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Review article

Minding mortality: A systematic review of the neural processing of death-related stimuli

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ABSTRACT

The human relationship with mortality has been widely studied in psychology, with extensive studies suggesting that death-related stimuli impact behavior even without reflective awareness. In recent decades, neuroimaging studies have yielded various contenders for brain regions underlying the online processing of death-related stimuli. To the best of our knowledge, we present here the first systematic review of these findings. We conducted a comprehensive search for studies where participants were presented with death-related and death-unrelated but negatively valenced (unpleasant) stimuli while undergoing functional brain imaging. We found seven functional magnetic resonance imaging studies with a total of 204 participants. Five of six within-group studies found that unpleasant stimuli consistently elicited increased insular activity, but only when it was unrelated to mortality. This novel finding—that insular deactivation alone marks the processing of death-related stimuli—suggests a critical difference between the neural processing of death-related and non-death related, unpleasant stimuli. We argue that preexisting explanatory frameworks fail to unite our results with findings on threat processing mechanisms in the insula or lack evolutionary plausibility. We present an alternative explanation: death might be unique in that it evades the insula's typical threat-assessment mechanisms.

Further research is needed to determine whether this neural signature is robust and what its function and consequences may be. A better understanding of how individuals process death-related information promises deeper insight into the human relationship with mortality, with significant implications for individuals and society, not least for mental health interventions and end-of-life care.

1. Introduction

Leo Tolstoy effectively captured the complex human relationship with mortality in *The death of Ivan Ilyich* (1886/1981, pp. 79–80):

> The syllogism he had learned from Kiesewetter's logic—"Caius is a man, men are mortal, therefore Caius is mortal"—had always seemed to him correct as applied to Caius, but by no means to himself. That man Caius represented man in the abstract, and so the reasoning was perfectly sound; but he was not Caius, not an abstract man… He had been little Vanya, with a mama and a papa… with all the joys, sorrows, and enthusiasms of his childhood, boyhood, youth. … Caius really was mortal, and it was only right that he should die, but for him, Vanya… with all his thoughts and feelings, it was something else again. And it simply was not possible that he should have to die …

Terror Management Theory (TMT; Greenberg et al., 1986; Solomon et al., 2015) has played a prominent role in psychological research on death awareness. TMT posits that the inevitability of death causes terror, managed through a dual mechanism of proximal and distal defenses (Pyszczynski et al., 1999). Proximal defenses are self-conscious efforts to avoid thoughts of death, such as distracting oneself by thinking about one's health or youth. Distal defenses, by contrast, are unconscious mechanisms that buffer against mortality awareness by bolstering self-esteem and reinforcing attachment to one's cultural worldview (Pyszczynski et al., 2004, p. 437). When an individual is confronted with death-related stimuli and then becomes distracted from them, the stimuli remain salient but the proximal defenses are, obviously, no

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longer available. The stimuli's continued salience triggers distal defenses, leading to changes in behavior as protection from mortality-related thoughts. Collectively, these predictions form the Mortality Salience Hypothesis (Harmon-Jones et al., 1997), which has been tested by priming participants with death-related stimuli and assessing the stimuli's effects on various outcomes, such as self-esteem (Arndt et al., 1997; Greenberg et al., 1994; Pyszczynski et al., 1999).

In a meta-analysis of two decades of mortality salience research, Burke et al. (2010) examined whether death-related stimuli have distinct effects on behavior compared to threats of pain, social rejection, and failure. They conclude that a large body of studies, with a range of experimental settings and participants, have reproduced the effects predicted by the mortality salience hypothesis; death-related stimuli affect behavior even without reflective awareness.[1] Burke et al. write that death is a "qualitatively unique threat" (p. 186) different from other threats in both degree and dimension. Which dimension (or dimensions) remains unclear, but the researchers argue that threats to one's sense of meaning in life elicit similar effects.

Nevertheless, Burke et al. (2010) argue that TMT is not the best explanatory framework for these effects because it fails to address individual differences arising from factors like age and gender. Navarrete and Fessler (2005) criticise TMT for not aligning with contemporary evolutionary approaches and not accounting for significant cultural variations in views on death. Kirkpatrick and Navarrete (2006) argue that the effects elicited by mortality salience are better explained by human beings' social nature: death-related thoughts activate defenses related more to the threat from other people than that from non-existence. It's not clear that TMT can explain variations *within* a culture, either; consider all those ailing elderly or terminally ill patients who seem prepared or even eager to die, all those who commit acts of self-sacrifice, and all those who appear recklessly fearless in the face of death (often enough with mortal consequences).

1.1. Death on the brain

Despite the extensive research on mortality salience in psychology, questions about the neural processing of death-related stimuli have only recently gained traction. Quirin et al. (2019) place these questions within existential neuroscience: a relatively new discipline at the intersection of existential philosophy and neuroscience. In contrast to other neuroscience research, which emphasizes the adaptive value of advanced cognitive abilities, existential neuroscience explores their potential side effects such as disorientation and dread. They review findings on the neural processing of mortality-related stimuli, concluding that two areas are central: the salience network and ventrolateral prefrontal cortex (VLPFC).

Comprising primarily the anterior insula and dorsal anterior cingulate cortex (ACC), the salience network has been thought to play a key role in dealing with novel, threatening, or otherwise urgent stimuli (Quirin et al., 2019). The insula is broadly understood to be central to sense of self and agency (for a meta-analysis, see Sperduti et al., 2011) and the ACC to various integrative functions concerning regulation of affect and cognition (for a review, see Bush et al., 2000). Seeley (2019) writes that the salience network might identify stimuli relevant to maintaining homeostasis and attributing to them positive (reinforcing) or negative (inhibiting) value. Quirin et al. (2019) write that insular deactivation has been observed in response to mortality-related stimuli and, in line with TMT, hypothesize that this might reflect suppression of self-referential processing as a coping mechanism.

Quirin et al. (2019) describe the right side of the VLPFC as involved in threat detection, emotional regulation, and avoidance behavior, while the left makes sense of novel experiences, integrating them into one's understanding of the world and self. Luo et al. (2014) found that mortality priming, compared to priming with negatively valenced stimuli, decreases activity in the dorsolateral prefrontal cortex (DLPFC) in response to suffering of others. This decrease was mediated by participants' ratings of their fear of death. The researchers propose that the suffering of others indicates an uncertain threat that requires evaluation of possible responses. This evaluative function, they argue, is hampered by mortality reminders, especially in individuals who fear death.

1.2. Emotion regulation: death and other threats

The observation that death-related stimuli have effects on behavior outside reflective awareness suggests that these stimuli trigger emotion-regulation strategies (Tritt et al., 2012). The question is, do these stimuli trigger a unique emotion-regulation strategy with a distinctive neural signature?

Tritt et al. (2012) propose that death anxiety might be an underlying cause of much human activity, but that it works like any other anxiety. They conclude that most nonhuman animals seem unaware of their mortality, while the idea that a specialized physiological fear-response system arose late in evolution makes little sense. They propose instead that the effects elicited by mortality cues are attributable to a generalized anxiety system evolved to respond to situations in which animals are unsure how to proceed. This same uncertainty-induced anxiety should be elicited when an individual encounters threats to basic psychological needs such as meaning, attachment, and sense of personal control.

Tritt et al. offer as a candidate for such an anxiety system the widely recognized behavioral inhibition system (Gray, 1984), which increases arousal and attention but — as the name suggests — inhibits behavior. It is activated when the best path forward is information gathering in response to incongruencies between what one expects and what one experiences. They predict that, if the behavioral inhibition system is the best explanation, the ACC and DLPFC should increase in activation when individuals are presented with cues related to psychological threat, including those posed by death-related stimuli.

1.3. This systematic review

This review examines the brain areas involved in processing death-related information and looks for a distinct neural signature accompanying its processing. To the best of our knowledge, no publication has attempted a systematic review of these findings. We looked for studies that used at least one comparative condition involving negatively valenced, death-unrelated (unpleasant) stimuli, where no measures were taken to distract participants. Our focus is on identifying measurable differences between the neural processing of death-related vs. unpleasant stimuli, so neuroimaging studies employing priming paradigms will be excluded, as these have additional experimental manipulations affecting the data.

2. Method

2.1. Search strategy

We conducted a literature search February 21, 2024, on Web of

[1] Phenomenologists are inclined to distinguish at least between pre-reflective consciousness and fully reflective self-consciousness (if not, indeed, allowing for a continuum between the two). It's the difference between "bare" conscious awareness and conscious awareness of conscious awareness. Whether these behavioral changes meet the threshold for pre-reflective consciousness or are truly pre-conscious we leave as an open question, though we have suggested elsewhere (Parthemore, 2011) a means for addressing that question by drawing the line at conceptually structured thought: that is, thoughts that meet the (largely agreed upon) desiderata for conceptually structured thought just are conscious thoughts; pre-conscious thoughts fail one or more of those desiderata, while reflective self-consciousness requires higher-order concepts: i.e., concepts of concepts.

Science, Scopus, and MEDLINE EBSCO, using the search string

> ("mortality salience" OR “death salience” OR "death-related stimuli" OR "mortality-related stimuli” OR "death-related linguistic cues") AND (insula* OR "amygdala" OR "prefrontal cortex" OR PFC OR "anterior cingulate cortex" OR "ACC" OR "salience network")

Articles needed to be peer-reviewed. The search was not restricted by year of publication.

Seventy-six results were exported to Rayyan (Ouzzani et al., 2016) for automatic duplicate detection backed by manual check, resulting in removal of 27 duplicates. Rayyan offers a blind mode, where reviewers cannot see each other’s decisions. With blind mode on, the first two authors independently screened records based on title and abstract. We then turned blind mode off to see that we agreed on all articles. Eighteen articles were removed for not reporting original empirical research. The remaining 49 were read in full, labeled, and excluded according to the same procedure: 14 for not looking at neural activation elicited by death-related stimuli on its own, four for failure to use death-related stimuli, three for using only EEG, and two for use of additional interventions, leaving seven articles for the review; see Fig. 1.

2.2. Inclusion/exclusion criteria

Our inclusion criteria were that 1) participants be healthy human adults 18 years or older 2) scanned using functional brain imaging while 3) presented with death-related stimuli and unpleasant stimuli. Our exclusion criteria were 1) use only of functional brain imaging with low spatial resolution (e.g., EEG) and 2) use of additional interventions such as drug administration (e.g., oxytocin) or psychological priming (e.g., nostalgia) prior to presentation of death-related stimuli.

2.3. Data extraction

Data extraction was guided by our PICO[2] model: in healthy human adults (18 years or older) (P), which brain areas are more or less active (O) when subjects are presented with death-related stimuli (I), compared to unpleasant stimuli (C)? We extracted information on sample size, gender, and age (including mean and, if available, standard deviation); type of functional brain imaging and analysis; type of death-related and unpleasant stimuli; results concerning activated/deactivated[3] brain areas (including correlation with stimuli presentations); correlation between neural activation and other relevant measures such as self-reported death anxiety (where available); and use of control conditions with neutral stimuli.

3. Results

3.1. Overview

See Table 1 for a summary. Two studies (Quirin et al., 2012; Qin et al., 2018) had all-male samples. One of these (Qin et al., 2018) investigated whether findings from an earlier study with all female participants (Han et al., 2010) could be replicated. Only one study (Yanagisawa et al., 2016) used a between-group design; all others were strictly within-group. The overall mean age of the study samples was low (M = 22), with the oldest sample (Quirin et al., 2012) averaging 23.7 years. While the other studies used at least three types of stimuli, two studies (Klackl et al., 2017; Quirin et al., 2012) only compared death-related stimuli to unpleasant stimuli. All studies used fMRI. Most studies involved both whole-brain and region-of-interest (ROI) analysis.[4] All studies used the Montreal Neurological Institute (MNI) reference brain for normalization.

Five of six within-group studies found that death-related stimuli induced significantly less activation in the bilateral insula than unpleasant stimuli, whether using words (Han et al., 2010; Qin et al., 2018; Shi and Han, 2013) or statements (Klackl et al., 2014), even when the statements were related to another category of existential threat: namely, uncontrollability (Klackl et al., 2017). In three studies (Han et al., 2010; Shi and Han, 2013; Qin et al., 2018), insular activity was lower in the death-related condition than in the neutral valence condition.

Two studies (Klackl et al., 2017; Quirin et al., 2012) found increased ACC activation in the death-related condition compared to the unpleasant condition: i.e., while both conditions led to increased ACC activation, ACC activation was higher in the death-related condition. Two others (Han et al., 2010; Qin et al., 2018) found that only unpleasant stimuli elicited increased activation in this area. One study (Klackl et al., 2017) found that the posterior cingulate cortex (PCC) was more active in the death-related condition compared to the unpleasant condition, while two others (Han et al., 2010; Klackl et al., 2014) observed similar activation in the PCC in the death-related and unpleasant conditions. One study (Yanagisawa et al., 2016) found that death-related stimuli induced activity in the right VLPFC.

3.2. Study details

Han et al. (2010) investigated neural activation underlying the processing of death-related words. Three categories of words with 60 words in each category – death-related, unpleasant, and neutral – were validated by an independent group of 46 subjects rating death relevance and negative emotional valence. Death-related stimuli ranked highest in both, followed by unpleasant words. Twenty females underwent fMRI scanning while presented with the words in a Stroop-task format, where they were to identify the color of the words by pressing one of two buttons. The order of stimuli was counterbalanced across subjects. Each word was shown for 400ms.

After the scan, participants rated the stimuli on their death relevance and negative emotions evoked, and they were asked to estimate their fear of death. The researchers conducted whole-brain analysis of the fMRI data and derived ROIs based on their observations. Relative to neutral-valenced words, death-related and unpleasant words elicited similar increases in activation in areas such as the lateral prefrontal cortex and PCC, which the researchers describe as important for emotion processing. Whereas the unpleasant condition only induced increases in activation (including areas such as the ACC), death-related words decreased activation in the bilateral insula and midcingulate cortex. The extent of decrease in left-insular activation correlated with death-relevance ratings, while the decrease in right-insular activation correlated with participants’ ratings of stimuli-evoked negative emotion.

Qin et al. (2018) replicated their previous all-female study (Han et al., 2010) with an all-male sample to investigate potential gender differences. Whole-brain analysis showed that both unpleasant and death-related words increased activation in the medial prefrontal cortex. Death-related words decreased activation in the ACC and bilateral insula compared to unpleasant and neutral words. ROI analysis showed no difference between males and females concerning changes in activity associated with death-related words. Among other things, this means that the findings regarding insular lateralization in females were replicated.

Shi and Han (2013) based their methodology on their earlier study

[2] PICO, standing for **p**atient/**p**opulation, **i**ntervention, **c**omparison/**c**ontrol, **o**utcome, is a standard framework for structuring clinical questions in health-care contexts.

[3] “Activated” we use as a shorthand for “increase in activation” and “deactivated” as a shorthand for “decrease in activation”.

[4] ROI-based analysis averages signals in the voxels of a predefined area, which increases the signal-to-noise ratio but discards potentially relevant information (see, e.g., Korhonen et al., 2017).

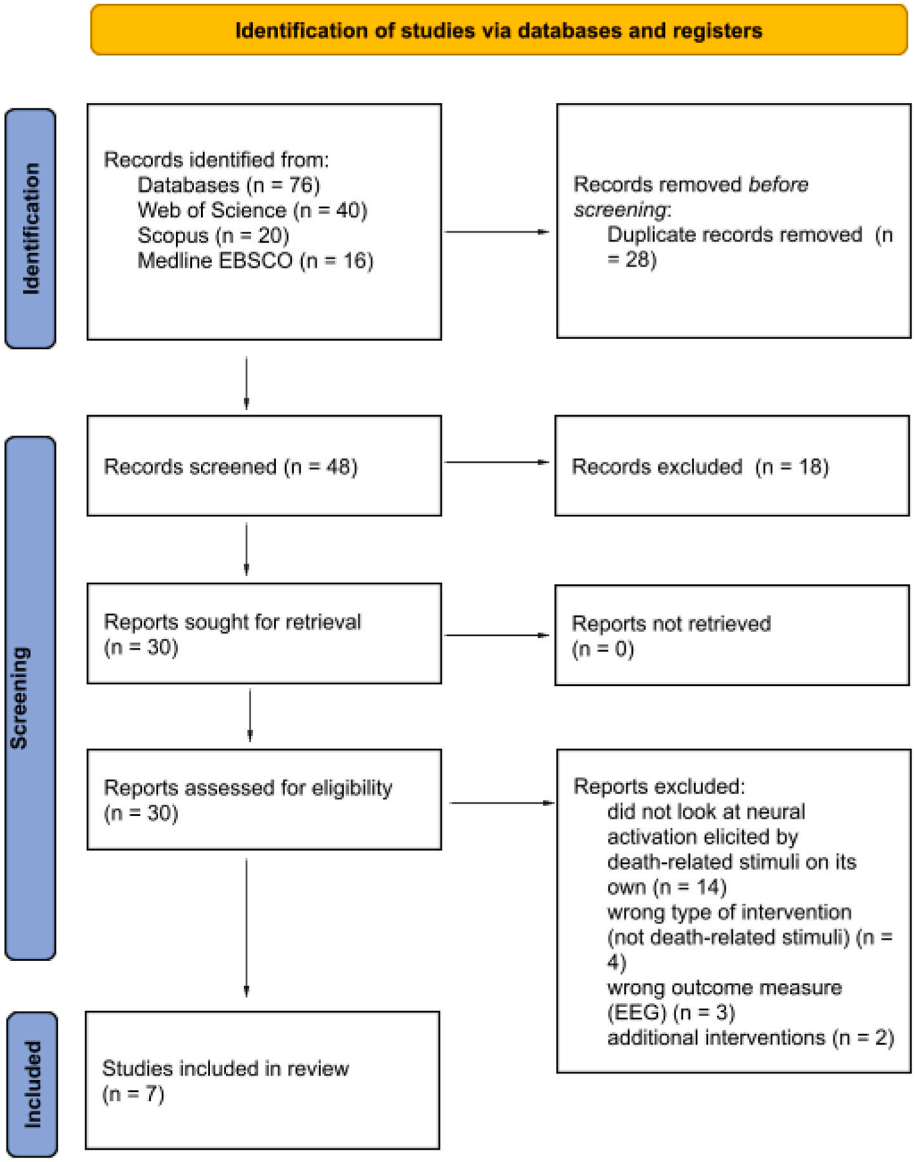

Fig. 1. PRISMA (Haddaway et al., 2022) flow diagram of the study selection process.

(Han et al., 2010) while seeking to discriminate between transient and sustained neural responses to death-related words. Twenty-four participants underwent fMRI scanning while presented with 300 words from five categories over three sessions. Each session contained a category pair: death-related vs. neutral words, life-related vs. life-unrelated words, or unpleasant vs. neutral words (validated in Han et al., 2010, with the new categories validated by an independent group of 24 judges). In these sessions, participants were to judge the stimuli according to different measures, depending on the category pair: death relevance, life relevance, and valence respectively.

Analysis of brain activation during participants' death relevance ratings revealed highly intercorrelated transient activity in left frontoparietal areas including the medial prefrontal cortex for death-related relative to death-unrelated words. These areas were averaged into a composite ROI for further analysis. Death-relevance judgment sessions, relative to life-relevance and valence judgment sessions, showed decreased activity in the bilateral insula and subcortical regions. The researchers found that sustained decrease in activity in the different insular regions was highly intercorrelated and again combined the results into a composite ROI for analysis. Investigating correlations between these two ROIs (frontoparietal and insular) by means of moderator analysis (examining whether a link between two variables is affected by a third variable), the researchers found that the transient increase modulated the sustained decrease.

Klackl et al. (2014) investigated whether earlier findings on death-related stimuli processing (Han et al., 2012; Quirin et al., 2012; Shi and Han, 2013) could be replicated and what role, if any, self-esteem plays in neural responses to such stimuli. The researchers used three categories of similar sentences – death-related, unpleasant, and neutral – validated in a pretest by an independent group of 19 participants. Analysis of pretest ratings showed that death-related and unpleasant sentences did not differ in arousal or negative valence.

While undergoing fMRI scanning, 30 participants read and rated how much they were aroused by each sentence. Using whole-brain analysis, the researchers found that death-related and unpleasant stimuli elicited similar activation in areas including the left prefrontal cortex. Comparing the two in a direct contrast analysis, unpleasant sentences induced increased activation in areas including the left posterior insula, whereas death-related sentences only induced decreased activation. Using ROI-based analysis based on coordinates from the three previous studies, the researchers could not replicate Quirin et al.'s (2012) findings but did find insular deactivation in the death-related relative to

Table 1
Summary of results.

Reference (country)	Total (males)	Study design	Mean age in years (SD)	Death-related stimuli (example (s))	Unpleasant stimuli (example (s))	Other condition (example(s))	Main findings on death-related stimuli (compared to unpleasant)	Language of stimuli
Qin et al., (2018) (China)	(20)	within-group	22 (1.84)	same as Han et al., (2010)	same as Han et al., (2010)	same as Han et al., (2010)	↑ left frontal cortex ↓ bilateral insula, ACC	Chinese
Klackl et al., (2017) (Austria)	30 (10)	within-group	22.03 (2.71)	sentences ("thinking about the finitude of life frightens me")	sentences: uncontrollability ("I'm afraid of things I cannot control") and dental pain ("I'm scared of going to the dentist")	neutral sentences ("I sometimes find it hard to speak fluently and without errors") (condition discarded in analyses)	↑ ACC ↓ precuneus	German
Yanagisawa et al., (2016) (Japan)	60 (30)	between-group	21.6 (not reported)	words ("mourning", "grave", "funeral")	words ("evil", "suffer", "scary")	neutral words ("spell", "phrase", "word")	↑ VLPFC	Kanji
Klackl et al., (2014) (Austria)	30 (12)	within-group	21.80 (2.09)	sentences ("the worker had a fatal work accident")	sentences ("the worker received an instant dismissal")	neutral sentences ("'the worker received new work clothes")	↓ bilateral insula	German
Shi and Han (2013) (China)	24 (12)	within-group	22.54 (2.04)	words ("coffin", "dirge", "asphyxiate")	words ("corruption", "shame", "lie")	neutral words: ("river, "cup", "gather") life-related words: ("eagle", "lotus") life-unrelated words: ("shoe", "shirt")	↓ bilateral insula	Chinese
Quirin et al., (2012) (Germany)	(20)	within-group	23.7 (2.97)	sentences (''I am afraid of a painful death'')	sentences ("I am getting panicked when I am sitting in the dentist's waiting room")	none	↑ right amygdala, left rostral ACC, tail of right CN	German
Han et al., (2010) (China)	20	within-group	21.8 (2.28)	words ("graveyard", "cremate", "corpse")	words ("corruption", "slander", "humiliate")	neutral words ("air", "bus", "wash)	↓ bilateral insula, mid-cingulate cortex	Chinese

Note. SD = standard deviation, ROI = region of interest, ACC = anterior cingulate cortex, VLPFC = ventrolateral prefrontal cortex, CN = caudate nucleus.

unpleasant condition, as observed by Han et al. (2010) and Shi and Han (2013). Insular activity increased in the unpleasant condition but did not differ between the death-related and neutral conditions.

Quirin et al. (2012) examined the involvement of ACC, amygdala, and caudate nucleus in processing statements relating to one's own death. While undergoing fMRI scanning, twenty male participants responded to 21 items on a fear-of-death scale, as well as 21 statements relating to fear of dental pain. Participants were instructed to press a key (left or right counterbalanced across subjects) to answer "yes" or "no", depending on whether they felt the statements applied to them. Each sentence was presented and responded to during 9s trials arranged in four mortality blocks (three, four, five, and nine trials) and four dental pain blocks (three, five, five, and eight trials) presented in pseudo-randomized order. The proportion of participants who agreed with the statements did not differ between the death and dental-pain statements. In line with their hypothesis, death-related statements elicited greater activation in the right amygdala and left rostral ACC, as well as around the tail of the right caudate nucleus.

Klackl et al. (2017) hypothesized that the behavioral inhibition system responds to sentences relating to existential threat, including mortality. Fifteen sentences from each of four categories – mortality, uncontrollability, dental pain, and neutral – were tested on arousal, emotional valence, and death relevance in separate pretest surveys with 10, 12, and 10 participants respectively. While undergoing fMRI scanning, 30 participants chose whether they agreed or disagreed with each statement using a response pad. Each sentence was presented visually for 3s. The neutral condition was excluded from analysis as the stimuli were rated relatively positive and high in arousal in the pretest surveys, such that they did not meet the researchers' criteria for a control condition. The dental-pain condition was used as a reference to investigate neural activation related to uncontrollability and mortality, both of which the researchers interpreted as posing existential threats, based on their background research.

The researchers found that mortality-related statements resulted in greater activation than uncontrollability statements in areas including the PCC. Compared to dental pain, uncontrollability and mortality led to increased activation in areas such as the dorsal ACC (dACC). However, for those participants who agreed with the dental-pain statements, dACC activation levels were not elevated. Mortality was associated with more activation in areas such as the PCC, uncontrollability with more activation in the right insula.

Yanagisawa et al. (2016) investigated the impact of self-esteem on brain activity in response to death-related and unpleasant stimuli. Three categories of stimuli – death-related, unpleasant, and neutral – with eight words each were used, validated by an independent group rating death relevance, emotional valence, and arousal. Death relevance was greatest for death-related words but also significantly higher for unpleasant than neutral words. Death-related and unpleasant words did not differ significantly in emotional valence or arousal.

Sixty participants were divided into two groups: one presented with death-related and neutral stimuli, the other with unpleasant and neutral stimuli. Participants performed word-relationship tasks while undergoing fMRI scanning.

Comparing fMRI data between groups, the researchers found increased activation in the right VLPFC for the death-related stimuli group. The unpleasant-stimuli group showed no changes in activation elicited by the unpleasant compared to neutral stimuli. Higher self-esteem in the death-related stimuli group was associated with decreased left amygdala activity and further increased VLPFC activity, in response to death-related stimuli.

4. Discussion

This systematic review examined the brain areas that respond to death-related stimuli compared to unpleasant stimuli, and how they do so. No currently proposed model seems up to the task. While Tritt et al.'s

(2012) model offers a potentially valuable alternative to TMT, it will not be the central focus of discussion, nor will we attempt a comprehensive evaluation. We will, however, look at two of its core claims: 1) death is processed like other uncertainty threats (i.e., death-related stimuli do not elicit distinct responses), and 2) death and other uncertain threats trigger activation in both the ACC and DLPFC.

4.1. Findings concerning the ACC and prefrontal cortex

Our findings on the ACC were, at best, inconsistent, perhaps driven in part by the variation in stimuli and methodology. Only two studies (Klackl et al., 2017; Quirin et al., 2012) reported that the mortality condition, compared to the unpleasant-stimuli condition, led to increased ACC activation. Both studies raise significant issues, and their results should be approached with caution.

Klackl et al. (2017) found that participants who disagreed with the dental-pain statements (e.g., "I'm scared of going to the dentist") showed relatively increased ACC activation under the existential-threat conditions (uncontrollability and mortality). The researchers sought to use the unpleasant condition (dental pain) as a general threat-control condition to compare with the existential-threat conditions. The neutral control condition was discarded for being too high in arousal and too positive in valence; it cannot be ensured that ACC activation among those participants who disagreed with the dental-pain statements was any different from that elicited by neutral stimuli. Nothing suggests that the participants who disagreed with the dental-pain statements perceived these statements as unpleasant. For participants who reported perceiving the dental-pain statements as threat related, ACC activation was comparable in the three conditions. The researchers' claim that increased ACC activation for the existential-threat conditions represents a unique marker for existential threat – rather than a marker for anything threat-related – seems to lack adequate support.

Quirin et al. (2012) also found ACC activation in the mortality condition, but their findings are again problematic. The researchers conducted no pretest validation of the dental-pain statements, and they did not have participants report any distress. This is important, because the point of the unpleasant stimuli was to elicit negative affect comparable to the death-related stimuli. The researchers argue that the lack of significant difference in proportion of "agree" responses to statements in the two categories implies that participants did not experience any difference in affect between the two conditions. This is surely insufficient, as both precise nature and magnitude of affect might well differ. The researchers claim that previous findings suggest no significant affective difference between fear of death and fear of dental pain, but this could simply be indicative of inadequate measures of affect. Finally, Klackl et al. (2014) were not able to replicate these findings despite explicitly attempting to do so, while they were able to replicate findings from two other studies (Han et al., 2010; Shi and Han, 2013).

One study (Yanagisawa et al., 2016) found increased activation in parts of the VLPFC in response to death-related stimuli. The researchers found no significant differences in brain activation between unpleasant and neutral conditions, despite their pretest showing that unpleasant words were rated significantly higher in death relevance than neutral words. Yanagisawa et al. describe this as a limitation of their study. Notably, the study used only eight words, compared to the set of 60 in the other studies that used words instead of statements. The repetitive structure of the experiment may have led to habituation to the unpleasant stimuli, while the death-related words may have triggered an emotion-regulation process that was not death-specific. At least half the words seem imbued with significance beyond a mere mortality reminder, conjuring something arguably more reminiscent of grief than mortality as such: "mourning", "funeral", "death anniversary", and "news of death" (Yanagisawa et al., 2016, p. 283).[5] Another factor that hampers comparison between unpleasant and death-related conditions is the researchers' use of a between-group design, which is not standard practice in fMRI studies given the great variability across individuals in multiple factors that affect fMRI data (see, e.g., Samanez-Larkin and D'Esposito, 2008).

Our findings do not point toward activation/deactivation in *any* part of the prefrontal cortex being a marker of death-related information processing. Three studies (Han et al., 2010; Klackl et al., 2014; Qin et al., 2018) found significantly increased activation somewhere in this area compared to the neutral condition, but under both death-related and unpleasant conditions. As all three articles explain, this finding is consistent with the understanding that this area is central to emotion regulation (particularly, of course, the VLPFC and orbitofrontal cortex).

4.2. Findings concerning the insula

Our findings suggest that the marker of death-related stimuli processing relative to other stimuli is insular deactivation. Unpleasant stimuli consistently elicited increased insular activation, while death-related stimuli did not (Han et al., 2010; Klackl et al., 2014, 2017; Shi and Han, 2013; Qin et al., 2018). That increased activation is consistent with other studies (e.g., Caria et al., 2010) that have observed a positive correlation between insular activation and ratings of negative valence. Death-related stimuli were generally rated as negative as the unpleasant stimuli in the studies reviewed here, so one would expect a comparable increase in insular activity, yet this was not observed. Even if valence could, conceivably, explain part of the insular deactivation observed, it cannot explain all of that effect. While there is evidence that insular activity increases when individuals are reminded of the loss of a relative (Bryant et al., 2021; Michel et al., 2024), that may have more to do with the unpleasantness of the loss than the connection to death.

The only study with a neutral control condition in which death-related and unpleasant stimuli were matched for negative valence – Klackl et al. (2014) – found no significant difference in insular activation between the death-related and neutral conditions, but *did* observe a relative decrease in insular activity for death-related compared to unpleasant stimuli. This finding is important in light of Han et al. (2010), who interpreted reduced insular activation in response to death-related stimuli as evidence of *inhibition*, partly because they observed a decrease relative to neutral stimuli. Klackl et al. challenge that interpretation by showing that insular activity in the death-related condition does not fall below baseline (neutral). If those findings are reproducible, it is possible that inhibition of the insula is not what marks death-related information processing; rather, lack of insular activation may be indicative of processes that, while responding to (other) unpleasant information, for some reason do *not* respond to death-related information.

Tritt et al. (2012) propose that death poses a threat similar to other psychological threats in that there is an element of uncertainty, such that the behavioral inhibition system might step in to inhibit action in favor of further information gathering. The researchers do not mention the insula, and an uncertainty-based account would not seem to explain the present findings on insular activation. Studies have consistently indicated that, as with generally unpleasant stimuli, uncertainty elicits not decreased but *increased* insular activation (for a meta-analysis, see Feng et al., 2022; also see, e.g., Motzkin et al., 2014; Sarinopoulos et al., 2010). The one study in our systematic review that included an uncontrollability condition (Klackl et al., 2017) observed increased insular activation under this condition.

Perini et al. 's (2018) study of a different kind of psychological threat – social pain – found that insular activity increased when social judgment was perceived to be aimed at oneself, regardless of whether the

[5] Michel et al. (2024) found that increases in VLPFC and DLPFC activation accompanied reminders of the death of a close relative.

judgment was negative or positive. Similarly, stimuli relating to social disgust and socially disapproved behaviour lead to increased insular activity, particularly in posterior areas (Borg et al., 2013; Vicario et al., 2017). Alvarez et al. (2015) found that individuals prone to anxiety exhibit heightened activation in the insula when anticipating unpredictable threats, probably driven by a reduced sense of control. Like uncontrollability, social pain/social judgment entails – in many if not most cases – a high degree of uncertainty. (Is the judgment deserved? How should I respond? Is it okay to feel what I am feeling?)

It seems that insular deactivation in response to death-related stimuli cannot be explained by negative valence, uncertainty, or classification as a psychological threat; our findings suggest that it is, in fact, a distinctive marker of response to death-related stimuli. Given the insula's role in sense of self and the way that death seems to necessitate a loss of self,[6] such a conclusion makes sense.

TMT proponents would likely explain insular deactivation in terms of a conflict between death-related stimuli and commitment to one's sense of a persistent "I". In line with TMT, Quirin et al. (2019) propose that insular deactivation indicates suppression of self-referential processing as a coping mechanism. As noted in the introduction, TMT faces significant challenges including how an explanation relying solely on suppression of self accounts for the lack of observation of deactivation in other areas central to self-related processing, including parts of the prefrontal cortex (see Northoff et al., 2006, for a meta-analysis) and midline regions in the midbrain and brainstem (see Heatherton, 2011's review).

Research suggests that, besides its role in sense of self, the insula has an important role in assessing potential threats; but the mechanism underlying its role is unknown (see Fiddick, 2011, for a review). The insula has been found to activate when imagining oneself and others in pain (see, e.g., Jackson et al., 2005). It has been claimed to play a key role in the proposed (albeit controversial) mirror-neuron system, the idea being that the neurons activate as if one is experiencing or acting oneself when observing these same actions and experiences in others (see Rizzolatti et al., 2009, for a review). Singer et al. (2009) suggest that the insula has an important predictive function, helping individuals anticipate and prepare for how emotional experiences and bodily sensations will feel. All these possible roles complicate interpretation of the insula's lack of activation in response to death-related stimuli.

Medford (2012) reports that individuals with depersonalization disorder exhibit an underactive insula in response to negatively valenced stimuli – an underactivation that suggests disruption in processes for generating subjective states and maintaining a coherent sense of self. It seems that insular activation is central to understanding not just how something would feel, but how it would feel *to me*.

Perceiving or simulating threats to self and avoiding them is a fundamental, evolutionarily important survival skill. At the same time, evolution has no interest in the survival of any given individual (beyond living long enough to reproduce), only of the genome that marks the species. If threat-related information is processed in the insula through self-related simulation and prediction, it could make sense that it deactivates in response to mortality cues, at least in individuals for whom death means an inevitable end to their existence. The deactivation would not indicate an evolutionary function – it is far from clear what purpose deactivation would serve in evolutionary terms – but simply the insula's inability to process death.

Insofar as death-related cognition is marked by fear and a sense of potential immediacy (as opposed to abstract future possibility), it remains possible, in line with TMT, that the insular deactivation we have observed marks the evolution of an advanced defense mechanism already observed in simpler form among other mammals for whom acute threats to life result in tonic immobility. That evolutionarily older defence offers selective advantage, because predators often disengage if their prey appears dead. The idea would be that, in the human as in the simpler mammalian case, depersonalization (associated with tonic immobility) means that the self is detached from the mortally dangerous situation. This is, of course, necessarily speculative. Nevertheless, Cantor (2009) offers a possible explanation for post-traumatic stress disorder that follows similar lines, and it might be used as a model.

Nichols (2007) among many others argues that there is an immovable obstacle preventing human beings from imagining non-existence: it is logically impossible to do so; there is nothing for non-existence to be like, no experience to understand. He sees belief in immortality as a natural consequence: humans cannot imagine non-existence and are therefore prone to believe it will not happen.[7] As Tolstoy notes, one might have a strong feeling that the "I" cannot cease to exist, even if one is convinced that all humans do.

A final note of caution concerning our results: the unpleasant stimuli in the included studies often related to socially disapproved actions – ones that trigger widespread social condemnation while fostering guilt or shame in the individual responsible for them – while the death-related stimuli generally did not describe actions at all, never mind socially disapproved ones; the death-related stimuli did not relate in any way to morality. This might explain some amount of the lack of insular activation in response to the death-related stimuli. However, we take it as highly unlikely that it can explain all of the difference in activation.

4.3. Limitations

Among the limitations to this review is the naming of specific brain areas in the search string. This was done to enable a more thorough evaluation of the areas that, based on initial research, seemed central. The downside of this decision is that it is impossible to draw conclusions about the involvement of other areas.

A major limitation to the generalizability of the present findings is that all studies had samples with relatively low mean ages; the overall mean was 22 years, with a small standard deviation. Considering the impact of age on brain activity (see Spreng et al., 2010, for a meta-analysis) and the relatively late development of the prefrontal cortex (see Kolk and Rakic, 2021, for a review), conclusions risk being limited to young people, particularly where those conclusions relate in some way to the prefrontal cortex. It is further possible – indeed, likely – that people in their early 20s have different concerns, different fears, and different attitudes toward death compared to younger or older age groups.

Event-related potential (ERP) findings point to age-related differences in the processing of death-related stimuli. While younger adults exhibit larger late positive potential (LPP) amplitudes[8] in response to death-related words compared to equally negatively valenced non-death-related words (Klackl et al., 2013),[9] older adults show the opposite pattern (Bluntschli et al., 2015).

Another limitation concerns the use by all studies of either individual words or complete sentences as stimuli: a standard procedure for

[6] … Or at least a severe disruption/alteration to that self: e.g., Hofstadter (2007) argues for a substantive continuation of self through the memories one leaves behind and the behavioural impressions one imprints onto those who are nearest. Whatever self that constitutes though, it is not the self that went before.

[7] In opposition to this, one can observe that belief in immortality or the existence of an afterlife of any kind is far from universal among world religions, which one might expect that it should be if belief in immortality *just is* a natural consequence of the inability to imagine non-existence. Even those religions that allow immortality as a possibility do not always place any emphasis on it; Judaism historically has not.

[8] … An ERP component thought to reflect attention allocation to stimuli based on their emotionality (Hajcak et al., 2010).

[9] Findings in other ERP components corroborate that younger adults show heightened emotional response to death relative to fear-related words (Huang et al., 2021).

neuroimaging studies in this area. This is done to enable more reliable between-study comparison but, at the same time, can be seen to limit generalizability. The words/phrases used differ greatly in emotional intensity, length, and language of presentation, which might explain some of the inconsistencies observed between studies. Future research should explore cultural variability in death-related processing by using languages appropriate to each culture and taking as interdisciplinary an approach as possible (see, e.g., Luo et al., 2024).

Narrowing the criteria to include only studies using words or only those using sentences would have resulted in an unworkably small set. Restricting stimuli to a standardized set matched on key features – valence, arousal, frequency, category (social vs. non-social), concreteness/abstractness and imageability – simply wasn't a possibility, as no such standardized stimuli set exists.[10]

On the other hand, these differences make the consistency of results on insular (de-)activation all the more striking. Indeed, they significantly strengthen that finding, through converging evidence and generalization across the variation in stimuli. Future research should examine whether the findings reported here are reproducible with other kinds of stimuli: non-linguistic auditory cues (e.g., the sound of a heart monitor when the heart has stopped), tactile cues, or smells. (Death has, obviously, a very distinct smell; but the smell of death also varies between species.)

For all its relatively small size (contributing to the lack of emphasis on it historically), the insula is far from homogeneous; it is a complex lobe with functionally distinct subregions (see Craig, 2009, for a review). Taking the subregions into account was beyond the scope of this review and probably would not be possible anyway within the current literature on death-related stimuli. Future research should explore how the subregions' distinct roles lend nuance to the present findings or cause them to be reinterpreted.

Finally, future research should do much more to investigate individual psychological and physiological differences in responding to death-related information. Psychological differences could include differences in personality along with philosophical or religious beliefs and formative experiences. What makes people different is just as important as what they have in common; too much attention to the latter, as often happens in neuroscience research involving use of fMRI, comes at the expense of too little attention to the former.

Understanding the neural processing of death-related information has major societal implications for mental-health interventions, public-health messaging, open societal conversations around death, and end-of-life care. To prevent or, at least, alleviate death anxiety, it is necessary to understand how human beings deal with mortality, in all their diverse ways: many useful but some to varying degrees dysfunctional. Particular care should be taken with those most exposed to death, including front-line soldiers, end-of-life patients along with their families, and health-care workers.

5. Conclusion

This systematic review is the first to investigate whether there is something distinctive about how the brain processes death-related compared to unpleasant stimuli. In this way, it makes a distinctive contribution to the budding field of existential neuroscience. Five out of six within-group studies found death-related stimuli processing to be marked by insular deactivation. The presence of a neural signature for this processing is all the more striking given the diversity of ways in which people reflect upon and respond to death. Existing explanatory models either fail to integrate the present findings with broader research on insula function or rely on theories that lack evolutionary plausibility. Based on our findings, we propose that the insula's role in threat assessment depends on its capacity to simulate experiences and predict how they will feel to the individual. As non-existence is by definition non-experiential and so logically impossible to imagine, death might evade the insula's usual processing mechanisms.

CRediT authorship contribution statement

Anna Bengtson: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Conceptualization. **Ida Nordin:** Writing – review & editing, Writing – original draft, Investigation. **Joel Parthemore:** Writing – review & editing, Supervision, Conceptualization. **Antti Revonsuo:** Writing – review & editing, Supervision.

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The authors have no conflict of interest to declare.

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Data availability

Review did not generate new data.

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[10] Even if a standardized set might improve generalizability and reproducibility of results, it would create problems as well, including ecological validity.

[11] The studies included in this systematic review are marked with asterisks.

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