Functional Brain Mapping of Extraversion and Neuroticism: Learning From Individual Differences in Emotion Processing

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ABSTRACT This review outlines how functional brain imaging, using an individual-differences approach in the processing of emotional stimuli, has begun to reveal the neural basis of extraversion (E) and neuroticism (N), two traits that are linked to both emotion and health. Studies using functional magnetic resonance imaging have shown that individual differences in participants' E and N scores are correlated with individual differences in brain activation in specific brain regions that are engaged during cognitive-affective tasks. Imaging studies using genotyped participants have begun to address the molecular mechanisms that may underlie these individual differences. The multidisciplinary integration of brain imaging and molecular genetic methods offers an exciting and novel approach for investigators who seek to uncover the biological mechanisms by which personality and health are interrelated.

Investigations of the biological basis of personality have led to the development of several influential models of personality, such as those by Eysenck (Eysenck, 1967, 1990), Gray (Gray, 1982; Pickering & Gray, 1999), Cloninger (Cloninger, Svrakic, & Przybeck, 1993), and Zuckerman (Zuckerman, 1991). Studies have been conducted with respect to the heritability of traits, the role of neurotransmitters, and the identification of neural structures that mediate trait-typical behaviors and have been reviewed elsewhere (Cloninger, 1986; Cloninger et al., 1993; Davidson, 2001; Depue & Collins, 1999; Eysenck, 1967, 1990; Gray, 1970, 1987; Panksepp, 1982, 1998; Pickering & Gray, 1999; Plomin, Owen, & McGuffin, 1994; Zuckerman, 1991). Recent advances in noninvasive brain imaging and molecular

Journal of Personality 72:6, December 2004.
Blackwell Publishing 2004

genetics have now opened the gates for novel and interdisciplinary approaches to the neuroscience of personality, which will be reviewed here.

Specifically, I will focus on imaging studies of extraversion (E) and neuroticism (N). The association between these traits, emotion, and health is intriguing, but the biological mechanisms underlying these associations are still poorly understood. One approach is to identify brain systems that are associated with E, N, and the processing of emotional stimuli. I will discuss recent work that has used functional magnetic resonance imaging (fMRI) to correlate individual differences in participants' E and N scores with brain activation differences during the processing of emotional stimuli. This will lead to the question by what mechanism individual differences in participants' E and N scores affect brain activation levels. I will discuss one exciting new line of research that combines functional neuroimaging with molecular genetics in human participants in order to develop molecular models of individual brain activation differences. The insights that can be gained from such multidisciplinary approaches to personality may also extend into the clinical realm. I will therefore conclude with a speculative outlook on clinical applications that may eventually reveal the biological mechanisms by which E and N affect health.

Extraversion, Neuroticism, and Emotion

Extraverted and neurotic individuals are characterized by positive and negative affect, respectively. In an analysis of multiple samples (the total sample size was 4457), Watson and colleagues (Watson, Wiese, Vaidya, & Tellegen, 1999) reported a correlation of 0.58 between N and the Negative Affect scale of the PANAS (Watson, Clark, & Tellegen, 1988) and a correlation of 0.51 between E and the Positive Affect scale. Costa and McCrae (1980) reported that participants who scored high in E reported more positive affect in their daily life than more introverted individuals and that participants who scored high in N reported more negative daily affect than those who score low. Indeed, measures of E and N predicted positive and negative affect in everyday life for periods of up to 10 years. Larsen and Ketelaar (1991) found that E and N were associated with greater responsiveness to the effects of positive and negative mood induction procedures, respectively.

Could the association between these two dimensions of personality and two dimensions of affect simply reflect a tautology, perhaps due to the use of similar terms in measurement instruments? Gross, Sutton, and Ketalaar (1998) caution of this possibility but also provide data that suggest some independence of the two constructs. They measured self-reported positive and negative affect prior to, during, and after a set of mood-induction film clips were shown and correlated these state levels of affect with E and N, as well as dispositional Positive and Negative Affect. They found that acute affective state, especially in response to the film clips, was more strongly associated with E and N than with dispositional affect.

Another line of research has shown differences between E, N, and positive and negative affectivity using a longitudinal design. Vaidya and colleagues in Watson's laboratory (Vaidya, Gray, Haig, & Watson, 2002) studied the temporal stability of the Big Five personality traits and positive and negative trait affect. They reported that affective traits were less stable than personality traits: over a 2.5-year period, the median stability coefficient for affective trait scales was 0.49, whereas the stability coefficients for E and N were 0.72 and 0.61, respectively. Life experiences played a moderating effect but were stronger for affective traits than for E and N (with betas approximately twice as large for general positive and negative affect as for E and N). This finding, along with the study by Gross, Sutton, and Ketelaar (1998), suggests that personality and affect are dissociable constructs.

The association between E and N (and related constructs) and emotion may be mediated, in part, by cognitive biases in the processing of emotional stimuli (Matthews & Deary, 1998). Such biases can be captured with cognitive tasks designed to measure attention to, or memory for, emotionally salient stimuli (Gotlib, Gilboa, & Kaplan-Sommerfeld, 2000). For example, attention can be assessed in a variant of the classic Stroop color-naming task (Stroop, 1935), the emotional Stroop. In this task, participants view emotional or neutral words that are printed in colored fonts and are asked to name the color of the word. Reaction times are slower in neurotic, trait-anxious, or depressed subjects when word stimuli are negative, compared to when they are neutral (Derryberry & Reed, 1998; Gotlib, McLachlan, & Katz, 1988; Richards, French, Johnson, Naparstek, & Williams, 1992; Wells & Matthews, 1994), presumably due to interference by automatic semantic processing systems that usurp attentional

resources. Attentional bias as a function of E has received far less attention, but Derryberry and Reed (1994) reported that extraverted subjects who participated in a target-detection task were slow to shift attention away from cue locations associated with positive reward.

Tasks such as the emotional Stroop have been used by cognitive neuroscientists in brain-imaging studies of healthy and patient populations (George et al., 1997; Isenberg et al., 1999; Shin et al., 2001; Whalen, Bush et al., 1998). We (Amin, Constable, & Canli, in press; Canli, Haas, Amin, & Constable, 2003) have begun to use these types of tasks to identify brain regions where individual differences in brain activation in response to emotional stimuli are correlated with participants' E and N scores. The utility of this individual differences approach in cognitive neuroscience will be discussed in the next section.

Using an Individual Differences Approach in Cognitive Neuroscience to Reveal Underlying Mechanisms

As Plomin and Kosslyn (2001) noted, biological studies of cognition have traditionally treated individual differences as unwanted statistical noise. Yet these individual differences can sometimes exhibit a remarkable stability within subjects, suggesting that they are not just random fluctuations. For example, participants who were scanned during a memory-retrieval task differed considerably from one another in their brain activation patterns, but were stable within individuals over time (Miller et al., 2002). The authors proposed that, rather than reflecting random noise, these individual differences may instead reflect the use of cognitive strategies that are different between, but consistent within, individuals.

The view that individual differences can reveal the underlying structure of psychological processes was endorsed in an article by Underwood almost 30 years ago (Underwood, 1975), but only in recent years has there been an interest in applying this approach to cognitive neuroscience. Some of these efforts have been summarized in an article (Kosslyn et al., 2002) that illustrated the utility of this approach in identifying underlying mechanisms of cognitive function, mediating factors in intersubject variability to emotional stimuli, and nonadditive effects in the interaction between two processes.

One application of this approach has been to relate individual differences in brain activation to individual differences in behavior

or task performance so that behavior can be predicted on the basis of brain activation. In the domain of emotion, for example, Davidson and colleagues have shown that individual differences in the laterality pattern of baseline prefrontal EEG activation predict dispositional affect and reactivity to emotional stimuli (Sutton & Davidson, 1997; Tomarken, Davidson, & Henriques, 1990; Tomarken, Davidson, Wheeler, & Doss, 1992). In studies of the biological basis of emotional memory, individual differences in amygdala activation during encoding predicted participants' ability to remember emotionally salient, but not neutral, stimuli weeks and even months later (Cahill et al., 1996; Cahill et al., 2001; Canli, Desmond, Zhao, & Gabrieli, 2002; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Hamann, Ely, Grafton, & Kilts, 1999). Perhaps the most dramatic application has been in patient populations, where individual differences in brain activation have been used to predict response to treatment (Buchsbaum et al., 1997; Little et al., 1996; Mayberg et al., 1997; Pizzagalli et al., 2001; Wu et al., 1999).

Brain activation differences across subjects can be associated with personality traits. Fischer and colleagues (Fischer, Tillfors, Furmark, & Fredrikson, 2001) showed film clips of snakes to (non-snake-phobic) individuals and reported that amygdala activation across subjects was correlated with dispositional pessimism. Other imaging studies have correlated personality measures with brain activation at rest or during cognitive tasks (Ebmeier et al., 1994; Haier, Sokolski, Katz, & Buchsbaum, 1987; Johnson et al., 1999; Stenberg, Risberg, Warkentin, & Rosen, 1990; Sugiura et al., 2000). We have begun a research program that focused specifically on the personality traits of E and N in the context of emotional processing, which will be discussed in the next section.

A Brain Imaging Approach to Individual Differences in Emotion Processing

Brain Imaging of E and N

Passive viewing of emotional scenes

Given that E is associated with reactivity to positive emotional stimuli and N with reactivity to negative emotional stimuli, we (Canli et al., 2001) hypothesized that a similar relationship should exist at

the brain systems level of analysis. Using fMRI, we predicted that greater E scores across participants should correlate with greater brain activation to positive images in regions known to play a role in affective processing. We made a similar prediction for participants with higher N scores and brain activation to negative stimuli.

Fourteen women completed a self-report measure of the Big Five personality traits (Costa & McCrae, 1992) and participated in an fMRI study in which blocked presentations of emotionally negative and positive images were presented in the scanner. These images were taken from a library of normed affective stimuli, the International Affective Picture Series (IAPS) (Lang & Greenwald, 1993). Participants were scanned as they passively viewed images that were presented for 6 seconds each. After the scan, a manipulation check was conducted to verify that the stimuli produced the intended emotional response in each subject.

Brain activation to positive and negative images across participants was correlated with their respective E and N scores. The resultant correlation map revealed regions where greater activation to emotional images was significantly correlated with higher scores in either E or N. Figure 1 shows a scatter plot from one region, the right amygdala. It illustrates that greater activation to positive, relative to negative, pictures was associated with higher scores in E across subjects. Similar correlations were seen in other subcortical and cortical regions, but the example of the amygdala is of particular interest because this structure is primarily associated with the processing of negative affect. This was the first demonstration that individual differences in amygdala activation to positive stimuli vary as a function of E.

Several features of this correlation map were noteworthy. First, the correlations were very robust, especially given the relatively small sample size, compared to behavioral studies. Second, the correlations were in the expected direction, such that greater activation to positive stimuli was associated with E (but not N) and greater activation to negative stimuli was associated with N (but not E). Third, both cortical and subcortical regions exhibited these correlations, suggesting that neural systems associated with personality are not confined to higher-level executive brain regions, but rather represented at all levels of neural processing.

The interpretation of these findings is constrained by several limitations, some of which are inherent to fMRI in general. First, the

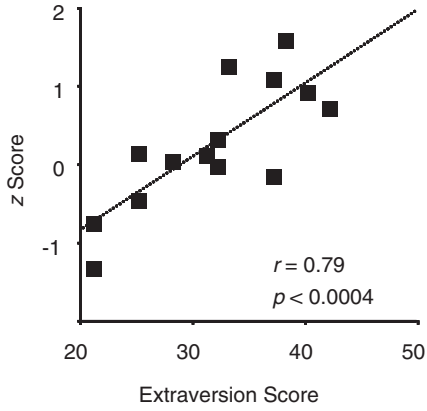

Figure 1
Brain response to positive stimuli correlates with participants' E scores. Scatter plot from the left amygdala, showing correlation between E and brain activation to valenced stimuli. Positive *z* scores denote significance level of grater activation to positive, relative to negative, pictures. Negative *z* scores denote significance level of grater activation to negative, relative to positive, pictures.

relation between the recorded signal (blood oxygenation) and underlying neural activity remains a matter of debate: although it is commonly assumed that it represents excitatory neural activity, there is disagreement about whether it cannot also represent inhibitory neural activity (Heeger, Boynton, Demb, Seidemann, & Newsome, 1999; Waldvogel et al., 2000). Second, the determination of significant signal change is based on the relative comparison between two conditions, rather than some absolute measure. Therefore, an increase in activation during one condition is equivalent to a decrease during the other condition. In our study, what was interpreted as an increase in activation to positive pictures could instead have represented a decrease in activation to negative pictures.

Another concern was whether the correlation clusters we observed could have emerged by chance. Significant loci might represent type-I errors because the data set contained a large number of voxels (three-dimensional pixels that comprise the brain space to be analyzed). We addressed this concern by way of a cluster analysis technique (Xiong, Gao, Lancaster, & Fox, 1995) that limited the chance of type-I errors. In addition, we conducted a correlation analysis using randomly generated dummy variables that failed to produce any significant clusters.

Other limitations and concerns are inherent to the study. One was that there was no neutral control condition. This was a deliberate choice in the design of the study because affect generated during the negative or positive blocks might not dissipate fast enough and could therefore contaminate the presumed control condition. The drawback is that it is not possible to establish whether a change in activation to positive or negative pictures represents an increase or decrease relative to a neutral condition. However, the inclusion of a neutral condition does not remove the ambiguity that is inherent in fMRI analyses based on the relative contrast between two conditions: for example, an increase in activation to the positive stimuli could instead represent a decrease in activation to neutral stimuli.

Another limitation was that scores were collected for the broad dimensions of E and N, but not for specific facets. It is therefore possible that some regions that were associated with E reflect different facets of this personality trait. Indeed, one could speculate that brain regions associated with aggression may relate to the facet of "assertiveness," but brain regions associated with attachment would be related to the facet of "warmth." Future studies should, therefore, measure facets of E and N and include different conditions designed to capture distinguishing features of these facets.

A final concern was the nature of the task and its relation to the observed brain regions. Because the task was unconstrained, any number of mental processes may have been engaged. Although it is likely that the observed brain activations represent emotional experience (since subjects reported emotional responses to the images), it is unclear how this experience was generated, whether participants attempted to regulate it, and whether additional processes, such as retrieval of autobiographical memories, were activated during the viewing.

Perception of emotional faces

Our second study focused on emotion perception, rather then emotional experience, and used a highly constrained task design that targeted one a priori region of interest. The study focused on the processing of emotional faces and activation in the amygdala. Studies of brain-damaged patients and functional neuroimaging studies of healthy participants have consistently reported amygdala involvement in the processing of facial expressions of fear (Adolphs, Tranel,

Damasio, & Damasio, 1994; Adolphs, Tranel, Damasio, & Damasio, 1995; Broks et al., 1998; Calder et al., 1996; Dolan, Morris, & de Gelder, 2001; Killgore & Yurgelun-Todd, 2001; Morris, deBonis, & Dolan, 2002; Morris et al., 1996; Whalen, Rauch et al., 1998). The response of the amygdala to facial expressions of other emotions, however, was found to be less consistent. For instance, Breiter and colleagues (1996) reported increases in amygdala activation to happy versus neutral faces, whereas Morris et al. (1996) and Whalen and colleagues (Whalen, Rauch et al., 1998) found decreases in amygdala activation when comparing happy versus fearful faces. Did this inconsistency reflect random variation or the presence of a previously uncontrolled determinant of individual differences?

Based on our previous study, we predicted that E would turn out to be a critical variable in amygdala activation. Specifically, we expected that amygdala activation to happy (but not fearful) faces would vary as a function of E. Participants answered a self-report assessment of personality characteristics (Costa & McCrae, 1992) and were then scanned while viewing blocks of photographs of emotional facial expressions (angry, fearful, happy, and sad, along with neutral faces).

The analysis of the fMRI data confirmed our expectations. Analyzing data in the traditional way (i.e., grouped activations, not taking individual personality scores into account), we found significant amygdala activation to fearful (relative to neutral) faces, but not to any other facial emotion. This finding was consistent with prior reports of amygdala sensitivity towards facial expressions of fear. The critical test of our hypothesis was whether there would be a significant correlation between participants' E scores and amygdala activation to happy faces. Figure 2 shows that this was indeed the case. Furthermore, additional analyses revealed that this correlation was specific to happy faces and E; none of the other facial emotions were correlated with E, nor were any of the remaining Big Five personality traits correlated significantly with greater amygdala activation to any of the emotional faces.

One clear limitation of this study is its focus on one brain structure. It is, therefore, not clear how activation in the amygdala relates to other regions. For example, it is possible that amygdala activation was due to modulatory influences from other, perhaps cortical, regions. Evidence for such modulatory influences comes from a study by Hariri and colleagues (Hariri, Bookheimer, & Mazziotta, 2000).

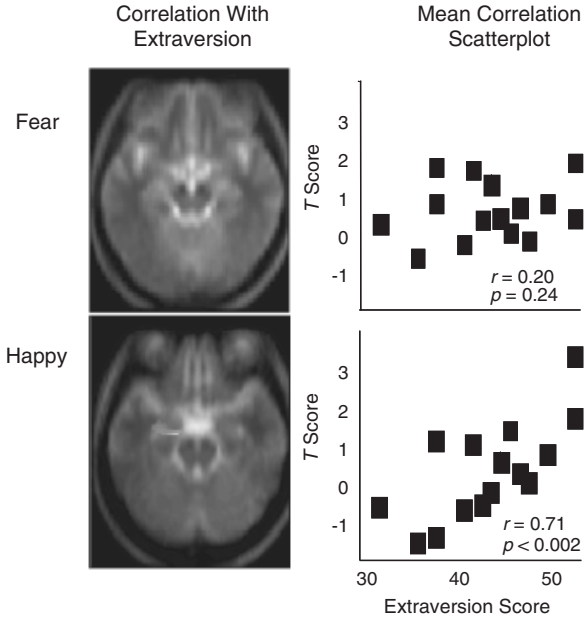

Figure 2
Amygdala response to happy, but not fearful, faces correlates with E. Amygdala response to happy and fearful faces as a function of E. A significant correlation was seen only in response to happy-neutral, but not fearful-neutral, faces (left column). Scatterplots in the right column show significance of amygdala activation for each of the fifteen participants as a function of their E scores.

These investigators presented emotional face pictures (target faces) and asked participants to select a matching face stimulus (a perceptual task) or word label (a linguistic task) from two given choices. Robust amygdala activation to angry or fearful target faces was observed when participants engaged in a perceptual matching task, but was diminished when they engaged in a linguistic matching task. The decrease in amygdala activation was correlated with an increase in the right prefrontal cortex. This study suggests that activation in higher cortical areas can inhibit amygdala response to stimuli that would otherwise drive it. Additional evidence comes from a study by Ochsner and colleagues (Ochsner, Bunge, Gross, & Gabrieli, 2002) who scanned subjects as they attended to, or reappraised, highly negative images. Reappraisal was associated with increased activation in prefrontal cortical regions, which have previously been

associated with cognitive control (Miller & Cohen, 2001; Smith & Jonides, 1999) and self-monitoring (Gusnard, Akbudak, Shulman, & Raichle, 2001). Activation in these regions was negatively correlated with activation in the amygdala. The authors suggested that the reappraisal task engaged cortical areas that then modulated activity in other regions associated with emotion processing.

Attention to emotional stimuli

We conducted two studies of attentional processes, one based on the emotional Stroop task (Canli et al., 2003) and one based on the dot-probe target detection task (Amin et al., in press). Similar to the study on face processing, these experiments focused on a priori regions of interest associated with attentional processes.

During the emotional Stroop task, participants were scanned while viewing words on a screen that are displayed in different colors. Their task was to indicate, as quickly and accurately as possible, the color in which each word was printed by pressing a corresponding key on a button box. Although the semantic meaning of the word was irrelevant to the task, the valence of the word did not seem to go unnoticed by the brain. A prior imaging study showed that participants exhibit greater activation to negative than neutral words in the anterior cingulate (Whalen, Bush et al., 1998), a brain region associated with emotional experience and awareness (Canli et al., 2002; Lane, Fink, Chau, & Dolan, 1997; Lane et al., 1998). Activation in this region to positive, relative to negative, pictures was also found to correlate with E (Canli et al., 2001). We, therefore, predicted that during the emotional Stroop task, greater activation to positive stimuli should correlate with E in the anterior cingulate. This was found to be the case. Additional analyses are currently underway to investigate the interaction of the anterior cingulate with other brain regions that play a role in attention and/or emotional processing.

Subjects in the dot-probe task were asked to respond to a probe stimulus that was initially hidden from view behind one of two stimuli, but revealed when both stimuli disappeared. In behavioral studies, a fast reaction time (RT) implies that the participant's attention is directed at the stimulus that obscures the probe, whereas a slow reaction time suggests that attention is drawn away from the stimulus that obscures the probe. In this imaging study, we focused on a priori regions of interest to ask the question whether activation in

these regions to positive and negative stimuli would correlate with E and N, respectively. Based on imaging studies of emotion and attention, we focused on the amygdala, anterior cingulate cortex, parietal regions, and fusiform gyrus (Davis & Whalen, 2001; Donner et al., 2000; Whalen, Bush et al., 1998).

Stimuli were presented in pairs of pictures that were negative and neutral (neg/neut), positive and neutral (pos/neut), or neutral and neutral (neut/neut). The probe was placed behind either item of the pair (both the placement of the probe and the placement of valenced and neutral items were counterbalanced across trials) so that, for any given trial, the probe was either behind a positive, negative, or neutral item. The analyses were based on contrasts where only the location of the probe differed between the two conditions. For example, one analysis identified brain regions that were significantly more activated when the probe was behind the positive item of a pos/neut pair, relative to when it was behind the neutral item. It needs to be stressed how subtle the difference between these two conditions was: both showed pairs of positive and neutral pictures, both showed a probe; both presented all stimuli for exactly the same amount of time; both required the same response; in both cases, the subject had no knowledge where the probe would appear.

We found that for pos/neut stimulus presentations, there was significantly greater activation, as a function of E, in the right fusiform gyrus when the probe was obscured by the neutral stimulus than when it was obscured by the positive stimulus (see Figure 3). For neg/neut stimulus presentations, there was significantly greater activation, as a function of E, in the right fusiform gyrus when the probe was obscured by the negative stimulus than when it was obscured by the neutral stimulus.

Activation in the right fusiform gyrus has previously been associated with visual search (Donner et al., 2000). We therefore speculated that greater activation in extraverted subjects in this region represented greater effort to search for the probe. This would be a reasonable interpretation if it were shown that highly extraverted subjects were less likely to look at the negative item of a neg/neut pair or the neutral item of a pos/neut pair than less extraverted subjects. Indeed, analysis of RT data showed that E was correlated with significantly faster RTs when the probe was placed behind the neutral than the negative stimulus, suggesting that highly extraverted participants avoided attending to the negative item of neg/neut pairs.

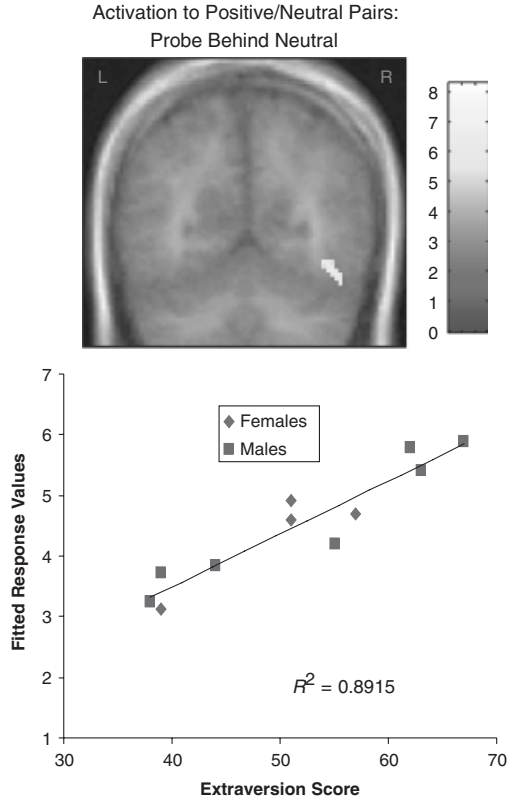

Figure 3

Correlations between E and brain activation in the right fusiform gyrus as a function of probe placement for pos/neut stimulus presentations. Brain activation is based on a contrast behind pos/neut pair presentations when the probe is obscured by the neutral versus positive item of the stimulus pair. When the probe was obscured by the neutral item, greater activation in the fusiform was seen as a function of E. L/R denotes left-right orientation of the image which is a coronal cut through posterior regions of the brain. Color bar indicates level of statistical significance (in T scores). Scatter plot shows degree of fusiform activation as a function of E.

Yet a clear limitation of this study is the lack of independent verification of gaze direction. Future work should combine functional imaging with eye tracking to determine which item of a stimulus pair was attended to.

Furthermore, the fusiform gyrus is involved in a wide range of behaviors, so that alternative interpretations need to be ruled out. For

example, activation in the right fusiform gyrus is also associated with autonomic arousal (Critchley, Elliott, Mathias, & Dolan, 2000). It is therefore possible that the correlations observed in this study reflect increased arousal associated with the regulation of affect, rather than greater effort in visual search. Concurrent measures of brain activation with autonomic arousal could address this possibility.

Some comments on localizing the neural basis of E and N

The mapping of psychological processes onto specific brain regions has been likened by Uttal as a form of "new phrenology" (Uttal, 2001). Such skepticism is buoyed by presentations that imply that complex psychological processes are represented by a single brain region, such as "fear is processed by the amygdala." Under the constraints of limited journal space, and with few a priori regions of interest, it is not uncommon to limit the discussion to a small number of regions. Yet one striking aspect of our first study (Canli et al., 2001) was the number of regions that exhibited a significant correlation; we listed 15 clusters where greater activation to positive, relative to negative, pictures correlated with E. This illustrates how distributed the neural representation of personality traits is likely to be.

Indeed, it has been suggested that the role that one region plays in the neural representation of a psychological function depends on the activity in other regions at that same time, a concept that has been named "neural context" (McIntosh, 1998). A related idea is that of "functional connectivity" (Friston et al., 1997) or "effective connectivity" (Friston, Harrison, & Penny, 2003). These terms refer to the idea that the activation in one brain region is the result of an interaction between another brain region and some other (e.g., psychological or experimenter-controlled) factor. Examples include brain-imaging studies demonstrating that the connectivity between different brain regions can vary as a function of attention (Friston & Buchel, 2000) or learning (Buchel, Coull, & Friston, 1999). To give a specific example, Buchel, Coull, and Friston (1999) used fMRI to show that associative learning of visual objects and their locations was associated with an increase in effective connectivity between brain regions involved in spatial and object processing. Subjects who performed best also showed the highest degree of effective connectivity, suggesting that the ability to make associations depended on functional interactions between these brain areas.

Could personality serve as a factor that modulates effective connectivity between brain regions? To the extent that personality traits are viewed as stable within individuals, the answer should be "no." Effective connectivity is capricious. Its temporal dynamics can change rapidly, as the subject enters a different mind state or focuses on different inputs. Presumably, traits like E and N don't exhibit these kinds of rapid fluctuations within subjects. On the other hand, I speculate that, between individuals, effective connectivity may very well be associated with personality. For example, it is possible that positive mood induction can dramatically change effective connectivity between two brain regions in individuals who are highly extraverted, but not in individuals who are introverted. As this speculation illustrates, current thinking in function imaging on topics like effective connectivity can inspire much new work in personality neuroscience.

Brain Imaging of Genotyped Individuals

Genetic contributions to personality have long been recognized (Bouchard, 1994; Ebstein, Benjamin, & Belmaker, 2000; Heath, Cloninger, & Martin, 1994; Plomin et al., 1994; Reif & Lesch, 2003; Zuckerman, 1991). This section will focus on functional brain imaging studies in which allelic variation in genes is associated with individual differences in brain activation. This approach has been called "imaging genomics" (Hariri & Weinberger, 2003).

The gene that has received the most attention so far, at least with respect to personality, is the serotonin (5-HT) transporter gene (referred to as 5HTT or SERT). Lesch and colleagues (Lesch et al., 1996) reported an association between individual differences in the structure of this gene (polymorphism) and participants' neuroticism scores. The 5HTT comes in two variants, which are physically longer (l) or shorter (s), due to the inclusion or deletion of a number of base pairs in the promotor region of the gene. The s variant is functional, but produces less of the transporter molecule that is responsible for removing serotonin from the synaptic cleft between two neurons (Lesch et al., 1996). Because participants carry two copies (alleles) of each gene, one from each parent, they can be homozygous for s (s/s), homozygous for l (l/l), or heterozygous (s/l). It was found that participants who carry at least one copy of the s-allele had significantly higher Harm Avoidance and N scores (Lesch et al., 1996) and

significantly lower Agreeableness scores (Greenberg et al., 2000) than participants who were homozygous for the l-allele.

These molecular studies of gene-personality relations, however, have been hampered by replication concerns. As discussed by Reif and Lesch (2003), more than 20 studies have investigated the relation between personality and the 5-HTT polymorphism. Only about half of them replicated the original finding. How can one explain such inconsistency?

Reif and Lesch (2003) identified several critical variables that may have contributed to null results in failed replication studies. First, they noted that only two replication attempts studied large samples ($N > 400$) as did the original study (Lesch et al., 1996) ($N = 505$). Second, several nonreplication studies examined unusual populations (e.g., alcoholic violent offenders, participants with substance dependence or personality disorders). Third, different studies used different measures to quantify personality traits. In that context, of particular interest is the assertion by Reif and Lesch that the contribution of the 5-HTT polymorphism to neuroticism is greatest in the central range of the distribution and least robust at the extremes (Sirota, Greenberg, Murphy, & Hamer, 1999), which may explain why two studies that selected extreme high- and low-scoring participants failed to replicate the original study. A fourth reason for poor replication across studies was that ethnic differences in study populations may also have been a factor. Two nonreplication studies of Japanese individuals reported a population frequency of the l/l allele of only 6% (compared to 32% in Caucasians, Lesch et al., 1996), yielding low statistical power to detect genotype-related differences.

Finally, and perhaps most importantly, molecular geneticists readily acknowledge that the contributions of individual genes to personality will likely be very modest. Based on twin studies, genetic factors contribute about 40%–60% of the variance in N and other personality traits (Bergeman, Plomin, McClearn, Pedersen, & Friberg, 1988; Bouchard, 1994; Heath et al., 1994; Lander & Schork, 1994; Loehlin, 1989; Loehlin, McCrae, Costa, & John, 1998; Pedersen, Plomin, McClearn, & Friberg, 1988; Plomin et al., 1994). The 5-HTT polymorphism was found to account for 3%–4% of the total variance and 7%–9% of the genetic variance (Lesch et al., 1996). Assuming that other genes make similar contributions to the observed variance, one would expect about 10–15 genes to be associated with personality measures (Lesch et al., 1996; Lesch & Mossner, 1998).

By combining molecular genetic approaches with functional imaging, the modest contributions of specific genes may be better isolated. In "Rethinking Behavior Genetics," Hamer (2002) made the point that a genetic explanation of human behavior is oversimplified if it relies on a direct linear relationship between genes and behavior. Rather, he suggested, one needs to incorporate the brain, the environment, and gene expression networks in future models. He pointed to a study by Hariri and colleagues (Hariri et al., 2002) to illustrate the power of combining the genotyping and functional neuroimaging approaches: using fMRI data, genotype accounted for 20% of the total variance, or about five to seven times the effect size of Lesch's original study using behavioral measures.

The study referred to by Hamer (2002) was conducted by Hariri and colleagues (Hariri et al., 2002) and asked the question, "If the 5-HTT polymorphism is indeed associated with N or anxiety-related behavior, could it be associated with individual differences in brain activation to fear-related stimuli?" If this is so, then amygdala activation to these stimuli should be greater in participants who carry at least one copy of the s-form than participants who are instead homozygous for the l-form. This was indeed found to be the case. Remarkably, this finding was established with two independent samples of only a total of 28 participants, whereas behavioral genetic studies typically require hundreds of participants to attain statistical significance. Importantly, this study has been replicated by two independent groups in Germany and Italy (Hariri, personal communication), as well as by Hariri and colleagues in a third and larger sample (Hariri et al., 2003). Together, these studies argue strongly that the 5HTT polymorphism is a determinant of amygdala reactivity to fear-related stimuli.

This focus on genetic contributions to brain activation and behavior does in no way imply that environmental factors are not equally important. Indeed, recent work by Caspi and colleagues firmly makes the point that it is the interaction between environmental and genetic factors that shapes behavioral outcomes (Caspi et al., 2002; Caspi et al., 2003). For example, Caspi and colleagues (Caspi et al., 2003) conducted a longitudinal (23-year) study of a large cohort ($N = 1037$ at time one, 96% retention over 23 years) to assess the interaction of life stress and the serotonin transporter polymorphism. They found that a significantly greater proportion of carriers of the s-allele responded to stressful life events with depressive symptoms

or diagnosed depression than homozygous l-allele carriers. For example, among participants who had encountered four or more stressful life events, 33% who carried at least one copy of the s-allele became depressed, versus 17% of homozygous l-allele carriers. Importantly, there were no significant differences in the number of stressful life events across groups, and the alternative hypothesis that exposure to life events is influenced by the 5HTT gene polymorphism was tested and could be rejected. Based on these observations and additional analyses, the authors concluded that the 5HTT polymorphism moderates individuals' response to stressful life events.

What is exciting about this work is that it begins to offer molecular hypotheses about the biological basis of personality traits. Whereas prior work noted an association between genetic variation (in the 5HTT gene) and a complex behavioral trait (N), imaging genomics relates these variations to specific brain structures that are associated with the processing of stimuli that are relevant to the trait (e.g., fear-related stimuli in the amygdala). Future work will then need to address the mechanisms by which individual differences in genotype scale up to individual differences in brain activations.

Applications to Health

The utility of understanding the neural basis of E and N extends beyond basic research to clinical applications. These are motivated, in part, by studies that have identified personality traits associated with E and N as resilience or vulnerability factors for certain kinds of psychopathologies. For example, cross-sectional studies reported elevated likelihood of substance-abuse disorders in individuals with high levels of novelty or sensation seeking, especially when coupled with high levels of impulsiveness (Acton, 2003; Bardo, Donohew, & Harrington, 1996; Franques et al., 2003).

More powerful demonstrations of personality–health relations come from prospective designs. For example, an 18-month prospective study showed that subjects in the top quartile of N scores were 3.3 times more likely to develop an eating disorder than lower scorers and that N was a better predictor than low self-esteem (Cervera et al., 2003). A 1-year prospective study showed that patients with high N scores had a 4.6-times-higher risk of developing post-stroke depression than patients with low N scores, regardless of stroke

location (Aben et al., 2002). A study of burn survivors found that those who developed post-traumatic stress disorder 12 months after treatment had higher N and lower E than those who did not develop the disorder (Fauerbach, Lawrence, Schmidt, Munster, & Costa, 2000). In a study of short-term (6-week) outcome of depression treatment, N was associated with unfavorable outcome and E was associated with positive outcome (Geerts & Bouhuys, 1998).

What kinds of mechanisms may play a role in the association between personality traits and health? Some may be behavioral. For example, Geerts and Bouhuys (1998) found that the association between E and N and depression treatment outcome was mediated, in part, by a nonverbal communication channel. There is an emergent interest in social cognitive neuroscience (Ochsner & Lieberman, 2001), which may, in the future, contribute to understanding the biological underpinnings that relate E and N to individual differences in social behavior.

Other mechanisms may be cognitive. For example, participants who scored high in N exhibited better recall memory for negative trait adjectives following a negative mood-induction procedure (Bradley, Mogg, Galbraith, & Perrett, 1993). Rusting (1999) reported that E and N were associated with participants' ability to retrieve positive and negative memories and make positive and negative judgments, respectively. This ability was mediated in some conditions by mood. Rogers and Revelle (1998) used a judgment task and found that E and N influenced the evaluation of emotional words in the absence of any interaction with induced mood and even interacted with each other. Derryberry and Reed (1994) reported that participants who scored high in E were slow to shift attention away from locations associated with positive incentives, whereas participants who scored low in E were slow to shift attention away from locations associated with negative incentives. This effect was most pronounced in participants who scored high in N, suggesting an interaction between these traits.

First steps have been taken towards understanding the neural basis of these cognitive processes in the context of E and N (see previous section). However, studies such as those by Derryberry and Reed (1994), Rogers and Revelle (1998), and Rusting (1999) suggest that imaging studies need to be designed and analyzed to take mood-personality interactions, and interactions between personality traits, into account.

Genetic influences will also provide mechanisms linking E, N, and health. This is suggested by findings that relate some of the same gene polymorphisms to personality traits and to different psychopathologies. For example, N is a risk factor for depression (Martin, 1985) and the 5HTT polymorphism is associated both with N (Lesch et al., 1996) and with depression (Mossner et al., 2001). A recent study found that individual differences in the 5HTT polymorphism predicted treatment response to serotonin reuptake inhibitors in depressed individuals (Rausch et al., 2002). Another example is the association between N and stress reactivity, which may also be related to the 5HTT polymorphism. A recent study reported that the genetic expression of the 5HT transporter in response to administration of dexamethasone, a glucocorticosteroid hormone associated with the stress response, is modulated by the 5HTT polymorphism (Glatz, Mossner, Heils, & Lesch, 2003). This may add a biological explanation of why individuals differ in stress reactivity. One of the great challenges for future work will be to understand the causal relationship between personality traits, genetic variation, and health and address how individual differences in serotonergic transmission may affect activation levels in brain regions associated with the processing of emotional signals.

This is not to suggest that there is a one-to-one correspondence between complex traits and psychopathologies, on the one hand, and single-gene polymorphisms, on the other. It is far more likely that any single-gene polymorphism will be involved in multiple psychopathologies and that any specific psychopathology will be the result of multiple gene–gene and gene–environment interactions. For example, gene–gene interactions were reported for the personality trait of reward dependence between the serotonin 5HT2c polymorphism and the dopamine DRD4 polymorphisms (Kuhn et al., 1999). An example for gene–environment interactions is provided by Caspi and colleagues (Caspi et al., 2003) who found an interaction between the s-form of the 5HTT polymorphism and life stress as predictors of depression. Future imaging genomics studies will need to feature factorial designs that make it possible to dissociate genetic and environmental contributions to individual differences in brain activation. This will require far larger sample sizes than is currently common in functional imaging studies.

Clearly, there is much that neuroscience can contribute to understanding the neural mechanisms that underlie personality–health relations. One of the major challenges will be to design studies that

can capture the complex interactions between genetic and environmental variables and to devise paradigms that capture the behavioral and cognitive mechanisms underlying personality–health relations in the scanning environment. This will require increased interactions and collaborations between neuroscientists and social, personality, and health psychologists, and continued efforts to communicate recent and exciting developments across disciplines.

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