Brain Science Advances
https://doi.org/10.26599/BSA.2025.905001
ISSN 2096-5958
CN 10-1534/R
REVIEW

Unraveling the Neurobiology of Grief: Insights into Brain and Behavior–Narrative Review

Nikolaos Statharakos[1,2] (✉)

[1] *General Hospital of Thessaloniki G. Papanikolaou, Papanikolaou Blvrd, Thessaloniki 57010, Greece*
[2] *Psychiatric Hospital of Thessaloniki, 196 Lagkada Blvd, Thessaloniki 56430, Greece*

ARTICLE INFO

Received: 06 January 2025
Revised: 08 March 2025
Accepted: 03 June 2025

KEYWORDS

Grief, Prolonged grief disorder, Neurobiology, Neural circuits, Hormones

ABSTRACT

Grief is a universal yet multifaceted emotional response to loss, profoundly affecting psychological and biological systems. This review aims to examine the neurobiological mechanisms underlying grief, with a particular focus on prolonged grief disorder, a condition characterized by persistent, maladaptive grief symptoms that extend beyond culturally normative grieving periods. This narrative review synthesizes recent findings on the neurobiology of grief. Hormonal dysregulation, such as elevated oxytocin and cortisol levels, plays a significant role in the physiological response to grief. Epigenetic modifications of stress-related genes further contribute to individual variability in grief responses. Neural alterations are observed in key brain regions associated with memory, emotion regulation, and attachment, including the amygdala, hippocampus, and prefrontal cortex. Dysfunction of the hypothalamic-pituitary-adrenal axis, coupled with disruptions in the default mode network and reward systems, have been implicated in the persistence of pathological grief symptoms. These neurobiological disruptions reflect the interplay among emotional processing, cognitive regulation, and the stress response during grief. By improving our understanding of the biological basis of maladaptive grief responses, these findings provide a foundation for developing targeted therapeutic interventions and guiding future research to better address the needs of individuals experiencing prolonged grief.

1 Introduction

Grief is a natural and adaptive process that enables individuals to cope with the emotional pain of losing a loved one [1]. It is often described as a journey or learning experience in which the brain gradually adapts to the absence of a loved one. In this process, the brain must update its expectations and emotional responses, moving from an attachment-based anticipation of reunion to the painful realization of loss. Initially, individuals may experience acute grief characterized by intense emotional pain and longing for the deceased [2]. Over time, many people begin to

Corresponding author: Nikolaos Statharakos, E-mail: nicstath@gmail.com

adapt as their brains form new neural connections that help them cope with their loss [3].

However, in some cases, grief can become prolonged and impair daily functioning, leading to a condition now recognized as prolonged grief disorder (PGD). PGD is officially recognized in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) and International classification of diseases, 11th revision (ICD-11) as a distinct clinical condition. In the DSM-5-TR, it is defined as a persistent and pervasive grief response lasting at least 12 months in adults (or 6 months in children), with symptoms such as intense yearning, emotional numbness, identity disruption, and social or occupational impairment [4]. Similarly, the ICD-11 classifies PGD as a disorder of persistent and disabling grief beyond 6 months, characterized by profound longing and difficulty adapting to loss [5]. These criteria distinguish PGD from normal bereavement, post-traumatic stress disorder (PTSD), and major depressive disorder (MDD), all of which involve grief-related distress but exhibit distinct neurobiological features [6]. This condition reflects a failure of the adaptive mechanisms of the brain to reconcile the loss, potentially leading to further psychological distress [3].

While grief has traditionally been studied through psychological and sociocultural lenses, recent advances in neuroscience have begun to unravel the biological underpinnings of this complex phenomenon [3]. Emerging research suggests that grief is not solely a psychological phenomenon, but involves distinct neurobiological mechanisms that influence emotional processing, cognitive function, and stress regulation [7]. This review synthesizes current findings to provide an integrated understanding of the neurobiology of grief, distinguishing normal grief from pathological manifestations such as PGD.

2 Methodology

A systematic search was conducted using PubMed and Scopus, focusing on studies published in peer-reviewed journals. The search query included the term “prolonged grief disorder” in combination with the terms “neurobiology”, “neuroanatomy”, “neuroimaging”, “hormones” with the Boolean term AND with. The articles were selected based on relevance, recentness, and methodological rigor. The search was restricted to human studies, and only peer-reviewed articles were considered. Additional studies were identified through citation tracking of key papers.

The inclusion criteria were as follows: (1) Neuroimaging studies assessing grief-related brain function or structure; (2) Neuroendocrine studies examining cortisol, oxytocin, or inflammatory markers in bereaved individuals; (3) Comparative studies of PGD, normal grief, and other psychiatric disorders (e.g., PTSD, MDD); (4) Longitudinal or cross-sectional studies examining changes in grief-related neurobiology over time; (5) Clinical trials investigating pharmacological or psychotherapeutic interventions targeting grief-related neurobiological processes; and (6)Reviews.

The exclusion criteria were as follows: (1) Studies without neurobiological data (e.g., purely psychological self-report studies); (2) Case reports, letters, conference abstracts, or non-peer-reviewed studies; (3)Studies focusing on animal models rather than human participants; and (4)Articles published in languages other than English.

The final selection comprised 47 articles, which were categorized into five primary domains: Distinct Neural Signatures, Neuronal Circuits, Hormonal and Neurochemical Alterations in Grief, Epigenetics, and Promising Interventions for PGD.

3 Results and Discussion

Grief has profound effects on the brain, triggering neurobiological changes that reshape how individuals cope with loss. Dr. O'Connor explained that grief is akin to a learning process, where the brain adapts and rewires itself to manage the absence of a loved one [2]. This adaptation involves key brain regions, such as the anterior cingulate cortex (ACC) and the amygdala, which are associated with emotional regulation and memory processing [8]. Grief can also manifest physically, increasing stress hormones and the heart rate, impacting overall health. The attachment bonds formed during relationships lead to lasting epigenetic changes [9], making it difficult for the brain to fully accept the loss. Neurochemical responses, including oxytocin release, persist even after the person is gone, reinforcing the pain of grief [10]. Furthermore, grief often manifests physically, increasing stress hormones such as cortisol, which can elevate the heart rate and negatively impact overall health [11]. Understanding these neurobiological mechanisms can help individuals navigate grief more effectively and facilitate the healing process. This knowledge highlights the importance of supporting the natural ability of the brain to adapt to loss while also addressing the physical and emotional challenges that grief presents.

3.1 Distinct neural signatures

Different stages of grief are associated with varying levels of activity in specific brain regions, reflecting the complex neurobiological processes involved in emotional responses to loss. Grief is a learning process that requires neural adaptation [2]. Research has identified several key areas that show distinct activation patterns during grief. The key brain regions involved in processing grief interact with one another to shape the complex emotion of grief (see Table 1).

- Amygdala: This region is crucial for emotional processing, particularly for fear and sadness. During grief, activity in the amygdala increases,

Table 1 Stages of grief and activation patterns of key brain areas

Brain Area	Acute Grief	Prolonged Grief Disorder	Acceptance
Amygdala	Increased activity: heightened emotional distress (anxiety, sadness, fear)	Increased activity: ongoing emotional intensity	Decreased activity: emotional responses begin to stabilize
Prefrontal Cortex	Underactive: difficulty regulating emotions, cognitive dysregulation	Reduced activity: difficulty regulating emotions, cognitive dysregulation persists	Gradual recovery: improved emotional regulation and decision-making
Hippocampus	Underactive: difficulty forming/retrieving memories, confusion	Further underactivity: memory-related distress remains	Improved function: memory retrieval becomes more stable
Nucleus Accumbens	Relatively low activity: emotional responses are more acute	Increased activity: craving-like response, reinforcing emotional attachment	Decreased activity: reduced attachment reinforcement, emotional processing stabilizes
Anterior Cingulate Cortex	Increased activity: heightened emotional and pain processing	Reduced activity: difficulty disengaging from grief-related thoughts	More stable activity: improved emotional processing and regulation
Posterior Cingulate Cortex	Increased activity: processing emotional memories and connecting to loss	Sustained activity: ongoing emotional and physical connection to the deceased	Decreased activity: reduced emotional connection to the past
Supramarginal Gyrus	Increased activation: heightened emotional distress and difficulty integrating grief-related information	Sustained hyperactivation: associated with impaired cognitive inhibition and persistent grief symptoms	Decreased activity: improved cognitive processing of grief-related information

intensifying emotional responses such as anxiety, sadness, and distress. Increased functional connectivity between the amygdala and other brain regions has been observed, indicating its role in emotional regulation during grief [8, 12–15].

- Prefrontal Cortex: The prefrontal cortex is responsible for higher cognitive functions such as decision-making, emotional regulation, and social behavior; it typically shows reduced activity during grief. This reduction can lead to difficulties in regulating emotions, making decisions, and maintaining cognitive clarity. The medial prefrontal cortex is involved in self-referential thinking and emotional regulation. Its activation occurs when individuals process emotions related to their loss, indicating its importance in managing grief responses [12, 14–17].
- Supramarginal gyrus: The supramarginal gyrus plays a critical role in phonological processing and verbal working memory, particularly during language-related tasks. In grieving parents, atrophy in the supramarginal gyrus is linked to deficits in cognitive inhibition, potentially contributing to intrusive thoughts and difficulties disengaging from grief-related memories [17].
- Hippocampus: The hippocampus is involved in memory formation and retrieval. During the grieving process, the hippocampus often becomes underactive, leading to difficulties in both forming new memories and retrieving old ones. This underactivity can result in confusion, disorientation, and a distorted sense of time. The emotional memories associated with grief are stored in the hippocampus, which can trigger strong emotional reactions when recalling these memories. This interplay between memory and emotion can exacerbate feelings of sadness and longing, further complicating the grieving experience [18].
- Nucleus accumbens: The nucleus accumbens is associated with reward processing. In cases of PGD, the nucleus accumbens shows increased activity. This activation suggests that reminders of the deceased may trigger a craving-like response, complicating the grieving process by reinforcing attachment to memories of the deceased [8, 12].
- Anterior cingulate cortex: The ACC is engaged in regulating pain and emotional responses to stress. It is often more active during grief, reflecting the brain attempting to process and manage the emotional pain associated with loss. The ACC shows reduced activity in individuals experiencing PGD, indicating a difficulty in disengaging from grief-related thoughts and emotions. This underactivity can hinder effective emotional regulation, leading to persistent feelings of sadness and yearning. Conversely, those with non-complicated grief may exhibit more robust ACC activation, facilitating better emotional processing and adaptation to loss [12, 16, 19, 20].
- Posterior cingulate cortex: The posterior cingulate cortex plays a crucial role in grief processing, particularly in the retrieval of autobiographical memories, facilitating the emotional connection to those memories, and it processes both emotional and physical sensations related to loss [12, 19, 20].

3.2 Neuronal circuits

Grief alters cognitive and emotional regulation by disrupting the default mode network (DMN) and reward systems, leading to persistent negative emotions and difficulty in emotional processing [21]. These disruptions are similar to those observed in various psychiatric conditions, highlighting the importance of these networks in maintaining

emotional balance. Understanding these neural disruptions can assist therapeutic strategies to mitigate the impact of grief.

The DMN plays a central role in self-referential processing and emotional regulation, and its disruption is a hallmark of PGD. Studies show that individuals with PGD exhibit hyperconnectivity between the DMN and reward processing regions, leading to persistent mental fixation on the deceased [22]. PGD is associated with reduced dopamine activity, leading to persistent craving and yearning for the deceased, similar to addiction [23]. Alterations in the DMN have been linked to emotional-cognitive disturbances, such as those seen in MDD, where reduced negative blood oxygenation level dependent responses in the DMN correlate with depression severity and negative emotions [21]. In contrast, PTSD is characterized by hypoactivation of prefrontal inhibitory circuits, whereas MDD shows global DMN hypoactivity, contributing to rumination [24].

The DMN interacts with other networks such as the central executive and salience networks, which regulate its activity. Disruptions in these interactions can lead to poorly regulated information processing, a hallmark of many neuropsychiatric disorders. The interplay between the DMN and other networks is crucial for emotional and reward processing, affecting decision-making and emotional regulation [25].

3.3 Hormonal and neurochemical alterations in grief

Grief can be seen as a type of "learning process," where the brain struggles to reconcile the memories of the deceased with the new reality of their absence [2]. This conflict between the familiar presence of the loved one and their physical absence disrupts emotional regulation and cognitive function. The brain finds it challenging to adapt to life without the loved one, making grief an ongoing, dynamic process [3]. Moreover, the concept of continuing bonds illustrates how the attachment formed during the relationship does not disappear with death. Instead, individuals maintain emotional connections with the deceased, further influencing the grieving process. These enduring neural and emotional ties highlight the complexity of grief and the lasting impact of attachment on how the loss is processed [26].

As the body experiences stress from the emotional pain of loss, the hypothalamic-pituitary-adrenal (HPA) axis is activated, leading to an increase in cortisol production. Unlike normal grief, where cortisol levels decline over time, individuals with PGD maintain elevated cortisol levels, reflecting prolonged stress activation [27]. This distinguishes PGD from MDD, where blunted HPA axis responses are more common [28, 29]. Cortisol, known as the stress hormone, significantly impacts the brain during grief. During grief, elevated cortisol levels can have profound effects on the brain and body [27].

Studies have shown that individuals experiencing prolonged grief demonstrate altered diurnal cortisol slopes, where elevated cortisol levels persist over time, unlike in normal grief, where cortisol gradually normalizes [30, 31]. Elevated cortisol levels are associated with memory impairments, cardiovascular strain, increased immune vulnerability, and disrupted sleeping patterns [32, 33]. These physical health risks can complicate the grieving process and affect long-term well-being. Thus, the hormonal imbalance caused by cortisol during grief not only affects emotional and cognitive functions but also compromises overall health, making the grieving process more challenging [28].

Furthermore, gender differences in cortisol responses have been noted in grief studies. Men typically exhibit greater cortisol reactivity, whereas women demonstrate a blunted cortisol response, likely modulated by estrogen and oxytocin

interactions. These differences may influence coping strategies, with women relying more on social support networks, while men may be prone to maladaptive stress responses [34].

The attachment neurobiology of the brain plays a pivotal role in shaping our experience of grief. When we form emotional bonds with loved ones, neurochemical systems, particularly involving oxytocin, solidify this attachment [35]. Upon loss, the neural circuits in the brain associated with these bonds become activated, leading to intense emotional responses. Oxytocin plays a crucial role in the attachment neurobiology of grief by reinforcing emotional bonds and influencing the experience of loss. This neuropeptide is associated with social bonding and attachment, promoting feelings of connection and security with loved ones. Emerging evidence suggests that individuals with PGD exhibit persistently elevated oxytocin levels, which reinforce attachment bonds and inhibit emotional detachment from the deceased [35, 36]. This characteristic distinguishes PGD from MDD, where oxytocin dysregulation occurs without persistent attachment activation [37]. A resting state functional magnetic resonance imaging study emphasized that individuals with PGD showed altered resting-state connectivity in regions associated with self-referential thinking and emotional regulation, particularly in the DMN. Oxytocin administration led to changes in DMN connectivity, suggesting that this neuropeptide may influence grief-related rumination and attachment processing [38]. Elevated oxytocin levels correlate with increased nucleus accumbens activity, suggesting a neurobiological mechanism for prolonged yearning [39] (Table 2).

Furthermore, interactions among the κ-opioid system, corticotropin-releasing factor (CRF), and oxytocin have been shown to modulate grief intensity. Increased κ-opioid activity following the loss of a partner is linked to negative emotional states, dysphoria, and heightened stress responses. The CRF system, which regulates stress reactivity, is upregulated in grief, contributing to increased distress and prolonged emotional pain. The interplay between these systems suggests that grief is not just an emotional experience but a deeply embedded neurobiological process that affects stress regulation and reward processing [40]. The CRF-oxytocin system is particularly active in maternal grief, where loss-induced hormonal dysregulation leads to persistent emotional pain [39, 40]. Brain imaging has shown that oxytocin interacts with the reward and stress networks in bereaved mothers, possibly maintaining an internal representation of the lost individual [41].

3.4 Epigenetic changes

Epigenetic changes in the brain significantly influence our perception of grief by altering gene expression in response to loss [10]. When a loved one dies, the brain undergoes epigenetic modifications that can affect emotional and cognitive processing, particularly in areas such as the nucleus accumbens, which is involved in attachment and reward pathways. These changes can lead to heightened sensitivity to stress and

Table 2 Hormonal changes in grief

Hormone/Neurochemical	Role in Grief	Effects
Cortisol	Stress hormone, elevated during grief	Impairs cognitive function (e.g., memory, concentration), weakens immune response, and disrupts sleep. Elevated levels contribute to emotional dysregulation.
Oxytocin	Involved in social bonding and attachment	Higher levels are associated with yearning and difficulty in letting go of the deceased. May enhance social support-seeking behavior.

emotional pain, making it difficult for individuals to adapt to their loss [42]. Furthermore, prior life stressors can interact with these epigenetic alterations, increasing vulnerability to health issues and complicating the grieving process [43]. Grief-related epigenetic changes can affect several genes, particularly those involved in the stress response and immune function. Some of the key genes influenced by grief are shown in Table 3.

- *FKBP5*: This gene plays a crucial role in regulating the HPA axis and the stress response of the body. Epigenetic modifications of *FKBP5* can lead to heightened cortisol secretion, increasing susceptibility to prolonged stress and psychiatric conditions, which are common in complicated grief [42].
- *Nr3c1*: This gene encodes the glucocorticoid receptor, a key component in the bodily response to cortisol. Stress-related epigenetic changes often result in the downregulation of *Nr3c1*, reducing the ability of the body to effectively regulate the stress response [43].
- *Type I interferon-related transcripts*: These genes are involved in immune responses. Differential expression patterns of these transcripts have been observed between individuals experiencing complicated grief and those with more typical grief reactions, highlighting alterations in immune function in response to grief [10].

3.5 Promising interventions for PGD

Interventions for PGD must address the underlying neurobiological, hormonal, and cognitive mechanisms that sustain persistent grief-related distress. Given the complex interplay among attachment systems, stress regulation, and reward processing, effective treatments should integrate behavioral, cognitive, pharmacological, and neuromodulatory approaches. Though it is necessary to mention that most of the data are explorative and preliminary.

Mindfulness-Based Cognitive Therapy (MBCT) and Mindfulness-Based Stress Reduction have emerged as promising interventions for regulating maladaptive grief responses. MBCT has been shown to modulate DMN activity, particularly in the medial prefrontal cortex, reducing self-referential rumination and excessive preoccupation with loss [44, 45]. Mindfulness practices normalize HPA axis function, leading to reduced cortisol reactivity, which is often heightened in PGD [46]. MBCT enhances cognitive flexibility and emotional regulation, helping individuals shift from persistent yearning to adaptive acceptance of loss.

Social support plays a critical role in buffering grief-related stress, influencing both psychological resilience and neuroendocrine regulation. Group therapy and bereavement support groups have been linked to lower cortisol levels, suggesting that social connection may attenuate prolonged HPA axis activation [47]. Neuroimaging studies indicate that strong social networks enhance prefrontal regulatory control, improving emotional modulation and cognitive reappraisal of grief-related memories [48]. Expressive Writing and

Table 3 Epigenetic alterations in grief

Gene	Function	Epigenetic Changes
FKBP5	Regulates the hypothalamic-pituitary-adrenal axis and stress responses	DNA methylation changes lead to heightened cortisol secretion and increased vulnerability to stress
Nr3c1	Encodes the glucocorticoid receptor critical for cortisol regulation	Downregulated expression reduces the ability of the body to effectively regulate stress responses
Type I Interferon-related Transcripts	Mediates immune responses	Differential expression patterns observed in complicated grief versus normal grief

Narrative Therapy help individuals restructure loss narratives, decreasing amygdala hyperreactivity to grief-related stimuli [30].

Grief-focused Cognitive-Behavioral Therapy (CBT) has demonstrated effectiveness in helping individuals adapt to loss. CBT encourages individuals to replace maladaptive thoughts with adaptive coping mechanisms, facilitating the integration of loss into personal identity. Research shows that CBT strengthens prefrontal executive control, improving top-down regulation of limbic structures such as the amygdala [49]. Randomized controlled trials indicate that CBT reduces intrusive grief thoughts and excessive longing, which correlate with diminished nucleus accumbens hyperactivity [50].

Pharmacological approaches for PGD primarily target dysfunctional reward processing, HPA axis dysregulation, and attachment neurobiology. Given the heightened nucleus accumbens activity in PGD, opioid receptor antagonists such as naltrexone have gained attention as potential treatments. Persistent attachment cravings in PGD share neurobiological similarities with addiction-like reward reinforcement, suggesting that opioid antagonism could reduce maladaptive yearning [8]. A randomized controlled trial investigating naltrexone for PGD found that it diminished grief intensity by interrupting the neural feedback loop that sustains prolonged attachment distress [51].

Oxytocin administration has been found to modulate DMN activity, reducing grief-related intrusive thoughts [38]. While oxytocin may facilitate emotional healing, excessive oxytocin signaling has been linked to reinforced attachment distress, necessitating careful consideration of its therapeutic use [40].

Given the prolonged cortisol elevation in PGD, cortisol-regulating treatments have been hypothesised as potential therapeutic options. Metyrapone, an HPA axis modulator, has been hypothesised to reduce prolonged stress responses in treatment resistant depression by suppressing excessive cortisol production [52]. An extrapolation of this hypothesis can be tested for PGD. Although selective serotonin reuptake inhibitors are widely used for MDD, they have limited efficacy in PGD and thus the rationale of their use is for comorbidities or adjunct to psychotherapy [53].

Emerging research suggests that grief-induced neuroplasticity plays a pivotal role in long-term adaptation to loss. Repetitive transcranial magnetic stimulation has been shown to enhance prefrontal-limbic connectivity, which may help counteract the overactivation of grief-related circuits in PGD [54].

By combining cognitive interventions, neuroplasticity-based therapies, and pharmacological treatments, a more comprehensive and personalized approach to PGD treatment can be developed. Future research should prioritize identifying individual biomarkers for treatment responsiveness, thus optimizing precision medicine approaches for grief disorders.

4 Conclusion

The neurobiology of grief provides a compelling framework for understanding the profound psychological and physical impact of loss. Hormonal changes, such as elevated oxytocin levels, indicate the continued activation of attachment systems in individuals with PGD, reflecting their difficulty in emotionally adapting to loss. Epigenetic modifications in stress-related genes underline the long-term physiological consequences of grief, influencing both stress response and immune function. Neural disruptions in key circuits, including the DMN and reward systems, reveal how grief alters cognitive and

emotional regulation, perpetuating the experience of loss.

These findings highlight the potential of biomarkers, such as oxytocin levels and epigenetic markers, to predict vulnerability to PGD and guide early intervention strategies. Moreover, the interplay between neural mechanisms and hormonal pathways underscores the importance of integrated therapeutic approaches that address both the psychological and biological dimensions of grief. Future research should focus on longitudinal studies to track the progression of neurobiological changes over time and explore interventions targeting these mechanisms to alleviate the burden of pathological grief. By advancing our understanding of the neurobiology of grief, we can enhance the support and care provided to those navigating the complex journey of bereavement.

Acknowledgments

None.

Funding Information

None.

Author Contribution

Nikolaos Statharakos: Conceptualization, Methodology, Analysis, Original draft, Review, Editing.

Declaration of Conflicting interests

The author declares no conflict of interest.

Data Availability Statement

Data derived from public domain databases.

Ethics Statement

Not applicable.

Informed Consent

Not applicable.

References

[1] Shear MK. Grief and mourning gone awry: pathway and course of complicated grief. *Dialogues Clin Neurosci*. 2012, **14**(2): 119–128. doi:10.31887/DCNS.2012.14.2.mshear

[2] O'Connor MF, Seeley SH. Grieving as a form of learning: insights from neuroscience applied to grief and loss. *Curr Opin Psychol*. 2022, **43**: 317–322. doi: 10.1016/j.copsyc.2021.08.019.

[3] O'Connor MF. Grief: a brief history of research on how body, mind, and brain adapt. *Psychosom Med*. 2019, **81**(8): 731–738. doi: 10.1097/psy.0000000000000717.

[4] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Text revision. Washington, DC: American Psychiatric Publishing; 2022.

[5] World Health Organization. *International classification of diseases, 11th revision (ICD-11)*. Geneva: World Health Organization; 2019. Available from: https://icd.who.int/

[6] Bryant R. Current knowledge about prolonged grief disorder. *Grief Matters: The Australian Journal of Grief and Bereavement*. 2018, **21**(1): 21–26. doi: 10.3316/informit.883344658978547.

[7] Ratcliffe M, Velasco PF. The nature of grief: implications for the neurobiology of emotion. *Neurosci Conscious*. 2024, **2024**(1): niae041. doi: 10.1093/nc/niae041.

[8] O'Connor MF, Wellisch DK, Stanton AL, et al. Craving love?Enduring grief activates brain's reward center. *Neuroimage*. 2008, **42**(2): 969–972. doi: 10.1016/j.neuroimage.2008.04.256.

[9] O'Connor MF, McConnell M. Grief reactions: A neurobiological approach. In: Barrett JE, editor. Stress and Mental Disorder. Springer; 2018. p. 45-62. doi:10.1007/978-3-319-65241-2_3

[10] O'Connor MF, Schultze-Florey CR, Irwin MR, et al. Divergent gene expression responses to complicated grief and non-complicated grief. *Brain Behav Immun*. 2014, **37**: 78–83. doi: 10.1016/j.bbi.2013.12.017.

[11] Bui E, Hellberg SN, Hoeppner SS, et al. Circulating levels of oxytocin may be elevated in complicated grief: a pilot study. *Eur J Psychotraumatol*. 2019, **10**(1): 1646603. doi: 10.1080/20008198.2019.1646603.

[12] Silva AC, de Oliveira Ribeiro NP, de Mello Schier AR, et al. Neurological aspects of grief. *CNS Neurol Disord Drug Targets*. 2014, **13**(6): 930–936. doi: 10.2174/1871527313666140612120018.

[13] Chen G, Ward BD, Claesges SA, et al. Amygdala functional connectivity features in grief: a pilot longitudinal study. *Am J Geriatr Psychiatry*. 2020, **28**(10): 1089–1101. doi: 10.1016/j.jagp.2020.02.014.

[14] Bryant RA, Andrew E, Korgaonkar MS. Distinct neural mechanisms of emotional processing in prolonged grief disorder. *Psychol Med*. 2021, **51**(4): 587–595. doi: 10.1017/s0033291719003507.

[15] Hwang G, Blair NP, Ward BD, et al. Amygdala-centered emotional processing in prolonged grief disorder: relationship with clinical symptomatology. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2024: S2451-9022(24)00384-7. doi: 10.1016/j.bpsc.2024.12.008.

[16] Arizmendi B, Kaszniak AW, O'Connor MF. Disrupted prefrontal activity during emotion processing in complicated grief: an fMRI investigation. *Neuroimage*. 2016, **124**(pt a): 968–976. doi: 10.1016/j.neuroimage.2015.09.054.

[17] Shi Y, Shi G, Zhao S, et al. Atrophy in the supramarginal gyrus associated with impaired cognitive inhibition in grieving Chinese Shidu parents. *Eur J Psychotraumatol*. 2024, **15**(1): 2403250. doi: 10.1080/20008066.2024.2403250.

[18] Grimm S, Boesiger P, Beck J, et al. Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. *Neuropsychopharmacology*. 2009, **34**(4): 932–943. doi: 10.1038/npp.2008.81.

[19] Gündel H, O'Connor MF, Littrell L, et al. Functional neuroanatomy of grief: an FMRI study. *Am J Psychiatry*. 2003, **160**(11): 1946–1953. doi: 10.1176/appi.ajp.160.11.1946.

[20] Kakarala SE, Roberts KE, Rogers M, et al. The neurobiological reward system in prolonged grief disorder (PGD): a systematic review. *Psychiatry Res Neuroimaging*. 2020, **303**: 111135. doi: 10.1016/j.pscychresns.2020.111135.

[21] Grimm S, Boesiger P, Beck J, et al. Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. *Neuropsychopharmacology*. 2009, **34**(4): 932–943. doi: 10.1038/npp.2008.81.

[22] Tye KM, Mirzabekov JJ, Warden MR, et al. Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature*. 2013, **493**(7433): 537–541. doi: 10.1038/nature11740.

[23] Blair NP, Cohen AD, Ward BD, et al. Ventral striatal subregional dysfunction in late-life grief: Relationships with yearning and depressive symptoms. *J Psychiatr Res*. 2022, **156**: 252–260. doi: 10.1016/j.jpsychires.2022.10.031.

[24] Broyd SJ, Demanuele C, Debener S, et al. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev*. 2009, **33**(3): 279–296. doi: 10.1016/j.neubiorev.2008.09.002.

[25] Chen AC, Oathes DJ, Chang C, et al. Causal interactions between *Fronto*-parietal central executive and default-mode networks in humans. *Proc Natl Acad Sci USA*. 2013, **110**(49): 19944–19949. doi: 10.1073/pnas.1311772110.

[26] Hewson H, Galbraith N, Jones C, et al. The impact of continuing bonds following bereavement: a systematic review. *Death Stud*. 2024, **48**(10): 1001–1014. doi: 10.1080/07481187.2023.2223593.

[27] Mason TM, Duffy AR. Complicated grief and Cortisol response: an integrative review of the literature. *J Am Psychiatr Nurses Assoc*. 2019, **25**(3): 181–188. doi: 10.1177/1078390318807966.

[28] Hopf D, Eckstein M, Aguilar-Raab C, et al. Neuroendocrine mechanisms of grief and bereavement: a systematic review and implications for future interventions. *J Neuroendocrinol*. 2020, **32**(8): e12887. doi: 10.1111/jne.12887.

[29] Donaldson ZR, Shear MK. Neurobiology and treatment advances for prolonged grief disorder. *Neuropsychopharmacology*. 2024, **49**(1): 309–310. doi: 10.1038/s41386-023-01663-8.

[30] Holland JM, Rozalski V, Thompson KL, et al. The

unique impact of late-life bereavement and prolonged grief on diurnal Cortisol. *J Gerontol B Psychol Sci Soc Sci*. 2014, **69**(1): 4–11. doi: 10.1093/geronb/gbt051.

[31] O'Connor MF, Wellisch DK, Stanton AL, et al. Diurnal Cortisol in complicated and non-complicated grief: slope differences across the day. *Psychoneuroendocrinology*. 2012, **37**(5): 725–728. doi: 10.1016/j.psyneuen.2011.08.009.

[32] Saavedra Pérez HC, Direk N, Milic J, et al. The impact of complicated grief on diurnal Cortisol levels two years after loss: a population-based study. *Psychosom Med*. 2017, **79**(4): 426–433. doi: 10.1097/psy.0000000000000422.

[33] Bell JM, Mason TM, Buck HG, et al. Challenges in obtaining and assessing salivary Cortisol and α-amylase in an over 60 population undergoing psychotherapeutic treatment for complicated grief: lessons learned. *Clin Nurs Res*. 2021, **30**(5): 680–689. doi: 10.1177/1054773820973274.

[34] Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: a review. *Biol Psychol*. 2005, **69**(1):113-132. doi:10.1016/j.biopsycho.2004.11.009.

[35] Bui E, Hellberg SN, Hoeppner SS, et al. Circulating levels of oxytocin may be elevated in complicated grief: a pilot study. *Eur J Psychotraumatol*. 2019, **10**(1): 1646603. doi: 10.1080/20008198.2019.1646603.

[36] Bottemanne H, English I, Bottemanne L, et al. From love to pain: is oxytocin the key to grief complications?*Encephale*. 2024, **50**(1): 85–90. doi: 10.1016/j.encep.2023.08.006.

[37] Hurlemann R, Scheele D. Dissecting the role of oxytocin in the formation and loss of social relationships. *Biol Psychiatry*. 2016, **79**(3): 185–193. doi: 10.1016/j.biopsych.2015.05.013.

[38] Seeley SH, Andrews-Hanna JR, Allen JJB, et al. Dwelling in prolonged grief: Resting state functional connectivity during oxytocin and placebo administration. *Hum Brain Mapp*. 2023, **44**(1): 245–257. doi: 10.1002/hbm.26071. Erratum in: Hum Brain Mapp. 2024, **45**(2): e26594. doi: 10.1002/hbm.26594.

[39] Demarchi L, Pawluski JL, Bosch OJ. The brain oxytocin and corticotropin-releasing factor systems in grieving mothers: What we know and what we need to learn. *Peptides*. 2021, **143**: 170593. doi: 10.1016/j.peptides.2021.170593.

[40] Bales KL, Rogers FD. Interactions between the κ opioid system, corticotropin-releasing hormone and oxytocin in partner loss. *Philos Trans R Soc Lond B Biol Sci*. 2022, **377**(1858): 20210061. doi: 10.1098/rstb.2021.0061.

[41] Kark SM, Adams JG, Sathishkumar M, et al. Why do mothers never stop grieving for their deceased children?Enduring alterations of brain connectivity and function. *Front Hum Neurosci*. 2022, **16**: 925242. doi: 10.3389/fnhum.2022.925242.

[42] Zannas AS, Wiechmann T, Gassen NC, et al. Gene-stress-epigenetic regulation of FKBP5 clinical and translational implications. *Neuropsychopharmacology*. 2016, **41**(1): 261–274. doi: 10.1038/npp.2015.235.

[43] Dee G, Ryznar R, Dee C. Epigenetic changes associated with different types of stressors and suicide. *Cells*. 2023, **12**(9): 1258. doi: 10.3390/cells12091258.

[44] Huang FY, Hsu AL, Chao YP, et al. Mindfulness-based cognitive therapy on bereavement grief: Alterations of resting-state network connectivity associate with changes of anxiety and mindfulness. *Hum Brain Mapp*. 2021, **42**(2): 510–520. doi: 10.1002/hbm.25240.

[45] Chou T, Deckersbach T, Dougherty DD, Hooley JM. The default mode network and rumination in individuals at risk for depression. *Soc Cogn Affect Neurosci*. 2023, **18**(1): nsad032. doi:10.1093/scan/nsad032.

[46] Vargas-Uricoechea H, Castellanos-Pinedo A, Urrego-Noguera K, et al. Mindfulness-Based Interventions and the Hypothalamic-Pituitary-Adrenal Axis: A Systematic Review. *Neurol Int*. 2024, **16**(6): 1552–1584. doi:10.3390/neurolint16060115.

[47] Buckley T, Sunari D, Marshall A, et al. Physiological correlates of bereavement and the impact of bereavement interventions. *Dialogues Clin Neurosci*. 2012, **14**(2): 129–139. doi:10.31887/DCNS.2012.14.2/tbuckley.

[48] O'Connor MF. Immunological and neuroimaging biomarkers of complicated grief. *Dialogues Clin Neurosci*. 2012, **14**(2): 141–148. doi:10.31887/DCNS.2012.14.2/mfoconnor.

[49] Shou H, Yang Z, Satterthwaite TD, et al. Cognitive behavioral therapy increases amygdala connectivity with the cognitive control network in both MDD and PTSD. *Neuroimage Clin*. 2017, **14**: 464–470. doi: 10.1016/j.nicl.2017.01.030.

[50] Komischke-Konnerup KB, Zachariae R, Boelen PA,

Marello MM, O'Connor M. Grief-focused cognitive behavioral therapies for prolonged grief symptoms: A systematic review and meta-analysis. *J Consult Clin Psychol*. 2024, **92**(4): 236–248. doi:10.1037/ccp0000884.

[51] Gang J, Kocsis J, Avery J, et al. Naltrexone treatment for prolonged grief disorder: study protocol for a randomized, triple-blinded, placebo-controlled trial. *Trials*. 2021, **22**(1): 110. doi: 10.1186/s13063-021-05044-8.

[52] Sigalas PD, Garg H, Watson S, McAllister-Williams RH, Ferrier IN. Metyrapone in treatment-resistant depression. *Ther Adv Psychopharmacol*. 2012, **2**(4): 139–149. doi:10.1177/2045125312436597.

[53] Szuhany KL, Malgaroli M, Miron CD, et al. Prolonged grief disorder: course, diagnosis, assessment, and treatment. *Focus*: *Am Psychiatr Publ*. 2021, **19**(2): 161–172. doi: 10.1176/appi.focus.20200052.

[54] Han X, Zhu Z, Luan J, et al. Effects of repetitive transcranial magnetic stimulation and their underlying neural mechanisms evaluated with magnetic resonance imaging-based brain connectivity network analyses. *Eur J Radiol Open*. 2023, **10**: 100495. doi: 10.1016/j.ejro.2023.100495.