Anterior insula reactivity during certain decisions is associated with neuroticism

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Neuroticism is a core personality trait that profoundly affects how individuals interpret and interact with their environment. Understanding neuroticism at a neurobiological level will be an important step toward identifying novel vulnerability factors for psychiatric illnesses such as depression and anxiety. Along these lines, recent work has identified neural activation patterns within the right anterior insula that correlates with an individual's degree of neuroticism. The present study aims to further characterize the circumstances under which neuroticism modulates insular activity. Sixteen healthy participants underwent functional magnetic resonance imaging while playing a card game with varying degrees of outcome uncertainty. Activation within the bilateral anterior insula was found during all decisions, irrespective of uncertainty. However, a significant positive correlation between neuroticism and anterior insula activity was found only during 'certain decisions' (i.e. situations where the most probable outcome was clearly evident). Moreover, an increase in the right anterior insula activity during certain decisions was related to a behavioral mirroring effect such that the response latency for certain decisions approached the response latency for uncertain decisions. These findings suggest that increasing levels of neuroticism modulate neural activation in such a way that the brain interprets certainty as uncertain.

**Keywords:** functional magnetic resonance imaging (fMRI); decision-making; uncertainty; personality; individual differences

**INTRODUCTION**

Neuroticism is a core personality trait that refers to one's tendency to experience negative feelings (Costa and McCrae, 1991). Increased levels of neuroticism are strongly correlated with a number of psychiatric illnesses including depression (Kendler et al., 1993), bipolar disorder (Solomon et al., 1996), and anxiety disorders (Bienvenu and Stein, 2003; Kendler et al., 2002). Moreover, healthy individuals with high levels of neuroticism are at an increased risk for developing depressive and anxiety disorders (Bienvenu et al., 2003; Kendler et al., 1993).

Over the past 5 years, a number of neuroimaging studies have attempted to understand how neuroticism is linked to functional brain activity (for review see, Canli, 2004; Canli and Amin, 2002). These studies have revealed that the degree of activation in a small number of brain regions is significantly correlated with a subject's degree of neuroticism. These regions include the dorsolateral prefrontal cortex (dLPFC) (Canli et al., 2001) and the dorsal anterior cingulate (Eisenberger et al., 2005). In addition, our laboratory has found a strong positive correlation between neuroticism and activation in the right anterior insula during risky decision-making (Paulus et al., 2003).

Interestingly, the magnitude of anterior insula activation also predicted the likelihood that a subject would revert to a safe response following punishment. This finding has recently been replicated in a study showing anterior insula activity that predicted a switch from a risky to a safe choice (Kuhnen and Knutson, 2005). A growing literature also suggests that the insular cortex plays a critical role in the development and maintenance of anxiety (for review see, Paulus and Stein, 2006). Based on this data, it appears that increased levels of neuroticism and anxiety are associated with increased levels of anterior insula activity, and this activity can play a powerful role in guiding our choice of behavior toward safer, less risky situations.

An important construct in understanding risk is outcome uncertainty. Decision-making in the presence of uncertainty can be considered a state of conflict where there is a discrepancy between choosing the best option among two or more choices (Paulus et al., 2001). A number of brain regions have been implicated in processing uncertainty, including the anterior cingulate, anterior insula, amygdala, posterior parietal cortex, and regions within the medial, orbitofrontal and dorsolateral prefrontal cortices (Bechara et al., 1999; Critchley et al., 2001; Elliott et al., 1999; Ernst et al., 2002; Hsu et al., 2005; Huettel et al., 2005; Paulus et al., 2001; Paulus et al., 2003; Volz et al., 2003; Volz et al., 2004). This uncertainty network comprises many of the same brain regions associated with neuroticism, including the anterior insula, anterior cingulate and dorsolateral prefrontal cortices.
Anterior insula and neuroticism

The present study aims to further explore the relationship between neuroticism, brain activation and uncertain decision-making. To accomplish this we used a simple card paradigm that was originally applied toward measuring neural activity during varying degrees of anticipation and arousal (Critchley et al., 2001). During each trial, the subject is presented with a standard playing card, decides whether the next card in the deck will be lower or higher, and receives feedback after a fixed delay. The paradigm was designed so that the brain activity immediately preceding a decision (i.e. the action selection phase of decision-making) could be analyzed to detect two different patterns of brain activation: (i) activity specific to processing uncertainty during action selection and (ii) activity specific to action selection, irrespective of a decision’s degree of uncertainty. This analysis focused on finding activity that was significantly correlated with a subject’s degree of neuroticism.

METHODS

Participants

Sixteen right-handed healthy subjects (8 males and 8 females) participated in the study [an average age of 35.4 years (SD ± 5.82) and an average education of 15.1 years (SD ± 1.57)]. Participants were required to be free from medical or psychiatric disorders as determined by a physical examination and a structured clinical interview for DSM-IV-TR diagnoses. Prior to participation, all subjects gave their informed, written consent to participate in the study. The UCSD Institutional Review Board approved all study procedures.

Task

The card paradigm (Figure 1) uses standard playing cards numbered 2–10 (excluding all face cards and aces). The subject is instructed that these cards are drawn from a regular deck and randomly shuffled. The goal for the subject is to predict whether the face value of a feedback card will be lower or higher than the initially presented cue card. During the task, cue cards and feedback cards were presented in a pseudorandomized order with two constraints: (i) in all trials, the feedback card was either lower or higher than the cue card (i.e. no ‘ties’), and (ii) the probability of the feedback card being lower or higher than the cue card approximated the true probability of a randomly shuffled deck of cards. There were a total of 36 trials in the paradigm. Uncertain decision situations were over-sampled such that the cue card had a face value of ‘5’ on four trials, ‘6’ on eight trials, and ‘7’ on four trials. All subjects were presented with the same pseudorandomized stimulus presentation. The card paradigm was presented to the subjects during the functional magnetic resonance imaging (fMRI). The images were back projected (using an LCD projector) onto a screen near the subject’s feet, which could be seen via a mirror attached to the head coil (visual angle ~4°). Subjects requiring corrective lenses were provided with a pair of plastic-framed lenses that approximated their degree of correction. All subjects wore a pair of headphones in order to hear the auditory feedback. Motor responses were made with the right hand using a response box.

fMRI protocol and image analysis pathway

One fMRI run sensitive to blood oxygenation level-dependent (BOLD) contrast was collected for each subject using a 1.5-Tesla Siemens (Erlangen, Germany) scanner (T2*-weighted echo-planar imaging, TR = 2000 ms, TE = 40 ms, 64 × 64 matrix, 20 4 mm axial slices, 256 scans). During the same experimental session, a T1-weighted image (MPRAGE, TR = 11.4 ms, TE = 4.4 ms, flip angle = 10°, FOV = 256 × 256, 1 mm3 voxels) was obtained for anatomical reference. In all subjects, T2*-weighted echo-planar images provided coverage of the majority of the cortex. However, significant signal dropout in the medial orbitofrontal cortex limited any inferences about task-related activity in this region.

All data were preprocessed, normalized to Talairach coordinates (Talairach and Tournoux, 1988) and analyzed with the AFNI software package (Cox, 1996). For preprocessing, voxel time series data were interpolated to correct for non-simultaneous slice acquisition within each volume and corrected for 3D motion. Motion-corrected voxel time series data were visually inspected to remove large movement artifacts. Preprocessed time series data for each subject were analyzed using a multiple regression model. Three regressors were used to model residual motion (in the roll, pitch and yaw direction). Two regressors, a baseline and a linear trend, were used to eliminate slow signal drifts. There were three regressors of interest: (i) action selection during uncertain trials, (ii) action selection during certain trials and (iii) the outcome phase of the task. Uncertain trials comprise all trials where the face value of the cue card is a 5, 6 or 7. Certain trials comprise all trials where the face value of the cue card is a 2, 3, 4, 8, 9 or 10. The distinction between uncertain and certain trials was based on the subjects’ behavioral responses (see ‘Results’ section). These three regressors of interest were created using each subject’s individual response patterns. Thus, during each trial, two subject-specific regressors were created (Figure 1): (i) the action selection regressor begins at the onset of the cue card and ends when the subject selects a response and (ii) the outcome regressor begins at the onset of the feedback card and ends at the onset of the fixation cross. Each of the regressors was convolved with a modified gamma variate function modeling a prototypical hemodynamic response prior to inclusion in the regression model.
The AFNI program 3dDeconvolve (Cox, 1996) was used to calculate the estimated voxel-wise impulse response function. A Gaussian filter with FWHM 6 mm was applied to voxel-wise percent signal change data to account for individual variations of anatomical landmarks. A threshold adjustment method based on Monte Carlo simulations was used to guard against identifying false positive areas of activation (Forman et al., 1995). Based on these simulations, it was determined that a voxel-wise a priori probability of 0.05 would result in a corrected cluster-wise activation probability of 0.05 if a minimum cluster volume of 1024 ml and a connectivity radius of 4.0 mm was considered.

The voxel-wise percent signal change data for each comparison was entered into a mixed model analysis of variance with task condition as a fixed factor and subjects as a random factor. There were two main comparisons: (i) action selection (uncertain trials vs certain trials) and (ii) action selection (during all trials) vs outcome (during all trials). Each subject’s BOLD signal in each cluster of activation was extracted separately for uncertain trials and certain trials and then inputted into the correlation analysis.

**Personality measures**

All subjects were given the Neuroticism Extraversion Openness Five-Factor Inventory (NEO-FFI) (Costa and McCrae, 1991), a widely-used self-report measure of personality, and asked to return the questionnaire in a stamped envelope. The NEO-FFI consists of 60 statements that are rated by the subject on a 5-point scale from ‘strongly agree’ to ‘strongly disagree’. The NEO-FFI can be used to extract five personality factors: neuroticism, extraversion, openness, agreeableness and conscientiousness. For the purposes of this study, only the neuroticism factor was analyzed. Each subject’s neuroticism score was converted to a normalized T-score and then correlated with the BOLD signal.

**Correlation analysis**

All correlations were carried out with SPSS 10.0 (Norusis, 1990) using the Pearson correlation coefficient. In order to ensure that significant correlations were not due to extreme data points, an outlier screening process was used. All behavioral and personality data >2 SDs from the mean were considered outliers, and thus excluded from the correlation analysis. This process yielded two outliers within the response latency correlations and no outliers within the personality correlations.

**RESULTS**

**Behavioral results**

Behavioral measures of response selection and response latency were collected during fMRI scanning. Figure 2A displays the response selection characteristics of the subjects. When the cue card was a 2, 3 or 4, subjects predominantly predicted that the next card would be higher. Likewise, when the cue card was an 8, 9 or 10, subjects predominantly predicted that the next card would be lower. However, when the cue card was a 5, 6 or 7, subject responses wavered between lower and higher. As shown in Figure 2B, trials with a cue card of a 5, 6 or 7, were denoted ‘uncertain trials’, accounting for >83% of the total uncertainty. Trials with a cue card of either 2–4 or 8–10 were denoted ‘certain trials’, accounting for <17% of the total uncertainty. If uncertain trials require more cognitive or affective resources, one...
might expect increased response latency when the cue card is a 5, 6 or 7. The data supported this hypothesis (Figure 2C); it took the subjects significantly longer to select a response during uncertain trials when compared with certain trials $[F(1,15) = 4.75, P<0.05]$.

### fMRI results

The dLPFC was significantly more active during the action selection period of uncertain vs certain trials (Table 1). No brain regions were significantly more active during the action selection period of certain vs uncertain trials. Although a whole-brain analysis yielded no significant clusters of activation in other regions known to process uncertainty, this does not preclude the possibility of finding brain regions that are significantly active during action selection irrespective of a trial's degree of uncertainty. For example, recent evidence suggests that the anterior insula may be preferentially engaged during action selection when compared with the outcome phase of decision-making (Paulus et al., 2005). In order to test for this possibility, a second contrast was performed between the action selection and the outcome phase of the task. This second contrast yielded two clusters of activation within the bilateral anterior insula (Table 1). As predicted, the anterior insula was significantly more active during action selection, irrespective of trial type. Importantly, the average group activation was not significantly different during certain and uncertain trials, thereby explaining the negative finding in the first contrast analysis.

### Neuroticism

All subjects completed the NEO-FFI. Their mean T-score for neuroticism was 44.27 (SD = 8.3; range 30–56). This sample's scores were slightly lower than the average range of the normative NEO-FFI population (standardized to have a T-score mean of 50, SD = 10).

### Correlation results

There was significant between-subjects variability in BOLD activation, bilaterally in the anterior insula and dLPFC, during the action selection period of both certain and uncertain trials. We utilized the personality scores to account for the between-subjects variability in neural activity in these structures. As shown in Table 2, individual differences in activation during certain trials significantly correlated with neuroticism in all four clusters of activation. On the other hand, individual differences in activation during uncertain trials did not significantly correlate with neuroticism. Scatter plots for the significant correlations are shown in Figure 3 (dLPFC) and Figure 4 (anterior insula).

A similar variability was found in individual response latency differences between uncertain and certain trials. On average, the group took significantly longer to select a response during uncertain trials (Figure 2C). However, subjects who showed smaller differences in response latency between uncertain and certain trial types showed more activation in the right anterior insula relative to those who responded quicker during certain trials and slower during uncertain trials (Table 2 and Figure 5).
This investigation showed that activation within the anterior insula and dLPFC during the action selection phase of a simple decision-making task was positively correlated with neuroticism. This correlation was only significant during certain decisions and not during uncertain decisions. In addition, this pattern of results was found in brain regions specific to processing uncertainty (i.e. the dLPFC) and in brain regions found to be involved in decision-making irrespective of uncertainty (i.e. the anterior insula). Furthermore, the correlations were found bilaterally in both brain regions, making it less likely that these findings were obtained by chance. These results add to a growing number of studies documenting the strong associations between personality and brain activation (Canli et al., 2001; Eisenberger et al., 2005; Paulus et al., 2003). The specificity of these findings to certainty is noteworthy because intuitively certain decisions are easier (e.g. when presented a 2, the next card must be higher) than uncertain decisions (e.g. when presented a 6, the next card can be higher or lower). This finding is consistent with the notion that increased levels of neuroticism are associated with the allocation of more processing resources to decision-making during times in which there is little chance of incorrect responding (Paulus et al., 2004).

This study provides converging evidence that activation in the anterior insula during decision-making is highly modulated by an individual’s degree of neuroticism (Paulus et al., 2003). Our findings also replicate previous results showing a significant correlation between neuroticism

### Table 1 Significant clusters of neural activation ($P < 0.05$)

| Cluster volume ($mm^3$) | Coordinates (Center of cluster) | L/R | Cortical areas (within cluster) | BA | T-value |
|-------------------------|---------------------------------|-----|---------------------------------|----|---------|
| Action selection: Uncertain trials > Certain trials | 4032 | $-45, 32, 27$ L | Middle frontal gyrus | 9/46 | 2.83 |
| 1088 | $41, 31, 29$ R | Middle frontal gyrus | 9 | 3.02 |
| Action selection > Outcome | 1856 | $32, 15, 11$ R | Anterior insula | 13 | 2.98 |
| 1344 | $-32, 13, 12$ L | Anterior insula | 13 | 4.68 |

All coordinates are Talairach coordinates ($x, y, z$). Cortical areas are based on Talairach Daemon software. L/R, left/right; BA, Brodmann’s area.

### Table 2 Correlations

| Brain region | Trial type | Neuroticism T-score | Certain minus Uncertain response latency |
|--------------|------------|---------------------|----------------------------------------|
| Right anterior insula | Certain | 0.591* | 0.710** |
| Uncertain | 0.431 | 0.133 |
| Left anterior insula | Certain | 0.664*** | 0.455 |
| Uncertain | 0.127 | -0.224 |
| Right dLPFC | Certain | 0.572* | 0.443 |
| Uncertain | 0.207 | 0.252 |
| Left dLPFC | Certain | 0.552* | 0.511 |
| Uncertain | 0.193 | -0.054 |

The Pearson correlation ($r$-value) is shown for each correlation. Scatter plots for each significant correlation are shown in Figure 3–5.

*Correlation is significant at the 0.05 level (two-tailed).

**Correlation is significant at the 0.01 level (two-tailed).
and activation of the dLPFC (Canli et al., 2001). One possible interpretation of this finding is that individuals with higher neuroticism scores subjectively interpret certain decisions as uncertain. This is consistent with neurotic people’s tendency to respond emotionally to events that would not affect most people and interpret ordinary situations as threatening and difficult to resolve. Unfortunately, we did not obtain any measure of self-report that specifically assesses the subject’s interpretation of uncertainty. However, a proxy measure for the degree of uncertainty inherent in a decision is the latency to select a response. For example, if a particular trial engenders the same degree of subjective uncertainty as another trial, one would predict similar response latencies between these trials. The significant correlation between the degree of right anterior insula activation and the response latency difference supports this prediction (Figure 5). Specifically, the higher a subject’s insula activation during certain decisions, the closer their response latency on certain trials matched their response latency on uncertain trials.

Fig. 5 The scatter plot displays each subject’s average activation within the right anterior insula during the action selection period of certain trials and his or her respective response latency difference (in milliseconds) between certain and uncertain trials. There is a significant positive correlation, such that the higher a subject’s insula activation, the closer their response latency on certain trials matched their response latency on uncertain trials.

The results of this study highlight a number of possibilities for further investigation. Additional replication, with larger sample sizes, will further clarify the role of the insular cortex in neuroticism. Also, the somewhat counterintuitive finding of increased activation during certain decisions (but not uncertain decisions) correlating with neuroticism needs to be further explored. Very little research has investigated the relationship between certainty and neuroticism. Future studies should consider obtaining a subjective measure of uncertainty, like the Intolerance of Uncertainty Scale (Freeston et al., 1994), which would complement the neural and behavioral measures obtained in the present study. Intolerance to uncertainty is characterized by a tendency to perceive ambiguous situations as threatening and has been identified as an important variable related to the acquisition and maintenance of excessive worry (a hallmark feature of generalized anxiety disorder) (Dugas and Ladouceur, 2000; Ladouceur et al., 2000; Sexton et al., 2003). Along these lines, it is still unknown whether a specific facet of neuroticism (e.g. anxiety) is more involved than other facets (e.g. self-consciousness) in producing the present findings (Eisenberger et al., 2005). Likewise, recent work has highlighted the close relationship between neuroticism, negative affect and fMRI activation (Canli et al., 2004). Future fMRI studies should attempt to parse out the state vs trait influence on neural activity. It is also important to point out that the subjects used in this study all scored within or slightly below the average range of neuroticism scores obtained from the general population. Thus, future studies should attempt to characterize individual differences in anterior insula reactivity using a subject pool with a much wider range of personality scores. Such an approach will provide a more comprehensive picture of how neuroticism and other personality traits are instantiated within the brain. Furthermore, it may illuminate specific neural signatures related to the vulnerability for psychiatric illness.

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