

Transient and sustained neural responses to death-related linguistic cues

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Recent research showed that perception of death-related vs death-unrelated linguistic cues produced increased frontoparietal activity but decreased insular activity. This study investigated (i) whether the increased frontoparietal and decreased insular activities are, respectively, associated with transient trial-specific processes of death-related linguistic cues and sustained death-related thought during death-relevance judgments on linguistic cues and (ii) whether the neural activity underlying death-related thought can predict individuals' dispositional death anxiety. Participants were presented with death-related/unrelated words, life-related/unrelated words, and negative-valence/neutral words in separate sessions. Participants were scanned using functional magnetic resonance imaging while performing death-relevance, life-relevance, and valence judgments on the words, respectively. The contrast of death-related vs death-unrelated words during death-relevance judgments revealed transient increased activity in the left inferior parietal lobule, the right frontal eye field, and the right superior parietal lobule. The contrast of death-relevance judgments vs life-relevance/valence judgments showed decreased activity in the bilateral insula. The sustained insular activity was correlated with dispositional death anxiety, but only in those with weak transient frontoparietal responses to death-related words. Our results dissociate the transient and sustained neural responses to death-related linguistic cues and suggest that the combination of the transient and sustained neural activities can predict dispositional death anxiety.

Keywords: death-related thought; anxiety; fMRI; frontoparietal cortex; insula

INTRODUCTION

It has been known since long that humans are troubled by being aware of the fact that all living things including humans ultimately die (Kierkegaard, 1844/1957). Death-related thought can be easily induced by exposure of scenes or words that are associated with death (e.g. Pyszczynski *et al.*, 1996; Arndt *et al.*, 1997). Reminders of death lead to powerful effects on behavior and thought in healthy individuals. For example, reminders of mortality influence social psychological phenomena, such as altruism (Jonas *et al.*, 2002), aggression (McGregor *et al.*, 1998), risk taking (Rosenbloom, 2003), and attitude toward goals (Kosloff and Greenberg, 2009). People with affective disorders such as mild depression (Simon *et al.*, 1996) and posttraumatic stress disorder (Pyszczynski and Kesebir, 2011) are even more vulnerable to death-related thought compared to healthy controls due to lack of seeking defense from cultural worldview.

Although death-related thought is strongly associated with mental health, surprisingly, little has been known about its underlying neural mechanisms. To uncover the neural substrates of death-related thought is undoubtedly critical for understanding why and how death-related thought influences human behavior and for developing appropriate strategy to cope with human death anxiety. An early functional magnetic resonance imaging (fMRI) study found that viewing photographs of a deceased loved one *vs* a stranger, combined with words specific to the death event *vs* neutral words, activated the precuneus, left medial and superior frontal gyrus, posterior cingulate gyrus, right precentral gyrus, right superior lingual gyrus, right insula, right anterior cingulate cortex, left inferior temporal gyrus and left fusiform gyrus (Gündel *et al.*, 2003). The findings suggest that grief induced by viewing a deceased loved one may consist of affect processing, mentalizing, episodic memory retrieval, processing

of familiar faces, visual imagery and autonomic regulation. These processes, however, may not be specific to death-related thought.

A recent fMRI research scanned adults while they were presented with words related or unrelated to death (Han *et al.*, 2010). It was found that, relative to death-unrelated words, death-related words were associated with increased activity in the precuneus/posterior cingulate and lateral frontal cortex but decreased activity in the bilateral insula. This finding is consistent with proposition that the effect of reminders of death cannot be simply interpreted by elicitation of other aversive experiences such as negative affect/arousal (Hayes *et al.*, 2010) because negative affect/arousal is related to increased rather than decreased insular activity (Anders *et al.*, 2004; Schmidt *et al.*, 2009). Because the insula plays a key role in representation and integration of multiple feelings that constitute the entirety of an individual or the sentient self (Craig, 2009, 2010), Han *et al.* (2010) suggested that the decreased insular activity induced by death-related words may characterize a specific process involved in death-related thought—suppression of the sentient self-awareness.

Because the previous fMRI study employed a box-car design in which death related and unrelated words were presented in separate sessions (Han *et al.*, 2010), it is unclear whether the increased frontoparietal and decreased insular activities were, respectively, associated with transient trial-specific processes and sustained death-related thought linked to linguistic cues of death. Moreover, it is unknown whether the transient or sustained neural activity underlying death-related thought can predict dispositional death anxiety. This study addressed these issues using a hybrid design that is capable of parsing transient/item-related and sustained/epoch-related neural activities (Visscher *et al.*, 2003). Participants were presented with death-related/unrelated words, life-related/unrelated words, and negative-valence/neutral words in separate sessions. They were scanned using fMRI while they performed death-relevance, life-relevance, and valence judgments on the words, respectively. Since thinking of death may lead to dialectic evaluation of life (King *et al.*, 2009) and negative affect (Arndt *et al.*, 2001), death-relevance judgments on death-related/unrelated words may engage the processes of life-relevance and valence of words besides the suppression of the sentient self-awareness. Thus,

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life-relevance and valence judgments were used to control for the process of life-relevance and word valence in order to identify the neural activity that specifically characterizes death-related thoughts during death-relevance judgments. The contrast of death-related vs death-unrelated words during death-relevance judgments revealed transient brain activity linked to trial-specific processes of death-relevance of stimuli. The contrast of death-relevance judgments vs life-relevance/valence judgments identified brain activity specifically associated with continued death-related thought. After scanning participants were asked to complete the Death Anxiety Scale (Templer, 1970) to measure their dispositional death anxiety. This allowed us to assess whether the transient, sustained, and the combination of both can predict individuals' dispositional death anxiety.

METHODS

Participants

Twenty-four undergraduate or graduate students (12 female; 17–25 years of age, mean \pm s.d. = 22.54 \pm 2.04) participated in this study as paid volunteers. All were right-handed, had normal or corrected-to-normal vision and reported no neurological or psychiatric history. Subjects were given informed consent prior to the study. This study was approved by a local ethics committee.

Stimuli and procedure

Three hundred words with each consisting of two Chinese characters were classified into five categories: (i) death-related words consisted of 30 nouns (e.g. coffin, dirge and hell) and 30 verbs (e.g. asphyxiate, suicide and drown) describing events or behaviors associated with death; (ii) negative words consisted of 30 nouns (e.g. corruption, shame and idiot) and 30 verbs (e.g. degenerate, lie and plagiarize) describing negative events or behaviors that were not associated with death; (iii) death-unrelated or neutral words consisted of 30 nouns (e.g. river, cup and guest) and 30 verbs (e.g. shut, gather and repair) describing neutral events or behaviors; (iv) life-related words consisted of 30 animal names (e.g. eagle, bear and elephant) and 30 plant names (e.g. lotus, strawberry, and willow); (v) life-unrelated words consisted of 30 clothing names (e.g. shoe, skirt and pants) and 30 furniture or commodity names (e.g. desk, soap and bench). Word frequencies were matched for words of different categories (Sun *et al.*, 1997). An independent group of 46 subjects were recruited to rate semantic death-relevance of death-related, death-unrelated and negative words on an 11-point Likert scale ('To what degree do you think this word is related to death?', 0 = not related at all, 10 = extremely related) and the degree of arousal invoked by each word on an 11-point Likert scale ('How strong is your negative feeling induced by this word?', 0 = not at all, 10 = extremely strong). The scores of death-relevance were higher for death-related words (8.55 \pm 1.07) than for death-unrelated (0.26 \pm 0.46) and negative valence (1.11 \pm 1.41) words [$t(45) = 43.35$ and 28.13, both $P < 0.001$]. The scores of arousal were also higher for death-related words (6.30 \pm 2.22) than for death-unrelated (0.32 \pm 0.48) and negative (4.16 \pm 2.06) words [$t(45) = 17.92$ and 5.278, both $P < 0.001$]. The scores of arousal were higher for negative words than for death-unrelated words [$t(45) = 13.39$, $P < 0.001$]. An independent group of 24 subjects were asked to rate life-related and life-unrelated words in terms of life-relevance ('How is this word relevant to life?' 0 = not at all relevant, 10 = extremely relevant) and arousal ('How strong is your feeling induced by this word?' 0 = not at all, 10 = extremely strong) on an 11-point Likert scale. Life-relevance was rated significantly higher for life-related than life-unrelated words [7.72 \pm 1.95 vs 2.55 \pm 2.24, $t(23) = 10.89$, $P < 0.001$]. Rating scores of arousal were slightly higher for life-related than life-unrelated words [1.21 \pm 1.09 vs 0.61 \pm 1.14, $t(23) = 4.896$, $P < 0.001$].

Each word with a 60 size bold-face font and a visual angle of 2.2° \times 3.0° (width \times height) at a viewing distance of 80 cm was presented in the center of a screen against a gray background. Functional images were obtained from nine experimental runs. Each run consisted of three sessions of death-relevance judgment task, valence judgment task and life-relevance judgment task. The order of different tasks was counterbalanced across runs using Latin-square design. Before each session, a fixation was shown for 7 s followed by a 3-s task instruction (i.e. death-relevance judgment, valence judgment or life-relevance judgment). In each session for death-relevance judgment, subjects were presented with 10 death-related words and 10 death-unrelated words in a randomized order and had to judge whether each one was semantically associated with death by pressing one of two buttons with the right index or middle finger. Both response speed and accuracy were emphasized. Likewise, in each session for valence judgments or life-relevance judgments, subjects judged the valence of 10 negative and 10 neutral words, or the life-relevance of 10 life-related and 10 life-unrelated words. Each word was presented for 400 ms, and was followed by an inter-trial interval varying randomly among 800, 1000, 1200 and 1400 ms. The responding fingers were counterbalanced across subjects.

After the scanning procedure, subjects rated their subjective feeling of semantic death-relevance of death-related and death-unrelated words on an 11-point Likert scale (0 = not at all related, 10 = extremely related) and arousal of negative emotion invoked by each word on an 11-point Likert scale (0 = not at all, 10 = extremely strong). The 15-item Death Anxiety Scale (Templer, 1970) with true/false format was administered to measure individuals' degree of dispositional death anxiety.

fMRI data acquisition and analysis

Scanning was performed on a GE 3T scanner with a standard head coil in Peking University First Hospital. Thirty-two transverse slices of functional images covering the whole brain were acquired using a gradient-echo-echo-planar pulse sequence (64 \times 64 \times 32 matrix with 3.75 \times 3.75 \times 4 mm spatial resolution, inter-slice gap = 1 mm, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, field of view (FOV) = 24 \times 24 cm, flip angle = 90°). Anatomical images were obtained using a 3D FSPGR T1 sequence (256 \times 256 \times 128 matrix with a spatial resolution of 0.938 \times 0.938 \times 1.4 mm, TR = 7.4 ms, inversion time (TI) = 450 ms, TE = 3.0 ms, flip angle = 20°).

SPM2 (the Wellcome Trust Centre for Neuroimaging, London, UK) was used for imaging data processing and analysis. The functional images were adjusted for slice timing and realigned to the first scan to correct for head motion between scans. The anatomical image was co-registered with the mean functional image produced during the process of realignment. All images were normalized to a 2 \times 2 \times 2 mm Montreal Neurological Institute (MNI) template. Functional images were spatially smoothed using a Gaussian filter with the full-width/half-maximum parameter (FWHM) set to 8 mm. We then modeled trials of death-related words, death-unrelated words, negative words, neutral words, life-related words, and life-unrelated words by including six regressors convolved with canonical hemodynamic response function (HRF) as well as their temporal derivatives in the general linear model (GLM) to estimate different event-related effects. Epoch-based effects were estimated by convolving three box-car functions with canonical HRF and including them as regressors in the GLM to represent sustained effects of death-relevance judgments, valence judgments and life-relevance judgments. Six movement parameters (translation: x , y , z ; rotation: pitch, roll, yaw) were included in the statistical model. Regionally specific effects were identified using linear contrasts in individual participants with a fixed effect model. Random

effect analyses were then conducted using one-sample *t*-test based on statistical parameter maps from each individual participant to allow population inference. Areas of significant activation were identified using a threshold of $P < 0.05$ (FDR corrected for multiple comparisons). Specifically, event-related (i.e. transient) activation was calculated by contrasting death-related vs death-unrelated stimuli within the sessions of death-relevance judgment. Epoch-based (i.e. sustained) activation was attained by comparing sessions of death-relevance judgment to those of life-relevance/valence judgments. Contrast values of death-related vs death-unrelated words or death-relevance vs life-relevance/valence judgments within the regions of interest (ROIs) with radii of 5 mm and centered at the peak voxels of activations were extracted to allow further regression analyses.

RESULTS

Behavioral results

Rating scores of death-relevance from one subject was missing due to technical failure and this subject was excluded from the correlation analysis. A repeated measures multivariate analysis of variance (MANOVA) revealed a significant difference among death-related words, negative words and neutral words with regard to subjective ratings of semantic death-relevance and emotional arousal (Pillai's Trace = 1.65, $F(4, 92) = 104.36$, $P < 0.001$). A repeated measures analysis of variance (ANOVA) was conducted and confirmed the effect of word category on rating scores of death-relevance [$F(2, 44) = 570.42$, $P < 0.001$]. Post-hoc analysis revealed that death-relevance ratings of death-related words were higher than those of negative words (8.89 ± 0.95 vs 1.11 ± 1.58 , $P < 0.001$) and those of neutral words (0.27 ± 0.47 , $P < 0.001$), and death-relevance ratings of negative words were slightly greater than those of neutral words ($P < 0.05$). We also conducted an ANOVA to examine the difference of arousal ratings on death-related, negative, and neutral words. A significant effect of word category was found [$F(2, 44) = 103.6$, $P < 0.001$], and post-hoc comparisons confirmed that death-related words did not significantly differ from negative words (5.8 ± 2.2 vs 4.8 ± 1.9 , $P > 0.05$), whereas both death-related words and negative words were rated more arousing than neutral words (0.3 ± 0.5 , P 's < 0.001). Response accuracy (mean \pm s.d. = $93.09 \pm 2.89\%$) was high in the current study and did not differ significantly between different judgments tasks. Reaction times (RTs) for correct responses to each word category were calculated and subject to a 3×2 (ANOVA) with task (death-relevance judgment/valence judgment/life-relevance judgment) and response (yes/no) as within-subjects variable. There were significant main effects of task [$F(2, 46) = 36.14$, $P < 0.001$] and response [$F(1, 23) = 17.77$, $P < 0.001$], as well as a significant interaction of the two [$F(2, 46) = 8.80$, $P < 0.001$]. Pair-wise contrasts showed that RTs to life-relevance judgments did not differ from those to death-relevance judgments (673 ± 92 vs 683 ± 95 ms, $P > 0.05$), which were shorter than those to valence judgments (711 ± 94 ms, P 's < 0.001). Pair-wise contrasts also revealed shorter RTs to death-related words than to death-unrelated words during death-relevance judgments (658 ± 97 vs 708 ± 99 ms, $P < 0.001$), to life-related words than to life-unrelated words (661 ± 95 vs 686 ± 91 ms, $P < 0.005$), but no significant difference between negative words and neutral words (703 ± 94 vs 719 ± 100 ms, $P > 0.1$).

Transient neural activity

The contrast of death-related vs death-unrelated words within the sessions of death-relevance judgments revealed transient increased activity in the left inferior parietal lobule (LIPL), the right frontal eye field (RFEF), the right superior parietal lobule (RSPL), and the medial prefrontal cortex (MPFC; Figure 1a and Table 1). The reverse contrast did

not show any significant activation. Similar analyses were conducted with the sessions of valence judgments and life-relevance judgments but failed to show any significant transient activations linked to negative or life-related words at the threshold of $P < 0.05$ (FDR corrected for multiple comparisons). The contrast of negative vs neutral words showed increased activity in the left insula ($x/y/z = -32/10/-4$, $k = 43$, $Z = 3.82$) at the threshold of $P < 0.001$, uncorrected. To examine how specifically the frontoparietal regions and MPFC were engaged in death-related processing, two masks were created by contrasting negative vs neutral words and life-related vs life-unrelated words using a liberal threshold of $P < 0.1$. These were then applied to the contrast of death-related vs death-unrelated words as exclusive masks. Whereas activations in the LIPL, RFEF and RSPL were retained after the exclusive masking, the MPFC activation was eliminated.

The contrast values of death-related vs death-unrelated words were highly inter-correlated within the three frontoparietal ROIs (Cronbach's $\alpha = 0.835$), suggesting similar functional roles of these activations. We thus combined the three frontoparietal ROIs into a composite by averaging the contrast values in the three brain regions for the following correlation and regression analyses.

Sustained neural activity

We first contrasted death-relevance vs life-relevance judgments and death-relevance vs valence-judgments to control for the process of life-relevance and word valence, respectively. Both contrasts showed significantly decreased activity in the bilateral insula and subcortical regions (Table 1). We used the contrast of death-relevance vs (life-relevance and valence) judgments to control for two processes life-relevance and word valence and produced a single index of insular deactivation for the following correlation and regression analyses. Similarly, this contrast showed significantly decreased activity in the left anterior insula/putamen (LAIns), the left posterior insula (LPIns), the right anterior insula/putamen (RAIns) and the right posterior insula (RPIns; Table 1 and Figure 1b).

We examined the correlation within the decreased insular activity in the four ROIs (LAIns, LPIns, RAIns and RPIns) and found that they were highly inter-correlated with each other (Cronbach's $\alpha = 0.887$). Thus, we combined the four ROIs into a composite by averaging their contrast values for the following correlation and regression analyses.

Correlation between transient and sustained death-related neural activities

A correlation analysis showed a significantly positive correlation between the transient frontoparietal activity and the sustained insular activity ($r = 0.630$, $P < 0.001$; Figure 1c). The higher transient activation in the frontoparietal regions was associated with a greater sustained decreased activity in the insular regions across subjects. This association was further confirmed by separate correlation analyses between each of the three frontoparietal ROIs (LIPL, RFEF and RSPL) and each of the four insular ROIs (LAIns, LPIns, RAIns and RPIns), which demonstrated that out of the 12 ROI pairs, 9 showed significant correlations ($r = 0.405$ – 0.699 , P 's < 0.05) and 3 marginally significant correlations (LIPL and LAIns, $r = 0.380$, $P = 0.067$; LIPL and RAIns, $r = 0.361$, $P = 0.083$; LIPL and LPIns, $r = 0.375$, $P = 0.071$).

Neural activities involved in death-related processing and subjective feelings of death-relevance

Differential rating scores on semantic death-relevance for death-related vs death-unrelated words were first transformed into ranks due to a significant violation of normality (Shapiro–Wilk test, $W = 0.891$,

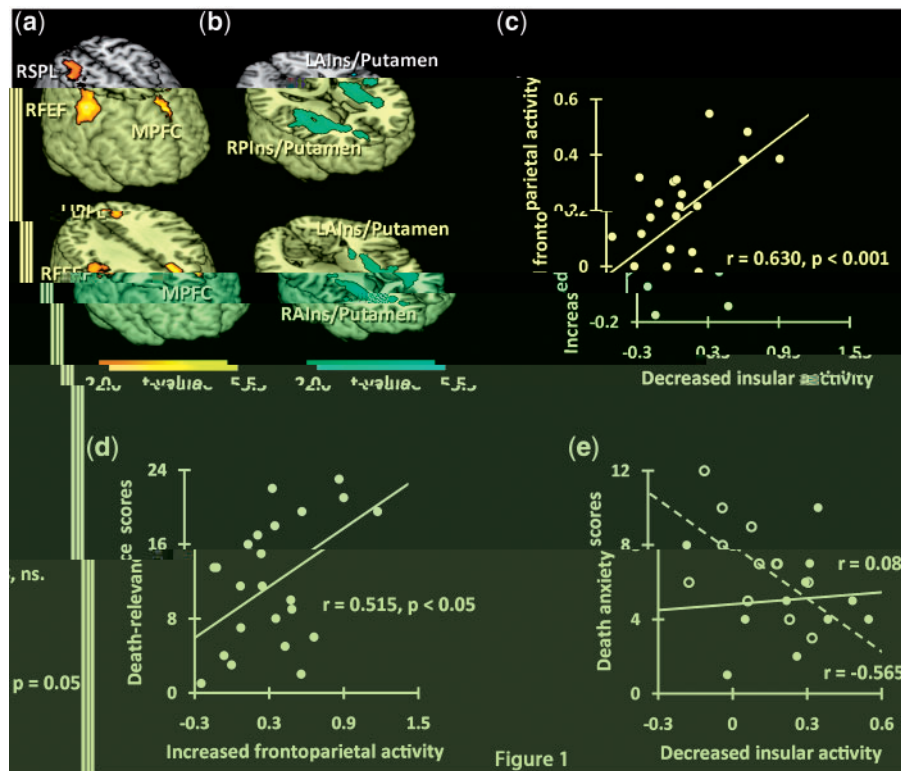


Fig. 1 Brain imaging results. (a) Transient increased frontoparietal activity to death-related words vs death-unrelated words in frontoparietal regions. (b) Sustained decreased activity in the bilateral insula to death-relevance judgments compared to the control tasks. (c) The correlation between transient frontoparietal activity and sustained decreased insular activity. (d) The correlation between the transient frontoparietal activity and rank of rating scores on death-relevance of death-related words vs death-unrelated words. (e) The correlation between the sustained insular activity and DAS scores in individuals with weak (dots and solid line) and strong (circles and dashed line) transient frontoparietal activity. LIPL, left inferior parietal lobule; RFEF, right frontal eye field; RSPL, right superior parietal lobule; MPFC, medial prefrontal cortex. LAIns, left anterior insula; LPIIns, left posterior insula; RAIns, right anterior insula; RPIIns, right posterior insula.

Table 1 Transient and sustained brain activity related to death-related words and death-relevance judgments

Regions	x	y	z	k	Z
Transient activity: Death-related words > Death-unrelated words					
L posterior intraparietal sulcus	-24	-70	32	181	3.85
R frontal eye field	52	-10	48	746	4.27
R anterior intraparietal sulcus	36	-38	62	221	3.66
Sustained activity: Valence judgments > Death-relevance judgments					
L insula/putamen	-38	16	10	613	3.93
L insula	-42	-18	20	181	3.59
R insula/putamen	24	16	8	937	3.82
R inferior occipitotemporal cortex	48	-56	-10	228	3.85
Sustained activity: Life-relevance judgments > Death-relevance judgments					
L insula/putamen	-30	-14	12	446	3.64
R insula/putamen/thalamus	20	-24	2	844	4.16
R temporoparietal junction	50	-42	26	209	3.87
Sustained activity: (Valence and life-relevance judgments) > Death-relevance judgments					
L anterior insula/putamen	-36	16	12	2441	3.96
L posterior insula	-32	-14	14	^a	4.01
R anterior insula/putamen	42	16	14	3036	3.93
R posterior insula	40	-8	18	^a	4.37

^aAnterior insula/putamen and posterior insula were in the same cluster. L: Left. R: Right.

$P < 0.05$). A correlation analysis was then conducted and showed a significant correlation between the rating scores of death-relevance and the frontoparietal activation (frontoparietal ROI composite, $r = 0.515$, $P < 0.05$; Figure 1d). This association was further confirmed by calculating correlations between the rating scores and the neural activity in each brain region (LIPL, $r = 0.553$, $P < 0.01$; RFEF, $r = 0.402$, $P = 0.057$; RSPL, $r = 0.429$, $P < 0.05$). Subjective ratings of

death-relevance did not correlate significantly with the sustained decreased insular activity ($r = 0.079-0.345$, P 's > 0.1). Ratings of emotional arousal did not significantly correlate with the transient increased activity ($r = 0.214-0.360$, P 's > 0.09) or with the sustained decreased activity ($r = 0.017-0.146$, P 's > 0.05).

Neural activities involved in death-related processing and dispositional death anxiety

As neither the transient frontoparietal activity nor the sustained decreased insular activity was significantly correlated with the DAS scores ($r = 0.143$ and 0.298 , P 's > 0.1), we conducted a hierarchical regression analysis (Baron and Kenny, 1986; Frazier *et al.*, 2004) to assess whether the interaction of the transient and sustained neural activity was associated with the DAS scores. All variables (DAS scores, contrast values indexing frontoparietal ROI composite activation, and contrast values indexing decreased insular ROI composite activity) were first standardized using z -transformation. The frontoparietal and insular activities were regressed in the first step and their interaction was included in the second step. The first-step analysis failed to show significant main effects of the frontoparietal and insular activity (frontoparietal activity: $\beta = -0.046$, $P > 0.8$; insular activity: $\beta = -0.279$, $P > 0.3$; $R^2 = 9.6\%$, $F(2, 21) = 1.116$, $P > 0.3$). The second-step analysis, however, showed a significant interaction of the frontoparietal and insular activity ($\beta = 0.420$, $P = 0.05$; $\Delta R^2 = 15.8\%$, $\Delta F(1, 20) = 4.223$, $P = 0.05$). This moderator effect was also confirmed using separate frontoparietal ROIs (LIPL, RFEF, and RSPL) and insular ROIs (LAIns, LPIIns, RAIns and RPIIns). Significant interactions were only observed between right frontoparietal areas (RFEF and

RSPL) and anterior insula (LAIIns and RAIIns) ($\Delta R^2 = 16.9\text{--}34.5\%$, $\Delta F(1, 20) = 4.451\text{--}12.78$, $P's < 0.05$). Similar analyses including LIPL, LPIIns and RPIIns did not show significant effect of interactions ($\Delta R^2's < 8.90\%$, $\Delta F's(1, 20) < 2.125$, $P's > 0.1$).

This moderator effect was further elaborated by mean splitting all 24 subjects into two groups according to their right frontoparietal activation magnitude. For those with weak transient right frontoparietal responses to death-related words, their sustained decreased anterior insular activity was negatively correlated with the DAS scores ($r = -0.653$ to -0.541 , $P's = 0.02\text{--}0.069$); whereas for those with strong transient responses in the right frontoparietal cortex to death-related words, no such correlation was observed ($r = 0.021\text{--}0.182$, $P's > 0.5$; Figure 1e).

DISCUSSION

The high response accuracy of death-relevance judgments and subjective ratings of death-relevance of words indicate that death-related words indeed induced death-related thought during scanning. The fMRI results showed increased transient activity to death-related vs death-unrelated words in the bilateral parietal lobe and the right frontal eye field. The increased frontoparietal activity was also observed in our previous study that employed a block design (Han *et al.*, 2010). This study, however, indicates that the frontoparietal activity was specific to the event-related component of neural responses to death-related words. In addition, the correlation analysis suggested an association between the transient frontoparietal activity and subjective feelings of death-relevance of words.

The frontoparietal network is engaged in multiple brain functions. Most closely related to this study, perceiving physical threat to oneself (Lloyd *et al.*, 2006) and encoding social threat cues (Han *et al.*, 2008) activated the lateral frontoparietal cortices. The frontoparietal network engaged in the processing of threatening stimuli partially overlaps with the frontoparietal circuit involved in voluntary allocation of attention (Corbetta and Shulman, 2002). These brain imaging results are consistent with the behavioral findings that threatening objects are more attracting than neutral ones (Öhman *et al.*, 2001) and it takes longer time to disengage attention from the location of threats (Koster *et al.*, 2004). Death-related words are threatening in terms of their meanings related to life. Thus, it is not surprising that the prior knowledge about death may bias attention to death-related words and thus recruit the frontoparietal network. The human brain may evolve a stimulus-driven transient neural mechanism that helps to detect death-related information efficiently.

The sustained activity was characterized by the bilateral decreased insular activity. The insula plays a key role in affective processing. The left anterior insular activity increased with reported negative valence of emotional pictures (Anders *et al.*, 2004). Emotional arousal induced by pictures was associated with increased activity in the bilateral ventrolateral prefrontal and insular regions (Schmidt *et al.*, 2009). Grief induced by viewing a deceased loved one also activated the right insula and other brain regions (Gündel *et al.*, 2003). Similarly, using a lenient threshold, we observed increased activity in the left insula associated with the processing of negative vs neutral valence words. Thus, regardless of using pictures or words, negative affect/arousal is associated with increased insular activity. Death-relevance judgments modulated the insular activity in an opposite direction compared to the effect of negative valence and arousal, leading to decreased rather than increased insular activity. This effect cannot be explained by the assumption that death-related thought simply induces negative emotion or arousal.

The insula also plays a central role in perception and awareness of multiple aspects of one's body (Craig 2002, 2009) and the

representation of the interoceptive body in the anterior insula is essential for subjective feelings of the sentient self (Craig, 2010). This study extended the previous research by showing that the decreased insular activity is a sustained neural process involved in death-related thought during death-relevance judgments rather than a transient neural response locked to the onset of each death-related word. If the decreased insular activity reflected continuous suppression of the sentient self-awareness (Han *et al.*, 2010), it may provide a neural mechanism of the avoidance of self-focus after being reminded of mortality (Arndt *et al.*, 1998). Self-focused state may require the existence of a feeling of bodily self. The weakened sense of the sentient self arising from online death-related thought makes the feeling of bodily self degenerate and thus impairs the entity for self-focusing. Apparently, long-lasting decreased insular activity associated with the sentient self-awareness may induce mental problems. A recent study has shown that major depressive disorder patients showed reduced neural activity in the bilateral anterior insula during rest periods relative to healthy controls (Wiebking *et al.*, 2010). As the previous studies have reported high lifetime risks of suicide for affective disorder such as depression (e.g. Inskip *et al.*, 1998), future research should investigate the relation between the neural activity underlying death-related thought and abnormal behaviors such as self-harm and suicide in individuals with affective disorder.

Interestingly, we found that the transient increased frontoparietal activity was positively correlated with the sustained decreased insular activity associated with death-related thought. Thus, the transient and sustained activity underlying death-related thought induced by linguistic cues was not independent but was associated with each other. The results suggest that individuals with stronger stimulus-driven attentional bias to death-related information may experience greater persistent decrease of the sentient self-awareness. Previous studies suggest that individuals who have undergone and survived deadly threats have recognition of new possibilities or path's for one's own life (Tedeschi and Calhoun, 1996) and transcendent attitudes about existential issues (Tedeschi and Calhoun, 2004; Cozzolino, 2006). An interesting question for future research is whether and how the neural mechanisms underlying death-related thoughts dissociated in our work is associated with the change of attitudes toward oneself during post-traumatic growth.

One major goal of studies of death is to understand the fear of death or death anxiety. Behavioral studies have developed questionnaires to measure death anxiety (e.g. Templer, 1970; Conte *et al.*, 1982) that is a prominent concern in groups characterized by psychopathology (Pollak, 1980) and has been associated with depression (e.g. Templer, 1971). However, we have known little about the neural mechanisms underlying death anxiety. The current work addressed this issue by examining whether the neural activity involved in death-related thought can predict individual differences in dispositional death anxiety. The regression analysis showed that neither the transient increased frontoparietal activity nor the sustained decreased insular activity alone was able to account for one's dispositional death anxiety. Instead, death anxiety was predicted by the interaction of the transient and sustained activity. Specifically, we showed that greater decreased insular activity was associated with lower death anxiety, but only in those who showed weak transient frontoparietal activity. It is possible that it may be unnecessary to resort to suppression of self-awareness to reduce death anxiety if death-related information can efficiently invoke one's attention. However, for those whose voluntary attention to death-related information is weak, a decreased sense of the sentient self may then contribute to reduce death anxiety. Otherwise, under the circumstance that neither strategy is functional, death anxiety would be high and psychological well-being would be jeopardized. Hayes *et al.*'s (2010) recent work suggests that death

anxiety constitutes different aspects such as mortality salience, death association, anxiety-buffer threat, and dispositional death-thought accessibility. The Death Anxiety Scale used in the current work assessed general death anxiety rather than different aspects of death anxiety. Future research may dissociate the neural activities that are associated with different aspects of death anxiety.

A recent fMRI study found increased activity in the right amygdala, left rostral anterior cingulate cortex, and right caudate nucleus during mortality salience priming that required reading sentences like 'I am afraid of a painful death' relative to a control condition (Quirin *et al.*, 2012). Such mortality salience priming functions as reminders of death toward oneself (i.e. to remind one's own death) and activated the emotional neural network. The paradigm used in our work, however, required judgments on whether a number of words were generally related to death and thus the death-related thoughts induced in such paradigm were not directly oriented toward oneself. These findings together implicate that the neural activity underlying death-related thoughts may be modulated by whether leading death-related thoughts directly toward oneself.

In summary, our fMRI results decomposed the neurocognitive processing of death-related linguistic cues into two subcomponents. The transient component was characterized by the increased frontoparietal activity and the sustained component was reflected in the decreased insular activity. The transient and sustained activities were associated with each other and their interaction was able to predict individual's dispositional death anxiety. Our findings contribute to the understanding of the neural substrates of death-related thought and death anxiety. Future research should further investigate the relation between the neural activity involved in death-related thought and affective disorder so as to understand the neural mechanisms of mental health from the perspective of existence concern.

Conflict of Interest

None declared.

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