predispose to separation anxiety, but are not themselves anxiety circuitry in the usual sense, may merit exploration.

As social interaction is central to separation anxiety, we must identify neural circuitry involved in "separation-sensitive" social representations or schemas, schemas that predict danger when separation occurs. Extant evidence suggests that the temporal cortex and areas specifically important for social cognition may organize such heteromodal schemas (97). Affective evaluation may be lower than normal in individuals with avoidant attachment and greater than normal in those who are anxiously attached (22).

Conclusions

The apparent clinical centrality of separation anxiety and anxious attachment underscores the need to better understand their significance in empirically delineating the developmental path of anxiety. Separation anxiety must relate to emotion regulation circuits in human psychopathology, epitomized in the emotional processes of attachment and separation. The challenge is to move from clinical observations to a sophisticated understanding of risk, vulnerability, and symptom expression that might hone targeting of interventions.

The description of separation anxiety in this article has been necessarily schematic. Basic information is sparse even in key areas such as prevalence of separation anxiety among patients with mood and anxiety disorders and differential treatment response associated with separation anxiety. The field requires additional research to corroborate or disprove the preceding argument. Results, however, might prove exciting. Closely monitoring separation anxiety may uncover different mechanisms of vulnerability to anxiety and to anxiety that responds poorly to standard treatment interventions. For example, is exposure-based fear extinction more or less effective in individuals with separation anxiety? As a clinical marker for pathological dysregulation of the anxiolytic, stress-buffering effect of close relationships, separation anxiety and its treatment could provide an important window to neural circuits and other biological processes associated with internalization of social support (35, 98).

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Clinical Guidance: Separation Anxiety and Treatment for Anxiety Disorders

Psychotherapies focusing on relationships and separation anxiety may be helpful for adults with anxiety disorders who experienced separation anxiety in childhood. The fear extinction model of anxiety calls for desensitization to threatening stimuli and does not consider the role of earlier childhood separation anxiety disorder in adult panic disorder and other anxiety disorders. In these patients, unaddressed separation anxiety lessens the effects of both medication and psychotherapy. Milrod et al. add that patients may be unaware of separation anxiety, as it clusters in families and may be considered normal behavior.