

Research article

Assessing the heritability of attentional networks

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Abstract

Background: Current efforts to study the genetics of higher functions have been lacking appropriate phenotypes to describe cognition. One of the problems is that many cognitive concepts for which there is a single word (e.g. attention) have been shown to be related to several anatomical networks. Recently we have developed an Attention Network Test (ANT) that provides a separate measure for each of three anatomically defined attention networks. In this small scale study, we ran 26 pairs of MZ and DZ twins in an effort to determine if any of these networks show sufficient evidence of heritability to warrant further exploration of their genetic basis.

Results: The efficiency of the executive attention network, that mediates stimulus and response conflict, shows sufficient heritability to warrant further study. Alerting and overall reaction time show some evidence for heritability and in our study the orienting network shows no evidence of heritability.

Conclusions: These results suggest that genetic variation contributes to normal individual differences in higher order executive attention involving dopamine rich frontal areas including the anterior cingulate. At least the executive portion of the ANT may serve as a valid endophenotype for larger twin studies and subsequent molecular genetic analysis in normal subject populations.

Background

In order to foster genetic studies there has been increased emphasis on the development of appropriate phenotypes to describe cognitive functions such as attention (see, for example, [1]). In general these efforts have used tasks that do not distinguish between different functions of attention. However, imaging studies have revealed quite specific anatomical networks for functions of attention such as orienting to sensory events, developing and maintaining the alert state and executive control used in resolving conflict between stimuli and responses (for a review of these networks see [2]). We seek to use this anatomical information to define appropriate endophenotypes for genetic studies of attention.

Imaging studies show that the alerting network depends largely on frontal and parietal areas of the right hemisphere [3,4]. The orienting network has important involvement of superior and inferior parts of the parietal lobe in conjunction with frontal and subcortical structures related to eye movements [5]. The executive control network involves frontal areas including the anterior cingulate and lateral prefrontal cortex [6].

Each of the networks is also differentially dependent on a particular neuromodulator. Studies of alert monkeys suggest that the effectiveness of alerting produced by a warning signal can be eliminated by drugs that block noradrenaline [7]. Lesions of the cholinergic system [8] and

of drugs blocking ACh transmission have effects on orienting of visual attention in monkeys [9]. The executive network involves dopamine rich areas of the prefrontal cortex and anterior cingulate. Lesions in the cell bodies of dopamine (DA) neurons [10] as well as in the terminals located in prefrontal cortex [11] result in cognitive deficits in executive function tasks.

There is considerable evidence that insults to parts of the brain containing these networks or to the neuromodulators involved can produce specific neurological or psychiatric deficits. For example, strokes to the posterior parietal lobe involved in orienting produce neglect of the contralesional space and specific deficits in tasks involved the orienting network [12]. Reductions in striatal dopamine seen in Parkinson's disease result in an inability to shift sets from one instruction to another, possibly reflecting a difficulty in control of conflict [13]. Many psychiatric disorders whose anatomical origins may not be well understood also show deficits in attention. For example, patients with schizophrenia exhibit difficulties in sensorimotor gating [14], smooth pursuit eye-tracking [15], set-shifting [16], and working memory tasks [17]. Children with attention-deficit/hyperactivity disorder (ADHD) exhibit abnormal performance in sustained attention tasks [18] and studies on autism reveal slowed covert orienting of visual spatial attention [19]. Patients with Alzheimer's disease show covert orienting deficits in visual attention tasks [20]. Interestingly, many of these disorders show familial patterns of inheritance and increased concordance in monozygotic (MZ) vs. dizygotic (DZ) twins suggesting genetic origins [21].

There is evidence that some kinds of variation in attention in normal subject and patient populations involves genetic variation. Studies using the Continuous Performance Task (CPT) have shown that the d' signal detection component of CPT performance has a heritability among normal subjects of 0.49 [22]. The Span of Apprehension task (SPAN), a visual search task, has been shown to have an heritability among normal subjects of 0.65 [23] and the P/N ratio of the Spontaneous Selective Attention Task (SSAT) was shown to have an heritability among normal subjects of 0.41 [24]. Twin studies using discordant twins affected with schizophrenia show that spatial working memory, divided attention, choice reaction time and selective attention [25] and attentional set-shifting [26] are underlain by inherited factors. Studies on infants suggest that effortful control and duration of orienting are heritable as well [27].

Recent studies have proceeded to associate genetic variation with performance variation in attentional function. For example, persons homozygous for the $\epsilon 4$ allele *apoe* gene, who are asymptomatic, but at risk for Alzheimer's

disease have been shown to have a specific deficit in orienting of attention that is in the same direction as the Alzheimer's patients [28]. Other studies using endophenotypic measures of attention have linked variation in the *chrna7* gene with sensorimotor gating performance [29] and variation in the *drd4* gene with attention deficits [30]. However, the tasks used in these studies have not generally involved either the orienting network alone, or the task involves an undefined combination of different networks.

In previous work we have provided an Attention Network Test (ANT) for measuring the efficiency of the alerting, orienting and conflict networks [31]. The advantage of this measure over other neuropsychological measures of attention is that it provides a rapid measure of the efficiency of each of the attention networks which have been linked to a specific anatomy and specific chemical modulators. The ANT task is a combination of the cued reaction time [32] and the flanker task [33]. Its simple design permits use with adults, children, non-human primates, and patients with various abnormalities of attention. Our previous paper [31] and other studies using the flanker task suggest that performance on this task follows a roughly normal distribution. Performance is also stable within normal adult subjects across a wide age range and not detectably different in males and females. It has also been shown that practice or previous experience has little impact on the attentional measures although the overall reaction time is reduced. In this small scale preliminary study we take a step toward the use of the ANT as an endophenotype in genetic studies by exploring the heritability of each of the networks studied by the test.

Results

The mean efficiency scores for each of the three attention networks were calculated according to the operational definitions described below (see Materials and Methods). Table 1 shows means and standard deviations (SD) for each of the attention networks and overall reaction times (RT) separately for MZ and DZ twins.

The values obtained for the three attentional networks were similar to those found previously [31]. To determine if these values or the overall RT differed between members of a twin pair or between twin type (MZ or DZ), we carried out a 4 (three effects and mean RT) \times 2 (2 twins in each pair) \times 2 (MZ and DZ) analysis of variance (ANOVA) with twin type as between subject factor. There were no significant differences between twins in the pair, $[F(1, 50) = 2.74, MSe = 912.98, p > .10]$, and twin type (MZ and DZ), $[F(1, 50) = 2.79, MSe = 3553.27, p > .10]$.

Table 1: Means and standard deviations (SD) for each of the attention network and mean RT.

	Alerting	Orienting	Conflict	Mean RT
MZ twins (n = 52)				
Mean (msec)	42	60	71	482
SD (msec)	16	14	25	50
DZ twins (n = 52)				
Mean (msec)	38	52	90	513
SD (msec)	15	19	38	78
Combined (n = 104)				
Mean (msec)	40	56	80	498
SD (msec)	16	17	34	67

The study consisted of two sessions which permitted analysis of reliability in the present sample. The test-retest reliability for alerting, orienting, and conflict were .36, .41, and .81 respectively. They were significant ($p < .01$). Since the means of the two test sessions were used, the expected reliability composite of two measures were .53, .58, and .90 for alerting, orienting, and conflict respectively.

The alerting, orienting, and conflict scores may be influenced directly or indirectly by the overall mean RT. Generally one expects larger subtractions when the RTs are longer. In order to reduce these effects, ratio scores (effect divided by overall RT) were used in the correlation analysis and the estimations of the heritability of the three networks. Table 2 shows the correlation values between twin pairs of MZ and DZ twins for each network.

Table 2: Correlation values between twin pairs of MZ and DZ twins for each network.

Twin type	Alerting	Orienting	Conflict	RT
MZ	.465*	.099	.727**	.740**
DZ	.375	.395*	.281	.659**

Note: * $p < .05$; ** $p < .01$

Heritability is generally thought to be the proportion of variance that can be attributed to genetic rather than strictly environmental factors. Most often it is estimated by comparing monozygotic and dizygotic twins [34]. Although there remains controversy in how purely genetic these calculation are [35] and the best way compute heritability [36] we chose to calculate heritability in two ways. First, using the classical approach, the proportion of variance attributed to additive genetic factors (narrow sense heritability) was estimated by doubling the difference in correlation between MZ and DZ twins. This approach provides a simple and reliable index for twin studies which vary across time and culture [37]. This method however, is ineffective at disentangling non-additive genetic factors and epistatic components as well and unique and shared environmental components. Table 3 shows the efficiency of the conflict network is heritable ($h_F^2 = 0.89$, $h_H^2 = .62$) while low heritabilities were observed for alerting and median reaction time ($h_F^2 = 0.18$ and 0.16 respectively, and $h_H^2 = 0.14$ and 0.24 respectively). The orienting response shows no evidence of heritability. The orienting response shows a higher correlation in DZ twins than MZ twins

Table 3: Heritability estimates for three attentional networks and mean RT

Heritability measure	Alerting	Orienting	Conflict	RT
$h_F^2 = 2(r_{MZ} - r_{DZ})$.18 (-.73, 1.10)	-.59 (-1.56, .41)	.89 (.09, 1.70)	.16(-.42, .75)
$h_H^2 = (r_{MZ} - r_{DZ}) / (1 - r_{DZ})$.14	-.49	.62	.24
ML fit:				
H	.43 (-.85, .85)	.00 (-.69, .69)	.85 (.29, .93)	.40(-.90, .90)
h^2	.18	.00	.72	.16
c	.53 (-.79, .79)	.50 (-.70, .70)	.00 (-.72, .72)	.76(-.90, .90)
c^2	.28	.25	.00	.58
e	.73 (.53, .91)	.86 (.70, 1.00)	-.53 (-.73, -.38)	-.51(-1.00,-.36)
e^2	.53	.74	.28	.26

Note: Confidence intervals of h_F^2 were estimated based on Appendix 6 (reference[54]); h_H^2 was cited in (reference[55]); ML, Maximum Likelihood fit, (reference[56]); h: path coefficient for additive genetic; c: path coefficient for shared environment; and e: path coefficient for specific environment.

In addition to the classical estimation of h^2 , we applied the structural equation modeling package Mx [38] which allows the explicit representation of observed and latent variables. The advantage of this method lies in the ability to best fit the observed data according to path models that hypothesize varying degrees of additive and non-additive contributions as well as shared and unique environmental contributions. We chose a conservative approach, setting, the expected genetic correlation among DZ twins, to 0.5 and used the standard twin analysis path. Table 3 shows the heritability estimates for three attentional networks and mean RT (and 95% confidence limits). The contributions to the additive genetic variance (h^2), common environmental variance (c^2) and unique environmental variance (e^2) values are given. Interestingly, the h^2 s were in agreement with those calculated using the classical approach. The effect of conflict was highly heritable ($h^2 = 0.72$) while low heritabilities were observed for alerting and reaction time and ($h^2 = 0.18$ and 0.16 respectively).

Discussion

Because of the small Ns involved in this study, only the effect of conflict is significantly different than 0 and this is due to the very small correlation found in the DZ twins. The correlation among DZ twins in conflict is suspiciously low because it is a smaller number than for any of the other networks this, of course, would inflate the overall heritability of the conflict network. To compare the heritability of the various networks would take a much larger study. For example, a power calculation suggests that with the current size of the effect it would take more than 600 pairs to reach significance for the alerting network.

Nonetheless there is some indication favoring the heritability of the executive network. The heritability of the executive network has been observed in other conflict tasks such as the Stroop color-word task [39] which also activates the cingulate and other frontal areas [6]. However, the flanker task has an advantage over the Stroop in that it does not involve language and our results show considerably higher heritability.

The heritability of reaction time has also been observed in other twin studies on normal subjects [25]. In genetic studies where cognitive assays for executive control or general intelligence depend on reaction time measures, the heritability of lower levels of processing involved in RT may thus influence the performance scores. To avoid this we normalized all efficiency scores as a function of median RT.

There have been no reported twin studies on the alerting response *per se*, but this function, namely the maintenance of the alert state is inherently a part of many neu-

ropsychological tasks. Interestingly, studies on depression and mood have shown deficits in simple reaction time tasks in patients that report sadness or depression [40,41]. These RT deficits are specific to left visual field (right hemisphere) and are consistent with the right frontal and parietal networks involved in alerting. Changes in the efficiency of the alerting network as a consequence of mood and depression are further supported by the findings of Liotti and Tucker [42] where subjects induced into sadness showed no improvement in RT when given alerting cues before target stimuli were presented. The mean probandwise MZ concordance rate for unipolar depression (40%) is more than twice that for DZ twins (17%) [43] as well as for narrowly defined depression (50%:29%) [44] suggesting the presence of genetic determinants.

In our study there is no evidence of heritability for the orienting network. This may be because of low power of this small study. There is evidence that genes can influence orienting in a task similar to ours. Alzheimer's Disease is a heritable condition with a well described visual orienting deficit and where associations have been found in unaffected relatives between visual orienting and the *apoe* gene [28]. In order to keep the ANT simple the peripheral orienting cues are 100% valid. This differs from similar tasks of visual orienting where usually only 80% of the orienting cues are valid. In the visual orienting studies of Greenwood *et al.*, [28] the association with the *apoe* gene was observed only when this validity manipulation was utilized. It is possible that the use of 100% validity and the lack of any specific instruction may have made use of the cues a matter of individual strategy and thus both relatively unreliable and less subject to genetic influences. Future genetic studies may be more fruitful when the validity manipulation is included in the ANT.

While it is likely that our failure to find any evidence of heritability of the orienting network is due to either the small scale of our study or weaknesses in our assay, it is certainly possible that low correlations among MZ twins reflects differential experiences that these twin pairs undergo [45].

The advantage of using an endophenotypic measure can be extended when information about the neuroanatomy physiology and development underlying performance on the task is available. Knowledge of brain structures involved in performance will serve to constrain candidate gene identity and function and thus facilitate the integration of genetic information. In the case of the executive attention network, multiple imaging studies have shown activation of midline and lateral frontal areas. These areas are strongly modulated by dopamine and suggest the importance of examining genes that modulate

dopamine. One of these genes the dopamine D4 receptor gene has been repeatedly associated with attentional disorders (see [46] for a review). While one allele of this gene (the 7 repeat) has been found not to be associated with abnormalities in interference in the Stroop effect, it is reasonable to examine other variants of this gene and other genes related to the dopamine system.

Studies of human development have shown that the executive attention network is related to effortful control as measured from caregiver reports of their child's behavior [47]. Effortful control has also been shown to be heritable in twin studies [27] using larger numbers of subjects and has been linked by behavioral studies to the ability to delay gratification, development of conscience and other aspects of self regulation [48].

Conclusions

We have developed phenotypic measures for the three aspects of attention: alerting, orienting and executive control that have been the best described anatomically. Our small scale preliminary study of twins suggests that at least the dopamine rich executive network is appropriate for use in molecular genetic studies.

Materials and Methods

Subjects

Twenty six MZ twin pairs and 26 DZ same sex pairs participated in the study. Twins were recruited in the vicinity of Peking University via newspaper advertisement. Paid volunteer pairs traveled to the Department of Psychology to undergo a pre-test interview by a resident psychologist. Subjects with a history of psychopathology and/or taking medication were excluded. A total of 60 twin pairs interviewed, 52 aged matched pairs from ages 14–42 years old met inclusion criteria. All participants reported normal or corrected to normal vision. Zygosity status was determined by close inspection of physical features, birth records, parental interview and genotyping of buccal swab DNA at 6 polymorphic genetic loci: *maoa*, *drd3*, *dbh*, *maoa*, *b1adr* and *gsalpha*[49–53].

Procedure

The ANT was performed as previously described [31]. Briefly, participants viewed the stimuli and responses were collected via two response buttons. Stimuli consisted of a row of 5 visually presented horizontal black lines, with arrowheads pointing leftward or rightward, against a gray background where the target was a leftward or rightward arrowhead at the center. This target was flanked on either side by two arrows in the same direction (congruent condition), or in the opposite direction (incongruent condition), or by lines (neutral condition).

The participants' task was to identify the direction of the centrally presented arrow by pressing one button for the left direction and a second button for the right direction. Cues consisted of a 100 msec asterisk presented 400 msec before the target. There were four cue conditions: (1) no-cue, participants were shown a cross which was the same as the first fixation for 100 ms; (2) central-cue, which was at the central fixation point; (3) double-cue, in which cues were presented on the two possible target locations simultaneously (both above and below the fixation point); and (4) spatial-cue, cue was presented right on the target location (either above, below the central fixation point).

A session consisted of a 24-trial practice block and three experimental blocks of trials. Each experimental block consisted of 96 trials (48 conditions: 4 warning levels x 2 target locations x 2 target directions x 3 congruency conditions, with 2 repetitions). The presentation of trials was in a random order. Participants were instructed to focus on a centrally located fixation cross throughout the task, and to respond as fast, also as accurately as possible. Twin pair participants performed 2 sessions of the ANT allowing a break in between sessions while the other member of the pair performed the task.

Calculation of attention network efficiencies

Values for attention network efficiency were calculated from the raw reaction time data as previously described [31]. Medians were calculated for each test conditions (12 conditions in total: 4 cue levels by 3 target levels, combined target locations and target directions) to avoid the influence of the outliers. The alerting effect was calculated by subtracting the mean RT of the conditions with double cue from the mean RT of the conditions with no cue. Since neither of these conditions provides information on the spatial location of the target, the subtraction gives a pure measure of alerting. The orienting effect was calculated by subtracting the mean RT of the conditions with spatial cue from the mean RT of the conditions with center cue. In both conditions the subject is alert but only the spatial cue provided spatial information on where to orient. The conflict (executive) effect was calculated by subtracting the mean RT of congruent conditions from the mean RT of incongruent conditions.

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