The brain with death in mind: A quantitative meta-analysis of the neural substrates underpinning mortality salience

By

Ishan Charith Walpola

A THESIS
SUBMITTED TO THE FACULTY OF MEDICINE
DEPARTMENT OF PSYCHIATRY
MCGILL UNIVERSITY, MONTREAL
NOVEMBER 2015
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE
DEGREE OF MASTER OF SCIENCE

The brain with death in mind: A quantitative meta-analysis of the neural substrates underpinning mortality salience

Ishan Walpola

Master of Science

Department of Psychiatry

McGill Unviersity

2015

Abstract

Existentialism offers a perspectival stance that reorients the inquiry of any discipline, be it philosophy, psychology, or neuroscience, from the abstract and theoretical to the direct and immediate concerns most central and proximal to human beings. Unique among these concerns is the inevitability of one's own death, which is always a pressing possibility that threatens to eliminate the all other possibilities for one's life. In the present manuscript, we conducted an Activation Likelihood Estimation (ALE) meta-analysis of the functional neuroimaging literature investigating the processing of linguistic stimuli relevant to death (i.e., mortality salience). Several of these studies have taken the name "Existential Neuroscience". We hoped that ALE analysis would offer a means to mediate the ongoing debate over whether mortality salience was a unique threat in the sense of involving a unique neurobiological signature. We supplemented ALE with seed-based intrinsic connectivity network analysis and computation of posterior probability of psychological functions associated with the peak coordinates of significant

ALE clusters. Our results suggest that deactivation of the bilateral posterior insula is an important signature of existential threat over and above other kinds of threat (e.g., negative affect). Furthermore, these brain regions are members of the brain's salience network and are associated with a collection of psychological processes that fall under the rubric of interoceptive processing. We propose that an existential neuroscience does not reduce existential concerns to mere variations in neural activity, but could harness insights garnered through neuroscience in order to improve our understanding of the embodied mechanisms underlying existential threat and investigate candidate interventions to protect against the harmful consequences of existential terror.

Résumé

L'existentialisme offre une perspective qui réoriente la recherche de toute discipline, que ce soit la philosophie, la psychologie, ou les neurosciences, de l'abstrait et du théorique, vers les préoccupations directes et immédiates les plus centrales et proximales aux êtres humains. Parmi ces préoccupations, l'inéluctabilité de sa propre mort est particulièrement unique, car elle représente toujours une possibilité pressante qui menace d'éliminer les toutes les autres possibilités de sa propre vie. Dans ce présent manuscrit, nous avons mené à partir de l'« Estimation de Probabilité d'Activation » (en anglais Activation Likelihood Estimation, ALE) une méta-analyse de la littérature de la neuro-imagerie fonctionnelle enquêtant sur le traitement des stimuli linguistiques pertinents à la mort (saillance de la mortalité). Plusieurs de ces études ont pris le nom de << Neuroscience existentielle>>. Nous espérions que l'analyse ALE apporterait des éléments au débat en cours pour déterminer si la saillance de la mortalité est une menace unique, dans le sens

où elle implique une signature neurobiologique unique. Nous avons complété l'ALE par une analyse intrinsèque de réseaux de connectivité fonctionnelle avec souche, ainsi que par le calcul de la probabilité postérieure des fonctions psychologiques associées aux coordonnées cardinales des groupes significatifs d'ALE. Nos résultats suggèrent que la désactivation de l'insula postérieure bilatérale est la signature importante de la menace existentielle bien au delà d'autres types de menace (par exemple, l'affect négatif). En outre, ces régions du cerveau font partie du réseau de saillance du cerveau et sont associés à un ensemble de processus psychologiques qui entrent dans la catégorie du traitement intéroceptif. Nous proposons qu'une neuroscience existentielle ne réduit pas les préoccupations existentielles à de simples variations de l'activité neuronale, mais permettrait d'exploiter des connaissances acquises par la neuroscience afin d'améliorer notre compréhension des mécanismes incorporés sous-jacents à la menace existentielle, et d'enquêter sur les interventions de candidats pour se protéger contre les conséquences néfastes de la terreur existentielle.

Contribution of Authors

Ishan Walpola conducted all analyses included herein, wrote and prepared the manuscript in Chapter 2 under the joint supervision of Dr. Vasavan Nair and Dr. Pedro Rosa-Neto.

Acknowledgements

I am deeply grateful to my primary advisor, Dr. Vasavan Nair, upon whose advice I first decided to explore existentialism as a philosophical complement to a neuroscience interested in understanding human experience. His unwavering support and guidance has allowed me to learn many new methods without losing sight of the “bigger questions”. I look forward to investigating the impact of meditation and yoga on the healthy and pathological aging process together.

It is thanks to my co-supervisor, Dr. Pedro Rosa-Neto, that any of this was possible at all. He first introduced me to Dr. Vasavan Nair upon recognizing my unconventional neuroscientific interests, such as meditation and the deeper questions of human experience. His methodological acumen and excitement by a diversity of questions has proved both instructional and inspirational. Again, I look forward to future work together.

I am grateful beyond measure to my dear friend Tara Campbell, who has read and provided invaluable feedback on this thesis and much of my other scientific work.

Thank you to my family: Devni, Indira, and Piyal Walpola, who support me in all that I do.

Finally, with gratitude to Dr. Oliver Sacks whose writing taught me to never lose sight of the human being for the human brain. In the words of W. H. Auden that came to you when your own death was in mind, “Let your last thinks all be thanks.”

Table of Contents

List of Tables

List of Figures

Chapter 1

“To be honest, I really don’t give a damn about the brain. I care about the human soul. However, I happen to believe that the soul is in the mind, and that the mind is a functional process instantiated by the brain with its interactions with the body and the environment. Hence, I study the human brain.” – Marco Iacoboni

1 Background

Inspired by the writings of cultural anthropologist Ernest Becker, specifically his 1973 book *The Denial of Death*, Terror Management Theory (TMT) emerged as an attempt to explain the uniquely human drive to secure meaning and self-esteem that appears to arise, at least in part, from an equally unique awareness of our impending mortality (Greenberg, Pyszczynski, & Solomon, 1986). TMT traditionally manipulates mortality salience by priming participants with the idea of death compared to a control topic (e.g., dental pain or negative affect), either by writing or reading about these topics, before investigating the impact of a mortality salience process that is proposed to operate outside or beneath conscious awareness on behaviour. Mortality salience is believed to trigger “death defenses”, such as strengthening cultural worldviews or fleeing the physical body, in order to attenuate the existential terror that results from encountering reminders of one’s own demise.

1.1 Terror management theory

In almost three decades since the proposal of TMT, an expansive social psychology literature has proliferated that explores core tenants of TMT and their implications for human behaviour. TMT takes the drive for self-preservation, conserved across all animal species, as a fundamental assumption. However, humans are identified as unique among animals due to an awareness of both their physical vulnerability and the inevitability of their own death. In order to manage the terror and anxiety that results, TMT suggests that humans turn to culture in order to secure a symbolic immortality that is not afforded by more temporary solutions such as seeking to improve health and longevity. Typically, then, TMT holds that for culture to provide a buffer against existential terror or anxiety, individuals must: 1) have faith in a cultural worldview, and 2) believe they meet the ideals of espoused cultural worldviews (self-esteem). By achieving a confident sense of identification with a culture that will presumably outlive their mortal embodiment, an individual's existential terror is expected to resolve, at least temporarily. However, reminders of one's own mortality, both subtle and ostensible, are frequently encountered in the dynamic landscape that human beings traverse. As such, terror management by means of cultural worldview defense and self-esteem striving are processes that must constantly be enacted. Further, as cultural worldviews must be interpersonally established, validated, and reinforced to provide relief from existential concerns, it follows that one would not take kindly–and indeed potentially react aggressively–to others who violate or dispute the validity of (and thereby undermine the existentially relief offered by) one's espoused worldviews. As such, the majority of TMT research has focused on worldview defense (e.g., increased identification with worldviews or increased antagonism towards others with conflicting worldviews) as a dependent variable. When confronted with the physical body's vulnerability to inevitable death and decay, TMT has also observed a tendency for individuals to flee identification with the body and even pleasurable corporeal sensations (Goldenberg, Pyszczynski, Greenberg, & Solomon, 2000). Taken together, these findings suggest that investment in a cultural system that outlives the dying physical body may serve to buffer or manage existential terror–but with potentially negative consequences to the wellbeing of oneself and relationships with certain others.

Presented at the level of conscious awareness, concerns about death engage rationalizing strategies and attempts to suppress thoughts about death that have been termed *proximal defenses* (Pyszczynski, Greenberg, & Solomon, 1999). Implicit presentation or priming of death awareness, as well as a period of temporal distance or distraction following explicit presentation, engages *distal defenses* such as worldview defense, self-esteem striving, or fleeing the body (Pyszczynski, Greenberg, & Solomon, 1999). Rigorous empirical investigation of *distal defenses* constitutes the greater proportion of TMT's contribution to the understanding of existential threat, and is generally induced by manipulation of mortality's salience.

1.1.1 Mortality salience

TMT compares the psychological and behavioural consequences of mortality's salience by comparing the impact of first priming participants with the idea of either death or a control topic (e.g., pain or negative affect) before they engage in an experimental task of interest. A recent large-scale meta-analysis including 164 articles containing 277 experiments reported moderate effects of mortality salience ($r = .35$) on dependent variables pertaining to worldview defense and self-esteem striving (Burke, Martens, & Fucher, 2010). Another smaller meta-analysis (Jost, Glaser, Kriglanski, & Sulloway, 2003), comprised of 8 experiments focusing specifically on the dependent variable of political conservatism as a form of worldview defense, found that mortality salience induced changes in the dependent measures with a large effect size (r = .50). The larger meta-analysis found several factors that influenced differential strength of mortality salience effects between studies: duration of delay, control condition, and the dependent variable measured. Longer delays between the induction of mortality salience and experimental testing produces larger effect sizes, supporting TMT's claim that concerns about death exert more robust influences on distal defenses when there is more time provided for death concerns to fade from awareness and operate below the threshold of conscious awareness (i.e., unconsciously). Control conditions interestingly did not vary according to affective valence (e.g., neutral vs. negative control threat). If this had been the case, it would support the contention that death is merely a quantitatively different affective threat with magnitude of effect increasing according to affective valence from neutral, to negative-valence, to death-related threats. However, the results of the meta-analysis indicate that death may in fact be a qualitatively unique threat. Control conditions that most reduced the effect of mortality salience (i.e., produced effects more similar to mortality salience) on dependent variables were impactful meaning threats (suggesting the importance of meaning threat over valence threat). Finally, the dependent variable showed differences in effect size with greater effects observed for the impact of mortality salience on attitudes toward other people than on other attitudes or an individual's own affect. The limited impact of mortality salience on conscious reports of an individual’s affect has perpetuated an “affect-free” claim that has recently been called into question (Lambert et al., 2014). This claim serves as major support for the identification of mortality salience as a unique form of threat, and might need to be re-evaluated in light of evidence that fear, but not the correlated construct of anxiety, is elicited to a greater degree by mortality salience than control conditions; furthermore, anger is elicited to a lesser degree (Lambert et al., 2014). However, this study notably lacks information regarding whether or not a delay period was provided during the course of the experiment before dependent measures were collected. It might then be the case that heightened affect, specifically fear, is engaged as a proximal defense, but does not survive as a distal defense when experimental designs provide a sufficient period of delay between the induction of mortality salience and the measurement of dependent variables. It should also be noted that the mortality salience manipulation in the study questioning the “affect-free” claim involved explicit and conscious consideration of one’s own death, which might differ in the degree of affect elicited and available to subjective awareness when compared with manipulations that more implicitly or unconsciously introduce the specter of one’s own impending mortality (the latter form of manipulation is employed in the preponderance of mortality salience studies under the framework of TMT). Thus, mortality may become implicitly salient and induce behavioural effects without generating a demonstrably heightened, subjectively experienced, affect.

1.2 Existential neuroscience

The mirror neuron researcher Dr. Marco Iacoboni first identified the emergence of an "existential neuroscience" in 2007, describing what he called a "quiet revolution" that challenges the central dogmas of cognitive neuroscience (Iacoboni, 2007). Twenty-two years earlier, the neurologist and author Dr. Oliver Sacks had already called for an "existential neurology" in his 1984 book *A Leg to Stand On*–prompted by his own crisis of embodied identity following a close encounter with mortality and the illness which ensued (Sacks, 1984). An existential study of the human brain would endeavour to take concerns most pressing to the human conditions, i.e., old age, sickness and death, as the central focus of study, without conceptually excising the human subject from her social and cultural milieu. Thus, the existential perspective understands the brain not as a "meaning-giving", but "meaning-mediating" organ, dependent upon a body that exists in a world of shared social norms (Iacoboni, 2007; Fuchs, 2011). Despite the promise of an existential approach to understanding the function of the brain and the brain's contribution to our uniquely human existence, identified by proponents like Iacoboni and Sacks, attempts to develop rigorous empirical investigations from an existential perspective have been markedly few in number. Although Iacoboni borrows many ideas from the philosopher Martin Heidegger in his description of an existential approach to neuroscience, a core notion of Heidegger's existential philosophy–the encounter with the finitude of human existence and the inevitability of one's own death (Heidegger, 1962)–is entirely overlooked. Fortunately for the discipline of existential neuroscience, eleven studies published from 2009-2015 have explored this fundamental existential phenomenon, an encounter with death through reminders of one’s own mortality, building upon foundational work in TMT to explore the neuroscience of mortality salience.

1.2.1 The neuroscience of mortality salience

A neuroscience literature is emerging that manipulates mortality salience through means analogous to those established by the social psychology literature on Terror Management Theory (Ayars, Lifshin, & Greenberg, 2015). At present, the neuroscientific study of mortality salience consists of four electroencephalography (EEG) studies, three employing the methodology of event-related potentials (ERPs; Henry, Bartholow, & Arndt, 2009; Klackl, Jonas, & Kronbichler, 2012; Liu, Shi, Ma, Qin, & Han, 2013), one exploring slow wave modulation for nociceptive stimulation (Valentini, Koch, Nicolardi, & Aglioti, 2015) and seven functional magnetic resonance imaging (fMRI) studies (Table 1; Han, Qin, & Ma, 2010; Quirin et al., 2012; Graupman et al., 2013; Silveira et al., 2013; Klackl et al., 2013; Shi & Han, 2013; Luo et al., 2014). Of these studies, four have used the term “Existential neuroscience” in their title, highlighting both a commitment to an existential approach to neuroscience and the existential significance of death awareness, or mortality salience.

1.2.1.1 Evidence from electroencephalography

EEG provides a unique methodology to be able to noninvasively capture bioelectric signatures of neurocognitive processes with millisecond temporal resolution. Due to this feature, EEG is uniquely poised to interrogate temporal dynamics of postulated mortality salience processes operating both below (or prior) and at (or following) the threshold for conscious access to information (Del Cul, Baillet, Dehaene, 2007).

The first of these studies used EEG recordings time-locked to stimulus presentation and averaged over repeated trials in order to obtain ERPs associated with neurocognitive biases in person perception, specifically the P200/ N200 (believed to reflect early direction of selective attention) and P300 (believed to be reflect evaluative categorization) ERP components (Henry, Bartholow, & Arndt, 2009). The mortality salience induction involved writing about one's emotional response towards death and thoughts about the process of physical death. The control condition entailed writing about dental pain. A brief delay during which participants read an "innocuous passage" was then provided to allow thoughts about death and dental pain to fade into the periphery of conscious awareness. Stimuli consisted of faces with black or white skin tone, and the visual oddball task required identifying 'target' happy, angry, or morphed (part happy, part angry) faces amidst faces displaying a neutral expression. One finding that supports a qualitative (of kind) rather than quantitative (of degree) neurocognitive difference in person processing following mortality salience is the interaction of racial group x facial expression for the amplitude of both early ERP components of interest (P200 and N200). The authors suggest that participants primed by mortality salience believe threatening ingroup members are less likely to be encountered than threatening outgroup members (despite objective equivalence in proportion encountered during the experiment). Consistent with this interpretation, latency of the later component of interest (P300), which is expected to exhibit longer latencies for stereotype-violating targets, was longer for angry ingroup targets and shorter for happy ingroup targets. Interestingly, no neurocognitive indices of bias were found between manipulation conditions (mortality vs. dental pain) for outgroup members, suggesting mortality salience specifically impacted ingroup bias in a favorable direction by acting upon electrophysiological signatures of early attentional and later categorization processes.

Another study employed two tasks to investigate neurocognitive processing, via ERPs, associated with *proximal defenses* as opposed to the *distal defenses* probed by the former study (Klackl, Jonas, & Kronbichler, 2012). Specifically, this group investigated whether the late positive potential (LPP), an index of depth-of-processing, could differentiate between death-related, pleasant, unpleasant, and neutral words. Results of the first task indicated that death-related words elicited greater LPP amplitudes compared to neutral, pleasant and unpleasant words. The second task yielded greater amplitudes of death-related words as compared with unpleasant and neutral words, but similar results to positive words. One speculative interpretation provided by the authors for the latter finding rests on prior work demonstrating that reminders of death result in automatic and unconscious tuning to information of a positive affective nature (De Wall & Baumeister, 1997). The authors cautiously conclude that it would be premature to claim that LPP amplitude ‘directly’ reflects the *proximal defense* of death-thought suppression. Instead, they outline future studies to investigate *distal defenses* that are believed to be engaged when to a greater extent when death-thought suppression (a *proximal defense*) has pushed mortality salience below the threshold for conscious access to further support the tentative link between LPP and *distal defenses*.

Following their group's prior work with fMRI that will be detailed below, one study used ERPs to determine the time course of neural processing of death-related linguistic cues (Liu, Shi, Ma, Qin, & Han, 2013). Note: this study does not claim to investigate either *proximal defenses* or *distal defenses,* but agnostically examines neural processing that might underpin both of these phenomena. When comparing death-related to death-unrelated linguistic cues, a decreased N1 was observed that positively correlated with subjective reports of arousal and pessimism (though these two subjective measures were not inter-correlated), and a greater P1 was observed that might indicate attentional enhancements of visual extrastriate activity. An increased P2 was also observed that was expected due to the similarity between the comparison of death-related and neutral valence (death-unrelated) words and previous studies of emotional Stroop processing. Finally, the authors also found increased P3 amplitudes suggesting enhanced recruitment of evaluative processes to categorize death-related words even when the semantic meaning of words was irrelevant to the task at hand (this P3 effect was also found in a comparison between negative and neutral valence words–suggesting a general effect associated with aversive stimuli). Thus, in this study, the effects most specific to death-related linguistic cues were observed in earlier temporal windows of neurocognitive processing, supporting the claim that mortality salience might operate on both the brain and behavior though largely unconscious or pre-conscious means.

The most recent EEG study examined the influence of mortality salience, compared to reminders of failing an exam (“exam salience”), on slow wave (SW) ERPs and delta oscillations (the main frequency representation of slow waves) associated with affective and motivational processes (Valentini, Koch, Nicolardi, & Aglioti, 2015). The authors observed an increase in ratings of both nociceptive intensity and threat concomitant with enhanced SW ERPs, event-related delta synchronization (ERS; at contralateral frontopolar electrode), and event-related delta desynchronization (ERD; at scalp vertex). Enhanced SW negativity correlated with greater state anxiety and negative mood, as well as lower levels of self-esteem. Increased delta band ERS correlated with positive mood following mortality salience induction and greater levels of self-esteem. Taken together, the authors interpret their findings as indicating that mortality salience impacts perception of repeated and threatening painful stimuli, and that slow brain responses to these stimuli index the engagement of both *proximal* and *distal defenses*. The authors conclude that their findings reveal a robust impact of mortality salience on the processing of nociceptive, but not auditory, threats–suggesting sensory events inherently related to representation of the body may be tightly linked to the representation of death in the brain. This interpretation is consistent with the findings from fMRI studies demonstrating qualitatively unique deactivation during mortality salience processing in a brain region crucial to bodily processing–the insula–that will be described in further detail in the following section.

1.2.1.2 Evidence from functional magnetic resonance imaging

While EEG affords excellent temporal resolution, fMRI provides exemplary spatial precision, allowing for the attribution of functional neurocognitive processing to anatomical regions with a high degree of confidence. However, this comes at the compromise of temporal resolution, which fMRI captures on the order of seconds (compared to the millisecond resolution of EEG), limiting an understanding of more fine-grained neural dynamics. Nonetheless, it is the only truly noninvasive technique that allows for elucidating whole-brain functional anatomy or the neural substrates underpinning cognitive processing.

The first fMRI study of mortality salience employed a modified Stroop task in which participants were asked to name the colour of words that were either death-related, negative-valence, or neutral-valence words (Han, Qin, & Ma, 2010). The goal of the Stroop task was to identify the anatomical location of neural substrates supporting automatic semantic processes specifically associated with implicit processing of death-related information. The authors found that both death-related and negative-valence words activated directly overlapping regions such as the posterior cingulate cortex (PCC) and middle right middle frontal cortex as well as several adjacent regions (e.g., the medial prefrontal cortex and subgenual anterior cingulate cortex) in the frontal and parietal cortex, relative to neutral-valence words. The authors also found that significant deactivations were elicited only by death-related words. These deactivations were located at the bilateral insular cortex relative to neutral-valence words, and at the bilateral insular cortex and the mid-cingulate cortex relative to negative-valence words. Negative-valence words did not show any decreased activity compared with neutral-valence words. Taken together, these deactivations are evidence of distinct and specific effects of mortality salience upon neural activity. Thus, this study supports the proposition of a qualitatively distinct neurobiological mechanism involved in mortality salience, undermining the contention that death is merely quantitatively different from other threats (e.g., pain or negative affect) and should not therefore be biologically unique (Tritt, Inzlicht, & Harmon-Jones, 2012)–a contention speculatively derived from evolutionary theorizing rather than empirical observation. Furthermore, subjective valuations of death-relevance of each word correlated with left insula deactivation observed in the neutral-valence vs. death-relevance contrast; ratings of negative emotion for each word correlated with right insula deactivation and bilateral parietal cortex activation observed in the associated contrasts between death-relevant and neutral-valence words. No similar correlations were observed for negative-valence vs. neutral valence condition. On the basis of these fMRI results, the authors suggest unique neurocognitive mechanisms are engaged during the processing of death-related information, the core process involved in mortality salience. As a double dissociation was present between death-relevant and negative-valence words, the authors posit that the observed deactivations cannot be accounted for by enhanced arousal elicited by negative emotion alone. Instead, the authors speculatively interpret their findings, specifically the observation of decreased insular activity, as suggesting modulations of the sense of oneself as a sentient being on the basis of a review of insular function (Craig, 2009). The authors found mid-cingulate cortex deactivation unexpected, but a recent case study causally connecting the mid-cingulate to the “will to persevere” as well as characterizing its functional connectivity with the bilateral insular cortex, together comprising core nodes of the brain’s salience network (Parvizi, Rangarajan, Shirer, Desai, & Greicius, 2015), might parsimoniously explain this finding in terms of network-level deactivation of the salience network specific to mortality salience.

Another study investigated differential neural activity associated with explicit and conscious consideration of one’s death (mortality salience) compared to dental pain (a control condition) in a paradigm that was as faithful to TMT manipulations as possible while simultaneously modified to accommodate the constraints of fMRI experimentation (Quirin et al., 2012). Here, the authors found significantly greater activation in the right amygdala, left rostral anterior cingulate cortex, and tail of the right caudate nucleus extending to the dormedial thalamaic nucleus for the death-related vs. dental pain-related condition. No significant results were obtained for the reverse contrast. The authors interpret these findings as supporting the claim that mortality salience operates at an unconscious level of processing due to the involvement of limbic structures associated with unconscious processing in other studies. However, as neuroimaging occurred during the explicit and conscious consideration of death, this interpretation based solely upon reverse inference may be somewhat dubious. Accordingly, the authors acknowledge that future experiments employing alternative designs will be necessary to advance confidence in the interpretations for potential mechanistic accounts underlying the neural substrates that have demonstrated to be engaged in mortality salience relative to dental pain.

One study endeavored to characterize the neurobiological correlates of *distal defenses* in terms of cultural worldview defense following the presentation of mortality salience priming compared with meaning-threat primes, and neutral (meaning) primes. Images that were independently determined by pilot testing to positively depict a participant's culture were used to examine worldview affirmation. During prime conditions, a prime appeared for 200 milliseconds before the worldview affirmation or neutral image. During the non-prime condition, only the image was presented. Results specific to the impact of mortality salience on cultural worldview affirmation involved a contrast between the mortality salience prime and meaning threat prime condition, revealing greater activation in the left prefrontal cortex (middle and inferior frontal gyrus). This again supports the notion of specific neural mechanisms and substrates involved in mortality salience, but this time providing a neurobiological account of cultural worldview affirmation, a *distal defense*, and a core finding of TMT.

A recent study examined how mortality salience impacts neural correlates associated with the perception of potential mating partners (Silveira et al., 2013). Again, this serves as an investigation of *distal defenses.* Heterosexual male and female participants viewed opposite-sex faces and made either implicit (whether or not the participant would like to meet the presented person) or explicit (rating of attractiveness) judgments of attractiveness following either no prime or a mortality salience prime consisting of death-related linguistic cues. No differences in neural activity were found between the no prime and mortality salience prime conditions for explicit judgment of sexual preferences. However, significantly higher activation was found in the left insula and left prefrontal cortex in both men and women during implicit judgments of sexual preference following death-related priming compared to no priming. No significant "gender" effects were observed. The authors interpret this finding as indicating enhanced approach motivation following mortality salience, and corroborating previous demonstrations of lPFC activations following mortality salience priming (Graupmann et al., 2013). The observed insular activations are reconciled with other work demonstrating insular deactivation to death-related linguistic stimuli, interpreted as reflecting compromised interoceptive processing, by suggesting that the present results may represent the direction of uncomfortable bodily sensations into the culturally meaningful social tendency of potential mating partner determination. However, the results suggest that this transference mechanism operates implicitly, as explicit sexual partner preference produced no concomitant changes in neural activity following mortality salience priming compared to the no prime condition.

Using a hybrid design that allowed parsing neural activity into transient/item-related and sustained/epoch-related brain activity, one study investigated neural dynamics associated with mortality salience during the processing of death-relevant compared to life-relevant and valence-relevant linguistic cues (Shi & Han, 2013). Transient activity was observed in frontoparietal regions including the left inferior parietal lobule, the right superior parietal lobule, the right frontal eye field and the medial prefrontal cortex for death related vs. death-unrelated words. At a threshold that controlled for multiple comparisons using false discovery rate ($P<0.05$, FDR), other contrasts did not reveal significant transient activations. However increased transient activation was found at the left insula for negative vs. neutral words at a threshold of $P<0.001$, uncorrected. Collective transient frontoparietal activity (not including the medial prefrontal cortex) significantly correlated with participant-rated death-relevance scores of word stimuli. Sustained activity was found during both death-relevance vs. life-relevance (to control for life-relevance processing) and death-relevance vs. valence (to control for valence processing) judgments in brain regions including the bilateral insula. A contrast of sustained activity combining both control conditions, i.e., death relevance vs. (valence and life-relevance), revealed sustained decreases in activity at the bilateral anterior insula/putamen and bilateral posterior insula. Collective insular deactivations did not significantly correlate with participant-rated death-relevance scores of word stimuli. However, significant correlations were observed between transient frontoparietal activity and sustained insular deactivations. In order to determine whether interactions between transient and sustained neural activity correlated with death anxiety scores, hierarchical regression analysis was conducted. This analysis first constrained the examination of significant interactions to the right frontal eye field and right superior parietal lobule of the fontroparietal areas (transient activity) and the bilateral anterior insula (sustained activity). Groups were then mean-split according to frontoparietal activation magnitude. The authors found that for those participants with weak frontoparietal activation to death-related words, sustained anterior insular activity was negatively correlated with death anxiety scores, but no significant correlation was observed in those with strong frontoparietal activation. The authors provide the interpretation that it might be unnecessary to resort to suppression of self-awareness (inferred from decreased insular activity) if death-related information can efficiently invoke one's attention (inferred from increased frontoparietal activation). Given that the gradient of information flow from posterior to anterior insula is believed to reflect information flow from unconscious representation to conscious re-representation, another possibility is that in the weak frontoparietal activation group, the weaker activation might reflect a diminished ability of executive control regions to inhibit posterior insula activity. Thus, this would allow information to flow form the posterior insula to the anterior insula and engage subjective awareness of death anxiety, which is proportionally related to degree of anterior insular activation. Support for this interpretation comes from a causal demonstration with transcranial magnetic stimulation that the frontoparietal central executive network exerts inhibitory control over other large-scale cortical networks (Chen et al., 2013), and is further supported by recent work utilizing the effective connectivity metric of Granger Causality to show that at rest, the salience network exerts an excitatory influence on the frontoparietal central executive network and the fontroparietal central executive network exerts an inhibitory influence on the salience network (anchored in the insula; Palanyiappan et al., 2013) . The application of network-level analytic procedures involving measures of effective connectivity between the frontroparietal activity and insular activity in future mortality salience neuroimaging studies could assist in selecting between these candidate interpretations.

According to TMT, self-esteem, in addition to cultural worldview defense, is believed to serve as a cultural anxiety buffer to mortality salience. This position is supported by empirical evidence of diminished worldview defense (Harmon-Jones et al., 1997) and death anxiety (Davis et al., 1983) as a function of self-esteem. The first neuroimaging study to examine whether self-esteem moderates neural responses to mortality-related stimuli used sentences that described death-related, death-unrelated negative, or neutral situations. Voxel-based analysis of the death related vs. unpleasant contrast revealed deactivations in the bilateral lingual gyri and the border between posterior aspects of the left superior temporal cortex and left posterior insula. Furthermore, using ROIs from previous studies, the authors were able to subject putative neural substrates of mortality salience processing to independent validation with a different paradigm. Of coordinates reported by Quirin et al. (2011), only the right caudate nucleus was sensitive to the present manipulation, and only the contrast between death-related and neutral sentences. Both left and right ROIs from Han et al. (2010) were less active to death-related than unpleasant sentences in the present study (corroborating previous results), yet here no differences were found between death-related and neutral sentences (diverging from previous results). Coordinates for anterior insula from Shi & Han (2013) exhibited no deactivations for death-related over unpleasant (diverging from previous results), but bilateral posterior insula coordinates did (corroborating previous results). Voxel-based correlation analyses revealed that low self-esteem predicted enhanced neural responses to death-related over unpleasant sentences in bilateral ventrolateral prefrontal cortex, left orbitofrontal cortex, left ventromedial prefrontal cortex and the left anterior insula. Using ROI correlation analysis, higher self-esteem only significantly predicted decreased activity for death-related compared with unpleasant sentences in the right anterior insula. Both anterior insula (ROI and voxel-based) and prefrontal cortex correlations between brain activity and self-esteem scores bore a negative relationship such that decreased activity correlated with greater self-esteem. Thus, the authors interpret these results as demonstrating that self-esteem plays an important role on brain deactivation to death-related stimuli. The relationship between self-esteem and activity in the insula region is posited to represent a diminished 'global emotional moment' and the relationship with prefrontal cortical regions are explained as reflecting decreased effortful emotion regulation to suppress negative emotional states in the face of existential threat. It is important to note, as the authors do, that these interpretations rely entirely on qualitative reverse inference. Finally, this study reports novel deactivations in the superior and middle temporal as well as bilateral lingual gyri to death-related vs. unpleasant sentences–again, speculatively interpreted on the basis of reverse inference as reflecting decreased auditory and visual processing due to these regions being adjacent to primary auditory and visual cortex respectively.

The most recent fMRI study in this literature sought to characterize the impact of mortality salience on neural processing during social cognition and to clarify its relationship to prosocial behaviour (Luo et al., 2014). Two groups of participants received either a mortality salience or negative affect (fear/anxiety) prime and were scanned prior to and following receipt of these primes while viewing video clips during which another individual undergoes a painful (a face being punctured by a needle and expressing pain) or non-painful (a face being stroked by a Q-tip and maintaining a neutral expression) experience. In order to subsequently examine prosocial behavior, participants were asked to decide the intensity of an electric shock (from mild intensities that “produce sensory feelings” to high intensities that “produce intolerant painful feelings”) that would be administered to others in a pseudo-experiment. Neuroimaging results demonstrated that an established neural circuit activated by empathy (Bernhardt & Singer, 2012) was recruited in both groups during viewing of others experiencing pain. Activations of the midcingulate cortex (MCC)/dosomedial prefrontal cortex (dMPFC) and bilateral anterior insula (AI)/inferior frontal gyrus (IFG) were able to predict prosocial behavior (intensity of shocks administered), suggesting a relationship between neural activity in these regions and altruistic behaviour. However, mortality salience priming did not differentially impact this behavioural index. Compared to the negative affect group, the mortality salience group exhibited significantly less brain activity in the MCC/dMPFC post-priming. Activity in the MCC/dMPFC also significantly decreased in the post-prime vs. pre-prime in the mortality salience group, but not the negative affect group. In order to support the notion that this decrease in activity does not merely reflect sustained neural response to the processing of mortality salience primes, but a reduction in empathic neural responses, the authors separated mortality salience priming and the post-priming sessions by a 5-minute calculation task. This resulted in the unexpected findings of increased middle temporal gyrus

(MTG)/superior temporal sulcus (STS) activity in the mortality salience group as compared to the negative affect group as well as in the mortality salience group post-priming vs. pre-priming that was not found in the negative affect group. The authors interpret decreased MCC/dMPFC activity as indicating decreased affect and regulation processing and increased MTG/STS activity as an index of enhanced perceptual feature processing. They further suggest that these two processes may be interrelated and support this hypothesis by demonstrating a significant negative correlation found between changes in neural activity of the respective regions (individuals with greater decreases in MCC/dMPFC activity also exhibited increases in MTG/STS activity). Subjective rating of fear of death significantly mediated the mortality salience group's decrease in MCC/dMPFC activity, such that the effect of group membership (mortality salience or negative affect) was significantly reduced when ratings of fear of death were included in the regression model. To assess whether fear of death following mortality salience moderated inter-regional neural activity between the two brain regions that predicted prosocial behavior in the present study, co-variation between the BOLD signal time-course from each region was examined as a measure of functional connectivity. Analysis confirmed that fear of death significantly moderated this co-variation (functional connectivity) across the pre- and post-priming scans. Further analysis revealed positive correlations between co-variance during the pre-priming and post-priming session in individuals with low fear of death but no significant correlation in individuals with high fear of death. Furthermore, this pre-priming and post-priming correlation in co-variance was significant for the negative affect group, but not the mortality salience group. These results provide the first evidence that morality salience does not merely affect brain activity within isolated regions, but also functional connectivity between regions in a neural network involved in empathy that predicts prosocial behaviour. It should also be noted that the midcingulate cortex and insula are core nodes of the brain's salience network (Seeley et al., 2007; Taylor, Seminowicz, & Davis, 2009; Menon & Uddin, 2010). As such, an interpretation that posits diminished "salience" of the other's suffering at the level of neural activity and connectivity following priming that bolsters the salience of one's own mortality should also be considered.

1.3 Overview of experiment

The purpose of the present experiment is to mediate an ongoing debate surrounding putative qualitatively unique neurobiological mechanisms engaged during mortality salience processing by leveraging the quantitative meta-analytic method of activation likelihood estimation (ALE) to provide an empirical synthesis of the fMRI literature on mortality salience processing. In our study, we begin by entering reported foci of statistical significance from whole-brain analyses of a mortality salience paradigm, both activation and deactivations, greater during the mortality condition vs. the control condition into GingerALE 2.3 (San Antonio, TX: UT Health Science Center Research Imaging). GingerALE implements a quantitative, random-effects meta-analytic method (Eickhoff et al., 2009; Eickhoff et al., 2012; Turkeltaub et al., 2002; Turkeltaub et al., 2012). This provides us with clusters of meta-analytic activations or deactivations where the convergence is greater than would be expected at chance-level if foci were independently distributed. With the peak ALE coordinates of meta-analytic clusters, we were able to determine intrinsic network membership of these clusters using seed-based correlation analysis. By calculating the posterior probability of a psychological function being reported given activation at peak ALE coordinates, we were able to identify prominent psychological functions associated with meta-analytic clusters. This represents a principled and quantitative approach to reverse inference (Chang, Yarkoni, Khaw, & Sanfey, 2012; Poldrack, 2006).

We found that only the bilateral posterior insula exhibits converging deactivation specific to mortality salience. Furthermore, peak ALE coordinates from these clusters belong to the brain's salience network and are associated with a host of psychological phenomena that can be collectively termed interoceptive processing. These results provide the first quantitative meta-analysis of this nascent literature. Furthermore, they identify a robust and unique neurobiological signature, reveal functional networks that may be implicated, and point towards a constellation of interoceptive functions that might be compromised as a result of the impact of mortality salience processing on regional brain activity. Thus, our ALE meta-analysis affords the possibility of empirically directing future hypotheses and improving the precision of experimental designs to further elucidate how mortality salience impacts brain, behavior and phenomenology. It could also facilitate the selection of interventions that might protect against established deleterious consequences for individual health arising from certain forms of existential defense against mortality salience, to be thoroughly investigated by future studies.

Chapter 2

2. The brain with death in mind: A quantitative meta-analysis of the neural substrates underpinning mortality salience (Walpola, Rosa-Neto & Nair, *In Preparation)*

2.1 Introduction

Life entails death, and yet coming to terms with the inevitability of one's own mortality can be a cause of profound anxiety and distress. Nonetheless, reminders of life's transience abound. The impact of these reminders of mortality upon human behavior, termed mortality salience, has been extensively studied within the framework of Terror Management Theory (Greenberg, Pyszczynski, & Solomon, 1986) in social psychology over the last two decades. The basic premise, built upon the work of cultural anthropologist Ernest Becker, is that the uniquely human foresight into one's eventual demise results in behaviours aimed at managing existential terror arising from this confrontation with one's inevitable death (Greenberg, Pyszczynski, & Solomon, 1986). A corpus of research spanning twenty different countries with varying means of inducing mortality salience has demonstrated a propensity for individuals to engage in vigorous defense of their cultural worldviews in order to manage existential terror. This is believed to reflect attempts at securing symbolic immortality through culture–even at the expense of compromising one's own wellbeing and the wellbeing of others who hold opposing or incompatible worldviews (Greenberg et al., 2008).

Despite an extensive body of work in social psychology, only a handful of studies have investigated the neurobiological correlates of mortality salience and all have done so within the last five years. This literature has employed both electroencephalography (EEG; Henry, Bartholow, & Arndt, 2009; Klackl, Jonas, & Kronbichler, 2012; Liu, Shi, Ma, Qin, & Han, 2013, Valentini, Koch, Nicolardi, & Aglioti, 2015) and functional magnetic resonance imaging (fMRI; Han, Qin, & Ma, 2010; Quirin et al., 2012; Graupman et al., 2013; Silveira et al., 2013; Klackl et al., 2013; Shi & Han, 2013; Luo et al., 2014), however we shall focus on the fMRI studies for the purposes of this meta-analysis. Seven fMRI studies (see **Table 1** for a list of the studies) have probed the neurobiology of mortality saleince with unparalleled anatomical precision in order to understand the impact of processing death-related linguistic cues, a core component of mortality salience processing, upon activity patterns in specific regions of the human brain.

Table 1.
fMRI studies of mortality salience (* denotes studies included in ALE meta-analysis)

Title	Authors	Journal	Year	PMID
*Neurocognitive processes of linguistic cues related to death.	Han, Qin & Ma	Neuropychologia	2010	20667490
*Existential neuroscience: a functional magnetic resonance imaging investigation of neural responses to reminders of one's mortality.	Quirin et al.	Social cognitive and affective neuroscience	2012	21266462

Culture and its neurofunctional correlates when death is in mind.	Graupmann et al.	Neuroscience letters	2013	23752131
Existential neuroscience: effects of mortality salience on the neurocognitive processing of attractive opposite-sex faces.	Silveira et al.	Social cognitive and affective neuroscience	2013	24078106
*Existential neuroscience: self-esteem moderates neuronal responses to mortality-related stimuli.	Klackl et al.	Social cognitive and affective neuroscience	2013	24222712
*Transient and sustained neural responses to death-related linguistic cues.	Shi & Han	Social cognitive and affective neuroscience	2013	22422804
Reminders of mortality decrease midcingulate activity in response to others' suffering	Luo et al.	Social cognitive and affective neuroscience	2014	23327932

It should be noted that many studies in this emerging fMRI literature, and all studies included in this quantitative meta-analysis, depart significantly from the majority of the behavioral mortality salience literature. In the behavioral literature, participants are generally first primed with death-related cues and then engaged in some sort of distraction to allow thoughts of mortality to fade into the periphery of awareness before participants are tested to measure some variable of interest such as their propensity to defend cultural worldviews. This procedure has been shown to bolster the impact of mortality salience on variables of interest. However, one of the novel and potentially important contributions of investigating mortality salience with fMRI is to understand how the act of processing death-related words itself impacts online brain activity in specific areas of the brain during mortality salience processing, rather than limiting investigation to probing downstream behavioral consequences–elucidating neurocognitive processes underpinning mortality salience for the first time. Furthermore, if, as several studies have suggested (Han, Qin, & Ma, 2010; Klackl et al., 2013; Shi & Han, 2013), death-related linguistic cues affect brain activity differently from negative affective cues, then negative affect induced by mortality salience cannot alone account for these effects–suggesting that mortality salience might be distinct from other kinds of negative affective salience or threat. As noted by previous researchers, "the notion of separate and distinct biological mechanisms of mortality salience effects on the one hand and all other threat on the other runs counter to prevailing views in neuroscience" (Tritt, Inzlicht, & Harmon-Jones, 2012). In order to empirically mediate the debate over the possibility of a distinct neurobiological mechanism, we conducted a quantitative meta-analysis using activation likelihood estimation (Eickhoff et al., 2009; Trkeltaub et al., 2002, 2012) of the 4 functional neuroimaging studies investigating neural activity during mortality salience processing (see **Table 2** for a list of the studies).

Table 2.
Studies included in ALE meta-analysis

Study	Mortality Stimuli	Control Stimuli	Subjects	Significant Contrasts
Han, Qin, & Ma (2010)	Death-related Chinese words (Colour Stroop task)	1) Negative affect words 2) Neutral affect words	20 female students	1) Death-related>neutral (activation) 2) Negative> death-related (deactivation)
Quirin et al. (2012)	Mortality statements	Dental pain statements	20 male students	1) Mortality>dental pain (activation)
Klackl et al. (2013)	Death-related sentences	1) Negative sentences 2) Neutral sentences	30 students (18 female)	1) Death>neutral (activation) 2) Unpleasant>death (deactivation)
Shi & Han (2013)	Death-related words	1) Death-unrelated/neutral affect words 2) Negative affect words 3) Life-related words 4) Life-unrelated words	24 students (12 female)	1) Death-related>Death-unrelated (activation) 2) Valence>Death-relevance (deactivation) 3) Life relevance>death relevance (deactivation) 4) (Valence and life relevance)>death relevance (deactivation)

2.2 Methods

2.2.1 Search strategy

In order to identify neuroimaging studies investigating mortality awareness, we conducted a systematic search of the extant literature using MEDLINE (pubmed.com), Google Scholar (scholar.google.com) and Neurosynth (neurosynth.org) for papers containing the keywords ‘mortality’, ‘mortality salience’ or ‘existential neuroscience’. We used the additional keywords “fMRI” and “functional magnetic resonance imaging” to filter the literature from MEDLINE and Google Scholar to only those that employed functional neuroimaging. Abstracts of all the resulting studies were carefully examined to ensure that functional magnetic resonance imaging was conducted. Studies using electroencephalography were not considered. In order to ensure that our search was comprehensive, reference lists of all retrieved studies were also examined.

2.2.2 Inclusion criteria

Only studies that performed fMRI acquisition while participants were processing death-related linguistic cues (mortality salience processing) as well as a control linguistic cue (e.g., neutral or negative affective cues) were included (Table 2). As a consequence of these inclusion criteria, three of the seven published fMRI studies were excluded from subsequent analysis, yielding 4 studies in total to be included in the ALE procedure.

2.2.3 Activation likelihood estimation (ALE) meta-analysis

We conducted ALE using a quantitative, random-effects meta-analytic method (Eickhoff et al., 2009; Eickhoff et al., 2012; Turkeltaub et al., 2002; Turkeltaub et al., 2012) implemented in GingerALE 2.3 (San Antonio, TX: UT Health Science Center Research Imaging). The ALE algorithm proceeds by testing whether the clustering of peak foci included in the meta-analysis occurs above chance by comparing these entered peak foci with a null distribution that includes the same number of peak foci distributed randomly throughout the brain's gray matter. A Gaussian blur with a full-width half maximum (FWHM) kernel empirically determined by sample size (larger samples result in smaller smoothing kernels) of the experiment from which foci are reported is applied (Eickhoff et al., 2012). The statistical maps are illustrative of clusters where the convergence of activation foci is greater than would be expected at chance-level if foci were independently distributed.

Our analysis included a total of 41 foci from 4 neuroimaging studies with an aggregate of 91 participants (Table 2). Only coordinates from whole-brain analyses were included. As it has been demonstrated that uncorrected P value thresholds and FDR corrected thresholds are not optimal for the ALE procedure (Eickhoff et al., 2012), we resorted to statistical thresholds determined by a cluster-forming value of $P<0.001$ and a cluster-level inference of $P<0.01$. Regions were classified according to the Multi-Image Analysis GUI ('Mango') image-viewing software (UT Health Science Center Research Imaging Institute) and corroborated using the xjView toolbox (http://www.alivelearn.net/xjview). Fig. 1 was created in Mango (UT Health

Science Center Research Imaging Institute).

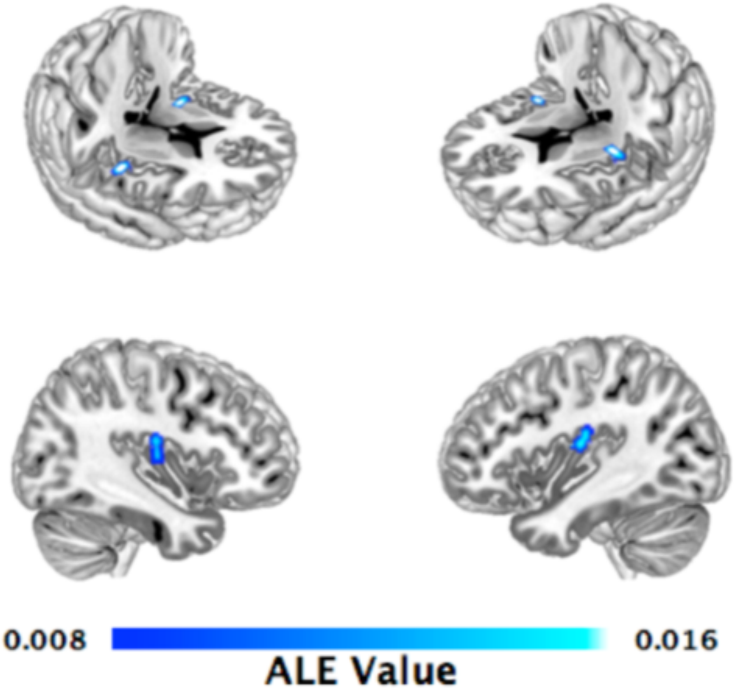

Fig.1. Peaks of meta-analytic clusters of activation associated with mortality salience.
Left: right posterior insula; Right: left posterior insula (largest cluster).
Colour bar indicates ALE likelihood values (see Methods). See Table 3 for detailed quantitative results.

2.2.4 Intrinsic connectivity network membership and posterior probability of ALE peak coordinates

We submitted the MNI coordinates of peak ALE values to Neurosynth (http://www.neurosynth.org) in order to determine intrinsic connectivity network membership of significant clusters through seed-based functional connectivity analysis in a sample of 1,000 participants (For details, see Yeo et al., 2011) and posterior probability (i.e., P(Term|Activation)) of distinct psychological processes associated with activation at specific coordinates. Figure 2 was created using the software package MRIcro (http://www.mccauslandcenter.sc.edu/CRNL/tools/mricro) and projecting masks of intrinsic functional connectivity on the cortical surface.

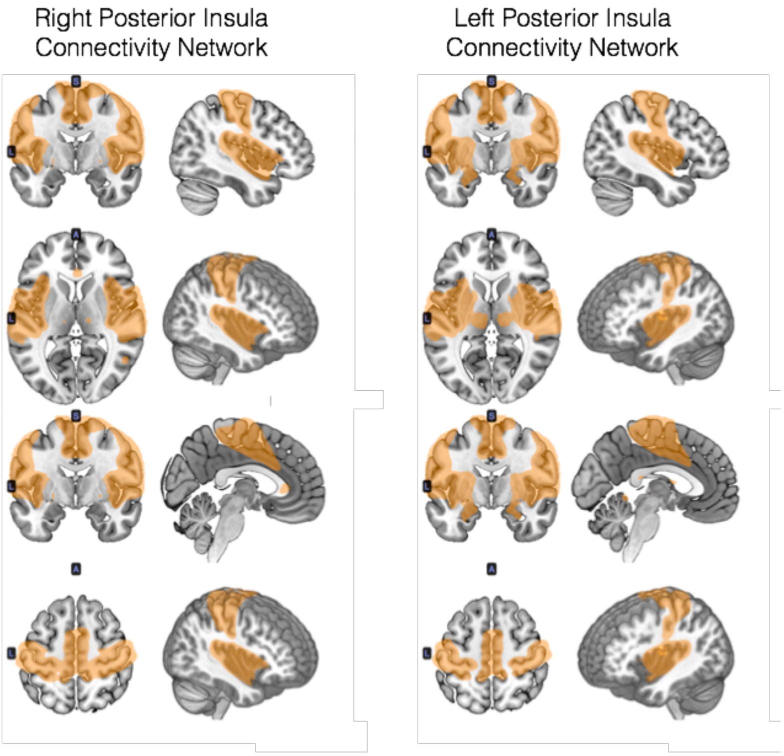

Fig. 2. Intrinsic connectivity network membership of meta-analytic peak coordinates. Maps depict a network spatially overlapping with the brain's Salience Network involving bilateral insula, midcingulate, supplementary motor area and somatosensory cortices.

2.3 Results

We found clusters in the bilateral posterior insula (BA 13; Table 3; Fig. 1) to be reliably involved in mortality salience processing–all contributing foci were deactivations. Intrinsic functional connectivity of peak ALE coordinates for each insula cluster reveals a network of brain regions (Fig. 2) spatially overlapping with the salience network and involved in central autonomic processing, specifically linked to regulation of the sympathetic division (Beissner, Meissner, Bär, & Napadow, 2013).

Table 3.
ALE results of deactivation during mortality salience processing (control > death stimuli)

Region	Cluster Size (mm^3)	Peak ALE Value	Peak in MNI Space	Brodmann Area
Left Posterior Insula	896	0.016402	-32, -14, 14	13
Right Posterior Insula	480	0.012048	44, -8, 10	13

Distinct psychological processes associated with significant activation of peak coordinates with the five greatest posterior probabilities (Table 4) are consistent with the involvement of these regions in primary interoceptive processing (Craig 2002; Craig 2009). We report the first five independent psychological terms with the greatest posterior probability. Overlapping terms and methodological terms are not reported.

Table 4.
Posterior probability (z-score) of associated psychological processes at peak coordinates

Region	Process #1	Process #3	Process #3	Process #4	Process #5
Left Posterior Insula	Heat (0.87)	Nociceptive (0.85)	Taste (0.85)	Anticipatory (0.79)	Autonomic (0.79)
Right Posterior Insula	Heat (0.89)	Bodily (0.86)	Noxious (0.85)	Pressure (0.83)	Taste (0.83)

2.4 Discussion

2.4.1 Overview

The aim of our meta-analysis was to synthesize the modest literature on the neuroimaging of mortality salience, that is to say studies investigating brain activity during the processing of death-related linguistic cues, in order to inform the debate regarding the possibility of a “separate and distinct” neurobiological mechanism for mortality salience processing. Our results provide the first quantitative evidence that the most statistically robust convergent finding in the extant literature, bilateral posterior insula deactivation during mortality salience processing compared to negative affective processing, does indeed suggest a neurobiological mechanism for mortality salience distinct from that observed during negative affect or anxiety.

2.4.2 Is death (anxiety) special?

A recent qualitative review exploring biological mechanisms underlying mortality salience proposed that these mechanisms reflect a “general form of anxiety, no different from other anxieties” (Tritt, Inzlicht, & Harmon-Jones, 2012). However, accounts of anxiety that highlight the insula’s crucial role as a cortical structure involved in the initiation and maintenance of anxiety indicate that it is *heightened* activity in the insula that corresponds to the “anxiety phenome” (Paulus & Stein, 2013). Furthermore, where subdivisions of the insula have been specified, it is the *anterior* insula, believed to integrate, among other sources of input, viscera-somatic information from the posterior insula (Craig, 2002) that has been linked to the subjective feeling of anxiety. In contrast to these neurobiological accounts of anxiety, our ALE meta-analysis found bilateral deactivation in the posterior insula during mortality salience compared with negative affective processing (Fig. 1, Table 3)– suggesting that an account of the mechanisms underlying mortality salience as merely a general form of negative affect or anxiety with no unique neurobiological mechanism is unlikely to remain tenable.

2.4.3 The functional role of the posterior insula

There is markedly less known about the functional role of the posterior insula in human cognition than the anterior insula. It has been noted that information from the autonomic nervous system representing bodily homeostatic afferent input is first projected to the mid/posterior insula before it is “re-represented” in the anterior insula and provides the neurobiological foundation for subjective interoceptive awareness (Craig, 2002; Craig, 2009). We linked five predominant psychological functions to peak ALE coordinates by investigating the posterior probability, or likelihood of the term denoting a psychological process appearing together with activation at the voxel’s coordinate (Table 4). The results are consistent with the involvement of the bilateral posterior insula in interoceptive processing. Functional MRI studies have linked activity in the posterior insula to pain processing (Brooks, Zambreanu, Godinez, & Tracey, 2005; Baumgärtner et al., 2010). Furthermore, a recent arterial spin-labelling study (Segerdahl, Mezue, Okell, Farrar, & Tracey, 2015) posits that the dorsal posterior insula is first brain region to be identified as specific to pain, a finding further supported by a study demonstrating, for the first time, the ability to elicit pain through direct electrical cortical stimulation which applied stimulation to the posterior insula (Ostrowsky et al., 2002). Activation in the posterior insula has also been implicated in innocuous thermosensation (Craig, Chen, Bandy, & Reiman, 2000; Hua, Strigo, Baxter, Johnson, & Craig, 2005), vestibular function (Fasold et al., 2002; Fink et al., 2003), motor tasks (Johnsen-Berg & Matthews, 2002), mind wandering during a practiced task (Mason et al., 2007), time perception (Witmann, Simmons, Aron & Paulus, 2010) and perhaps most notably for the present investigation, interoceptive attention (Farb, Segal, & Anderson, 2012; Farb, Segal, & Anderson, 2013) and body ownership (Tsakiris, Hesse, Boy, Haggard, & Fink, 2007). However, it should be noted that all these studies refer to activation, or increased activity of the posterior insula, so a deactivation, or decreased activity, might suggest a relative inhibition of these interoceptive neural processes during the processing of death-related linguistic cues that elicit mortality salience. Supporting this hypothesis, one study found that diminishing sense of agency or feeling of bodily control was related to a decreased activity in the posterior insula (Farrer at el., 2003). Lesion mapping studies support the importance of posterior insula function in bodily awareness, indicating that the right posterior insula is commonly damaged in hemiparesis patients exhibiting anosognosia (lack of self-awareness about limb functioning), but is less often damaged in those without anosognosia (Cereda et al., 2002; Karnath et al., 2005; Baier and Karnath, 2008).

Task-induced deactivations are routinely observed in a constellation of brain regions collectively termed the “default-mode network” (DMN), or sometimes, due to this effect, misleadingly referred to as the “task-negative network” (Spreng, 2012). During highly demanding tasks, however, deactivations are observed beyond the DMN–most notably in the posterior insula (Harrison et al., 2011). The same study demonstrated a step-wise increase in posterior insula deactivation–increasing with task-difficulty–and found that low performing participants could be distinguished from the high performing participants by the degree of posterior-to-mid insular deactivation. The authors interpret these findings in light of work conducted on pain processing in the posterior insula (Magnin, Mauguière, & Garcia-Larrea, 2007) that suggest the posterior insula's continuous multimodal integrative processing might establish a "background activity" rendering it relatively insensitive to activation or deactivation by stimuli that are not "sufficiently salient".

2.4.4 The posterior insula, mortality salience and fleeing the body

Terror management theorists hold that the body is a problem for humans because it reminds us of our vulnerability to death (Goldenberg, Pyszczynski, Greenberg, & Solomon, 2000). Mortality salience has been shown to lead individuals high in neuroticism to flee from bodily sensations, even including pleasurable ones (Goldenberg et al., 2006). Furthermore, these effects do not appear to be exclusive to those high in neuroticism (Goldenberg, Cox, Pyszczynski, Greenberg, & Solomon, 2002). This proclivity for disembodiment in the face of our own mortality can have serious adverse health consequences. For example, one study found that women reminded of the physicality of the body and then exposed to mortality salience decreased their intentions to perform breast self-exams (Goldenberg, Arndt, Routledge, & Hart, 2005). Finally, it is important to note that the behavioral impact of mortality salience is most effective when thoughts of death are acting unconsciously or implicitly rather than consciously or explicitly.

Although admittedly speculative, these findings may shed some light on the present ALE findings, especially in light of the posterior insula's putative role as primary interoceptive cortex (Craig, 2002; Craig, 2009; Farb, Segal, & Anderson, 2012; Farb, Segal, & Anderson, 2013) and its relationship to body ownership (Tsakiris, Hesse, Boy, Haggard, & Fink, 2007). Most specifically, manipulations that decreased participants' sense of bodily control over sensorimotor events also decreased activity in the posterior insula (Farrer at el., 2003). It is possible on the basis of these lines of research that the inhibition of interoceptive attention or attention to bodily states is neurobiologically mediated by decreased activity in the bilateral posterior insula, and this in turn facilitated the fleeing of the body that has been demonstrated in Terror Management Theory. The role of the posterior insula in providing the primary representation of the body through multisensory integration, before this information is made consciously accessible through re-representation in the anterior insula is also in accordance with the consistent with the well-established finding that mortality salience exerts its most robust impact while operating below the threshold of conscious access. This potential link between posterior insula deactivation during mortality salience and fleeing bodily sensation through interoceptive suppression provides an avenue for future research to elucidate the direct relevance of our ALE results to the morality salience literature and improve our understanding of a putative neurobiological mechanism unique to processing one's own imminent mortality.

2.4.5 Mortality salience and the brain's salience network

Our ALE meta-analysis also allowed us to probe the intrinsic connectivity network membership of significant clusters, namely the bilateral posterior insula (Fig. 2). To date, the literature on mortality salience has refrained from applying a large-scale network analysis, but has highlighted the involvement of key cortical regions belonging to the brain's "Salience Network" (Seeley et al., 2007): i.e., deactivation of the bilateral insula during mortality salience processing compare to negative affect (Han, Qin, & Ma, 2010; Klackl et al., 2013; Shi & Han, 2013) and diminished midcingulate activation during responses to others' suffering following priming with mortality salience but not negative affect (Luo et al., 2014). In fact, it has even shown impaired functional connectivity between two regions belonging to the salience network (the anterior insula and midcingulate cortex) following mortality salience priming (Luo et al., 2014). However, it should be noted that another study found greater activation in regions of the salience network following mortality threat than pain threat in regions such as the rostral anterior cingulate, amygdala and caudate nucleus (Quirin et al., 2010). A possible explanation for this discrepancy is that death-relevance was implicit and impersonal in the stimuli used by the former studies while those used by the latter were explicit and self-referential. Nonetheless, it appears that regions of the salience network are uniquely implicated in mortality salience as compared with other threatening or negative affective stimuli, and our results confirm that many of these regions are functionally connected to regions of the posterior insula identified by ALE. A posterior insula functional connectivity network adjacent but distinct from the anterior insula functional connectivity network traditionally identified as the salience network, has been described in previous work (Cauda, et al., 2011; Deen, Pitskel, & Pelphrey, 2011; Chang, Yarkoni, Khaw, & Sanfey, 2012 Taylor, Seminowicz, & Davis, 2013) and bears notable spatial similarity to the networks described in our connectivity analysis (Fig. 2). One study (Chang, Yarkoni, Khaw, & Sanfey, 2012) found a posterior insula network to be primarily associated with pain, sensorimotor and language-related topics by using meta-analytic decoding of network function on the Neurosynth database. Another study used ALE to characterize a central autonomic network that exhibits notable spatial overlap with the posterior insula functional connectivity network described here and by others (Beissner, Meissner, Bär, & Napadow, 2013). Future studies investigating mortality salience should apply large-scale network analyses in order to understand how processing of death-related linguistic cues affects both resting-state and task-related functional connectivity in and beyond the brain's salience network–a perspective that has recently been described as necessary to understand how the brain gives rise to cognition (Bressler & Menon, 2010).

2.4.6 Are these results culture-bound?

Given that all coordinates contributing to significant clusters in our ALE analysis were drawn from studies with participants of Chinese origin and residence, it warrants consideration whether these results may be exclusively culture-bound. One piece of evidence that this may not be the case, however, comes from a study using middle European (German-speaking) participants, which found bilateral posterior insula deactivations using a region-of-interest (ROI) analysis (Klackl et al., 2013). As we only included whole brain analyses in our ALE, these results were not considered and serve as an independent validation of posterior insula deactivation that might hold cross-culturally. Future work is necessary to determine whether these results generalize beyond Chinese and middle European participants–and it remains unclear why whole-brain analyses did not reveal deactivation with European participants (Klackl et al., 2013), while these were present for Chinese participants (Han, Qin, & Ma, 2010; Shi & Han, 2013).

2.4.7 Limitations of the present meta-analysis

It is important to note several limitations of the meta-analytic methods employed herein and the modest size of the research literature forming the basis for the meta-analysis. Firstly, only four (Table 2) of the seven fMRI studies (Table 1) investigating mortality salience were included in this meta-analysis due to inclusion criteria determined by our interest in brain activity during the actual processing of mortality-related stimuli rather than during downstream behavioural tasks. However, the importance of a quantitative meta-analysis yielding a significant result is to guide this literature, still in its infancy, towards identifying key neural substrates and associated psychological functions to probe with greater nuance and clarity in future studies. Secondly, even within this rather limited sample of studies, heterogeneity of study design is a cause for concern, assuaged in part by the similarity of contrasts employed (Table 2). Third, calculation of the posterior probability of psychological terms associated with activation at peak ALE coordinates suffers from the ability to identify only coarse-grained cognitive processes (e.g., pain), admittedly with demonstrable utility at this level of detail (Yarkoni et al., 2011). Finally, the studies contributing foci to the significant clusters in the present meta-analysis included only Chinese participants. However, as discussed in more detail above, convergent findings in a German-speaking middle European population support the notion that these findings are not exclusively culture-bound.

2.4.8 Conclusions and future directions

The aim of the present meta-analysis was to mediate a debate on the possibility of unique neurobiological mechanisms involved in the processing of mortality salience as opposed to other forms of threat (e.g., negative affect or pain) by applying the quantitative activation likelihood estimate (ALE) procedure to the extant functional neuroimaging literature specifically investigating this phenomenon. To this end, we successfully identified two significant clusters, one at each of the bilateral posterior insula (Fig. 1, Table 3) with peak foci derived from deactivations observed during the processing of mortality-related stimuli in contrast to negatively or neutrally affective stimuli. These findings support the possibility of a unique neurobiological mechanism involved in mortality salience implicating brain regions belonging to the brain's salience network (Fig 2) potentially impacting psychological and cognitive processes requiring primary interoceptive processing (Table 4).

Our understanding of the neurobiology underpinning the phenomenon of mortality salience is currently still in its infancy, but it is already providing clues that might prove crucial to elucidating both why death appears to be a unique threat and how it leads to the behavioral effects that populate much of the literature on Terror Management Theory. These studies and future research in the same vein can form the cornerstone of an “Existential Neuroscience”, but a more nuanced approach to characterizing both behavior and subjective experience will be necessary for it to be truly deserving of the name. On the basis of our findings, one key direction for future research will be to investigate how mortality salience affects bodily self-consciousness and interoceptive processing, and to do so in a way that does not require conscious awareness and explicit reporting. Carefully designed experimental protocols such as those used in the literature on predictive coding mechanisms underlying interoception and bodily presence (Apps & Tsakiris, 2014; Seth, 2013; Tsakiris, Hesse, Boy, Haggard, & Fink) may be particularly useful in the effort to empirically understand these mechanisms and the neural computations involved.

Finally, given the potential negative health consequences resulting from mortality salience and fleeing one’s body, future studies might consider investigating the protective role of practices that enhance embodiment and interoceptive attention as well as neural structure and function of the posterior insula such as yoga (Villemure, Čeko, Cotton, & Bushnell) and mindfulness meditation (Farb et al., 2007; Farb, Segal, & Anderson, 2012) against the impact of mortality salience–especially in light of recent studies demonstrating that trait mindfulness reduces defensive responses to the threat of mortality salience (Niemiec et al., 2010; Kashdan et al., 2011).

Taken together, there are many opportunities for the young discipline of existential neuroscience. Our meta-analysis of the functional brain imaging literature on mortality salience processing identifies an important early finding, considers its implications, and suggests a way forward in light of these considerations. By elucidating the neurobiological processes underlying existential threat, an existential neuroscience may have important consequences for understanding existential anxiety afflicting those with terminal diagnoses. The investigation of interventions that target identified neurobiological substrates, for example, by promoting mindfulness, may engender a change in perspective that reduces the hold of mortality salience over the individual–shifting the emphasis from fearing the day of one’s fateful death to enriching the experiential fullness of each day and every moment of one’s life.

Chapter 3

3. General Discussion

Our study was designed to leverage the ALE meta-analytic method, seed-based functional connectivity, and to attribute psychological function via calculation of posterior probability to quantitatively synthesize the functional neuroimaging literature on mortality salience. In so doing, we aimed to identify neural substrates robustly underpinning mortality salience and point towards new investigative vistas for an existential neuroscience. The ALE results revealed two significant clusters, one in each of the bilateral posterior insula–reflecting deactivation during mortality salience compared to control conditions. This suggests the qualitatively unique neural signature of bilateral insular deactivation during mortality salience processing advanced by several studies (Han, Qin, & Ma, 2010; Klackl et al., 2013; Shi & Han, 2013) is robust to the stringent statistical procedure of ALE, and that this effect can be specifically localized to a posterior insular region bilaterally. These results emphasize the heterogeneity of insular function and support the notion that the unconscious impact of mortality salience on brain and behaviour, and the conscious subjective awareness of existential terror (e.g., fear and anxiety) may be largely subserved by the posterior and anterior insula, respectively; specifically, our study revealed the impact of mortality salience processing to be robustly localized within the posterior subdivision.

3.1 Notes on the posterior insula in mortality salience

On the basis of our results, the extant neuroscience literature on mortality salience, and prior summaries of insular functional organization (Craig, 2002; Craig, 2004; Craig, 2010), we might hypothesize that mortality salience processing interrupts interoceptive reports of the human organism's homeostatic state, which first converge cortically in the posterior insula (putative primary interoceptive cortex). Then, the degree of this deactivation should subsequently reduce re-representation in the anterior insula, limiting subjective awareness of existential terror, and thus the ability to provide conscious reports. Furthermore, behaviours linked to activity in these brain regions (i.e, interoceptive processing) may be compromised and serve as implicit indices of existential terror management, a basic premise of TMT (Goldenberg, Pyszczynski, Greenberg, & Solomon, 2000; Goldenberg, Cox, Pyszczynski, Greenberg, & Solomon, 2002; Goldenberg et al., 2006). One study suggests that the degree of transient frontoparietal activity also plays a crucial role in this hypothesized mechanism, because a mean-split group with weak frontoparietal activity exhibited a negative correlation between sustained anterior insula activation to death-related words and death anxiety scores (Shi & Han, 2013). However, no significant correlation was observed in those with strong frontoparietal activation. The anterior insula is believed to convey subjective experience of homeostatic bodily signals first integrated in the primary interoceptive cortex of the posterior insula (Craig, 2002; Craig, 2004; Craig, 2010). Thus, if death anxiety produces a deactivation of the posterior insula, one would expect decreased flow of information to the anterior insula and thus a negative correlation between subjective awareness of death anxiety and anterior insula activity. The group with stronger frontoparietal activation might not have exhibited a correlation with conscious access to death anxiety due to the correlation observed between transient frontoparietal activation and sustained insula deactivation–indicating less insula activity in those with higher frontoparietal activity. On the basis of the anterior insula's established role in integrating a global subjective state, decreased activity this brain region should correspond to attenuated awareness of feelings including death anxiety (Craig, 2002; Craig, 2004; Craig, 2010). The authors of this paper interpret this relationship as reflecting greater persistent decrease in sentient self-awareness in individuals with stronger attention driven attentional bias. However, an interaction between the frontoparietal and salience network–partially anchored in the bilateral insula–should also be considered, as previous work has found that frontoparietal network activation can casually influence other large-scale networks (Chen et al., 2015). Furthermore, effective connectivity reveals that the frontoparietal network exerts a causal inhibitory influence over the salience network and that the salience network in exerts a causal excitatory influence over the frontoparietal central executive network at rest (Planiyappan et al., 2013). These potential interpretations are not necessarily antagonistic and may both be involved in the observed effect. Nonetheless, future investigation employing a network-level perspective and measures of effective connectivity will be necessary in order to empirically validate either or both of these theories.

It should also be noted that TMT has provided evidence of "fleeing the body", i.e., avoiding bodily sensations that are both pleasurable and unpleasurable (Goldenberg, Pyszczynski, Greenberg, & Solomon, 2000; Goldenberg, Cox, Pyszczynski, Greenberg, & Solomon, 2002; Goldenberg et al., 2006) and avoidance of a "self-focused state" (Arndt et al., 1998)–both of which are predictable consequences of posterior insula deactivation (Craig, 2002; Craig , 2004; Craig, 2010). These established experimental methodologies from TMT might be adapted by future efforts in existential neuroscience to further elucidate whether the functional significance of posterior insula deactivation can be confidently linked to interoception and self-awareness.

3.2 The importance of adopting a network perspective

Of the extant neuroscience literature on mortality salience, only one study (Luo et al., 2014) employed an analytic method to move beyond characterizing activity *within* a region or collection of regions, and instead understand shared patterns of activity *between* regions (i.e, functional connectivity)–and even this was limited to functional connectivity between only two ROIs. This study provided evidence for functional decoupling between two brain regions (insula and midcingulate cortex), typically described as core nodes of the brain's salience network (Seeley et al., 2007) in the mortality salience group. Furthermore, the degree of this decoupling was correlated with subjective reports of fear of death. These functional connectivity results only reflect downstream effects of mortality salience, and no characterization of mortality salience processing as such on large-scale functional brain networks has yet occurred. This identifies a lacuna in the existential neuroscience literature, as contemporary views in human neuroscience suggest understanding the role of the human brain in cognitive processes crucially depends upon an understanding of large-scale brain network organization (Bressler & Menon, 2010). Furthermore, recent work has begun to investigate interactions between these networks–moving away from localizationist and modular perspectives towards a more global and holistic understanding of the neural coordination underpinning cognition (Barch, 2013).

For our part, we established network membership (Figure 2) using seed-based correlation analysis of the peak ALE coordinates in the bilateral posterior insula clusters (Figure 1) identified as deactivated during mortality salience processing. With both seed coordinates, we found a network (Figure 2) that spatially overlaps with the salience network, similar to other studies that have examined posterior insula connectivity (Cauda, et al., 2011; Deen, Pitskel, & Pelphrey, 2011; Chang, Yarkoni, Khaw, & Sanfey, 2012 Taylor, Seminowicz, & Davis, 2013) and the central autonomic network (Beissner, Meissner, Bär, & Napadow, 2013). On the basis of our results and the work of others (Luo et al, 2014), it can be reasonably hypothesized that the salience network is at least one large-scale network that is likely to be involved in mortality salience processing. How exactly the salience network is affected by mortality salience processing and whether networks anchored in the anterior and posterior insula are differentially impacted should be investigated through future studies. Furthermore, on the basis of an established relationship between a collection of frontoparietal regions and bilateral insula (Shi & Han, 2013) and the causal influence others have observed these networks to exert upon each other (Palaniyappan et al., 2013), it is important to examine directional interactions between large-scale networks to which these regions belong (i.e., frontoparietal central executive network and salience network, respectively) by using measures of effective connectivity (e.g., Granger Causality).

3.3 Limitations

Our meta-analysis is subject to several limitations. First, only a subset of an already modestly sized literature could be included in our ALE analysis due to inclusion criteria derived from our interest in characterizing variations in regional brain activity specifically elicited by mortality salience processing. Nonetheless, a significant meta-analytic result with contributing foci from a few early studies using different mortality salience paradigms is a promising early indication of convergence upon a neural correlate of mortality salience processing (Han, Qin, & Ma, 2010; Shi & Han, 2013). Furthermore, these results were independently corroborated by *a priori* ROI analysis using yet another mortality salience paradigm (Klackl et al., 2013; albeit all employing death-related linguistic stimuli) in a cohort with a different cultural background. This suggests that decreased posterior insula activity is a robust effect of mortality salience processing compared to negative affective processing–constituting a qualitatively unique neural signature of mortality salience not accounted for by other forms of affective threat.

Second, it should be noted that our connectivity analysis was not able to account for variations in connectivity elicited by mortality salience processing, but could only indicate network membership of peak ALE coordinates from significant meta-analytic clusters specific to mortality salience processing in a large independent cohort (Yeo et al., 2011). As such, large-scale network-level effects of mortality salience have yet to be elucidated, and should be characterized by future studies in existential neuroscience.

Finally, the functional role of the posterior insula is still poorly characterized in contrast to that of the anterior insula, which has received considerable attention as of late. In order to be able to provide some understanding of the psychological functions that may be associated with the peak ALE coordinates of posterior insula clusters deactivated during mortality salience, we reported the first five distinct psychological functions with the greatest posterior probability. Although this represents a principled approach to reverse inference, it needs to be supplemented by experiments designed to examine whether the psychological functions we have found to be associated with posterior insula activity, collectively falling under the rubric of interoception, are indeed specifically impaired during and/or following mortality salience processing.

3.4 A future for existential neuroscience?

The limitations of our meta-analysis could also be read as future directions for the fledgling discipline of existential neuroscience. The convergence we observed upon deactivation of the insula, specifically the posterior division, during mortality salience processing represents the most statistically robust thread for future studies to follow. Although others have made the observation of consistent insular deactivation across early studies of mortality salience processing on a qualitative basis (Klackl et al., 2013), our ALE meta-analysis provides the first quantitatively derived evidence for this claim.

What are the behavioural and qualitative consequences of posterior insula deactivation? Is deactivation in the posterior insula related to decreased activity in the anterior insula and thus gating of conscious access to the impact of mortality salience (i.e., reportability of experienced death anxiety/existential terror)? These are questions that, as of yet, remain unanswered, but may serve as grounds for future studies. With respect to adopting a network perspective, future work will need to characterize whether large-scale functional connectivity of the salience network is impaired during mortality salience processing and whether dynamic inter-network interactions, specifically directional influences of one network over the other (e.g., central executive network upon the salience network), occur during the processing of death-relevant information. Finally, the putative role of the posterior insula as primary interoceptive cortex, corroborated by our examination of posterior probability, should be further examined by experimental designs that can elucidate whether interoception in general, or only specific sub-processes may be affected by mortality salience processing. Experimental paradigms from the TMT literature on "fleeing the body" (Goldenberg, Pyszczynski, Greenberg, & Solomon, 2000; Goldenberg, Cox, Pyszczynski, Greenberg, & Solomon, 2002; Goldenberg et al., 2006) and "avoiding a self-focused state" (Arndt et al., 1998) could prove instructive in designing future studies linking changes in brain activity during mortality salience processing to interoceptive functions intimately tied to a sentient self. Furthermore, established means of enhancing interoceptive accuracy and strengthening neural circuitry underlying interoception (Farb et al., 2007; Farb, Segal, & Anderson, 2012), such as mindfulness training, should be investigated by an existential neuroscience that not only describes the impact of mortality salience, but also endeavours to provide a means of attenuating its potentially deleterious consequences–especially in light of demonstrations that mindfulness buffers against the certain consequences of mortality salience that may be harmful to oneself and others (Niemiec et al., 2010; Kashdan et al., 2011).

At first glance, the existential neuroscience that forms the basis of this meta-analysis more closely resembles the circumstances that prompted Oliver Sacks to call for an existential neurology (Sacks, 1984) than the social neuroscience literature that motivated Marco Iacoboni to identify an emerging existential neuroscience (Iacoboni, 2007). Nonetheless, we refer to this literature as existential neuroscience because multiple publications herein have taken the name "Existential Neuroscience" in their titles to indicate a debt to the existential perspective notably found in the philosopher Martin Heidegger, upon whom Marco Iacoboni also draws and in whose philosophy human awareness of one's own mortality plays a central role (Heidegger, 1962). Furthermore, at least a few papers in this literature that were not included in the present meta-analysis are existential in both the sense that one's continued existence is threatened during mortality salience (Sacks, 1984) and the social aspects (Iacoboni, 2007) of one's existence such as attraction to (Silveira et al., 2013) and empathy for (Luo et al., 2014) the other are affected. As such, this literature is already undermining conventional distinctions between stimuli that affect self- and other-processing in cognitive neuroscience, thus challenging implicitly held assumptions.

Most importantly, existential neuroscience offers a fresh perspective for the cognitive neurosciences, bringing pressing matters of everyday human existence (such as the inevitability of death), to the fore. This young discipline is already beginning to bring together other paradigmatic shifts in perspective for cognitive neuroscience including embodied cognition (Seth, 2013) and social neuroscience (Adolphs, 2003; Uddin, Iacoboni, Lange, & Keenan, 2007) in order to expand the purview of what is considered amenable to cognitive neuroscientific inquiry. Only time will tell if this novel perspective for cognitive science, composed of a currently modest literature, will achieve a stable purchase in cognitive neuroscience and proliferate as its predecessors have done before. Nonetheless, one thing that has already been made apparent is this: if we hope to understand the relationships between neurobiology and those matters of concern most immediately and proximally significant to human beings–an existential neuroscience must be the way forward.

References

Adolphs, R. (2003). Cognitive neuroscience of human social behaviour. *Nature Reviews Neuroscience*, *4*(3), 165-178.

Apps, M. A., & Tsakiris, M. (2014). The free-energy self: a predictive coding account of self-recognition. *Neuroscience & Biobehavioral Reviews*, *41*, 85-97.

Ayars, A., Lifshin, U., & Greenberg, J. (2015). Terror Management Theory.*Emerging Trends in the Social and Behavioral Sciences: An Interdisciplinary, Searchable, and Linkable Resource*.

Arndt, J., Greenberg, J., Simon, L., Pyszczynski, T., & Solomon, S. (1998). Terror management and self-awareness: Evidence that mortality salience provokes avoidance of the self-focused state. *Personality and Social Psychology Bulletin*, *24*(11), 1216-1227.

Baier, B., & Karnath, H. O. (2008). Tight link between our sense of limb ownership and self-awareness of actions. *Stroke*, *39*(2), 486-488.

Barch, D. M. (2013). Brain network interactions in health and disease. *Trends in cognitive sciences*, *17*(12), 603-605.

Baumgärtner, U., Iannetti, G. D., Zambreanu, L., Stoeter, P., Treede, R. D., & Tracey, I. (2010). Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: a high-resolution fMRI study. *Journal of neurophysiology*, *104*(5), 2863-2872.

Beissner, F., Meissner, K., Bär, K. J., & Napadow, V. (2013). The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *The Journal of Neuroscience*, *33*(25), 10503-10511.

Bernhardt, B. C., & Singer, T. (2012). The neural basis of empathy. Annual review of neuroscience, 35, 1-23.

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends in cognitive sciences*, *14*(6), 277-290.

Brooks, J. C. W., Zambreanu, L., Godinez, A., & Tracey, I. (2005). Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage*, *27*(1), 201-209.

Burke, B. L., Martens, A., & Faucher, E. H. (2010). Two decades of terror management theory: A meta-analysis of mortality salience research. *Personality and Social Psychology Review*, *14*(2), 155-195.

Chang, L. J., Yarkoni, T., Khaw, M. W., & Sanfey, A. G. (2012). Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cerebral Cortex*, bhs065.

Chen, A. C., Oathes, D. J., Chang, C., Bradley, T., Zhou, Z. W., Williams, L. M., ... & Etkin, A. (2013). Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proceedings of the National Academy of Sciences*, *110*(49), 19944-19949.

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature reviews neuroscience*, *3*(8), 655-666.

Craig, A. D. (2004). Human feelings: why are some more aware than others?.*Trends in cognitive sciences*, *8*(6), 239-241.

Craig, A. D. (2010). The sentient self. *Brain structure and function*, 1-15.

Davis, S. F., Bremer, S. A., Anderson, B. J., & Tramill, J. L. (1983). The interrelationships of ego strength, self-esteem, death anxiety, and gender in undergraduate college students. *The Journal of general psychology*, *108*(1), 55-59.

Eickhoff, S. B., Laird, A. R., Grefkes, C., Wang, L. E., Zilles, K., & Fox, P. T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Human brain mapping*, *30*(9), 2907-2926.

Eickhoff, S. B., Bzdok, D., Laird, A. R., Kurth, F., & Fox, P. T. (2012). Activation likelihood estimation meta-analysis revisited. *Neuroimage*, *59*(3), 2349-2361.

Farb, N. A., Segal, Z. V., Mayberg, H., Bean, J., McKeon, D., Fatima, Z., & Anderson, A. K. (2007). Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. *Social cognitive and affective neuroscience*, *2*(4), 313-322.

Farb, N. A., Segal, Z. V., & Anderson, A. K. (2012). Mindfulness meditation training alters cortical representations of interoceptive attention. *Social cognitive and affective neuroscience*, nss066.

Farb, N. A., Segal, Z. V., & Anderson, A. K. (2013). Attentional modulation of primary interoceptive and exteroceptive cortices. *Cerebral cortex*, *23*(1), 114-126.

Farrer, C., Franck, N., Georgieff, N., Frith, C. D., Decety, J., & Jeannerod, M. (2003). Modulating the experience of agency: a positron emission tomography study. *Neuroimage*, *18*(2), 324-333.

Fasold, O., von Brevern, M., Kuhberg, M., Ploner, C. J., Villringer, A., Lempert, T., & Wenzel, R. (2002). Human vestibular cortex as identified with caloric stimulation in functional magnetic resonance imaging. *Neuroimage*, *17*(3), 1384-1393.

Fink, G. R., Marshall, J. C., Weiss, P. H., Stephan, T., Grefkes, C., Shah, N. J., ... & Dieterich, M. (2003). Performing allocentric visuospatial judgments with induced distortion of the egocentric reference frame: an fMRI study with clinical implications. *Neuroimage*, *20*(3), 1505-1517.

Graupmann, V., Peres, I., Michaely, T., Meindl, T., Frey, D., Reiser, M., ... & Gutyrchik, E. (2013). Culture and its neurofunctional correlates when death is in mind. *Neuroscience letters*, *548*, 239-243.

Greenberg, J., Pyszczynski, T., & Solomon, S. (1986). The causes and consequences of a need for self-esteem: A terror management theory. In *Public self and private self* (pp. 189-212). Springer New York.

Goldenberg, J. L., Arndt, J., Hart, J., & Routledge, C. (2008). Uncovering an existential barrier to breast self-exam behavior. *Journal of experimental social psychology*, *44*(2), 260-274.

Goldenberg, J. L., Cox, C. R., Pyszczynski, T., Greenberg, J., & Solomon, S. (2002). Understanding human ambivalence about sex: The effects of stripping sex of meaning. *Journal of sex research*, *39*(4), 310-320.

Goldenberg, J. L., Hart, J., Pyszczynski, T., Warnica, G. M., Landau, M., & Thomas, L. (2006). Ambivalence toward the body: Death, neuroticism, and the flight from physical sensation. *Personality and Social Psychology Bulletin*,*32*(9), 1264-1277.

Goldenberg, J. L., Pyszczynski, T., Greenberg, J., & Solomon, S. (2000). Fleeing the body: A terror management perspective on the problem of human corporeality. *Personality and social psychology review*, *4*(3), 200-218.

Han, S., Qin, J., & Ma, Y. (2010). Neurocognitive processes of linguistic cues related to death. *Neuropsychologia*, *48*(12), 3436-3442.

Harrison, B. J., Pujol, J., Contreras-Rodríguez, O., Soriano-Mas, C., López-Solà, M., Deus, J., ... & Menchón, J. M. (2011). Task-induced deactivation from rest extends beyond the default mode brain network. *PLoS One*, *6*(7), e22964-e22964.

Harmon-Jones, E., Simon, L., Greenberg, J., Pyszczynski, T., Solomon, S., & McGregor, H. (1997). Terror management theory and self-esteem: Evidence that increased self-esteem reduced mortality salience effects. *Journal of personality and social psychology*, *72*(1), 24.

Heidegger, M. (1962). Being and Time, trans. J. Macquarrie and E. Robinson.

Henry, E. A., Bartholow, B. D., & Arndt, J. (2009). Death on the brain: effects of mortality salience on the neural correlates of ingroup and outgroup categorization. *Social cognitive and affective neuroscience*, nsp041.

Iacoboni, M. (2007). The quiet revolution of existential neuroscience. *Social neuroscience: Integrating biological and psychological explanations of social behavior*, 439-453.

Johansen-Berg, H., & Matthews, P. (2002). Attention to movement modulates activity in sensori-motor areas, including primary motor cortex. *Experimental brain research*, *142*(1), 13-24.

Kashdan, T. B., Afram, A., Brown, K. W., Birnbeck, M., & Drvoshanov, M. (2011). Curiosity enhances the role of mindfulness in reducing defensive responses to existential threat. *Personality and Individual Differences*, *50*(8), 1227-1232.

Klackl, J., Jonas, E., & Kronbichler, M. (2012). Existential neuroscience: neurophysiological correlates of proximal defenses against death-related thoughts. *Social cognitive and affective neuroscience*, nss003.

Klackl, J., Jonas, E., & Kronbichler, M. (2013). Existential Neuroscience: Self-esteem moderates neuronal responses to mortality-related stimuli. *Social cognitive and affective neuroscience*, nst167.

Langer, K. G. (2009). Babinski's anosognosia for hemiplegia in early twentieth-century French neurology. *Journal of the History of the Neurosciences*, *18*(4), 387-405.

Lambert, A. J., Eadeh, F. R., Peak, S. A., Scherer, L. D., Schott, J. P., & Slochower, J. M. (2014). Toward a greater understanding of the emotional dynamics of the mortality salience manipulation: Revisiting the “affect-free” claim of terror management research. *Journal of personality and social psychology, 106*(5), 655.

Liu, X., Shi, Z., Ma, Y., Qin, J., & Han, S. (2013). Dynamic Neural Processing of Linguistic Cues Related to Death. *PloS one*, *8*(6), e67905.

Luo, S., Shi, Z., Yang, X., Wang, X., & Han, S. (2014). Reminders of mortality decrease midcingulate activity in response to others’ suffering. *Social cognitive and affective neuroscience*, *9*(4), 477-486.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science*, *315*(5810), 393-395.

Niemiec, C. P., Brown, K. W., Kashdan, T. B., Cozzolino, P. J., Breen, W. E., Levesque-Bristol, C., & Ryan, R. M. (2010). Being present in the face of existential threat: The role of trait mindfulness in reducing defensive responses to mortality salience. *Journal of personality and social psychology*, *99*(2), 344.

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M., & Mauguière, F. (2002). Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cerebral Cortex*,*12*(4), 376-385.

Palaniyappan, L., Simmonite, M., White, T. P., Liddle, E. B., & Liddle, P. F. (2013). Neural primacy of the salience processing system in schizophrenia. *Neuron*, *79*(4), 814-828.

Pyszczynski, T., Greenberg, J., & Solomon, S. (1999). A dual-process model of defense against conscious and unconscious death-related thoughts: an extension of terror management theory. *Psychological review*, *106*(4), 835.

Quirin, M., Loktyushin, A., Arndt, J., Küstermann, E., Lo, Y. Y., Kuhl, J., & Eggert, L. (2011). Existential neuroscience: a functional magnetic resonance imaging investigation of neural responses to reminders of one's mortality. *Social Cognitive and Affective Neuroscience*, nsq106.

Sacks, O. (1984). *A leg to stand on*. Simon and Schuster.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ... & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of neuroscience*, *27*(9), 2349-2356.

Segerdahl, A. R., Mezue, M., Okell, T. W., Farrar, J. T., & Tracey, I. (2015). The dorsal posterior insula subserves a fundamental role in human pain. *Nature neuroscience*.

Seth, A. K. (2013). Interoceptive inference, emotion, and the embodied self.*Trends in cognitive sciences*, *17*(11), 565-573.

Shi, Z., & Han, S. (2013). Transient and sustained neural responses to death-related linguistic cues. *Social cognitive and affective neuroscience*, *8*(5), 573-578.

Silveira, S., Graupmann, V., Agthe, M., Gutyrchik, E., Blautzik, J., Demirçapa, I., ... & Hennig-Fast, K. (2013). Existential neuroscience: effects of mortality salience on the neurocognitive processing of attractive opposite-sex faces.*Social cognitive and affective neuroscience*, nst157.

Taylor, K. S., Seminowicz, D. A., & Davis, K. D. (2009). Two systems of resting state connectivity between the insula and cingulate cortex. *Human brain mapping*, *30*(9), 2731-2745.

Tritt, S. M., Inzlicht, M., & Harmon-Jones, E. (2012). Toward a biological understanding of mortality salience (and other threat compensation processes).*Social Cognition*, *30*(6), 715-733.

Tsakiris, M., Hesse, M. D., Boy, C., Haggard, P., & Fink, G. R. (2007). Neural signatures of body ownership: a sensory network for bodily self-consciousness.*Cerebral cortex*, *17*(10), 2235-2244.

Turkeltaub, P. E., Eden, G. F., Jones, K. M., & Zeffiro, T. A. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage*, *16*(3), 765-780.

Turkeltaub, P. E., Eickhoff, S. B., Laird, A. R., Fox, M., Wiener, M., & Fox, P. (2012). Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. *Human brain mapping*, *33*(1), 1-13.

Uddin, L. Q., Iacoboni, M., Lange, C., & Keenan, J. P. (2007). The self and social cognition: the role of cortical midline structures and mirror neurons. *Trends in cognitive sciences*, *11*(4), 153-157.

Valentini, E., Koch, K., Nicolardi, V., & Aglioti, S. M. (2015). Mortality salience modulates cortical responses to painful somatosensory stimulation: Evidence from slow wave and delta band activity. *NeuroImage*, *120*, 12-24.

Villemure, C., Čeko, M., Cotton, V. A., & Bushnell, M. C. (2013). Insular cortex mediates increased pain tolerance in yoga practitioners. *Cerebral Cortex*, bht124.

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature methods*, *8*(8), 665-670.

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., ... & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of neurophysiology*, *106*(3), 1125-1165.