Disposed to Distraction: Genetic Variation in the Cholinergic System Influences Distractibility But Not Time-on-Task Effects

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Abstract

■ Both the passage of time and external distraction make it difficult to keep attention on the task at hand. We tested the hypothesis that time-on-task and external distraction pose independent challenges to attention and that the brain's cholinergic system selectively modulates our ability to resist distraction. Participants with a polymorphism limiting cholinergic capacity (Ile89Val variant [rs1013940] of the choline transporter gene *SLC5A7*) and matched controls completed self-report measures of attention and a laboratory task that measured decrements in sustained attention with and without distraction. We found evidence that distraction and time-on-task effects are independent and that the cholinergic system is strongly linked to greater vulnerability to distraction. Ile89Val participants reported more distraction during everyday life than controls, and their task performance was more severely impacted by the presence of an ecologically valid video distractor (similar to a television playing in the background). These results are the first to demonstrate a specific impairment in cognitive control associated with the Ile89Val polymorphism and add to behavioral and cognitive neuroscience studies indicating the cholinergic system's critical role in overcoming distraction. ■

INTRODUCTION

"Pay attention!" You may have given yourself this exhortation during a long, boring drive as you realized both your mind and your car were drifting off the road or received it from your conversation partner when they noticed your eyes wandering toward an attractive stimulus walking by. Both extended task periods and external distractors challenge our ability to remain focused on the task at hand, and individuals with psychiatric disorders such as schizophrenia and attention deficit hyperactivity disorder (ADHD) may be especially vulnerable to such challenges. Effective treatment of these vulnerabilities will require a better understanding of whether they reflect general declines in cognitive control or more specific processing deficits and of the underlying neural systems that may be targets for pharmaceutical intervention. Here we present evidence that performance declines caused by time-on-task demands and external distraction are independent and that the cholinergic system plays an especially important role in resisting external distraction.

Intuitively, one might expect that any demand on cognitive control, regardless of its source, would reduce performance, and that compounding such demands would have an especially detrimental effect. That is, external distractors might be especially tempting when one is already having difficulty maintaining attention on an attended task. In turn, competition from external distractors may make it especially difficult to maintain focus, causing steeper time-on-task declines. However, the reality is much more complex. Vulnerability to external distraction is typically increased by cognitive load but decreased by perceptual load (Lavie, 2010; Lavie, Hirst, de Fockert, & Viding, 2004). Time-on-task performance declines have been attributed by some to overloads of attention and by others to underloads of attention (see discussion by Pattyn, Neyt, Heridericlcx, & Soetens, 2008), suggesting opposite predictions for the effects of adding an additional cognitive load in the form of external distraction.

Previous attempts to test potential interactions between distraction and time-on-task effects have yielded ambiguous results. Rosenberg, Noonan, DeGutis, and Esterman (2013) used a continuous performance test (detect female target faces vs. male nontarget faces) that showed significant declines in both accuracy and RT stability over a 12-min period and manipulated whether or not the background consisted of distracting scenes. This manipulation did not affect performance overall or the slope of time-on-task declines, but did alter individual differences factors: Only in the distraction condition did mindfulness scores predict time-on-task declines. In another study, Breckel, Giessing, and Thiel (2011) added motion distractors (moving vs. stationary dots) to a simple signal

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detection task. However, these "distractors" did not affect time-on-task declines on the minute scale and paradoxically alleviated performance declines associated with long intertarget intervals on no distractor (stationary) trials. The distraction manipulation also had no effect on brain activity (measured using fMRI) related to time-on-task effects and intertarget interval. Looking in the other direction, activity related to processing the motion distractors was not affected by time-on-task, and there were mixed results in regions involved in motion processing (some areas increasing, others decreasing) as a function of intertarget interval.

In short, the bulk of the evidence from these studies suggests that time-on-task and external distractor effects are independent. However, the lack of an overall performance decrement as a result of the nominal distractor manipulations in these studies reduces the support for this conclusion. That is, without a reliable main effect of distraction, it is hard to know whether distractor effects might interact with time-on-task effects. The neuroimaging data are also somewhat ambiguous, as it is hard to distinguish which changes represent the engagement of cognitive control to inhibit distractor processing from those that may represent increased distractor processing because such inhibition has failed (see also Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011).

We therefore took a different approach, applying a manipulation that creates robust distractor effects to a task with rapid time-on-task performance declines and asked whether time-on-task and distractor effects might be related to different neuromodulatory systems. This approach also has a translational advantage: Developing effective drug treatments for specific aspects of attentional function will require understanding their links to the neuromodulator systems targeted by such treatments. Time-on-task effects have been linked to genetic variation in the dopaminergic system (Lim et al., 2012); here we asked whether distraction effects might be linked to genetic variation in the cholinergic system.

The basal forebrain cholinergic system projects throughout neocortex and modulates several neurocognitive functions, including both perceptual and goal-driven aspects of attention (e.g., Rokem, Landau, Garg, Prinzmetal, & Silver, 2010; Silver, Shenhav, & D'Esposito, 2008; see Demeter & Sarter, 2013, for a recent review). Although the cholinergic system has been traditionally described as a diffuse neuromodulatory system contributing to arousal, plasticity, and improved signal-to-noise ratio (see Picciotto, Higley, & Mineur, 2012, for a recent review of this evidence), current models suggest that acetylcholine is also capable of mediating specific cognitive operations through spatially restricted signaling (Hasselmo & Sarter, 2011).

In particular, rodent studies indicate that right-lateralized frontoparietal cholinergic circuitry mediates the ability to resist distraction (St. Peters, Demeter, Lustig, Bruno, & Sarter, 2011; Broussard, Karelina, Sarter, & Givens, 2009; Gill, Sarter, & Givens, 2000). When humans are tested in the same paradigm, they show increased right prefrontal activation during the distraction condition, paralleling rodents' increase in right prefrontal acetylcholine levels. Translational studies using human clinical populations (e.g., Demeter, Guthrie, Taylor, Sarter, & Lustig, 2013; Pa et al., 2013) and animal models (see reviews by Lustig, Kozak, Sarter, Young, & Robbins, 2012; Sarter, Martinez, & Kozak, 2009) also suggest that cholinergic pathways play a critical role in the increased vulnerability to distraction seen in neurological disorders including schizophrenia and mild cognitive impairment.

We tested the hypothesis that increased vulnerability to distraction would be associated with genetic variation affecting the high-affinity choline transporter (CHT), which is responsible for transporting choline into the nerve terminal for the synthesis of acetylcholine (ACh). Mice with reduced CHT expression have normal ACh release and choline clearance at baseline but are impaired on both these measures in response to task demands (Parikh, St. Peters, Blakely, & Sarter, 2013). In humans, the Ile89Val variant (rs1013940) of the CHT gene *SLC5A7* reduces the rate of choline transport by approximately 40–60% compared with the major allele (Okuda, Okamura, Kaitsuka, Haga, & Gurwitz, 2002). The frequency of the Ile89Val variant in normal White participants in the United States, ~6% (English et al., 2009), is equivalent to a prevalence of over 10 million individuals. This variant occurs more often in ADHD patients than controls and has been linked to greater symptom severity in depressed patients (English et al., 2009; Hahn et al., 2008).

The link to depression suggests that individuals with the Ile89Val allele might be more likely to engage in rumination and mind-wandering but based on previous human and animal data linking the cholinergic system to distraction, we expected an increased susceptibility to distraction to be their major difference from control participants without the allele. To preview our results, Ile89Val participants showed an increased vulnerability to distraction on both self-report measures and laboratory task performance but were spared on other measures of attentional control, including those involved in maintaining performance over time. These results indicate that time-on-task demands and external distraction tax at least partially dissociable components of cognitive control and that the cholinergic system plays a particularly important role in resisting distraction.

EXPERIMENT 1

Methods

Participants

Six hundred seventeen individuals recruited from the greater Ann Arbor community completed the Poor Attentional Control questionnaire (Huba, Singer, Aneshensel, & Antrobus, 1982; see description below) and contributed saliva samples for genotyping. From this larger pool,

67 Ile89Val heterozygotes were identified and compared with age, sex, and education-matched controls. See Table 1 for demographics.

Genotyping Methods

CHT SNP genotyping was carried out using the procedures described in English et al. (2009). Briefly, DNA was extracted from saliva samples using a commercial DNA isolation kit (Gentra Systems, Minneapolis, MN) as previously described (Mazei-Robinson, Couch, Shelton, Stein, & Blakely, 2005). An allelic discrimination assay was performed in the Vanderbilt Center for Human Genetics Research DNA Resources Core using TaqMan SNP Genotyping Assay reagents (Applied Biosystems, Inc., Foster City, CA). Four nanograms of DNA were used as template in reactions containing 1× TaqMan Universal PCR Master Mix and 900 nM forward (5′-TGTACCAGGTTATGGCCTAGCTT-3′) and reverse (5′-ACTGAGATTTGCACTTTCACTTACCT-3′) amplification primers, 200 nM VIC (5′-CAGGCACCAATTGGATA-3′) and FAM (5′-AGGCACCAGTTGGATA-3′) dye-labeled probes. Thermal cycling (95°C for 10 min, followed by 50 cycles of 92°C for 15 sec and 60°C for 1 min) and product detection were accomplished using the ABI 7900HT Real-Time PCR System (ABI). Quality control analyses showed that the results were consistent with recommended guidelines (e.g., Edenberg & Liu, 2009). The call rate (rate of at which samples could be successfully assigned a genotype) in our sample was >95% with TaqMan, with 100% consistency when TaqMan was compared with gel-based genotyping. No-call TaqMan samples were reanalyzed using gel-based genotyping.

Attention Questionnaire Measure

Trait attention. Participants completed 36 items from the Imaginal Processes Inventory (Singer & Antrobus, 1970). Each item consisted of a statement about cognitive function in everyday life (e.g. "I find it difficult to concentrate when the TV or radio is on"), and participants rated the degree to which they identified with each statement on a scale from 1 to 5. Our analyses focus on the 15 items that make up the Poor Attentional Control (PAC) subscale identified in a later factor analysis (Huba et al., 1982).

The PAC has good internal consistency (coefficient alpha = .83) and test–retest reliability (r = .73; see also Tanaka & Huba, 1985/1986). It can be subdivided into subscales (five questions each) of distractibility, mind-wandering, and boredom. Although Huba et al. (1982) do not provide psychometric data on these subscales, analyses of a large data set from our laboratory (N = 510; see Berry, Li, Lin, & Lustig, 2014) indicate good internal consistency within subscales (mind-wandering coefficient alpha = .84, distraction coefficient alpha = .79, boredom coefficient alpha = .77). The subscales also have reasonable discriminant validity (average correlation between subscale total and items not in that subscale all $r < .49$ compared with items in that subscale all $r > .72$).

Results and Discussion

As illustrated in Table 1, Ile89Val participants reported experiencing more distractibility and mind-wandering in everyday life than did controls, but not more boredom. The groups' equivalence on boredom is important, as it indicates that Ile89Val participants were not simply interpreting the scale differently and marking all items higher than controls.

The Ile89Val participants' higher ratings for distraction were in line with our predictions based on the cholinergic system's role in resisting distraction as described in the Introduction. The higher ratings for mind-wandering were somewhat less expected. However, in everyday life, it may be difficult to disentangle the subjective experiences of mind-wandering and distraction. For example, in factor analyses "I notice all the other things around me I could be doing" groups with the distraction factor and involves external distractors whereas "thoughts unrelated to my work always creep in" groups with the mind-wandering factor and involves only internal experiences. Despite these distinctions on a principled basis (external vs. internal) and in large-scale factor analyses, it is easy to see how they might overlap or become confused in individual participants' self-reports.

Table 1. Demographics and Self-reported Everyday Attention Function (PAC Measures; Huba et al., 1982) for Ile89Val Participants and Controls

	Control	*Ile89Val*	*t Test*	*Effect Size (Cohen's d)*
Age (years)				
M	42.49	42.33	$t < 1$	d = .01
SD	*17.20*	*17.33*	p = .96	
Edu (years)				
M	16.08	16.50	$t < 1$	d = .14
SD	*2.50*	*3.49*	p = .43	
Distractibility				
M	13.43	15.16	t = 2.36	d = .41
SD	*4.04*	*4.43*	p = .02*	
Mind-wandering				
M	12.93	14.45	t = 2.16	d = .36
SD	*3.46*	*4.77*	p = .05*	
Boredom				
M	12.64	12.97	$t < 1$	d = .09
SD	*3.26*	*4.12*	p = .61	

Each group included 67 participants (41 women, 26 men).

*Significant difference between groups.

We therefore conducted a second experiment with a clearer operationalization of external distraction versus other, presumably internal challenges to attentional control and performance, including those that result from extended time on task. In particular, when asked about distractibility, Experiment 1 participants regardless of genotype gave high ratings to items such as "Faced with a tedious job, I notice all the other things around me I could be doing" and "I find it difficult to concentrate when the TV or radio is on." These responses guided the design of the experimental task we used in Experiment 2.

Specifically, we added an external distractor to the Continuous Temporal Expectancy Test (CTET; O'Connell et al., 2009) and examined its effect on overall performance and time-on-task declines. The CTET is a duration judgment task: On most trials, a grid pattern rotates after a standard duration (800 msec), but on target trials it takes slightly longer (1070 msec). Because the grid pattern is the same for target and nontarget trials, there is no bottom–up perceptual change signaling the presence of a target. Instead, duration judgments require continuous, focused attention to time and are exquisitely sensitive to fluctuations in attention; in some cases, performance declines may occur in as few as four trials (Lustig & Meck, 2005; Penney, Gibbon, & Meck, 2000; Zakay & Block, 1997). O'Connell et al. found that the ability to detect the target declined linearly over 3 min and that failures to detect the target were predicted up to 20 sec beforehand by trends in alpha-band activity (measured using EEG) thought to index mind-wandering.

The CTET thus constituted the "tedious task" described in the self-report data. To mimic the distraction caused by the TV or radio, next to the main task computer, we placed a laptop playing a series of distracting video clips. This compelling distractor, similar to the situations that participants described as most distracting in everyday life, allowed us to test for potential interactions between distraction and time-on-task demands with greater sensitivity than previous studies that did not find overall distractor effects. To preview our results, we found that both distraction and time-on-task had robust but independent effects on performance and that Ile89Val participants were especially susceptible to distraction.

EXPERIMENT 2

Methods

Participants

Thirty-two Ile89Val heterozygotes agreed to return for additional testing including the CTET with distractor and more questionnaire measures. The control group consisted of 32 individuals homozygous for the major allele and matched with the heterozygotes on age, gender, education, and PAC scores (Table 2). We matched participants on PAC score to reduce potential concerns that a finding of increased distractibility by Ile89Val participants on the laboratory task might be an artifact of selection bias. That is, if we had not matched the samples for this experiment on PAC score, there might have been concerns that we happened to pick low-distractibility participants from the control population and high-distractibility participants from the Ile89Val population and thereby inflated our chances of finding a group difference on the laboratory task. Instead, by matching the groups on PAC score, we conducted a conservative test, as any selection bias created using this method would be against our preferred hypothesis (i.e., we have likely picked control participants relatively high in the distractibility distribution for their population and Ile89Val participants relatively low in the distractibility distribution for their population). Our results may thus underestimate the size of the group difference in the distraction effect. Ile89Val has been associated with ADHD and depression, so to maintain sample size, we matched participants as closely as possible on history of diagnosis rather than excluding on this basis. (Analyses excluding these participants gave similar results with slightly reduced power.)

Additional Screening Measures

Depression. Hahn et al. (2008) found that Ile89Val was associated with depression severity (though not incidence) in a clinical population. We therefore matched participants on depression ratings using the Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001). Participants respond to each of the nine symptom questions using a scale of 0–3. Possible scores range from 0 to 27, with 0 indicating no self-reported experience of depression and 27 reflecting severe depression symptoms.

Sleep and other health measures. Because the cholinergic system is also involved in the sleep/wake cycle and sleep quality can affect attention, we wanted to ensure that our groups were also matched on this front. The Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) consists of 10 multicomponent questions. Scores range from 0 to 21, with 0 indicating the best sleep quality. The Berlin Sleep Questionnaire (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999) consists of 10 questions relating to snoring, sleep problems, and blood pressure, as well as age and body mass index. Participants are considered at high risk for sleep apnea if they have a positive score (more than 2 points) in two categories. Participants also completed the standard health, demographics, and screening form used in our laboratory, which asks questions about medications and medical or psychiatric conditions that could affect performance.

Table 2. Demographic and PAC Questionnaire Measures for Participants Completing the CTET with Distraction Task

	Control	*Ile89Val*	*t Test*	*Effect Size (Cohen's d)*
Demographic and Health Measures				
Age (years)				
M	45.13	44.66	$t < 1$	$d = .03$
SD	*16.85*	*16.99*	$p = .91$	
Education (years)				
M	16.73	16.53	$t < 1$	$d = .06$
SD	2.57	3.59	$p = .80$	
History of ADHD/depression/anxiety (*n*)	6	7	–	–
Psychotropic medications (*n*)	6	5	–	–
PHQ-9 depression score				
M	3.50	3.47	$t < 1$	$d = .01$
SD	3.97	4.12	$p = .98$	
Pittsburgh Sleep Quality Index				
M	5.91	4.75	$t = 1.17$	$d = .29$
SD	4.32	3.54	$p = .25$	
Self-report Everyday Attention Measures (PAC)				
Distractibility				
M	13.50	14.59	$t = 1.01$	$d = .25$
SD	4.21	4.45	$p = .32$	
Mind-wandering				
M	12.91	13.38	$t < 1$	$d = .11$
SD	3.77	4.47	$p = .65$	
Boredom				
M	12.94	12.25	$t < 1$	$d = .18$
SD	3.30	4.21	$p = .47$	

t test and Cohen's *d* refer to the comparison between control and lle89Val participants. Each group included 19 women and 13 men, for a total $n = 32$ per group.

CTET with Video Distractor

CTET procedures generally followed those used by O'Connell et al. (2009), with some modifications (e.g., target and standard durations, response window) based on pilot testing to make it feasible for participants with a wide range of ability. The task was presented on a Dell PC using Presentation software (Neurobehavioral Systems, Inc., Berkeley, CA). On each trial, participants were presented with a black and white 10 × 10 grid of square tiles (15 mm^2 each) divided diagonally into black and white halves. On standard trials, the grid randomly changed rotation (90°, 180°, or 270°) after 800 msec; on target trials it rotated after 1070 msec (Figure 1). Participants were instructed to press the spacebar as soon as they detected the target.

The distraction manipulation was implemented using a laptop oriented 32° to the left of the CTET task and 65 cm from the participant. In the No Distractor condition, the laptop was silent and displayed a gray screen. In the Distractor condition, the laptop played a series of 30-sec video clips from various sources (e.g., cartoons, movies, sports) with sound presented via headphones. None of the videos contained music or other obviously rhythmic content or overtly violent or sexual content.

Responses were recorded as correct (hits) up to 1.5 sec following target offset. Responses outside this window were coded as false alarms (FAs). Participants received feedback at the end of each run. Before beginning the experiment, participants were given six practice runs that contained three targets each. For the first practice run, the duration difference between target and standard trials was exaggerated to ensure participants understood the task rules (standard: 800 msec; target: 1600 msec). Participants were informed that the timing parameters of

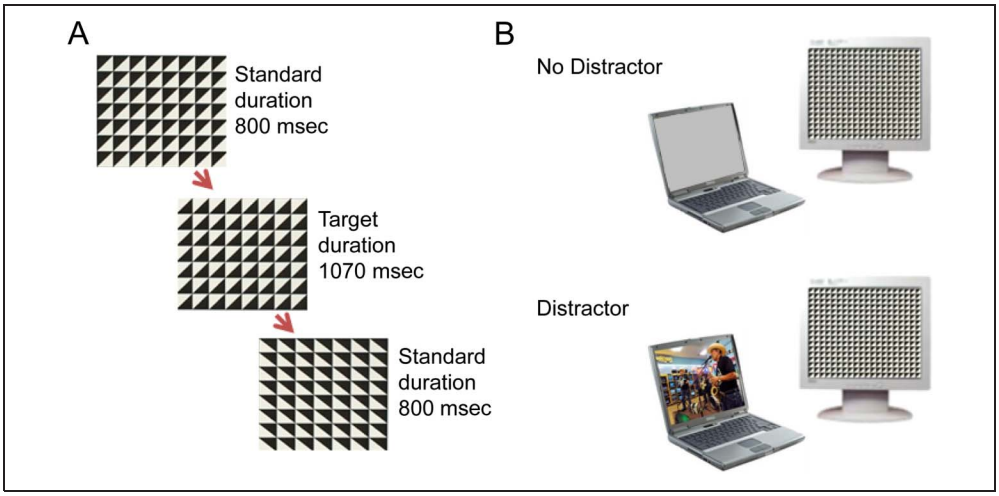

Figure 1. CTET with video distractor. As shown in (A) each trial consisted of a black and white grid made up of squares divided into triangles. At the end of the trial, the triangles rotated (90°, 180°, or 270°, chosen randomly) to start the next trial. The participant's task was to press the spacebar when they realized that the grid had taken longer than usual (1070 msec rather than the standard 800 msec) to rotate. (B) The distractor manipulation was implemented using a laptop oriented 32° to the left of the main task computer. In the No Distractor condition, the laptop was silent and displayed a gray screen. In the Distractor condition, it played video clips with sound.

the subsequent five practice runs would be more challenging and identical to the test runs (standard: 800 msec; target: 1070 msec). To ensure participants were able to discriminate between standard and target durations, they were required to continue practice until they achieved 100% (3/3 targets detected) if they had not already reached this criterion in the mandated five practice runs.

Participants then performed nine task runs (4 min each) with 24 targets per run.[1] Stimuli were pseudorandomly intermixed, with four to eight target trials presented per minute and 7–14 standard duration stimuli presented between each target. Participants took a 1-min break between each experimental run. For each participant, four runs were presented in the No Distractor condition, and four runs were presented in the Distractor condition. Distractor and No Distractor runs alternated, and their order was counterbalanced across participants. Participants completed one additional "Boring Distractor" run for piloting purposes that is not included in the present analysis. The single Boring Distractor run was inserted as either the first, third, sixth, or ninth run.

Post Experiment Questionnaire

Distractor video content. After the CTET, participants completed a surprise 15-item multiple-choice quiz assessing memory for the video content. Similar procedures have revealed relationships between memory for the distracting stimuli and the impact of distraction on performance, as well as experimental group differences (Berry et al., 2014; Biss, Ngo, Hasher, Campbell, & Rowe, 2013; Clapp & Gazzaley, 2012; Gazzaley, Cooney, Rissman, & D'Esposito, 2005).

State attention. After completing the CTET and the quiz for memory of the distractors, participants rated the level of distractibility, mind-wandering, and boredom they experienced during the task. These questions were intended to be similar in form and content to items from the PAC trait attention measure. Participants were given five statements and asked to rate the degree to which they identified with each statement on a scale from 1 to 5 (see Table 3). Questions 1, 2, and 4 measured mind-wandering, Question 3 measured boredom, and Question 5 measured distractibility. We emphasized mind-wandering (three questions) when constructing the questionnaire as that had been the focus of the original O'Connell et al. (2009) article. However, subsequent analyses pooling across CTET experiments in our laboratory show that Question 4 consistently shows the highest correlations with the PAC mind-wandering score and with CTET performance. For that reason and so that an equal number of items are used for the mind-wandering, distractibility, and boredom scores, as in prior work (Berry et al., 2014), we focus on Question 4 as the "state" measure of mind-wandering.

Results and Discussion

Consistent with previous articles (Berry et al., 2014; O'Connell et al., 2009), analyses of CTET performance focused on hits (correct target detections); analyses of d' measures yield similar results. Greenhouse–Geisser sphericity correction was applied as needed for reporting p values, but degrees of freedom are reported as integers in the text for easier reading. Effect sizes are reported using η^2_G (Bakeman, 2005), which gives smaller values than the frequently used η^2_P but is preferable as it reduces error when comparing across studies (Fritz, Morris, & Richler, 2012).

As seen in Figure 2, external distraction and time-on-task effects were independent, and heterozygotes showed

Table 3. Post Experiment Questionnaire Measures for Participants Completing the CTET with Distraction Task

1. At times of this task, it was hard for me to keep my mind from wandering.				
M	2.63	3.53	$t = 3.02$	$d = .75$
SD	*1.21*	*1.19*	$p = .004$*	
2. (Reverse scored) During the task, my thoughts seldom shifted from the subject in front of me.				
M	2.81	3.31	$t = 1.7$	$d = .43$
SD	*1.12*	*1.23*	$p = .09$	
3. I was easily bored during this task.				
M	2.47	2.63	$t < 1$	$d = .12$
SD	*1.19*	*1.43*	$p = .64$	
4. I had difficulty in keeping my attention focused on this long, tedious task.				
M	2.59	3.09	$t = 1.76$	$d = .44$
SD	*0.98*	*1.28*	$p = .08$	
5. No matter how hard I tried to concentrate, I felt easily distracted by the videos playing.				
M	2.47	3.09	$t = 2.11$	$d = .53$
SD	*1.16*	*1.20*	$p = .04$*	
Recognition memory for distractor content (% correct)				
M	0.60	0.71	$t = 0.193$	$d = .46$
SD	*0.26*	*0.22*	$p = .06$	

t test and Cohen's *d* refer to the comparison between control and lle89Val participants.

*Significant difference between groups.

a specific sensitivity to distraction. ANOVA results with within-participant factors Distraction (No Distractor, Distractor), Time (Minutes 1, 2, 3, 4), and between-participant factor Genotype (Control, Ile89Val) revealed main effects of Distraction, $F(1, 62) = 59.27$, $p < .0005$, $\eta^2_G = .07$, and Time-on-task, $F(3, 186) = 21.35$, $p < .0005$, $\eta^2_G = .03$, that did not interact, $F < 1$ (Figure 2). Of primary interest, heterozygotes were more sensitive than controls to distraction, $F(1, 62) = 11.65$, $p = .001$, $\eta^2_G = .01$, but not time-on-task, $F < 1$.[2] The three-way interaction between Distraction, Time-on-task, and Genotype did not approach significance, $F < 1$. Although groups were matched on PAC distractibility, the CTET with distraction was sensitive to group differences in distractor vulnerability, suggesting that the PAC and laboratory performance measures captured at least partially distinct aspects of distractibility.

FA rates were low and did not differ across groups. An ANOVA with within-participant factors Distraction (No Distractor, Distractor) and Time (Minutes 1, 2, 3, 4) and between-participant factor Genotype (Control, Ile89Val) revealed only a main effect of Distraction, $F(1, 62) = 5.10$, $p = .03$, $\eta^2_G < 0.01$, such that FA rates were higher during distraction (No Distractor $M = 0.94\%$, $SD = 1.7$; Distractor $M = 1.15\%$, $SD = 2.04$). There was no effect of Time or Genotype and no interactions (all Fs < 1).

Post experiment ratings of subjective experience generally followed the patterns seen for ratings of everyday attentional function (PAC scores) in Experiment 1: Ile89Val participants tended to give higher ratings for items concerning mind-wandering and distractibility, but not boredom (Table 3). Although these effects are small, they are notable given that, in selecting our participants, we had matched Ile89Val and control participants as closely as possibly in their PAC subjective ratings of everyday attention.

Thus, although the Ile89Val participants tested in this experiment were selected to give similar ratings as controls for attentional function in everyday life, they still tended to show an increased subjective as well as objective susceptibility to distraction during the experimental task. In addition, Ile89Val participants tended to have better memory for the video contents. Together with the CTET performance data, these patterns suggest that Ile89Val individuals are more susceptible to distraction but may benefit from better memory for nominally irrelevant information.

To determine how task performance related to subjective measures of attention, we examined how CTET performance correlated with the self-report measures of attention in everyday life and state of attention during the task. To reduce the number of comparisons and ensure replication across data sets, unless otherwise noted we restrict our analyses to those of theoretical interest and also examined in a previous experiment using an undergraduate sample (Berry et al., 2014).

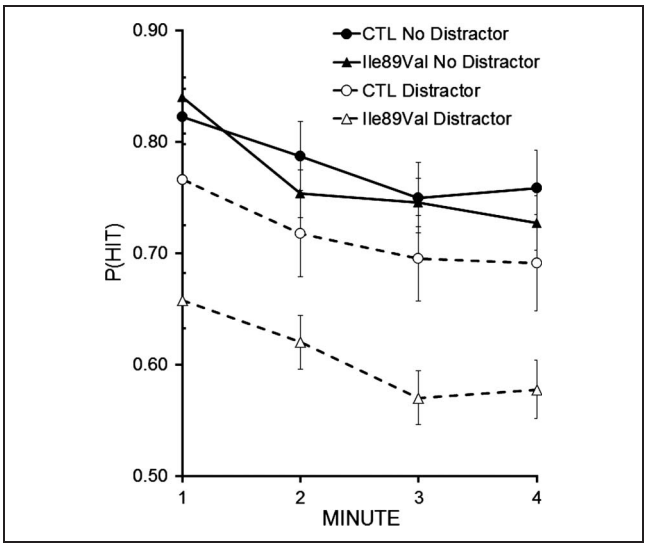

Figure 2. CTET performance with and without video distractor. Markers represent mean proportion of hits for each minute; error bars represent *SEM*. Both groups exhibit time-on-task and distraction effects that do not interact, and the distractor effect is larger for IIeVal89 participants.

In the text, we note the consistencies and discrepancies compared with Berry et al. so that the reader can weigh results accordingly. Full correlation tables for the combined group and each subgroup are available upon request.

We first asked how performance correlated with the PAC "trait" measures of attention, with particular interest in those measures related to distraction (Figure 3). Across both groups, there was a small-to-moderate correlation such that participants who reported more distractibility in everyday life also showed a greater distractor-related drop in performance on the CTET, $r = .25$, $p = .05$. In a previous experiment using an undergraduate sample (Berry et al., 2014), this correlation was in the same direction but did not reach significance. The greater variance in the distraction effect in this study (due to Ile89Val participants' distractor vulnerability) may have contributed to this difference. In our undergraduate sample, self-reported mind-wandering negatively correlated with overall performance in the No Distractor condition, but this relationship did not reach significance in the current sample ($r = -.19$, $p = .13$). Thus, across studies, correlations between performance and self-reported everyday attentional function are of modest size but in the expected direction.

Likewise consistent with the Berry et al. (2014) undergraduate sample, in this community sample stronger correlations were found between task performance and post experiment ratings (Table 3; Figure 3). Target detection in the No Distractor condition was negatively related to difficulty keeping attention focused ($r = -.40$, $p = .001$). Greater performance declines as a result of the video distractor correlated with greater self-rated distraction by the videos, $r = .27$, $p = .03$, and to better memory for the videos' content, $r = .33$, $p = .008$.

A reviewer noted that the mean group differences in the size of the distractor effect on performance might have inflated the size of the cross-group correlations with this effect. To examine this possibility, we calculated the correlations with this factor for each group. For the correlation with trait distractibility as measured by the PAC subscale, the difference between the groups was relatively small ($r = .16$ for controls, $r = .27$ for Ile89Val participants), perhaps because we had matched the groups on PAC scores. However, for both self-rated distraction ($r = -.01$ for controls, $r = .34$ for Ile89Val participants) and memory for the videos' content ($r = -.004$ for controls, $r = .53$ for Ile89Val participants), correlations with the distractor effect on performance were largely driven by Ile89Val participants. In other words, in addition to being more vulnerable to distraction's detrimental effects on performance, Ile89Val participants were also more sensitive to its subjective effects and its potential benefits to later memory.

GENERAL DISCUSSION

The present results reveal three major findings. First, although both distraction and time-on-task reduce performance, their effects are independent. This seems inconsistent with simple "underload" or "overload" resource explanations of vigilance decrements. Instead, these different types of demand appear to tap dissociable attention control processes. Although neuroimaging studies suggest a core network involved in stable task control (e.g., Dosenbach et al., 2006), recent studies focused on time-on-task or fatigue effects show substantial variance in the neural correlates of such effects indicating fatigue of specific task-dependent processes (e.g., Persson, Larsson, & Reuter-Lorenz, 2013; Lim et al., 2010). The task used here may provide a useful tool for examining these processes in clinical and individual differences research.

Second, in a community-based sample, genetic variation in cholinergic function was related to self-reported everyday (trait) distractibility and mind-wandering, but not boredom. There are legitimate concerns about the degree to which a single nucleotide polymorphism (SNP) can be linked to cognitive processes, as genes are not

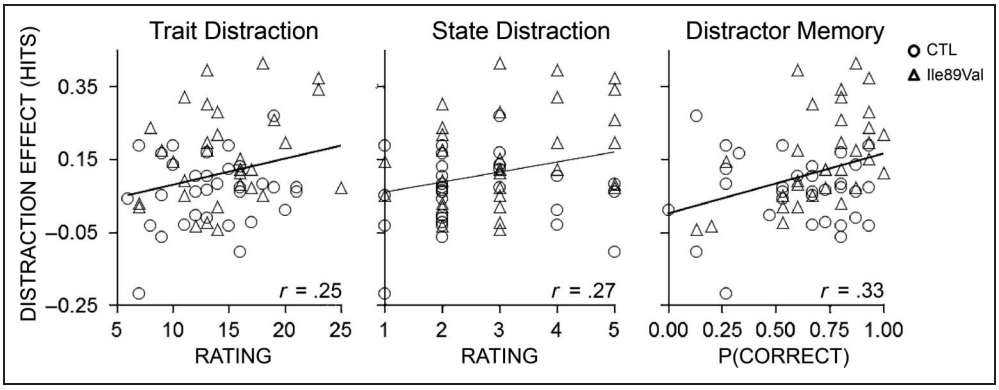

Figure 3. Correlations between distractor-related performance declines in the CTET, self-rated "trait" distractibility measured using the PAC, self-rated "state" distractibility measured using the post experiment questionnaire and performance on the post experiment quiz for memory of the content of the distracting videos. Larger numbers indicate greater distractibility. If the data from the control participant in the lower left corner are excluded, the correlations remain in the same direction as indicated in the main text at reduced effect size ($r = .20$ for trait distraction, $r = .22$ for state distraction, and $r = .29$ for distractor memory).

solitary mediators of behavior. Instead, gene–behavior relationships likely take the form of complex interactions that include other genes and the environment (Thomas, 2010). However, the pattern found here, especially increased distractibility, was predicted a priori from prior research and can be interpreted in the context of evidence about its neurobiological impact. When first describing the Ile89Val SNP, Okuda et al. (2002) noted that the effects of reduced choline transport might be especially evident under demanding conditions, consistent with rodent studies that show that responding to the demands imposed by distraction depends critically on the right basal forebrain cholinergic system (St. Peters et al., 2011; Gill et al., 2000). These findings, as well as parallel human neuroimaging studies showing increased right prefrontal activation in the same conditions that produce increased right prefrontal ACh in rodents, converge to predict the present association between Ile89Val and distractibility.

Third, even after matching participants on self-report measures of distraction in everyday life, Ile89Val participants showed a specific vulnerability to distraction on a laboratory task (the CTET). A distraction score of 12% discriminated the groups with 63% sensitivity and 72% specificity. Conceptually replicating the group differences on the trait measures, when asked about their attentional state during the task, Ile89Val participants gave higher ratings on items concerning distractibility and mind-wandering, but not boredom. The equivalent state and trait boredom scores, No Distractor task performance, and time-on-task declines, as well as superior performance on the memory test, indicate that Ile89Val participants are not generally impaired but have a particular vulnerability to distraction.

To summarize, the association between Ile89Val and distractibility is predicted from molecular, systems, and cognitive neuroscience and replicates across self-report measures of everyday attention, laboratory task performance, and self-report ratings of attention during the task. In contrast, the link to mind-wandering is more tenuous. It is not clear how mind-wandering relates to the mechanism (attenuated cholinergic response to high task demands) indicated by molecular and cellular studies, and although Ile89Val participants consistently indicated higher rates of mind-wandering on the self-report measures, they did not show worse task performance overall or steeper time-on-task declines. A potential reason for the discrepancy between the self-report and performance measures is that, although the former ask about off-track thoughts, those thoughts may not always disrupt performance. Esterman, Noonan, Rosenberg, and DeGutis (2013) recently reported different neural correlates and timescales for vigilance declines, off-track thought, and performance lapses. Of particular interest, default network activity putatively related to off-track thought had a nonlinear relationship to performance lapses depending on the stability of goal-directed attention. Future investigations using experience-sampling techniques and neural measures with Ile89Val participants may resolve this issue.

The more robust link between Ile89Val and distractibility found here is to our knowledge the first evidence linking this polymorphism to a specific cognitive process and the first indicating its role in normal cognitive variation beyond clinical conditions such as ADHD. Besides their vulnerability to the distractor's detrimental effects, Ile89Val participants' better memory for the distractor is reminiscent of findings from older adults showing that increased processing of nominally irrelevant information provides an advantage if that information becomes useful later on (Biss et al., 2013; Clapp & Gazzaley, 2012; Gazzaley et al., 2005). Increased processing of irrelevant information has been linked to creativity in ADHD (White & Shah, 2011); an interesting question for future studies is whether this advantage extends to Ile89Val.

As noted above, understanding the role that any SNP, including Ile89Val, plays in normal cognition and cognitive disorders requires consideration of its interaction with other genetic and environmental factors. For example, variation at a nearby SNP (G to T substitution at CHT 3′ UTR) has been linked to corticolimbic reactivity (Neumann et al., 2006), and this variation paired with Ile89Val was especially common in the combined subtype of ADHD (English et al., 2009). Recent evidence from a mouse model suggests that reduced CHT function in combination with dopamine depletion may explain why some Parkinson's patients show pronounced cognitive declines (Zurkovsky et al., 2013) and links between the amyloid precursor protein and CHT indicate a potential role in Alzheimer's disease (Wang, Yang, Wang, & Zheng, 2007).

The present results suggest that the cholinergic system plays an important and specific role in susceptibility to distraction in everyday life (Experiment 1) and on a laboratory task (Experiment 2). They add to a growing body of research that integrates findings from several areas of psychology and neuroscience to clarify links between cognitive functions and the neural systems that underlie them (see also Howe et al., 2013). This integrative approach holds promise for improving our understanding of how genes influence cognition and behavior and for developing more effective, precisely targeted treatments when these processes are disordered (Insel et al., 2010).

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Notes

1. In this and other studies, time-on-task effects occur within runs; there are no systematic differences between runs (i.e., performance is not worse in Run 5 than in Run 1; see also Berry et al., 2014; O'Connell et al., 2009).
2. As a check of reliability, we split each group in half (even/odd pairs) and reran the analysis on the subsamples; effects were in the same direction and of similar effect size as those reported here.

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