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Assessing the heritability of attentional networks

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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

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

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.

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
$h^2_F = 2\,(r_{MZ} - r_{DZ})$	.18 (-.73, 1.10)	-.59 (-1.56, .41)	.89 (.09, 1.70)	.16(-.42, .75)
$h^2_H = (r_{MZ} - r_{DZ})/\,(1 - r_{DZ})$	.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^2_F were estimated based on Appendix 6 (reference[54];) h^2_H 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^2s 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 0.19 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 900 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 [9]. 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 neuropsychological 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 response 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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