

Anterior Cingulate Activation in High Trait Anxious Subjects Is Related to Altered Error Processing During Decision Making

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Background: Individuals with high trait anxiety (HTA) can be studied to examine the effect of elevated levels of anxiety on the processing of stimuli and the selection of actions. The anterior cingulate cortex has been implicated in the detection and processing of errors. This investigation examined the hypothesis that HTA subjects are more sensitive to errors than nonanxious comparison subjects during a simple decision-making task and show increased activation in the anterior cingulate, particularly at low error rates.

Methods: Thirteen HTA subjects were compared with 13 normal trait anxiety (NTA: 40th–60th percentile) subjects during functional magnetic resonance imaging while performing a two-choice prediction task at three different error rates.

Results: Both HTA and NTA subjects performed similarly during a simple two-choice prediction task; however, during the low-error-rate condition, activation in the anterior cingulate and medial prefrontal cortex was significantly higher in HTA subjects and was correlated with trait but not state anxiety.

Conclusions: These results support the idea that HTA subjects devote more processing resources to decision making than do NTA subjects during times in which there is little chance of incorrect responding (i.e., the low-error-rate condition). The extent to which this altered activation within the anterior cingulate contributes to anxiety-proneness remains to be determined.

Key Words: Anxiety, decision making, error sensitivity, functional neuroimaging

Anxiety has been viewed traditionally as an emotional state that is based on a perceived apprehension of danger or threat (Lang and Cuthbert 1984; Mogg et al 1989). Alternatively, anxiety can be defined as a future-oriented cognitive and emotional state/trait characteristic involving several components, such as anxious apprehension, worry, affective or behavioral conflicts, and altered approach/avoidance behaviors. A number of different experimental approaches have been used to examine these components, which involve basic cognitive paradigms probing attention (Mathews et al 1989) and working memory (Bradley et al 1994; Calvo and Eysenck 1996), behavioral control processes (Mogg et al 1989), conflict exposure (Boucsein and Wendt-Suhl 1976), uncertainty processing (Ladouceur et al 2000), implicit emotional face processing (Mogg et al 1995), and decision making (Aftanas et al 1996; Pury and Mineka 2001; Schmitt et al 1999.)

One approach to examining the effects of anxiety on such processes is to study individuals with high trait anxiety (HTA) (Spielberger et al 1999), which can be defined as a general predisposition to respond anxiously (Spielberger and Smith 1966). High trait anxiety, defined here as being in the upper 15th percentile on measures of trait anxiety, can be used to examine the effect of elevated levels of anxiety on the processing of stimuli and the selection of actions. Subjects with HTA are at risk for a number of different psychiatric conditions (Comeau et al 2001; Willinger et al 2002), including the full spectrum of anxiety disorders (Bennet and Stirling 1998). Investigating subjects with

HTA provides a unique opportunity to examine the neural systems that are important for mediating increased levels of anxiety and that might, in addition, provide insight into processes that might be responsible for the development of anxiety disorders. This strategy also has the advantage of enabling the study of individuals in the relative absence of potential confounding factors, such as medical and complicated psychiatric comorbidity and psychopharmacologic drug therapy.

Several investigators have shown that subjects with HTA are more sensitive to detect threat-related material (Bradley et al 1997; McNally and Palfai 2001). Others have found that HTA is due to a lower threshold for appraising threat rather than a bias in the direction of attention deployment (Mogg and Bradley 1999). High trait anxiety subjects show a bias to encode (Pury and Mineka 2001) and recall (Reidy and Richards 1997; Russo et al 2001) task-irrelevant but affectively salient information. Subjects with HTA also showed heightened shock expectancy (Chan and Lovibond 1996), increased sensitivity to punishment (Corr et al 1997), increased sensitivity to recognizing fear in morphed ambiguous faces (Richards et al 2002), and increased sensitivity to contextual information (Blanchette and Richards 2003). This altered threshold for threat-related material, bias for the recollection of affectively salient information, and increased sensitivity to punishment might, therefore, have important implications for the evaluation of different options in decision-making situations.

Decision making is an important and complex process in daily life. Decision making consists of several steps that involve assessment of the available options, the execution of an action, and the processing of the outcome associated with the decision. In a narrow sense, decision making involves the selection of an action from several available options on the basis of an underlying rule or heuristic. Not surprisingly, in experimental decision-making studies, people choose the option that is most likely to be associated with a preferred outcome (Calfee and Atkinson 1966; Goulet and Barclay 1967; Ludvigson 1966). This behavior is consistent with the notion that anticipated "success" or "failure" critically influences decision making (Egeman et al 1998); however, the degree to which people are sensitive to feedback varies widely and might be a basis for large interindividual decision-making differences (for review, see Luce 1959; Mellers et al

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1998). Therefore, an altered expectancy of “success” or “failure” in HTA subjects might critically affect decision-making processes in these subjects.

Functional neuroimaging studies inducing anxiety and comparing HTA subjects (and subjects with anxiety disorders) with normal comparison subjects have revealed a neural circuitry that involves orbitofrontal cortex (Grachev and Apkarian 2000), inferior prefrontal cortex (Rauch et al 1997), insular cortex (Liotti et al 2000), hippocampus (Ploghaus et al 2001), medial prefrontal cortex (Simpson et al 2001a, 2001b), and adjacent anterior cingulate cortex (Chua et al 1999). The elements of this neural circuitry involve many of the components of the neural system that underlies decision making. Specifically, functional neuroimaging studies have shown that decision making is critically dependent on the activation of inferior prefrontal cortex (Ernst et al 2002; Paulus et al 2001), ventromedial and ventrolateral frontal cortex (Elliott et al 1999, 2000a; Rogers et al 1999), anterior cingulate (Elliott et al 2000a), insula (Critchley et al 2001), and parietal cortex (Paulus et al 2001).

In particular, when the frequency of “correct” prediction (error rate) is experimentally controlled in a simple two-choice prediction task, differential activation was found in the striatum, posterior parietal cortex (Verney et al 2003), and anterior cingulate (Paulus et al 2002). Although the outcome of this task is inherently unpredictable, subjects do not select a choice randomly but rather match the frequency of response alterations to the frequency of errors (Ludvigson 1966). Previous studies have found that the expectation of an outcome has an important effect on that outcome’s ability to disrupt performance (e.g., infrequent errors seem to be particularly disruptive) (Tzelgov et al 1992). Therefore, at low error rates, increased fronto-parietal-cingulate activation might signal the error-related switch from a predominant response strategy to alternative strategies during decision making (Paulus et al 2002).

Previously, we found that response sequences generated by patients with panic disorder were more unpredictable during a simple two-choice prediction task at low error rates (Ludwig et al 2003). One explanation for the increased unpredictability is that an “incorrect” prediction, albeit infrequent, is more likely to initiate a different response strategy in panic disorder patients. The present study aimed to extend this finding to HTA subjects by determining whether these subjects show increased unpredictability, particularly at low error rates, and whether brain activation patterns during this task reflect altered processing at low error rates. Specifically, we expected to find error-related differences between HTA and nonanxious comparison subjects in four key structures that are relevant for decision making: the anterior cingulate, the posterior parietal cortex, the prefrontal cortex, and the striatum. Consistent with our previous findings, we hypothesized that, if HTA subjects are hypersensitive to processing errors, one would expect to see increased activation at low error rates in the cingulate, parietal, and prefrontal cortices.

Methods and Materials

Participants

This study was approved by the University of California San Diego and the San Diego State University (SDSU) institutional review boards, and all subjects signed informed consent. Initially, a sample of SDSU undergraduate psychology students participated in mass screening with the Spielberger Trait Anxiety Questionnaire (Spielberger 1983). Subsequently, subjects who

scored high in trait anxiety (in the upper 15th percentile of the distribution) and subjects who had normative levels of trait anxiety (from the 40th to the 60th percentile of the distribution) were selected for further screening. All subjects were subsequently interviewed with a structured diagnostic interview (First et al 1995), modified to enable us to document the presence of subthreshold anxiety and mood disorders. Only subjects who did not have a DSM-IV (American Psychiatric Association 1994) diagnosis were included in this study (though subjects with subthreshold disorders were permitted to participate). Twenty-six subjects were studied: 13 subjects (12 female, 1 male) with normal trait anxiety (NTA) scores and 13 subjects (12 female, 1 male) with HTA scores. The HTA subjects were very similar to the NTA subjects in terms of age (mean [SD]: HTA: 18.31 [.85] years; NTA: 18.54 [.88] years) and years of education (HTA: 13.15 [.38] years; NTA: 13.46 [.88] years). All subjects were trained to perform the two-choice prediction and two-choice response tasks before testing during functional magnetic resonance imaging (fMRI) scanning and received \$50 for participation. No restrictions were placed on the consumption of caffeine-containing beverages; none of the subjects were smokers.

Measures

Subjects completed the NEO Five Factor Inventory (NEO-FFI) (Costa and McCrae 1992, 1997), which consists of 60 statements that are rated by the subjects 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. These NEO-FFI factors were transformed to normalized *z* scores. Subjects also completed the Anxiety Sensitivity Index, a 16-item measure of the propensity to view anxiety symptoms as threatening (Reiss et al 1986), which has been shown to predict later onset of panic attacks (Schmidt et al 1997, 1999). Moreover, all subjects completed the Zuckerman Sensation Seeking Scale, a questionnaire to assess engagement in high-risk activities (Zuckerman 1986), and the Barratt Impulsivity Scale, which measures different components of impulsivity (Barratt et al 1999).

Task

In the two-choice prediction task (Paulus et al 1994, 1996, 2001), the image of a house that is flanked by a person to the left and right is presented on a computer screen. The goal for the subject is to decide on which side of the house a car will be presented. Each trial is self-paced to maximize self-determined action (Frith et al 1991), thus the subject determines the number of trials by the latency to select a response. Immediately after the subject’s response, the car is presented for 300 msec on the far left or right side of the screen, which provides the feedback as to whether the prediction was correct (i.e., the person and car are on the same side) or incorrect (i.e., the person and car are on opposite sides). Immediately after the presentation of the car, the next trial begins. Unbeknownst to the participants, the computer determines the response based on the participant’s selection. Three error-rate block types were presented (see also Figure 1): high (80% of responses were “incorrect”), chance-level (50% of responses were “incorrect”), and low (20% of responses were “incorrect”). Because error rates are a property of sequences of trials, a parametric fMRI block design was used. The three task conditions (20%, 50%, or 80% error rate) were presented four times, yielding 12 blocks, which varied in duration between 21 and 24 sec. Each block type occurred in a pseudorandom order (50%, R [rest], 20%, R, 80%, R, 20%, R, 50%, R, 80%, R, 50%, R,

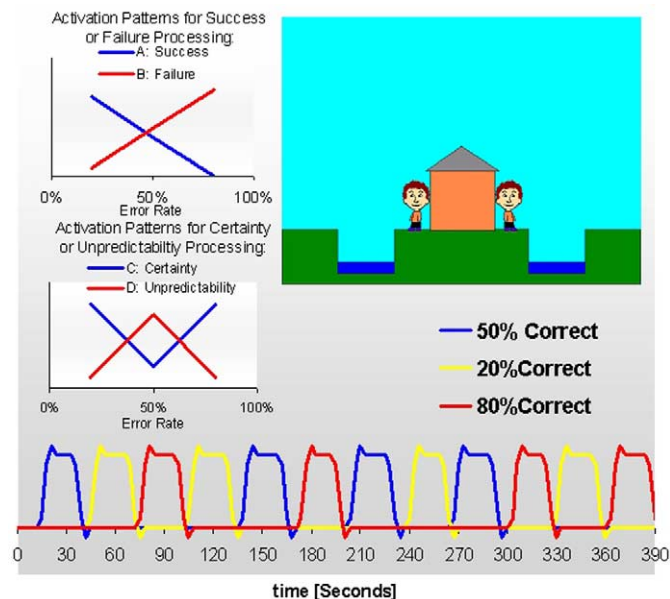


Figure 1. fMRI block design for two-choice prediction task. The insets show the predicted activation patterns according to success or failure processing, as well as certainty or unpredictability processing. These processing patterns are assessed by planned linear and quadratic contrasts, respectively.

20%, R, 50%, R, 80%, R, 20%, R, 80%) and was separated by a resting condition (presentation of the background stimulus, no response required), which lasted 6–12 sec.

Behavioral Measures

For each trial, the selection by the participant (right or left), computer-selected response (right or left), and response latency were obtained. The strategies of decision making in the presence of uncertainty were assessed by two sets of measures: 1) general response biases: the number of left or right responses and stay responses (e.g., left response followed by another left response) versus switch responses (e.g., left response followed by right response); and 2) the degree to which the current response was determined by the previous response, the previous stimulus, or a combination of both, as quantified by mutual information measures (Herzel and Grosse 1995). Mutual information functions (Herzel and Grosse 1997) are based on the logarithmic likelihood ratio between the observed frequency and the expected frequency of an event (i.e., the more likely two events co-occur the higher their mutual information).

fMRI Protocol and Image Analysis Pathway

Magnetic resonance images were obtained with a 1.5-T whole-body system (Siemens, Erlangen, Germany). Anatomical T1-weighted images of the whole brain (magnetization prepared rapid acquisition gradient echo; repetition time = 11.4 msec, echo time [TE] = 4.4 msec, flip angle 10°, field of view [FOV] 256 × 256, 1-mm³ voxels) were obtained sagittally. Thirty-two slices of T2*-weighted images were obtained in the axial plane with gradient-recalled echo-planar imaging (TE = 40 msec, flip angle 90°, 64 × 64-pixel FOV = 256 × 256 mm, 4-mm contiguous slice thickness) every 3000 msec for 128 repetitions, yielding a voxel size of 4 mm³.

All structural and functional image processing was done with the Analysis of Functional Neuroimages software package (AFNI; Cox 1996). A multivariate regressor approach was used to relate changes in echoplanar image intensity (EPI) to differences in task

characteristics. Echoplanar image intensity images were coregistered with a three-dimensional coregistration algorithm that has been developed to minimize the amount of image translation and rotation relative to all other images. Specifically, average motion parameters were obtained for registration to each EPI image and were ranked for all images. The final registration was conducted with the EPI image that produced the smallest adjustment in the six motion parameters (dx, dy, dz, droll, dpitch, dyaw). High trait anxiety subjects did not differ from NTA subjects on any of the movement parameters [multivariate analysis of variance (MANOVA) $F(1,24) = .04, p = .91$]. In addition, the time series of motion parameters was used to obtain an average for these six motion parameters for each subject. Three motion parameters (droll, dpitch, dyaw) were used as regressors to adjust EPI intensity changes due to motion artifacts. Three regressors of interest (20%, 50%, and 80% error-rate blocks) were convolved with a gamma variate function that models a prototypical hemodynamic response and normalized. The regressors of interest and the motion regressors were entered into 3dDeconvolve, an AFNI program, to determine the height of each regressor for each subject. The regressor height was divided by the 0th-order regressor to obtain the normalized voxelwise relative signal change (percent signal change). This percent signal change was the main dependent measure. A Gaussian filter with full-width half maximum 6 mm was applied to voxelwise percentage signal change data to account for individual variations of the anatomical landmarks. Data from each subject were normalized to Talairach coordinates. The percent signal difference between the two-choice prediction task and rest was entered into a mixed-model (fixed factor: error rate; random factor: subjects) ANOVA. A threshold adjustment method based on Monte-Carlo simulations was used to guard against identifying false-positive areas of activation (Forman et al 1995). On the basis of these simulations, it was determined that a voxelwise a priori probability of .025 would result in a corrected clusterwise activation probability of .01 if a minimum volume of 1536 μL (or 24 connected voxels) was considered. Talairach Demon software (Lancaster et al 2000) was used to determine brain labels for activation clusters.

Statistical Analysis

All behavioral analyses were carried out with SPSS 10.0 (Norusis 1990). A repeated-measures MANOVA, with error rate (20%, 50%, or 80%) as the within-subjects factor, was used to analyze the behavioral measures and neural activation patterns. Two main contrasts were considered. First, as shown in Figure 1, changes in behavior or patterns of activation that are due to failure- or success-related processing should show linear increases or decreases with error rates, respectively (e.g., behavioral or neuroimaging change proportional to error rate would point to failure-related processing). Second, as shown in Figure 1, predicted changes in behavior or neural substrate activation that are due to the degree of outcome predictability should show a quadratic relationship to error rates (i.e., the most unpredictable condition [50% error rate] should show the most profound effect on behavior or neural substrate activation).

Results

Subject Assessments

High trait anxiety and NTA subjects did not differ from each other on measures of sensation seeking, motor and non-planning impulsiveness, NEO-FFI extraversion, and conscientiousness levels (Table 1). There was a trend for HTA anxiety subjects to show

Table 1. Behavioral Assessments and SDs for Different Error Rate Conditions for NTA and HTA Subjects

Measures	NTA (n = 13)		HTA (n = 13)		t Test	p
	Mean	SD	Mean	SD		
SSS						
Thrill and adventure seeking	6.46	2.60	6.67	2.74	-.192	.849
Experience seeking	4.46	2.30	4.69	1.89	-.28	.782
Disinhibition	5.08	2.84	5.73	2.33	-.606	.551
Boredom susceptibility	1.92	1.55	3.17	2.25	-1.62	.119
BIS						
Attentional impulsiveness	23.31	4.55	27.15	4.51	-2.165	.041 ^a
Motor impulsiveness	21.11	3.53	20.23	3.77	.615	.545
Non-planning impulsiveness	15.85	3.46	17.77	3.30	-1.451	.16
NEO-FFI						
Neuroticism	38.42	7.32	56.84	5.91	-7.057	.00005 ^a
Extraversion	49.64	11.45	42.65	12.51	1.487	.15
Openness	52.42	9.32	45.71	9.34	1.836	.079
Agreeableness	55.97	8.74	48.5	10.70	1.949	.063
Conscientiousness	50.84	7.76	45.59	13.52	1.213	.237
STAI						
Trait	40.81	2.74	53.85	11.31	-4.04	.0005 ^a
State	30.16	7.57	44.54	10.14	-4.097	.0004 ^a
ASI	13.00	5.70	21.09	6.58	-3.229	.004 ^a

NTA, normal trait anxiety; HTA, high trait anxiety; SSS, Zucherman Sensation Seeking Scale; BIS, Barratt Impulsivity Scale; NEO-FFI, NEO Five Factor Inventory; STAI, State-Trait Anxiety Inventory; ASI, Anxiety Sensitivity Index.

^aSignificant at $p < .05$.

lower NEO-FFI openness and agreeableness scores compared with NTA subjects. As expected, not only did HTA subjects differ on the Spielberger Trait Anxiety Inventory, they also showed higher state anxiety levels, higher NEO-FFI neuroticism scores, and increased anxiety sensitivity (Table 1).

Behavioral Results

Consistent with previous findings, which have shown that subjects do not randomly respond to this task but rather make choices that are highly responsive to the experimental conditions (Paulus et al 1994), error rate significantly affected basic response

characteristics during the two-choice prediction task in both groups (Table 2). The error rate effects on response biases and mutual information functions were similar for both HTA and NTA subjects (Tables 2 and 3). First, response latencies were longest when the outcome was most unpredictable (i.e., at chance [50%] error rates; see Table 3), although this did not differ between HTA and NTA subjects [see Table 1; $F(1,28) = 1.7$, ns]. Second, a linear relationship between the error rate and the behavioral response was found for both response switching [linear trend: $F(1,23) = 33.8$, $p < .01$] and mutual information [linear trend: $F(1,23) = 11.4$, $p < .01$; Tables 2 and 3]. Specifically, the degree

Table 2. Two-Choice Prediction Task Measures and SDs for Different Error Rate Conditions for NTA and HTA Subjects

Measures	NTA Subjects (n = 13)		HTA Subjects (n = 13)		t Test	p
	Mean	SD	Mean	SD		
20% Error Rate						
Response latency	805.12	317.46	848.75	385.13	-.32	.76
Response switching	.34	.17	.34	.17	-.70	.49
Mutual Information	.11	.09	.10	.10	.35	.73
Win-stay lose-shift MI	.20	.09	.13	.08	1.90	.07
50% Error Rate						
Response latency	918.09	286.35	869.07	282.78	.44	.66
Response switching	.48	.11	.48	.07	-.15	.88
Mutual information	.07	.05	.04	.03	1.86	.08
Win-stay lose-shift MI	.19	.06	.16	.10	.79	.44
80% Error Rate						
Response latency	840.39	248.13	853.46	307.21	-.12	.91
Response switching	.53	.08	.54	.06	-.41	.69
Mutual information	.06	.05	.04	.03	.98	.34
Win-stay lose-shift MI	.12	.08	.10	.05	.81	.43

NTA, normal trait anxiety; HTA, high trait anxiety; MI, mutual information.

Table 3. Statistical Analysis of the Behavioral Results for the Two-Choice Prediction Task

Measure	Error Rate			Group			Error Rate × Group		
	<i>F</i>	<i>p</i>	η^2	<i>F</i>	<i>p</i>	η^2	<i>F</i>	<i>p</i>	η^2
Response Latency	4.39	.021	.155		.983		2.091	.135	.080
Response Switching	29.932	.000	.555	.323	.575	.013	.337	.639	.014
Mutual Information	7.557	.003	.239	1.298	.266	.051	.100	.862	.004
Win-Stay Lose-Shift MI	9.012	.001	.273	1.099	.336	.044	2.161	.155	.083

All *F* values are Greenhouse-Geisser corrected where appropriate. MI, mutual information.

to which the current response predicted the next response (mutual information) was highest at low error rates; however, there were no differential effects of error rate in HTA versus NTA subjects (Table 3). There was a statistical trend ($p < .10$) for HTA subjects to utilize win-stay/lose-shift consistent response strategies less frequently at 20% error rates.

Functional Neuroimaging Results

Effect of Error Rate on Activation Patterns. There were five areas that showed similar error rate–related activation differences for both HTA and NTA subjects. As shown in Table 4 and Figure 2, a large cluster in the right occipital/temporal area and the left middle frontal gyrus showed activation patterns that were most consistent with failure-related processing (i.e., the relative degree of activation was proportional to the number of incorrect predictions). In comparison, bilateral striatum (extending into the parahippocampal area), right precentral gyrus, and right superior frontal gyrus showed activation patterns that were consistent with certainty-related processing (i.e., the relative activation was larger when the outcome was more predictable at 20% and 80% error rates) (see Figures 1 and 2).

Group × Error-Rate Interactions. Error rate–related activation patterns of HTA subjects differed from those observed in NTA subjects in seven areas. In particular, a success- or failure-related

interaction was found in the medial frontal gyrus/anterior cingulate, the left precuneus, the right medial frontal gyrus, and the right superior frontal gyrus (Table 4). In each case, as shown in Figure 3, HTA as opposed to NTA subjects showed relatively more activation when the error rate was low (20%) than when the error rate was high (80%). A certainty- or unpredictability-related interaction was observed in the angular gyrus, the posterior cingulate, the left precuneus, and the left middle frontal gyrus. In these areas HTA subjects showed relatively more activation when the outcome was uncertain, whereas NTA subjects showed more activation when the outcome was more predictable (as shown in Figure 3 for the posterior cingulate). Taken together, the observed neural substrate activation differences between HTA and NTA subjects are consistent with the idea that HTA subjects devote more processing resources to the low-error-rate condition and when the outcome is most unpredictable.

Brain Behavior Relationships

The activation in the anterior cingulate at 20% error rates for the HTA and NTA subjects was correlated with the Spielberger Trait Anxiety Inventory score ($r = .56, p < .01$, for all 26 subjects and $r = .57, p < .05$ for the 13 HTA subjects only; Figure 3B). In comparison, the Spielberger State Anxiety Inventory score did

Table 4. Volume and Center of Mass for Mixed ANOVA Clusters of Task-Related Activation

Volume	x	y	z	L/R	BA	Label	Success or Failure		Certainty or Unpredictability	
							<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Task × Error-Rate Effect										
17,344	32	−61	6	R	19	Occipital Temporal area	26.4 ^a	<.01	1.1	.22
8704	−2	9	1		39	Striatum Parahippocampal area	4.6	.04	33.5 ^a	<.01
3520	33	−25	68	R	4	Precentral gyrus	3.7	.06	25.5 ^a	<.01
2688	−27	−3	61	L	6/9	Middle frontal gyrus	25.8 ^a	<.01	3.3	.08
1728	36	54	24	R	10	Superior frontal gyrus	3.8	.06	6.2 ^a	.02
Task × Group × Error-Rate Effect										
9344	−31	−59	33	R	39	Angular gyrus	4.6	.04	28.5 ^a	<.01
5120	0	−49	22		23	Posterior cingulate	.03	.96	24.0 ^a	<.01
4544	−14	9	59		32	Medial frontal gyrus Anterior cingulate	26.8 ^a	<.01	.96	.33
2432	12	−55	51	L	7	Precuneus	12.0 ^a	<.01	17.4 ^a	<.01
1856	16	4	63	R	6	Medial frontal gyrus	19.4 ^a	<.01	1.58	.67
1600	21	58	24	R	10	Superior frontal gyrus	14.5 ^a	<.01	2.31	.14
1600	−40	18	42	L	8	Middle frontal gyrus	4.17	.05	8.11 ^a	<.01

The success- or failure-related activation and the certainty- or unpredictability-related activation differences refer to planned linear and quadratic contrasts, respectively. Labels are based on Talairach Demon software (Lancaster et al 2000). ANOVA, analysis of variance; L/R, left/right; BA, Brodmann's area.

^aSignificant *F* score.

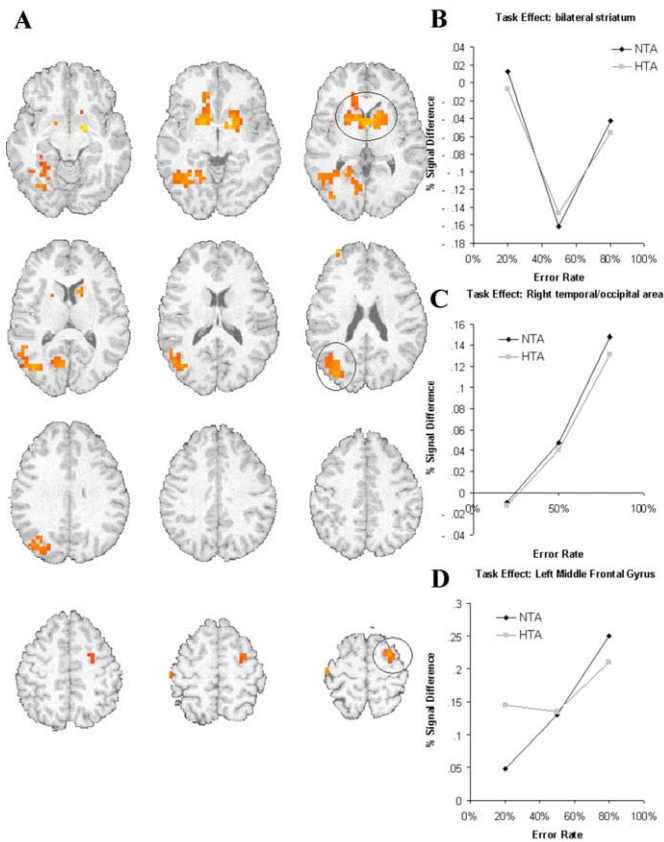


Figure 2. (A) Main effect of error rate: axial sections of cluster-thresholded *F*-maps of the error rate-related activation common to both groups. (B-D) Cluster-averaged percent signal change in the striatum, right temporo-occipital area, and left middle frontal gyrus for high trait anxiety (HTA) subjects (gray) and normal trait anxiety (NTA) subjects (black).

not correlate with activation in this area ($r = .17$, ns, for all 26 subjects and $r = .15$, ns, for the 13 HTA subjects only). Moreover, the activation in this area was also correlated with the frequency of lose-shift responses for both groups ($r = -.52$, $n = 26$, $p < .01$) but not for the HTA subjects alone ($r = -.18$, $n = 13$, ns).

Discussion

This investigation yielded three main results. First, HTA and NTA subjects did not differ significantly in their behavioral responses: during the two-choice prediction task, subjects in both groups similarly increased response switching proportional to the error rate, showed the longest latencies, the least predictable actions, and the fewest win-stay/lose-shift consistent responses when the outcome was most uncertain. Second, brain activation patterns of HTA individuals relative to NTA subjects showed relatively more activation when the outcome was most uncertain or when the error rate was low. Third, HTA subjects showed increased activation at low error rates in the anterior cingulate and medial prefrontal cortex, which was correlated with trait but not state anxiety and was associated with fewer lose-shift consistent responses. In combination, these results support the hypothesis that high trait anxiety, although not associated with altered behavioral patterns of decision making, is associated with altered neural substrate processing in areas that

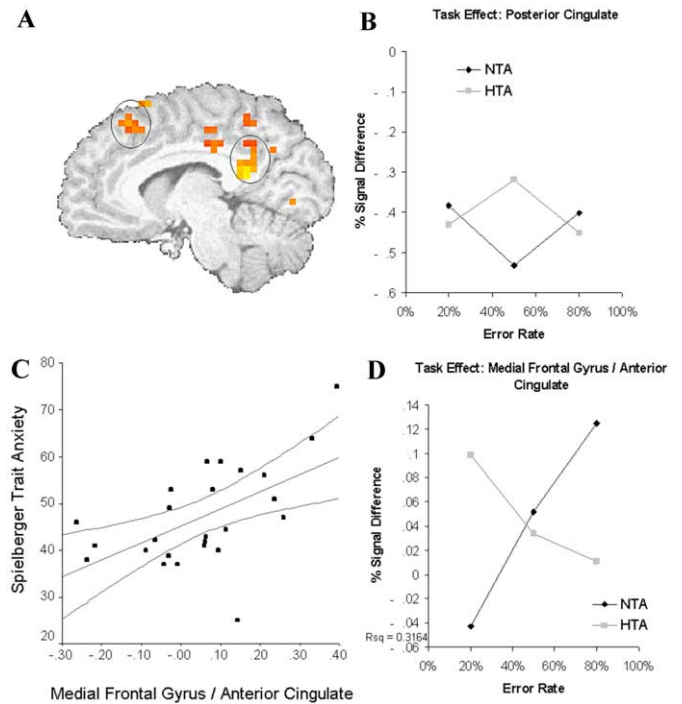


Figure 3. (A) Activation cluster in anterior cingulate/medial prefrontal cortex and posterior cingulate. (B) Cluster-averaged percent signal change in the posterior cingulate for high trait anxiety (HTA) subjects (gray) and normal trait anxiety (NTA) subjects (black). (C) Scatter-plot and regression between activation in the anterior cingulate at low error rates and trait anxiety. (D) Cluster-averaged percent signal change in the anterior cingulate for HTA subjects (gray) and NTA subjects (black).

have previously been implicated in the pathophysiology of anxiety disorders. It is of particular interest that the anterior cingulate cortex, the area that was most closely associated with levels of trait anxiety in the present study, has been implicated in error and conflict processing (Carter et al 1998; Jones et al 2002). Thus, enhanced activation in this area when errors are infrequent in a decision-making situation, in which the only indication for “correct” performance is the feedback of previous outcomes, suggests that HTA subjects might be more sensitive to incorrect predictions. Increased sensitivity to incorrect predictions fits well, conceptually, with the notion that anxiety-prone individuals are harm avoidant (Bienvenu and Stein 2003); an aversive response to incorrectly predicted circumstances might underlie this trait.

Feedback of an adverse outcome is important for adjusting behavioral strategies as part of the decision-making process. In simple decision-making tasks, stimulus frequency and payoffs primarily determine response selection (Swenson and Edwards 1971). Accordingly, subjects adjust their response strategy consistent with an error-correction set of rules (Myung and Busemeyer 1989), that is, they select actions that are different from those that have previously resulted in errors or incorrect predictions. Both groups exhibited this type of behavior by increasing their response-switching rate proportional to the error rate. In addition, however, subjects also adjusted their strategy in accordance with the general predictability of the outcome. Most notably, both groups took longer to make a decision when the outcome

was more unpredictable and were less likely to adhere to the otherwise dominant win-stay/lose-shift strategy. These behavioral findings support the notion that situations are not just processed for success and failure or reward and punishment but are also processed for their general unpredictability. Consistent with this idea, Fiorillo et al (2003) reported dopaminergic neural firing patterns that are modulated both by reward and by uncertainty.

We were not able to extend our previous findings that response sequences generated by panic disorder patients were more unpredictable than those of healthy control subjects to the behavior of HTA individuals. Apart from the different magnitude and patterns of anxiety occurring in HTA subjects relative to panic disorder patients, there are several other explanations. First, the impact of the different error rates on the behavioral measures was quite strong (effect sizes $\eta^2 \approx .5-.6$), which might have obscured other processing differences across groups. Second, the reward or punishment saliency of the outcome was quite low, which might have attenuated outcome-related difference in both groups. Third, because of the limited number of decision options, differences in processing of the situation might not result in the selection of different strategies. Therefore, future investigations might require modifications of the current paradigm, involving other contingencies (such as varying the probability and magnitude of monetary reward or punishment), to modify the decision-making characteristics and provide more decision alternatives.

We hypothesized the finding of error-related neural activation differences between HTA and NTA subjects in the anterior cingulate, the posterior parietal cortex, the prefrontal cortex, and the striatum. In fact, HTA subjects did show altered processing in three of these four areas but not in the striatum. The activation pattern differences were consistent with two different processing approaches. First, in contrast to NTA subjects, HTA individuals showed more activation at low error rates, which might suggest that they use more processing resources when errors are infrequent. Second, whereas NTA subjects showed activation patterns consistent with increased processing of certain outcomes (predictably correct or incorrect), HTA subjects showed more activation when the outcome was maximally uncertain. Previous studies have shown that infrequent errors seem to be particularly disruptive (Tzelgov et al 1992), thus, the relatively larger activation in the anterior cingulate during low error rates is consistent with the notion of an increased processing of potentially more disruptive errors.

It has been proposed that the anterior cingulate cortex contributes to performance monitoring by detecting errors (Carter et al 1998) and processing appetitive (Bush et al 2002) but also aversive conflicts (Buchel et al 1999). Specifically, the anterior cingulate is thought to provide on-line detection of processing conflicts that might be associated with deteriorating performance (Carter et al 1999). Using a number of different task conditions, some investigators have proposed that the anterior cingulate serves as a generic detector of processing conflict when low frequency responses must be executed (Braver et al 2001). Apart from the anterior cingulate's involvement in error detection and cognitive control, others have suggested that this structure is probably critical for anticipatory anxiety (Chua et al 1999), error-correcting action selection (Gehring and Knight 2000), adaptive response selection to changing conditions (Allman et al 2001), and reward-related decision making (Bush et al 2002; Gehring and Willoughby 2002; Shima and Tanji 1998). Thus, the increased activation in the anterior cingulate during low error

rates in HTA subjects might reflect the propensity to be more engaged in feedback-related processing, which might then increase anticipation of adverse outcomes and error and contribute to fearfulness (and, potentially, avoidance) of future conflict processing.

Some investigators have proposed a "risk-as-feelings" hypothesis, which highlights the role of affect experienced at the moment of decision making (Loewenstein et al 2001), consistent with the emerging view that the anterior cingulate and the anterior insula might be critical for the integration of afferent interoceptive information about impending external stimuli and internal emotional states (Craig 2002, 2003). According to these and other related models, brain-generated body-feeling states might be critical determinants for the evaluation of different options during decision-making situations and result in establishing a value system based on these body-feeling states. This formulation is completely analogous to the somatic marker hypothesis proposed by Damasio (1996). According to this formulation, anticipated outcomes associated with available actions are translated into different body states on the basis of previous experiences. This process critically depends on the intact orbitofrontal cortex, insula, amygdala, and anterior cingulate. In fact, reduced anterior cingulate activation has been related to attenuated top-down control of threat-related distractors (Bishop et al 2004). In HTA subjects, an increased representation of anticipated body states associated with adverse outcome might result in anterior cingulate hyperactivity. To examine this hypothesis, however, future studies will need to include measures of autonomic arousal as covariates during decision-making situations.

This study has several limitations. First, although brain pattern activation during the two-choice prediction task differed between HTA and NTA subjects, there was no behavioral difference observed between these subjects. The effect size analysis, however, showed that the behavioral differences between HTA and NTA subjects are similar to those reported in other studies (Mogg and Bradley 1999), but the current study might not have had enough power to detect these differences. Second, contrary to our hypothesis, there were no significant differences between HTA and NTA subjects in activation in the anterior insula. Insula activation occurs in a wide variety of task conditions frequently associated with aversive states. For example, insula-related activation has been reported during the processing of fearful (Morris et al 1998) or disgusted (Phillips et al 1998) faces, during the anticipation of electric shocks (Chua et al 1999), as well as during script-induced sad mood induction (Liotti et al 2000). Moreover, insula activity is modulated by perceptual awareness of threat (Critchley et al 2002), penalty (Elliott et al 2000b), or error-related processes (Menon et al 2001). Our group has recently reported an association between neuroticism and anterior insula activation, using a different risk-taking decision-making task (Paulus et al 2003). Thus, several behavioral decision-making probes might provide complementary information about the neural circuits critical for the mediation of anxiety. Third, the current paradigm was not intended to tease apart different component processes of decision making. Each decision-making situation can be decomposed into three phases: assessment of information, selection of action, and evaluation of outcome. An event-related fMRI design would be necessary to evaluate whether the increased anterior cingulate activation seen in the current study is due to altered assessment, execution, or evaluation.

In conclusion, altered activation patterns in the anterior

cingulate and other brain areas during decision making in HTA subjects might help us to understand how an altered top-down control process underlies anxiety as a trait and, by inference, the development and/or maintenance of anxiety disorders. Although there are many candidate processes (e.g., altered appraisal processes [Mogg and Bradley 1999], encoding and recall biases [Pury and Mineka 2001; Reidy and Richards 1997; Russo et al 2001], expectancy changes [Chan and Lovibond 1996], increased sensitivity to punishment [Corr et al 1997], and biases in processing of facial expressions [Richards et al 2002] or emotional contextual information [Blanchette and Richards 2003]), error sensitivity as measured by a simple behavioral probe, such as the two-choice prediction task, might provide additional insights into brain systems mediating pathologic anxiety.

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- Aftanas LI, Koshkarov VI, Pokrovskaja VL, Lotova NV, Mordvintsev YN (1996): Pre- and post-stimulus processes in affective task and event-related desynchronization (ERD): Do they discriminate anxiety coping styles? *Int J Psychophysiol* 24:197–212.
- Allman JM, Hakeem A, Erwin JM, Nimchinsky E, Hof P (2001): The anterior cingulate cortex. The evolution of an interface between emotion and cognition. *Ann N Y Acad Sci* 935:107–117.
- American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)*. Washington, DC: The American Psychiatric Association.
- Barratt ES, Stanford MS, Dowdy L, Liebman MJ, Kent TA (1999): Impulsive and premeditated aggression: A factor analysis of self-reported acts. *Psychiatry Res* 86:163–173.
- Bennet A, Stirling J (1998): Vulnerability factors in the anxiety disorders. *Br J Med Psychol* 71(pt 3):311–321.
- Bienvenu OJ, Stein MB (2003): Personality and anxiety disorders: A review. *J Personal Disord* 17:139–151.
- Bishop S, Duncan J, Brett M, Lawrence AD (2004): Prefrontal cortical function and anxiety: Controlling attention to threat-related stimuli. *Nat Neurosci* 7:184–188.
- Blanchette I, Richards A (2003): Anxiety and the interpretation of ambiguous information: Beyond the emotion-congruent effect. *J Exp Psychol Gen* 132:294–309.
- Boucsein W, Wendt-Suhl G (1976): The effect of chlordiazepoxide on the anticipation of electric shocks. *Psychopharmacology (Berl)* 48:303–306.
- Bradley BP, Mogg K, Lee SC (1997): Attentional biases for negative information in induced and naturally occurring dysphoria. *Behav Res Ther* 35:911–927.
- Bradley BP, Mogg K, Williams R (1994): Implicit and explicit memory for emotional information in non-clinical subjects. *Behav Res Ther* 32:65–78.
- Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A (2001): Anterior cingulate cortex and response conflict: Effects of frequency, inhibition and errors. *Cereb Cortex* 11:825–836.
- Buchel C, Dolan RJ, Armony JL, Friston KJ (1999): Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *J Neurosci* 19:10869–10876.
- Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR (2002): Dorsal anterior cingulate cortex: A role in reward-based decision making. *Proc Natl Acad Sci U S A* 99:523–528.
- Calfee RC, Atkinson RC (1966): Two-choice behavior under limiting cases of contingent reinforcement schedules. *J Comp Physiol Psychol* 62:193–200.
- Calvo MG, Eysenck MW (1996): Phonological working memory and reading in test anxiety. *Memory* 4:289–305.
- Carter CS, Botvinick MM, Cohen JD (1999): The contribution of the anterior cingulate cortex to executive processes in cognition. *Rev Neurosci* 10:49–57.
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998): Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.
- Chan CK, Lovibond PF (1996): Expectancy bias in trait anxiety. *J Abnorm Psychol* 105:637–647.
- Chua P, Krams M, Toni I, Passingham R, Dolan R (1999): A functional anatomy of anticipatory anxiety. *Neuroimage* 9:563–571.
- Comeau N, Stewart SH, Loba P (2001): The relations of trait anxiety, anxiety sensitivity, and sensation seeking to adolescents' motivations for alcohol, cigarette, and marijuana use. *Addict Behav* 26:803–825.
- Corr PJ, Pickering AD, Gray JA (1997): Personality, punishment, and procedural learning: A test of J.A. Gray's anxiety theory. *J Pers Soc Psychol* 73:337–344.
- Costa PT, McCrae RR (1992): Normal personality assessment in clinical practice: The NEO Personality Inventory. *Psychol Assess* 4:5–13.
- Costa PT Jr, McCrae RR (1997): Stability and change in personality assessment: The revised NEO Personality Inventory in the year 2000. *J Pers Assess* 68:86–94.
- Cox RW (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29:162–173.
- Craig AD (2002): How do you feel? Interoception: The sense of the physiological condition of the body. *Nat Rev Neurosci* 3:655–666.
- Craig AD (2003): A new view of pain as a homeostatic emotion. *Trends Neurosci* 26:303–307.
- Critchley HD, Mathias CJ, Dolan RJ (2001): Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron* 29:537–545.
- Critchley HD, Mathias CJ, Dolan RJ (2002): Fear conditioning in humans: The influence of awareness and autonomic arousal on functional neuroanatomy. *Neuron* 33:653–663.
- Damasio AR (1996): The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci* 351:1413–1420.
- Egelman DM, Person C, Montague PR (1998): A computational role for dopamine delivery in human decision-making. *J Cogn Neurosci* 10:623–630.
- Elliott R, Dolan RJ, Frith CD (2000a): Dissociable functions in the medial and lateral orbitofrontal cortex: Evidence from human neuroimaging studies. *Cereb Cortex* 10:308–317.
- Elliott R, Friston KJ, Dolan RJ (2000b): Dissociable neural responses in human reward systems. *J Neurosci* 20:6159–6165.
- Elliott R, Rees G, Dolan RJ (1999): Ventromedial prefrontal cortex mediates guessing. *Neuropsychologia* 37:403–411.
- Ernst M, Bolla K, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, et al (2002): Decision-making in a risk-taking task. A PET study. *Neuropsychopharmacology* 26:682–691.
- Fiorillo CD, Tobler PN, Schultz W (2003): Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 299:1898–1902.
- First MB, Spitzer RL, Gibbon M, Williams JB (1995): *Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID-I/P), Version 2.0*. New York: New York State Psychiatric Institute, Biometrics Research Department.
- Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995): Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magn Reson Med* 33:636–647.
- Frith CD, Friston K, Liddle PF, Frackowiak RS (1991): Willed action and the prefrontal cortex in man: A study with PET. *Proc R Soc Lond B Biol Sci* 244:241–246.
- Gehring WJ, Knight RT (2000): Prefrontal-cingulate interactions in action monitoring. *Nat Neurosci* 3:516–520.
- Gehring WJ, Willoughby AR (2002): The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 295:2279–2282.
- Goulet LR, Barclay A (1967): Guessing behavior of normal and retarded children under two random reinforcement conditions. *Child Dev* 38:545–552.
- Grachev ID, Apkarian AV (2000): Anxiety in healthy humans is associated with orbital frontal chemistry. *Mol Psychiatry* 5:482–488.
- Herzel H, Grosse I (1997): Correlations in DNA sequences: The role of protein coding segments. *Phys Rev E* 55:800–810.
- Herzel HP, Grosse I (1995): Measuring correlations in symbol sequences. *Physica A* 216:518–542.
- Jones AD, Cho RY, Nystrom LE, Cohen JD, Braver TS (2002): A computational model of anterior cingulate function in speeded response tasks: Effects

- of frequency, sequence, and conflict. *Cogn Affect Behav Neurosci* 2:300–317.
- Ladouceur R, Gosselin P, Dugas MJ (2000): Experimental manipulation of intolerance of uncertainty: A study of a theoretical model of worry. *Behav Res Ther* 38:933–941.
- Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, et al (2000): Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp* 10:120–131.
- Lang PJ, Cuthbert BN (1984): Affective information processing and the assessment of anxiety. *J Behav Assess* 6:369–395.
- Liotti M, Mayberg HS, Brannan SK, McGinnis S, Jerabek P, Fox PT (2000): Differential limbic–cortical correlates of sadness and anxiety in healthy subjects: Implications for affective disorders. *Biol Psychiatry* 48:30–42.
- Loewenstein GF, Weber EU, Hsee CK, Welch N (2001): Risk as feelings. *Psychol Bull* 127:267–286.
- Luce RD (1959): *Individual Choice Behavior: A Theoretical Analysis*. New York: John Wiley & Sons.
- Ludewig S, Paulus MP, Ludewig K, Vollenweider FX (2003): Decision-making strategies by panic disorder subjects are more sensitive to errors. *J Affect Disord* 76:183–189.
- Ludvigson HW (1966): Response units in the prediction of simple event patterns. *J Exp Psychol* 72:335–360.
- Mathews A, Mogg K, May J, Eysenck M (1989): Implicit and explicit memory bias in anxiety. *J Abnorm Psychol* 98:236–240.
- McNally AM, Palfai TP (2001): Negative emotional expectancies and readiness to change among college student binge drinkers. *Addict Behav* 26:721–734.
- Mellers BA, Schwartz A, Cooke ADJ (1998): Judgment and decision making. *Ann Rev Psychol* 49:447–477.
- Menon V, Adelman NE, White CD, Glover GH, Reiss AL (2001): Error-related brain activation during a Go/NoGo response inhibition task. *Hum Brain Mapp* 12:131–143.
- Mogg K, Bradley BP (1999): Some methodological issues in assessing attentional biases for threatening faces in anxiety: A replication study using a modified version of the probe detection task. *Behav Res Ther* 37:595–604.
- Mogg K, Bradley BP, Williams R (1995): Attentional bias in anxiety and depression: The role of awareness. *Br J Clin Psychol* 34(pt 1):17–36.
- Mogg K, Mathews A, Weinman J (1989): Selective processing of threat cues in anxiety states: A replication. *Behav Res Ther* 27:317–323.
- Morris JS, Friston KJ, Buechel C, Frith CD, Young AW, Calder AJ, Dolan RJ (1998): A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain* 121:47–57.
- Myung IJ, Busemeyer JR (1989): Criterion learning in a deferred decision-making task. *Am J Psychol* 102:1–16.
- Norusis MJ (1990): *SPSS Base System User's Guide*. Chicago IL: SPSS.
- Paulus MP, Geyer MA, Braff DL (1994): The assessment of sequential response organization in schizophrenic and control subjects. *Prog Neuropsychopharmacol Biol Psychiatry* 18:1169–1185.
- Paulus MP, Geyer MA, Braff DL (1996): Use of methods from chaos theory to quantify a fundamental dysfunction in the behavioral organization of schizophrenic patients. *Am J Psychiatry* 153:714–717.
- Paulus MP, Hozack N, Frank L, Brown GG (2002): Error rate and outcome predictability affect neural activation in prefrontal cortex and anterior cingulate during decision-making. *Neuroimage* 15:836–846.
- Paulus MP, Hozack N, Zauscher B, McDowell JE, Frank L, Brown GG, Braff DL (2001): Prefrontal, parietal, and temporal cortex networks underlie decision-making in the presence of uncertainty. *Neuroimage* 13:91–100.
- Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB (2003): Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage* 19:1439–1448.
- Phillips ML, Young AW, Scott SK, Calder AJ, Andrew C, Giampietro V, et al (1998): Neural responses to facial and vocal expressions of fear and disgust. *Proc R Soc Lond B Biol Sci* 265:1809–1817.
- Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, et al (2001): Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci* 21:9896–9903.
- Pury CLS, Mineka S (2001): Differential encoding of affective and nonaffective content information in trait anxiety. *Cognition Emotion* 15:659–693.
- Rauch SL, Savage CR, Alpert NM, Fischman AJ, Jenike MA (1997): The functional neuroanatomy of anxiety: A study of three disorders using positron emission tomography and symptom provocation. *Biol Psychiatry* 42:446–452.
- Reidy J, Richards A (1997): Anxiety and memory: A recall bias for threatening words in high anxiety. *Behav Res Ther* 35:531–542.
- Reiss S, Peterson RA, Gursky DM, McNally RJ (1986): Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behav Res Ther* 24:1–8.
- Richards A, French CC, Calder AJ, Webb B, Fox R, Young AW (2002): Anxiety-related bias in the classification of emotionally ambiguous facial expressions. *Emotion* 2:273–287.
- Rogers RD, Owen AM, Middleton HC, Williams EJ, Pickard JD, Sahakian BJ, Robbins TW (1999): Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *J Neurosci* 19:9029–9038.
- Russo R, Fox E, Bellinger L, Nguyen-Van-Tam DP (2001): Mood-congruent free recall bias in anxiety. *Cognition Emotion* 15:419–433.
- Schmitt WA, Brinkley CA, Newman JP (1999): Testing Damasio's somatic marker hypothesis with psychopathic individuals: Risk takers or risk averse? *J Abnorm Psychol* 108:538–543.
- Schmidt NB, Lerew DR, Jackson RJ (1997): The role of anxiety sensitivity in the pathogenesis of panic: prospective evaluation of spontaneous panic attacks during acute stress. *J Abnorm Psychol* 106:355–364.
- Schmidt NB, Lerew DR, Jackson RJ (1999): Prospective evaluation of anxiety sensitivity in the pathogenesis of panic: replication and extension. *J Abnorm Psychol* 108:532–537.
- Shima K, Tanji J (1998): Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* 282:1335–8.
- Simpson JRJ, Drevets WC, Snyder AZ, Gusnard DA, Raichle ME (2001a): Emotion-induced changes in human medial prefrontal cortex: II. During anticipatory anxiety. *Proc Natl Acad Sci U S A* 98:688–693.
- Simpson JRJ, Snyder AZ, Gusnard DA, Raichle ME (2001b): Emotion-induced changes in human medial prefrontal cortex: I. During cognitive task performance. *Proc Natl Acad Sci U S A* 98:683–687.
- Spielberger CD (1983): *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologists Press.
- Spielberger CD, Smith LH (1966): Anxiety (drive), stress, and serial-position effects in serial-verbal learning. *J Exp Psychol* 72:589–595.
- Spielberger CD (1983): *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologists Press.
- Swenson RG, Edwards W (1971): Response strategies in a two-choice reaction task with a continuous cost for time. *J Exp Psychol* 88:67–81.
- Tzelgov J, Henik A, Berger J (1992): Controlling Stroop effects by manipulating expectations for color words. *Mem Cognit* 20:727–735.
- Verney SP, Brown GG, Frank L, Paulus MP (2003): Error-rate-related caudate and parietal cortex activation during decision making. *Neuroreport* 14:923–928.
- Willinger U, Lenzinger E, Hornik K, Fischer G, Schonbeck G, Aschauer HN, Meszaros K (2002): Anxiety as a predictor of relapse in detoxified alcohol-dependent patients. *Alcohol Alcohol* 37:609–612.
- Zuckerman M (1986): Sensation seeking and the endogenous deficit theory of drug abuse. *NIDA Res Monogr* 74:59–70.