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Tracking Deceased-Related Thinking With Neural Pattern Decoding of a Cortical-Basal Ganglia Circuit

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ABSTRACT

BACKGROUND: Deceased-related thinking is central to grieving and potentially critical to processing of the loss. Self-report measurements might fail to capture important elements of deceased-related thinking and processing. Here, we used a machine learning approach applied to functional magnetic resonance imaging—known as neural decoding—to develop a measure of ongoing deceased-related processing.

METHODS: Twenty-three subjects grieving the loss of a first-degree relative, spouse, or partner within 14 months underwent two functional magnetic resonance imaging tasks. They first viewed pictures and stories related to the deceased, a living control person, and a demographic control figure while providing ongoing valence and arousal ratings. Second, they performed a 10-minute Sustained Attention to Response Task with thought probes every 25 to 35 seconds to identify deceased, living, and self-related thoughts.

RESULTS: A conjunction analysis, controlling for valence/arousal, identified neural clusters in basal ganglia, orbital prefrontal cortex, and insula associated with both types of deceased-related stimuli versus the two control conditions in the first task. This pattern was applied to functional magnetic resonance imaging data collected during the Sustained Attention to Response Task and discriminated deceased-related but not living or self-related thoughts, independently of grief severity and time since loss. Deceased-related thoughts on the Sustained Attention to Response Task correlated with self-reported avoidance. The neural model predicted avoidance over and above deceased-related thoughts.

CONCLUSIONS: A neural pattern trained to identify mental representations of the deceased tracked deceased-related thinking during a sustained attention task and also predicted subject-level avoidance. This approach provides a new imaging tool to be used as an index of processing the deceased for future studies of complicated grief.

Keywords: Grieving, Insula, MVPA, Neural decoding, Rumination, Thought prediction

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Recurrent thoughts of a deceased loved one are common following a loss (1,2). These thoughts are considered a part of normal grief (1). The evolution of one's feelings toward the deceased is described as grief work, or processing of the loss (3,4). Existing theories of grieving emphasize the importance of grief work, requiring thinking about the deceased (1,4,5). Excessive thinking about the deceased is associated with poorer grief outcomes in some studies (6) but not in others (7,8). Furthermore, reductions in avoidance (i.e., more thinking about loss) correlate with positive outcomes (9). In part, these mixed findings likely stem from the different aspects of deceased-related thinking in each study (i.e., worry, rumination, contemplation, avoidance). However, another reason for disagreeing results may be the way these thoughts are measured.

Current methods for assessing deceased-related thinking depend on self-report. Self-report is vulnerable to biases that might influence accuracy (10–12). Furthermore, self-report is limited to thoughts that are consciously experienced and remembered later. However, processing of loss that does not occur consciously or is later forgotten may be especially relevant to psychiatric outcomes (13,14). We therefore sought to identify a neural signal that could predict ongoing self-generated thoughts of the deceased. This might serve as a better proxy for actual grief work and processing of the loss than self-reported deceased related thoughts.

To do this, we used a two-step technique known as neural decoding where machine-learning methods are used on a first set of functional magnetic resonance imaging (fMRI) data to detect a pattern of brain activity associated with a target mental process. This pattern is then applied to a second set of data to track the occurrence of that mental process. Neural decoding has been used to track ongoing perceptions (15), memory (16), and emotional processes (17,18). To our knowledge it has not been used to track the occurrence of a specific type of thought.

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To accomplish these goals, we first used machine learning applied to fMRI to identify a neural pattern associated with mental representations of the deceased in subjects grieving a loss. This voxel pattern was then applied to a second set of fMRI data obtained from a 10-minute sustained attention task where subjects reported the occurrence of deceased-related thoughts. The neural model was used to discriminate instances when subjects reported thinking about the loss.

Deceased-related thinking may be experienced in multiple ways, including as an image (19), an autobiographical memory (20), or a sense of being with the person (21). We therefore sought to identify a neural network responsive to representations of the loss across these three visual, memory, and relational modalities, which we term a transmodal mental representation of the deceased. Prior studies have identified basal ganglia activity in response to pictures of the deceased (22). Nevertheless, it remains unclear if this pattern is specific to representing a deceased figure or applies to any close attachment. We therefore aimed to determine the neural circuitry of mental representations of the deceased across multiple perceptual modalities while also controlling for demographic and attachment-related representations. To do that, we used memories and images of a living relative and of a fictional but demographically comparable avatar.

We recruited subjects bereaved of a first-degree family member in the previous 14 months who underwent two fMRI tasks: 1) a multimodal representations of the deceased task that controlled for attachment and demographic factors and 2) a Sustained Attention to Response Task (SART) (23) interspersed with thought probes about deceased-related thinking. We hypothesized that we would identify a model of transmodal neural representations of the deceased and that neural decoding implemented with this model during the SART would detect deceased-related thinking.

METHODS AND MATERIALS

Participants

Twenty-three subjects bereaved of a first-degree relative 3 to 14 months ago (mean 7.7 ± 4.1 months) participated in this study. This study was part of a larger study comparing suicide- and non–suicide-bereaved individuals. As a result, we recruited subjects across a relatively wide range of times since loss and still capture a moderate to severe degree of grieving severity. Subjects were 18 to 65 years old (mean 46 ± 13.6 years) and four subjects were men. All participants had normal-color vision and spoke English as a first language. Recruitment was done through social media websites and reaching out to people listed as relatives in obituaries. All subjects were medically healthy as determined by medical history, examination, and standard blood and urine tests. Exclusion criteria were recent bipolar disorder (manic episode within the previous year), recent substance use disorder (met criteria within previous 6 months), current obsessive-compulsive disorder, lifetime schizophrenia, or schizoaffective disorder assessed with the Structured Clinical Interview for DSM-IV Axis I. Subjects who were taking psychiatric medications were required to be on a stable dose for 2 weeks prior to scanning. The New York State Psychiatric Institute Institutional Review Board approved this study and all subjects gave written informed consent.

Procedure

Subjects underwent a diagnostic interview, a prescan interview, an MRI scan, and then a postscan interview. During the MRI scan subjects performed the representations of deceased task followed by the SART. Grief severity was measured by the Inventory of Complicated Grief (ICG) (24) and avoidance of reminders of the loss was measured using the Impact of Event avoidance subscale (25); both scales were administered during the postscan interview.

Stimulus Acquisition and Preparation

Stimuli for the representations of the deceased task were acquired during the prescan interview. Subjects were asked to think of a living person who became the living control person. This person could be a brother, sister, friend, or anyone that the subject deemed to have a similar relationship as they did with the deceased. Subjects provided two front-facing pictures of the deceased and living control person taken within the past five years as well as three stories about the deceased and the living control person. Participants were instructed to tell stories that "make you think of that person." Stories were then reduced to three lines each ranging from 30 to 50 characters, including spaces.

A demographic control figure was then created to match the demographic features (age, ethnicity, gender) of the deceased. Pictures for the demographic control figure were obtained from the FERET (Facial Recognition Technology) database (http://www.itl.nist.gov/iad/humanid/feret/feret_master.html) and were selected to match the pictures of the deceased in terms of age, ethnicity, gender, and facial expression. A parallel set of stories was composed corresponding to the demographic control figure. These stories always described the same relational dyads as the one described in the deceased stories (father-son, mother-daughter), with the demographic control figure occupying the same part of dyad as the deceased. Stimuli were preprocessed to equalize visual features (pictures) and valence and arousal (demographic control figure stories). Details of stimulus preprocessing are included in the Supplement.

Representations of Deceased Task

Four runs of the representations of deceased task were administered. Each run consisted of two blocks each of the three persons: deceased, living control person, and demographic control figure (Figure 1A). Each person block lasted for 46.5 seconds and comprised three modalities: picture, story, and think. In the picture modality two pictures corresponding to the person-condition were displayed for 7.5 seconds each. In the story modality one of the three stories was presented in successive phrases of three lines with each line being presented for 5 seconds. The stories were alternated across blocks. In the think modality subjects were instructed to imagine being with the person for 15 seconds. Each modality was separated by a 500-ms fixation and each person-condition block was followed by valence (1 = very sad,

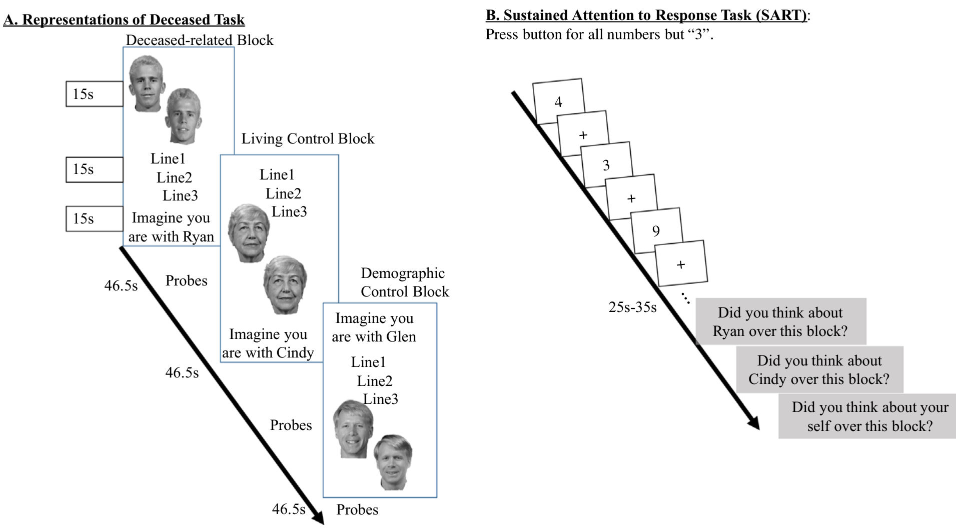

Figure 1. **(A)** Representations of deceased task: in this task three person blocks (deceased, living control person, demographic control figure) were presented in a permuted order twice per run across four runs. Each block comprised three modalities (picture, story, think). For the picture modality two pictures were presented for 7.5 seconds each. For the story modality one story was presented in three lines, with each line being presented for 5 seconds each. Stories alternated across blocks. In the think modality subjects were instructed to think about the deceased for 15 seconds. Five-hundred-millisecond fixations were presented in between each modality. Hence, each person block lasted 46.5 seconds. Within each block the ordering of modalities was randomized. Valence and arousal probes were presented following each block. To protect confidentiality, sample images for this figure are all taken from the FERET database of facial images collected under the FERET program, sponsored by the Department of Defense Counterdrug Technology Development Program Office (37). **(B)** Sustained Attention to Response Task (SART): the SART was presented following the representations of deceased task. During SART trials subjects were instructed to press a button every time a number aside from 3 was presented. Numbers were presented for 1.5 seconds with a fixation jitter of around 2 seconds. Blocks lasted for 25 to 35 seconds. Following each block subjects were probed regarding deceased- and living control person–related thinking. Sixteen SART blocks were performed per subject.

2 = sad, 3 = neutral, 4 = happy, 5 = very happy) and arousal (1 = very relaxed, 2 = relaxed, 3 = neutral, 4 = aroused, 5 = very aroused) probes. Presentation order of person blocks was permuted across the four runs. Presentation of modalities within blocks was randomized. Before the first presentation of the demographic control figure a slide was presented introducing the subject to the demographic control figure.

Sustained Attention to Response Task

The SART was always performed following the representations of deceased task (Figure 1B). In the SART, subjects were instructed to press a button every time a number came on screen except for the number 3. Numbers were presented on screen for 1.5 seconds with an intertrial jitter averaging 2 seconds. The number 3 was presented 11% of the time to ensure subjects remained engaged in the task. To limit predictability of thought probes, the length of each block of this task was randomly selected from a range of 25 to 35 seconds. Subjects completed 16 blocks. Following each block, thought probes were presented as follows: 1) Did you think about [name of deceased] over the past block (Yes/No)? 2) Did you think about [name of living control person] over the past block (Yes/No)? 3) Did you think about yourself over the past block (Yes/No)? This is similar to the usage of the SART to detect mind-wandering in a number of prior studies (26,27).

Image parameters and preprocessing are provided in the Supplement.

Feature Selection

Univariate Analysis of Representations of Deceased Task. The full workflow for this study is presented in Supplemental Figure S1. We sought to identify a mask of voxels involved in transmodal mental representations of the deceased (Supplemental Figure S1, step 1). Multiple mental processes are likely to occur during presentation of the person-related stimuli, such as person representation as well as self-related thoughts. We were interested in the representation of the person, which likely occurs first. Therefore, the first 5 seconds of each trial were modeled, with the remaining 10 seconds modeled via a nuisance regressor. Nevertheless, a 15-second block was used to display the stimuli to create the expectation for extended exposure to each stimulus and allow subjects to immerse themselves. Standard 6° motion regressors were included as covariates in all analyses.

A least squares deconvolution method (least squares–separate) and registration were applied and described in the Supplement.

To conduct univariate analyses, we compared parameter estimates of the deceased (D) and control living and demographic (CLD) conditions across the three modalities of picture (PIC), story (STO), and think (THI), thus producing the following groups: (D_PIC, D_STO, D_THI, CLD_PIC, CLD_STO, CLD_THI). Results from *t* tests were calculated as follows: picture (D_PIC > CLD_PIC), story (D_STO > CLD_STO), think (D_THI > CLD_THI). This analysis was conducted while controlling for valence and arousal ratings. A voxelwise threshold of $p < .001$ and a cluster-size threshold of $p < .05$ was applied with the cluster command in FSL. The rationale for using *t* tests on standardized data rather than mixed-effect models is also provided in the Supplement.

Conjunction Analysis. Conjunction analysis was used (28) to identify a transmodal mask for mental representations of the deceased (Supplemental Figure S1, step 2). The conjunction analysis tests the degree to which there is an effect for both task A and task B. The non–cluster-corrected results for the contrast between deceased-related stories versus control stories and the contrast between deceased-related pictures and control pictures were input to the conjunction analysis ((D_PIC > CLD_PIC) and (D_STO > CLD_STO)). Only the picture and story modalities were input into the conjunction analysis because the think condition did not produce significant results.

We applied a voxelwise threshold of $p < .001$. We did not apply a cluster correction to this mask because we sought to identify a large set of clusters, thereby increasing signal to noise ratio for subsequent multivoxel pattern analysis analyses. This is similar to the approach employed in prior conjunction studies (29,30). To identify a more stringent conjunction mask we employed a cluster threshold of $p < .05$.

Model Training. To identify a pattern for representations of the deceased in the conjunction results we calculated a logistic regression multivoxel pattern analysis model discriminating deceased related and control picture and story blocks within these voxels controlling for valence/arousal (Supplemental Figure S1, step 3). We used fast simultaneous training of generalized linear models (31) to obtain an optimal penalization constant to predict the condition type of hold-out data across 100 out-of-sample cross-validation runs. Full details of the classification approach are provided in the Supplement. Additional control analyses were conducted on two null regions to highlight the specificity of conjunction based model training. Full details of these analyses are provided in the Supplement.

Model Application: Neural Decoding of the SART Data

In addition to standard preprocessing, four-dimensional time series of SART data were registered to standard space and motion effects were regressed out using standard FSL 6° motion regressors. Each SART time series was also standardized by its own mean and standard deviation.

Neural decoding was implemented by applying the model developed in the representations of deceased task to the SART data (Supplemental Figure S1, step 4). Model application entails voxelwise multiplication of regression weights in the conjunction mask with the values for the new blood oxygen level–dependent data from the SART, followed by a linear summation across voxels. This produces a one-dimensional repetition time (TR) by TR neural prediction of the pattern similarity between the new data and the pattern that optimally corresponds to mental representations of the deceased. To account for the hemodynamic response delay we applied the model starting at the fourth TR following each probes period and into the second TR into the next probes period. Blockwise model output was given as the mean for model output over all the TRs in each block (Supplemental Figure S1, step 5).

Thought Prediction: Prediction of Deceased-Related Thinking

A linear mixed-effects logistic regression was implemented in R 2.15.13 (32) to predict deceased-related thinking from average blockwise model output (Supplemental Figure S1, step 6). Subject identity was modeled as a random intercept. The average model output for a block was entered into the model as a continuous predictor of responses to the binary deceased thoughts probe.

Blocks of SART trials with errors (i.e., commissions or omissions) were excluded from this analysis because the neural processes occurring during nonerror blocks are likely to be more homogenous as compared with those that occur during blocks with errors. As a result, comparing across a set of more homogenous blocks is likely to yield a better discrimination between blocks with and without deceased-related thinking on the basis of neural data.

RESULTS

Reliability was acceptable for both the ICG scale ($\alpha = .96$) and the Impact of Event avoidance subscale ($\alpha = .76$). Subjects were experiencing a considerable amount of grief, with average ICG score of 26.5 (SD = 13.4). ICG score correlated with avoidance, arousal during the mental representations of deceased task, frequency of thinking about the deceased on the SART, and average motion during the SART (Table 1).

Table 1. Correlation Matrix of Clinical Variables and Performance Characteristics

	1	2	3	4	5	6	7
ICG	1						
Avoidance (IES)	.442[a]	1					
Valence	–.178	–.132	1				
Arousal	.460[a]	.11	–.584[b]	1			
Deceased-Related Thinking (SART)	.586[b]	.483[a]	.166	.078	1		
Total Errors (SART)	.240	.251	–.382	.492[a]	.232	1	
Motion (SART)	.498[a]	–.076	–.121	.323	.395	.245	1
Motion (Mental Rep-Task)	.263	–.213	.159	–.021	.336	.105	.695[b]

Valence and arousal data show subject-level average of valence and arousal as measured by the probes in the mental representations of deceased task. Deceased-related thinking data shows percentage of nonerror blocks on the Sustained Attention to Response Task (SART) in which deceased-related thinking was reported. Total errors row data show total number of errors made on the SART. Motion row data show average degree of frame-to-frame displacement for each functional magnetic resonance imaging task.

ICG, Inventory of Complicated Grief; IES, Impact of Event Scale.

[a]Significant at the .05 level (two tailed).

[b]Significant at the .01 level (two tailed).

Representations of the Deceased Task

Figure 2 describes characteristics of responses to the representations of deceased task. Deceased-related blocks evoked more valence and arousal than did both types of control blocks. The story modality displayed a widely distributed set of clusters associated with the deceased versus control conditions (D_STO > CLD_STO), including the anterior and posterior cingulate, insula, orbital frontal cortex (OFC), and basal ganglia (Figure 3A, Supplemental Table S1). In the picture modality, activity in a single contiguous cluster extending across the right putamen, caudate, insula, and OFC was associated with viewing pictures of the deceased as compared with viewing pictures of the control figures (D_PIC > CLD_PIC) (Figure 3B, Supplemental Table S2). The think modality showed no significant clusters associated with thinking about the deceased. Neural analyses controlled for self-reported valence and arousal. To demonstrate the effect of this control we highlight the voxels that were excluded by accounting for valence/arousal (Supplemental Figure S3). There were no clusters whose activity was greater for the control conditions as compared with deceased condition.

Conjunction Analysis

The conjunction analysis identified voxels in the bilateral putamen, caudate, insula, and OFC and left posterior cingulate whose activity was conjointly associated with viewing pictures and stories of the deceased as compared with viewing pictures and stories of the control figures at a threshold of voxel $p < .001$ ((D_PIC > CLD_PIC) and (D_STO > CLD_STO)) (Figure 3C, Table 2). There were a number of very small clusters ranging in size from 1 to 12 voxels. We therefore applied a lenient cluster correction of cluster $p < .1$ to remove very small clusters whose activity was unlikely to be biologically significant. This threshold removed the small clusters. When applying a more stringent cluster correction ($p < .05$) the cluster in the right putamen, insula, and OFC remains significant (Figure 3C, green): cluster center (x, y, z) = 58, 69, 32; voxels = 147; average z score = 3.33.

Classification Results

On the representations of deceased task data, the multivariate logistic regression model achieved significant cross-validated average out-of-sample classification accuracy ($p < .01$) across a large range of regularization constants. The maximum accuracy achieved (area under the curve) was 0.63.

SART

Twenty-one of 23 subjects completed the SART task. One subject completed only 14 SART blocks owing to timing limitations. Of a total of 334 SART blocks there were 209 that did not include an error. The average number of error-free blocks was 9.9 (SD = 2.8, range = 3–14). An additional three blocks had insufficient neural data and were excluded from subsequent neural analyses. A chi-square test showed no association between a block having errors and deceased-related thinking (χ^2_1= 0.003, p = .96). Errors were associated with arousal as measured on the mental representations task but no other clinical variables like grief severity or valence (Table 1).

Deceased-related thinking occurred on 68 (32%) of 209 blocks. There were 49 (23%) living control person reports of thinking and 93 (44%) self-related reports of thinking. Blocks with deceased-related thinking were also more likely to contain living control person (χ^2_1 = 0.48, $p < .001$) and self-related (χ^2_1 = 0.13, p = .045) thinking (Figure 4). To identify subject-level correlates of thinking about the deceased we calculated the percentage of reported thoughts of loss out of total nonerror SART blocks (mean [SD] = 0.33 [0.38], range = 0–1). Percentage of thinking about the deceased correlated with grief severity and avoidance but not valence/arousal, motion, or errors (Table 1).

Greater blockwise output of the neural model predicted higher odds of thinking about the deceased on that block (B_{203} = 2.92, SE = 1.39, p = .035; Figure 5). These findings persisted after controlling for ICG score and time since loss (B_{201} = 2.89, SE = 1.37, p = .033) as well as valence/arousal and average motion (B_{200} = 3.01, SE = 1.38, p = .02). The output of a model trained in the voxels defined by the more stringent conjunction results also predicted deceased-related thinking although only at a trend level (B_{203} = 2.96,

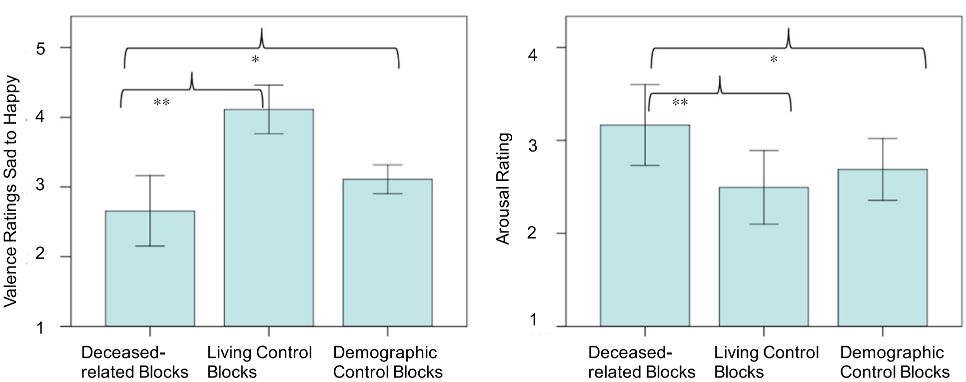

Figure 2. Representations of deceased task valence and arousal. Average valence and arousal ratings for deceased-related, living control person, and demographic control figure blocks. Paired samples t tests show that deceased-related blocks evoked greater valence as compared with both living control person (t_{22} = –5.6, $p < .001$) and demographic control figure (t_{22} = –2.2, p = .031) blocks. Deceased-related blocks were more arousing than living control person (t_{22} = 3.15, p = .005) and demographic control figure (t_{22} = 2.16, p = .041) blocks. Valence ratings were given as the following: 1 = very sad, 2 = sad, 3 = neutral, 4 = happy, 5 = very happy. Arousal ratings were given as the following: 1 = very relaxed, 2 = relaxed, 3 = neutral, 4 = aroused, 5 = very aroused. *$p < .05$, **$p < .01$.

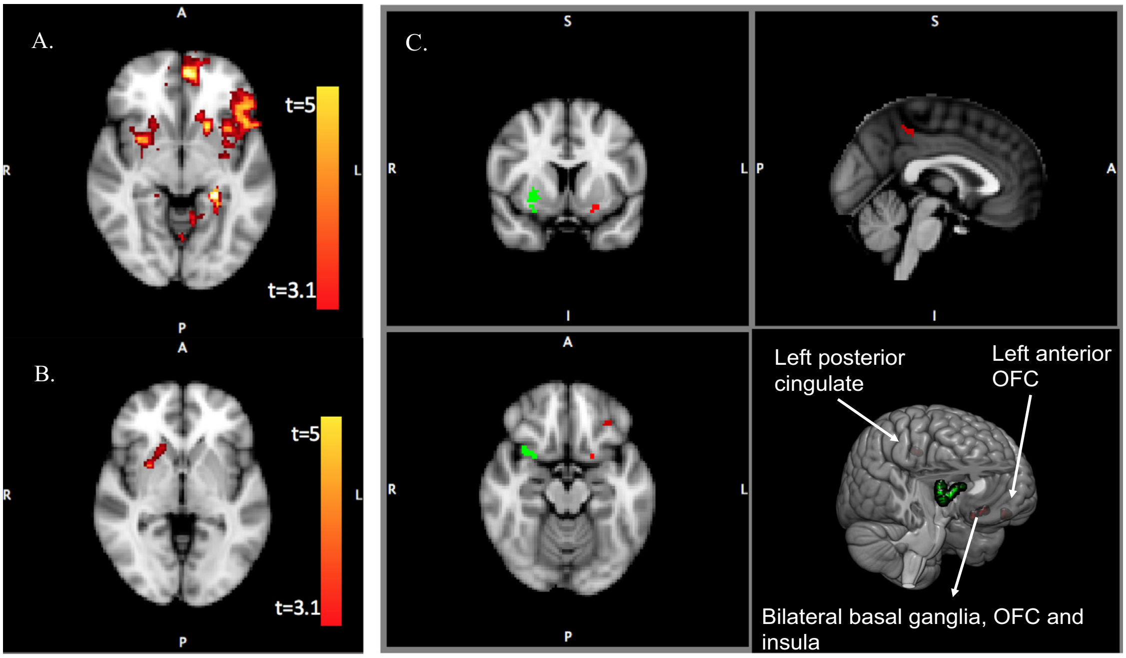

Figure 3. Neural circuitry of mental representations of the deceased. **(A)** Clusters showing greater response to deceased-related stories as compared with control stories (D_STO > CLD_STO). Clusters are significant at a voxelwise threshold of $t_{523} = 3.1$, $p < .001$, and cluster corrected with a threshold of $p < .05$. A large cluster in the right insula as well as a distributed network across the anterior and posterior cingulate, orbital prefrontal cortex (OFC), and bilateral basal ganglia are seen. Image coordinates (x, y, z = 25, 70, 33). **(B)** Cluster in the right putamen, insula, and caudate whose activity is associated with viewing pictures of the deceased as compared with viewing pictures of the control figures (D_PIC > CLD_PIC) of $t_{522} = 3.1$, $p < .001$, cluster $p < .05$. Image coordinates (x, y, z = 60, 67, 35). **(C)** Red and green maps together display clusters in the bilateral basal ganglia, OFC, and insula as well as the left anterior OFC and posterior cingulate conjointly activated by pictures and stories of the deceased as compared with the control conditions ((D_STO > CLD_STO) and (D_PIC > CLD_PIC)) (voxel $p < .001$, cluster $p < .1$). Green mask highlighted by three-dimensional rendering displays the larger cluster on the right that survived a more stringent cluster-size threshold of $p < .05$ and was previously seen in cluster-corrected story and picture results. Image coordinates (x, y, z = 45, 67, 28). CLD, control living and demographic; D, deceased; PIC, picture; STO, story.

SE = 1.59, p = .063). The effect of model output was not significant for thinking about the living control person (B_{203} = –0.04, SE = 1.36, p = .97) or predicting self-related thoughts (B_{203} = 1.01, SE = 0.99, p = .31).

Avoidance is a cognitive strategy that provides respite from frequent painful thoughts of loss (1). Consistent with prior work (33,34), subject-level avoidance correlated with more frequent thoughts of the deceased on the SART (Table 1) and higher model output (Figure 6; r_{21} = .54, p = .01). Deceased-related thinking also correlated with intrusion (r_{21} = .44, p = .04) while model output did not (r_{21} = .05, p = .82). In a simultaneous regression analysis, model output was a predictor of avoidance (B = 0.43, t_{18} = 2.25, p = .03) while deceased-related thinking on the SART was not statistically significant (B = 0.34, t_{18} = 1.77, p = .09). The prediction of avoidance from neural model output remained significant while controlling for ICG (t_{18} = 3.11, p < .01). Because both motion during the SART and arousal were associated with ICG, we calculated the prediction of avoidance from model output while controlling for these (t_{17} = 2.64, p = .01).

Table 2. Clusters Conjointly Activated by Deceased-Related Pictures and Stories as Compared With Control Pictures and Stories

Region	No. of Voxels	x	y	z
Left Posterior Cingulate (and Precuneus)	26	44.31	43.24	59.85
Bilateral Frontal Orbital Cortex	76	38.51	72.67	29.35
Bilateral Insula	28	34.50	68.67	30.67
Left Putamen	6	44.24	42.35	60.41
Right Caudate	9	52.89	73.22	35.78
Right Putamen	78	57.18	67.88	33.87

Regions in which neural activity was conjointly activated by pictures and stories of the deceased as compared with the control conditions ((D_STO > CLD_STO) and (D_PIC > CLD_PIC)) (voxel $p < .001$, cluster $p < .1$). CLD, control living and demographic; D, deceased; PIC, picture; STO, story.

DISCUSSION

This study identified a neural pattern in the insula, basal ganglia, and OFC involved in the transmodal mental representation of a deceased loved one independently of valence/arousal. Neural decoding of this pattern during a sustained attention task tracked ongoing deceased-related thinking.

A generic grief effect was seen in the correlation of grief severity with experiential avoidance, arousal, and motion. Nevertheless, the neural pattern of mental representations of the deceased predicted thinking about the loss and experiential avoidance independently of these generic grief factors (i.e., ICG, motion, arousal). These findings point to a specific

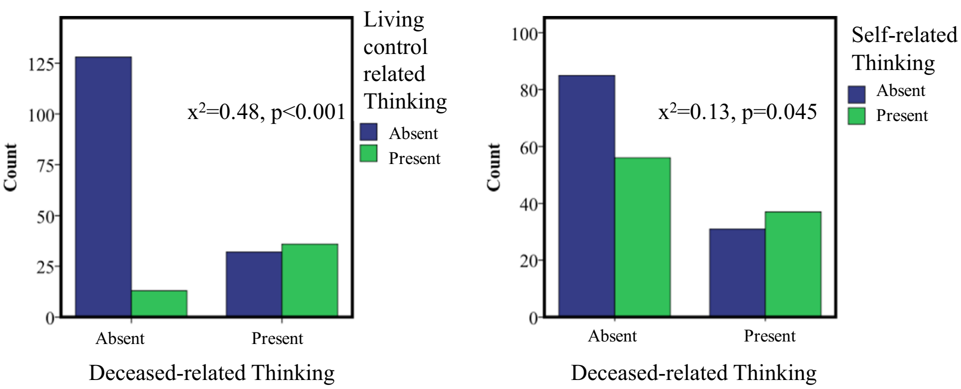

Figure 4. Mind-wandering during the Sustained Attention to Response Task (SART). Bar graphs display the co-occurrence of self- and living control person–related thinking with deceased-related thinking during the SART. Chi-square tests show that self- and living control person–related thinking were more likely to occur during blocks in which deceased-related thinking had also been reported.

relationship among mental representations of the deceased, deceased-related thinking, and experiential avoidance that is distinct from generic grief severity. The independence of these relationships from generic grief severity suggests a potential subtype of grieving. This subtype would be characterized by greater experiential avoidance and a stronger relationship between mental representations of the deceased and experienced thoughts of loss. This neural probe can be used to further understand the relationship among mental representations of the deceased, thoughts of loss, and experiential avoidance.

While we interpret our findings as a measure of mental representations of the deceased it remains possible that the neural pattern detected valence/arousal occurring during the SART. The neural tracker was developed controlling for valence/arousal as reported during the first task. The fact that deceased-related blocks evoked more valence/arousal suggests that these probes were successful, and subsequently controlling for them would exclude voxels associated with valence/arousal (Supplemental Figure S3). Nevertheless, probes were presented at the end of each block rather than after each stimulus. Certain stimuli (i.e., stories, pictures) may have evoked more valence/arousal than was measured in the probes and these processes may then have been included in the subsequent neural marker. Future studies should measure valence/arousal occurring at each stimulus and during the SART to ensure that the process being tracked is truly specific to grief rather than a generic valence/arousal process.

The regions activated by the representations of deceased task provide insight into the type of the deceased-related processing potentially identified by the neural pattern. The involvement of both approach-related regions (i.e., basal ganglia) as seen in prior work (22) and regulation-related regions (i.e., insula and OFC) may indicate the simultaneous yearning toward the deceased as well as distancing from the deceased that is unique to grieving (35). By controlling for a living attachment and an anonymous demographic avatar this task specifically targeted the unique combination of attachment (i.e., deceased-attachment vs. anonymous) as well as loss (i.e., deceased-attachment vs. living-attachment) that is present in grieving.

We build on prior neural decoding studies in two ways: neural decoding 1) predicted a specific thought rather than a general cognitive or emotional process (15–18) and 2) was applied during a cognitively active task rather than a rest period. Neural tracking of thoughts during an active cognitive state rather than a rest state may provide a better analogue for the types of irrelevant thoughts or mind-wandering that occurs outside of the laboratory which often happens during states of activity and not just rest (36).

The specificity of our model training as well as decoding is underscored by the tracking of thoughts of the deceased but

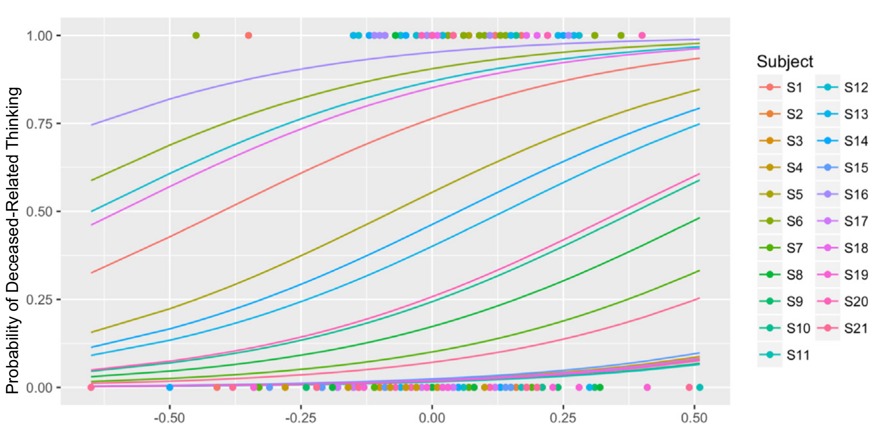

Figure 5. Prediction of deceased-related thinking during the Sustained Attention to Response Task (SART). Deceased-related thinking during the SART was predicted by neural decoding of SART functional magnetic resonance imaging (fMRI). Higher model output in a given SART block indicates that the pattern of neural activity in that block was more similar to the pattern linked to mental representations of the deceased. Higher pattern similarity in a given block predicted a higher chance of subsequent self-reported deceased-related thinking. Individual slopes are displayed for each subject (S).

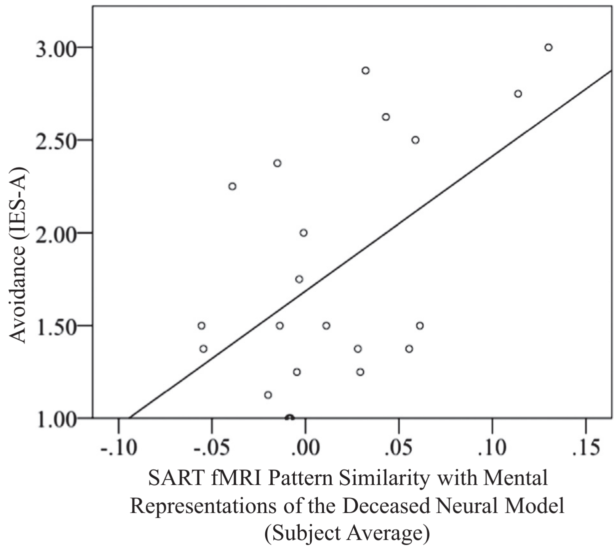

Figure 6. Mental representations of deceased during the Sustained Attention to Response Task (SART) and avoidance. Subjects who showed higher mental representations of the deceased model output during the SART also had higher avoidance scores. fMRI, functional magnetic resonance imaging; IES-A, Impact of Event avoidance subscale.

not by the tracking of thoughts of the living control person or self. Task-irrelevant thoughts occurred as a general process by which self and living control person–related thoughts were more likely to occur during blocks with deceased-related thoughts. Despite these relationships among self-related, living control person–related and deceased-related thinking, our model only predicted deceased-related thinking.

Limitations

To maximize recruitment, we recruited from months 3 to 14 postloss. However, this time period spans acute and integrated grief stages. Controlling for time since loss and complicated grief inventory scores gave more confidence in the results but it would be ideal to begin recruitment at 6 months postloss to avoid blurring across these stages. Furthermore, the sample size is small and these findings should be replicated in a larger sample. The instruction of "imagine being with [person]" that was used in the think condition may have elicited more variable responses across subjects (i.e., visual imagination, memory elicitation) and therefore failed to yield a consistent neural circuit. Future studies should use a more concrete stimulus such as the person's name or an instruction to think about an aspect of his or her personality. As mentioned above, valence/arousal probes could be included in the SART and after each stimulus presentation in the mental representations task to ensure that the neural pattern is specific to grief rather than to tracking more generic processes. An additional alternative would be a physiological measure of arousal.

Conclusions

We identified clusters of neural activity in the insula, OFC, and basal ganglia associated with transmodal representation of the deceased versus living attachment and demographic control figures in grieving subjects. These findings were independent of general emotional and arousal reactivity. A model trained in these clusters was used to decode neural data produced during a sustained attention task. Neural decoding predicted the occurrence of deceased-related thinking occurring during this task. The neural marker of deceased-related thinking predicted subject-level avoidance over and above the prediction by deceased-related thinking on the SART. These findings present a new measure of mental representations of the deceased that can be used for predicting the risk of complicated grief and further developed into a tracker of deceased-related thinking.

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REFERENCES

1. Shear MK (2010): Exploring the role of experiential avoidance from the perspective of attachment theory and the dual process model. Omega 61:357–369.
2. Zisook S, Shear K (2009): Grief and bereavement: What psychiatrists need to know. World Psychiatry 8:67–74.
3. Bonanno GA, Kaltman S (1999): Toward an integrative perspective on bereavement. Psychol Bull 125:760–776.
4. Stroebe M, Boelen PA, van den Hout M, Stroebe W, Salemink E, van den Bout J (2007): Ruminative coping as avoidance: A reinterpretation of its function in adjustment to bereavement. Eur Arch Psychiatry Clin Neurosci 257:462–472.
5. Stroebe M, Schut H (2010): The dual process model of coping with bereavement: A decade on. Omega 61:273–289.
6. Bonanno GA, Papa A, Lalande K, Zhang N, Noll JG (2005): Grief processing and deliberate grief avoidance: A prospective comparison of bereaved spouses and parents in the United States and the People's Republic of China. J Consult Clin Psychol 73:86–98.

7. Moore MM, Cerel J, Jobes DA (2015): Fruits of trauma? Posttraumatic growth among suicide-bereaved parents. Crisis 36:241–248.
8. Eisma MC, Stroebe MS, Schut HA, Stroebe W, Boelen PA, van den Bout J (2013): Avoidance processes mediate the relationship between rumination and symptoms of complicated grief and depression following loss. J Abnorm Psychol 122:961–970.
9. Glickman K, Shear MK, Wall MM (2016): Mediators of outcome in complicated grief treatment [published online ahead of print Oct 18]. J Clin Psychol.
10. Fyock J, Stangor C (1994): The role of memory biases in stereotype maintenance. Br J Soc Psychol 33:331–343.
11. Holmes DS (1970): Differential change in affective intensity and the forgetting of unpleasant personal experiences. J Pers Soc Psychol 15:234–239.
12. Tversky A, Kahneman D (1974): Judgment under uncertainty: Heuristics and biases. Science 185:1124–1131.
13. Baird B, Smallwood J, Fishman DJ, Mrazek MD, Schooler JW (2013): Unnoticed intrusions: Dissociations of meta-consciousness in thought suppression. Conscious Cogn 22:1003–1012.
14. Takarangi MK, Strange D, Lindsay DS (2014): Self-report may underestimate trauma intrusions. Conscious Cogn 27:297–305.
15. Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P (2001): Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293:2425–2430.
16. Harrison SA, Tong F (2009): Decoding reveals the contents of visual working memory in early visual areas. Nature 458:632–635.
17. Kragel PA, Knodt AR, Hariri AR, LaBar KS (2016): Decoding spontaneous emotional states in the human brain. PLoS Biol 14:e2000106.
18. Tusche A, Smallwood J, Bernhardt BC, Singer T (2014): Classifying the wandering mind: revealing the affective content of thoughts during task-free rest periods. Neuroimage 97:107–116.
19. Boelen PA, Huntjens RJ (2008): Intrusive images in grief: An exploratory study. Clin Psychol Psychother 15:217–226.
20. Maccallum F, Bryant RA (2013): A cognitive attachment model of prolonged grief: Integrating attachments, memory, and identity. Clin Psychol Rev 33:713–727.
21. Boelen PA, Stroebe MS, Schut HA, Zijerveld AM (2006): Continuing bonds and grief: A prospective analysis. Death Stud 30:767–776.
22. O'Connor MF, Wellisch DK, Stanton AL, Eisenberger NI, Irwin MR, Lieberman MD (2008): Craving love? Enduring grief activates brain's reward center. Neuroimage 42:969–972.
23. Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J (1997): 'Oops!': Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia 35:747–758.
24. Prigerson HG, Maciejewski PK, Reynolds CF 3rd, Bierhals AJ, Newsom JT, Fasiczka A, *et al*. (1995): Inventory of Complicated Grief: A scale to measure maladaptive symptoms of loss. Psychiatry Res 59:65–79.
25. Baumert J, Simon H, Gundel H, Schmitt C, Ladwig KH (2004): The Impact of Event Scale–Revised: Evaluation of the subscales and correlations to psychophysiological startle response patterns in survivors of a life-threatening cardiac event: an analysis of 129 patients with an implanted cardioverter defibrillator. J Affect Disord 82:29–41.
26. McVay JC, Kane MJ (2013): Dispatching the wandering mind? Toward a laboratory method for cuing "spontaneous" off-task thought. Front Psychol 4:570.
27. Marchetti I, Koster EH, De Raedt R (2012): Mindwandering heightens the accessibility of negative relative to positive thought. Conscious Cogn 21:1517–1525.
28. Nichols T, Brett M, Andersson J, Wager T, Poline JB (2005): Valid conjunction inference with the minimum statistic. Neuroimage 25: 653–660.
29. Norbury A, Valton V, Rees G, Roiser JP, Husain M (2016): Shared neural mechanisms for the evaluation of intense sensory stimulation and economic reward, dependent on stimulation-seeking behavior. J Neurosci 36:10026–10038.
30. Badre D, Poldrack RA, Pare-Blagoev EJ, Insler RZ, Wagner AD (2005): Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. Neuron 47:907–918.
31. Conroy BR, Walz JM, Sajda P (2013): Fast bootstrapping and permutation testing for assessing reproducibility and interpretability of multivariate fMRI decoding models. PLoS One 8: e79271.
32. R Development Core Team (2012): A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing.
33. Eisma MC, Rinck M, Stroebe MS, Schut HA, Boelen PA, Stroebe W, *et al*. (2015): Rumination and implicit avoidance following bereavement: An approach avoidance task investigation. J Behav Ther Exp Psychiatry 47:84–91.
34. Eisma MC, Schut HA, Stroebe MS, van den Bout J, Stroebe W, Boelen PA (2014): Is rumination after bereavement linked with loss avoidance? Evidence from eye-tracking. PLoS One 9:e104980.
35. Maccallum F, Sawday S, Rinck M, Bryant RA (2015): The push and pull of grief: Approach and avoidance in bereavement. J Behav Ther Exp Psychiatry 48:105–109.
36. Killingsworth MA, Gilbert DT (2010): A wandering mind is an unhappy mind. Science 330:932.
37. Phillips PJ, Wechsler H, Huang J, Rauss P (1998): The FERET database and evaluation procedure for face recognition algorithms. Image Vision Comput J 16:295–306.