Mapping the genetic variation of executive attention onto brain activity

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A popular theory of cognitive control suggests that the dorsal anterior cingulate is part of a network involved in handling conflict between neural areas (1, 2). In support of this general idea, a number of neuroimaging studies have shown activation of the dorsal anterior cingulate in tasks requiring people to respond to one dimension of a stimulus rather than a strong conflicting dimension (1–3). One task in which this has been found (1, 4) involves the person responding to the direction of a central arrow when flanking arrows could point either in the same (congruent) or the opposite (incongruent) direction.

The Attention Network Test (ANT) uses the flanker task to measure conflict and shows strong activation in the dorsal anterior cingulate (4, 5). Because the cingulate is modulated by the ventral tegmental dopamine system (6–8), we previously tested 200 normal persons with the ANT and genotyped them for a number of genes related to the dopamine system (9). We found polymorphisms in two genes were significantly related to the efficiency of conflict. These were the gene ( ) and ( ) genes.

In the current study, we ran 16 unselected normal subjects on the ANT with event-related functional MRI (fMRI). We collected cheek cells to search for polymorphisms in the two genes which we previously found to be related to performance on the conflict network of the ANT (9). We considered only alleles possessed by at least six of our subjects, and which we thought might influence dopamine modulation within the conflict network. There were sufficient data to test one such polymorphism in each of the two previously identified genes. One of these is a 30-bp repeat polymorphism in the promoter of the gene. The other is a single-nucleotide insertion/deletion polymorphism in the 5′ region of the gene.

One of the advantages of the molecular genetic method used here is that it can noninvasively probe genes that have been shown to result in variation in protein levels or biochemical activity. For example, transfection experiments show that the three-repeat allele of the 30-bp repeat in the promoter results in a 5-fold lower transcriptional induction than the four-repeat allele (10). This finding suggests that those subjects with the three-repeat allele may have relatively lower levels of active enzyme and thus relatively higher levels of dopamine. Some polymorphisms in the gene have been shown to confer differences in biochemical activity (11) and have been related to behavior (12). The −1217G insertion/deletion polymorphism resides in the upstream region of the gene and may affect transcriptional efficiency; however, biochemical evidence in this case has not been reported.

Both of these polymorphisms did show some tendency toward association with behavioral performance when we examined our larger population of 200 subjects. We ask whether they will be associated with different levels of activation in the dorsal anterior cingulate during performance of the ANT, as would be expected if the candidate genes are truly related to monitoring and processing conflict.

Methods

Participants. Participants in the behavioral–genetic study were recruited from advertisements in the New York area and Beijing (for more details, see ref. 9). Participants in the fMRI study were

the fixation point. To measure the alerting or

class, conflict error, 0.040; SE, 0.005; t (168) = −0.033, p = 0.973].

In Fig. 1 , subjects were grouped according to whether they were homozygous for the insertion of a guanosine residue at position −1217 (insertion class, n = 112) of the gene or whether they were heterozygous for the "G" insertion/deletion polymorphism at this site (deletion class, n = 71). Between these two groups, the difference on ratio score of conflict effect was significant [insertion class: conflict RT ratio, 0.165, SE, 0.006; deletion class, conflict RT ratio, 0.185, SE, 0.009; t (181) = 1.97, p = 0.051, two-tailed]. The differences in conflict effect of error rate (see Fig. 1) were not significant [insertion class: conflict error rate, 0.048, SE, 0.008; deletion class: conflict error rate, 0.040, SE, 0.006; t (181) = 0.713, p = 0.433]. For all above statistics, analyses of covariance with age and gender as the covariates did not show significant changes.

Fig. 2 shows the behavioral results of the fMRI study. Although the subjects were grouped in the same fashion and showed trends (differences between genotypic groups) similar to the larger sample, no trend was significant in the sample of fMRI study.

fMRI Results. Fig. 2 and shows the significant differences of conflict effect in ACC between genotypic groups for the and polymorphisms, respectively. Tables 1 and 2 show other areas in the brain where greater conflict effect was found. In the case of , the four-repeat genotypic group (n = 8) showed greater conflict effect than the three-repeat group (n = 8) in the ACC. Further analysis of the conflict effect showed that the significant interaction between allele (two groups) and task conditions (congruent and incongruent) occurred because the four-repeat class showed greater conflict effect (greater activity for the incongruent than for the congruent condition), whereas the three-repeat class showed no significant conflict effect. The difference between the two groups was not significant for the congruent condition. The difference between the two groups was significant for the incongruent condition.

In the case of , the insertion class (n = 6) showed greater conflict effect than deletion class (n = 10) in the ACC. The difference between two groups in ACC arose because the insertion class showed significantly greater conflict effect, whereas the deletion class did not. ACC activation of the insertion class was less than that of the deletion class for the congruent condition. However, there was no significant ACC activation difference between the two groups for the incongruent condition.

A cluster of ACC activation was extracted. Analysis of covariance with ACC activation as the dependent variable and gender, age, conflict effect calculated using the ratio scores, and conflict

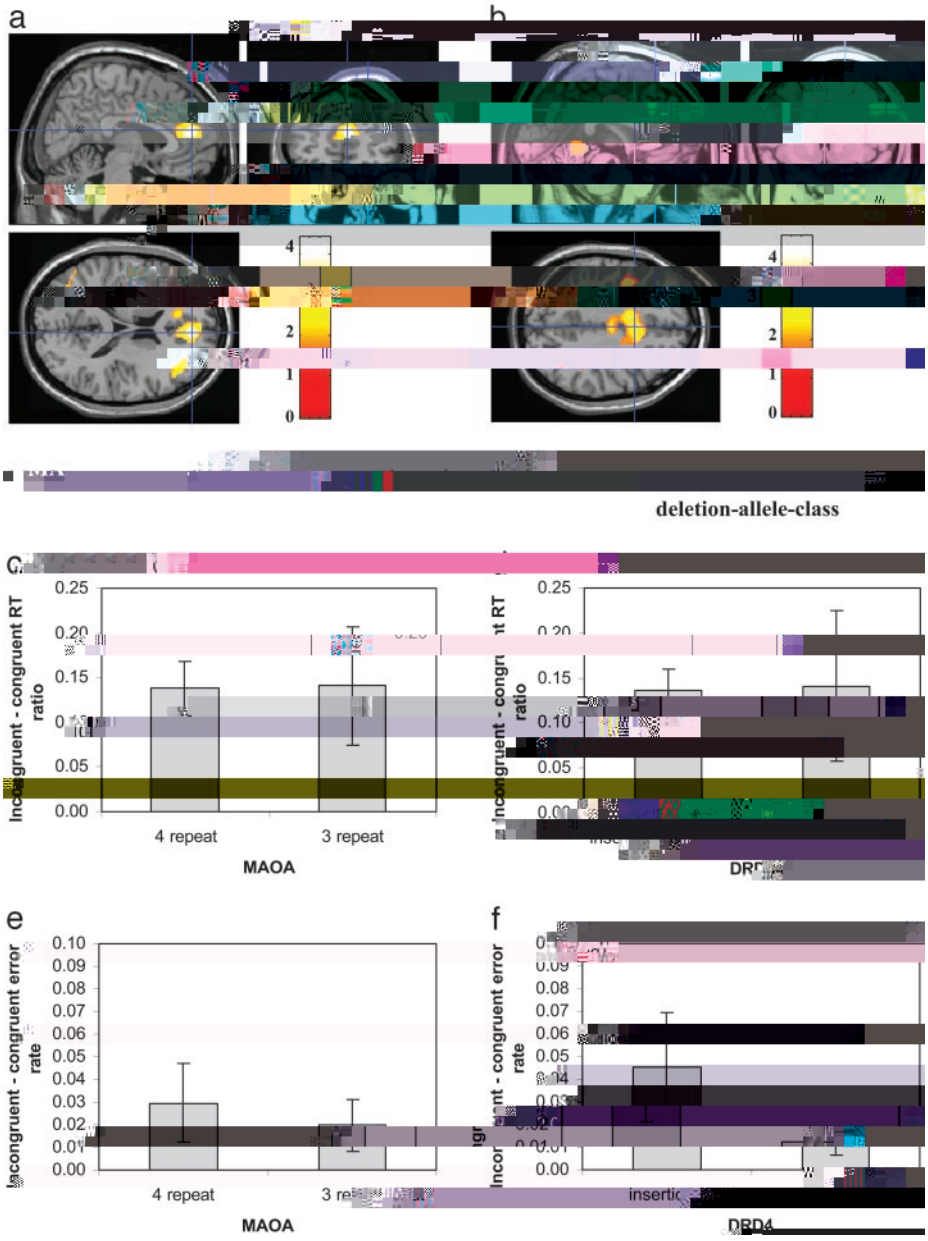

Fig. 2. Genetic variation in *MAOA* and *DRD4* and brain activity. (*a*) Greater brain activity among subjects who were grouped according to genotype at the *MAOA* LPR four-repeat class ($n = 8$) in comparison with three-repeat class ($n = 8$). (*b*) Greater brain activity among subjects who were grouped according to genotype at the *DRD4* insertion class ($n = 6$) in comparison with deletion class ($n = 10$). The color bar represents the level of *t* value. (*c* and *d*) The *y* axis shows the conflict effect based on the difference between incongruent and congruent conditions on ratio scores of RT for subjects in the corresponding genetic groups. (*e* and *f*) The *y* axis shows the error rate differences between incongruent and congruent conditions for each genetic group. (Error bar = ± 1 SE.)

Discussion

Many cognitive processes have been studied at the network level by neuroimaging. These include attentional networks (1–5), word reading (17, 18), music (19), faces (20), episodic memory (21), and many others. Each of these networks involves different anatomical areas, and each has its own time course of development. Although the general anatomy of each network is relatively fixed, there are clearly individual anatomical variations (22) and behavioral differences in the efficiency of their operation (13).

We have been working with attentional networks, particularly the executive attention network, which is involved in control of cognition and emotion (1) and is frequently activated by conflict (2). The most commonly activated node of this network is the anterior cingulate gyrus. Because this is a dopamine-rich brain area, we have surveyed a number of dopaminergic genes to see whether they influence performance on a RT test known to tap activity in the anterior cingulate.

We have found two genes that influence the efficiency with which normal people handle conflict (9). Although our imaging study did not have sufficient subjects in each genotypic class to examine these two polymorphisms, we did have enough to examine two other polymorphisms in these genes. These two polymorphisms showed similar but nonsignificant differences in the conflict network of the ANT. However, we did find that the two polymorphisms produced significant differences in the degree of activation in an important node of the executive attention network. This finding closes the loop in showing that

genes involved in modulating behavioral performance influence brain activity in a node of the network that mediates that performance. We expect that, in a larger study, we would find similar activation differences for the other alleles of the , , , and

the performance of normal people on a learning task. The authors suggest that it may be possible to apply this method to other cognitive networks, and that relatively fewer subjects may be needed to detect differences in fMRI than would be required to see these effects in behavior. Our results support both of these ideas. The attention networks involve brain areas quite distinct from the hippocampal area. In these networks, we also find that specific polymorphisms influence local activation within the network. In our case as well, much larger samples would have been required to obtain statistical significance than was true for the fMRI result. These results support the use of candidate genes as an approach to understanding the individual development of cognitive networks.

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