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 monamine 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.

Abstract

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 were thought might influence dopamine modulation within the conflict network. We used event-related fMRI to study the changes in brain activity of these anterior networks corresponding to the task conditions. We isolated brain activity associated with the subtraction of the congluent condition from congluent condition for the measurement of the conflict effect. ANOVA was used 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 nucletide insertion/deletion polymorphism in the 5’ region of the DRD4 gene. Both of these polymorphisms showed a strong correlation 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 can select unselected normal subjects in an event related fMRI study of the ANT. We collected cheek cells to genotype 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 attention network.

Introduction

The ANT is a single neuroimaging technique that has been used for the last decade to study the neural network used to control voluntary behaviors in response to both exogenous and endogenous conflict. The ANT parameters were optimized for the fMRI study [4]. The ANT task consists of 16 trials, each consisting of a central fixation point and two flankers. The flankers are presented to the left and right of the central fixation point and flankers are presented in the left-right and right-left conditions. In each condition, the flankers are congruent or incongruent with the central stimulus. Congruent trials are defined as those where the target and flankers point in the same direction, whereas incongruent trials are defined as those where the target and flankers point in different directions. The ANT task was developed by Posner et al. [1] and has been used extensively to study the neural networks involved in conflict monitoring and resolution.

Methods

Participants

Participants in the behavioral genetic study were recruited from 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 neurological or psychiatric illness were excluded. Participants in the fMRI study consisted of sixteen right-handed normal adults (mean age = 27.2 years, SD = 5.7, range = 16-36 years, 6 female, 10 male). The ANT task was performed in a dimly lit room, with participants seated in a comfortable chair. The task consisted of 16 trials, each consisting of a central fixation point and two flankers. The flankers are presented to the left and right of the central fixation point and flankers are presented in the left-right and right-left conditions. In each condition, the flankers are congruent or incongruent with the central stimulus. Congruent trials are defined as those where the target and flankers point in the same direction, whereas incongruent trials are defined as those where the target and flankers point in different directions. The ANT task was developed by Posner et al. [1] and has been used extensively to study the neural networks involved in conflict monitoring and resolution.

Results

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. The target can be presented at any time, and the participant responds with a button press, but no longer than 1700 ms. The target is followed by a post-target fixation cross for a variable duration. The duration between the onset of the target and the start of the next target is 2800 ms. The ANT is a single neuroimaging technique that has been used for the last decade to study the neural network used to control voluntary behaviors in response to both exogenous and endogenous conflict.

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

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.

We tested two recent 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.

References


Acknowledgement

Supported by N01 grant BCS 99070021 and by a DAFIP Wallace-Reader’s Digest Fellowship in Psychiatry and a grant from the James L. McDonnell Foundation to the Sackler Institute. Support to J. Fossella is via MER 1 F32 MH63601-01A1 and NASA Young Investigator Award.

Poster request

Please send email to Jin Fan: jf2004@med.cornell.edu or download from www.sacklinfo institute.org/jjin