# Sadness and Loss: Toward a Neurobiopsychosocial Model

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## Case Description

**A** previously untreated 25-year-old female graduate student with masochistic traits but no axis I or II disorder entered twice-weekly psychodynamic psychotherapy with a stated goal of ending an abusive romantic relationship with a colleague. In the early months, sessions were filled with the patient's childhood memories of emotional mistreatment by her parents, whose constant fighting left her feeling abandoned and terrified. She contrasted these memories with loving memories of her grandmother, in whose nearby house she recalled afternoons of calm play, cookies, and attentive nurturance. The patient's grandmother was elderly when treatment began, and in the fourth month of treatment she became unexpectedly ill. The patient visited her daily and was with her when she died. The patient then entered a period of grief, spending much of each day thinking about her grandmother. However, she continued to be productive at work, did not develop a major depressive episode, and retained the capacity for pleasure and socialization.

Therapy sessions followed a pattern: the patient would arrive in a euthymic state and begin to talk about her grandmother. The therapist responded with supportive clarification and mirroring, using phrases such as "you really loved her" or "she was the one who understood how scared you were." Sometimes as a result of such comments, and others the patient made spontaneously, the patient would blurt out, "I cannot believe she's dead!" followed by crying of varying intensity, lasting 3–10 minutes. During this introspective period, she would lower her face, cover her eyes, and break off communication with the therapist. She reported feeling intensely sad during these periods, being flooded by loving memories of how her grandmother looked, sounded, and felt, and understanding the reality and finality of the loss. Further empathic comments by the therapist, such as "You really miss her," prolonged these episodes; typically the therapist would attend silently. After several minutes, the patient would reengage by drying her eyes, adjusting her clothes and hair, and resuming eye contact while talking about how lonely the world was without

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her grandmother. To this the therapist typically responded with reflective statements, such as "It feels like you will not ever be known in that kind of warm way again," which often led the patient either to further but more muted episodes of tearfulness or, more frequently, to the somewhat comforting idea that her grandmother's spirit was watching over her. By session's end the patient was no longer tearful; she would smile politely as she left to return to work. She reported many similar episodes outside of therapy, estimating that there had been at least several hundred over the few months following her grandmother's death. Over a 3-month period, the frequency and intensity of these minutes-long sadness episodes decreased; by the fourth month of bereavement, she discussed her grandmother only occasionally and focused largely on current relationships and concerns.

The therapist did not offer the patient medication or advice on coping, because he considered her grief process to be normal, spontaneous, and healthy. During the therapy termination 2 years later (the therapist was graduating from training), dreams in which the grandmother was dying recurred and were interpreted in the context of dealing with loss of the therapeutic relationship. This led to brief episodes of sad crying during sessions about the loss of the therapist.

## The Clinical Problem

Despite their clinical frequency, minutes-long episodes of intense sadness are rarely studied and poorly understood (1). Psychiatry's familiarity with major depression and bereavement, both of which feature sadness, leads to the false impression that minutes-long episodes of sadness are understood scientifically. In fact, in comparison with our knowledge of the neurobiology and adaptive function of other brief, intense, normal emotions, such as anger and anxiety, our understanding of sadness remains rudimentary. What is the function of sadness? This question has yet to be answered, and it raises four further questions that have clinical implications:

1. Does sad emotion, like anxiety or anger, provide an adaptive benefit, such as actively assisting the process of grief or coping with loss?

2. If sadness is adaptive, what are its psychological and neurobiological mechanisms of action? In particular, does it increase or decrease yearning for the deceased?

3. Can sadness in bereavement give way to depressed mood and major depression? If so, is the clinician advised

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to suppress sadness? Or, alternatively, is sadness a cathartic aspect of grief that the clinician should encourage?

4. Do normal sadness and major depression lie along a continuum, and is major depression a "sadness disorder"?

In the case presented, the therapist faced each of these unanswered questions and grappled with a clinical choice: to encourage the patient's sadness episodes to arise and unfold without interruption over the course of her bereavement or to use medications or cognitive reframing to suppress them. In choosing the former, he demonstrated adherence to the "detachment model" of sadness, in which sad emotion is believed to play a useful role in "accepting" and thereby recovering from loss. However, an alternative model suggests that sadness is designed to promote reunion, not detachment; according to this model, the psychiatrist in the case presented may have inadvertently prolonged the patient's grief by encouraging sadness, thereby placing her at risk of developing complicated bereavement or major depression. There is ongoing debate over which of these models is correct (2), but little work has been done to resolve it.

In this article, we present psychological, neurobiological, and brain circuitry evidence related to sadness and emphasize that the lack of integration of these data reflects the absence of a common theoretical model for testing rival theories of sadness. We propose that sadness be interpreted as a mechanism for altering the incentive salience of cues related to the deceased and that rival theories argue alternatively that sadness increases or decreases incentive salience. We propose ways of experimentally testing hypothesized models of loss and the role of sadness in grief resolution.

## Phenomenology of Sadness

Sad emotion occurs commonly in the normal population; it lasts for minutes, and it must be distinguished both from sad mood, which persists for hours to months, and from "pangs of grief," which are marked primarily by intense yearning. While the latter two may be components of grief and mood disorders, which are more complex phenomena (3), sad emotion in psychiatrically healthy persons, typically in the context of loss, is a distinct phenomenon, and that is the focus of this article.

The stimuli that trigger sadness, such as photographs, memories, and needs that were formerly met by the deceased, may trigger other emotions as well, including anger, anxiety, and yearning (4, 5). These distinct emotions may overlap, making it difficult to formulate a definition of sadness (6, 7). However, several features appear to be unique to sadness. Sad emotion begins with an awareness of loss, typically that of an attachment figure, goal, or valued aspect of the self (8, 9). Many people experiencing sadness become anergic, sit still, or hold on to others and avert or cover their eyes (9). Linguistic communication decreases in duration and complexity. The corners of the mouth are drawn down and the inner corners of the brows

move up and inward (9, 10). Weeping may occur, consisting of stereotyped patterns of respiration, vocalization, and lacrimation (11). Attention turns inward toward thoughts or reminders of the deceased (12). Cues or reminders of the deceased may more broadly trigger "pangs of grief" that include yearning and searching behaviors in addition to sadness (13–17). The mixture of yearning and sadness may underlie a "bittersweet" awareness of the value of what has been lost (5, 6). Additionally, the idea that the loss is unfair is not uncommon in Western cultures (12). Related feelings include nonlocalized psychic "pain" (18, 19); anhedonia (20); bodily sensations including chest and limb heaviness; increased pain sensitivity; and a fullness in the throat and behind the eyes, perhaps related to tears (21). Thinking may take on a ruminative quality (6). A bias toward perceiving one's own helplessness and sensitization to risks over rewards may emerge (22). Memory encoding and retrieval and attributions of causality and efficacy become heightened (23, 24) and favor retrieval of other sad memories.

Shifting of attention to external matters or unexpected reunion with the lost attachment figure can terminate sadness (6, 25). But sadness episodes are self-limiting after minutes, even in the absence of conscious efforts to end them. After an episode, many people report feeling "clearer" or "relieved" (21). A central question, addressed below, is what the purpose of the phenomenology described above might be.

## Neurobiology of Sadness

Unlike major depression, little is known of the neurobiology of minutes-long human sadness episodes. Animal work (26, 27) has identified three neurotransmitter systems that mediate attachment and may be relevant to human sadness; future research may show that a disruption of their baseline function is correlated with the emotion. First, endogenous opioid transmission may decrease during sadness. It is known to increase during exposure to attachment figures (28–30), and transient sad mood is associated with lower opioid transmission in the rostral anterior cingulate cortex (19). Second, oxytocin transmission may be reduced during sadness. It is released after imagining, touching, or interacting with a loved one (31, 32), and its administration reduces separation distress (33); memory-induced sadness in humans lowers serum oxytocin levels in female subjects (34). Third, the feelings of missing and yearning for the deceased that co-occur with sadness may involve dopamine release in response to cues reminiscent of the deceased. This hypothesis is based on the speculation that yearning for and attention to reminders of an attachment are mediated by the same neural systems that mediate subjective drug craving and automatic attention toward drug-related cues (28, 33, 35). The general term used to describe the perception of reward value in a cue, leading to reward-seeking behaviors, is *incentive salience* (28).

TABLE 1. Frequencies of Reported Activation and Deactivation of Brain Regions During Induced Sadness Across 22 Studies

| Brain Region | Studies Reporting Activation | | Studies Reporting Deactivation | |
|---|---|---|---|---|
| | N | % | N | % |
| Basal ganglia | 10 | 46 | 1 | 4 |
| Anterior cingulate cortex (Brodmann's area 32, 24, 25) | 9 | 43 | 2 | 11 |
| Cerebellum | 9 | 43 | 0 | 0 |
| Ventral prefrontal cortex (Brodmann's area 47) | 9 | 39 | 0 | 0 |
| Insula | 8 | 36 | 1 | 4 |
| Occipital cortex, any | 7 | 32 | 4 | 18 |
| Middle temporal gyrus | 7 | 32 | 4 | 18 |
| Superior temporal gyrus | 7 | 32 | 2 | 11 |
| Motor and premotor (Brodmann's area 4, 6) | 6 | 29 | 2 | 7 |
| Brainstem | 6 | 29 | 0 | 0 |
| Posterior cingulate cortex | 6 | 29 | 3 | 14 |
| Lateral prefrontal cortex (Brodmann's area 10) | 6 | 25 | 6 | 29 |
| Dorsolateral prefrontal cortex (Brodmann's area 9) | 6 | 25 | 5 | 21 |
| Thalamus | 6 | 25 | 1 | 4 |
| Inferior temporal gyrus | 5 | 21 | 2 | 11 |
| Anterior temporal pole | 4 | 18 | 1 | 4 |
| Amygdala | 4 | 18 | 1 | 4 |
| Subgenual anterior cingulate cortex | 3 | 14 | 0 | 0 |
| Orbitofrontal cortex (Brodmann's area 11) | 2 | 11 | 2 | 7 |
| Lateral prefrontal cortex (Brodmann's area 45, 46) | 2 | 7 | 2 | 11 |
| Parietal cortex (Brodmann's area 7, 40) | 2 | 7 | 5 | 21 |
| Hypothalamus | 2 | 7 | 0 | 0 |
| Hippocampus and parahippocampus | 1 | 4 | 2 | 7 |
| Sensory cortex (secondary somatosensory cortex or Brodmann's area 1, 2) | 1 | 4 | 1 | 4 |
| Brodmann's area 8 (lateral prefrontal cortex) | 1 | 4 | 0 | 0 |
| Lenticular nucleus | 1 | 4 | 0 | 0 |
| Fornix | 1 | 4 | 0 | 0 |

## Neural Circuitry of Sadness

Induction of sad mood in nondepressed volunteers has been reported to alter activity in more than 70 brain regions, with only modest agreement across studies (summarized in Table 1). Likely reasons for this variation are that induction methods, study populations, imaging modalities, and data analysis vary from study to study. In addition, subjects may vary in their capacity for emotional introspection, and the lack of objective measures of sadness may prevent the detection of differences in what subjective states subjects label as sad. Finally, there may be a difference between real-time sadness following a recent loss and recollected or empathic sadness. Only two (36, 37) of 22 relevant studies (Table 1) used brain imaging in people currently mourning a loss. Most studies induce sadness either through personal, autobiographical memories or empathically, through the viewing of sad movies or photographs. Empathic and autobiographical sadness may be mediated by neural mechanisms distinct from each other as well as from those of spontaneous sadness.

Eleven brain regions showed activation in over 30% of studies (Table 1). Since no published study has suggested a functional explanation for sadness, we have only a partial understanding of these activations. Prominent regions include the anterior cingulate cortex, involved in cognitive and emotional conflict, perception of pain (38–41), and social isolation (18); the posterior cingulate cortex, involved in emotional memories; the ventrolateral prefrontal cortex, involved in reward processing; the lateral and dorsolateral prefrontal cortex, involved in executive attention; the superior and middle temporal gyri and insula, involved in subjective emotional experience, bodily sensations, and

emotional decision making (42–45); and areas of the basal ganglia and cerebellum, which may have a role in the social display of emotion. Many of these regions overlap with regions known to be hypoactive or hyperactive in imaging studies of major depression, suggesting that sadness and depressed mood may share a common functional neuroanatomy (46). Dopaminergic neurons project from the ventral tegmental area to several of these structures, including the orbitofrontal cortex (47–49) and anterior cingulate cortex (50, 51).

In addition to human functional data, animal models of distress vocalizations (52–57) and lesion studies in human subjects that produce pseudobulbar palsy (45) provide some information about the neuroanatomy of sadness. They indicate the presence of a circuit in which descending tracts from the anterior cingulate cortex and cerebellum control the periaqueductal gray and cranial nerve nuclei, particularly of nerve VII, that produce the vocalizations, respiratory patterns, facial expressions, and lacrimation seen in sadness.

## Models of Sadness

Although sadness is a universal response to the loss of an attachment relationship, there is marked disagreement over whether it is part of the protest or despair phase of separation distress (7, 58–60). The distinction matters. The protest phase is marked by autonomic arousal, hyperactivity, distress vocalizations, and, in human beings, by subjective yearning, and it is adapted to preserve attachments. If sadness is a protest behavior, it serves no purpose after permanent loss. In contrast, the despair phase is marked by quiescence, anergia, decreased speech, and

introversion. The evolutionary purpose of despair is unclear. Some authors suggest that it represents loss of homeostasis in systems regulated by the lost attachment (27), and others imply that it represents an adaptive mechanism for facilitating detachment (61). If the latter is correct, it may be adaptive in bereavement. Thus, the assignment of sadness to the protest or despair phase determines whether it is understood as adaptive or maladaptive in bereavement.

As noted earlier, there are few published models or studies of sadness per se, but we identified three distinct models in the literature. The caregiving model (62) places sadness in the protest phase. It proposes that sadness strengthens attachments by inducing empathy in others, leading them to reunite with and/or meet the needs of the sad person. The major deficiency of this model is that it does not propose an intrapsychic function for sadness, and it places all adaptive power on the contingency that care is elicited from others. This model is at odds both with people's subjective experience of a change in thinking over the course of an episode and with the finding of intrapsychic advantages in other emotions.

The reunion model (35, 63, 64) also places sadness in the protest phase but suggests an intrapsychic function: sadness is an internally generated punishment. Sadness teaches that separation from loved ones is painful and motivates efforts at reunion, as seen in homesickness. This model implies that sadness after irreversible loss is maladaptive and represents the "cost" of its adaptive benefit when reunion is possible. An important prediction of this model is that sad persons should feel that reunion is possible following an episode.

In contrast to the caregiving and reunion models, the disengagement model (65–67) places sadness in the despair phase of separation distress and suggests that it facilitates detachment rather than attachment. Sadness is an affect that accompanies awareness that the attachment cannot be restored, and the sad person consciously works through a process of detachment from the loved one or object. A problem with published models is an emphasis on conscious signal processing: the sad person must consciously renounce their attachment. This is at odds with evidence that most emotions produce automatic changes in perception, attention, and behavior. Studies are needed to determine whether there is an automatic function whereby sadness mediates detachment.

Much of the literature on grief and depression does not propose any function for sadness but portrays it simply as an emotion that occurs in the context of loss and emphasizes that coping with sadness is a major task of bereavement (25). We suggest an active role for sadness in the process of bereavement.

## Toward a Neurobiopsychosocial Model of Sadness Following Permanent Loss

In the preceding sections, the phenomenology, neurobiology, and functional neuroanatomy of sadness were reviewed separately, a presentation that reflects the fact that psychiatry has not integrated the data and theory of sadness into a coherent neurobiopsychosocial model. In addition, it was noted that rival models of sadness were not reconciled to these data and that functional studies of sadness are not hypothesis driven and do not propose a function for the circuits mediating it, which provides more evidence that an integrated model has not been developed.

We propose that the concept of incentive salience may offer a framework for producing a neurobiopsychosocial model. When an attachment figure is absent, the incentive salience of the cues they leave behind persists; memories, photographs, and other reminders automatically bias attention toward and trigger subjective yearning (6, 17, 25). Coping with this elevated incentive salience is a major task of separation—in order to accept the loss, incentive salience must be reduced; but if reunion is possible, preserving and acting upon it is adaptive. Whether sadness is seen as a protest behavior designed to produce reunion or a despair behavior designed to produce detachment determines whether incentive salience is predicted to decrease or increase after an episode. The reunion model proposes that sadness increases yearning for the deceased, motivating reunion, while the disengagement model proposes that it decreases yearning and attachment, facilitating detachment.

It is plausible that by examining the biological, psychological, and behavioral correlates of incentive salience before and after an episode of sadness, the function of sadness may be clarified. Biologically, incentive salience may involve reward-processing brain regions that are known to be involved in recoding the reward value of cues and are targets of ascending mesolimbic dopamine pathways—including the anterior cingulate cortex, orbitofrontal cortex, and amygdala (50, 68). Psychologically, incentive salience involves yearning, such as that experienced in "pangs of grief." Behaviorally, incentive salience triggers attentional bias toward rewarding cues (51, 69–74). These three measures can therefore be used to test rival hypotheses, as outlined in Table 2.

Table 2 describes a set of predictions that can be tested in the service of the development of an integrated neurobiopsychosocial model that would address the questions raised at the beginning of this article. If sadness episodes reduce incentive salience, this would be adaptive in bereavement by decreasing yearning for and attention toward the deceased. Reduction of yearning for the deceased, mediated by a reduction in incentive salience, is not equivalent to forgetting the deceased. On the contrary, such a reduction may allow the bereaved to encounter memories without an overwhelming sense of loss or need, thereby permitting more pleasurable emotional associations and a sense of a continuing bond. Alternatively, if sadness episodes increase or leave incentive salience unchanged, they may be understood as a part of protest phase behavior that is optimal for temporary separations but serves no useful purpose in the face of permanent loss (questions 1 and 2). If sadness is adaptive, as in the first option, then psychiatrists should help patients express

TABLE 2. Key Questions on How Sadness Affects Incentive Salience and the Answers Predicted by Two Intrapsychic Models of Sadness

| Question | Predicted Answers | |
| --- | --- | --- |
| | Reunion Model | Disengagement Model |
| Theoretical | | |
| 1. Is sadness an aspect of protest or despair? | Protest | Despair |
| 2. Does sadness promote attachment or detachment? | Attachment | Detachment |
| Psychological | | |
| 3. Will subjects report that yearning for the deceased increases or decreases following sadness? | Increases | Decreases |
| Behavioral | | |
| 4. Will sadness correlate with sympathetic or parasympathetic tone (as measured by skin conductance and respiratory sinus arrhythmia)? | Sympathetic | Parasympathetic |
| 5. Does sadness increase or decrease attention toward reminders of the deceased? | Increase | Decrease |
| Neurobiological | | |
| 6. Will administration of oxytocin, opioids, or dopamine-blocking agents increase or decrease sadness in response to exposure to cues reminiscent of a loss? | Decrease | Increase |
| Functional neuroanatomical | | |
| 7. Does a sadness episode increase or decrease activation of the ventral tegmental area, nucleus accumbens, anterior cingulate cortex, orbitofrontal cortex, or amygdala in response to cues reminiscent of the deceased? | Increase | Decrease |
| Clinical | | |
| 8. Should psychiatrists use treatments that facilitate the suppression or the expression of sadness during bereavement? | Suppression | Expression |

sadness; if sadness is not adaptive—if it has no effect on incentive salience—then there is no advantage in encouraging expression of sadness during bereavement (question 3). And if sadness is shown to reduce incentive salience and the neurocircuitry of minutes-long episodes of sadness overlaps with that of sustained periods of depression, it may be plausible that depression is in part a "sadness disorder" in which incentive salience, hopefulness, motivation, and goal-directed activities are all reduced as a result of the inappropriate triggering of this sadness mechanism (question 4).

When the desire for reunion with a deceased loved one is both overpowering and maladaptive, a mechanism that inhibits reward seeking and down-regulates yearning and attentional bias is useful. Sadness may be such a mechanism. However, if sadness does not perform such a function, further inquiry is needed into the mechanisms by which bereaved persons decouple outdated stimulus-reward associations while allowing the memory of the deceased loved one to live on. Such detachment plays an important role in the resolution of bereavement, as it may allow the bereaved person to reframe the memories of the deceased in terms of a past physical and current spiritual relationship without the ongoing pain of grief and loss.

## Conclusion

Faced with a tearful patient who has suffered the loss of an attachment, the psychiatrist must choose between helping them to express or, alternatively, to suppress, their affect. In the case presented, the therapist chose to encourage the patient to explore her yearning and sadness. This was done with comments that emphasized the grandmother's capacity to be warm, to know and understand the patient, and to be worthy of love—in short, by reminding the patient of the high incentive salience of the deceased. These comments reliably triggered sadness. Once episodes began, the therapist passively allowed the

patient to experience her associations and feelings silently and waited for her to resume eye contact and verbal communication. After a sadness episode, comments about the grandmother's high reward value were less likely to trigger a second episode, although second episodes did sometimes occur. By the end of each session, the patient had composed herself and was able to return to work. In following this sequence of interventions, the therapist implicitly endorsed the disengagement model of sadness. The patient's sadness was treated as an endogenous mechanism for reducing high incentive salience associated with the grandmother. The therapeutic method was to trigger sadness and then allow it to unfold without interruption.

An alternative strategy, based on the reunion model, would have treated sadness as a mechanism that could maladaptively increase incentive salience and prolong grief. The therapist would have avoided such triggering comments and interrupted or redirected the patient's attention if she became sad. Medications could also have been used, such as selective serotonin reuptake inhibitors, which are known to reduce crying in pseudobulbar palsy and mood disorders. Such management would have been consistent with findings that over the course of bereavement, high sadness intensity is predictive of complicated bereavement, not recovery (75).

In the case presented, the evolution of the patient's grief process was normal: she experienced a reduction in both yearning and thinking about her grandmother, a decrease in frequency and intensity of sadness episodes, and continued bonds with her grandmother in the form of a sense that her spirit was still with her. This outcome is in keeping with the literature on healthy bereavement, which emphasizes the importance of reworking one's relationship to the deceased (25). An important question is whether the patient's sadness episodes helped, hindered, or had no role in this process. The effect of sadness on incentive salience

and its capacity to alter yearning for and attention toward reminders of the deceased calls for the empirical study of the effects of sadness on the grief process.

## CME Disclosure

Drs. Freed and Mann report no competing interests.

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