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Grief and bereavement: A pre-registered systematic review of neuroimaging studies☆

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ABSTRACT

Grief is a universally experienced response to the loss of a significant person, representing a profoundly stressful life event that can have lasting impacts on mental and physical health. Despite its inevitability, the neural mechanisms underlying grief remain poorly understood, hindering the development of effective interventions to improve outcomes for individuals coping with loss. To address this gap, we systematically reviewed functional and structural magnetic resonance imaging (MRI) studies related to brain connectivity, structural changes, peripheral physiology, and neuroendocrine, immune, and psychological correlates of grief. Functional MRI (fMRI) studies have consistently found associations between grief and neural activity, connectivity, and structure in networks related to emotion regulation, reward processing, and cognitive control, with some studies documenting heightened reactivity in regions such as the posterior and subgenual anterior cingulate cortex, medial/superior frontal gyrus, cerebellum, and amygdala. In turn, structural MRI studies have found reductions or differences in hippocampal, amygdala and supramarginal gyrus volumes, white matter abnormalities, and potential cognitive decline in those with prolonged grief. These neurobiological measures have been associated with clinical outcomes, including prolonged grief disorder, posttraumatic stress disorder, depressive disorders, and increased risk of cardiovascular disease. Studies focusing on individuals with PTSD or prolonged grief, especially following the loss of a child or spouse, have revealed hippocampal atrophy and an increased risk for brain pathologies, including neurodegenerative diseases. Future research should use longitudinal, multi-modal, and prospective study designs to identify neurobiological markers of prolonged grief. Integrating these findings with interventional research may help inform individualized strategies to promote neuroimmune resilience and improve grief management.

1. Introduction

The death of a close relative or friend is a highly stressful life event that can have significant psychological and emotional effects including pervasive grief and yearning. A representative sampling study of 914 participants reported 3.3 %–4.2 % prolonged grief disorder (PGD) among the bereaved subgroup (Rosner et al., 2021) whereas a large self-selected survey found higher rates in specific subgroups, highest in bereaved parents, followed by spouses/partners and then siblings (Thieleman et al., 2023). Moreover, 2024 was subject to a significant surge in civilian casualties resulting from violence and war in regions including Ukraine, Gaza, Lebanon, Sudan and Myanmar, with civilian casualties from explosive weapons increasing by 67 % in 2024 vs 2023 (Action on Armed Violence., 2025). Grief reactions are instantiated by neural activity (Bryant et al., 2021; Freed et al., 2009) and neuroanatomy (Luo et al., 2017; Luo et al., 2016), as well as by the autonomic (Buckley et al., 2011; O'Connor et al., 2002), neuroendocrine (Gerra et al., 2003), and immune systems (Brown et al., 2022; Knowles et al.,

☆ Trial registration: This review protocol was pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration No. CRD42024531868).

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2019; Seiler et al., 2018), thereby increasing the risk of a variety of mental and physical health problems (Stroebe et al., 2007).

The complex and multifaceted nature of the response to bereavement can predispose individuals to an increased risk of a variety of morbidities, including cardiovascular diseases (CVD) (Buckley et al., 2011; Chen et al., 2020; Chen et al., 2023; Fagundes and Wu, 2020) as well as to the development of posttraumatic stress disorder (PTSD), depressive disorders, and prolonged grief disorder[1] (O'Connor, 2019; O'Connor et al., 2002; Prigerson et al., 1997; Stahl et al., 2016). These statistics underscore the widespread nature of grief and its profound impact on both mental and physical health, highlighting the need for effective interventions and support systems worldwide. Understanding the neural and peripheral mechanisms—and the neuroendocrine, immune, and psychological processes associated with grief—is critical for the development of effective interventions to support individuals and improve physical and mental health outcomes.

Although grief is a distinct experience, its impact on the brain and body overlaps with processes studied extensively in stress research, suggesting that this literature can inform our understanding of bereavement-related mechanisms. Stress research accumulating over the past decades has revealed a complex interplay between stress, the brain, and the neuroendocrine and immune systems (Haykin and Rolls, 2021; Slavich, 2020, 2022; Slavich et al., 2023). These findings provide valuable insights into the neurobiological and physiological mechanisms underlying the effect of stress on emotion, cognition, and behavior (Dantzer et al., 1993; Moriarity et al., 2023; Ojha et al., 2023; Shields et al., 2024). However, the complex crosstalk between the neural networks and the neuroendocrine and immune systems during grief and bereavement remains underexplored. Specifically, the use of functional magnetic resonance imaging (fMRI) to investigate the neural correlates of grief alongside neuroendocrine and immune biomarkers remains a small area of research (O'Connor et al., 2009).

The earliest study on the functional neuroanatomy of grief was published by Gündel et al. in 2003. This study demonstrated a complex response to elicitation of grief in a magnetic resonance imaging (MRI) scanner that employs neural networks associated with emotional processing, memory retrieval, and autonomic regulation, providing valuable insights into the (mental) health implications of early grief (Gündel et al., 2003). Since then, neuroimaging research on grief has emphasized the role of neural activity within attachment, reward, and pain circuitry systems (O'Connor et al., 2008). Additionally, it has been observed that prolonged grief constitutes a distinct syndrome despite significant overlap in the neural circuits implicated in PTSD and depression (Bryant et al., 2021). Studies have also revealed how grief extends its effects beyond the brain and mind, influencing multiple organismic systems, particularly the immune system (Knowles et al., 2019). However, the broader clinical implications of these findings remain insufficiently explored.

1.1. Present study

To address this gap, we conducted the present review to systematically evaluate for the first time associations between functional neural response, changes in brain structure, peripheral physiology, and emotional correlates of grief using both structural and functional MRI studies. Given the complexity of grief as an emotional, cognitive, and physiological process, we hypothesize that grief is associated with multiple alterations in brain activity, connectivity, and structure, which both influence and are influenced by the neuroendocrine and immune systems.

The aims of this article are two-fold. The first aim is to summarize the current understanding of the anatomical and functional neural networks involved in grief and bereavement as assessed through MRI. The second aim is to examine associations between emotional processing, neuroendocrine, and immune system responses, and brain activation during grief and bereavement. In this context, we discuss key findings relating to alterations in brain activity, connectivity patterns, volume changes, autonomic, neuroendocrine, and immune markers within the context of acute grief, typical grief, and prolonged grief, as well as grief coupled with PTSD. The terminology used to describe these conditions has varied across time and diagnostic systems. Earlier research frequently employed the term *complicated grief* to describe persistent, impairing grief reactions. More recently, the DSM-5-TR and ICD-11 formally introduced the diagnosis of *prolonged grief disorder* (PGD), which captures the same underlying phenomenon with standardized diagnostic criteria. Although many of the studies we review employ the older term, "complicated grief," we use "prolonged grief disorder" throughout this paper for consistency with current diagnostic manuals.

To accomplish these aims, we first summarize key findings from studies investigating brain structure and neural connectivity employing structural MRI techniques in bereaved populations, including those also diagnosed with PTSD. Second, we examine studies that employed functional MRI across a range of tasks in bereaved populations, including a grief elicitation task, emotional-Stroop task, standardized affective stimuli, and in a resting state. We examine the role of grief-related neuroendocrine and immune mechanisms in these neuroimaging studies as well as cognitive and emotional responses to grief and bereavement, including attentional bias, empathy, and emotion regulation, while including grief-related disorders such as PTSD and prolonged grief. Finally, we draw conclusions on the current state of research on these topics, identify gaps and limitations, and propose directions for future studies to further enhance current understanding of grief and how this may improve clinical outcomes.

2. Method

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). The review protocol was pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration No. CRD42024531868).

2.1. Study selection strategy

Searches were completed on MEDLINE (PubMed) and EMBASE (Ovid) through December 31, 2024. The search strategy included a combination of subject headings, as well as free text terms including: "bereavement", "grief", "neuroanatomy", "neuroanatomical", "magnetic resonance imaging", "MRI", "functional magnetic resonance imaging", "fMRI", "brain", "cerebral", and "neural", and encompassed synonyms, abbreviations, and spelling variations. The chosen terms related to grief with terms related to neuroanatomy, neural processing, and fMRI. Boolean operators were applied to combine individual search terms. The search terms were selected based on their relevance to the aim of the paper and were combined in a way to ensure the chance of finding relevant articles was maximized, whilst also reducing the risk of missing important publications. The complete search strategy can be seen in

[1] According to the current ICD-11 and DSM-5-TR diagnostic manuals, which include 'prolonged grief disorder' Prigerson, H. G., Horowitz, M. J., Jacobs, S. C., Parkes, C. M., Aslan, M., Goodkin, K., Raphael, B., Marwit, S. J., Wortman, C., Neimeyer, R. A., Bonanno, G. A., Block, S. D., Kissane, D., Boelen, P., Maercker, A., Litz, B. T., Johnson, J. G., First, M. B., & Maciejewski, P. K. (2009). Prolonged grief disorder: Psychometric validation of criteria proposed for DSM-V and ICD-11. *PLoS Med*, *6*(8), e1000121. https://doi.org/10.1371/journal.pmed.1000121 we use this term instead of the older term, 'complicated grief', although the latter was used in most of the reviewed studies. Both terms, however, largely refer to the same phenomenon Prigerson, H. G., Kakarala, S., Gang, J., & Maciejewski, P. K. (2021). History and Status of Prolonged Grief Disorder as a Psychiatric Diagnosis. In (Vol. 17, pp. 109–126).

Table 1
Search strategy and hits.

Search Number	Search Topic	Search Terms	PubMed (MEDLINE)	Ovid (EMBASE)
#1	Bereavement	"bereavement [Title/Abstract]" OR "grief[Title/Abstract]" Filters: time (2003–2024), English	11,092	14,560
#2	Neuroanatomical imaging	"neuroanatomy [Title/Abstract]" OR "neuroanatomical [Title/Abstract]" OR "FMRI[Title/Abstract]" OR "MRI[Title/Abstract]" OR "functional magnetic resonance imaging [Title/Abstract]" OR "magnetic resonance imaging [Title/Abstract]" OR "brain[Title/Abstract]" OR "cerebral[Title/Abstract]" OR "neural[Title/Abstract]" Filters: time (2003–2024), English	1564,707	2220,915
#3	Combined searches	#1 AND #2 Filters: time (2003–2024), English	279	504

Table 1. The search was limited to articles published from January 1, 2003 to December 31, 2024. This time frame was deemed appropriate as the first study to investigate the functional neuroanatomy of grief was published in 2003. Search strategy and number of publications found with specific terms and their combinations in relevant literature databases.

2.2. Eligibility criteria

When screening titles and abstracts, the following inclusion criteria were applied: (1) articles published between 1/1/2003 and 12/31/2024, (2) abstract available, (3) written in English, (4) related to (f)MRI studies on grief or bereavement, OR (5) related to neuroendocrine and immune system activity. The following exclusion criteria were applied: (1) solely non-bereaved participants, (2) grief related to pet bereavement, (3) grief related to unborn child grief, (4) employed machine learning (to avoid introducing a different analytical framework to the conventional imaging techniques), (5) investigated neurobiological markers outside the scope of this review (e.g., specific hormonal systems such as oxytocin), (6) no full text available, and (7) systematic reviews or meta-analyses. These inclusion and exclusion criteria were selected to generate a library of literature that would include a wide range of publications in the field but refrain from yielding publications not specific to the aim of this review.

The review was focused on grief following the loss of a significant person (e.g., family members, partners, close friends) to maintain a coherent scope of human interpersonal bereavement. Studies examining grief following the loss of an unborn child were excluded because this type of bereavement often involves unique psychological, social, and cultural processes that differ from grief after the death of a significant person, and including these studies could confound interpretations of neurobiological mechanisms in prolonged grief disorder. Studies of pet bereavement were excluded because these experiences, while emotionally significant, may involve distinct neurobiological, social, and cultural mechanisms that differ from interpersonal loss in humans. Finally, since our aim was to focus on observational studies, studies involving the administration of substances were considered outside the scope of this review. Searching three databases including MEDLINE and EMBASE ensured that there was thorough and rigorous coverage of articles for this review. Following the screening of the title and abstract, eligible articles were screened in full text, applying the same eligibility criteria. The PRISMA flow diagram of the publications is presented in Fig. 1.

2.3. Data selection and extraction

All titles and abstracts were independently evaluated by two researchers (S.R.E., A.S.) against the inclusion and exclusion criteria. For any discrepancies between the two reviewers, a third researcher was consulted, and disagreements were resolved through consensus discussion (4). After screening by titles and abstracts, full-text articles were obtained for all abstracts meeting the inclusion criteria for further assessment, and for articles that could not be rejected with certainty. The data extracted included the author's first name, publication year, title, primary purpose of the review, methodology, and key findings.

2.4. Quality appraisal

A specific quality appraisal tool, The Newcastle-Ottawa Scale (NOS) (Wells et al., 2014), was used for the assessment of nonrandomised studies. This tool provided a structured and transparent approach to assessing the quality and validity of articles. It was used to identify any potential sources of bias or limitations. The criteria assessed in the NOS for assessing the quality of nonrandomised studies (case control study version) is comprised of three sections: selection, comparability, and exposure (Wells et al., 2014). The selection section allows for a maximum of four stars to be awarded and assesses the definition of the case, representation of the case, selection of control, and definition of controls (Wells et al., 2014). For example, studies that did not include a control group therefore scored lower in this category than studies that did include a control group. The comparability section can award a maximum of two stars and assesses the comparability of cases and controls on the basis of the design or analysis, taking into account covariates (Wells et al., 2014). Finally, the exposure sections allows for a maximum of four stars to be awarded and assesses the ascertainment of exposure, if the method of ascertainment is the same for cases and controls, and the non-response rate (Wells et al., 2014). In total, the scale allows for a maximum of 10 stars to be awarded across the three categories.

2.5. Data analysis

Data were extracted from the included articles and tabulated into two tables via an Excel document. The evaluation of data was processed by means of qualitative description. Results are summarized in tables and presented in a narrative form.

3. Results

3.1. Identification of included studies

The search returned a total of 783 published articles across two databases: PubMed ($n = 279$) and EMBASE ($n = 504$). After removing duplicative entires ($n = 233$), the title and abstract of records were screened ($n = 550$). Following exclusion of articles based on title and abstract screening ($n = 518$), articles were screened in full text ($n = 32$).

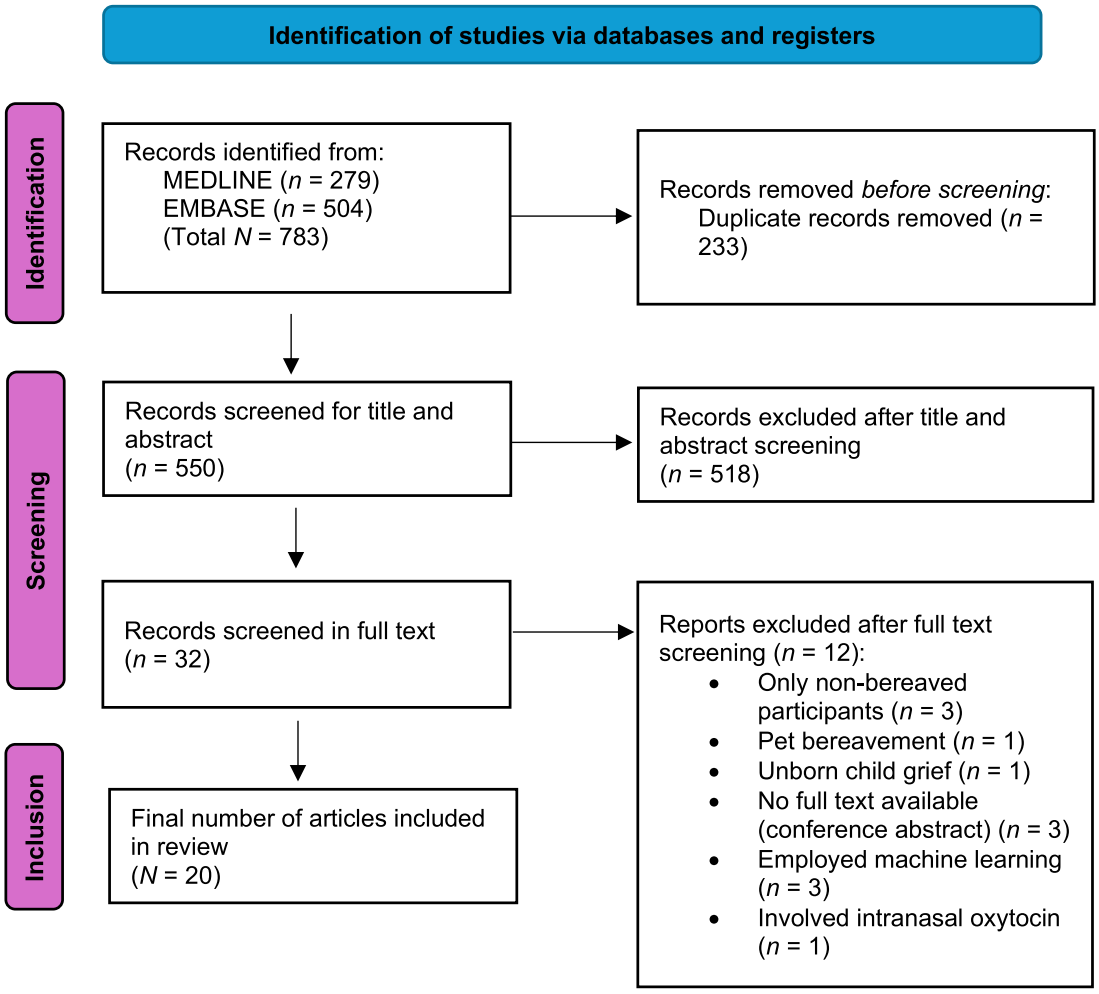

Fig. 1. PRISMA flow diagram.

During full-text screening, 12 review articles were excluded. The final review included 20 unique articles (Fig. 1).

3.2. Characteristics of included studies

The included articles were published from 2003 to 2024, with an increasing trend over this time frame. All included articles addressed the functional or structural neurobiology of grief and bereavement, in populations that included bereaved humans. Although animal models can offer valuable insights into the general mechanisms of stress and emotional regulation, they do not fully capture the complex and unique aspects of human bereavement, such as the social, cultural, and cognitive factors that contribute to grief responses, and were therefore not included in this review. All included articles employed methodology that included MRI or fMRI assessment. While techniques such as positron emission tomography (PET), electroencephalography (EEG), and magnetoencephalography (MEG) provide valuable insights into brain activity, they do not offer the same spatial resolution or ability to assess deep brain structures as MRI, which is particularly important in studying grief-related changes in emotion regulation, brain structure, and connectivity. By focusing solely on MRI-based studies, this review ensures consistency in the data analyzed, allowing for a more integrated and comprehensive understanding of the neural mechanisms underlying grief.

All articles were published in English and consisted of empirical studies. The studies included in this review were conducted in the USA ($n = 12$), China ($n = 3$), Australia ($n = 1$), Spain ($n = 1$), South Korea ($n = 1$), Japan ($n = 1$), and the Netherlands ($n = 1$). The studies included samples of predominantly women (60 % or greater) ($n = 18$), with one included study having a male dominant cohort (18.3 % female) ($n = 1$), whilst one study did not declare gender ($n = 1$). The mean age of participants was 40 years or older for all studies except for one ($n = 19$). One study did not report on age ($n = 1$).

The defined study populations included a non-bereaved control group in some studies ($n = 10$), whilst other studies did not include a control group, or the control group was bereaved but not experiencing prolonged grief ($n = 10$). The average time since the loss of a significant person had passed was less than one year ($n = 7$), over 18 months ($n = 10$), or a lifetime experience ($n = 1$). Two studies did not declare the amount of time that had passed between the loss of the loved one and the participation in the study. Some studies included as part of their sample those bereaved by a traumatic death including suicide, accident, violent death, and chronic or sudden illness ($n = 9$), with five studies including samples which were entirely grieving such a traumatic death. Eleven articles did not report on the nature of the death. The kinship relationships of the study populations to the deceased included a spouse or partner ($n = 13$), a first-degree relative ($n = 17$), other ($n = 4$), or was not mentioned ($n = 1$).

Some of the articles included medication status as a covariate to account for potential confounding effects. The use of psychiatric medications amongst participants, including but not limited to selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines, with an indicated stable dosage period prior to undertaking the study was indicated in six

studies. Thirteen studies did not mention medication use or were not explicit in which medications were taken and if they were, if a stabilization period prior to the study was introduced. One study excluded participants taking psychotropic medications which were started since the death event ($n = 1$). An overview of the included articles and their characteristics can be found in Table 2 (structural MRI studies) and 3 (fMRI and other studies).

3.3. Quality appraisal

Quality appraisal data are presented in Appendix A, and the details of the evaluation tool can be viewed in Appendix B. On a scale of 0–10 with higher scores indicating better study quality, studies scored between 4 and 9, with half of the included studies scoring a 9 ($n = 10$). It is important to note that when studies scored 6 or lower on this scale, this was primarily due to the absence of a non-bereaved control group ($n = 10$), which prevented awarding three stars. The second reason for variation between the scores was found in the comparability section, with one star awarded for the control of one confounding factor ($n = 1$), or two stars awarded for the control of additional confounders ($n = 14$). All studies provided an adequate case definition, adequate representation, and adequate ascertainment of death exposure ($n = 20$).

3.4. Structural MRI studies

Five articles employed structural MRI in samples of bereaved participants compared to samples of non-bereaved participants (Kim et al., 2022; Luo et al., 2017; Luo et al., 2016; Saavedra Pérez et al., 2015; Shi et al., 2024). One sample (Luo et al., 2016, and Luo et al., 2017) showed significant hippocampal atrophy in parents whose only child had died and were no longer able to conceive. Shi et al. (2024) identified reduced grey matter volume in the left supramarginal gyrus and right amygdala in Chinese Shidu parents, with supramarginal gyrus atrophy mediating the association between grief intensity and impaired cognitive inhibition (Shi et al., 2024). White matter abnormalities and poorer cognitive performance were observed in individuals with prolonged grief (Saavedra Pérez et al., 2015), whilst a higher risk of neurodegeneration in older adults who had experienced spousal bereavement was also observed (Kim et al., 2022).

3.5. Functional MRI studies

Fifteen articles employed fMRI in samples of bereaved participants. Seven studies employed a grief elicitation task, all conducted in samples experiencing acute or early grief (Gündel et al., 2003; Kark et al., 2022; McConnell et al., 2018; O'Connor et al., 2007; O'Connor et al., 2009;

Table 2
Characteristics of studies and included populations using structural MRI.

First Author, Year	Country	Defined Study Populations	Methods	Mean Age	% Female	Medication Use	Mean Time Since Death	Relation of Deceased	Nature of Death
Saavedra Pérez et al. (2015)	Netherlands	Three groups: normal grief, prolonged grief, and no grief	• MRI to measure general structural parameters (white matter, gray matter), and white matter lesions. • Cognitive testing (Mini-Mental State Examination, Letter–Digit Substitution Test, Stroop Test, Word Fluency Task, Word Learning Test – immediate and delayed recall)	62.2	74	NA	Normal grief: lifetime bereavement and low grief severity; prolonged grief: high grief severity and > 6 months since death	Partner, child, parent, sibling, other	NA
Luo et al. (2016)	China	Three groups: bereaved with PTSD, bereaved without PTSD, and control group	• Hippocampal and amygdala volumes were examined using MRI	57.6	60	No history of psychotropic drugs	93.8 months	Parents who lost their only child and could no longer conceive	Accident, illness, suicide, other
Luo et al. (2017) (same sample as Luo et al. 2016)	China	Three groups: bereaved with PTSD, bereaved without PTSD, and control group	• Hippocampal subfields were examined using MRI	57.6	60	No history of psychotropic drugs	93.8 months	Parents who lost their only child and could no longer conceive	Accident, illness, suicide, other
Kim et al. (2022)	South Korea	Two groups: spouse bereavement vs no spouse bereavement	• Participants underwent positron emission tomography PET and MRI and clinical assessment to assess the presence of brain pathologies, including markers of neurodegeneration such as Alzheimer's disease	76.1	79.7	NA	Lifetime experience	Spouse	NA
Shi et al. (2024)	China	Two groups: prolonged grief disorder and non-bereaved control group	• Voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) to assess structural alterations and correlation with cognitive inhibition, measured by Stroop interference scores • Prolonged Grief Questionnaire (PG-13) and Physical Health Questionnaire (PHQ-9)	63.5	65	NA	174 months	Shidu parents (Chinese parents who lost their only child)	NA

Table 3
Characteristics of studies and included populations using functional MRI and/or peripheral physiology.

First Author, Year	Country	Defined Study Populations	Methods	Mean Age (Years)	% Female	Psychotropic Medication Use	Mean Time Since Death	Relation of Deceased	Nature of Death
Gündel et al. (2003)	USA	One group: bereaved (no comparison group)	• Grief Elicitation Task: Photos of deceased loved one provided by participant were matched with photos of strangers. Fifteen autobiographical grief-related words were selected from participant interviews about the death and matched with 15 neutral words. • Photos and words were combined to create 60 composites in a 2 × 2 factorial design, creating four conditions: (1) deceased with grief words, (2) stranger with grief words, (3) deceased with neutral words, and (4) stranger with neutral words.	41.9	100	NA	8.5 months	First degree relative or spouse	NA
O'Connor et al. (2007) (O'Connor et al. (2008) subsample)	USA	One group: bereaved (no control group)	• Grief Elicitation Task (O'Connor et al. 2008). • Respiratory sinus arrhythmia (RSA) was measured by electrocardiogram prior to scanning.	NA	100	NA	30 months (range 2–59 months)	Mother, sister	Breast cancer
O'Connor et al. (2008)	USA	Two groups: prolonged grief and non-prolonged grief	• Grief Elicitation Task: Photos of the deceased loved one were matched with photos of strangers. Fifteen autobiographical grief-related words were selected from participant interviews about the death and matched with 15 neutral words.	43.7	100	NA	30 months (range 2–59 months)	Mother, sister	Breast cancer
O'Connor et al. (2009) (O'Connor et al. (2008) subsample)	USA	One group: bereaved (no control group)	• Grief Elicitation Task (O'Connor et al. 2008). • Local inflammation (IL-1β and TNF-α) was measured in saliva	44.3	100	NA	30 months (range 2–59 months)	Mother, sister	Breast cancer
Arizmendi et al. (2016)	USA	Three groups: prolonged grief, non-prolonged grief, and non-bereaved	• E-Stroop task using grief-related and neutral words	71.9	81	Excluded those with use of psychotropic medications initiated since the death event	Range: past 36 months	NA	NA
Schneck et al. (2018)	USA	One group: bereaved *ranked by severity of prolonged grief symptoms	• E-Stroop task, using words related to a deceased or a living attachment figure, and a standard Stroop task. • Subjects rated word sadness, prolonged grief symptoms, depression severity, attachment style, emotional pain, non-acceptance, yearning, and intrusions	45	NA	Psychiatric medication stable for two weeks prior to scanning	8.0 months	First degree relative or partner	76 % by suicide, 24 % non-suicide
Chen et al. (2020)	USA	Two groups: bereaved and non-bereaved controls	• Resting state fMRI at multiple time points following their loss to track changes in brain connectivity over time	69.5	73	34 % on SSRI, SNRI, benzodiazepine or combination antidepressant, doses stable for at	5.5 months	Spouse, child, parent, other	NA

(*continued on next page*)

Table 3 (*continued*)

First Author, Year	Country	Defined Study Populations	Methods	Mean Age (Years)	% Female	Psychotropic Medication Use	Mean Time Since Death	Relation of Deceased	Nature of Death
						least four weeks prior to scanning			
			• Grief symptoms and emotional states were assessed using standardized psychological scales at each time point						
Fernández-Alcántara et al. (2020)	Spain	Two groups: prolonged grief and non-bereaved	• Standardized affective picture task including positive valence, negative valence, and death-related • Participants completed a picture-recognition task after scanning, and valence, arousal, and dominance ratings were obtained	39.9	89.5	No mention of specific antidepressant use (only overall drug consumption – 15.8 %)	41.6 months	Son, spouse, parent, sibling, grandparent	NA
Bryant et al. (2021)	Australia	Four groups: prolonged grief disorder, PTSD, MDD, and bereaved controls (*MDD and PTSD groups were not bereaved)	• Standardized passive face viewing task with facial expressions including sadness, happiness, and neutral	41.2	18.3	23.9 % using SSRIs, stable dosage for at least 2 months prior to scanning	6.8 months	Partner, parent, child, sibling	Chronic illness, sudden illness, traumatic death, suicide
Blair et al. (2022)	USA	Two groups: high and low prolonged grief	• Resting state fMRI used to map ventral caudate and nucleus accumbens functional connectivity	66.1	69	Antidepressants and/or low doses of benzodiazepines allowed if stable dosage for at least 4 weeks prior to scanning	5 months	Spouse, parent, child, grandchild, other	NA
Kark et al. (2022)	USA	Two groups: bereaved mothers and control group	• Grief Elicitation Task: Participants viewed images of their child, recently deceased celebrities, and unfamiliar individuals, rating their emotional response during scan • Participants underwent cognitive tests and self-report assessments	61.8	100	NA	38 months	Mothers who had lost an adult child unexpectedly	Suicide or accident
Yoshiike et al. (2023)	Japan	One group: bereaved	• Grief Elicitation Task: Participants were primed with facial stimuli (pictures of their deceased or living relative or a stranger) followed by a visual pain stimulus • Empathy levels were measured using standardized scales or self-report questionnaires to assess participants' ability to empathize with others' emotions	49.5	93	17.9 % on psychiatric medication	102 months	Spouse, child, parent, sibling, grandparent	50 % by sudden or violent loss
Hwang et al. (2024)	USA	Two groups: prolonged grief disorder and integrated grief	• Resting-state fMRI to assess intrinsic functional connectivity • Standardized passive face viewing task with facial expressions including fearful and angry versus shapes, to	61.5	~76	Allowed if stable dosage for six weeks prior to scanning	36.5 months	Spouse, child, parent, other	NA

(*continued on next page*)

Table 3 (*continued*)

First Author, Year	Country	Defined Study Populations	Methods	Mean Age (Years)	% Female	Psychotropic Medication Use	Mean Time Since Death	Relation of Deceased	Nature of Death
			probe negative affect reactivity • Clinical assessment of PGD symptoms						

Note. NA, no data available. PGD = prolonged grief disorder

O'Connor et al., 2008; Yoshiike et al., 2023), three used the e-Stroop task (Arizmendi et al., 2016; Michel et al., 2024; Schneck et al., 2018), three used standardized affective stimuli (Bryant et al., 2021; Fernández-Alcántara et al., 2020; Hwang et al., 2024), and three used resting state fMRI (Blair et al., 2022; Chen et al., 2020; Hwang et al., 2024). Neuroimaging protocols for the grief elicitation and e-Stroop tasks are published to ensure future replicability of these task designs (Singer et al., 2024). Resting state and task-based fMRI studies showed disruptions in emotion regulation, reward processing, and regions implicated in cognitive control and attachment circuits. Resting-state studies also identified differences in functional connectivity associated with grief intensity. For example, Blair et al. (2022) examined individuals in early bereavement, grouped by high vs. low grief intensity, and found that participants with higher grief intensity showed higher connectivity between ventral caudate and nucleus accumbens seeds and other brain regions (Blair et al., 2022). Additionally, emotional processing tasks showed heightened neural reactivity in response to grief related stimuli, with heightened activation in the posterior and subgenual anterior cingulate cortex, medial/superior frontal gyrus, cerebellum, and amygdala (Gündel et al., 2003; Hwang et al., 2024; Kark et al., 2022; McConnell et al., 2018).

Further, two articles focused on aspects relating to the peripheral physiology associated with neural activity during grief (O'Connor et al., 2007; O'Connor et al., 2009). O'Connor et al. (2007) found that individuals with lower baseline parasympathetic activity, as indexed by respiratory sinus arrythmia (RSA), exhibited greater ventral posterior cingulate cortex (vPCC) activity when processing grief, thereby indicating a possible connection between autonomic nervous system regulation and emotional processing related to grief (O'Connor et al., 2007). Additionally, O'Connor et al. (2009) showed that local inflammation, as indexed by IL-1β and TNF-α from a saliva sample, was positively associated with greater sACC activation (O'Connor et al., 2009). A summary of the findings is presented in Fig. 2.

4. Discussion

This systematic review provides a comprehensive synthesis of structural and functional MRI studies in grief and bereavement, highlighting novel associations between functional neural response, changes in brain structure, peripheral physiology, and emotional correlates of

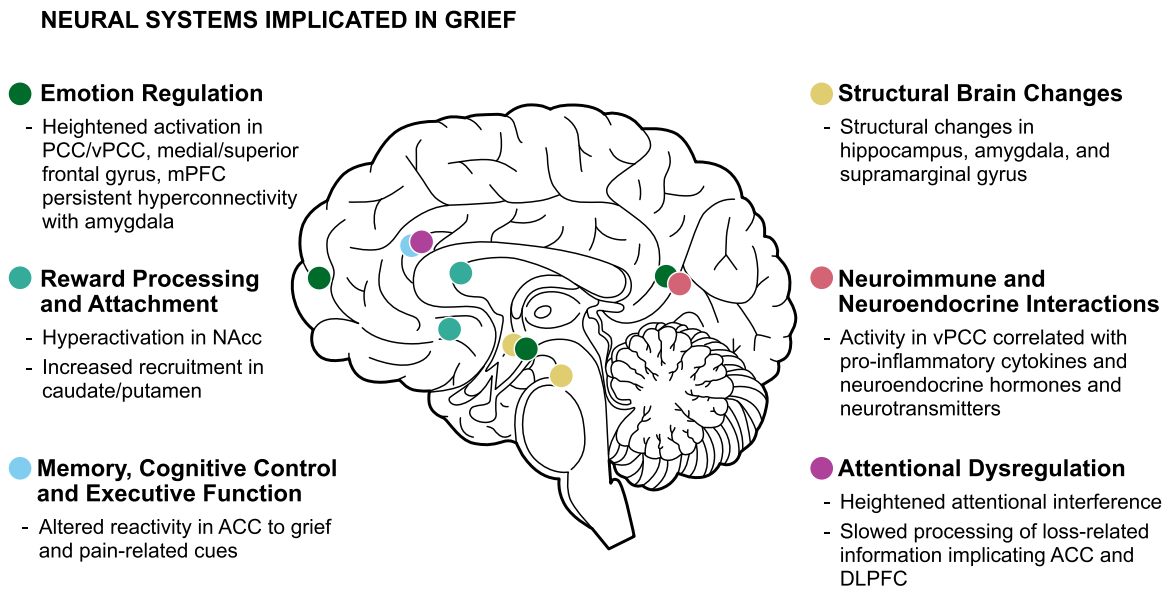

Fig. 2. Neural systems implicated in grief. Note: Fig. 2 highlights the major brain regions and functional networks affected during grief, organised into six thematic domains. Emotion regulation involves heightened activation in the posterior cingulate cortex (PCC), ventral posterior cingulate cortex (vPCC), medial and superior frontal gyri, and persistent hyperconnectivity between the medial prefrontal cortex (mPFC) and amygdala. Increased activation in the medial and superior frontal gyri and persistent hyperconnectivity between the medial prefrontal cortex (mPFC) and the amygdala reflect altered regulation of self-relevant emotional content. Reward processing and attachment mechanisms include hyperactivation of the nucleus accumbens (NAcc) when viewing images of the deceased, heightened connectivity within the ventral striatum (including the caudate nucleus and NAcc) during early intense grief, and increased recruitment of the caudate and putamen during subliminal processing of sad facial expressions in prolonged grief disorder (PGD). Memory, cognitive control, and executive function alterations include altered subgenual and dorsal anterior cingulate cortex (ACC) responses to grief and pain-related cues. Structural brain changes associated with grief are observed in the hippocampus, amygdala, and supramarginal gyrus. Neuroimmune and autonomic interactions are represented by correlations between vPCC activity and elevated pro-inflammatory cytokines, alongside stress-sensitive changes in the mPFC, amygdala, and hippocampus associated with neuroimmune dysregulation. Neuroimmune interactions are represented by correlations between vPCC activity and pro-inflammatory cytokines. Attentional dysregulation is characterised by frontoparietal network involvement, with grief severity linked to increased attentional interference for grief-related words and slowed processing of loss-related information implicating executive-control regions such as the ACC and dorsolateral prefrontal cortex (DLPFC).

grief. We found that bereavement and grief severity are evident in neural responses to grief-specific and general emotional stimuli, functional connectivity, and brain structure.

Grief is a complex emotional and physiological response to loss, with increasing evidence suggesting that prolonged grief is associated with distinct neurobiological alterations. This systematic review examined functional and structural MRI studies investigating the neural correlates of bereavement, revealing consistent disruptions in emotion regulation, reward processing, and cognitive control networks. FMRI studies demonstrated heightened neural reactivity to grief-related stimuli, particularly in the posterior and subgenual anterior cingulate cortex, medial/superior frontal gyrus, cerebellum, and amygdala (Gündel et al., 2003; Hwang et al., 2024; Kark et al., 2022; McConnell et al., 2018). Structural MRI studies further highlighted reductions in hippocampal, amygdala and supramarginal gyrus volumes, as well as white matter abnormalities and potential cognitive decline in individuals experiencing prolonged grief (Kim et al., 2022; Luo et al., 2017; Luo et al., 2016; Saavedra Pérez et al., 2015; Shi et al., 2024). These findings suggest that bereavement, especially prolonged grief, may contribute to neural changes, with potential lasting implications for mental and cognitive health.

4.1. Structural MRI studies

Saavedra Pérez et al. (2015) demonstrated cognitive impairments and structural brain changes in individuals with prolonged grief, underscoring the need for comprehensive assessments and interventions to support cognitive function and overall well-being in those experiencing grief (Saavedra Pérez et al., 2015). Similarly, Shi et al. (2024) reported reduced grey matter volume in the left supramarginal gyrus and right amygdala among Chinese Shidu parents, with supramarginal gyrus atrophy mediating the association between grief intensity and impaired cognitive inhibition (Shi et al., 2024). These findings extend previous evidence of grief-related cognitive deficits by identifying specific structural substrates linking emotional distress and executive dysfunction.

Further, in two studies, Luo et al. (2016), (2017) specifically examined the neurobiological impact of losing an only child, including in parents with PTSD in the aftermath of this trauma (Luo et al., 2017; Luo et al., 2016). Their research revealed significant atrophy and asymmetry in hippocampal subfield structures, with a pronounced volume reduction in the left hippocampus. These structural changes were more severe in parents with PTSD and correlated with the severity of grief and PTSD symptoms (Luo et al., 2017; Luo et al., 2016). The observed structural changes in the hippocampus suggest potential disruptions in memory consolidation and emotional regulation processes, which are commonly affected in PTSD. This research thus highlights the complex interplay between grief, PTSD, and brain structure alterations, emphasizing the importance of early interventions to mitigate structural changes and alleviate symptoms.

Further, Kim et al. (2022) highlighted the significant association between spouse bereavement and an increased risk of brain pathologies, including neurodegenerative diseases (Kim et al., 2022). Their findings suggest that the emotional and psychological stress of losing a spouse can have profound effects on brain health, emphasizing the importance of providing psychological and social support to mitigate these risks (Kim et al., 2022). This work underscores the broader impact of bereavement on long-term brain health and the necessity for supportive interventions. Collectively, these studies highlight the intricate interplay between emotional regulation and brain structure alterations following bereavement and its implications for brain and mental health.

4.2. Functional MRI studies

4.2.1. Grief elicitation task

A number of studies in this review employed variations of a grief elicitation task, providing evidence of the neural, physiological, and emotional mechanisms underlying grief processing (Gündel et al., 2003; Kark et al., 2022; McConnell et al., 2018; O'Connor et al., 2007; O'Connor et al., 2009; O'Connor et al., 2008; Yoshiike et al., 2023). Gündel et al. (2003) first demonstrated that viewing images and words related to the deceased elicited heightened activation in three distinct brain regions, being the posterior cingulate cortex, medial/superior frontal gyrus, and cerebellum, highlighting a specific neural signature of grief (Gündel et al., 2003). O'Connor et al. (2008) found that individuals with prolonged grief exhibited greater activation in the nucleus accumbens when viewing images of their deceased loved one, indicating that prolonged grief may involve dysregulation of reward processing (O'Connor et al., 2008). Similarly, Kark et al. (2022) found that bereaved mothers exhibited distinct neural responses, such as heightened activation in areas associated with emotional processing and memory when viewing images of their deceased child. These responses further support the role of the attachment system in grief processing, as these brain regions are critical for emotional bonds (Kark et al., 2022). Beyond neural responses, Yoshiike et al. (2023) explored the relation between grief, pain perception, and empathy by priming bereaved individuals with images of their deceased or living relatives before exposing them to an image designed to evoke a sensation of pain or discomfort. The study found that grief-related priming dampened neural responses in the dorsal anterior cingulate cortex and superior medial frontal gyrus to pain cues that were primed by images of living relatives or strangers, compared with priming using images of the deceased. These findings suggest that grief alters the neural evaluation of others' pain-related cues rather than enhancing pain sensitivity directly (Seiler et al., 2018; Seiler et al., 2020; Yoshiike et al., 2023).

4.2.2. Neuroimmune interactions

The CNS regulates peripheral immune responses via hormonal and neuronal circuits. Neuroendocrine stress responses, triggered by infections or trauma, typically suppress systemic immune functions (Sternberg, 2006). Both the sympathetic and parasympathetic nervous system detect injury or infection locally and modulate immune activity through adrenergic and cholinergic anti-inflammatory pathways. Importantly, the neuroendocrine hormones and neurotransmitters that regulate peripheral immunity also influence CNS cell functions, responding not only to immune stimuli but also to stress and emotional arousal, enabling individuals to adapt to environmental changes (Tracey, 2009).

Similarly, emotional traumatic stress such as the loss of a significant person, can lead to widespread changes in brain function, structure, and plasticity, as well as in neuroendocrine and immune responses within the CNS (Bremner, 2006). Dysregulation of this close neuroimmune crosstalk can adversely affect cognitive and emotional functioning, and influence behavior (Dantzer, 2018). Grief, in particular, triggers inflammatory activity (Slavich and Irwin, 2014), which may impact immune-to-brain signaling resulting in profound effects on emotion, cognition, and behavior (Seiler et al., 2020). Evidence suggests that bereavement may alter immune functioning, including increased and sustained secretion of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. Additionally, bereavement is associated with an impaired immune response, characterized by a reduced T-lymphocyte activity and decreased natural killer (NK) cell function (Hansel et al., 2010; Irwin et al., 1988; Knowles et al., 2019; Seiler et al., 2018).

Although the impact of stress on immune function has been discussed in the literature, including forward-looking conceptual reviews such as Knowles et al. (2019) (Knowles et al., 2019), research on how the neural correlates of grief influence immune system function—or vice versa—remains limited. In contrast, studies on depression and PTSD reveal similar alterations in the neuroendocrine and immune systems and report consistent changes in brain areas like the hippocampus, amygdala, and the medial prefrontal cortex. These parallels may help explain the high comorbidity and prevalence of these conditions in bereaved

individuals (Bremner, 2006; Yehuda et al., 1996). Importantly, however, many of these neurobiological and immune patterns may reflect general stress responses rather than grief-specific effects. To delineate grief-related mechanisms more precisely, future studies should employ longitudinal designs with appropriate control groups to disentangle markers of bereavement from those associated with broader stress processes.

O'Connor et al. (2009) provided a unique perspective by linking pro-inflammatory cytokine levels with regional brain activation in grief (O'Connor et al., 2009). This study highlights the complex interplay between biological markers of inflammation and emotional processing during bereavement. A better understanding of the neuroimmune crosstalk in the CNS and its role in mental health disorders following loss, grief, and bereavement may help inform the development of interventions aimed at reducing inflammation and regulate neural changes and improving health in bereaved individuals.

In an additional study, O'Connor et al. (2007) showed that individuals with lower baseline parasympathetic activity, which is indicative of reduced cardiac parasympathetic control and often associated with higher psychophysiological arousal, exhibit greater vPCC activity in response to grief stimuli (O'Connor et al., 2007). This suggests that the PCC processes self-relevant emotional information, linking vPCC activity with autonomic arousal. Together, these findings are suggestive of a connection between autonomic nervous system activity, immune function, and brain regions involved in emotional processing during grief, indicating potential targets for therapeutic interventions. These studies emphasize the intricate relations between grief, autonomic, and immune function, and brain activity, revealing potential neuro-immune pathways through which bereavement can affect both physical and mental health. Strategies to reduce inflammation, modulate autonomic arousal, and support the regulation of brain activity through biopsychosocial interventions are essential components of comprehensive grief management. Based on the findings of O'Connor et al. (2005) mind-body interventions and relaxation techniques that can increase vagal activity may effectively modulate autonomic and immune function, making them a promising adjunctive intervention (O'Connor et al., 2005).

4.2.3. E-Stroop task

The studies by Arizmendi et al. (2016), Schneck et al. (2018), and Michel et al. (2024) provide converging evidence that bereaved individuals exhibit attentional biases toward grief-related stimuli, as assessed through variations of the emotional Stroop (e-Stroop) task (Arizmendi et al., 2016; Michel et al., 2024; Schneck et al., 2018). Arizmendi et al. (2016) was the only study to focus explicitly on prolonged grief, reporting that individuals with prolonged grief demonstrated delayed reaction times when processing grief-related words compared to both non-prolonged grief and non-bereaved individuals, suggesting heightened cognitive interference by grief-related stimuli (Arizmendi et al., 2016).

Schneck et al. (2018) examined a broader bereaved sample and found that higher grief symptom severity, rather than a categorical diagnosis of prolonged grief, was associated with heightened attentional interference for words related to the deceased, as well as heightened subjective ratings of sadness and emotional distress (Schneck et al., 2018). Similarly, Michel et al. (2024) investigated individuals bereaved by suicide and observed that grief-related words elicited greater attentional interference than words related to a living attachment figure, reinforcing the idea that intrusive cognitive processing of loss may be particularly pronounced in this population (Michel et al., 2024).

Together, these studies indicate that attentional dysregulation, particularly difficulty disengaging from grief-related stimuli, may play a key role in the persistence or intensity of grief symptoms. While only one of these studies focused specifically on prolonged grief, this broader evidence from bereaved samples offers a useful foundation for understanding how cognitive biases may operate across the spectrum of grief responses. These findings have important clinical implications, suggesting that cognitive interventions designed to modify attentional biases may confer therapeutic benefit. However, the methodological heterogeneity of neuroimaging studies (e.g., group composition, different task conditions, etc.) limits cross-study comparability and underscores the need for research that directly and consistently examines prolonged grief.

4.2.4. General affective stimuli

Studies by Bryant et al. (2021) and Fernández-Alcántara et al. (2020) explored emotional processing in bereavement, using task-based fMRI paradigms to examine neural responses to facial expressions and emotionally valenced images, respectively (Bryant et al., 2021; Fernández-Alcántara et al., 2020). The study by Bryant et al. (2021) investigated distinctive neural processes underpinning emotion processing in participants with prolonged grief disorder (PGD), PTSD, and major depressive disorder (MDD) (Bryant et al., 2021). The study found that PGD individuals showed distinct neural recruitment patterns compared to individuals with either PTSD or MDD, showing greater recruitment of the medial orbitofrontal cortex during supraliminal processing of sad faces. Individuals with prolonged grief also showed greater activation in the left amygdala, caudate, and putamen during subliminal presentation of sad faces in comparison to individuals with MDD (Bryant et al., 2021). Whilst the PTSD and MDD groups also exhibited altered neural responses, the PGD group showed distinct patterns of hyperactivation, reinforcing the idea that prolonged grief involves unique neurobiological mechanisms (Bryant et al., 2021).

Similarly, Fernández-Alcántara et al. (2020) showed that individuals with prolonged grief exhibited heightened activity in the limbic system, particularly the amygdala, when viewing grief-related stimuli (Fernández-Alcántara et al., 2020). Additionally, their subjective emotional ratings showed heightened arousal and emotional intensity, suggesting that prolonged grief is associated with persistent and heightened sensitivity to grief-related emotional cues (Fernández-Alcántara et al., 2020). These studies highlight the importance of emotional processing biases in prolonged grief and suggest that interventions targeting maladaptive emotional responses could be beneficial. More recently, Hwang et al. (2024) employed a standardized emotional face-matching paradigm and reported heightened right amygdala reactivity to fearful and angry faces in individuals with PGD relative to integrated grief (Hwang et al., 2024). Importantly, this activation correlated positively with intrusive thoughts, while reduced task-dependent functional connectivity between the right amygdala and posterior midline structures was associated with avoidance of loss reminders (Hwang et al., 2024). Collectively, these studies may indicate that PGD is associated with lateralised amygdala hyperactivation, left amygdala reactivity to subliminal grief cues (Bryant et al., 2021) and right amygdala reactivity and connectivity alterations to general negative affective stimuli (Hwang et al., 2024), supporting the hypothesis of disorder-specific emotional processing biases.

4.2.5. Resting state fMRI

Blair et al. (2022) and Chen et al. (2020) used resting-state fMRI to investigate intrinsic brain connectivity in bereaved individuals (Blair et al., 2022;Chen et al., 2020). Blair et al. (2022) investigated early bereavement, categorizing participants into high- and low-intensity early-grief groups based on grief severity scores rather than prolonged

grief status (Blair et al., 2022). The authors examined functional connectivity of the ventral caudate and nucleus accumbens, key regions involved in reward processing and attachment, and found that individuals with higher early-grief intensity showed higher connectivity between ventral striatal seeds and prefrontal as well as limbic regions (Blair et al., 2022). These findings suggest that grief intensity during early bereavement is associated with distinct patterns of intrinsic connectivity, although not specific to prolonged grief.

Furthermore, Chen et al. (2020) included longitudinal clinical assessments following bereavement but collected imaging data at baseline only (Chen et al., 2020). The study compared bereaved individuals with non-bereaved healthy controls, assessing grief symptoms and emotional states alongside fMRI data. Results indicated that bereaved individuals showed initial hyperconnectivity within the limbic system, particularly in the amygdala and default mode network, which gradually lowered over time. The study reported initial hyperconnectivity within the limbic system, particularly the amygdala and default mode network (DMN), which was associated with acute grief responses. In participants with persistent grief symptoms, certain connectivity patterns, such as between the amygdala and medial prefrontal cortex, remained elevated. While these results cannot be interpreted as direct longitudinal evidence of neural changes, they do offer insights into potential mechanisms underlying prolonged grief (Chen et al., 2020).

Complementing these findings, Hwang et al. (2024) observed higher resting-state connectivity between the right amygdala and thalamus, which was inversely associated with loneliness in PGD (Hwang et al., 2024). These findings provide preliminary evidence that dysregulation in reward and emotion-related networks may be relevant to prolonged grief.

Overall, these resting-state studies indicate that grief intensity and emotional distress are associated with distinct patterns of intrinsic connectivity in reward and emotion-regulation circuits. However, the available evidence is derived largely from early bereavement or mixed bereaved samples and therefore cannot be assumed to reflect mechanisms specific to prolonged grief. Future longitudinal neuroimaging studies are needed to clarify whether these connectivity patterns persist over time, reflect trajectories toward prolonged grief, or instead represent normative responses to acute loss.

4.2.6. *Therapeutic implications*

The studies in this systematic review illustrate the intricate interplay between various brain regions and psychological factors in the experience of grief. The findings emphasize the need for multifaceted therapeutic approaches that address the neural, autonomic, immune, and cognitive and emotional components of grief. By targeting specific brain regions and neuroimmune processes, interventions may be tailored to support individuals in managing their grief more effectively, ultimately improving their emotional and mental well-being. Body-mind interventions and relaxation techniques may increase vagal activity, targeting some of the neurobiological paths linking altered brain activity with autonomic and immune regulation in prolonged grief. Further research is needed to refine these interventions and explore their efficacy in diverse bereaved populations, aiming to provide comprehensive support for those navigating the profound challenges of bereavement.

4.2.7. *Strengths and limitations*

This systematic review employed a robust search strategy and adhered to the PRISMA guidelines. Strict inclusion and exclusion criteria were applied by two independent authors to ensure methodological rigor. By integrating and analyzing findings from a diverse range of literature, the review provides a comprehensive overview of the current knowledge Furthermore, through the synthesis of empirical evidence across neurobiological, psychological, and clinical domains, this systematic review aims to enhance the understanding of grief mechanisms and identify evidence-based interventions to support individuals.

Nonetheless, the findings should be interpreted in light of several limitations. First, although some studies focused specifically on a population bereaved by a particular cause of death, or a specific relation to the deceased, this review synthesized data across a wide range of causes of death, relations to the deceased, and time since the loss. However, the available data was too scant to allow for a systematic investigation of the effect of these factors. Future studies should explore differences in neural correlates among populations bereaved by different circumstances of death, for example unexpected or traumatic death compared to anticipated death to expand on our understanding of the contextual effect of grief and its neural, neuroendocrine, and immune correlates. Second, although most studies reported the time elapsed since the loss, ranging from four and a half months to a lifetime experience, two studies did not disclose this information. This poses a limitation as definitive statements about causal associations between loss and neural changes cannot be made without accounting for this temporal factor.

Additionally, the majority of the included studies reported predominantly female participants (60 % or greater), with only one study featuring a male-dominant cohort (18 % female). Although studies with all-female samples reduce variability and enhance homogeneity, the lack of gender balance in others introduces potential variability, limiting the generalizability of findings. Given known biological and psychological differences between men and women in emotional processing and stress response (Kreibig et al., 2007; Wilhelm et al., 2017), future research should consider gender balance in study populations and examine potential gender differences in (f)MRI findings.

Another limitation involves the use of psychiatric medications amongst participants. Psychotropic medications, such as antidepressants, neuroleptics, or benzodiazepines, can modulate brain activity and may thus influence the (f)MRI results. Additionally, some of these medications have autonomic side effects that could further impact the findings. Although some studies explicitly mentioned the use of medications such as SSRI, SNRI, and benzodiazepines, others either did not report medication use or failed to clarify whether participants had paused their medication or undergone a stabilization period prior to the study. This lack of information introduces a potential confounding factor. One study excluded participants taking psychotropic medications which were started since the death event, but did not specify the treatment period since the loss (Arizmendi et al., 2016). Given that many bereaved individuals, particularly those with PTSD or prolonged grief, may be prescribed psychiatric medications, future studies should control for medication use, ensuring stabilization of doses, and accounting for this variable in the statistical analysis.

Finally, the mean age of participants in the included studies was 40 years or older with one study not reporting age (O'Connor et al., 2007). Future research could benefit from including a broader age range or focusing specifically on a younger age population. A longitudinal study incorporating (f)MRI to examine brain structures and functional connectivity in adolescents or young adults who experience a loss during their formative years could yield novel insights into the long-term impact of grief on their brain structure, functional connectivity, and brain aging.

4.2.8. Implications for future research

Future research aimed at identifying neurobiological markers and predictors of prolonged grief could benefit from longitudinal study designs that track neural activity, connectivity, and structure over time in bereaved individuals. Further, multi-modal approaches combining functional and structural MRI with neuroendocrine and immune measures may provide a more comprehensive understanding of the mechanisms underlying grief. Integrating these measures into a conceptual framework or model could help disentangle grief-specific mechanisms from broader stress responses and examine trajectories in cases of PGD both alone and when coupled with PTSD. Finally, prospective cohort studies could help identify early predictors of prolonged grief, while integration with intervention research, such as targeted psychotherapeutic trials, could inform individualized strategies to promote neuroimmune resilience and improve grief management. These approaches would allow for a more precise translation of neurobiological findings into clinical support and personalized care for those experiencing prolonged grief. The comprehensive understanding provided in this review may facilitate the development of multifaceted therapeutic approaches that address not only the emotional wellbeing of individuals experiencing grief and bereavement, but further, the neurobiological aspects of grief.

5. Conclusion

In conclusion, this systematic review highlights the significant impact of grief and bereavement on brain regions involved in the attachment, affective processing, pain, and reward systems, including the amygdala, hippocampus, and prefrontal cortex. The loss of a significant person, one of life's most stressful events, can result in lasting changes in these brain areas. These alterations may lead to dysregulation of both the neuroendocrine and immune systems, contributing to disruption in emotional, cognitive, and behavioral functioning. By synthesizing findings from 20 empirical studies, this work underscores the multidimensional nature of grief and advocates for interdisciplinary approaches to advance research. It further highlights the need for psychological interventions aimed at promoting neuroimmune resilience and enhancing clinical practices in grief management and support.

Author contributions

SRE developed the concept for this article. The initial draft was written by SRE, and subsequently reviewed and edited by AS. GMS, MFO, FW, and DB edited the article, and all authors read and approved the final version for publication.

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Declaration of Competing Interest

The authors declare no conflicts of interest with respect to this work.

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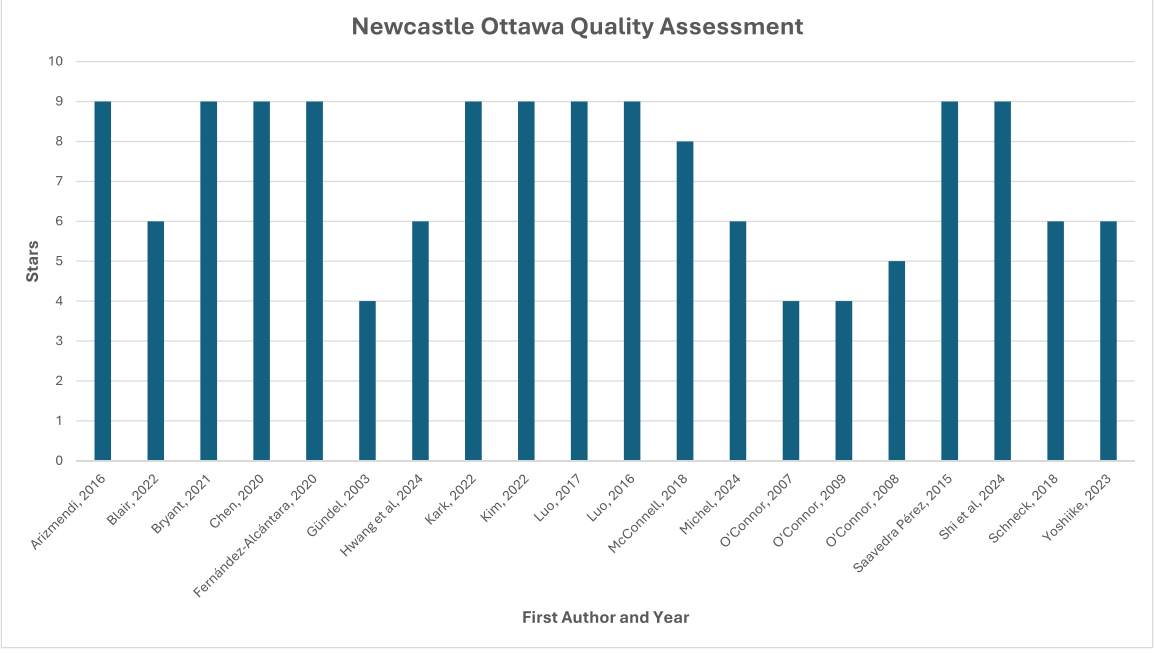
Appendix A. Newcastle-Ottawa Scale Ratings



Appendix B. Newcastle-Ottawa Coding Manual

Newcastle-Ottawa Quality Assessment Scale
Case-Control Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) Yes, with independent validation *
   b) Yes, e.g., record linkage or based on self report
   c) No description

2) Representativeness of the cases
   a) Consecutive or obviously representative series of cases *
   b) Potential for selection biases or not stated

3) Selection of Controls
   a) Community controls *
   b) Hospital controls
   c) No description

4) Definition of Controls
   a) No history of disease (endpoint) *
   b) No description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) Study controls for_____ (select the most important factor). *
   b) Study controls for any additional factor * (These criteria could be modified to indicate specific control for a second important factor).

Exposure

1) Ascertainment of exposure
   a) Secure record (e.g., surgical records) *
   b) Structured interview where blind to case/control status *
   c) Interview not blinded to case/control status
   d) Written self report or medical record only
   e) No description

2) Same method of ascertainment for cases and controls
   a) Yes *
   b) No

3) Non-Response rate
   a) Same rate for both groups *
   b) Non-respondents described
   c) Rate different and no designation

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