



Published in final edited form as:

*Psychiatry Res Neuroimaging*. 2020 September 30; 303: 111135. doi:10.1016/j.pscychresns.2020.111135.

## The Neurobiological Reward System in Prolonged Grief Disorder (PGD): A Systematic Review

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### Abstract

Prolonged Grief Disorder (PGD) is a debilitating condition affecting between 7% and 10% of bereaved individuals. Past imaging and psychological studies have proposed links between PGD's characteristic symptoms - in particular, profound yearning - and the neural reward system. We conducted a systematic review to investigate this connection. On December 19, 2019, we searched six bibliographic databases for data on the neurobiology of grief and disordered grief. We excluded studies of the hypothalamic-pituitary-adrenal (HPA) axis, animal studies, and reviews. After abstract and full-text screening, twenty-four studies were included in the final review. We found diverse evidence for the activation of several reward-related regions of the brain in PGD. The data reviewed suggest that compared to normative grief, PGD involves a differential pattern of activity in the amygdala and orbitofrontal cortex (OFC); likely differential activity in the posterior cingulate cortex (PCC), rostral or subgenual anterior cingulate cortex (ACC), and basal ganglia overall, including the nucleus accumbens (NAc); and possible differential activity in the insula. It

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Conflicts of Interest Statement

Declarations of interest: none.

also appears that oxytocin signaling is altered in PGD, though the exact mechanism is unclear. Our findings appear to be consistent with, though not confirmative of, conceptualizing PGD as a disorder of reward, and identify directions for future research.

## Keywords

bereavement; Prolonged Grief Disorder (PGD); Complicated Grief (CG); neuroimaging; neurobiology

## 1. Introduction

Grief, the sorrow caused by the loss of a loved one, develops into an all-consuming, persistent, and debilitating condition for roughly 7–10% of bereaved survivors (Prigerson et al. 2009, Lundorff et al. 2017). This syndrome, referred to as Prolonged Grief Disorder (PGD), has been validated in numerous studies (Prigerson et al. 1997, Latham and Prigerson 2004, Prigerson et al. 2009), included in the International Classification of Diseases (ICD) –11 (ICD-11 for Mortality and Statistics, 2020), and approved by the Diagnostic and Statistical Manual (DSM) Steering Committee as a new mental disorder for inclusion in DSM-5-TR.<sup>1</sup> PGD is characterized by persistent yearning for the deceased and disabling symptoms, which can include emotional numbness, a sense of disbelief about the death, identity disruption, and an inability to move forward in life following the death of the significant other (Prigerson et al. 2009). Those who develop PGD are at an increased risk of suicide (Latham and Prigerson 2004; Maciejewski et al. 2016; Prigerson et al. 1999), acute and chronic medical conditions such as heart disease, myocardial infarction, and cancer (Prigerson et al. 1997; Prigerson et al. 2009; Tofler et al. 2019), substance misuse (Prigerson et al. 1997, Parisi et al. 2019), and impaired quality of life (Silverman et al. 2000; Boelen and Prigerson 2007, Maciejewski et al. 2016, MacCallum and Bryant 2020). There is a need to develop the evidence base of mental health interventions for vulnerable bereaved individuals. Research on the neural mechanisms of PGD can inform the development of interventions targeting this syndrome; it may be especially helpful for pharmacological treatments, as medication trials have had disparate and mixed results (Bui et al. 2012).

Studies of neurobiological correlates of PGD have hypothesized that the onset and maintenance of symptoms involve neural reward system activity associated with thoughts of the deceased (O'Connor 2012). The reward system (illustrated in Figure 1) facilitates the seeking of both intrinsic and extrinsic (learned) rewards through pathways that link dopaminergic neurons in the midbrain with limbic and cortical areas, which evaluate the motivational salience of a stimulus. Evidence suggests that reward system activation is linked to the mitigation of pain sensations, putatively by generating endorphins, a class of endogenous opioids (Younger 2010). Reward signaling integrates not only dopamine but also oxytocin (OT) – a neuropeptide hormone involved in social bonding and attachment – and the endogenous opioids. Among other areas, dopamine, oxytocin, and opioid receptors converge in the nucleus accumbens (NAc), a primary node of the reward system (Trezza et

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<sup>1</sup><https://www.psychiatry.org/psychiatrists/practice/dsm/proposed-changes>

al. 2011, facilitating interplay between extrinsic and intrinsic sources of reward and the formation of social bonds (Johnson et al. 2015). Reward signaling is not the only function of the NAc, which is also active during motion, avoidance, and complex behavioral decisions (Floresco 2015). Similarly, the anterior cingulate cortex (ACC), insula, and orbitofrontal cortex (OFC) activate during a wide variety of psychological processes, and are not exclusively indicative of reward signaling. We present their activity in the context of reward because the symptom profile of PGD may accord with a reward disorder and because animal microinjection studies (Bosch et al. 2016) have shown reward-related signaling cascades in the NAc to be integral to attachment and its disruption.

Love and loss are known to affect the reward system. Attachment figures play a psychological and physiological regulatory role, providing emotional stability during times of distress and acting as safe buoys in times of uncertainty (Coan et al. 2006, Fogel et al. 2007). Neurobiologically speaking, attachment offers not only security, but also sustained reward, facilitated by OT and mediated largely by endogenous opioids (Inagaki 2018), the withdrawal of which can send an individual into a state of psychological and physiological “disorganization” when facing a significant loss (Sbarra and Hazan 2008). Site-specific agonist studies in prairie voles (Bosch et al. 2009, Bosch et al. 2016) have found that a drop in OT levels in the NAc, mediated by corticotropin-releasing factor (CRF), induces a depressive-like response in male voles separated from their partners.

PGD, then, may be associated with a persistent disruption in reward signaling. An elegant 2019 review by LeRoy et al. (2019) proposed that in order for an individual’s attachment hierarchy to be adaptively reorganized, and for the individual to reach homeostasis after a loss, the individual must pass from disorganization to a “protest” stage, in which they are first disoriented and then agitated and angered over deprivation of the deceased, to a “despair” stage, characterized by depression and lack of motivation or withdrawal. LeRoy et al. (2019) suggested that dysregulated or prolonged grief develops when bereaved individuals continue to rely on the deceased as a primary attachment figure, with motivational activity in the reward system causing them to yearn for the deceased – a core symptom of PGD. The bereaved individual experiences despair presumably because the deceased attachment figure is unavailable to fulfill the same interpersonal functions that they had previously.

That the reward system is vulnerable to such disruptions is evident from its role in addiction, which develops as overall dopamine levels in the mesolimbic reward system drop, prompting the compulsive reward-seeking typical of addiction in order to achieve equilibrium (Edwards and Koob 2010). Functional neuroimaging studies show that brain regions associated with reward and substance addiction also activate upon viewing stimuli related to an attachment figure, such as a romantic partner (Fisher et al. 2010, Younger et al. 2010). Anecdotally, Dr. Prigerson is aware of three patients with PGD who received naltrexone, a competitive opioid antagonist commonly used to treat addiction, and who all rapidly (within two days of initiation) exhibited dramatic alterations in their behavior and reduction of their PGD symptoms. Within days of starting naltrexone, each of these three bereaved family members who had met criteria for PGD became able to put away mementos and venture outside of their home in contrast to former behavior in which they had been

home-bound and spent the day viewing pictures or videos of the deceased (personal communication). Taken together, this led us to hypothesize that naltrexone would make the rewarding stimulus (e.g., images of the deceased) and behaviors (e.g., ruminations of times together with the deceased) markedly less pleasurable, thereby freeing them from the hold they had and permitting an openness to explore other activities and develop relationships outside the home. Admittedly scant, these examples suggested to us that the reward system might be implicated in PGD and prompted us to review the neurobiological research in support of this scientific premise.

Behaviorally, PGD manifests in some behaviors that resemble disorders of reward. People with PGD seek out connection with the deceased (approach); this is complicated by the tendency for them to simultaneously avoid painful reminders that the person they lost is gone (avoidance). The conflict between approach and avoidance characterizes substance addiction (Breiner et al. 1999). Research by MacCallum and colleagues (2015) found that individuals with PGD show an approach bias in an approach-avoidance task, responding more quickly to grief-related stimuli than to neutral stimuli. Those with PGD also showed attentional bias to grief-related cues over neutral cues during an emotional counting Stroop (ecStroop) task study (MacCallum and Bryant 2010). MacCallum et al. (2015) suggested that negative affect in PGD is maintained by consistent attentional bias toward the loss, a process that is also observed in substance addiction (Field et al. 2009).

The notion that the neurological reward system underlies craving for the deceased gained empirical support from a 2008 fMRI study by O'Connor and colleagues (2008), who found that participants with PGD had heightened activation of the NAc when viewing grief-related stimuli. It is important to note that the seminal O'Connor et al. (2008) study used a cluster correction of 10 voxels to account for multiple comparisons across the brain. On its own, this approach has been shown to have unacceptably high false positive rates (see Eklund et al. 2016). However, subsequent neuroimaging studies observed activity in other areas involved in reward signaling, such as the dorsal anterior cingulate cortex (dACC), in those with PGD (O'Connor 2012). More recent work has suggested differences in OT signaling in PGD (Bui et al. 2019), further implicating the reward system. While the role of this system in PGD is of increasing interest, a comprehensive examination of the research in this area has been lacking. The purpose of this systematic review is to summarize the state of the science and review the literature to evaluate the extent to which neurological reward pathways are associated with PGD.

## 2. Methods

All procedures were conducted according to guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Moher et al. 2015). On December 19, 2019, a comprehensive electronic literature search was conducted using the following six databases: Medline/PubMed (legacy), [Embase.com](https://www.embase.com), Scopus, Web of Science, PsycInfo (Ovid), and the Cochrane Central Register of Controlled Trials. The search strategy consisted of two components, related to bereavement/grief and relevant neurological/biological phenomena, respectively. The search terms used were subject headings (MeSH, Emtree, APA's Thesaurus of Psychological Index Terms) and/or keywords in the title,

abstract and author keywords fields. Boolean Operators OR and AND were used to combine the search terms and the search strategy components. The searches in all databases except for Cochrane CENTRAL were limited to the English language. Results were not restricted by date, in order to capture all existing literature. Search results were compiled using the citation management tool EndNote and duplicates were removed following the Bramer method (2017). Covidence was utilized to facilitate article screening and selection. For a complete overview of the search strategy, see the accompanying PubMed search displayed in Appendix A.

Studies were deemed eligible for inclusion if they described neurological pathways, structures or components and their association with grief, prolonged grief, or complicated grief. Studies describing other biological associations with grief (e.g., HPA axis, cortisol activation, genetic factors, neurocognitive effects, cardiac effects) were excluded from this review. Studies that did not clearly indicate that they were focused on grief, in contrast to other outcomes such as depression or anxiety, were excluded.

After duplicates were removed, seven members of the study team independently reviewed a random selection of titles/abstracts for initial eligibility. In addition to the above inclusion and exclusion criteria, non-human animal studies were excluded, as were reviews and chapters. Each article was reviewed by two coders and any discrepancies were resolved in a consensus meeting with the entire coding team. The full text of the remaining articles was reviewed by two independent coders each to determine if each article met inclusion criteria. Discrepancies were again discussed in a consensus meeting with the entire coding team. Finally, the first author completed a spreadsheet to extract prespecified information about the sample, instruments used, methods, and results from the included articles.

Two articles were added from outside the original search. One (Bryant et al. 2020) was found when the authors conducted an informal search on March 20, 2020, using the original search terms, to ensure the review included the most up-to-date material. The second (Fernández-Alcántara et al. 2020) was identified on publication because it cited work by two of the authors. (See Figure 2 for the PRISMA flow diagram.)

### 3. Results

#### 3.1 Overview of Utilized Assessment Tools

The 24 included studies varied in their use of the terms “prolonged grief” and “complicated grief,” as well as in their choice of instruments to assess grief and other constructs of interest. In this review, we use the term Prolonged Grief Disorder (PGD) for consistency and clarity. In all, 8 of the 24 included studies used neuroimaging to investigate PGD specifically. Eight of these studies assessed PGD caseness using the Inventory of Complicated Grief (ICG), with one (Bui et al. 2019) including ICG-diagnosed patients as well as those with “probable” PGD as assessed by the Structured Clinical Interview for Complicated Grief in analyses. All studies using the ICG applied a cutoff score of 30 for PGD diagnosis, except for two: one by Saavedra-Perez and colleagues that conducted separate analyses using cutoffs of 22 and 30 (Saavedra Perez et al. 2015); and a study by Fernández-Alcántara and colleagues (2020) that used a cutoff of score of 25 but confirmed

diagnoses by a clinical interview. A 2008 neuroimaging study by O'Connor et al. (2008) diagnosed PGD using an early structured clinical interview (SCI), The Traumatic Grief Evaluation of Response to Loss (Prigerson and Jacobs 2001), for what was then termed “traumatic grief,” rather than the ICG. Bryant et al. (2020) used the Prolonged Grief-13 scale to assess PGD.

Of the non-neuroimaging studies we reviewed, three investigated the role of OT in PGD, offering indirect support for the activity of the reward system in the disorder. One study measured the effect of intranasal OT on approach and avoidance in PGD using a joystick push-pull task (Arizmendi 2018). Another study measured peripheral (bloodstream) OT levels in PGD as scored by the ICG (Bui et al. 2019). A separate study examined genomics: participants were genotyped for a polymorphism possibly affecting oxytocin binding in PGD, which was assessed using the ICG (Schiele et al. 2018).

Four studies did not explicitly investigate PGD caseness, but rather used the ICG to measure “grief severity” (Schneck et al. 2017, 2018, 2019a, 2019b) and the Impact of Events Scale (IES) to measure intrusive thoughts and avoidance – a measure of posttraumatic stress disorder (PTSD) symptoms. One study of neurobiological correlates of adult attachment style (AAS) in grief (Acosta et al. 2018) used the anxiety and avoidance subscales of the Relationship Scales Questionnaire (RSQ) to examine attachment style, and the List of Threatening Experiences Questionnaire (LTE-Q) to tally affective losses in the past five years. Three studies focused on the neurobiology of normative grief, measured by the Texas Revised Inventory of Grief (TRIG) (Huang et al. 2019); levels of inflammation (O'Connor et al. 2009); and subjective grief ratings on a scale of 1 to 10 (O'Connor et al. 2007), respectively. Another study examining individuals who had lost a pet (Freed et al. 2009) used the Texas Revised Inventory of Grief (TRIG) to measure grief intensity and the Impact of Event Scale-Revised (IES-R) to measure intrusive and avoidant thoughts as predictors of grief intensity (though it should be noted that the IES is a measure of PTSD, not PGD). Of two other papers, one examined anticipatory grief, measured by the Marwit and Meuser Caregiver Grief intensity scale (Jain et al. 2019), and the other examined grief following a romantic break-up, using the ICG (Najib et al. 2004).

Below, we summarize study findings from our review, organizing them according to the brain regions implicated. Although the wide variety of methods and samples in our studies preclude us from reaching specific conclusions about any one region, we found diverse evidence that neural structures associated with the reward system are active in PGD. The areas for which we found some evidence for differential activity in PGD are the basal ganglia, including the NAc; the amygdala; the insula; the cingulate cortex, with specific support for the subgenual anterior cingulate cortex (sgACC); and the orbitofrontal cortex (OFC). We also found evidence for differential OT signaling in PGD, some of which indicated a possible genetic component to the disorder. We recognize that the activation of these brain regions and the presence of differential OT signaling do not necessarily implicate neural reward signaling. We present these findings to evaluate the evidence in support of a connection to the reward system and to suggest potentially fruitful areas of future research. A summary of studies is found in Table 1.

### 3.2 The Basal Ganglia

The basal ganglia are a multifarious group of nuclei, including the NAc, that bridge the midbrain and forebrain. They play a significant role in movement: for example, degeneration of dopaminergic neurons in the basal ganglia is responsible for disordered movements like those observed in Parkinson's disease (Blandini et al. 2000). Most relevant to this review, however, the basal ganglia form the chief part of the mesolimbic reward pathway. Regions of the basal ganglia such as the subthalamic nucleus and the NAc process and integrate reward signals. Specifically, the basal ganglia integrate impulses from the midbrain and cortical regions to determine incentive salience (Lanciego et al. 2012, Berridge and Kringelbach 2015). In addition, they allow an addictive substance to gain incentive salience, and diminish dopamine and opioid signaling in its absence (Koob and Volkow 2016).

In bereaved individuals, the basal ganglia may be activated when thinking of the deceased. Two included studies by Schneck and colleagues (2017, 2018) applied neural network-based pattern identification to fMRI data from bereaved participants completing sustained-attention tasks and ecStroop tasks (which measure participants' response latency when counting words that have either emotional or neutral valence). The authors identified neural patterns of activation that were associated with mental representation of the deceased (d-MR) and the suppression of deceased-related thoughts (deceased-related selective attention, or d-SA). Schneck et al. (2017) identified an activation pattern for d-MR that involved the basal ganglia and orbitofrontal cortex. This pattern was associated with experiential avoidance, as measured by scores on the Avoidance subscale of the IES, and frequency of thoughts about the deceased during a sustained attention task, both predictors of poorer grief outcomes. Because the activation pattern predicted deceased-related thinking independent of total ICG score, Schneck et al. (2018) proposed that the pattern may be indicative of a subtype of PGD.

A second study by the same group (Schneck et al. 2019b) identified two separate patterns characteristic of *avoidant* grievers, as indicated by the IES: a frontotemporoparietal network for deceased-related selective attention (d-SA) and the aforementioned basal ganglia-orbitofrontal network for mental representation of the deceased (d-MR). Schneck et al. suggested that these two networks are responsible for the avoid-approach conflict characteristic of avoidant grief, with the d-SA network monitoring for cues related to the deceased in order to prevent the d-MR network activating. Paradoxically, the study found that in the absence of a cue, participants with avoidant grief, as indicated by the IES, had more frequent intrusive thoughts about the deceased than those with normative grief, suggesting that heightened d-SA primes the brain for deceased-related thoughts (Schneck et al. 2019b).

The NAc, a basal ganglia nucleus, has received considerable attention in grief research because of its role in the reward pathway. A striatal area receiving dopaminergic input from the Ventral Tegmental Area (VTA) and OT and opioid signals from other areas, the NAc modulates signaling from the midbrain to the limbic system, facilitating motivated behavior (Salamone et al. 2007). Animal studies in the prairie vole, a monogamous mammal, implicate the NAc in the systemic response to partner loss. Vole research has found that increased levels of corticotropin-releasing factor (CRF) following partner separation mediate

depressive behavior, akin to Bowlby's "despair" phase (Bowlby 1973), by causing OT levels in the NAc to drop precipitously (Bosch and Young 2017).

Human research has painted a murkier picture. An early influential study by O'Connor et al. (2008) implicated the NAc in the maintenance of PGD. The authors compared fMRI data from 11 subjects with PGD to 12 with normative grief and observed higher activity in the NAc among participants with PGD than without when viewing a picture of the deceased. The NAc co-activated with areas associated with pain, such as the insula and periaqueductal grey, prompting O'Connor et al. (2008) to suggest that "craving" for the deceased was experienced as an affliction, as in addiction. A subsequent study attempted to replicate this finding with an older sample, but found no significant difference in NAc activation between PGD and non-PGD groups (McConnell et al. 2018). The authors suggested this null finding may have been due to a small sample size or to the age of the subjects (the average age was 71 years, as opposed to 44 years in their 2008 paper), citing non-human animal research that shows a decline in certain NAc activity with advancing age (Ruegsegger et al. 2017). However, it is unknown whether the animal findings extend to humans, or whether they would be detectable in an fMRI. Furthermore, the high false positive rate associated with the statistical method used by O'Connor et al. (2008) may cast doubt upon that paper's findings. Thus, the role of the NAc in PGD remains unclear.

### 3.3 Amygdala

The amygdala, a key node of the limbic system, contributes to emotional learning and the formation of desire and aversion (Clark 1995). Importantly, the amygdala sends glutamatergic projections to the NAc, which are active in determining emotional salience (Nieh et al. 2013). Because of its dual roles in avoiding unpleasant stimuli and seeking pleasure (Fernando et al. 2013), one would expect to see activation in the amygdala in response to grief stimuli in PGD.

Functional neuroimaging studies show simultaneous activation of the amygdala with reward-oriented areas of the brain in PGD. Arizmendi et al. (2016) found heightened activation in the amygdala as well as in the orbitofrontal cortex (OFC), a reward-related region discussed in greater detail below, when individuals with PGD were exposed to a deceased-related cue. In their study of pet loss, Freed et al. (2009) found that functional connectivity between the amygdala and prefrontal cortex (PFC) was indeed inversely correlated with intrusive thoughts and avoidance as measured by the IES-R. The authors proposed that altered regulation of the amygdala could lead to pathological grief symptoms, although their data showed that amygdala activity alone predicted sadness, not yearning (the latter being more uniquely characteristic of PGD). Bryant et al. (2020) found heightened activity in the amygdala in those with PGD viewing sad faces, but this activity was also observed in participants with Post-Traumatic Stress Disorder (PTSD), leading the authors to suggest that amygdala activation reflects a separate network active in multiple disorders. This finding is supported to some extent by a study conducted by Fernández-Alcántara et al. (2020) in which the authors found higher activity in the amygdala of participants with PGD while viewing death-valenced images. However, the latter study (Fernández-Alcántara 2020) is limited by an entirely nonbereaved control group; it is therefore unclear whether its finding



of heightened amygdala activity is distinct in PGD or merely reflective of normative grief. In addition, the general role of the amygdala in strong emotion (Clark 1995) precludes interpretation specific to PGD.

Heightened amygdala activation is consistent with findings from two non-fMRI papers we reviewed. The first tested circulating catecholamine levels in participants with PGD in a trial comparing Interpersonal Therapy to Complicated Grief Treatment (O'Connor et al. 2013). The study found that higher levels of peripheral epinephrine predicted higher PGD symptomatology after therapy, regardless of intervention assignment. Circulating catecholamines are a measure of stress (O'Neill 2019), which the amygdala integrates into memory consolidation and recall through its connections with the hippocampal complex and prefrontal cortex (Roosendaal et al. 2009). The second paper, by Saavedra Pérez et al. (2015), reported cross-sectional analyses of psychometric tests and volumetric analyses of MRI data across an aging cohort of over 5,000 individuals enrolled in the Rotterdam Study (Hofman et al. 1991). Saavedra Pérez et al. (2015) tentatively suggest that aging-related synaptic loss in the amygdala (among other regions) may predispose older adult patients to PGD by reducing their ability to regulate the stress of grieving and mourning.

### 3.4 Insula

A wide range of functions are credited to the insula, which is known to be active in sensing social and physical pain as well as in interoception, salience, and reward anticipation (Tsurumi et al. 2014, Uddin et al. 2017). Studies linking damage to the insula with the cessation of addictive craving make it highly relevant to research on dysregulated reward signaling in other disorders (Naqvi and Bechara 2009, Droutman et al. 2015). However, perhaps due to the heterogeneity in its functions, evidence for the insula's involvement in PGD is mixed. In a recent fMRI study comparing PGD, PTSD, and Major Depressive Disorder (MDD; the latter two disorders in nonbereaved participants), Bryant et al. (2020) found heightened insula activity across all three disorders during subliminal processing of happy faces, which were displayed in rapid succession. In their examination of grief, the two neural pattern recognition studies introduced above (Schneck et al. 2017, 2018) identified increased activity in the insula as part of the basal ganglia-orbitofrontal d-MR pattern. The pattern predicted both experiential avoidance and thoughts about the deceased (which, when intense and frequent, are symptoms of PGD), even when controlling for total ICG score (Schneck et al. 2018). On the other hand, in their 2008 study demonstrating increased activity in the NAc among those with PGD, O'Connor et al. (2008) found that participants with PGD had *lower* insula activity during grief elicitation than those without PGD. These studies used similar methods to elicit grief, but with distinct samples. Both neural pattern identification studies (Schneck et al. 2017, 2018) were performed with a cohort with a high proportion of suicide-bereaved participants and a high average score on the ICG (26.5; PGD caseness was not assessed), while the O'Connor et al. (2008) study included women who had lost a mother or a sister to breast cancer, half of whom met criteria for PGD based on a structured clinical interview.

### 3.5 Cingulate Cortex

The anterior cingulate cortex (ACC) integrates stimulus evaluation with emotional and physiological affect. It interacts directly with the reward system through a projection to the NAc, as well as with autonomic areas, including the amygdala, hypothalamus, and brainstem (Stevens et al. 2011). The evidence for differential activation of the ACC in PGD is mixed and reflects the likelihood - according to basic neurobiological studies - that the several subregions comprising the ACC perform different roles (Jin et al. 2018, Tang et al. 2019).

Two included studies revealed no evidence for differential activation of the ACC on the basis of PGD diagnosis. O'Connor et al. (2008) found no significant difference in ACC activation between subjects with PGD and without during grief elicitation, which used picture-word composites. An fMRI study by the same group (O'Connor et al. 2007) examined neural correlates of baseline parasympathetic arousal (inversely measured by respiratory sinus arrhythmia) in bereaved women and found that ACC activation was not associated with parasympathetic activity. The authors note that this decreased parasympathetic activity is a common feature of disorders such as MDD and PTSD, though participants with Axis I disorders diagnosable by a structured clinical interview were excluded in this study and participants were not screened for PGD.

The evidence concerning subregions of the ACC is more nuanced. One study testing Mentalizing Imagery Therapy (MIT), a mindfulness intervention, for anticipatory grief in dementia caregivers (Jain et al. 2019), found activation of the dorsal ACC (dACC) during grief elicitation at baseline; the authors suggested that this region is activated in social pain. However, the level of activation of the broader cingulate gyrus during grief elicitation after completing MIT predicted lower grief intensity. This may mean that both regions of the cingulate cortex are associated with anticipatory grief. An fMRI study of 8 bereaved women exhibiting normative grief (Gundel et al. 2003) found that the dACC was activated by viewing pictures of the deceased loved one. The authors suggested that dACC activation is associated with intense feelings of grief, because the dACC is known to be active in awareness of emotion (Stevens et al. 2011) and the engagement of attention (Gundel et al. 2003). Arizmendi et al. (2016) observed significantly lower recruitment of the rostral ACC (rACC) among participants with PGD during an ecStroop task. The authors suggested that those with PGD process grief stimuli via different pathways than those without PGD. As the task progressed through repeated rounds of words, they saw greater activation in the dACC in participants with PGD and in nonbereaved controls, but not in those with normative grief, which the authors proposed means those with PGD lack an adaptation common to normative grief. The authors suggested that the dACC's role in self-awareness facilitates monitoring of error, and that while the rACC is recruited in normative grief, the dACC "turns on" in PGD to compensate for the failure of the rACC to activate (Arizmendi et al. 2016).

Subregions of the rACC may also be differentially implicated. A recent fMRI study (Bryant et al. 2020) found that compared to bereaved controls, participants with PGD had higher functional connectivity between the pregenual ACC (pgACC) and right pallidum, a region that inhibits reward processing, during subliminal processing of happy faces. However, pgACC activity in PGD did not differ from that in nonbereaved participants with PTSD or MDD. The difference in functional connectivity could therefore be indicative of reward

inhibition patterns in several psychological disorders (Price and Drevets 2010). The subgenual ACC (sgACC), which is the foremost area of the rostral section, may also play a role in symptomatic yearning in PGD. sgACC activation during grief elicitation was associated with circulating levels of inflammatory markers in a study of 18 women who had lost a mother or sister to breast cancer (O'Connor et al. 2009). The authors proposed that sgACC activation is associated with a stressful grief experience, though PGD was not assessed. A later study by McConnell et al. (2018) observed no significant differences in sgACC activation between those with PGD and those without. However, in a symptom-specific analysis of all bereaved participants, the authors found that yearning (as assessed by the yearning item in the ICG) was associated with activation in the sgACC, independent of other ICG items or total score (O'Connor et al. 2018). This result is consistent with other studies that have found the sgACC to be active in ruminative thought, both in depression (Cooney et al. 2010) and in grief (Eisma et al. 2015).

The role of the posterior cingulate cortex (PCC) in autobiographical memory and pain (Nielsen et al. 2005, Leech and Sharp 2014) makes it a candidate for grief-related activity. Though we found no evidence that its activation predicts PGD, differential reward-related PCC activation may be associated with the disorder. Four functional neuroimaging studies we reviewed found heightened PCC activity during grief elicitation in normatively grieving participants (Gundel et al. 2003, O'Connor 2007, Schneck et al. 2018, Jain et al. 2019). Gundel et al. (2003) and O'Connor et al. (2007) found that grief-related words significantly induced PCC activation; similarly, in Jain et al.'s (2019) study of anticipatory grief in dementia caregivers, pictures of a terminally ill loved one induced PCC activation. Schneck et al.'s (2017) machine learning study of neural activation patterns in grief identified the PCC as part of a pattern of mental representation of the deceased. Another study observed reduced PCC activity in grieving individuals completing an ecStroop task after they had taken a mindfulness course; the authors suggested that the PCC has a role in emotional distress and painful recall in acute normative grief (Huang et al. 2019).

The PCC's connectivity to the orbitofrontal cortex (OFC), which conducts reward processing (see next section), could implicate it in reward-related activity in grief, though a direct link to PGD is not evident. O'Connor et al. (2007) found that bereaved individuals with greater baseline arousal, as measured by respiratory sinus arrhythmia (RSA), had PCC activation when presented with cues reminding them of the deceased. The PCC activation was associated with activity in the OFC. Schneck et al. (2017) found PCC activity to be part of a larger network indicating mental representation of the deceased, which also included the OFC. This machine learning-generated pattern predicted participants' self-reported repetitive thinking about the loss and experiential avoidance. It is possible, therefore, that the PCC is recruited in patterns of repetitive thought that contribute to the clinical presentation of PGD.

### 3.6 Orbitofrontal Cortex

The OFC, the dysfunction of which is implicated in MDD, performs multiple functions in reward-oriented behavior. Lesion studies in macaques suggest that the lateral OFC links representations of reward to stimulus choice, while the ventromedial OFC facilitates

repeated choice based on the likelihood of reward (Noonan et al. 2012). Enhanced activity in the OFC has been observed in individuals with a drug addiction when exposed to a drug-related stimulus (Schoenbaum and Shahan 2008). As noted above in the review of evidence for activity in the PCC, the OFC has been implicated in repetitive thinking about the deceased (O'Connor et al. 2007, Schneck et al. 2017). Two additional studies have demonstrated dysregulated OFC activity in PGD. In O'Connor et al.'s (2009) aforementioned study of inflammation in grief, participants with higher levels of inflammatory markers also had higher activation in the OFC upon recalling grief-related words. More recently, Arizmendi et al. (2016) found that a PGD diagnosis was associated with heightened activation in the OFC during a grief-eliciting Stroop task. In comparing participants with PGD to those with PTSD and MDD, Bryant et al. (2020) also found higher medial OFC activity in those with PGD while viewing sad faces, suggestive of reward processing. These data suggest heightened OFC activity in individuals with PGD thinking of their deceased loved one.

### 3.7 Oxytocin Signaling

Studies of OT signaling were included in this review because it is the neuropeptide hormone most directly responsible for emotional disequilibrium following partner loss in animals (Hurlemann and Scheele 2016), and because variations in OT levels and binding efficiency within the brain play a primary role in attachment (King et al. 2016). Variations in OT signaling appear to impact bereaved individuals' responses to their loss; however, the studies reviewed differed in their findings.

One study administered intranasal OT to participants with and without PGD before they engaged in an approach-avoidance task (Arizmendi 2018). Those with PGD, but not those without, were significantly slowed in their execution of the task with administration of OT, regardless of the image they were shown (a deceased loved one, a living loved one, or a stranger). The difference in reaction times suggests that OT signaling may uniquely influence the approach-avoidance calculus in PGD. An abstract included in our review reported similar results, with OT slowing participants with PGD in their responses to grief-related and neutral images (O'Connor 2018).

Attempts to measure overall levels of OT associated with PGD symptoms have been inconclusive. One study that examined circulating OT levels in bereaved participants with normative grief, PGD, and MDD (Bui et al. 2019) initially found that those with MDD had significantly lower OT levels than those without. In contrast, participants with ICG scores greater than 30, which has been used as the clinical cutoff for PGD in most studies, did not differ significantly from those with normative grief. However, a secondary analysis adding those with "probable" PGD as determined by the Structured Clinical Interview for Complicated Grief (SCI-CG) found that all participants with PGD, even those with comorbid MDD, had higher OT levels than those without. The authors proposed that these differences in levels of OT distinguish PGD, which was associated with higher levels, from MDD, which was associated with lower levels (Bui et al. 2019). However, this result must be interpreted with caution, as other research has found that peripheral OT levels may not accurately reflect central OT levels (Valstad et al. 2017).

Further studies examining genetic correlates of PGD may inform associations between OT signaling and PGD. One study in our review that used genomic sequencing in bereaved participants (Schiele et al. 2018) found that those bearing a particular single-nucleotide polymorphism (SNP) in the oxytocin receptor gene (*OXTR*), rs2254298, had higher ICG scores as a function of their levels of behavioral inhibition and separation anxiety. The region of *OXTR* affected is involved in epigenetic modification, putatively affecting GATA4 binding. The authors suggested a gene-by-environment effect, consistent with the Social Salience Hypothesis of Oxytocin: those with the SNP in question could be predisposed to develop PGD in the presence of certain environmental, experiential, or psychological factors (Schiele et al. 2018).

## 4. Discussion

### 4.1 Summary of Findings

The purpose of this review was to synthesize empirical investigations of neurobiological correlates of PGD, with a focus on the reward system in light of the growing body of research implicating its role in PGD in humans. The limited evidence synthesized in this review provides varied, though not abundant, support for the hypothesis that the reward system plays a role in the onset and maintenance of PGD symptoms. These findings suggested that reminders of the deceased are processed by the reward system, and that the protracted yearning characteristic of PGD may reflect a combination of craving (commonly observed in addiction disorders) and rumination (commonly observed in MDD and anxiety disorders).

A landmark 2008 finding by the O'Connor group of heightened NAc activity in subjects with PGD undergoing grief elicitation (O'Connor et al. 2008) spurred our interest in the role of the reward system in PGD. Notably, activation of the NAc did not emerge in other studies, including a recent attempt to replicate the O'Connor group's 2008 study (McConnell et al. 2018). What did emerge, however, was evidence for PGD-associated activity in the amygdala and OFC; likely in the PCC, rACC, sgACC, and basal ganglia overall; and possibly in the insula. Taken together, these data suggest a subcortical-cingulate-orbitofrontal pattern of activity related to PGD. The areas identified align with neural reward processing: for example, a comprehensive review of neuroimaging studies of addiction (Suckling and Nestor 2017) reported heightened activity in the OFC and cue reactivity in the ACC, amygdala, and ventral striatum (which contains the NAc). Our review therefore offers moderate support for conceptualizing PGD as similar to other reward-oriented disorders, such as substance abuse. The results of the review also suggest that OT signaling is altered in PGD, which would be consistent with animal studies of separation (Bosch and Young 2017) and with disorders involving the reward system. However, it is unclear exactly how OT signaling is altered, or which brain regions are affected. OT signaling interacts with dopamine and endogenous opioid systems, and all three are key in the response to the loss of a loved one: OT in trust and bond formation; opioids in creating a positive experience of social contact, such as touch; and dopamine in motivating one to pursue social contact (O'Connor 2012).

Conceptualizing PGD as a reward-system-based syndrome would be consistent with observations that individuals with PGD struggle to process their loss because the deceased is a source of both pleasure and pain. The empirical support for involvement of the reward system in this review helps elucidate the “pleasure” side of this paradox, with yearning as an analogue to craving, which we would expect in a condition mediated by dysregulated reward signaling. Such dysregulation is further supported by evidence for the approach-avoidance problem central to PGD (Schneck et al. 2017, 2018): a bereaved person simultaneously yearns for the deceased while avoiding thoughts that trigger their painful grief.

## 4.2 Study Design Considerations, Caveats, and Future Directions

It is important to consider critically the studies we reviewed and what the nascent evidence base suggests about future directions for researchers. Studies generally had small samples [in 15 of the 18 fMRI studies included,  $N$  was less than 30, the minimum recommended for replicability by a recent fMRI study (Turner et al. 2018)], limiting statistical power. Samples were also quite heterogeneous, with different causes of death (e.g., suicide vs. cancer), relationships to the deceased, and length of time since the loss occurred, as well as variability in how PGD was assessed. Some studies also did not directly link findings to PGD symptoms, limiting the conclusions that can be drawn.

Such diversity in study design makes it difficult to interpret the variation in findings observed. It is also important to note that 5 of the 7 fMRI studies of populations with PGD involved members of one research group (O’Connor et al. 2008 Arizmendi 2018, Arizmendi 2016, McConnell 2018, O’Connor and Arizmendi 2015). This reflects the relatively primitive stage of the field and punctuates how important it is for researchers to attempt to replicate findings and pursue research in this area.

At the risk of repeating ourselves, we reiterate that these results cannot be taken as incontrovertible evidence that PGD is a disorder of reward. OT and lesion studies in voles explicitly manipulate neural mechanisms, giving strong evidence that CRF and OT cascades in the NAc dictate post-separation behavior. By contrast, causal inference from the diverse human fMRI data we present is not possible. The Schneck et al. (2017, 2018, 20\_S1\_Reference8919a, 2\_S1\_Reference90019b) studies demonstrate that a machine learning model can predict certain psychological processes (i.e., intrusive thinking, approach avoidance, etc.) associated with PGD. Yet even here, we cannot conclude that the psychological function of these networks implicates reward processes specifically. Furthermore, the presence of reward signaling would not exclude other neural processes from important roles in PGD’s pathogenesis or symptom maintenance. While reward is an alluring conclusion, it should not be taken to be the only one.

More research on the role of the reward system, and the NAc in particular, in the development and maintenance of PGD symptoms is needed. It would also be helpful to explore functional connectivity patterns associated with PGD, as addiction researchers have shown, for example, that differences in functional connectivity between the NAc, insula, precuneus, and prefrontal cortex (PFC) reduce the ability of the PFC to regulate craving (Chen et al. 2016). Additionally, to our knowledge, no studies have examined baseline OFC activation in PGD, which may be of interest given its disproportionately low activation

during drug withdrawal and its heightened activation in addicted individuals exposed to a drug-related stimulus (Volkow and Fowler 2000).

### 4.3 Clinical Implications and Future Directions

The studies included in this review have implications for both pharmacological and psychosocial interventions. The existing evidence suggests that PGD's core symptoms – yearning for and preoccupation with the deceased – may be linked to reward signals that reinforce the deceased as a source of pleasure. It is possible, therefore, that psychopharmacological interventions targeting reward signaling, such as those used to address behavioral addictions and substance use disorders (e.g., naltrexone), may be helpful for individuals with PGD. A review of neurobiological correlates of addiction (Goldstein and Volkow 2011) found that dysregulated prefrontal activity – especially in the OFC – may be due in part to changes in dopamine receptor availability elsewhere in the brain. Endogenous opioid signaling also appeared to be involved: in those addicted to cocaine and alcohol, higher mu opiate binding in the ACC and PFC persists during abstinence and may predict treatment outcome (Goldstein and Volkow 2011). Naltrexone, a competitive opioid antagonist, has been a successful treatment for alcoholism (Helstrom et al. 2016) and for broadly defined behavioral addictions, such as gambling (Mouaffak et al. 2017). Guanfacine, an alternative treatment that may work by normalizing dysregulated prefrontal signaling, may also be of interest (Fredriksson et al. 2015), as could memantine, an NMDA receptor antagonist that reduced cue-induced alcohol craving in a small trial (Krupitsky et al. 2007).

However, treatment of PGD with medication is controversial for a variety of reasons. First, concerns about medicalizing PGD have been prominent in the literature; providers, researchers, theorists, and bereaved family members worry that a neurobiological conceptualization of PGD and its treatment may contribute to over-pathologizing and overmedicating the bereaved. Second, while the present review suggests a link between the neurobiological reward system and PGD, much about the etiology, onset, and maintenance of PGD remains unknown. Finally, despite the potential utility, little research has been done on potential psychopharmacological interventions for PGD. The findings from this review may serve to encourage efforts to explore pharmacological interventions, cautiously and conservatively.

Involvement of the reward system in PGD also has implications for psychosocial interventions. Psychotherapeutic approaches might include those shown to be effective in addiction research to address cravings and encourage adaptive behaviors (often in conjunction with pharmacological treatment). These include motivational interviewing (Nyamathi et al. 2011) and cognitive-behavioral strategies such as self-monitoring, goal setting, coping skill rehearsal, behavioral contracts, and positive reinforcement (Chawarski et al. 2011, Moore et al. 2013, Dugosh et al. 2016).

Although the literature examining neurobiological pathways associated with PGD is developing, adequate symptom assessment and identification of treatment moderators (e.g., symptom thresholds, type of loss, and duration and course of symptoms) remain central to the development of appropriate and effective treatments for PGD. While this review suggests there may be value in pursuing research on medications to treat the symptoms of PGD, in

parallel, it is critical to be able to identify those who are most likely to benefit from a psychopharmacological treatment.

#### 4.4 Conclusions

Studies in this systematic review suggest that activation of the neural reward system is associated with PGD. Reward signaling can be powerful, resulting in persistent and preoccupying yearning for the comforting, soothing connection to the deceased and hindering integration of the loss and adaptation. Conceptualizing PGD through a neurobiological lens can be validating for those struggling with debilitating grief reactions: it helps explain why they cannot simply “get over” their loss. However, this review also highlights the necessity for additional research in this area. Research using larger and more homogeneous samples, and consistent, psychometrically validated measures of PGD, is needed to replicate existing findings and further elucidate the role of the reward system in the neurobiology of PGD. In addition, researchers should explore adapting existing interventions that target the reward system, such as those used to treat addiction, to help those suffering from PGD.

#### Acknowledgements

We thank Dr. Mary-Frances O’Connor for her clarification of details regarding her work.

##### Funding

This work was supported by grants from the National Cancer Institute [CA106370 (Prigerson), CA197730 (Prigerson), CA218313 (Prigerson/Lichtenthal), CA009461 (Ostroff), P30CA008748 (Thompson)]; the National Institute of Minority Health Disparities [MD007652 (Maciejewski/Prigerson)]; the National Institute of Nursing Research [NR018693 (Prigerson/Epstein)]; the National Institute of Mental Health grant [MH095378 (Lichtenthal/Prigerson)]; the National Institute on Aging [AG049666 (Reid/Prigerson)]; and the National Center for Advancing Translation Sciences [UL1 TR002384 (Imperato-McGinley)]. The funding sources did not play a role in the conception or conduct of this research or the writing of this paper.

#### Appendix A: MeSH Search Terms Used in Systematic Review

(“Bereavement”[Mesh] OR bereavement[tiab] OR bereaved[tiab] OR bereave[tiab] OR bereaving[tiab] OR grief[tiab] OR grieved[tiab] OR grieve[tiab] OR grieving[tiab]) AND (“Gene Expression”[MeSH] OR “Gene Expression Regulation”[MeSH] OR “Biomarkers” [MeSH] OR “Inflammation”[MeSH] OR “Cytokines”[Mesh] OR “Biogenic Amines”[Mesh] OR “Receptors, Biogenic Amine”[Mesh] OR “Catecholamines”[Mesh] OR “Receptors, Catecholamine”[Mesh] OR “Neuropeptides”[Mesh] OR “Oxytocin”[MeSH] OR “Hydrocortisone”[MeSH] OR “hydrocortisone receptor” [Supplementary Concept] OR “Blood Cells”[Mesh] OR “Cerebrovascular Circulation”[Mesh] OR “Synaptic Transmission”[Mesh] OR “Nerve Net”[Mesh] OR “Neural Pathways”[MeSH] OR “Neurons”[Mesh] OR “Neurotransmitter Agents”[Mesh] OR “Receptors, Neurotransmitter” [Mesh] OR “Brain”[Mesh] OR “Neurosciences”[Mesh] OR “Neuroimaging”[MeSH] OR “Electroencephalography”[Mesh] OR “Tomography”[Mesh] OR “Radionuclide Imaging” [Mesh] OR psychobiology[tiab] OR psychobiological[tiab] OR psychobiologic[tiab] OR neuroanatomy[tiab] OR neuroanatomical[tiab] OR neuroanatomic[tiab] OR neurobiology[tiab] OR neurobiological[tiab] OR neurobiologic[tiab] OR neurophysiology[tiab] OR neurophysiological[tiab] OR neurochemistry[tiab] OR



neurochemical[tiab] OR neuroendocrine[tiab] OR neuroimmunomodulation[tiab] OR activation[tiab] OR psychoneuroimmunology[tiab] OR psychoneuroimmunological[tiab] OR psychoneuroimmunologic[tiab] OR biomarker[tiab] OR biomarkers[tiab] OR biological marker[tiab] OR biological markers[tiab] OR correlate[tiab] OR correlates[tiab] OR biogenic[tiab] OR biochemistry[tiab] OR biochemical[tiab] OR immunology[tiab] OR immunological[tiab] OR immunologic[tiab] OR immune[tiab] OR immunomodulation[tiab] OR inflammation[tiab] OR inflammatory[tiab] OR gene[tiab] OR genes[tiab] OR genotype[tiab] OR genotypes[tiab] OR phenotype[tiab] OR phenotypes[tiab] OR endocrine[tiab] OR endocrinology[tiab] OR endocrinological[tiab] OR endocrinologic[tiab] OR lipid[tiab] OR lipids[tiab] OR killer cell[tiab] OR killer cells[tiab] OR blood cell[tiab] OR blood cells[tiab] OR plasma[tiab] OR serum[tiab] OR platelet[tiab] OR platelets[tiab] OR erythrocyte[tiab] OR erythrocytes[tiab] OR leukocyte[tiab] OR leukocytes[tiab] OR lymphocyte[tiab] OR lymphocytes[tiab] OR neutrophil[tiab] OR neutrophils[tiab] OR serotonin[tiab] OR serotonergic[tiab] OR oxytocin[tiab] OR oxytocinergic[tiab] OR catecholamine[tiab] OR catecholamines[tiab] OR dopamine[tiab] OR acetylcholine[tiab] OR cortisol[tiab] OR cellular[tiab] OR intracellular[tiab] OR intercellular[tiab] OR protein[tiab] OR proteins[tiab] OR cytokine[tiab] OR cytokines[tiab] OR interleukin[tiab] OR interleukins[tiab] OR interferon[tiab] OR interferons[tiab] OR tumor necrosis factor[tiab] OR forebrain[tiab] OR brainstem[tiab] OR brain stem[tiab] OR nucleus accumbens[tiab] OR accumbens nucleus[tiab] OR hypothalamus[tiab] OR hypothalamic[tiab] OR thalamus[tiab] OR thalamic[tiab] OR cerebrum[tiab] OR cerebellum[tiab] OR hippocampus[tiab] OR hippocampal[tiab] OR parahippocampus[tiab] OR parahippocampal[tiab] OR cortex[tiab] OR cortical[tiab] OR subcortical[tiab] OR cingulum[tiab] OR cingulate[tiab] OR gyrus[tiab] OR gyri[tiab] OR lobe[tiab] OR lobes[tiab] OR frontal[tiab] OR fronto[tiab] OR prefrontal[tiab] OR gray matter[tiab] OR white matter[tiab] OR cerebral blood flow[tiab] OR cerebral circulation[tiab] OR hemisphere[tiab] OR hemispheres[tiab] OR caudate[tiab] OR amygdala[tiab] OR putamen[tiab] OR ganglion[tiab] OR ganglia[tiab] OR circuit[tiab] OR circuits[tiab] OR circuitry[tiab] OR pituitary[tiab] OR sympathetic[tiab] OR parasympathetic[tiab] OR neural[tiab] OR synapse[tiab] OR synapses[tiab] OR synaptic[tiab] OR neuronal[tiab] OR neurotransmitter[tiab] OR neurotransmitters[tiab] OR neurotransmission[tiab] OR neuropeptide[tiab] OR neuropeptides[tiab] OR neuroscience[tiab] OR tomography[tiab] OR tomogram[tiab] OR tomograms[tiab] OR magnetic resonance[tiab] OR mri[tiab] OR fmri[tiab] OR CT[tiab] OR SPECT[tiab] OR positron emission[tiab] OR neuroimaging[tiab] OR brain mapping[tiab] OR eeg[tiab] OR electroencephalography[tiab] OR electroencephalogram[tiab] OR electroencephalograms[tiab]) AND (English[lang])

### Abbreviations:

<b>AAP</b>	Adult Attachment Projective Picture System
<b>AAS</b>	Adult Attachment Scale
<b>ASA-27</b>	Adult Separation Anxiety Scale
<b>ANOVA</b>	Analysis of variance

<b>AAT</b>	Approach Avoid Task
<b>BDI BDI II</b>	Beck Depression Inventory
<b>BI</b>	Behavioral Inhibition
<b>BC</b>	Breast Cancer
<b>BSI</b>	Brief Symptom Inventory
<b>CG</b>	Complicated grief
<b>CRFR2</b>	Corticotropin-releasing factor receptor 2
<b>d-SA</b>	deceased-related selective attention
<b>DERS</b>	Difficulties in Emotional Regulation Scale
<b>dACC</b>	dorsal Anterior Cingulate Cortex
<b>DLPFC</b>	Dorsolateral prefrontal cortex
<b>ECG</b>	Electrocardiograph
<b>eCStroop</b>	Emotional Counting Stroop
<b>FEW</b>	Family-wise error correction
<b>FFMQ</b>	Five Factor Mindfulness Questionnaire
<b>FST</b>	Forced Swim Test
<b>fMRI</b>	Functional Magnetic Resonance Imaging
<b>GAD-7</b>	Generalized Anxiety Disorder-7
<b>IES-R</b>	Impact of Event Scale-Revised
<b>IL-1<math>\beta</math></b>	Interleukin 1 beta
<b>IU</b>	International Unit
<b>INT OT</b>	Intranasal Oxytocin
<b>ICG</b>	Inventory of Complicated Grief
<b>LDST</b>	Letter-Digit Substitution Test
<b>LTE-Q</b>	List of Threatening Experiences Questionnaire
<b>MIT</b>	Mentalizing Imagery Therapy
<b>MBCT</b>	Mindfulness-Based Cognitive Therapy
<b>MMSE</b>	Mini Mental State Exam
<b>MAO-A</b>	Monoamine Oxidase A

<b>MMQ</b>	Multidimensional Mood Questionnaire
<b>non-CG</b>	Non complicated grief
<b>NAcc</b>	Nucleus Accumbens
<b>OFC</b>	Orbitofrontal cortex
<b>OT</b>	Oxytocin
<b>OXTR</b>	Oxytocin Receptor
<b>PHG</b>	Parahippocampal gyrus
<b>PVN</b>	Paraventricular nucleus
<b>PHQ</b>	Patient Health Questionnaire
<b>PAG</b>	Periaqueductal gray
<b>PCC</b>	Posterior cingulate cortex
<b>PMR</b>	Progressive Muscle Relaxation
<b>QIDS</b>	Quick Inventory of Depressive Symptomatology
<b>RSQ</b>	Relationship Scales Questionnaire
<b>RSA</b>	Respiratory Sinus Arrhythmia
<b>RSRI</b>	Retrospective Self-Report of Inhibition
<b>rACC</b>	rostral Anterior Cingulate Cortex
<b>SART</b>	Selective Attention Related Thoughts
<b>SA</b>	Seperation Anxiety
<b>K-22</b>	Short Form of Social Support Questionnaire
<b>sTNFrII</b>	Soluble tumor necrosis factor receptor type II
<b>STAI</b>	State Trait Anxiety Index
<b>SCID</b>	Structural Clinical Interview for DSM-IV
<b>SCI-CG</b>	Structured Clinical Interview for Complicated Grief
<b>sACC</b>	subgenual Anterior Cingulate Cortex
<b>SCL-90</b>	Symptom Checklist-90
<b>TRIG</b>	Texas Revised Inventory of Grief

## Reference List

- Acosta H, Jansen A, Nuscheler B, Kircher T, 2018 A voxel-based morphometry study on adult attachment style and affective loss. *Neuroscience* 392, 219–229. doi: 10.1016/j.neuroscience.2018.06.045. [PubMed: 30005995]
- Arias-Carrión O, Stamelou M, Murillo-Rodríguez E, Menéndez-González M, Pöppel E, 2010 Dopaminergic reward system: a short integrative review *International Archives of Medicine* 3, 24. doi:10.1186/1755-7682-3-24.
- Arizmendi B, 2018 The effect of intranasal oxytocin on neural functioning in widow(er)s. Dissertation Abstracts International: Section B: The Sciences and Engineering.
- Arizmendi B, Kaszniak AW, O'Connor MF, 2016 Disrupted prefrontal activity during emotion processing in complicated grief: An fMRI investigation. *NeuroImage* 124, 968–976. doi: 10.1016/j.neuroimage.2015.09.054. [PubMed: 26434802]
- Berridge KC, Kringelbach ML, 2015 Pleasure systems in the brain. *Neuron* 86, 646–664. doi:10.1016/j.neuron.2015.02.018. [PubMed: 25950633]
- Blandini F, Nappi G, Tassorelli C, Martignoni E, 2000 Functional changes of the basal ganglia circuitry in Parkinson's disease. *Prog Neurobio* 62, 63–68. doi: 10.1016/s0301-0082(99)00067-2.
- Boelen PA, Prigerson HG, 2007 The influence of symptoms of prolonged grief disorder, depression, and anxiety on quality of life among bereaved adults: a prospective study. *Eur Arch Psychiatry Clin Neurosci*. 257, 444–52. [PubMed: 17629728]
- Bosch OJ, Dabrowska J, Modi ME, Johnson ZV, Keebaugh AC, Barrett CE, Ahern TH, Guo J, Grinevich V, Rainnie DG, Neumann ID, Young LJ, 2016 Oxytocin in the nucleus accumbens shell reverses CRFR2-evoked passive stress-coping after partner loss in monogamous male prairie voles. *Psychoneuroendocrinology* 64: 66–78. doi: 10.1016/j.psyneuen.2015.11.011. [PubMed: 26615473]
- Bosch OJ, Nair HP, Ahern TH, Neumann ID, Young LJ, 2009 The CRF system mediates increased passive stress-coping behavior following the loss of a bonded partner in a monogamous rodent. *Neuropsychopharmacology* 34(6): 1406–1415. doi: 10.1038/npp.2008.154. [PubMed: 18923404]
- Bosch OJ, Young LJ, 2017 Oxytocin and Social Relationships: From Attachment to Bond Disruption In: Hurlmann R, Grinevich V (eds) *Behavioral Pharmacology of Neuropeptides: Oxytocin. Current Topics in Behavioral Neurosciences*, vol 35 Springer, Cham.
- Bowlby J, 1973 *Attachment and Loss*, volume II: Separation Anxiety and Anger. Basic Books.
- Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T, 2017 De-duplication of database search results for systematic reviews in EndNote [published correction appears in *J Med Libr Assoc* 105, 1]. *J Med Libr Assoc* 104, 240–243. doi:10.3163/1536-5050.104.3.014.
- Bryant RA, Andrew E, Korgaonkar MS, 2020 Distinct neural mechanisms of emotional processing in prolonged grief disorder. *Psychological Medicine* 2020, 1–9. doi: 10.1017/S0033291719003507.
- Bui E, Nadal-Vicens M, Simon NM, 2012 Pharmacological approaches to the treatment of complicated grief: rationale and a brief review of the literature. *Dialogues Clin Neurosci* 14, 149–57. [PubMed: 22754287]
- Bui E, Hellberg SN, Hoepfner SS, Rosencrans P, Young A, Ross RA et al., 2019 Circulating levels of oxytocin may be elevated in complicated grief: A pilot study. *European Journal of Psychotraumatology* 10, 1646603. doi: 10.1080/20008198.2019.1646603. [PubMed: 31489134]
- Chawarski MC, Zhou W, Schottenfeld RS, 2011 Behavioral drug and HIV risk reduction counseling (BDRC) in MMT programs in Wuhan, China: A pilot randomized clinical trial. *Drug Alcohol Depend* 115, 237–239. doi: 10.1016/j.drugalcdep.2010.09.024. [PubMed: 21159452]
- Chen CY, Yen JY, Wang PW, Liu GC, Yen CF, Ko CH, 2016 Altered Functional Connectivity of the Insula and Nucleus Accumbens in Internet Gaming Disorder: A Resting State fMRI Study. *European Addiction Research* 22, 192–200. doi: 10.1159/000440716. [PubMed: 26863028]
- Clark GA, 1995 Emotional learning: Fear and loathing in the amygdala. *Current Biology* 5, 246–248. doi: 10.1016/S0960-9822(95)00050-9. [PubMed: 7780731]
- Coan JA, Schaefer HS, Davidson RJ, 2006 Lending a Hand: Social Regulation of the Neural Response to Threat. *Psychological Science* 17, 1032–1039. doi: 10.1111/j.1467-9280.2006.01832.x. [PubMed: 17201784]

- Cooney RE, Joormann J., Eugène F, Dennis EL, Gotlib IH, 2010 Neural correlates of rumination in depression. *Cogn Affect Behav Neurosci* 10, 77–100. doi: 10.3758/CABN.10.4.470
- Droutman V, Read SJ, Bechara A, 2015 Revisiting the role of the insula in addiction. *Trends Cogn Sci* 19, 414–420. doi: 10.1016/j.tics.2015.05.005. [PubMed: 26066588]
- Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D, 2016 A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction. *J Addict Med* 10, 93–103. doi: 10.1097/ADM.000000000000193. [PubMed: 26808307]
- Eklund A, Nichols TE, Knutsson H 2016 Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc. Natl. Acad. Sci. U.S.A* 113, 7900–7905. 10.1073/pnas.1602413113 [PubMed: 27357684]
- Edwards S, Koob GF, 2010 Neurobiology of dysregulated motivational systems in drug addiction. *Future Neurol.* 5, 393–401. doi: 10.2217/fnl.10.14. [PubMed: 20563312]
- Eisma MC, Schut HAW, Stroebe MS, Boelen PA, van den Bout J, Stroebe W, 2015 Adaptive and maladaptive rumination after loss: A three-wave longitudinal study. *Br J Clin Psychol* 54, 163–180. doi:10.1111/bjc.12067 [PubMed: 25229192]
- Fernández-Alcántara M, Verdejo-Román J, Cruz-Quintana F, Pérez-García M, Catena-Martínez A, Fernández-Ávalos MI et al., 2020 Increased amygdala activations during the emotional experience of death-related pictures in complicated grief: an fMRI study. *Journal of Clinical Medicine* 9, 851. doi: 10.3390/jcm9030851.
- Fernando AB, Murray JE, Milton AL, 2013 The amygdala: securing pleasure and avoiding pain. *Front Behav Neurosci* 7, 190. doi:10.3389/fnbeh.2013.00190. [PubMed: 24367307]
- Field M, Munafò MR, Franken IH, 2009 A meta-analytic investigation of the relationship between attentional bias and subjective craving in substance abuse. *Psychological bulletin* 135, 589–607. doi: 10.1037/a0015843. [PubMed: 19586163]
- Fisher HE, Brown LL, Aron A, Strong G, Mashek D, 2010 Reward, Addiction, and Emotion Regulation Systems Associated With Rejection in Love. *Journal of Neurophysiology* 104, 51–60. doi: 10.1152/jn.00784.2009. [PubMed: 20445032]
- Floresco SB, 2015 The nucleus accumbens: an interface between cognition, emotion, and action. *Annual Review of Psychology* 66: 25–52. doi: 10.1146/annurev-psych-010213-115159
- Fogel A, Garvey A, 2007 Alive communication. *Infant Behavior and Development* 30, 251–257. doi: 10.1016/j.infbeh.2007.02.007. [PubMed: 17376534]
- Fredriksson I, Jayaram-Lindström N, Wirf M et al., 2015 Evaluation of guanfacine as a potential medication for alcohol use disorder in long-term drinking rats: behavioral and electrophysiological findings. *Neuropsychopharmacology* 40, 1130–1140. doi: 10.1038/npp.2014.294 [PubMed: 25359257]
- Freed PJ, Yanagihara TK, Hirsch J, Mann JJ, 2009 Neural mechanisms of grief regulation. *Biological Psychiatry* 66, 33–40. doi: 10.1016/j.biopsych.2009.01.019. [PubMed: 19249748]
- Goldstein RZ, Volkow ND, 2011 Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci* 12, 652–669. doi: 10.1038/nrn3119. [PubMed: 22011681]
- Gündel H, O'Connor MF, Littrell L, Fort C, Lane RD, 2003 Functional neuroanatomy of grief: An FMRI study. *American Journal of Psychiatry* 160, 1946–1953. doi: 10.1176/appi.ajp.160.11.1946. [PubMed: 14594740]
- Helstrom AW, Blow FC, Slaymaker V, Kranzler HR, Leong S, Oslin D, 2016 Reductions in Alcohol Craving Following Naltrexone Treatment for Heavy Drinking. *Alcohol and Alcoholism* 51, 562–566. doi: 10.1093/alcalc/agw038. [PubMed: 27402770]
- Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA, 1991 Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *European Journal of Epidemiology* 7, 403–422. doi: 10.1007/bf00145007. [PubMed: 1833235]
- Huang FY, Hsu AL, Hsu LM, Tsai JS, Huang CM, Chao YP et al., 2019 Mindfulness improves emotion regulation and executive control on bereaved individuals: an fMRI study. *Frontiers in Human Neuroscience* 12, 541. doi: 10.3389/fnhum.2018.00541. [PubMed: 30745865]

- Hurlemann R and Scheele D, 2016 Dissecting the Role of Oxytocin in the Formation and Loss of Social Relationships. *Biological Psychiatry* 79, 185–193. doi: 10.1016/j.biopsych.2015.05.013. [PubMed: 26122876]
- ICD-11 for Mortality and Statistics. 6B42 Prolonged Grief Disorder. <https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1183832314>. [Accessed March 23, 2020]
- Inagaki TK, 2018 Opioids and Social Connection. *Current Directions in Psychological Science* 27, 85–90. doi: 10.1177/0963721417735531.
- Jain FA, Connolly CG, Christov-Moore L, Leuchter AF, Abrams M, Ben-Yelles RW et al., 2019 Grief, mindfulness and neural predictors of improvement in family dementia caregivers. *Frontiers in Human Neuroscience* 13, 155. doi: 10.3389/fnhum.2019.00155. [PubMed: 31156412]
- Jin F, Zheng P, Liu H, Guo H, Sun Z, 2018 Functional and anatomical connectivity-based parcellation of human cingulate cortex. *Brain Behav* 8, e01070. doi:10.1002/brb3.1070. [PubMed: 30039643]
- Johnson ZV, Young LJ, 2015 Neurobiological mechanisms of social attachment and pair bonding. *Curr Opin Behav Sci.* 3, 38–44. doi: 10.1016/j.cobeha.2015.01.009. [PubMed: 26146650]
- King LB, Walum H, Inoue K, Eyrich NW, Young LJ, 2016 Variation in the Oxytocin Receptor Gene Predicts Brain Region-Specific Expression and Social Attachment. *Biol Psychiatry* 80,160–169. doi:10.1016/j.biopsych.2015.12.008. [PubMed: 26893121]
- Koob GF, Volkow ND, 2016 Neurobiology of addiction: a neurocircuitry analysis. *The Lancet: Psychiatry* 3, 760–773. doi: 10.1016/S2215-0366(16)00104-8. [PubMed: 27475769]
- Krupitsky EM, Neznanova O, Masalov D, Burakov AM, Didenko T, Romanova T, 2007 Effect of Memantine on Cue-Induced Alcohol Craving in Recovering Alcohol-Dependent Patients. *American Journal of Psychiatry* 164, 519–523. doi: 10.1176/ajp.2007.164.3.519 [PubMed: 17329479]
- Lanciego JL, Luquin N, Obeso JA, 2012 Functional neuroanatomy of the basal ganglia. *Cold Spring Harb Perspect Med* 2, a009621. doi:10.1101/cshperspect.a009621. [PubMed: 23071379]
- Latham AE, Prigerson HG, 2004 Suicidality and bereavement: complicated grief as psychiatric disorder presenting greatest risk for suicidality. *Suicide Life Threat Behav.* 34, 350–362. doi:10.1521/suli.34.4.350.53737. [PubMed: 15585457]
- Leech R, Sharp DJ, 2014 The role of the posterior cingulate cortex in cognition and disease. *Brain* 137, 12–32. doi:10.1093/brain/awt162. [PubMed: 23869106]
- LeRoy AS, Knee CR, Derrick JL, Fagundes CP, 2019 Implications for Reward Processing in Differential Responses to Loss: Impacts on Attachment Hierarchy Reorganization. *Personality and Social Psychology Review* 23, 391–405. doi: 10.1177/1088868319853895. [PubMed: 31200625]
- Lundorff M, Holmgren H, Zachariae R, Farver-Vestergaard I, O'Connor M, 2017 Prevalence of prolonged grief disorder in adult bereavement: A systematic review and meta-analysis. *J Affect Disord* 212, 138–149. doi: 10.1016/j.jad.2017.01.030. [PubMed: 28167398]
- MacCallum F, Bryant RA, 2010 Attentional bias in complicated grief. *J Affect Disord* 125, 1–3. doi:10.1016/j.jad.2010.01.070. [PubMed: 19733913]
- MacCallum F, Bryant RA, 2020 A Network Approach to Understanding Quality of Life Impairments in Prolonged Grief Disorder. *J Trauma Stress* 33, 106–115. [PubMed: 30958609]
- MacCallum F, Sawday S, Rinck M, Bryant RA, 2015 The push and pull of grief: Approach and avoidance in bereavement. *J Behav Ther Exp Psychiatry* 48, 105–109. doi: 10.1016/j.jbtep.2015.02.010. [PubMed: 25797028]
- Maciejewski PK, Maercker A, Boelen PA, Prigerson HG, 2016 “Prolonged grief disorder” and “persistent complex bereavement disorder”, but not “complicated grief”, are one and the same diagnostic entity: an analysis of data from the Yale Bereavement Study. *World Psychiatry* 15, 266–275. doi: 10.1002/wps.20348. [PubMed: 27717273]
- McConnell MH, Killgore WD, O'Connor MF, 2018 Yearning predicts subgenual anterior cingulate activity in bereaved individuals. *Heliyon* 4, e00852. doi: 10.1016/j.heliyon.2018.e00852. [PubMed: 30364703]
- Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M et al., 2015 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 4, 1. doi:10.1186/2046-4053-4-1. [PubMed: 25554246]

- Moore BA, Fazzino T, Barry DT et al., 2013 The Recovery Line: A pilot trial of automated, telephone-based treatment for continued drug use in methadone maintenance. *J Subst Abuse Treat* 45, 63–69. doi: 10.1016/j.jsat.2012.12.011. [PubMed: 23375114]
- Mouaffak F, Leite C, Hamzaoui S, Benyamina A, Laqueille X, Kebir O, 2017 Naltrexone in the treatment of broadly defined behavioral addictions: a review and meta-analysis of randomized controlled trials. *European Addiction Research* 23, 204–210. doi: 10.1159/000480539. [PubMed: 28877518]
- Najib A, Lorberbaum JP, Kose S, Bohning DE, George MS, 2004 Regional brain activity in women grieving a romantic relationship breakup. *American Journal of Psychiatry* 161, 12:2245–2256. doi: 10.1176/appi.ajp.161.12.2245.
- Naqvi NH, Bechara A, 2009 The hidden island of addiction: the insula. *Trends Neurosci* 32, 56–57. doi: 10.1016/j.tins.2008.09.009. [PubMed: 18986715]
- Nieh EH, Kim SY, Namburi P, Tye KM, 2013 Optogenetic dissection of neural circuits underlying emotional valence and motivated behaviors. *Brain Res* 1511, 73–92. doi:10.1016/j.brainres.2012.11.001. [PubMed: 23142759]
- Nielsen FA, Balslev D, Hansen LK, 2005 Mining the posterior cingulate: Segregation between memory and pain components. *NeuroImage* 27, 520–532. doi: 10.1016/j.neuroimage.2005.04.034. [PubMed: 15946864]
- Noonan MP, Kolling N, Walton ME, Rushworth MF, 2012 Re-evaluating the role of the orbitofrontal cortex in reward and reinforcement. *European Journal of Neuroscience* 35, 997–1010. doi: 10.1111/j.1460-9568.2012.08023.x. [PubMed: 22487031]
- Nyamathi AM, Nandy K, Greengold B et al., 2011 Effectiveness of intervention on improvement of drug use among methadone maintained adults. *J Addict Dis* 30, 6–16. doi: 10.1080/10550887.2010.531669. [PubMed: 21218306]
- O'Connor MF, 2012 Immunological and neuroimaging biomarkers of complicated grief. *Dialogues Clin Neurosci*. 14, 141–8. [PubMed: 22754286]
- O'Connor MF, 2018 Biobehavioral processes underlying complicated grief. Abstracts of the 76<sup>th</sup> Annual Scientific Meeting: Psychosomatic Medicine 80, A140. doi: 10.1097/PSY.0000000000000578.
- O'Connor MF, Arizmendi B, 2015 Approach and avoidance in complicated grief: neuroscience results and clinical implications. *Journal of Psychosomatic Research* 6, 78. doi: 10.1016/j.jpsychores.2015.03.100.
- O'Connor MF, Gündel H, McRae K, Lane RD, 2007 Baseline vagal tone predicts BOLD response during elicitation of grief. *Neuropsychopharmacology* 32, 2184–2189. doi: 10.1038/sj.npp.1301342. [PubMed: 17299507]
- O'Connor MF, Irwin MR, Wellisch DK, 2009 When grief heats up: Pro-inflammatory cytokines predict regional brain activation. *Neuroimage* 47, 891–896. doi: 10.1016/j.neuroimage.2009.05.049. [PubMed: 19481155]
- O'Connor MF, Shear MK, Fox R, Skritskaya N, Campbell B, Ghesquiere A et al., 2013 Catecholamine predictors of complicated grief treatment outcomes. *International Journal of Psychophysiology* 88, 349–352. doi: 10.1016/j.ijpsycho.2012.09.014. [PubMed: 23044089]
- O'Connor MF, Wellisch DK, Stanton AL, Eisenberger NI, Irwin MR, Lieberman MD, 2008 Craving love? Enduring grief activates brain's reward center. *Neuroimage* 42, 969–972. doi: 10.1016/j.neuroimage.2008.04.256. [PubMed: 18559294]
- O'Neill HA, 2019 A review on the involvement of catecholamines in animal behaviour. *South African Journal of Animal Science* 49, 29–39. doi: 10.4314/sajas.v49i1.1
- Parisi A, Sharma A, Howard MO, Blank Wilson A, 2019 The relationship between substance misuse and complicated grief: A systematic review. *J Subst Abuse Treat* 103, 43–57. [PubMed: 31229191]
- Price JL, Drevets WC, 2010 Neurocircuitry of mood disorders. *Neuropsychopharmacology* 35, 192–216. doi:10.1038/npp.2009.104 [PubMed: 19693001]
- Prigerson HG, Bierhals AJ, Kasl SV, Reynolds CF, Shear MK, Day N, Beery LC, Newsom JT, Jacobs S, 1997 Traumatic grief as a risk factor for mental and physical morbidity. *Am J Psychiatry* 154, 616–23. [PubMed: 9137115]

- Prigerson HG, Horowitz MJ, Jacobs SC, Parkes CM, Aslan M, Goodkin K, Raphael B, Marwit SJ, Wortman C, Neimeyer RA, Bonanno GA, Block SD, Kissane D, Boelen P, Maercker A, Litz BT, Johnson JG, First MB, Maciejewski PK, 2009 Prolonged grief disorder: Psychometric validation of criteria proposed for DSM-V and ICD-11. *PLoS Med.* 2009, 6:e1000121. doi: 10.1371/journal.pmed.1000121. [PubMed: 19652695]
- Prigerson HG, Jacobs SC, 2001 Traumatic grief as a distinct disorder: a rationale, consensus criteria, and preliminary empirical test In: Stroebe MS, Hansson RO, Stroebe W, Schut H (Eds.), *Handbook of Bereavement Research: Consequences, Coping and Care.* American Psychological Association, Washington, D.C. pp. 613–645.
- Roozendaal B, McEwen B., Chattarji S, 2009 Stress, memory, and the amygdala. *Nat Rev Neurosci* 10, 423–433. doi: 10.1038/nrn2651. [PubMed: 19469026]
- Prigerson HG, Bridge J, Maciejewski PK, Beery LC, Rosenheck RA, et al. 1999 Influence of traumatic grief on suicidal ideation among young adults. *Am J Psychiatry* 156: 1994–1995. [PubMed: 10588419]
- Ruegsegger GN, Toedebusch RG, Childs TE, Grigsby KB, Booth FW, 2017 Loss of Cdk5 function in the nucleus accumbens decreases wheel running and may mediate age-related declines in voluntary physical activity. *J Physiol* 595, 363–384. doi:10.1113/JP272489. [PubMed: 27461471]
- Saavedra Perez H, Ikram A, Direk N, Prigerson H, Freak-Poli R, Verhaaren B, et al., 2015 Cognition, structural brain changes and complicated grief. A population-based study. *Psychological Medicine* 45, 1389–1399. doi: 10.1017/s0033291714002499. [PubMed: 25363662]
- Salamone JD, Correa M, Farrar A et al., 2007 Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology* 191, 461–482. doi: 10.1007/s00213-006-0668-9. [PubMed: 17225164]
- Sbarra DA, Hazan C, 2008 Coregulation, Dysregulation, Self-Regulation: An Integrative Analysis and Empirical Agenda for Understanding Adult Attachment, Separation, Loss, and Recovery. *Personality and Social Psychology Review* 12, 141–167. doi: 10.1177/1088868308315702. [PubMed: 18453476]
- Schiele MA, Costa B, Abelli M, Martini C, Baldwin DS, Domschke K, et al., 2018 Oxytocin receptor gene variation, behavioural inhibition, and adult separation anxiety: Role in complicated grief. *The World Journal of Biological Psychiatry* 19, 471–479. doi: 10.1080/15622975.2018.1430374. [PubMed: 29353531]
- Schneck N, Haufe S, Tu T, Bonanno GA, Ochsner KN, Sajda P et al., 2017 Tracking deceased-related thinking with neural pattern decoding of a cortical-basal ganglia circuit. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 2, 421–429. doi: 10.1016/j.bpsc.2017.02.004.
- Schneck N, Tu T, Michel CA, Bonanno GA, Sajda P, Mann JJ, 2018 Attentional bias to reminders of the deceased as compared with a living attachment in grieving. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 3, 107–115. doi: 10.1016/j.bpsc.2017.08.003.
- Schneck N, Tu T, Bonanno GA, Shear MK, Sajda P, Mann JJ, 2019a Self-generated unconscious processing of loss linked to less severe grieving. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 4, 271–279. doi: 10.1016/j.bpsc.2018.08.003.
- Schneck N, Tu T, Haufe S, Bonanno GA, GalfaIvy H, Ochsner KN et al., 2019b Ongoing monitoring of mindwandering in avoidant grief through cortico-basal-ganglia interactions. *Social Cognitive and Affective neuroscience* 14, 163–172. doi: 10.1093/scan/nsy114. [PubMed: 30535245]
- Schoenbaum G, Shaham Y, 2008 The role of orbitofrontal cortex in drug addiction: a review of preclinical studies. *Biol Psychiatry* 63, 256–262. doi:10.1016/j.biopsych.2007.06.003. [PubMed: 17719014]
- Stevens FL, Hurley RA, Taber KH, 2011 Anterior cingulate cortex: unique role in cognition and emotion. *Journal of Neuropsychiatry and Clinical Neuroscience* 23, 121–125. doi: 10.1176/jnp.23.2.jnp121.
- Silverman G Jacobs S, Kasl S, Shear M, Maciejewski P, Noaghuil S Prigerson H 2000 Quality of life impairments associated with diagnostic criteria for traumatic grief. *Psychological Medicine*, 30(4), 857–862. doi:10.1017/S0033291799002524 [PubMed: 11037094]



- Suckling J, Nestor LJ, 2017 The neurobiology of addiction: the perspective from magnetic resonance imaging present and future. *Addiction* 112, 360–369. doi:10.1111/add.13474. [PubMed: 27452960]
- Tang W, Jbabdi S, Zhu Z et al., 2019 A connectional hub in the rostral anterior cingulate cortex links areas of emotion and cognitive control. *Elife* 8, e43761. doi:10.7554/eLife.43761. [PubMed: 31215864]
- Tofler GH, Morel-Kopp MC, Spinaze M, Dent J, Ward C, McKinley S, et al. 2019 The effect of metoprolol and aspirin on cardiovascular risk in bereavement: A randomized controlled trial. *Am Heart Journal* 220:264–72. Epub 2020/01/11. doi: 10.1016/j.ahj.2019.11.003. [PubMed: 31923768]
- Trezza V, Damsteegt R, Achterberg EJ, Vanderschuren LJ, 2011 Nucleus accumbens  $\mu$ -opioid receptors mediate social reward. *J Neurosci*. 31, 6362–70. doi: 10.1523/JNEUROSCI.5492-10.2011 [PubMed: 21525276]
- Tsurumi K, Kawada R, Yokoyama N et al., 2014 Insular activation during reward anticipation reflects duration of illness in abstinent pathological gamblers. *Front Psychol* 5, 1013. doi: 10.3389/fpsyg.2014.01013. [PubMed: 25250011]
- Turner BO, Paul EJ, Miller MB et al., 2018 Small sample sizes reduce the replicability of task-based fMRI studies. *Commun Biol* 1, 62. doi: 10.1038/s42003-018-0073-z. [PubMed: 30271944]
- Uddin LQ, Nomi JS, Hébert-Seropian B, Ghaziri J, Boucher O, 2017 Structure and Function of the Human Insula. *J Clin Neurophysiol* 34, 300–306. doi:10.1097/WNP.0000000000000377. [PubMed: 28644199]
- Valstad M, Alvares GA, Egknud M, Matziorinis AM, Andreassen OA, Westlye LT, Quintana DS, 2017 The correlation between central and peripheral oxytocin concentrations: A systematic review and meta-analysis. *Neuroscience Biobehavioral Reviews* 78, 117–124. doi: 10.1016/j.neubiorev.2017.04.017. [PubMed: 28442403]
- Volkow ND, Fowler S, 2000 Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cerebral Cortex* 10, 318–325. doi: 10.1093/cercor/10.3.318. [PubMed: 10731226]
- Younger J, Aron A, Parke S, Chatterjee N, Mackey S, 2010 Viewing Pictures of a Romantic Partner Reduces Experimental Pain: Involvement of Neural Reward Systems. *PLOS ONE* 5, e13309. doi: 10.1371/journal.pone.0013309 [PubMed: 20967200]

### Highlights

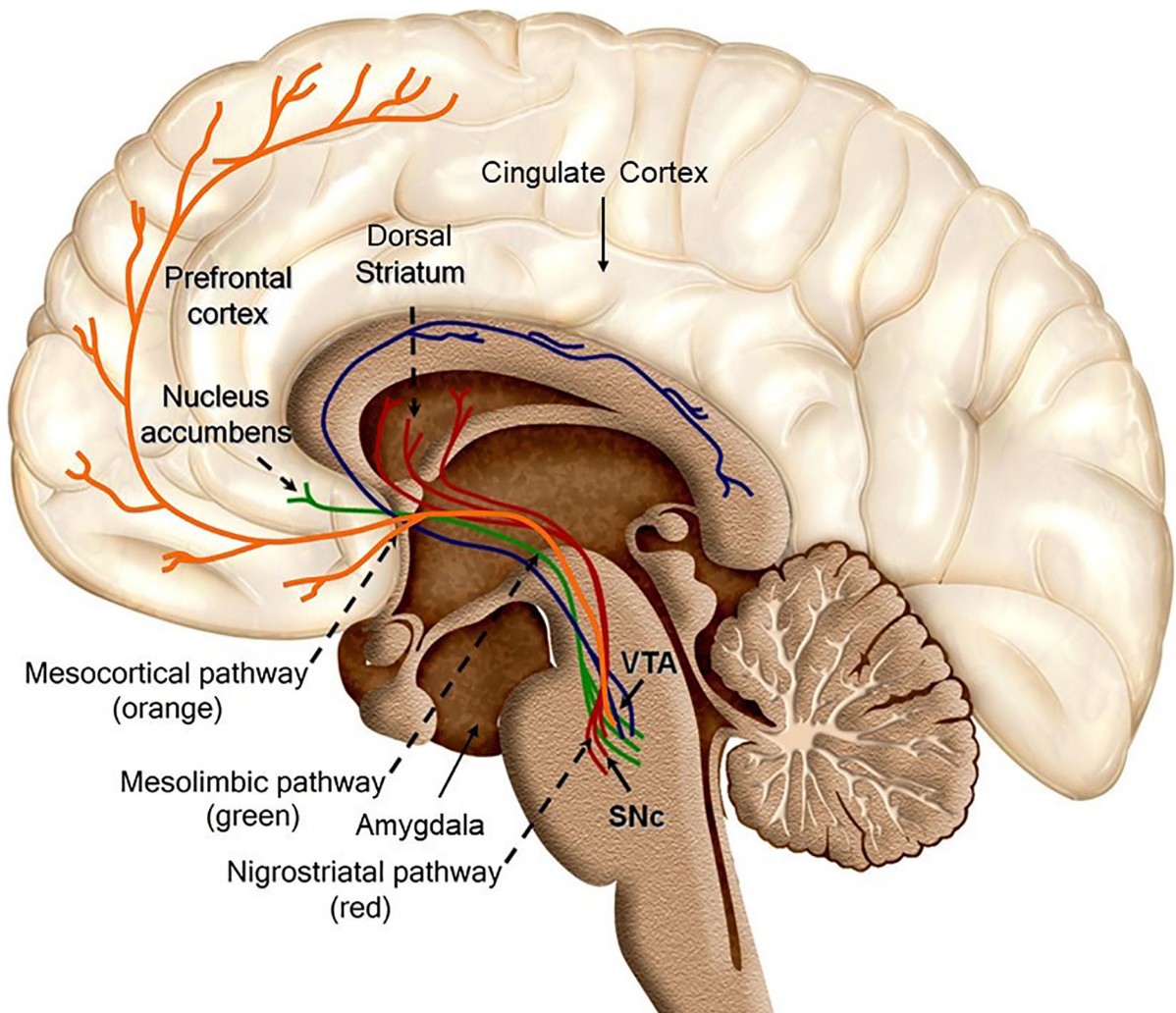
- Prolonged Grief Disorder (PGD) likely involves the neural reward system
- Evidence associates the mesolimbic dopamine system and cortical regions with PGD.
- Oxytocin function may also be altered in PGD.
- Further research on disordered reward processing in PGD is needed

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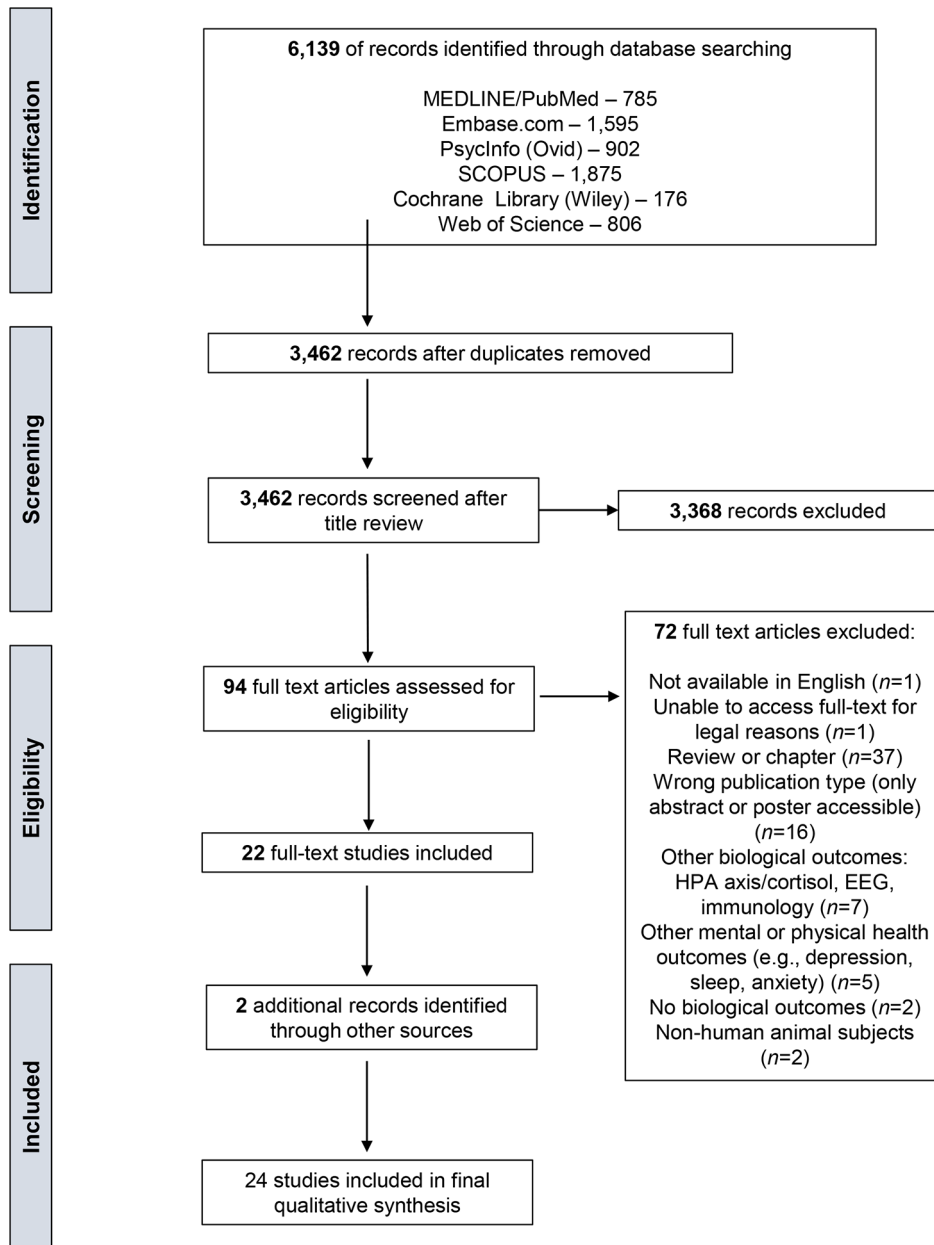
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**Figure 1:**

Key areas and pathways involved in neural reward signaling. (Image: JG, adapted from Wikimedia Commons. [Arias-Carrión O., Stamelou M., Murillo-Rodríguez E., Menéndez-González M., Pöppel E., 2010. Dopaminergic reward system: a short integrative review International Archives of Medicine 3, 24. doi:10.1186/1755-7682-3-24.])



**Figure 2:**  
PRISMA flow diagram outlining the systematic review process.

Table 1.

Description of design and outcomes of studies reviewed.

Author (Year)	Sample	Design/Method	Measures	Results	Grief Association Mechanisms
Acosta et al. (2018)	<ul style="list-style-type: none"> <li><math>N = 192</math></li> <li>Gender: females (<math>n = 96</math>), males (<math>n = 96</math>)</li> <li>Age range: 19–38</li> <li><math>M_{\text{age}} = 24.1</math></li> <li><math>SD = 3.2</math></li> <li>Type of loss: first-degree relative, spouse, or close friend; relationship or spousal breakup</li> <li>Time since loss: &lt; 5 years</li> </ul>	<ul style="list-style-type: none"> <li>Structural MRI</li> <li>Mini International Psychiatric Review</li> <li>Inclusion criteria: student status, age (18–40 years), right-handedness, no history of major psychiatric disorders</li> </ul>	<ul style="list-style-type: none"> <li>Adult Attachment Style (RSQ)</li> <li>Affective loss (e.g., loss of a spouse, relative, friend, or relationship breakup; LTE-Q)</li> </ul>	<ul style="list-style-type: none"> <li>Affective loss significantly associated with anxious attachment style (<math>r = .18</math>, <math>p &lt; .05</math>) but not avoidant attachment style (<math>r = -.10</math>, <math>p = .16</math>)</li> <li>Anxious attachment positively associated with gray matter volume in the left insula and in the pars opercularis of left inferior frontal gyrus</li> <li>No association between affective loss and brain gray matter volume</li> <li>Sex-specific effects indicated affective loss in men was significantly associated with brain gray matter in left middle cingulate cortex</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> </ul>
Arizmendi et al. (2016)*	<ul style="list-style-type: none"> <li><math>N = 28</math> (8 CG, 9 non-CG, 11 control)</li> <li>Control group: non-bereaved, married</li> <li>Gender: females (<math>n = 23</math>), males (<math>n = 5</math>)</li> <li>Age range: 62–82</li> <li><math>M_{\text{age}} = 71.9</math></li> <li><math>SD = 4.6</math></li> <li>Type of loss: not specified</li> <li>Time since loss: not specified</li> </ul>	<ul style="list-style-type: none"> <li>fMRI: eCStroop task including 73-grief related words matched with neutral words. Eight alternating blocks of grief-related and neutral words. Participants rated words most relevant to their grief experience</li> <li>Inclusion Criteria: No presence of current major psychiatric disorder, no use of psychotropic medications since loss</li> </ul>	<ul style="list-style-type: none"> <li>Depression (BDI II)</li> <li>eCStroop response latency</li> <li>Grief (ICG)</li> </ul>	<ul style="list-style-type: none"> <li>CG group had slower reaction times and worse performance over the course of eCStroop blocks; control participants improved over the course of the task</li> <li>Non-CG group showed greater activity in grief compared to neutral trials in the right medial OFC (<math>p = .001</math>) and the rACC (<math>p &lt; .005</math>) compared to controls. No differential rACC activity in the CG group compared to controls.</li> <li>CG and control groups showed significantly greater dACC activation in grief block 4 of the</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> </ul>

Author (Year)	Sample	Design/Method	Measures	Results	Grief Association Mechanisms
				<ul style="list-style-type: none"> <li>eCStroop compared to grief block 1</li> <li>dACC activity did not differ significantly between CG and control groups</li> </ul>	
Arizmendi et al. (2018) *	<ul style="list-style-type: none"> <li><math>N = 37</math> (CG 17, non-CG 20)</li> <li>Gender: females (<math>n = 28</math>), males (<math>n = 9</math>)</li> <li>Age range: 55–80</li> <li><math>M_{age}</math> CG = 69.29, <math>SD = 6.66</math>; <math>M_{age}</math> non-CG = 68.36, <math>SD = 6.44</math></li> <li>Type of loss: spousal</li> <li>Time since loss: between 6 months and 3 years</li> </ul>	<ul style="list-style-type: none"> <li>fMRI: AAT task with three stimulus categories (photos of spouse, stranger, and generic grief)</li> <li>INT OT/placebo manipulation (counterbalanced across two visits)</li> <li>Inclusion criteria: ages ranging from 25–80 years, not on psychotropic medications, not enrolled in therapy/support groups targeted toward grief</li> </ul>	<ul style="list-style-type: none"> <li>Implicit approach/avoidance behaviors (AAT response latency and accuracy)</li> </ul>	<ul style="list-style-type: none"> <li>INT OT condition showed an avoid bias for images of strangers (<math>\chi^2(1) = 4.35, p &lt; .05</math>)</li> <li>When viewing a spouse, CG/placebo group had increased activation in the right inferior frontal gyrus, precuneus, and right superior temporal sulcus (<math>p &lt; .001</math>) compared to non-CG/INT OT group</li> <li>CG/INT OT group showed slower reaction times across all stimuli types compared to the placebo (<math>F_{1,3299} = 42.21, p &lt; .001</math>) and non-CG/INT OT groups (<math>F_{1,3781} = 69.27, p &lt; .001</math>)</li> <li>Non-CG/INT OT group showed increased activation in the superior temporal sulcus and right inferior frontal gyrus compared to CG/placebo group</li> <li>When ICG was included as a covariate, participants showed increased neural activity in the orbitofrontal (<math>p &lt; .001</math>) and medial frontal/mid-cingulate regions when responding to generic grief compared to spouse stimuli</li> <li>No significant findings on NAcc activation</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> <li></li> <li></li> </ul>

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Author (Year)	Sample	Design/Method	Measures	Results	Grief Association Mechanisms
Bryant et al. (2020)*	<ul style="list-style-type: none"> <li>• <math>N = 117</math> (PGD 21, PTSD 45, MDD 26, Bereaved Control 25)</li> <li>• Gender: females (<math>n = 73</math>), males (<math>n = 44</math>)</li> <li>• Age range: Not specified</li> <li>• <math>M_{agePGD} = 47.8</math>, <math>M_{agePTSD} = 40.4</math>, <math>M_{ageMDD} = 31.5</math>, <math>M_{ageControl} = 45.1</math></li> <li>• <math>SD_{PGD} = 2.4</math>, <math>SD_{PTSD} = 11.9</math>, <math>SD_{MDD} = 11.4</math>, <math>SD_{Control} = 14.2</math></li> <li>• Type of loss: Deceased partner (<math>n = 4</math>), parent (<math>n = 8</math>), child (<math>n = 4</math>), sibling (<math>n = 5</math>)</li> <li>• Time since loss: Not specified</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI: Passive face viewing task using standardized facial expressions of fear, anger, disgust, sadness, happiness, and neutral.</li> <li>• Inclusion criteria: absence of neurological disorder, psychosis, or current substance dependence. No MDD or PTSD participants were bereaved.</li> </ul>	<ul style="list-style-type: none"> <li>• Depression (BDI)</li> <li>• Grief (ICD-11 criteria for PGD/ Prolonged Grief – 13)</li> <li>• MINI v5.5</li> <li>• Post-Traumatic Stress (DSM-IV criteria for PTSD/ Clinician Administered PTSD scale)</li> </ul>	<ul style="list-style-type: none"> <li>• Compared to bereaved control, PGD had greater activation in pregenual anterior cingulate cortex (<math>z = 3.52</math>, <math>p = 0.005</math>), left insula (<i>cluster size</i> = 872, <math>z = 3.42</math>, <math>p = 0.042</math>), right insula (<math>z = 3.46</math>, <math>p = 0.036</math>), left dorsolateral prefrontal cortex (<math>z = 3.11</math>, <math>p = 0.028</math>), right dorsolateral prefrontal cortex (<math>z = 3.14</math>, <math>p = 0.026</math>), right caudate (<math>z = 3.26</math>, <math>p = 0.037</math>), and pregenual anterior cingulate cortex-right palladium connectivity (<math>z = 2.87</math>, <math>p = 0.037</math>) during subliminal processing of happy faces</li> <li>• Compared to PTSD and MDD, PGD had greater activation of medial orbitofrontal cortex (<math>z = 3.18</math>, <math>p = 0.026</math>) during supraliminal processing of sad faces</li> <li>• Compared to MDD, PGD had greater activation in left amygdala (<math>z = 3.21</math>, <math>p = 0.013</math>), caudate (<math>z = 3.43</math>, <math>p = 0.024</math>), and left putamen (<math>z = 3.57</math>, <math>p = 0.014</math>) during subliminal processing of sad faces</li> <li>• No difference between PGD, PTSD, and MDD during processing of happy faces.</li> </ul>	<ul style="list-style-type: none"> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> </ul>
Bui et al. (2019)*	<ul style="list-style-type: none"> <li>• <math>N = 139</math> (Bereaved with CG = 47; bereaved with MDD = 46; bereaved without any mental disorder = 46)</li> <li>• Gender: females (<math>n = 97</math>), males (<math>n = 42</math>)</li> <li>• Age range: 21–70 years</li> </ul>	<ul style="list-style-type: none"> <li>• Peripheral blood samples used to examine comparison of plasma OT levels</li> <li>• Inclusion criteria: Loss of loved one within past 6 months</li> </ul>	<ul style="list-style-type: none"> <li>• Grief (ICG)</li> <li>• Presence/ absence of psychiatric disorders (SCI-CG)</li> </ul>	<ul style="list-style-type: none"> <li>• Unadjusted regression analyses indicated that OT levels were significantly higher for CG group compared to MDD (<math>p = .013</math>), but no significant findings emerged when compared to</li> </ul>	<ul style="list-style-type: none"> <li>•</li> </ul>

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Author (Year)	Sample	Design/Method	Measures	Results	Grief Association Mechanisms
	<ul style="list-style-type: none"> <li>• <math>M_{age}</math> CG = 49.49, <math>SD</math> = 12.87; <math>M_{age}</math> MDD = 49.33, <math>SD</math> = 13.27; <math>M_{age}</math> bereaved controls = 48.65, <math>SD</math> = 12.70)</li> <li>• Type of loss: death of a loved one</li> <li>• Time since loss: 6 months</li> </ul>	<ul style="list-style-type: none"> <li>• Control groups: Matched on age and sex</li> </ul>		<ul style="list-style-type: none"> <li>• bereaved control participants</li> <li>• Adjusted regression models indicate that primary or probable CG diagnosis (ICG 30) was associated with significantly higher oxytocin levels (<math>p = .001</math>)</li> </ul>	
Fernández-Alcántara et al. (2020)	<ul style="list-style-type: none"> <li>• <math>N = 38</math> (19 PGD, 19 nonbereaved)</li> <li>• Control group: nonbereaved, sociodemographically matched with study group</li> <li>• Gender: females (<math>n = 34</math>), males (<math>n = 38</math>)</li> <li>• Age range: 18–65</li> <li>• <math>M_{agePGD} = 40.42</math>; <math>M_{ageControl} = 39.42</math></li> <li>• <math>SD_{PGD} = 11.94</math>; <math>SD_{Control} = 12.42</math></li> <li>• Type of loss: any loved one</li> <li>• Time since loss: 18 months (control group: 3 years if any loss)</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI: Emotional Experience Task contrasting negative-, positive-, and death-valenced pictures (International Affective Picture System)</li> <li>• Inclusion criteria (PGD group): loss of loved one within 18 months; ICG score &gt; 25; no other psychiatric diagnoses</li> </ul>	<ul style="list-style-type: none"> <li>• PGD (ICG and ad-hoc clinical interview)</li> <li>• Grief severity, past and present (TRIG)</li> <li>• Depression and anxiety (SCL-90)</li> <li>• PTSD: Global Assessment of PTSD (Spanish)</li> <li>• Subjective emotional evaluation of pictures: Self-Assessment Manikin</li> </ul>	<ul style="list-style-type: none"> <li>• Amygdala and putamen activations in PGD group, but not in control group, correlated with TRIG-Present scores (<math>r = -0.570</math>, <math>p = 0.013</math> vs. <math>r = -0.490</math>, <math>p = 0.039</math>, respectively); middle frontal gyrus activation in PGD group, but not control group, correlated with TRIG-Past (<math>r = 0.522</math>, <math>p = 0.026</math> vs. <math>r = 0.014</math>, <math>p = 0.955</math>)</li> <li>• While viewing negative-valenced pictures compared to fixation cross, PGD group had significantly greater activation of right inferior temporal cortex; control group had significantly greater activation in association and primary visual cortices</li> <li>• Death vs. positive valence: PGD group had greater activation in amygdala, midbrain, PAG, cerebellum, and right hippocampus</li> <li>• Negative vs. positive valence: PGD group had greater activation of midbrain, PAG, and right hippocampus</li> <li>• No significant differences when comparing positive-valenced pictures to fixation</li> </ul>	<ul style="list-style-type: none"> <li>•</li> <li>•</li> <li>•</li> <li>•</li> </ul>

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Freed et al. (2009)	<ul style="list-style-type: none"> <li>• <math>N = 20</math></li> <li>• Gender: females (<math>n = 16</math>), males (<math>n = 4</math>)</li> <li>• Age range: 22–62</li> <li>• <math>M_{\text{age}} = 37.8</math></li> <li>• <math>SD = 13.1</math></li> <li>• Type of loss: pet bereavement</li> <li>• Time since loss: 3 months</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI: Emotional Stroop task contrasting deceased-related with control words</li> <li>• Inclusion criteria: loss of pet dog or cat within prior 3 months, no presence of psychiatric disorders</li> </ul>	<ul style="list-style-type: none"> <li>• Depression (BDI)</li> <li>• Grief Intensity (TRIG)</li> <li>• Intrusive and avoidance thoughts (IES-R)</li> <li>• Reaction time on Emotional Stroop task</li> </ul>	<ul style="list-style-type: none"> <li>• cross, or death-valenced to negative-valenced pictures</li> <li>• Attentional bias observed toward deceased-related words (<math>p = .001</math>). Participants made more errors during deceased word trials (<math>p = .027</math>). Bias magnitude associated with activity in right amygdala, insula, and DLPFC activity (<math>p &lt; .01</math>)</li> <li>• Intrusiveness was associated with TRIG (<math>r = .86, p &lt; .000</math>) and activation of ventral amygdala and rACC (<math>p &lt; .05</math>)</li> <li>• Amygdala activity was associated with induced sadness intensity (<math>p &lt; .05</math>)</li> <li>• Avoidance was associated with deactivation of the dorsal amygdala and DLPFC (<math>p &lt; .05</math>)</li> <li>• High DLPFC-amygdala functional connectivity associated with reduced attentional bias (<math>r = -.50</math>), while low rACC-amygdala functional connectivity predicted sadness intensity (<math>r = -.70</math>)</li> </ul>	<ul style="list-style-type: none"> <li>•</li> <li>•</li> <li>•</li> <li>•</li> </ul>
Gundel et al. (2003)	<ul style="list-style-type: none"> <li>• <math>N = 8</math></li> <li>• Gender: females (<math>n = 8</math>)</li> <li>• Age range: 19–58</li> <li>• <math>M_{\text{age}} = 41.9</math>.</li> <li>• <math>SD =</math> not specified</li> <li>• Type of loss: death of first-degree relative</li> <li>• Time since loss: &lt; 1 year</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI: 15 picture-word composites (grief versus neutral related words/photo of loved one versus a strange)</li> <li>• Skin conductance</li> <li>• Grief intensity</li> <li>• Inclusion criteria: female gender, right-handedness,</li> </ul>	<ul style="list-style-type: none"> <li>• Not specified</li> </ul>	<ul style="list-style-type: none"> <li>• Three brain regions were activated by the picture and word factors: posterior cingulate cortex, medial/superior frontal gyrus, and cerebellum</li> <li>• In the picture factor, the cuneus, superior lingual gyrus, insula, dACC, inferior temporal gyrus, and fusiform gyrus</li> </ul>	<ul style="list-style-type: none"> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> </ul>

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		<ul style="list-style-type: none"> <li>absence of psychiatric disorders</li> </ul>		<ul style="list-style-type: none"> <li>were activated (<math>p</math>s &lt;.001, uncorrected)</li> <li>In the word factor, the precuneus, precentral gyrus, midbrain, and vermis were activated (<math>p</math>s &lt;.001, uncorrected)</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> <li></li> </ul>
<p>Huang et al. (2018)</p>	<ul style="list-style-type: none"> <li><math>N = 23</math></li> <li>Gender: females (<math>n = 21</math>), males (<math>n = 2</math>)</li> <li>Age range: 25–66</li> <li><math>M_{\text{age}} = 48.35</math></li> <li><math>SD = 11.14</math></li> <li>Type of loss: relative</li> <li>Time since loss: 6 months to 4 years</li> </ul>	<ul style="list-style-type: none"> <li>8-week MBCT</li> <li>fMRI: Numerical Stroop task (pre- and post-intervention)</li> <li>Inclusion criteria: native Mandarin speakers, no previous experience with mindfulness meditation, no presence of psychiatric disorders</li> </ul>	<ul style="list-style-type: none"> <li>Anxiety (GAD-7)</li> <li>Depression (Taiwan Depression Scale)</li> <li>Difficulties in emotional regulation (DERS)</li> <li>Grief intensity (TRIG)</li> <li>Mindfulness (FFMQ)</li> <li>Stroop reaction time</li> </ul>	<ul style="list-style-type: none"> <li>Intervention reduced activation of the dorsal attentional network, including the middle frontal gyrus and superior parietal gyrus</li> <li>Improvements on reaction time in incongruent trials (<math>F_{1,18} = 6.73, p &lt; 0.018</math>)</li> <li>Activation of the posterior cingulate cortex (<math>r = .34, p &lt; .04</math>) and thalamus were associated with TRIG (<math>r = .33, p &lt; .05</math>). Anxiety associated with activity in the posterior cingulate cortex (<math>r = .36, p &lt; .03</math>).</li> <li>Lower grief and anxiety associated with reduced brain activations of posterior cingulate cortex or thalamus involved in the Stroop test</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> <li></li> </ul>
<p>Jain et al. (2019)</p>	<ul style="list-style-type: none"> <li><math>N = 17</math> at baseline, 9 at follow-up</li> <li>Age range: not specified</li> <li>Gender: not specified</li> <li><math>M_{\text{age}} = 60</math></li> <li><math>SD = 10-13</math></li> <li>Type of Loss: pre-loss population/ anticipatory grief</li> <li>Time since Loss: N/A</li> </ul>	<ul style="list-style-type: none"> <li>fMRI: involved 2x2 factorial design of picture-word composites of the caregivers' loved one or a stranger (matched for age, sex, and race) together with a grief-related or neutral word, dementia family caregivers enrolled in either 4 weeks of PMR or MIT</li> </ul>	<ul style="list-style-type: none"> <li>Depression (PHQ, QIDS)</li> <li>Grief (Marwit and Meuser Caregiver Grief Inventory - Short Form)</li> <li>Trait Mindfulness (FFMQ)</li> </ul>	<ul style="list-style-type: none"> <li>Significant negative association was found between grief and mindfulness (<math>r = -0.70, 95\% \text{ CI } -0.87 \text{ to } -0.41, p .01</math>)</li> <li>Picture-factor evoked two clusters of activation: left posterior cingulate/precuneus regions and bilateral anterior cingulate gyri (<math>p .025</math>)</li> <li>Word-factor evoked three</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> <li></li> </ul>

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		<ul style="list-style-type: none"> <li>Inclusion criteria: must be primary source of assistance or support for the care recipient, with a score of &gt; 9 on PHQ</li> </ul>		<ul style="list-style-type: none"> <li>clusters of activation: anterior cingulate cortex, posterior cingulate, and supramarginal gyrus (<math>p = .025</math>)</li> <li>Improvement in grief was associated with increased brain activation in the precuneus (<math>t = -4.78, d = -3.6</math>) and anterior cingulate (<math>t = -5.65, d = -4.3</math>)</li> </ul>	
McConnell et al. (2018)	<ul style="list-style-type: none"> <li><math>N = 25</math> (9 CG, 7 non-CG, 9 control)</li> <li>Control group: non-bereaved, married</li> <li>Age range: not specified</li> <li>Gender: females (<math>n = 21</math>), males (<math>n = 4</math>)</li> <li><math>M_{age} = 71.4</math></li> <li><math>SD =</math> not specified</li> <li>Type of Loss: spousal</li> <li>Time since Loss: <math>x = 21.19</math> months</li> </ul>	<ul style="list-style-type: none"> <li>fMRI: involved photos presented in an event-related design for 60 trials with 5 photos of participants' spouses and 5 photos of a stranger (matched for age, sex, race, and background), manipulation check post-scan</li> <li>Inclusion criteria: older adults, death of a spouse in the last 3 years, or non-bereaved married controls w/o any loss of first-degree relative in the past 3 years</li> </ul>	<ul style="list-style-type: none"> <li>Depression (BDI)</li> <li>Grief (ICG)</li> </ul>	<ul style="list-style-type: none"> <li>No significant difference in activity between the three groups for spouse vs. stranger or anticipation vs. photo</li> <li>Higher self-reported yearning predicted activation in the subgenual anterior cingulate during the anticipation period compared to viewing photo of spouse (<math>z = 3.11, p &lt; .005, cluster size = 25</math>)</li> <li>BDI showed no significant association with activation of sACC when included as regressor</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>
Najib et al. (2004)	<ul style="list-style-type: none"> <li><math>N = 9</math> (4 mod-CG)</li> <li>Age range: 18–40</li> <li>Gender: females (<math>n = 9</math>)</li> <li><math>M_{age} = 25.9</math></li> <li><math>SD = 5.8</math></li> <li>Type of Loss: romantic loss (break-up)</li> <li>Time since Loss: 16 weeks</li> </ul>	<ul style="list-style-type: none"> <li>BOLD fMRI: involved females who experienced upsetting romantic loss rating affect after viewing self-reported sad ruminative thought about ex-lover and neutral thought about an acquaintance</li> <li>Inclusion criteria: right-handed, premenopausal females, who had experienced a break-up/separation of relationship lasting 6</li> </ul>	<ul style="list-style-type: none"> <li>Anxiety (Hamilton Anxiety Rating Scale)</li> <li>Cloninger's Temperament and Character Inventory</li> <li>Depression (BDI, Hamilton Depression Rating Scale)</li> <li>Positive and Negative Affect Schedule</li> <li>Psychiatric History (SCID)</li> </ul>	<ul style="list-style-type: none"> <li>Significant increase in activation in cerebellum, posterior pons, posterior temporal cortex, posterior cingulate, parietal cortex, and occipital cortex during ruminative thought (<math>p &lt; .01</math>)</li> <li>Significant decrease in activation in the subcortex, medial and lateral temporal cortices, insula, anterior cingulate, and frontal cortex during ruminative thought (<math>p &lt; .01</math>)</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>

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		months, with absence of psychiatric disorder, psychotropic medication, pregnancy/lactation, and/or MRI contraindications	<ul style="list-style-type: none"> <li>Romantic loss/Grief (modified ICG)</li> </ul>	<ul style="list-style-type: none"> <li>Negative association between brain activity in regions of interest for ruminative thought and subject's baseline grief inventory score (<math>r = 0.93</math>, <math>df = 7</math>, <math>p = 0.0003</math>; <math>z = 3.48</math>)</li> </ul>	
O'Connor et al. (2018) <sup>##</sup>	<ul style="list-style-type: none"> <li><math>N = 37</math> (17 CG, 20 non-CG)</li> <li>Control group: placebo</li> <li>Age range: not specified</li> <li>Gender: not specified</li> <li><math>M_{age}</math> = not specified</li> <li><math>SD</math> = not specified</li> <li>Type of Loss: spousal</li> <li>Time since Loss: not specified</li> </ul>	<ul style="list-style-type: none"> <li>Idiographic Approach Avoidance Task response to images of deceased spouse, a living loved one, and a stranger (matched for age and sex) following placebo or OT in spousally bereaved older adults</li> <li>Inclusion criteria: not specified</li> </ul>	<ul style="list-style-type: none"> <li>Not specified</li> </ul>	<ul style="list-style-type: none"> <li>Analysis revealed a main effect of CG</li> <li>Those with CG responded more slowly in the OT condition (<math>p &lt; .01</math>), suggesting that neuropeptide oxytocin play a role in motivation systems of individuals with CG</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>
O'Connor et al. (2015) <sup>##</sup>	<ul style="list-style-type: none"> <li><math>N = 26</math> (8 CG, 9 non-CG, 9 controls)</li> <li>Age range: not specified</li> <li>Gender: not specified</li> <li><math>M_{age}</math> = not specified</li> <li><math>SD</math> = not specified</li> <li>Type of Loss: spousal</li> <li>Time since Loss: not specified</li> </ul>	<ul style="list-style-type: none"> <li>Event-related fMRI: involved photos presented of spouse (living or deceased) and a matched stranger.</li> <li>Inclusion criteria: not specified</li> </ul>	<ul style="list-style-type: none"> <li>Not specified</li> </ul>	<ul style="list-style-type: none"> <li>Bilateral hemodynamic responses in the amygdala and right orbitofrontal cortex were significantly activated (<math>z = 3.93</math>, <math>p &lt; .005</math>) in CG group compared to Non-CG group</li> <li>CG group showed activation in precuneus and mid-cingulate regions in comparison to Non-CG and control groups</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>
O'Connor et al. (2007)	<ul style="list-style-type: none"> <li><math>N = 8</math></li> <li>Age range: not specified</li> <li>Gender: females (<math>n = 8</math>)</li> <li><math>M_{age}</math> = not specified</li> <li><math>SD</math> = not specified</li> <li>Type of Loss: 1<sup>st</sup> degree relative</li> <li>Time since Loss: &lt; 1 year (<math>x = 6</math> months)</li> </ul>	<ul style="list-style-type: none"> <li>ECG and BOLD fMRI: involved 2x2 factorial design of picture-word composites of the caregivers' loved one or a stranger together with a grief-related or neutral word</li> <li>Inclusion Criteria: right-handed females, who had</li> </ul>	<ul style="list-style-type: none"> <li>Psychiatric History (SCID)</li> </ul>	<ul style="list-style-type: none"> <li>Participants with higher tonic RSA had lower subjective reports of grief during scanning (in a comparison of the grief and neutral conditions) (RSA (<math>6.16 \pm 1.11</math>), subjective rating of grief (<math>5.9 \pm 2.06</math>); <math>r = -0.74</math>, <math>p &lt; 0.05</math>)</li> <li>The PCC medial and superior frontal gyrus, and</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>

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Author (Year)	Sample	Design/Method	Measures	Results	Grief Association Mechanisms
		<p>experienced the loss of first-degree relative in the past year, with absence of Axis I psychiatric and medical disorders</p>		<p>cerebellum were all co-activated by grief words and photos of the bereaved</p> <ul style="list-style-type: none"> <li>A significant positive association was found with the right cuneus (<math>p = 0.009</math>) and a negative association was found with the right PCC (<math>p = 0.045</math>) with the activation of Deceased&gt;Stranger contrast</li> <li>A significant positive association was found with the left cuneus (<math>p = 0.001</math>) and PHG (<math>p = 0.043</math>) with the activation of Grief Word&gt;Neutral Word contrast</li> <li>A significant positive association was found between sACC/orbitofrontal cortex and posterior cingulate activity in the Deceased&gt;Stranger contrast (<math>p &lt; 0.001</math>)</li> </ul>	
O'Connor et al. (2009)	<ul style="list-style-type: none"> <li><math>N = 18</math></li> <li>Age range: 25–60</li> <li>Gender: females (<math>n = 18</math>)</li> <li><math>M_{age} = 44.3</math></li> <li><math>SD =</math> not specified</li> <li>Type of Loss: mother or sister</li> <li>Time since Loss: <math>&lt; 5</math> years (<math>x = 30</math> months)</li> </ul>	<ul style="list-style-type: none"> <li>Saliva collection and fMRI task: involved 2x2 factorial design of picture-word composites of the caregivers' loved one or a stranger (matched for age, sex, and race, environment) together with a grief-related or neutral word</li> <li>Inclusion criteria: females who had experienced loss of their sister or mother in the past 5 years, with absence of mood disorders, smoking and</li> </ul>	<ul style="list-style-type: none"> <li>Psychiatric History (SCID)</li> </ul>	<ul style="list-style-type: none"> <li>Inflammatory markers (IL-1<math>\beta</math> and sTNF<math>\alpha</math>) were positively associated with ventral prefrontal activation (sACC and OFC) as well as other regions important in the emotional task such as noun retrieval (temporal cortex), and visual processing (cuneus and fusiform gyrus) (<math>p &lt; .0001</math>)</li> <li>A significant positive association was found between sACC and freely recalled grief-related words (<math>r = 0.50, p &lt; 0.04</math>), and the association between sACC and freely recalled</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> <li></li> </ul>

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Author (Year)	Sample	Design/Method	Measures	Results	Grief Association Mechanisms
		diseases of the immune system		<ul style="list-style-type: none"> <li>neutral words (<math>r = 0.27, p &lt; 0.29</math>)</li> <li>No significant associations found in multiple regression analysis.</li> </ul>	
O'Connor et al. (2013)	<ul style="list-style-type: none"> <li><math>N = 16</math></li> <li>Age range: not specified</li> <li>Gender: females (<math>n = 14</math>), males (<math>n = 2</math>)</li> <li><math>M_{age} = 64</math></li> <li><math>SD = 4.3</math></li> <li>Type of Loss: any (44% parent, 31% spouse, 6% child, 13% sibling, and other)</li> <li>Time since Loss: <math>x = 87</math> months</li> </ul>	<ul style="list-style-type: none"> <li>Blood sample collection as part of an ongoing randomized trial of Interpersonal Therapy versus Complicated Grief Therapy</li> <li>Inclusion criteria: score of <math>\geq 30</math> on the ICG, participants were asked to abstain from food, caffeine, and smoking 4 hours prior to blood draw</li> </ul>	<ul style="list-style-type: none"> <li>Depression (BDI-II)</li> <li>Grief (ICG)</li> </ul>	<ul style="list-style-type: none"> <li>Paired-sample t-test revealed the ICG was significant (<math>t = 7.44, p &lt; .001</math>). The mean level ICG score at pre-treatment was 44.6 (<math>SD = 11.5</math>) and 23.5 (<math>SD = 11.0</math>) at post-treatment</li> <li>Epinephrine at pretreatment predicted the post-treatment ICG score, accounting for the pre-treatment ICG score (<math>F(16, 2) = 6.68, p = 0.01, \beta_{logE} = 0.53, \beta_{ICG} = 0.48</math>)</li> <li>Norepinephrine and dopamine levels at pre-treatment were not significant predictors of post-treatment ICG scores</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>
O'Connor et al. (2008) *	<ul style="list-style-type: none"> <li><math>N = 23</math> (11 CG, 12 Non-CG)</li> <li>Age range: not specified</li> <li>Gender: females (<math>n = 23</math>)</li> <li><math>M_{age} = 43.7</math></li> <li><math>SD = 10</math></li> <li>Type of Loss: mother or sister</li> <li>Time since Loss: <math>&lt; 5</math> years</li> </ul>	<ul style="list-style-type: none"> <li>Event-related fMRI task: involved <math>2 \times 2</math> factorial design of picture-word composites of the caregivers' loved one or a stranger (matched for age, sex, and race, environment) together with a grief-related or neutral word</li> <li>Inclusion criteria: females who had experienced loss of their sister or mother within 5 years, absence of Axis I disorders</li> </ul>	<ul style="list-style-type: none"> <li>Grief (ICG)</li> <li>Psychiatric History (SCID)</li> </ul>	<ul style="list-style-type: none"> <li>Greater reward-related activity occurred in the CG group relative to the Non-CG group</li> <li>The NAcc was more active after presented grief-related words than neutral words in CG group compared to Non-CG group (<math>t = 3.51, p &lt; 0.001, 15</math> voxels)</li> <li>A significant positive correlation was found between NAcc activation and self-reported yearning for the deceased in the grief word comparison (<math>r = .42, p &lt; .05</math>)</li> <li>Both CG (<math>p .05</math>) and non-CG (<math>p &lt; .01</math>) groups</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> <li></li> </ul>

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Author (Year)	Sample	Design/Method	Measures	Results	Grief Association Mechanisms
				<p>showed significant activity in (pain-related regions) dACC, insula, and PAG in the comparisons of the deceased vs. stranger pictures and grief vs. neutral words</p> <ul style="list-style-type: none"> <li>The left insula was found to be more active in the Non-CG group during the viewing of grief-related vs. neutral words (<math>t = 4.20, p &lt; 0.001, 87</math> voxels)</li> </ul>	
Saavedra Perez et al. (2015)*	<ul style="list-style-type: none"> <li><math>N = 5501</math></li> <li>Control group: individuals who were mourning over someone with severe disease/pet</li> <li>Age range: &gt; 45 years old</li> <li>Gender: females (<math>n = 2529</math>), males (<math>n = 2927</math>)</li> <li><math>M_{age\ control} = 60.7, M_{age\ non-CG} = 62.4, M_{age\ CG} = 61.9</math></li> <li><math>SD_{control} = 8.6, SD_{non-CG} = 9.3, SD_{CG} = 8.1</math></li> <li>Type of loss: not specified</li> <li>Time since Loss: not specified</li> </ul>	<ul style="list-style-type: none"> <li>fMRI: The study assessed differences in cognitive functions &amp; brain volume in individuals with either no, normal, or complicated grief.</li> <li>Population-Based</li> <li>Inclusion criteria: MMSE score &gt; 23, no major depression, ICG score &lt; 22, no missing data, no dementia</li> </ul>	<ul style="list-style-type: none"> <li>Attention, Concentration, Executive Function (Stroop Test)</li> <li>Cognitive Functions (MMSE)</li> <li>Grief (ICG)</li> <li>Processing Speed (LDST)</li> <li>Word Fluency Task</li> </ul>	<ul style="list-style-type: none"> <li>Complicated grief group performed worse in domains of executive function, &amp; information processing speed, &amp; had a lower total brain volume as measured by structural brain imaging.</li> <li>No significant differences found in cognition &amp; structural brain changes between persons with normal grief &amp; the controls</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> </ul>
Schiele et al. (2018)	<ul style="list-style-type: none"> <li><math>N = 96</math></li> <li>Age range: not specified</li> <li><math>M_{age} = 40.01</math></li> <li><math>SD = 12.74</math></li> <li>Gender: females (<math>n = 68</math>), males (<math>n = 25</math>)</li> <li>Type of loss: significant person</li> <li>Time since Loss: not specified</li> </ul>	<ul style="list-style-type: none"> <li>All participants were genotyped for OXTR rs2254298</li> <li>Population-Based</li> <li>Inclusion criteria: DSM-IV axis 1 mood &amp;/or anxiety disorders &amp; hx of bereavement</li> </ul>	<ul style="list-style-type: none"> <li>Behavioral Inhibition (RSRI)</li> <li>Grief (ICG)</li> <li>Separation Anxiety (ASA-27)</li> </ul>	<ul style="list-style-type: none"> <li>OXTR genotype interacted with BI &amp;, on a trend-level, with adult SA, to increase CG</li> <li>Higher levels on the RSRI &amp; ASA-27 scales, respectively, were related to higher ICG scores in GG genotype carriers</li> <li>Gender &amp; age had no significant associations</li> <li>No significant associations were observed between</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>

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Author (Year)	Sample	Design/Method	Measures	Results	Grief Association Mechanisms
				OXTR & RSRI or ASA-27	
Schneck et al. (2017)	<ul style="list-style-type: none"> <li><math>N = 23</math></li> <li>Age range: 18–65</li> <li>Gender: females (<math>n = 19</math>), males (<math>n = 4</math>)</li> <li><math>M_{age} = 46</math></li> <li><math>SD = 13.6</math></li> <li>Type of loss: 1<sup>st</sup> degree relative, spouse, or partner</li> <li>Time since Loss: 3–14 months</li> </ul>	<ul style="list-style-type: none"> <li>Measure Development: A machine learning approach was applied to fMRI (neural decoding) to develop a measure of ongoing deceased-related processing</li> <li>Population-Based</li> <li>Inclusion criteria: medically healthy, bereaved of a loved one 3–14 months ago</li> </ul>	<ul style="list-style-type: none"> <li>Avoidance of Reminders of Loss (IES)</li> <li>Deceased, Living, Self-Related Thought (SART)</li> <li>Grief (ICG)</li> <li>Mental representations of the deceased (fMRI)</li> </ul>	<ul style="list-style-type: none"> <li>Reliability was acceptable for both the ICG scale (<math>\alpha = .96</math>) &amp; IES avoidance subscale (<math>\alpha = .76</math>)</li> <li>ICG score associated with avoidance, arousal during the mental representations of deceased task, frequency of thinking about the deceased on the SART, &amp; average motion during the SART</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> </ul>
Schneck et al. (2019)	<ul style="list-style-type: none"> <li><math>N = 29</math></li> <li>Age range: 18–65</li> <li>Gender: females (<math>n = 23</math>), males (<math>n = 6</math>)</li> <li><math>M_{age} = 44.06</math></li> <li><math>SD = 13.65</math></li> <li>Type of loss: 1<sup>st</sup> degree relative or partner</li> <li>Time since Loss: 3–14 months</li> </ul>	<ul style="list-style-type: none"> <li>Observed ongoing interaction between deceased-related representational &amp; attentional systems during mind wandering</li> <li>Population-Based</li> <li>Inclusion criteria: bereaved by a loved one 3–14 months ago &amp; medically healthy</li> </ul>	<ul style="list-style-type: none"> <li>Avoidance of Reminders of Loss (IES)</li> <li>Grief (ICG)</li> <li>Spontaneous fluctuations in neural patterns during a neutral mind wandering task (fMRI)</li> </ul>	<ul style="list-style-type: none"> <li>Avoidant grievers monitor the contents of their mind wandering</li> <li>Monitoring was linked to a reduced likelihood that mental representations of the deceased, arising during mind wandering, would lead to a conscious thought of loss</li> <li>Avoidant grievers still displayed more intrusive thoughts of loss overall on the task</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> </ul>
Schneck et al. (2019)	<ul style="list-style-type: none"> <li><math>N = 29</math></li> <li>Age range: 18–65</li> <li>Gender: females (<math>n = 23</math>), males (<math>n = 6</math>)</li> <li><math>M_{age} = 44</math></li> <li><math>SD = 13</math></li> <li>Type of loss: 1<sup>st</sup> degree relative or partner</li> <li>Time since Loss: 3–14 months</li> </ul>	<ul style="list-style-type: none"> <li>Measured ongoing fluctuations in a neural proxy of d-SA during a neutral task to identify self-generated unconscious loss processing</li> <li>Population-Based</li> <li>Inclusion criteria: bereaved by a loved one 3–14 months ago &amp;</li> </ul>	<ul style="list-style-type: none"> <li>Deceased-related selective attention (d-SA)</li> <li>Grief (ICG)</li> </ul>	<ul style="list-style-type: none"> <li>Engagement of d-SA during a neutral task, in the absence of a conscious thought of the deceased, associated with less severe grieving (<math>r_{25} = -.711, p &lt; .001, 95\% \text{ CI} = -0.89 \text{ to } -0.42</math>)</li> <li>Concurrent neural activity in temporal parietal junction &amp; dorsolateral prefrontal cortex indicated</li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> </ul>

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Author (Year)	Sample	Design/Method	Measures	Results	Grief Association Mechanisms
		medically healthy		combination of social processing & conscious control	
Schneck et al. (2018)	<ul style="list-style-type: none"> <li>• <math>N = 25</math></li> <li>• Age range: 18–65</li> <li>• Gender: females (<math>n = 23</math>), males (<math>n = 2</math>)</li> <li>• <math>M_{age} = 45</math></li> <li>• <math>SD = 13</math></li> <li>• Type of loss: 1<sup>st</sup> degree relative or partner</li> <li>• Time since Loss: 3–14 months</li> </ul>	<ul style="list-style-type: none"> <li>• Emotional Stroop Task</li> <li>• Population-Based</li> <li>• Inclusion criteria: grieving 1<sup>st</sup> degree relative or partner within 3–14 months</li> </ul>	<ul style="list-style-type: none"> <li>• Attachment Style (AAS)</li> <li>• Complicated Grief (ICG)</li> <li>• Depression (BDI)</li> <li>• Emotional Pain (TRIG)</li> <li>• Emotional Selective Attention (Emotional Stroop Task)</li> <li>• General Selective Attention (Standard Stroop Task)</li> <li>• Intrusive Thinking (IES-R)</li> <li>• Neural circuitry (fMRI)</li> </ul>	<ul style="list-style-type: none"> <li>• Slower RT to deceased-related versus living-related words demonstrates attentional bias to deceased (<math>B = 0.012</math>, <math>t_{2831} = 2.73</math>, <math>p &lt; .006</math>, 95% confidence interval [CI], 0.003, Cohen's <math>d = 0.85</math>), which was associated with greater intrusive thinking &amp; general CG severity, but not emotional components of grief such as sadness, pain, &amp; yearning</li> <li>• Results remained significant when controlling for the effect of time since loss, CG severity, age, BDI score, number of prior major depressive episodes, suicide loss, &amp; medication use on RT</li> </ul>	<ul style="list-style-type: none"> <li>•</li> <li>•</li> <li>•</li> </ul>

\* includes mechanisms implicated in PGD,

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