Contributions of Genetic Variation in *CHT1* to Human Attention

by

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A Thesis Submitted in Partial Fulfillment of the

Requirements for the Degree of Bachelor of Arts

With Honors in Psychology from the

University of Michigan

2010

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Abstract

This study examined the contributions of genetic variation to individual differences in ability to pay attention. Specifically, we examined a subcapacity version (Ile89Val) of the high affinity choline transporter, a protein important in regulating the brain's acetylcholine levels, and tested the hypothesis that it would influence the ability to modulate attention. In Experiment 1, subjects were genotyped for this mutation, and completed questionnaires addressing attentional capacity. In Experiment 2, a subset of subjects heterozygous for the Ile89Val mutation and homozygous wild-type controls were brought back to complete the Attention Network Task. Results revealed a significant effect of genotype on self-reported tendency towards lapses of attention (as measured by the Distractibility measure of the Short Imaginal Processes Inventory). Moreover, genotype played a significant role in determining the magnitude of a subject's alerting effect on the ANT. Our results suggest that even a single nucleotide change in *CHT1* may be important for determining an individual's attentional ability.

Contributions of Variation in *CHT1* to Human Attention

Everyone experiences some degree of mind wandering and inattention from day to day, but individuals differ in their ability to control these tendencies. Part of this diversity may be attributable to genetic variation. Several studies have identified specific genetic components that contribute to pathologies of attention. For example, attention-deficit hyperactivity disorder has been linked to genes involved in the regulation of both norepinephrine and dopamine (Bobb et al., 2005; Kim et al., 2006; Roman et al., 2002). However, comparatively little work has been done to investigate the specific impact on human attentional capacity of another major neurotransmitter, acetylcholine. In the present study, we used a community sample to examine whether variation in a gene thought to regulate the efficiency of the cholinergic system may be related to variation in attention and mind-wandering. Although the gene in question has not been identified as a direct cause of any clinical disorders, it may contribute to normal variation in attentional control and increase the risk for disorders of attention including attention-deficit hyperactivity disorder.

The high-affinity choline transporter gene (*CHT1*) is involved in the regulation of acetylcholine (ACh), which is one of the primary neurotransmitters involved in modulating cognitive functions such as attention, memory, and optimization of task performance. Disruption of the cholinergic system may be implicated in disorders like schizophrenia and ADHD (Sarter, Nelson, & Bruno, 2005). Animal studies have shown that tasks demanding high levels of attention for sustained periods lead to increased release of ACh (Arnold, Burk, Hodgson, Sarter, & Bruno, 2002; Himmelheber, Sarter, & Bruno, 2000; Sarter, Hasselmo, Bruno, & Givens, 2005); thus, decreases in ACh regulation should be associated with inattention.

CHT1 may influence ACh function by affecting the rate at which the neurotransmitter can be produced. After ACh is released into the synapse, it is degraded into inactive metabolites – choline and acetate – by acetylcholinesterase. Choline is then taken back up into the cell, and recycled to synthesize new ACh in a reaction catalyzed by choline acyltransferase. The rate-limiting step in this process is thought to be the uptake of choline through the CHT1 protein (Okuda, Okamura, Kaitsuka, Haga, & Gurwitz, 2002). As a result, the rate of transport through CHT1 should be closely tied to the capacity of the cortical cholinergic system in mediating attention.

In the present study, we examine the impact that a single nucleotide polymorphism of the *CHT1* gene (Ile89Val; identified by Okuda et al., 2002) may have on attentional function. This polymorphism is thought to decrease the rate of choline transport in mammalian cells by 40-50%. Possessing this sub-capacity CHT1 variant may decrease a human subject's ability to maintain elevated levels of ACh, thus potentially impairing performance in situations demanding high attentional control. This research will compare the performance of subjects possessing a copy of the Ile89Val polymorphism to those who are homozygous for the wild type allele (Ile/Ile) in order to determine the overall functional significance of variation in *CHT1* on human attentional capacity.

Experiment 1

Experiment 1 focused on genotyping a sample of community participants in order to identify the presence of the Ile89Val mutation. In addition, participants were administered a battery of questionnaires in order to obtain data on self-reported attentional capacity and liability for cognitive failures.

Method

Participants. DNA from 164 participants (93 female; mean age = 38.4 years, *SD* = 12.2 years) was genotyped for the Ile89Val mutation. All subjects were between the ages of 18 and 60; none were excluded on the basis of medical or mental health conditions. Permanent residents of the Ann Arbor area were targeted, to ensure that participants would be available to return for follow-up tests if needed. A majority of participants (*n* = 147) completed full testing sessions involving both DNA collection and a battery of standardized questionnaires. These sessions lasted approximately 30 minutes to one hour, and were compensated at the rate of $15/hour. The remainder (*n* = 17) were University of Michigan faculty and staff members who opted to participate in uncompensated, shortened sessions involving only DNA collection.

Materials and Apparatus. DNA was obtained via saliva samples, using Oragene-DNA OG-250 disc format collection kits from DNA Genotek. The questionnaire battery included the Thought Occurrence Questionnaire (TOQ; I. Sarason, B. Sarason, Keefe, Hayes, & Shearin, 1986), Cognitive Failures Questionnaire (CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982), Behavioral Inhibition System/Behavioral Activation System Scales (BIS/BAS; Carver & White, 1994), items from the Poor Attentional Control scale of the Short Imaginal Processes Inventory (SIPI; Huba, Singer, Aneshensel, & Antrobus, 1982), and the Extended Range Vocabulary Test (ERVT; Educational Testing Service, 1976).

The TOQ contains 28 items related to the general tendency towards inattention due to intrusive thoughts on a day to day basis. Its three factors address thoughts of social relations or emotions that are unrelated to the task at hand, thoughts of escape from a task, and task-relevant worries. The CFQ contains 25 items about self-reported failures in perception, memory, and motor function; it was designed to measure general liability to everyday errors. The BIS/BAS is comprised of 24 items pertaining to four separate measures. One factor specifically relates to the

sensitivity of the behavioral inhibition system. The other three address separate aspects of the behavioral activation system: reward responsiveness, drive, and fun seeking. The SIPI, adapted from Singer and Antrobus (1966), assesses three scales: Positive-Constructive Daydreaming, Guilt and Fear-of-Failing Daydreaming, and Poor Attentional Control. We focused on the 15 items from the Poor Attentional Control scale, which were drawn from the Mind Wandering, Boredom Susceptibility, and Distractibility scales of the full Imaginal Processes Inventory (Singer & Antrobus, 1966). The TOQ, CFQ, and SIPI all contain items rated on a 5-point Likert scale, while the BIS/BAS uses a 4-point Likert scale. Finally, the ERVT tests verbal ability, providing a measure of general cognitive functioning that is unrelated to the specific capacity or failures of attention.

Procedure. All participants first completed written consent procedures, as outlined by the University of Michigan's Institutional Review Board. They next completed a short health and demographics questionnaire and then gave saliva samples.

Subjects refrained from eating or drinking for 30 minutes before donating saliva, and rinsed their mouths with water for 30 seconds immediately prior to collection. Participants were instructed to spit into the kits until the saliva reached a level indicated by a line inside the cup (approximately 2 mL). No time limit was imposed for saliva collection. Once donation was complete, subjects tightly capped the containers to release a preserving solution, and gently inverted the kits several times to mix this solution with the saliva sample. Samples were stored at room temperature and later shipped to Vanderbilt University for processing by a collaborating lab (PI: Dr. Randy Blakely).

Subjects who elected to participate in full study sessions were given the battery of standardized questionnaires described above. Completion of these questionnaires was self-paced.

Results

Genotyping identified 144 participants who were homozygous for the wild-type allele (79 female; average age = 38.5 years, *SD* = 12.2 years); 19 heterozygotes, possessing one copy of the wild-type-allele and one copy of the Ile89Val mutation (14 female; average age = 37.1 years, *SD* = 12.2 years); and one participant homozygous for the Ile89Val mutation (male; age 53). These totals yielded a frequency of 6.4% for the Ile89Val allele in the study population, in line with previous findings which also show a 6% frequency for this allele (English et al., 2009; Okuda et al. 2002). We then examined Ile89Val frequency by race and ethnic group as indicated on the demographics questionnaire (see Table 1). Of the 19 heterozygotes, 16 indicated their race as "White/Caucasian," and 3 indicated "Asian." The frequencies of Ile89Val in the White/Caucasian and Asian groups were 6.3% and 11.5% respectively. The single subject homozygous for Ile89Val indicated his ethnicity as "Hispanic/Latino." Since there was only one homozygous IIe89Val participant, all subsequent analyses focused on the heterozygotes and the homozygous wild-type controls.

Independent samples t-tests were run to compare means on various questionnaire measures between the group of 19 heterozygotes and 128 homozygous wild-type controls who completed questionnaires (72 female; mean age = 37.9 years, *SD* = 12.5 years). Individuals were excluded on a case-by-case basis for each analysis if they failed to complete a particular questionnaire. In general, results revealed that both groups were non-different on most

measures: no significant differences existed on various factors of the TOQ, the CFQ, any measure of the BIS/BAS, or the ERVT (see Table 2).

However, data from the SIPI did suggest group differences (see Figure 1). Heterozygotes tended to score higher on the Poor Attentional Control scale of the SIPI than controls, with $t(144) = 1.77$, $p = .08$. The mean scores were 45.5 ($SD = 10.8$) and 41.0 ($SD = 10.3$) respectively. We then broke these scores down into subcomponents, examining the total scores for the Mind Wandering, Boredom Susceptibility, and Distractibility subscales. Heterozygotes showed a trend of higher scores on Mind Wandering, with $t(144) = 1.71$, $p = .09$, but were not significantly different from controls on Boredom Susceptibility. Mean scores on Mind Wandering were 16.6 ($SD = 5.1$) for heterozygotes and 14.6 ($SD = 4.3$) for controls. Finally, the heterozygotes scored higher on Distractibility, with a mean of 16.0 ($SD = 3.6$), compared to controls ($M = 13.9$, $SD = 4.2$). This difference was significant, with $t(144) = 2.09$, $p < .05$.

Discussion

Experiment 1 showed that the Ile89Val mutation occurs at a low but detectable rate in a community sample, consistent with previous findings. Possessing even one copy of the Ile89Val mutation does seem to have a significant impact on everyday attentional capacity, as evidenced by the group differences in SIPI Distractibility scores. Moreover, the pattern of results seen in the SIPI Poor Attentional Control subcomponents suggests a specificity of effects – subjects possessing the Ile89Val polymorphism reported increased tendencies towards both mind wandering and distractibility, but were non-different in their reported susceptibility to boredom from homozygous wild-type controls. Additionally, the fact that ERVT scores were not different between groups emphasizes that heterozygotes are specifically impaired in certain domains of attention, rather than showing a blanket decrease in cognitive ability. Results from Experiment 1

thus suggest a significant effect of *CHT1* genotype on an individual's self-perceived attentional ability. To extend the findings of this experiment, further work is needed to determine whether these disruptions in everyday attentional processes translate to measurable differences on controlled laboratory tests of attention.

Experiment 2

Results from Experiment 1 demonstrated between-group differences in self-reported attentional capacity. As a follow-up, a subset of participants from Experiment 1 was brought back to determine whether these group differences persisted in laboratory measures of attention based on accuracy and reaction time.

Method

Participants. Experiment 2 compared a group of 15 heterozygous subjects possessing one copy of the Ile89Val allele and one copy of the wild-type allele (11 female; mean age = 38.5 years; *SD* = 12.3 years) to a group of 18 homozygous wild-type controls (13 female; mean age = 39.1 years; *SD* = 11.5 years). Controls were selected to be age-matched to heterozygotes within three years; two of the controls included in these analyses were matched to heterozygotes who had not yet completed testing at the time of writing. Data from one control participant were discarded due to outlying performance (see below). In the sample used for analysis here, the two groups were closely matched in age (heterozygous *M* = 38.5, *SD* = 12.3, range = 22-58; controls *M* = 38.3, *SD* = 11.3, range = 24-57). Controls were also pre-screened to exclude participants with medical conditions or mental health issues that might affect attention, such as anxiety or depression. Due to the very small number of participants possessing a copy of the Ile89Val allele who met these criteria, heterozygous subjects were *not* screened for medical or mental

health conditions. Moreover, work by our collaborators and others suggest that the variant may be more common in ADHD (English et al., 2009) and depressed (Hahn et al., 2008) populations.

Materials and Apparatus. We administered the Attention Network Task (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002), which provides measures of three different dimensions of attention: alerting, orienting, and executive control. Instructions were expanded slightly from the original task, but the task design and specific visual stimuli used remained the same.

Stimuli were presented on a personal computer running Windows XP, using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). They were displayed on a 17-inch monitor with resolution set to 1024x768 pixels for the duration of the experiment. Participants sat at a fixed distance of 60 cm away from the screen, so that a single arrow or line subtended a visual angle of 1.1°. A full row consisting of a central arrow and four flanking stimuli subtended a visual angle of 6.3°.

A small fixation cross was presented at the center of the screen throughout the entire experiment. Targets consisted of a single arrow pointing either right or left; these were surrounded by two flanking stimuli (either arrows or horizontal lines) to either side. Targets were horizontally centered and appeared in one of two locations: either 30 pixels above, or 30 pixels below the center of the screen. As outlined by Fan et al. (2002), each trial consisted of 1) a fixation period with a duration varying randomly between 400-1600 ms; 2) a warning event lasting 100 ms; 3) a second, brief fixation period (400 ms); 4) target presentation, lasting until a response was made (up to a maximum of 1700 ms); and 5) a post-trial fixation period with a duration depending on the durations of pre-trial fixation and target presentation, which brought the total trial duration up to 4000 ms (see Figure 2).

On all trials, participants received one of four different types of warning cues prior to target presentation: no cue, center cue, double cue, and spatial cue. The no-cue condition consisted of an additional 100 ms of fixation. In double-cue trials, the target was preceded by two asterisks presented together for 100 ms, one at each of the two possible target locations. Center-cue trials displayed a single asterisk in the center of the screen, briefly replacing the fixation cross. Finally, the spatial cue consisted of a single asterisk presented at only one of the possible target locations; half were presented above fixation, and the other half below. Spatial cues were always valid predictors of target location. Executive load was varied using three different flanker types: incongruent (one central arrow surrounded by flanking arrows pointing in the opposite direction from the target), congruent (the central arrow and flankers pointed in the same direction), and neutral (with nondirectional horizontal lines surrounding the target).

Performance measures (primarily reaction time) from the different warning and flanker types can be entered into formulae described by Fan et al. (2002) to obtain scores thought to relate to the function of different attention and brain networks (Posner & Rothbart, 2007). Alerting was measured by comparing performance on double-cue trials to no-cue trials, as both conditions were thought to keep attention diffused over the two possible target locations. Orienting was measured by comparing performance on spatial-cue trials to center-cue trials, as both of these conditions were expected to focus attention on a single location. Finally, the executive control measure was calculated by comparing trials with congruent flankers to trials with incongruent flankers. Congruent flanking distractors are generally thought to facilitate responding to the target relative to neutral flankers; conversely, incongruent flanking distractors impede processing of the target (Fan et al., 2002). Thus, subtracting reaction time for congruent

trials from reaction time for incongruent trials provides an assessment of conflict resolution (Posner & Rothbart, 2007).

Procedure. As before, participants first gave written consent and completed a short questionnaire on personal health and demographic information. Instructions for the ANT were displayed on the computer screen and explained verbally by the experimenter. Participants completed a practice session consisting of 24 trials, with feedback about accuracy and reaction time after each trial. Subjects were given the option to repeat this practice session if they did not feel comfortable with the task; however, no participant opted to repeat it. The test session consisted of three blocks, each of which contained 96 trials (two repetitions of all possible combinations of the four cue conditions, two target locations, two possible directions for the target arrow, and three flanker conditions) without feedback. Participants were instructed to take a self-paced break between blocks.

Results

The pattern of results for the SIPI and other questionnaire measures in this subsample were consistent with those found in the larger sample, although the differences in SIPI Distractibility (heterozygotes $M = 15.9$, $SD = 3.7$; controls $M = 13.2$, $SD = 4.7$) were now only marginally significant due in part to the reduced power at this smaller sample size, $t(30) = 1.79$, $p = .08$.

Overall accuracy on the ANT was quite high: mean accuracy for all subjects was 98.2% ($SD = 3.1\%$). One control subject had an average accuracy over five standard deviations below the group mean, and as a result was excluded from subsequent analyses. For the remaining subjects, accuracy ranged from 95%-100%, with a mean of 98.8% ($SD = 1.1\%$); the heterozygous and control groups were not significantly different (see Table 3). Since all subjects

were close to ceiling for accuracy, between-groups comparisons were run using reaction time as the primary outcome measure.

Independent samples t-tests were run to compare group means on various dimensions of the ANT. Heterozygotes and controls did not show significant differences in overall reaction time, nor did they differ on the orienting or executive control measures. The heterozygous group had a mean orienting effect of 57 ms (*SD* = 32 ms) and mean executive effect of 130 ms (*SD* = 49 ms); for controls, the means were 60 ms (*SD* = 32 ms) and 121 ms (*SD* = 60 ms) respectively. Heterozygotes did tend to show a lower alerting effect than controls, with $t(30) = -1.87$, $p = .07$. The group means for this effect were 30 ms (*SD* = 20 ms) and 45 ms (*SD* = 25 ms) respectively.

We next conducted a series of analyses to further explore the tendency towards group differences in the alerting effect and possible moderators of this effect. Two potential moderators of interest were chronological age and SIPI distractibility score.

Recent work by Jennings, Dagenbach, Engle, and Funke (2007) demonstrated a significant effect of age on the magnitude of the ANT alerting effect: older adults (61-87 years) showed a significantly lower alerting effect than did young adults (ages 18-21 years). In line with these findings, when we collapsed across genotype group, we saw a significant negative correlation between age and size of the alerting effect, $r(30) = -.37$, $p < .05$[1]. As described earlier, the two genotype groups also tended to differ on the SIPI Distractibility measure.

A repeated-measures analysis was used to examine the effects of age and SIPI score on potential group differences in alerting, and to examine which component of the alerting score might be affected. This analysis used reaction time on the double-cue trials and no-cue trials as a within-subjects factor, and included SIPI Distractibility scores and age as covariates. Results revealed a significant interaction between ANT measure (double-cue, no-cue) and group

(heterozygote, control), $F(1, 28) = 4.69$, $p < .05$. The estimated marginal means on double-cue trials were similar for both groups, but the heterozygotes were faster on no-cue trials than were the controls (see Figure 3).

Age was a significant covariate, $F(1,28) = 14.19$, $p < .05$, and also interacted significantly with ANT measure, $F(1,28) = 4.37$, $p < .05$. As suggested by the correlation analysis, increased age was associated with a reduction in the difference between the uncued and double-cued conditions. However, whether or not age was included in the model had little effect on whether the ANT score X group interaction was statistically significant. With SIPI Distractibility included in the model as a covariate, the group X ANT interaction was $F(1, 28) = 4.69$, $p < .05$ with age in the model as a covariate; it was $F(1, 28) = 4.72$, $p < .05$ if age was not included as a covariate. Although the SIPI Distractibility score did not interact significantly with ANT, $F < 1$, its presence in the model influenced whether or not the ANT X group effect was statistically significant. As mentioned previously, with age included in the model, the group X ANT interaction was $F(1,28) = 4.69$, $p < .05$ with SIPI Distractibility included as a covariate; this changed to $F(1,28) = 3.94$, $p = .07$ if SIPI Distractibility score was not included. Taken together, these patterns suggest that increased chronological age was related to a reduction in the size of the alerting effect, as described by Jennings et al. (2007), but that this effect did not significantly differ according to genetic group. In contrast, SIPI Distractibility appeared to moderate the relationship between genetic group and alerting.

Discussion

Experiment 2 supported the findings from Experiment 1, again demonstrating a significant effect of *CHT1* genotype on attentional capacity. Moreover, the pattern of specificity of effects seen in Experiment 1 was replicated, since heterozygotes were not different from

controls on measures of orienting or executive control, but were specifically impaired on the alerting dimension of the ANT. This pattern of results seems consistent with the fact that heterozygotes reported themselves to be more liable to inattention from Experiment 1. Orienting is more closely related to using sensory information to direct spatial attention, and the executive control measure of the ANT involves conflict resolution between incongruent flankers and the direction of the target arrow (Posner & Rothbart, 2007); however, neither directly involves distraction. Posner and Rothbart have defined alerting as "achieving and maintaining a state of high sensitivity to incoming stimuli." In Experiment 1, heterozygotes tended to score higher on the SIPI Mind Wandering subscale, and had significantly higher scores on the Distractibility – the sorts of attentional lapses and distractions addressed on these subscales might potentially match up with lapses in sensitivity to stimuli, and thus explain the group differences in alerting.

When we examined the ANT alerting measure further, heterozygotes were seen to be faster to respond to no-cue trials than controls. However, they were not able to speed up on double-cue trials to the same extent as controls, who showed a greater difference in reaction time between the two warning types. There are two potential interpretations of this pattern. One is that individuals with the variant allele may show a form of hypervigilance, since they are relatively fast to respond to the stimulus onset even without a warning cue. The other possibility is related to the suggestion of Jennings et al. (2007) that older adults overall have a reduced sensitivity to the warning cue and thus show fewer benefits from it; similarly, young adults who possess the variant allele may thus also have a reduced sensitivity to the cue and fail to benefit from the warning. In other words, possessing the Ile89Val mutation may have a "premature aging" effect on young adults. Further testing is needed to distinguish between these two hypotheses.

In addition, future work is needed to determine in which other dimensions of attention, if any, subjects with a copy of the Ile89Val allele are impaired. Follow-up testing to this study includes a rapid visual serial presentation paradigm testing contingent attentional capture, developed by Moore and Weissman (2009), which may provide a better laboratory approximation of liability to distraction. Other potential avenues for future research might include fMRI scans of subjects completing the ANT, which could provide insights into how the subcapacity variant of CHT1 might affect functional connectivity between brain regions in the various networks underlying the alerting, orienting, and executive control dimensions of attention. The results of this study highlight the importance of ACh in modulating human attention, and suggest that even a single nucleotide change can lead to observable differences in performance; future work would help to clarify the exact mechanisms and extent of these differences.

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Footnotes

[1]Although it was not the primary question of interest for this paper, we used linear regression analyses to better understand the effects of chronological age. Consistent with typical findings of age-related slowing (e.g., Salthouse, 1996), age was correlated with reaction time in both the no-cue ($r = .51$, $p < .01$) and double-cue ($r = .58$, $p < .001$) conditions. A linear regression analysis found that reaction time in the no-cue condition was the major predictor of reaction time in the double-cue condition, ($R^2 = .91$, $b^* = .89$, $t = 15.10$, $p < .0005$), and that age added a small but significant amount of predictive power even after accounting for no-cue reaction time (R^2 change = .01, $b^* = .12$, $t = 2.71$, $p < .05$). These results are consistent with the idea that with increased age, participants became slower in the double-cued condition (benefitted less from cueing) than would be predicted based on their no-cue reaction time.

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Many thanks to my research advisor, Dr. Cindy Lustig, for her guidance (and patience) in completing this research and preparing this paper. I also thank Elise Demeter for her advice in conducting experiments. In addition, I thank my peers in the Honors program, particularly Mary Winters and Halle Zucker, and my family members for their advice and support during this process. Finally, this research was supported in part by funding from the Tanner Memorial Award, and I received further financial support with the Anne Rudo Memorial Scholarship, both of which were extremely helpful to me for completing this project.

Table 1

Number of Subjects by Genotype, Broken Down by Race and Ethnicity

	Total	Homozygous (Wild-Type)	Heterozygous	Homozygous (Ile89Val)
N	164	144	19	1
Ethnicity				
Not Hispanic/Latino	157	138	19	0
Hispanic/Latino	6	5	0	1
Other/Unknown	1	1	0	0
Race				
American Indian/ Alaskan Native	3	3	0	0
Asian	13	10	3	0
Black/African American	17	17	0	0
White/Caucasian	127	111	16	0
Other/Unknown	4	3	0	1

Note. "Other/Unknown" collapses across subjects who selected "Other" and those who declined to respond.

Table 2

Between-Group Comparisons of Questionnaire Scores for Experiment 1

	Heterozygotes		Controls				
	M	*SD*	*M*	*SD*	*t*	*df*	*p*
TOQ Factor 1	21.4	9.6	19.6	9.0	0.74	138	0.46
TOQ Factor 2	8.1	6.6	7.0	5.4	0.76	138	0.45
TOQ Factor 3	5.9	6.9	15.9	6.4	0.01	138	0.99
TOQ Total Score	45.3	20.2	42.5	18.5	0.57	138	0.57
CFQ	30.7	13.9	36.5	14.6	-1.62	143	0.11
BAS Drive	11.2	3.2	11.8	6.1	-0.43	144	0.67
BAS Fun Seeking	12.0	2.5	11.8	2.4	0.33	144	0.74
BAS Reward Responsiveness	17.7	1.6	17.7	2.2	0.07	144	0.94
BIS	21.2	4.9	20.2	4.2	0.78	144	0.44
SIPI Mind Wandering	6.5	5.1	14.6	4.3	1.71	144	0.09
SIPI Boredom Susceptibility	13.0	3.9	12.5	4.0	0.53	144	0.59
SIPI Distractibility	16.0	3.6	13.9	4.2	2.09	144	0.04
SIPI Poor Attentional Control (Total)	45.5	10.8	41.0	10.2	1.77	144	0.08

Table 3

Group Means for Reaction Time (RT) and Accuracy by Warning Type and Flanker Condition

	Heterozygotes[a]				Controls[b]			
	RT (ms)		Accuracy		RT (ms)		Accuracy	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Cue Type								
No	634	85	0.99	0.01	646	65	0.98	0.02
Double	604	90	0.98	0.02	601	73	0.99	0.02
Center	607	82	0.98	0.02	609	75	0.99	0.01
Spatial	550	88	0.99	0.02	549	84	0.99	0.01
Flanker Type								
Congruent	558	82	1.00	0.01	565	58	1.00	0.01
Neutral	553	78	0.99	0.01	556	65	0.99	0.01
Incongruent	687	101	0.97	0.04	686	105	0.97	0.03
Calculated Measures								
Alerting	30	20			45	25		
Orienting	57	32			60	32		
Executive	130	49			121	60		

Note. Analyses focused on RT for calculating alerting, orienting, and executive measures; thus, only these values are presented.

[a]n = 15. [b]n = 17.

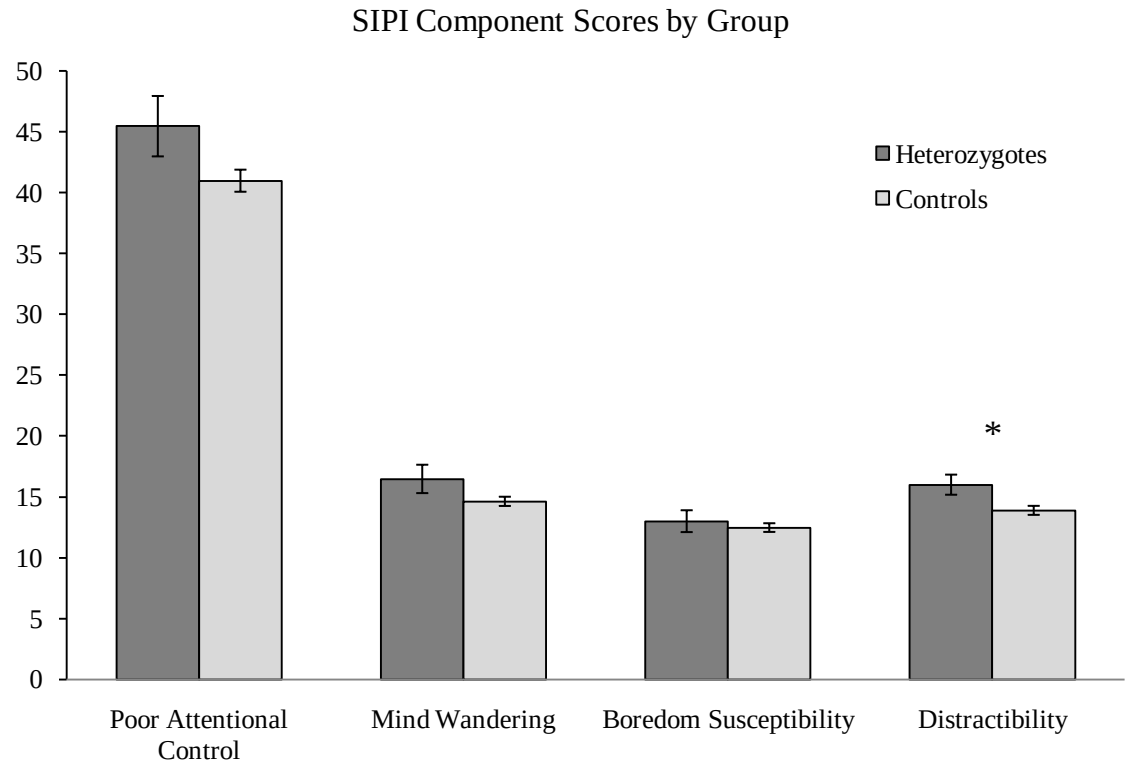

Figure 1. SIPI component scores by group. Heterozygotes tend to have higher Poor Attentional Control scores, with $t(144) = 1.77$, $p = .08$, and higher Mind Wandering scores, with $t(144) = 1.71$, $p = .09$ than controls. The two groups are not significantly different on Boredom Susceptibility. The asterisk (*) indicates that heterozygotes do score significantly higher than controls on the Distractibility subcomponent, with $t(144) = 2.09$, $p < .05$.

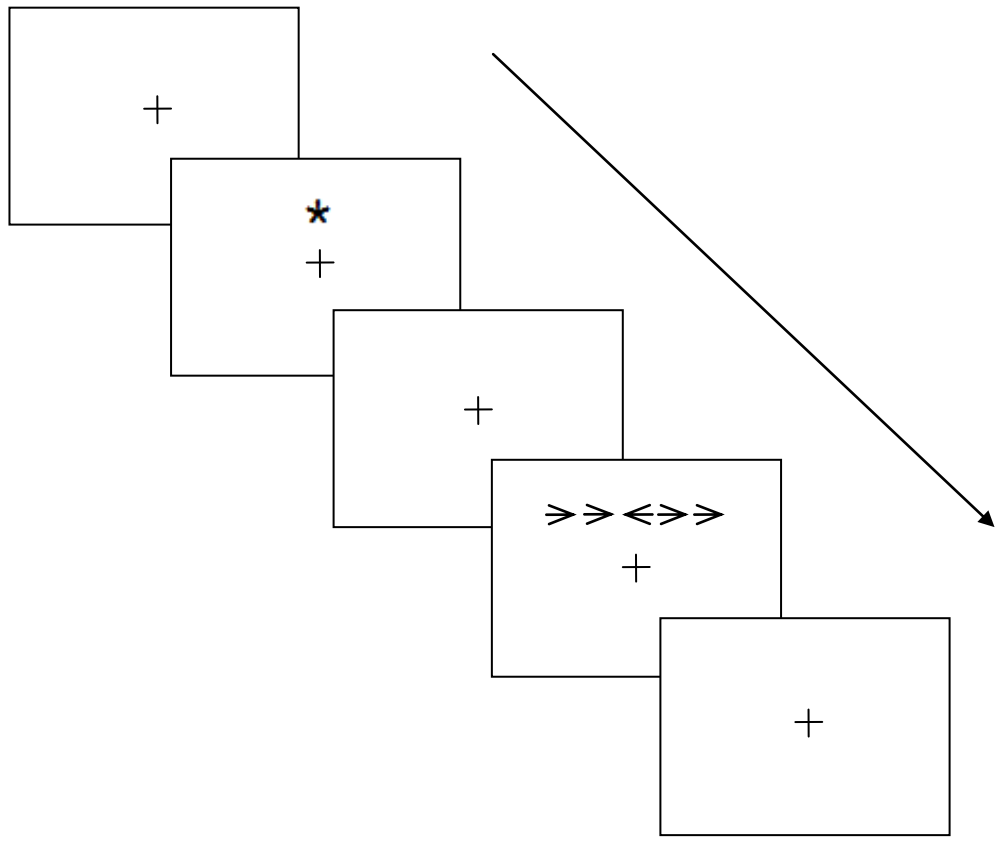

Figure 2. Sample trial progression for ANT

1) Initial fixation period; duration varies randomly between 400-1600 ms

2) Warning event (100 ms)

3) Second, brief fixation period (400 ms)

4) Target presentation, lasting until a response is made (up to a maximum of 1700 ms)

5) Post-trial fixation period. Duration varies depending on the durations of pre-trial fixation and target presentation, to bring total trial duration up to 4000 ms

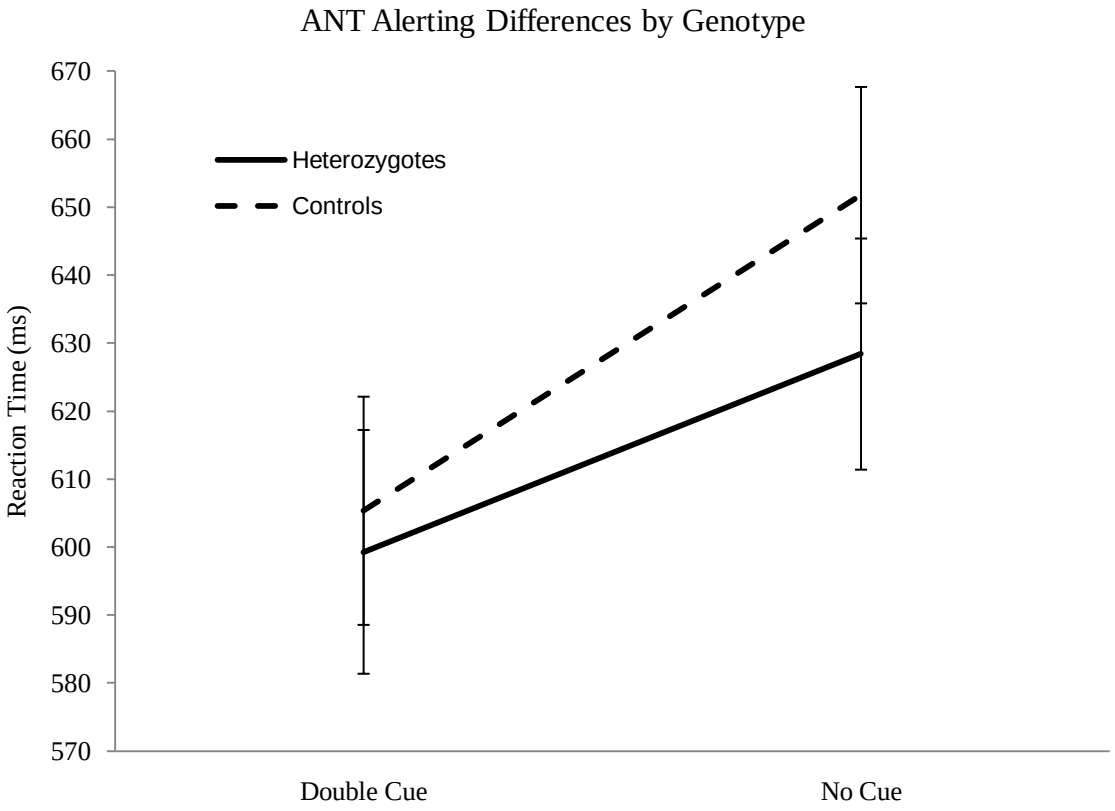

Figure 3. Components of the ANT Alerting measure by genotype (estimated marginal means). A repeated measures analysis revealed a significant interaction between ANT alerting component (double cue, no cue) and genotype group (heterozygotes, controls) when age and SIPI Distractibility scores were included as covariates, $F(1, 28) = 4.69$, $p < .05$.

Both heterozygotes and controls are similarly fast on double-cue trials, but heterozygotes are faster on no-cue trials. This pattern suggests that heterozygotes may either be hypervigilant, or show a decreased sensitivity to the warning cue and thus do not speed up to the same extent as controls.

Appendix

Items from the SIPI Poor Attentional Control Scale by Component

Items are rated on a 5-point Likert scale ranging from 1 ("definitely untrue or strongly uncharacteristic of me") to 5 ("very true or strongly characteristic of me"). Forward-scored items are indicated with (+); reverse-scored items are indicated by (-).

Mind Wandering
(+) I am the kind of person whose thoughts often wander.
(-) My mind seldom wanders from my work.
(+) No matter how hard I try to concentrate, thoughts unrelated to my work always creep in.
(-) My thoughts seldom drift from the subject before me.
(+) I have difficulty maintaining concentration for long periods of time.

Boredom Susceptibility
(-) I tend to be quite wrapped up and interested in whatever I am doing.
(+) I find that I easily lose interest in things that I have to do.
(-) I am seldom bored.
(-) I can work at something for a long time without feeling the least bit bored or restless.
(+) I tend to be easily bored.

Distractibility
(-) I am not easily distracted.
(-) My ability to concentrate is not impaired by someone talking in another part of my house or apartment.
(+) I find it difficult to concentrate when the TV or radio is on.
(+) Faced with a tedious job, I notice all the other things that I could be doing.
(+) I find it hard to read when someone is on the telephone in a neighboring room.