

Baseline Vagal Tone Predicts BOLD Response during Elicitation of Grief

Mary-Frances O'Connor^{*1}, Harald Gündel², Kateri McRae³ and Richard D Lane⁴

¹UCLA Neuropsychiatric Institute, Cousins Center for Psychoneuroimmunology, Los Angeles, CA, USA; ²Medizinische Hochschule Hannover, Hannover, Germany; ³Department of Psychology, University of Arizona, Tucson, AZ, USA; ⁴Department of Psychiatry, University of Arizona, Tucson, AZ, USA

Previous studies of the relationship between autonomic and central nervous system activity using fMRI have primarily utilized cognitive, motor or conditioning tasks. The present study investigated the association between the regional brain activity during the evocation of grief and baseline parasympathetic activity. Eight right-handed women who had experienced the death of a loved one in the past 18 months were scanned during the presentation of personalized pictures and words that evoked grief and had a measure of baseline parasympathetic activity taken. Greater posterior cingulate cortex (PCC) activity was associated with lower parasympathetic activity (eg more arousal). Connectivity has been demonstrated between the ventral PCC (vPCC) and the subgenual ACC (sACC), which then projects to the autonomic nuclei. In the present study, functional connectivity analysis revealed a positive correlation between vPCC and sACC/orbitofrontal cortical activity. Additionally, bilateral cuneus and parahippocampus were associated with higher baseline parasympathetic tone, important to visual perception in emotional processing and episodic memory respectively. Future studies should compare differences between central and peripheral arousal in complicated and non-complicated grief.

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INTRODUCTION

Recent neuroimaging studies have explored the relationship between peripheral autonomic activity and regional brain activity. Sympathetic activity, as measured by pupillary dilation (Critchley *et al*, 2005) and skin conductance responses (Nagai *et al*, 2004), have both been correlated with neural activation in the anterior cingulate cortex (ACC). Parasympathetic activity, as measured by the high-frequency component of heart rate variability, has also been associated with the ACC during fMRI tasks involving working memory and emotion (Gianaros *et al*, 2004; Lane *et al*, 2001; Matthews *et al*, 2004). The demonstrated relationship between autonomic activity indicative of arousal and ACC activity is consistent with the dense projections from the ACC to cell groups that regulate autonomic functions, such as the amygdala, hypothalamus, and brainstem nuclei (Neafsey *et al*, 1993). Other evidence

that arousal is associated with activity in the ACC comes from demonstrations of modulation in neural activity across stages of sleep and general anesthesia, suggesting that the activity of the ACC changes even in the absence of any overt cognitive activity (Paus, 2001).

Prior studies investigating the relationship between autonomic nervous system (ANS) activity and central nervous system (CNS) activity have been narrow in their approach. First, the tasks that have been used in demonstrating these relationships have primarily been cognitive, motor or conditioning tasks (eg Stroop, biofeedback, grip pressure, gambling, and fear conditioning). One exception is the demonstration of medial prefrontal activity associated with parasympathetic activity during emotion elicitation (Lane *et al*, 2001). The evocation of emotion relies on coordination of the CNS and ANS (Damasio, 1994), and very few studies have utilized emotion elicitation tasks in demonstrating the areas of brain activity that integrate these systems. Specifically, no studies examining the coordination of ANS and CNS have utilized personalized emotion stimuli. Stimuli that are personally relevant to the individual are likely to elicit strong emotion (such as pictures of family members), in part because of emotional memories. Most emotion elicited in every day life is triggered by a cue that is personally relevant (Ochsner and Gross, 2005).

*Correspondence: Dr M-F O'Connor, UCLA Neuropsychiatric Institute, Cousins Center for Psychoneuroimmunology, 300 Medical Plaza, Room 3156, Los Angeles, CA 90095-7076, USA, Tel: +1 310 825 1889, Fax: +1 310 794 9247,

E-mail: mfoconnor@mednet.ucla.edu

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A second way in which prior studies investigating relationships between CNS and ANS activity have been narrow is using task-related designs only. Another way to investigate these ANS–CNS relationships is to consider individual differences in autonomic activity. Personality traits and genetic subtypes are associated with differential brain activity, and it may be that individual traits in basal autonomic tone are also distinctly associated with regional brain activity. Individual differences in parasympathetic activity are integral to emotion and emotion regulation (Porges, 2003). Decreased parasympathetic activity has been observed in depression (Rechlin *et al*, 1994), generalized anxiety disorder (Borkovec *et al*, 1995), and post-traumatic stress disorder (PTSD) (Sack *et al*, 2004). These are all conditions associated with excessively intense or prolonged emotional responses and heightened autonomic arousal.

We have previously used personalized stimuli in eliciting grief in the imaging environment (Gündel *et al*, 2003). To expand the understanding of the CNS–ANS relationship, the present study investigated the association between the regional brain activity during the evocation of grief in these participants and unpublished data on their baseline parasympathetic activity. We hypothesized that those individuals who show lower baseline parasympathetic activity (greater arousal) will show greater activity in the ACC.

PARTICIPANTS AND METHODS

Study Participants

Eight right-handed women who had experienced the death of a first-degree relative (eg parents and spouses) in the past year (average of 6 months) participated. They were recruited through general advertisements in hospices, hospitals, mental health clinics, and university classes. Participants were interviewed about the diagnosis, course of illness, death, and memorial of their loved one from 24 to 72 h before scanning. Exclusion criteria included Axis I psychiatric disorders (including current depression) evaluated by a structured, clinical interview, and medical disorders. The Human Subjects Committee at the University of Arizona in Tucson, AZ, approved the study, and participants gave written informed consent.

Parasympathetic Activity Measurement

Before the day of scanning, resting electrocardiographic (ECG) data were recorded for 5 min. This initial recording is used in the analysis of present study; however, an additional 4 days of ECG measurement were recorded and used for reliability analysis. The ECG was recorded with a J&J amplifier system (Poulsbo, WA), using Ag–AgCl electrodes, sampled at 1024 Hz. Interbeat interval (IBI) series were derived from the raw ECG, using an R-spike detection algorithm, followed by hand screening with correction for artifacts. Heart rate variability in the high frequency band (0.12–0.40 Hz) was extracted using CMet software (Allen, 2002) as an estimate of respiratory sinus arrhythmia (RSA). RSA is a measure of parasympathetic activity, reflecting changes in beat-to-beat intervals of the heart. Variability in

the 0.12–0.40 Hz range is under vagal control. The natural log of the variance is reported.

Task Design and Stimuli

Participants provided one photograph of their deceased loved one. The deceased was the only or central figure in the photo; any other persons were digitally removed from the photo. Photos were then matched for sex, age, and environment with one photo of a stranger. Fifteen autobiographical grief-related words were chosen from participant interviews about the death (eg collapse, funeral, and loss). These 15 words were then matched for part of speech, number of letters, and frequency of usage in the English language with 15 neutral words (eg announce, ceiling, and list).

The grief-eliciting paradigm used a 2×2 factorial design creating four conditions: (1) the deceased with grief words, (2) the stranger with grief words, (3) the deceased with neutral words, and (4) the stranger with neutral words. Each condition consisted of 15 picture-word composites or 60 composites total (Figure 1a). Comparing conditions 1 and 3 (the deceased with keywords and neutral words) with conditions 2 and 4 (the stranger with keywords and neutral words) constituted the pictorial evocation of grief. Comparing conditions 1 and 2 (the keyword with the deceased and the stranger) with conditions 3 and 4 (the neutral word with the deceased and the stranger) constituted the verbal evocation of grief.

Composites were presented on MR Vision 2000 goggles (Resonance Technology Inc.). Each picture was presented for an average of 9 s, with a range of 7.5–10.5 s. The screen was blank during the 0.5 s interval between pictures. The picture-word composites were presented in a random order with regard to the four conditions. The randomization procedure was constrained so that there was an equal number of the four conditions every 20 pictures. Pictures were also counterbalanced so that half of the keywords were seen first with the deceased, and half were seen first with the stranger. The average length of presentation of each picture was also random, within the range noted above. The 60 pictures were presented continuously for a total average duration of 10.5 min.

Immediately following scanning, each composite was rated on a scale of 1 to 10 for subjective grief. The rating was completed following scanning so that it did not contaminate emotional experience or its neural substrates. As reported in Gündel *et al* (2003), the four conditions differed in subjective ratings of grief and skin conductance responses ($p < 0.05$), suggesting that the different conditions reliably elicited distinct levels of grief.

Data Acquisition

Whole brain imaging data were acquired on a 1.5 T GE Sigma Horizon system (Milwaukee, WI). Between 19 and 22 images were collected obliquely and aligned on the AC–PC plane (5 mm slice thickness, skip = 1 mm, 3.44×3.44 in plane resolution, TR = 3000, TE = 40, flip angle = 90). The imaging data were analyzed using statistical parametric mapping (SPM2) implemented in MATLAB (Mathworks Inc., Sherborn, MA, USA). Automated algorithms were used

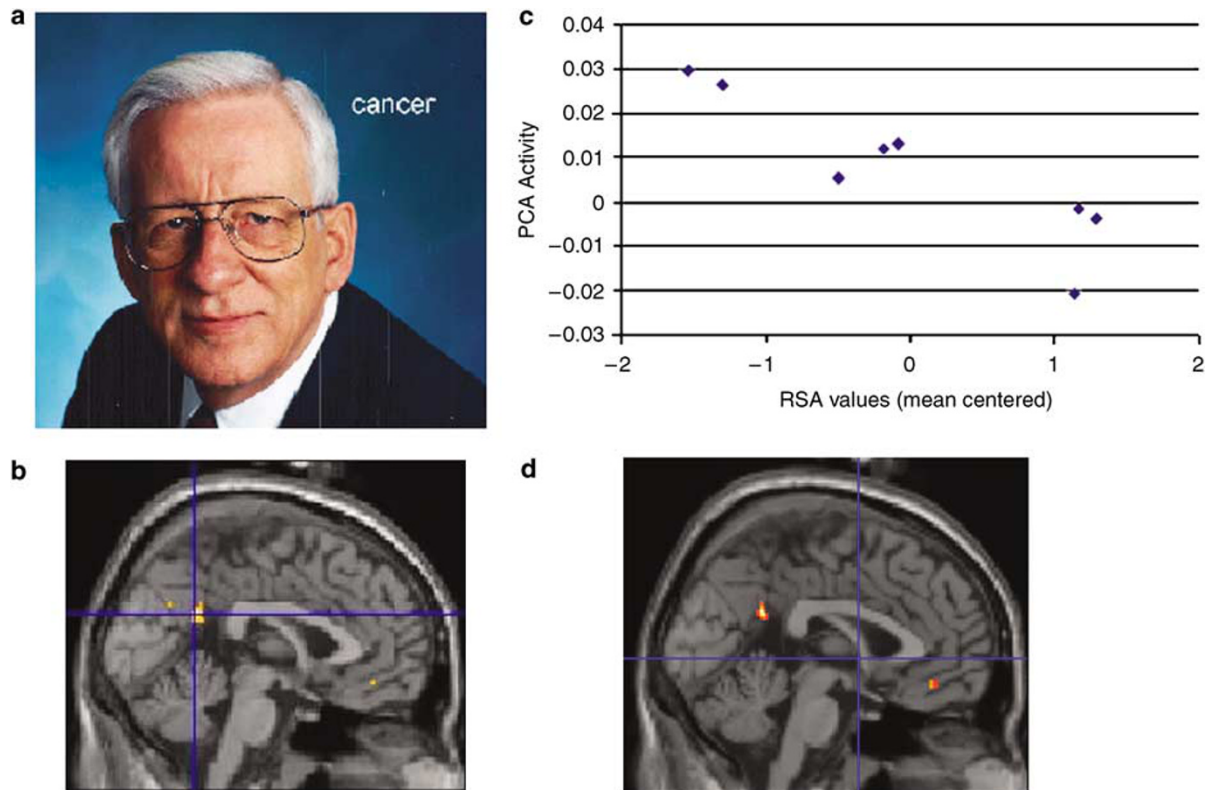


Figure 1 (a) Photo of the deceased with grief-related word. (b) Sagittal view of the vPCC (Talairach and Tournoux coordinates: 0, -54, 24). (c) Scatterplot of the negative relationship between vPCC activity and RSA (increased vPCC, decreased RSA) in the Deceased > Stranger condition. VPCC, ventral posterior cingulate cortex; RSA, respiratory sinus arrhythmia. (d) Brain regions resulting from functional connectivity analysis revealing positively correlated activity between the sACC/orbitofrontal cortex and posterior cingulate activity.

to align each subject's sequential MRI images, spatially normalized into the stereotactic space of Talairach and Tournoux (1988) using the 305 MNI (Montreal Neurological Institute) standard brain and smooth (8 mm FWHM) images.

Analysis was carried out using the general linear model in an event-related analysis. Subject-specific low-frequency drift was removed by a high-pass filter and global signal changes were removed by including a global covariate. Effects at each voxel were estimated and regionally specific effects were compared using linear contrasts. We investigated regional BOLD changes independent of variations in whole brain measurements, and generated separate normalized t -score (ie Z score) maps of BOLD increases during each of the four conditions. These t -statistics constituted a statistical parametric map (SPM{ Z }). Statistical inferences were based on a theory of random Gaussian fields. Contrasts for individual subjects were aggregated for the group in a random effects analysis. BOLD changes were considered statistically significant if they equaled or exceeded $p < 0.001$, uncorrected.

Data Analysis

The imaging data were first analyzed for main effects and are reported in Gündel *et al* (2003). For each participant, images taken during the Deceased and Stranger photos and images taken during the Neutral and Grief-related words were modeled as events. After the task was modeled for each

participant, planned comparisons were computed as linear contrasts to investigate Deceased > Stranger activity, and Grief Word > Neutral Word activity. To assess correlations between individual differences in RSA and neural activity, the measure of (mean-corrected) RSA was entered as a regressor into each random effects group analysis (Deceased > Stranger and Grief Word > Neutral Word). BOLD changes were considered statistically significant if they equaled or exceeded $p < 0.001$, corrected for multiple comparisons at the cluster level ($p < 0.05$).

Follow-up analyses examined functional connectivity with the posterior cingulate activation for the Deceased > Stranger contrast. Average values were extracted from each individual's Deceased > Stranger contrast image using a region of interest defined by the posterior cingulate cluster identified in the whole-brain contrast. These values were entered as a regressor into a random-effects group analysis with the same contrast to identify regions that covary with posterior cingulate activity across individuals.

RESULTS

Behavior and Physiology

The RSA values used reliably correlated with 4 days of baseline RSA recording subsequent to the imaging day ($p < 0.01$), indicating that these values represent a tonic level of parasympathetic activity. Those participants with higher tonic RSA had lower subjective reports of grief during

scanning (in a comparison of the grief and neutral conditions) (RSA (6.16 ± 1.11), subjective rating of grief (5.9 ± 2.06); $r = -0.74$, $p < 0.05$).

Brain Imaging

As previously published, the main contrasts showed three brain regions independently activated by the Deceased > Stranger and Grief Word > Neutral Word contrasts: PCC, medial/superior frontal gyrus, and cerebellum. Distinct regions were also activated by the two contrasts: Deceased > Stranger included the cuneus, superior lingual gyrus, insula, dorsal ACC, inferior temporal gyrus, and fusiform gyrus; Grief Word > Neutral Word included the precuneus, precentral gyrus, midbrain, and vermis.

In the regression analyses of the present study, using the RSA covariate with the activation of Deceased > Stranger, a positive relationship was found with the right cuneus, and a negative relationship was found with the right PCC (Table 1 and Figure 1b). Using the RSA covariate with the activation of Grief Word > Neutral Word, a positive relationship was found with the left cuneus and PHG. A scatterplot demonstrates that this effect was not due to outliers (Figure 1c).

To test the association between PCC and subgenual ACC (sACC) in the present study, a functional connectivity analysis that used the PCC activation ($x = 0$, $y = -54$, $z = 24$) as a seed region was conducted. This analysis revealed activity in the sACC/orbitofrontal cortex ($x = -2$, $y = 40$, $z = -14$, $z = 4.01$) that positively correlated with posterior cingulate activity in the Deceased > Stranger contrast, supporting our conclusion (Figure 1d).

DISCUSSION

The present study investigated the overlap between those individuals with higher baseline parasympathetic activity and brain activation during a personalized emotion-eliciting task. The results did not support our hypothesis that ACC would be negatively associated with individuals

with lower parasympathetic activity (greater baseline arousal). Instead, PCC activity was negatively associated with individual differences in parasympathetic activity in the context of grief elicitation. Although unexpected, this is an exciting new result, as recent projection studies have demonstrated specific connectivity between the PCC and the sACC (Vogt *et al*, 2006), which projects to the autonomic nuclei in the brainstem (Neafsey *et al*, 1993).

To the extent that arousal is associated with ACC, the task conditions that activate the ACC in prior studies are relevant. The stimulus conditions in the present experiment strongly pull for memories—the grief-related words are targeted for specific experiences in the past. This is in contrast to other studies that involve emotion \times attention interactions (eg focusing attention on feeling, or feelings capturing attention) or regulation of emotion (Ochsner *et al*, 2002) that involve ACC. Our original hypothesis was that we would observe ACC activity associated with tonic vagal tone based on prior studies; however, regional brain activity is always a product of the nature of the experimental conditions, and the experimental conditions in the present study differed importantly by eliciting personal emotional memories.

PCC activity is elicited by an interaction between emotion and memory (Maddock *et al*, 2003), specifically by the arousal dimension of emotional stimuli, and is important in monitoring the environment for emotionally salient events (Vogt *et al*, 1992). Comparison of these environmental events to memories utilizes the PCC (as suggested by its dense interconnections with the hippocampus and its role in the acquisition of familiarity; Kosaka *et al*, 2003).

Increased PCC activity has been demonstrated in participants who had experienced a bank robbery when the robbery video was contrasted with a control video (Fischer *et al*, 1996). PCC activity has also been shown in studies of participants with PTSD during an autobiographical trauma script, as compared to those without PTSD (Lanius *et al*, 2004). In the present study, the environmental cue (eg photo of loved one or autobiographical grief-related word) triggers retrieval of an emotional memory (eg the death event) in those with lower parasympathetic activity (eg more arousal).

The coordinates of the PCC in the present study clearly place it in the vPCC. Recent projection maps have shown that there are functional differences between the dorsal PCC (dPCC) and the ventral PCC (vPCC; Vogt *et al*, 2006). Vogt and colleagues propose a division between dPCC, which orients the body in space via the cingulate motor areas, and the vPCC, which interacts with sACC to process self-relevant emotional and nonemotional information and objects. The reciprocal connection between vPCC and ACC may explain the indirect association between the vPCC and lower parasympathetic autonomic activity in the present study. This is supported by the data from our functional connectivity analysis, demonstrating that activity in the sACC/orbitofrontal region is correlated with activity in the vPCC.

Those individuals with higher baseline RSA showed more cuneus activation in a covariate analysis with both the Deceased > Stranger contrast, and Grief Word > Neutral Word contrast. The cuneus is a region activated during tasks requiring emotional processing and visual perception,

Table 1 Brain Region Activity Associated with Respiratory Sinus Arrhythmia (RSA) during Grief Elicitation ($N = 8$)

Region	Coordinates (x, y, z)	Cluster size (p)	Z-score
(A) Areas of negative correlation between Deceased > Stranger and RSA (increased regional activity, decreased RSA)			
Ventral posterior cingulate cortex	0, -54, 24	42 (0.045)	3.81
(B) Areas of positive correlation between Deceased > Stranger and RSA (increased regional activity, increased RSA)			
Cuneus	20, -72, 8	57 (0.009)	5.04
(C) Areas of positive correlation between Grief Word > Neutral Word and RSA (increased regional activity, increased RSA)			
Cuneus	-16, -84, 24	102 (0.001)	4.51
Parahippocampal gyrus	-28, -4, -18	36 (0.043)	4.08

Coordinates as given according to Tailarach and Tournoux.

such as emotion induction elicited with visual stimuli (Ganis *et al*, 2004). We observed a correlation with right cuneus in the context of the Deceased > Stranger contrast and a correlation with left cuneus in association with the Grief Word > Neutral Word contrast. Given the hemispheric specialization that distinguishes visual and verbal tasks, the visual association areas activated may have been lateralized based on the nature of the exteroceptive input.

Those with higher baseline RSA showed more parahippocampal (PHG) activity with the Grief Word > Neutral Word contrast. The PHG is part of the hippocampal complex that underlies episodic memory (Squire *et al*, 2004). An earlier finding of a negative correlation between blood pressure and PHG activity has been interpreted to mean that the PHG and other medial lobe structures 'preferentially represent states of low sympathetic arousal and high parasympathetic tone (McEwen and Sapolsky, 1995, p 268)'. Our finding of PHG activation during high parasympathetic tone dove tails nicely with data.

CONCLUSION

The present study demonstrates greater activity in the vPCC in response to grief stimuli in individuals with lower baseline parasympathetic activity. This result lends support to the hypothesis that the vPCC processes self-relevant emotional information. The connection to sACC, and its role in autonomic arousal, may explain the association between the vPCC activity and lower baseline parasympathetic tone. Additionally, activity in the right and left cuneus and PHG were associated with higher baseline parasympathetic tone.

One limitation of the present study may be that the vagal tone was not measured during the grief-eliciting task in the scanner; however, we attempted to overcome this limitation by measuring the participants' RSA on multiple days to increase reliability of the vagal tone measure and therefore the likelihood that it would be very similar during scanning. Additional information could have been added by including a measure of sympathetic activity. Although other investigators have used the low-frequency component of heart rate variability as a proxy for sympathetic activity, there is controversy surrounding this usage (Malik *et al*, 1996). Consequently, we elected not to use it in the current study. Another limitation is the small number of participants; however, we used a conservative significance level ($p < 0.001$) and corrected for multiple comparisons to reduce the possibility that these observations were due to chance. In addition, the brain regions elicited were specific and distinct, rather than widespread activation. As this is the first study to examine at the peripheral and central arousal during grief elicitation it cannot be considered definitive, but rather informs future research through the development of testable hypotheses.

Future clinical research in this area should consider this individual physiological difference in comparing those with complicated and non-complicated grief (Prigerson *et al*, 1995). Peripheral parasympathetic arousal is associated with individual differences in grief response patterns (O'Connor *et al*, 2005), such that higher tonic vagal activity is associated with adaptation to bereavement. Comparing

the associations between central and peripheral arousal in complicated and non-complicated grief may elucidate the neural correlates of those individual differences.

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