

# EXECUTIVE ATTENTION: IMAGING AND GENETIC ANALYSIS

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## Abstract

Brain imaging data has repeatedly shown that the anterior cingulate gyrus (ACC) is an important node in the brain network mediating conflict. We previously reported that polymorphisms in the dopamine receptor (DRD4) and in monoamine oxidase A (MAOA) genes showed significant associations with efficiency of handling conflict as measured by reaction time (RT) differences in the Attention Network Test (ANT)[1]. To examine whether this genetic variation might contribute to differences in brain activation, we genotyped 16 subjects for the DRD4 and MAOA genes who had been scanned during the ANT. In each of the two genes previously associated with more efficient handling of conflict in RT experiments, we found a polymorphism in which persons with the allele with better behavioral performance showed significantly more activation in the anterior cingulate while performing the ANT than those with the allele associated with worse performance. The results demonstrate how genetic differences among individuals can be linked to individual differences in neuromodulators and in the efficiency of the operation of an appropriate attentional network.

## Introduction

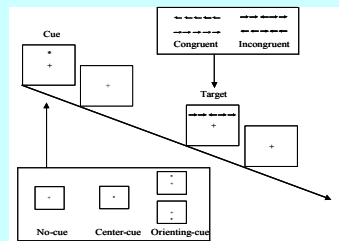
The Attention Network Test (ANT) [2] uses the flanker task to measure conflict and shows strong activation in the dorsal anterior cingulate [3, 4]. Since the cingulate is modulated by the ventral tegmental dopamine system [5, 6, 7], we previously tested 200 normal persons with the ANT and genotyped them for a number of genes related to the dopamine system. We found polymorphisms in two genes were significantly related to the efficiency of conflict [1]. These genes were the dopamine D4 receptor gene (DRD4) and monoamine oxidase A (MAOA). We only considered 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-base pair repeat polymorphism in the promoter of the MAOA gene. The other is a single nucleotide insertion/deletion polymorphism in the 5' region of the DRD4 gene. 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.

In the current fMRI study we ran sixteen unselected normal subjects in an event related fMRI study of the ANT. We collected cheek cells to search for polymorphisms in the two genes for which we previously found to be related to performance on the conflict network of the ANT.

## Methods

**Participants** Participants in the behavioral-genetic study were recruited from ads in the New York area and Beijing, China. For more details see [1]. Participants in the fMRI study were recruited from New York area. Participants with a history of psychopathology and/or taking medication were excluded. Participants in the fMRI study consisted of sixteen right-handed normal adults (mean age = 27.2 years, SD = 5.7, range: 18-36 years; 8 female, 8 male). They performed the ANT, see below, while being scanned in an event related fMRI experiment.

**ANT task** The details of ANT used in the behavioral genetic study are illustrated in [2]. The ANT parameters were optimized for the fMRI study [4].



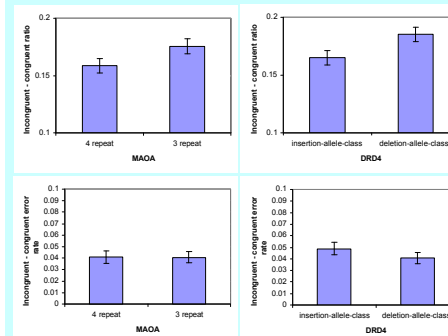
**Figure 1.** An illustration of the ANT in the fMRI study. In each trial, a fixation cross first appears in the center of the screen. At the same time, depending on the condition, a cue (a star sign) will (cued condition) or will not (no cue condition) be presented for 200 ms. After a variable duration (300 to 11800 ms, exponentially distributed with a mean interval of 2800 ms), the target and flankers will be presented until the participant responds with a button press, but for no longer than 1700 ms. After the participant makes a response, the target (the central arrow) and flankers disappear immediately and a post-target fixation cross appears for a variable duration. The duration between the onset of the target and the start time of the next trial is also a variable duration (300 to 15000 ms with a mean of 3000 ms, exponentially distributed).

**Functional magnetic resonance imaging** We used event-related fMRI to study the changes of brain activity of these attentional networks corresponding to the task conditions. We isolated brain activity associated with the subtraction of the congruent condition from incongruent condition for the measurement of the conflict effect. MR imaging was carried out using a GE Signa 3T scanner. Blood oxygenation-level dependent (BOLD) functional images were collected using a T2\*-weighted gradient echo planar imaging (EPI) sequence. Statistical Parametric Mapping (SPM) was conducted using SPM99. Region of interest (ROI) analysis was conducted to get the activation values of ACC.

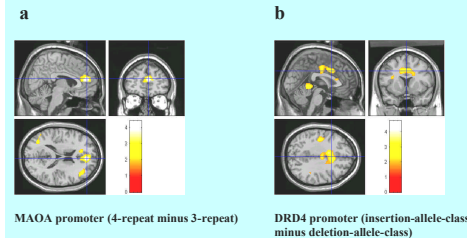
**Genotyping analysis** Buccal swabs were obtained via buccal cell brush from consenting subjects and prepared as directed by the manufacturer. For genotyping of the MAOA-LPR as described (10), Forward: 5'-ACAGCCTGACCGTGGAGAAG-3' and Reverse 5'-GAACGGACGCTCCATTCCGA-3' primers were used. The insertion/deletion of a guanosine or 'G' residue at upstream position -1217 was genotyped according to (11) using forward 5'-TGCAAGAGGACTGACCTGGCT-3' and reverse 5'-GCGGCGCACATCTGATGCTCTAGT-3' followed by digestion with BstEII.

## Results

Figure 2 shows the results of behavioral genetic study. The between group differences were significant or marginally significant for the ratio conflict scores but not for the error rates. Figure 3 shows the significant differences of the conflict effects between genotypic groups.



**Figure 2.** Genetic variation in MAOA and DRD4 and executive attention. The Y-axis of panels (a) and (b) shows the ratio conflict scores: (incongruent RT - congruent RT) / Mean RT. The X-axis in panels (a) and (c) indicates that subjects were grouped according to whether they were homozygous / hemizygous for the 4-repeat allele of the MAOA-LPR (4-repeat class, N=55) or, alternatively, whether they were homozygous / hemizygous or heterozygous for the MAOA LPR (3 repeat class, N=115). The X-axis in (b) and (d) indicates that subjects were grouped according to whether they were homozygous for the insertion of a guanosine residue at position -1217 (insertion class, N=112) or whether they were heterozygous for the 'G' insertion/deletion polymorphism at this site (deletion class, N=71).



**Figure 3.** Genetic variation in MAOA and DRD4 and brain activity. Panel (a) shows differences in brain activity among subjects who were grouped according to genotype at the MAOA-LPR 4-repeat class (N = 8) vs. 3-repeat class (N = 8). Panel (b) shows differences in brain activity among subjects who were grouped according to genotype at the DRD4 -1217G Ins/Del polymorphism insertion class (N = 6) and deletion class (N = 10). Color bar represents the level of t value.

## Discussion

We have found two genes that influence the efficiency with which normal people handle conflict [1]. Although our imaging study did not have sufficient subjects in each genotypic class to examine these two specific polymorphisms, we did have enough to examine two other polymorphisms in these genes. These two polymorphisms showed similar (but non significant) 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 in a larger study that we would find similar activation differences for the other alleles of the DRD4 and MAOA genes. These results support the use of candidate genes as an approach to understanding individual development of cognitive networks.

Two recent studies of cognitive networks [8, 9] underlying episodic and working memory provide examples of the strategy used in the current paper. 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.

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## Poster request

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