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Personality influences limbic-cortical interactions during sad mood induction

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Abstract

The current study examined limbic-cortical activation under transient emotional stress as a function of personality style. A ventral cingulate (Cg25)-centred limbic-cortical network was identified using positron emission tomography (PET) measures of regional cerebral blood flow (rCBF) during a sad mood challenge that demonstrated differences for individuals selected for specific patterns of Negative and Positive emotional traits, indexed by the NEO Personality Inventory-Revised. Healthy subjects scoring both low on the dispositional Depression facet of Neuroticism (N3) and high on the Positive Emotions facet of Extraversion (E6) were compared to those scoring high on the Depression facet (N3) and low on Positive Emotions (E6), a combination of traits previously linked to normal variations in mood reactivity. Scan analyses were designed to further characterize known variations in Cg25 activity previously reported in studies of negative mood in both healthy subjects and depressed patients. A multivariate technique, partial least squares (PLS) demonstrated a divergent Cg25-mediated network that differentiated temperamentally negative (NAS) from temperamentally positive (PAS) subjects providing a potential neural link between these specific combinations of trait affective styles and vulnerability to depression.
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Neurological bases for individual variability in normal characteristic styles of emotional reactivity (i.e., affective personality traits) are of growing research interest. These personality traits have been characterized in several systematic ways (Cloninger, 1987; Cloninger et al., 1993; Costa and McCrae, 1992). The Five Factor Model of Personality (FFM), used in this study, structures personality in terms of five broad traits: Neuroticism (N), Extraversion (E), Openess (O), Conscientiousness (C), and Agreeableness (A) (Costa and McCrae 1997). The personality traits of Extraversion (E) and Neuroticism (N) are strongly associated with positive and negative emotional experience, respectively (McCrae and Costa, 2003).

Individuals high on the extraversion dimension are often upbeat, optimistic, and enjoy social contact—they report more positive emotions in everyday life than less extraverted individuals (McCrae and Costa, 2003). Individuals who are high on the N dimension worry frequently, often appear to be anxious, and apprehensive—and report more negative emotions in everyday life than those scoring lower on N (McCrae and Costa, 2003). Furthermore, individuals can be characterized by their simultaneous standing or their location on several independent dimensions. Persons can be high or low in their propensity to experience negative affect and at the same time, be high or low in their tendency to experience positive affect. The present study explores the joint influence of both positive and negative emotional personality traits during a sad mood induction paradigm on limbic-cortical networks in healthy subjects.

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Recent studies have examined genetic links to the personality trait Neuroticism (Lesch and Mossner, 1998; Neumeister et al., 2002), and imaging studies have shown correlations between brain activity during selective cognitive tasks and variations in specific personality-trait markers (Canli et al., 2001; Moresco et al., 2002; Zubieta et al., 2003). Of specific interest to this study is the replicated link between high trait levels of Neuroticism and increased vulnerability to psychopathology including such syndromes as major depression, anxiety, and alcoholism. The more specific combination of high negative and low positive traits—typified by high Neuroticism and low Extraversion—appears to distinguish depression from other psychiatric syndromes (Clark and Watson, 1991).

In past functional neuroimaging studies of emotional reactivity, the involvement of subgenual cingulate (Cg25) is prominent (i.e., Liotti et al., 2002; Zald et al., 2002). Mood-challenge positron emission tomography (PET) studies have observed increased Cg25 activity with acute sad mood induction in healthy subjects (Mayberg et al., 1999; George et al. 1995; Damasio et al., 2000). A more complex interaction of Cg25 with frontal cortex has been demonstrated under comparable emotional stress in depressed patients where limbic increases are accompanied by decreased medial frontal activity not seen in healthy controls (Liotti et al., 2002). These converging findings suggest that interactions of Cg25 with medial and lateral prefrontal regions during emotional processing and experience may be sites of vulnerability critical to mood symptom expression in major depression (Mayberg, 2003). The involvement of Cg25 has been of further interest in depression studies since the combination of Cg25 suppression and dorsolateral prefrontal activation is characteristic of successful response to antidepressant medication (Mayberg et al., 2000).

The current study examined the influence of predefined personality traits on patterns of brain activity indexed with PET during acute sad mood induction in healthy volunteers. Two distinct personality groups (were defined based on specific positive and negative personality facets that best represent the personality style seen in major depression. The Negative Affect Style (NAS) group is hypothesized to be most vulnerable to the negative mood induction paradigm and to show activation of neural networks similar to those of remitted depressed patients. The Positive Affect Style (PAS) group is hypothesized to represent a "protective" personality style from major depression, and to be differentially affected by the sad mood induction procedure. Multivariate analyses identified the functional networks associated with task effects and activity in the Cg25 between groups.

Methods

Participants and group selection procedure

Personality traits were identified and quantified using the NEO Personality Inventory-Revised (NEO-PI-R), a vali-

dated tool that operationalizes the Five-Factor Model of Personality (Costa and McCrae, 1997). This inventory provides domain scores that correspond to the five orthogonal factors Neuroticism, Extraversion, Openness-to-Experience, Agreeableness, and Conscientiousness with six more specific or narrow facet scales within each factor (Costa and McCrae, 1997). The NEO-PI-R consists of 240 self-report items answered on a five-point Likert format, with six 8-item facet scales for each of the five domains. The five factors and the 30 facets have been shown to be present in psychiatric as well as normative samples (Bagby et al., 1999) and stability estimates for the domains and facets are substantial in both nonclinical (McCrae and Costa, 1992) and patient cohorts (Santor et al., 1997). In addition, recent evidence from twin studies in Canada and Germany indicate that each of the five broad trait domains and 26 of the 30 lower order facet traits have substantial and unique heritability coefficients (Jang et al., 1998).

The subjects that composed the Negative Affect Style and Positive Affect Style groups were selected using a two-tiered screening procedure. In the first phase, 131 subjects ages 18–50 were recruited at the University of Toronto and completed the NEO-PI-R. Subjects were informed that based on their results, they may qualify for a neuroimaging study examining personality and mood. Six subjects (3 males, 3 females, mean age = 29 years) who demonstrated a T score of 60 or greater (one standard deviation above the average score for the normative group) on the N3-Depression subscale and a T score of 40 or lower (one standard deviation below the average score for the normative group) on the E6-Positive Emotions subscale defined the negative affective style group. This personality pattern is hypothesized to be most vulnerable to the negative mood induction paradigm and to show activation of neural networks similar to those of remitted depressed patients.

Six individuals (6 females, mean age = 23 years) with the opposite pattern—positive affect style—were selected to have a T score less than 40 on N3-Depression and greater than 60 on E6-Positive Emotions and were hypothesized to be differentially affected by the sad mood induction. These 12 subjects (9 women, 3 men) were subsequently screened for current and lifetime episodes of any psychiatric disorder, including depression or mania, with the Structured Interview for DSM-IV Axis I Disorders (SCID). None had identifiable psychopathology by this criteria or a family history of such disorders. All were otherwise healthy and taking no medications. No other behavior measures were used as inclusion or exclusion criteria.

Table 1 displays the means and standard deviations for all five NEO-PI-R personality domain scores and the two facet scores N3 and E6 that make up the NAS and PAS groups. T tests confirmed expected significant differences between the two groups on N3 and E6. There were, however, no significant differences between the two groups for the remaining three personality domain scores.

Table 1
Means, standard deviations, *t* tests comparing the NAS group with the PAS group on the NEO PI-R domains and selected facets

	NAS group		PAS group		*t*
	M	SD	*M*	SD	
Neuroticism	65.44	5.98	43.60	6.22	6.21*
N3: Depression	69.66	6.43	43.33	3.08	9.05*
Extraversion	44.07	11.89	64.78	3.24	−4.12*
E6: Positive Emotions	39.91	5.75	60.81	5.00	−6.72*
Openness	56.10	17.32	71.41	10.83	−1.84
Agreeableness	37.87	12.84	48.38	6.71	−1.78
Conscientiousness	39.00	6.78	49.70	10.80	−2.06

* $P < 0.01$. Score are (standardized) *T* scores with a mean of 50 and a standard deviation of 10.

Imaging protocol

All positron emission tomography scans were acquired on a GEMS-Scanditronix PC 2048b brain PET scanner (15 parallel slices; 10 cm FOV; 6.5-mm center-to-center inter-slice distance) with measured attenuation correction (68Ge/68Ga transmission scans) and reconstructed to a final in-plane resolution of 7.0 mm full width at half-maximum. Regional cerebral blood flow (rCBF) was measured with PET using a $^{15}[0]$-water bolus technique (Fox et al., 1989), during two internally generated mood states—sad and neutral (2 scans each), with the 2 neutral conditions always presented first, in order to avoid any potential carryover effect from the sad to the neutral mood state. Thus, the sequence of conditions was Neutral-Neutral-Sad-Sad for all subjects. Past studies demonstrate no attenuation of signal with repeated scans of like conditions (i.e., Liotti et al., 2000, 2002). Prior to scanning, subjects were asked to provide a written neutral and a sad autobiographical script, which were used to provoke the specific mood state during scanning. The scripts were presented on a PC screen suspended over the PET table. The protocol allowed 8–10 min to achieve the maximum target mood. Past studies have consistently found that both healthy volunteers and depressed patients can achieve the appropriate state within approximately 7 min using this mood induction paradigm (Mayberg et al., 1999; Liotti et al., 2000, 2002). Once achieved, subjects were instructed to maintain the emotion without continued rumination on the content, for approximately 2 min before tracer injection. While monitoring of one's internal mood state (whether sad or neutral) was required for all conditions, the intent of the protocol was to minimize participation of brain regions mediating working memory. Scans were acquired during this peak sad state with the subjects' eyes closed. Subjects were debriefed and their mood was rated after completion of each 60-s scan. Mood-state was also rated every 2 min throughout the session with a visual analog scale and subjects' self-report (for more details about the sadness induction procedure, please see Liotti et al., 2000, 2002). Rest or neutral mood conditions required a 6 or 7 out of 7 on the calmness scale,

and a mandatory 0 out of 7 on the sadness scale to initiate scan acquisition; sad mood conditions required a minimum score of 6 or 7 on the sadness scale and most described near-tearfulness (i.e., a "lump in the throat sensation") or were actually tearful. Mood generally returned to a baseline euthymic state within 2–3 min after scan completion, well before initiation of the next condition. Scans were acquired approximately every 11–12 min to additionally allow for isotope decay from the previous injection. While subjects were told they could take as much time as needed to achieve a peak sad response (i.e., 6 or 7 on the sadness scale) before the radiotracer injection, all subjects achieved this peak sad state within approximately 7–8 min and as such, scanning was carried out at these fixed times.

Statistical analyses

Images were preprocessed in SPM99 (Friston et al., 1995), by first aligning all the images for a single subject to one another, and then normalizing the data using the SPM95 template, which transforms raw images into Talairach space (Talairach and Tournoux, 1988), and finally smoothing with a Gaussian kernel of 12 mm.

There were two steps in the image analysis. The first was to test for modulations of brain activity attributable to the task conditions and identify a ventral anterior cingulate voxel that could serve as a reference region for further functional connectivity analyses. The second step was to identify the more specific networks active during neutral and sad mood by determining the areas of the brain in which activity was correlated with that of the reference region, i.e., its functional connectivity (Friston et al., 1993; Horwitz, 1994; McIntosh, 1999; Grady et al., 2003).

Because all of these analytical steps are based on the assumption that behavior and cognition are the result of the integrated activity of dynamic brain networks rather than the action of any single region acting independently, the approach to the image data analysis was designed to reveal these networks through multivariate techniques. To this end, all analyses were performed using partial least squares (PLS) (Mcintosh et al., 1996) which is a multivariate analysis that identifies groups of brain regions distributed over the entire brain that together covary with some aspect of the experimental design. This is in contrast to the more typically used univariate analysis that assesses the significance of each region separately. PLS operates on the covariance between brain voxels and the experimental design, or a set of external measures, to identify a new set of variables [so-called latent variables (LVs)]. In this experiment a single task PLS analysis assessed differences across sad and neutral mood states in both groups simultaneously. The results of the PLS analysis are expressed in terms of LVs, each of which identifies a pattern of differences in brain activity across the tasks and the brain voxels showing this effect. Each brain voxel has a weight on each LV, known as a salience that indicates how that voxel is related to the LV.

Table 2
Talairach coordinates and bootstrap ratios for regions identified in Task and Seed Cg25 PLS

Region name (Brodmann area)	Task PLS, LV1[a]				Seed PLS, LV1[b]				Correlation with seed voxel			
	X	Y	Z	Bootstrap ratio[c]	X	Y	Z	Bootstrap ratio[c]	PAS Neu	PAS Sad	NAS Neu	NAS Sad
Subgenual cingulate (25)	2	26	−4	2.57	8	22	−4	+8	1.000	1.000	1.000	1.000
Parahippocampus (36)	−28	−36	−24	10.83								
Posterior cingulate (31)	14	−42	28	4.32	4	−22	32	3.26	0.906	0.894	−0.067	−0.055
	−18	−40	32	2.68								
Dorsolateral prefrontal (9)	38	20	36	−5.48	50	10	40	−6.27	−0.742	−0.760	0.788	−0.093
Dorsomedial prefrontal (9)	14	50	24	−3.23	−12	46	32	−8.53	−0.931	−0.937	0.298	0.367
Ventrolateral prefrontal (10)	30	50	12	−4.81	36	54	0	−2.98	−0.675	−0.563	0.804	0.581
	−24	50	12	−5.20	−28	48	−4	−2.59	−0.598	−0.853	−0.091	0.183
Premotor (6)	−28	−2	40	−2.83	32	4	40	−5.01	−0.554	−0.821	0.544	0.189
Ventral frontal (47/Insula)	40	28	−8	−5.72	40	22	−8	−8.65	−0.758	−0.952	0.479	0.335
					−42	18	4	−4.45	−0.774	−0.560	0.460	0.861
Anterior cingulate (24/32)	−12	30	16	−5.63	−16	16	24	2.75	0.630	0.685	0.005	−0.447
Ventromedial frontal (10)					20	66	12	3.58	0.900	0.822	0.468	−0.764
					16	66	12	3.32	0.836	0.923	0.581	−0.734
Orbital frontal (11)[d]					6	44	−12	4.91	0.928	0.848	−0.310	0.195
Brainstem					12	−22	−12	4.12	0.290	0.916	0.400	−0.356

Note. neu, neutral condition; sad, sad condition; PAS, low neuroticism, high extraversion; NAS, high neuroticism, low extraversion.

[a] Permutation test $P < 0.001$.

[b] Permutation test $P = 0.008$.

[c] Salience of each voxel/standard error; bootstrap ratio > 1.96, $P = 0.05$; > 2.58, $P = 0.01$; > 3.29, $P = 0.001$.

[d] Regions are contiguous with seed voxel at the threshold shown in Fig. 1 and reported in text.

A salience can be positive or negative, depending on whether the voxel shows a positive or negative relation with the overall pattern identified by the LV. Multiplying the rCBF value in each brain voxel for each subject by the salience for that voxel, and summing across all voxels, gives a latent variable score (called a "brain" score here) for each subject for each task condition on a given LV. The brain scores can be used to examine differences in brain activity across conditions, because greater activity in brain areas with positive (or negative) weights on a latent variable will yield positive (or negative) mean scores for a given condition. In addition, these scores can be correlated with external variables (see below).

The significance of each LV is assessed using a permutation test (Edgington, 1980; Mcintosh et al., 1996), using $P < 0.01$ as the statistical threshold. In addition to the permutation test, the reliability of the saliences for the brain voxels characterizing each LV is determined. To do this, all saliences in each analysis are submitted to a bootstrap estimation of the standard errors (SEs; Efron and Tibshirani, 1986; Sampson et al., 1989). A reliable contribution for a given voxel is further defined by a ratio of salience to SE ≥ 2.58, which corresponds to the 99% confidence interval ($P < 0.01$; Sampson et al., 1989). Because all saliences are calculated in a single analytical step, there is no need to correct for multiple comparisons, as is often done in univariate analyses (McIntosh et al., 1996). Local maxima for the reliable brain areas on each LV are then defined as the voxel with a bootstrap ratio higher than any other voxel in a 2-cm^3 volume centered on that voxel. Locations of these maxima are reported in terms of brain region, or gyrus, and estimated Brodmann area (BA) as defined in the Talairach and Tournoux atlas (1988).

Connectivity is then determined by means of a "seed voxel" analysis (Schreurs et al., 1997; McIntosh, 1999; Grady et al., 2003) in which the rCBF values from the seed are extracted, and the correlations between seed activity and activity in all brain voxels within each condition are calculated. For the functional connectivity or seed analysis, data from the neutral and sad mood states in both groups were used. In the seed PLS, the reference region, or "seed" was chosen directly from the results of the task PLS analysis where it was hypothesized that activity in the subgenual cingulate would be critical to task performance across groups. Therefore a region of subgenual cingulate that showed highly reliable task-related changes in both positive and negative affect style groups was sought. PLS is then used to contrast these correlations across conditions, in this case between the positive and negative affect style groups. Thus, with this analysis it can be seen whether the brain regions whose activity is correlated with activity in the seed are the same or different between groups and across task conditions. Permutation (significance) and bootstrap analyses (reliability) are similarly performed on the resulting LVs as described above.

Results

Both the NAS and PAS groups achieved the targeted maximum sad mood state (minimum 6 out of 7) for each of the sad scans.
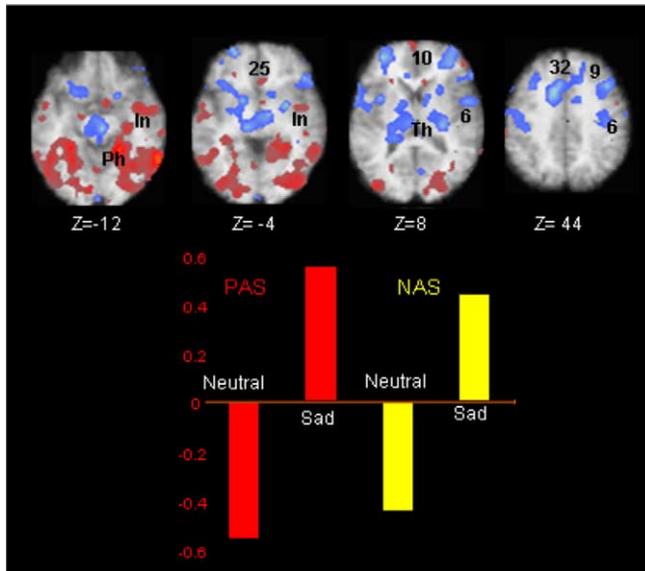
Fig. 1. Task PLS analysis. Brain areas with differential activity in the sad versus neutral mood conditions (areas with bootstrap ratios >2.0). Regions in red were more active during sad than in neutral; regions in blue were less active in sad. The graph show the mean brain scores of thte LVs. Positive mean brain scores were found in the sad condition for both groups. MRI brain slices for the images are in standard atlas space (Talairach and Tournoux, 1988). 6, Brodmann's area (BA6); 9, BA9; 10, BA10; 25, BA25; 32, BA32; In, insula; Ph, parahippocampus; Th, thalamus.

Level 1 analysis: Task PLS

The task PLS comparing the sad vs neutral mood induction for NAS vs PAS subjects isolated mood-specific changes common to the two groups (see Table 2, left). Common to both groups was a functional pattern (Fig. 1) accounting for 60.2% of the variance ($P < 0.0001$) that involved increases in subgenual cingulate (Cg25), parahippocampus, and posterior cingulate (BA31) and concurrent decreases in lateral prefrontal (BA10/BA9) and dorsal anterior cingulate (BA24b) (Table 2). This pattern is similar to that previously identified using univariate analyses in unselected normal volunteers (Mayberg, 1999; Liotti et al., 2000). No LV differentiated the NAS from PAS groups in either the emotionally passive (neutral) or emotionally provoked (sad) state and no independent patterns of covariance were identified for either group when the analyses were run separately.

Level 2 analysis: Seed PLS

The Cg25 seed PLS (performed to identify differences in Cg25-specific functional networks associated with both mood and personality) revealed one significant LV (Fig. 2) that accounted for 43% of the total variance ($P = 0.008$) and that distinguished PAS from NAS. In the PAS group, this covariance pattern was positively correlated with the seed and was similar for both the neutral and the sad conditions. In contrast, this pattern was generally reversed for the NAS

group particularly for the sad mood challenge condition. Regions (Table 2, right) more positively correlated with the Cg25 in NAS subjects included the dorsolateral and dorsomedial prefrontal (BA9 and BA 10), ventrolateral frontal (BA10/47/11), premotor (BA6) cortex, and insula with concurrent decreases in ventromedial (BA10) and orbital frontal (BA11), anterior cingulate (BA24), and posterior cingulate (BA31). Regions more negatively correlated with the right Cg25 in the PAS subjects during both sad and neutral mood states included the dorsolateral and dorsomedial prefrontal (BA9), ventromedial (BA10), and orbital frontal (BA11) cortices. In other words, sad stress unmasked a NAS-specific pattern involving increased activity in Cg25, linked to dorsal frontal increases (BA9, BA10, BA6) and limbic-paralimbic decreases (BA24, BA31, BA11). PAS subjects on the other hand maintain the same relationship among these regions with or without the stressor.

Discussion

The current study examined brain networks linking the subgenual cingulate (Cg25) to sad mood as a specific combination of personality traits. Subjects were divided into a negative affective style group (NAS; high Depression, N3, facet of Neuroticism and low Positive Emotion, E6, facet of Extraversion) versus a positive affective style group (PAS; low N3, high E6), according to their scores on the Revised NEO Personality Inventory. Participants were scanned using positron emission tomography to measure regional cerebral blood flow while performing sad and neutral mood induction tasks.

In both groups there was a common pattern of increased activity in subgenual cingulate (Cg25) and parahippocampus (BA36), and decreased activity in dorsolateral prefrontal cortex (BA9) associated with acute sadness (Table 2, left panel). This pattern is consistent with findings in healthy controls (George et al., 1995; Mayberg et al., 1999; Damasio et al., 2000; Liotti et al., 2000, 2002), suggesting that these common changes are critical to the effective regulation of acute changes in mood state. A second, group-specific pattern was seen only in the NAS group with sad mood, and involved increased activity in Cg25 but in association with decreased medial frontal activity, a pattern not seen in the PAS group.

The association of ventromedial frontal decreases seen uniquely in the NAS group (Table 2, right panel) and only during a provoked state is consistent with the pattern of change previously seen in both remitted and actively depressed patients (Liotti et al., 2002) and suggests a potential site of vulnerability linking a sad affective personality style to major depression. No rest-state (neutral condition) marker for the NAS group was identified; differences between the groups (NAS vs PAS) required the mood-induction probe. This further suggests that the behavior effects of variations in personality style in normal subjects are subtle,
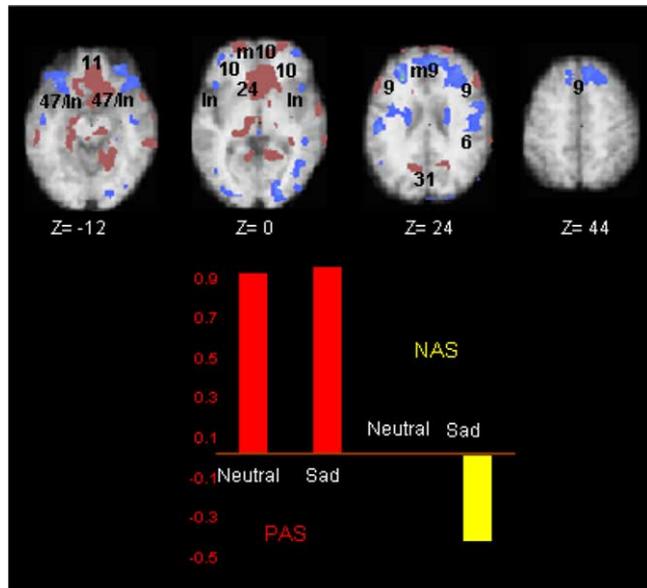
Fig. 2. Seed PLS analysis. Brain regions where activity during mood induction was correlated with activity in the subgenual cingulate (Cg25) are shown (areas with bootstrap ratios >2.0). The graph shows the correlations between brain scores and rCBF in the Cg25 seed in each condition for each group. Regions shown in red had the pattern of correlations shown in the graph. Red, positive correlation with Cg25 for PAS in both conditions but negative correlations for NAS (sad condition only); blue, positive correlations with Cg25 for NAS (sad condition only) and positive correlations for PAS (sad and neutral). MRI brain slices for the images are in standard atlas space (Talairach and Tournoux, 1988). 6, Brodmann's area (BA6); 9, BA9; m9, medial BA9; 10, BA10; m10, medial BA10; 11, BA11; 24, BA24; 47/In, BA47/Insula; 31, BA31.

and may require targeted provocations (such as mood induction) to reveal the potential contribution of personality style to the development of psychopathology.

The finding that the Cg25 seed PLS revealed the divergence in medial and lateral prefrontal engagement in response to sad mood for NAS and PAS, respectively, builds on past observations of changes with respect to emotional behavior in this region. Stimulation of Cg25 in monkeys, rats, and shrews is associated with reproducible maternal cry (MacLean, 1993) comparable to that seen with separation and loss in humans (Lorberbaum et al., 2002), and consistent with the level of emotion expression seen in this study. Cg25 connections to the brainstem, hypothalamus, spinal cord, and insula likely mediate these emotional vocalizations (MacLean, 1993). An integrative role for Cg25 in emotional regulation is further suggested by its nonlimbic afferent and efferent connections (Haber et al., 1995; Freedman et al., 2000). Reciprocal pathways linking Cg25 to orbitofrontal, medial, and dorsal prefrontal cortex, as well as various components of anterior and posterior cingulate cortex, identify plausible pathways by which primary autonomic and homeostatic processes influence various aspects of learning, memory, reward, and reinforcement (Haber et al., 1995; Vogt et al., 1995; Schultz, 2001; Bechara et al., 2000; Rolls, 2000).

The critical deactivations in medial frontal cortex in the NAS group are not only consistent with findings in depressed patients, but also patterns of behavior observed in patients with structural lesions in these regions (Grafman et al., 1986; Angrilli et al., 1999; Joseph, 1999). Damage specific to the medial orbital cortex (BA 10,11) can cause a disruption of social behavior including impulsivity and mood lability with sudden changes between euphoric and dysphoric mood states (Liotti et al., 2002; Starkstein et al., 1990). The maintenance of increased activity in medial frontal regions associated with emotion-cognition integration may further indicate pathways necessary to maintain emotional control, which, as seen in the PAS group, may reflect an adaptive and protective capacity in times of increased exogenous stress. While these divergent brain responses would appear to identify the differential influence of these affective traits in circumstances of extreme shifts in emotional state (as revealed by this specific mood provocation paradigm), these same traits may differentially influence alternative pathways in other cognitive or behavioral situations.

To anticipate future studies of depression vulnerability in at risk populations, this study focused on a specific combination of affective personality traits and used a challenge previously demonstrating depression-specific abnormal changes (Liotti et al., 2002). Previous studies investigating personality and brain functioning have used alternative strategies (i.e., Canli et al., 2001, 2002; Neumeister et al., 2002). Neuroticism has been associated with the presence of a functional polymorphism (s/s allele) in the promoter region of the sertotonin transporter gene (5HTTPR) (Lesch and Mossner, 1998; Tauscher et al., 2001; Neumeister et al., 2002). Direct links among gene, trait, specific behaviors and the brain are not yet confirmed (Mann et al., 2000). Comparisons of two common alleles of this functional polymorphism, using functional neuroimaging, have identified exaggerated amygdala responses to emotional stimuli in the s/s relative to the l/l genotype (Hariri et al., 2002). This study, however, did not address personality traits per se and findings emphasized magnitude differences in comparable regions rather than divergent network patterns, as demonstrated here.

Most directly relevant to this study, Neumeister et al. (2002) identified a significant influence of this same 5HTTPR polymorphism on mood reactivity using an acute dietary tryptophan depletion challenge. While no neuroimaging correlates were performed, one or two copies of the s allele were again associated with exaggerated behavioral responses to this second challenge. While speculative, potential differential neural correlates might be anticipated, similar to those seen in the NAS subjects here, particularly given the similarities of NAS changes to those seen with both tryptophan depletion and mood induction in recovered depressed patients (Bremner et al., 1997; Liotti et al., 2002). Furthermore, a recent PET study found a significant positive relationship between Cloninger's (1987) "harm avoidance"

dimension on the Tridimensional Personality Questionnaire and high values of 5HT(2) and D(2) receptor in vivo binding of 3-(2′-[^{18}F]fluoroethyl)spiperone (Moresco et al., 2002), indicating involvement of the serotoninergic system in this personality trait. While speculative, this recent PET finding further illustrates the differences in possible mechanisms of neurotransmission that could be related to the involvement of different cortical areas related to divergent personality types.

Neuroimaging studies more specifically focused on neuroticism (without considering genetic polymorphisms) have correlated scores on this single trait examining brain activity at rest without a specific behavior challenge (i.e., Johnson et al., 1999). None of these studies, however, considered specific combinations of personality traits, or even preselected subjects who score above the norm on a particular trait of interest (i.e., neuroticism and extraversion). The fact that neuroticism has been associated with specific genetic markers and a variety of psychopathologies with variable consistency suggests that a more complex analysis is required. Specifically, that consideration of the task and complexity of personality are needed to target disease vulnerability markers (Fanous et al., 2002; Kendler et al., 2002) a tactic consistent with the growing psychiatric and genetic literature suggesting that a single primary trait or genetic marker cannot clearly predict vulnerability to depression.

It is not yet clear if Neuroticism is an independent risk factor for depression. Neuroticism has nonetheless been repeatedly identified as a vulnerability factor (Ormel et al. 2001; Fanous et al., 2002) and as a predictor of relapse risk (O'Leary and Costello, 2001) and perhaps even an illness onset marker in as yet unaffected family members (Fanous et al., 2002). The considerable overlap of patterns of neural activation in the NAS group during sad mood and depressed patients under comparable stress would appear to suggest that this is an important focus for further research. Furthermore, it is these same divergent regions seen in the NAS group unmasked by emotional stress that are targeted by cognitive behavioral therapy (CBT) for major depression where patients are taught to reduce automatic emotional reactions to negative thoughts/attitudes (Goldapple et al., 2003).

Future investigations with larger numbers of subjects reflecting each personality style are needed, as the present study had a small sample size for each group ($n = 6$). A further limitation of the study is that a simple state measure of depression was not administered during screening. Our focus was on ensuring the absence of clinical symptoms indicative of an undiagnosed depressive disorder which might confound our results. It is a valid point that minor depressive symptoms may have been differentially present in the NAS group. It is noted, however, that all subjects endorsed a complete absence of sad mood (i.e., 0 out of 7) during screening and baseline (neutral mood) scanning blocks. In addition, the present study is gender biased, as only 3 of the 12 subjects were male. Thus, it is yet unclear

whether this apparent "vulnerability marker" is gender specific, given the higher incidence of depression in women (2:1). The current study precludes definitive conclusions regarding gender differences and neural networks characterizing personality traits in response to sad mood. While women generally report themselves to be higher in neuroticism than men (Costa et al., 2001), there is little evidence of a significant sex difference in the genetic correlation between neuroticism and major depression (Fanous et al., 2002). Furthermore, given the intriguing observation using the tryptophan depletion paradigm, that 5HTTPR polymorphism status may have a greater influence on mood reactivity in women than a family history of depression, additional studies of both men and women, known polymorphisms, specific personality traits, and various emotional challenges in family members at risk for depression are needed to dissect the relative contribution and interactions of these variables at the neural systems level.

In conclusion, the presence of a divergent medial/lateral prefrontal pattern in the NAS group with acute mood challenge provides new support for the hypothesis that high trait levels of negative affect along with the absence of positive emotion may be a risk factor for psychopathology, including depression, with mood provocation providing a controlled "environmental stressor" of a type often associated with illness onset or relapse in depressed patients. It also suggests that a potential moderating variable between negative affect and disease vulnerability may be an individual's level of positive emotionality. Direct comparisons of NAS persons and remitted depressed patients are needed to further test the hypothesis that mood provocation PET studies can serve as a preclinical depression "stress test" revealing fundamental disease-specific dysfunctional mood circuits.

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