Orbitofrontal thickness, retention of fear extinction, and extraversion

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People differ in their personality traits and in their ability to modulate fear. Does our personality determine how well we extinguish conditioned fear responses? Or is the opposite true? Herein, we examine the relationships between personality traits, memory for fear extinction, and cortical thickness as a measure of brain structure. We found that in healthy humans, extinction retention and thickness of the medial orbitofrontal cortex are positively correlated with extraversion. Path analysis indicates that extinction retention mediates the relationship between the medial orbitofrontal cortex thickness and extraversion, thereby illustrating one path through which brain structure influences personality. *NeuroReport* 16:1909–1912 © 2005 Lippincott Williams & Wilkins.

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Introduction

Increasing interest has been shown in the neuroscience of individual differences in the perception of, and reaction to, emotional stimuli [1]. Two major personality traits derived by Hans Eysenck, neuroticism and extraversion [2], have been invoked to link individual differences in personality to brain function. Functional neuroimaging studies of neuroticism and extraversion have found that these personality traits correlate with both baseline brain activity and reactivity to emotional stimuli [1,3]. For example, at rest, regional cerebral glucose metabolism in the anterior cingulate cortex and the orbitofrontal cortex is positively correlated with extraversion [4,5], whereas metabolism in the insular cortex is negatively correlated with neuroticism [5].

Eysenck [2] postulated that introverts, as a result of their higher arousal, acquire conditioned responses more easily, and extinguish them more slowly, than do extraverts. He also suggested that a key component of neurosis (now classified as anxiety disorder), which is characterized by high neuroticism and low extraversion, is the failure to extinguish aversive conditioned responses [2,6]. Although some psychophysiological laboratory evidence supports slower extinction of conditioned responses in introverts [7] and persons with anxiety disorders [8], such experiments typically measure extinction shortly following acquisition within the same experimental session. Recent animal research distinguishes between extinction learning (i.e. within-session extinction) and extinction retention, which appear to be mediated by different brain areas, namely, amygdala (e.g. [9]) and medial prefrontal cortex [10,11], respectively. To date, there have been no studies of the relationships between extinction retention and neuroticism or extraversion.

We devised and validated a psychophysiological procedure for the measurement of extinction retention of a conditioned fear response in humans [12]. We reported a significant correlation between thickness of the medial orbitofrontal cortex (mOFC) and extinction retention [13]. A thicker mOFC was associated with smaller skin conductance responses to a stimulus that had previously been aversively conditioned and then extinguished, and hence with greater retention of extinction memory [13]. Here, we report the relationships between extinction retention, mOFC thickness, and extraversion as well as neuroticism in study participants.

Methods

A total of 41 potential participants (20 men and 21 women) were recruited from the local community. Eleven participants were excluded because they did not demonstrate a measurable change in skin conductance level to *any* trial during the conditioning phase. Ten of the remaining 30 participants were conditioned but not extinguished and the data from this group were used for a different study [12]. Fourteen of the remaining 20 participants were randomly selected for the present study (eight men and six women; 21–34 years of age). Written, informed consent was obtained from all participants in accordance with the requirements of the Partners Healthcare System Human Research Committee.

The detailed experimental methods and psychophysiological responses of these participants were previously published [12–15]. Briefly, digital photographs of two different rooms constituted the visual contexts. Each room contained a lamp, and two different colors (blue and red) of the lighted lampshade constituted the conditioned stimulus (CS). The unconditioned stimulus was a 500 ms electric shock delivered through electrodes attached to the second and third fingers of the dominant hand. At the outset of the experiment, the intensity of the shock was adjusted for each participant so as to be 'highly annoying but not painful'. The experimental protocol was administered over two separate days. On day 1, the habituation phase consisted of eight trials, in which the to-be CS+ and to-be CS− (4 of each) were presented in a counterbalanced manner within either the to-be conditioning context or the to-be extinction context. The acquisition phase consisted of five CS+ and five CS− trials, all presented within the conditioning context. The unconditioned stimulus occurred immediately following each CS+ offset. The extinction phase was divided into two sub-phases: early and late, which were separated by an approximately 1-min rest period. Each subphase consisted of five CS+ and five CS− trials, all presented within the extinction context. No shocks were delivered during the extinction phase. The shock electrodes remained attached to the participant's fingers during the extinction phase and all subsequent phases of the experiment. On day 2, the recall phase was identical to an extinction sub-phase given on day 1.

To measure the magnitude of extinction retention, each participant's skin conditioned response to the first CS+ trial of the extinction recall phase was divided by their largest skin conditioned response to a CS+ trial during the conditioning phase and then multiplied by 100, yielding a percentage of maximal conditioned responding. This in turn was subtracted from 100% to yield an extinction retention index. Personality scores were measured with the NEO-Five Factor Inventory (NEO-FFI), a 60-item questionnaire that measures five personality dimensions: neuroticism, extraversion, openness, agreeableness, and conscientiousness [16]. Only scores from neuroticism and extraversion were analyzed in the present study.

We used the Sobel test [17] to examine the relationship between extinction retention, personality traits, and mOFC thickness. This tests whether a third variable (the mediator) influences the relationship between an independent and a dependent variable. A given variable may be considered as a mediator when all of the following conditions are satisfied: (1) the independent variable is correlated with the mediator; (2) the independent variable is correlated with the dependent variable; (3) the mediator is correlated with the dependent variable; and (4) the correlation between the independent variable and the dependent variable is significantly reduced upon the addition of the mediator to the model. Herein, we tested two models: (1) our *a priori* hypothesis that extinction retention is the mediator between mOFC cortical thickness and a personality trait (extraversion or neuroticism); and (2) an alternative hypothesis that the personality trait is the mediator between mOFC thickness and extinction retention.

Results

The average skin conditioned response magnitudes to the conditioned stimuli for the different phases of the experiment have been presented elsewhere [12]. We regressed the percentage extinction retention index onto extraversion and neuroticism *t*-scores (which adjust for sex difference). Extinction retention was positively correlated with extraversion (r=0.77, P=0.001) and negatively correlated with neuroticism (r=−0.61, P=0.02) (Fig. 1).

Elsewhere, we reported that a vertex-wise search of the brain revealed that the most statistically significant association between cortical thickness and extinction retention was found in right mOFC (Talairach coordinates [4, 31, −12]) [13]. We selected the cortical thickness values that we found to be maximally correlated with extinction retention and performed correlational analyses with extraversion and neuroticism *t*-scores. Cortical thickness at this locus was positively correlated with extraversion (r=0.60, P=0.02) and negatively correlated with neuroticism (r=−0.65, P=0.01). It could be argued, however, that this analysis was biased to yield significant correlations with the personality traits as a result of selecting the mOFC site that was maximally correlated with extinction retention. To resolve this, we ran an automated vertex-based analysis to identify the locations of the peak correlations between mOFC thickness and the two personality traits. The coordinates for the peak significant correlation between mOFC thickness and extraversion were 6, 28, −15 (r=0.65, P=0.01, Fig. 2), and for neuroticism were 5, 32, −16 (r=0.63, P=0.02, Fig. 2). The correlation between extinction retention and mOFC thickness at each of these loci remained highly significant: r=0.81 (P=0.0005) and r=0.76 (P=0.002), respectively. The coordinates for the peak vertex in the mOFC for the correlation between cortical thickness and extinction retention is very close to the peak vertices observed for the correlations between cortical thickness and both extraversion and neuroticism (all within one resolution unit, based on the spatial resolution of the methods employed).

Next, we investigated the causal nature of the relationships between mOFC thickness, extinction retention, and personality traits using the Sobel test. Cortical thickness values used for these analyses were extracted from the vertex found to be maximally correlated with extinction

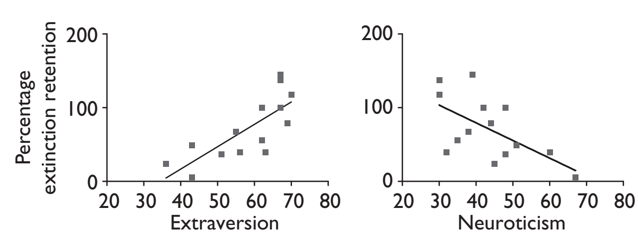

Fig. 1 Extinction is correlated with personality traits. Regression analysis between extraversion, neuroticism and the percentage retention of extinction memory.

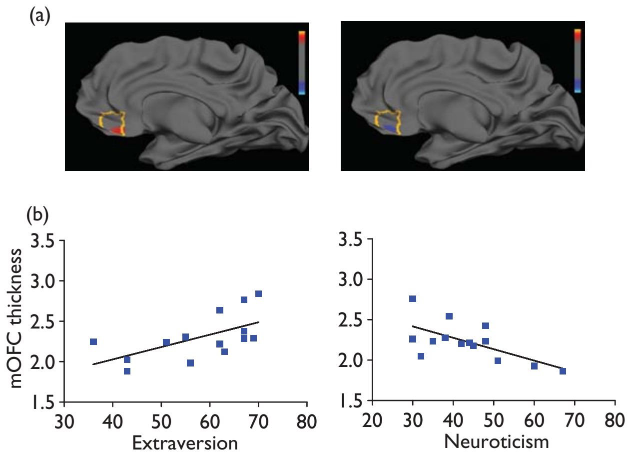

Fig. 2 Cortical thickness in the medial orbitofrontal cortex (mOFC) is correlated with extraversion and neuroticism. (a) Outline indicates the brain region of interest (mOFC), within which is a region found to be positively correlated with extraversion (left, red area) and negatively correlated with neuroticism (right, blue area). (b) Regression plots for the correlations between cortical thickness in the mOFC and extraversion (left) and neuroticism (right).

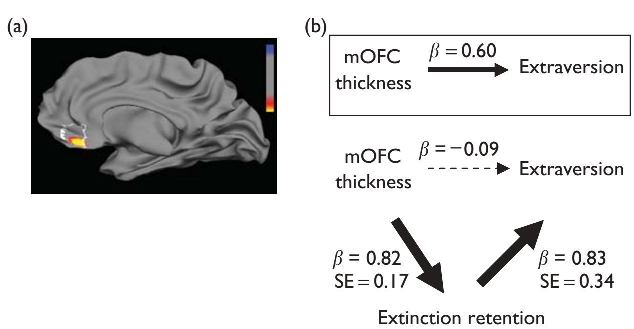

Fig. 3 Path analysis indicating that cortical thickness mediates extraversion via extinction retention. (a) Picture indicates the brain region of interest [medial orbitofrontal cortex (mOFC)], within which is a region found to be positively correlated with extinction retention (adapted from Milad *et al.* [13]). The mOFC thickness values used for the path analysis were obtained from the peak vertex found to be maximally correlated with extinction retention. (b) Path analysis representing a model showing that extinction retention mediates the mOFC correlation with extraversion. The dotted arrow indicates a path that is not significant.

retention (Fig. 3 [13]). In the first model (described in the methods section), when extinction retention was tested as the mediator, the coefficient between mOFC thickness and extraversion was reduced from β=0.60 to −0.09 (Fig. 3). The Sobel test revealed that extinction retention is a mediator of the relationship between mOFC thickness and extraversion (P=0.03). In the second model, when extraversion was tested as the mediator, the coefficient between mOFC thickness and extinction retention was only reduced from β=0.82 to 0.57. The Sobel test revealed that extraversion is not a significant mediator of the relationship between mOFC thickness and extinction retention (P=0.08). Regarding neuroticism, we found that extinction retention did not mediate the hypothetical path from mOFC thickness to neuroticism (P=0.57); nor did neuroticism mediate the hypothetical path from mOFC thickness to extinction retention (P=0.58).

Discussion

Whereas previous studies have linked the mOFC to extinction retention [10,11,18] and to extraversion [4,5], the data from the present study suggest a path through which these three variables are inter-related. Eysenck [2,6] postulated that extroverts have a superior inhibitory system. Animal research suggests that the ventromedial prefrontal cortex (vmPFC), of which the mOFC is a part, inhibits the expression of fear mediated by the amygdala [19]. If one presumes that a thicker mOFC is functionally more efficacious, and that this provides a better inhibitory system, then our results support this view of mOFC function. Specifically, a thicker and therefore more functional mOFC confers a better capacity to retain the extinction of fear responses. In turn, an enhanced capacity to limit fear responses leads the individual to be more extraverted.

The inverse correlation between mOFC thickness and neuroticism observed here is consistent with the fact that neurotic individuals are characterized as generally anxious and apprehensive, and they report more negative emotions. The fact that extinction retention did not mediate the hypothetical link between mOFC thickness and neuroticism, however, suggests that other physiological mechanisms and/or behavioral capabilities are involved in this association.

Although mOFC thickness is treated as the primary causal variable in the current model, the factors that determine cortical thickness in general and mOFC thickness in particular, remain to be established. Initial data suggest that both genetic and environmental factors can influence cortical structure in this area. For example, polymorphism of the serotonin transporter promoter region gene has been linked to the size (and function) of the vmPFC, such that carriers of the short allele form of the transporter, known to be linked with anxiety disorders, have smaller vmPFC volume [20]. From the environmental standpoint, exposure to chronic stress in animals has been found to damage the vmPFC [21]. Genetic and environmental factors that determine the size of the vmPFC could then influence our ability to extinguish fear. Although the genetic basis for extinction retention remains to be delineated, recent studies have suggested that the acquisition of conditioned fear has a genetic basis [22].

At the cellular level, the observed variance in mOFC thickness could be due to variance in the size or number of neurons or glia [23,24]. In particular, a greater number of neurons, or a more extensive neuropil [25], could better implement a function that the region subserves (e.g. in the case of the vmPFC), inhibiting the output of the amygdala in conditioned fear expression.

Several limitations are found to the interpretations of the data presented. First, the small sample size underscores the need for replication. Second, this demonstration of statistical mediation should not be equated with mechanistic mediation. Consequently, the implications of the path analyses should be considered with caution, given that correlations do not prove causality. Third, there is sufficient unexplained variance in all the observed associations to allow ample room for other causal influences and mediators. Finally, as extinction retention can only be meaningfully quantified in participants who exhibit significant fear conditioning, the current findings regarding the relationship between cortical thickness, extinction retention and personality traits cannot be readily extended to those individuals in whom fear conditioning cannot be demonstrated.

Conclusion

We show that extinction retention for conditioned fear represents a specific behavioral domain that is significantly determined by mOFC thickness and in turn mediates the relationship between mOFC thickness and the more complex human trait of extraversion.

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