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Individual Differences in Insular Sensitivity During Loss Anticipation Predict Avoidance Learning

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Abstract

The anterior insula has been implicated in both the experience and the anticipation of negative outcomes. Although individual differences in insular sensitivity have been associated with self-report measures of chronic anxiety, previous research has not examined whether individual differences in insular sensitivity predict learning to avoid aversive stimuli. In the present study, insular sensitivity was assessed as participants anticipated monetary losses while undergoing functional magnetic resonance imaging. We found that insular responsiveness to anticipated losses predicted participants' ability to learn to avoid losses (but not to approach gains) in a behavioral test several months later. These findings suggest that in addition to correlating with self-reported anxiety, heightened insular sensitivity may promote learning to avoid loss.

Detecting and avoiding threats arguably are the most basic of survival skills. In humans, avoidance learning is necessary not only to ensure survival in the face of basic threats (e.g., predators, rotten food), but also to promote optimal responses to more abstract threats in social (e.g., enemies) and economic (e.g., risky investments) domains. Although the ability to anticipate and avoid danger is critical to survival, excessive anticipatory anxiety may contribute to psychopathology.

Scientists have recently used brain-imaging techniques with enhanced spatial and temporal resolution to characterize neural circuitry implicated in anticipation of threats. One region that has consistently been associated with anticipation of threat is the anterior insula (Seymour, Singer, & Dolan, 2007), a region of polymodal association cortex tucked deep within the lateral sulcus between the lateral prefrontal cortex and striatum. Activation of the anterior insula has been observed not only in response to emotionally negative events, but also during anticipation of those events (Kim, Shimojo, & O'Doherty, 2006; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Samanez-Larkin et al., 2007; Seymour et al., 2005). In addition, anticipatory insula activation is associated with (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003) and predicts (Kuhnen & Knutson, 2005) behavioral avoidance of risky options in decision-making tasks.

Whereas insula activation exhibits within-individual variation related to task demands, chronic insular activation differs between individuals, and has been proposed as an endophenotypic marker of anxiety proneness (Paulus & Stein, 2006). Altered insular sensitivity has been observed in several clinical populations with anxiety disorders, including simple phobia, specific phobia, social phobia, posttraumatic stress disorder, obsessive-compulsive disorder, panic disorder, and generalized anxiety disorder (for a review, see Paulus & Stein, 2006). Moreover, studies of healthy, nonclinical samples have demonstrated significant relationships between insular sensitivity and self-report measures of anxiety, such as neuroticism and harm

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avoidance (Paulus et al., 2003; Stein, Simmons, Feinstein, & Paulus, 2007). In addition, animal studies have shown that specific lesions to insular cortex disrupt taste-aversion learning in rats (Cubero, Thiele, & Bernstein, 1999; Yamamoto, Shimura, Sako, Yasoshima, & Sakai, 1994).

Although there is converging evidence that activation of the insula plays a role in anticipatory anxiety, previous studies have not tested the functional hypothesis that anticipatory insular activation predicts learning to avoid loss. In the study reported here, we examined whether a neural index of insular sensitivity to anticipated loss would predict behavioral loss-avoidance learning several months later.

METHOD

Eleven younger (ages 19–27; 5 female, 6 male) and 12 older (ages 65–81; 6 female, 6 male) adults participated in two sessions. In the first, all 23 participants played a monetary incentive delay task while undergoing functional magnetic resonance imaging (fMRI) to localize brain regions involved in the anticipation of monetary incentives. On each trial, participants viewed one of six cues (lose $0.00, lose $0.50, lose $5.00, gain $0.00, gain $0.50, gain $5.00) on a computer monitor (2 s). After a delay (2–2.5 s), a star appeared briefly (100–400 ms), and participants attempted to press a button while the star was still present on the screen. An adaptive algorithm was used to control the hit rate by setting a deadline for each of the six trial types defined by the cues, such that individuals would respond while the star was present on approximately 66% of the trials for each cue type. When participants responded in time, they received feedback (2 s) that they had avoided losing ("−$0.00") or had gained ("+$0.00," "+$0.50," "+$5.00") the amount of money indicated by the preceding cue (in the loss and gain conditions, respectively); late responses produced feedback that participants had lost ("−$0.00," "−$0.50," "−$5.00") or had not gained ("+$0.00") money. Participants were told that their goal was to earn as much money as possible, and they were subsequently paid in real cash the cumulative amount of money they had won, as indicated by the outcomes displayed. There were 30 trials for each condition, ordered randomly.

Brain-imaging analyses focused on changes in activation during anticipation (i.e., after participants saw cues but before they responded to targets) and outcome (i.e., after participants received feedback about their success and monetary losses or gains), for both loss and gain trials. We conducted a whole-brain multiple regression analysis with four independent and orthogonal regressors of interest: loss versus nonloss anticipation, gain versus nongain anticipation, nonloss versus loss outcome, and gain versus nongain outcome.[1]

In the second session, administered 8 to 10 months later, participants performed a monetary incentive-learning task (functional imaging data were not collected in this session). On each trial, one of three pairs of fractal images was presented. In one pair (loss avoidance), choice of one image had a .6 probability of avoiding a $1 loss, and choice of the other had a .3 probability of avoiding a $1 loss. In a second pair (gain acquisition), choice of one image had a .6 probability of yielding a $1 gain, and choice of the other image had a .3 probability of yielding a $1 gain. In a third pair, neither image was associated with monetary outcomes. Assignment of pairs to conditions and images to outcomes was counterbalanced across participants.

Each trial began with a fixation cross (2 s), followed by a pair of images. Participants were given an unlimited amount of time to choose an image. The selected image was highlighted on the screen (2 s), and then the monetary outcome ("−$1," "$0," or "+$1") was displayed (2 s). There were 120 trials, consisting of 40 trials in each of the three conditions. Participants

[1]For a complete description of the task, fMRI acquisition parameters, and the full regression model used to localize changes in neural activation, see Samanez-Larkin et al. (2007).

were urged to earn as much money as possible by learning to choose the image with the higher probability of avoiding a $1 loss when the loss-avoidance pair was presented and the image with the higher probability of a $1 gain when the gain-acquisition pair was presented. Participants were paid in real cash the cumulative amount of money they won, as indicated by the outcomes displayed. Performance was calculated as the percentage of correct choices (i.e., the high-probability cue) in each monetary condition (loss avoidance, gain acquisition). Unlike in the first session, hit rate was not manipulated in this session. Group differences in performance were examined with independent-sample *t* tests.

To explore the relationship between neural activation in the first session and behavioral learning in the second, we conducted a whole-brain regression analysis that identified brain regions whose activation correlated significantly with subsequent incentive learning (i.e., correlation between voxel coefficients, from the whole-brain regression model described earlier, during each condition of the incentive-anticipation task and performance in each condition of the incentive-learning task). The threshold for statistical significance was set using a global family-wise error rate ($z > 3.89$, $p < .0001$ uncorrected) and required a minimum cluster of fifteen 2-mm^3 voxels. Confirmatory partial correlational analyses (controlling for age) were performed by extracting mean peak anticipatory signal change from regions identified in the whole-brain analysis (adjusted within individuals to ensure that regions contained gray matter only). The signal change score for each individual was computed as a measure of sensitivity (signal change on $0.50 and $5.00 trials minus signal change on $0.00 trials, separately for loss and gain).

RESULTS

Younger and older adults did not differ in their performance in any condition of the learning task, and so these groups were combined in the following analyses. Results of the whole-brain analysis revealed a significant association between activation in the right anterior insula (peak-voxel Talairach coordinates: 30, 20, 3) during loss anticipation and subsequent loss-avoidance learning, $z = 4.71$, $p_{rep} = .999$, effect size: $R^2 = .62$ (Fig. 1a). No other brain regions showed a significant association with loss-avoidance learning.

This relationship was confirmed in a volume-of-interest analysis, which revealed a significant partial correlation (controlling for age) between percentage signal change in the anterior insula during loss anticipation and subsequent behavioral loss-avoidance learning, $r = .45$, $p_{rep} = .897$ (Fig. 1b).[2] However, performance in gain-acquisition learning was not significantly correlated with activation in any brain region. Further, the correlation between insular activation during loss anticipation and future loss-avoidance learning ($r = .45$) was significantly greater than the correlation between insular activation during loss anticipation and future gain-acquisition learning ($r = -.10$), $z = 5.8$, $p_{rep} = .999$. Additionally, insular activation during gain anticipation was not significantly correlated with either gain-acquisition learning or loss-avoidance learning (*r*s = .11 and .04, respectively). The association between insular activation and loss-avoidance learning was specific to activation during anticipation, as insular activation in response to loss outcomes was not significantly related to learning of either gain acquisition or loss avoidance.

DISCUSSION

This is the first demonstration that individual differences in insular sensitivity presage future loss-avoidance behavior. Because the present study localized insular sensitivity with a task

[2]Controlling for age did not reduce the significance of this effect. The simple correlation between anterior insular activation and avoidance learning was also significant, $r = .50$, $p_{rep} = .939$.

devoid of performance differences, individual differences in insular sensitivity cannot be attributed to differential incentive outcomes. The results are consistent with the recent hypothesis that a loss-prediction signal (i.e., heightened anxiety during loss anticipation), rather than global sensitivity to loss (i.e., heightened anxiety during both loss anticipation and loss outcomes), can promote avoidance behavior (Paulus & Stein, 2006). The findings also provide neural evidence consistent with the historic hypothesis that a loss-prediction signal that generates increased anxiety can promote instrumental avoidance behavior (Mowrer, 1956).

These results suggest that a neural endophenotypic marker of the affective experience of anxiety may also promote avoidance learning—a skill that can confer survival value in threatening environments. This potential functional advantage may help to explain why anxiety-related traits persist in humanity's genetic endowment, even as environmental threats vary.

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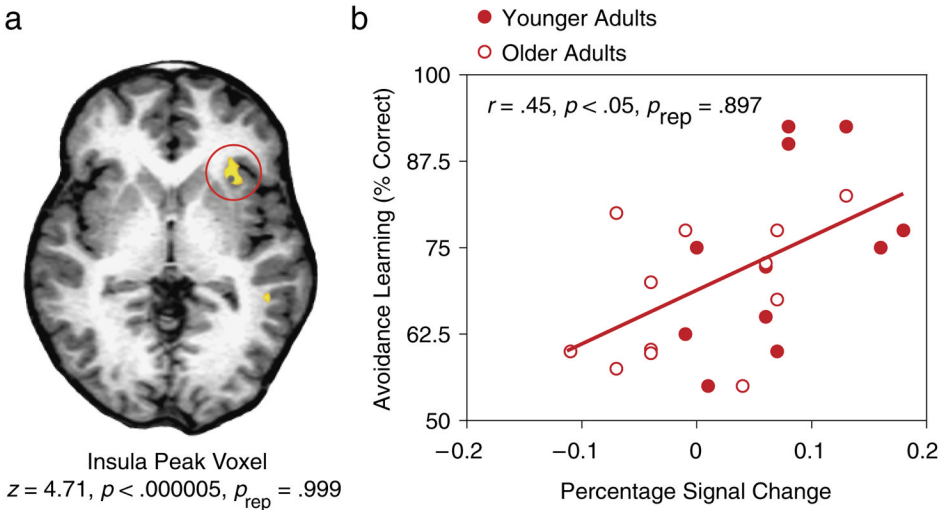

Fig. 1.

Correlation between insular activation during loss anticipation and behavioral loss-avoidance learning. The illustration (a) depicts the location and corresponding statistics for the peak cluster of activation in the right anterior insula, identified during the whole-brain analysis (map threshold: $p < .0005$). The scatter plot (b) reveals the correlation (and corresponding statistics, controlling for age) between mean percentage signal change (*x*-axis) extracted from anatomically defined regions of interest in the anterior insula in individual participants and subsequent loss-avoidance learning (percentage correct; *y*-axis). The trend line depicts the correlation across all participants, but individual results for younger adults and older adults are labeled with separate markers.