Neuropsychology

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Online First Publication, April 28, 2016. http://dx.doi.org/10.1037/neu0000277

CITATION

A Role for Attention During Wilderness Navigation: Comparing Effects of BDNF, KIBRA, and CHRNA4

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Objective: To better understand what influences interindividual differences in ability to navigate in the wilderness, we hypothesized that better performance would be seen in (a) BDNF (rs6265) Val/Val homozygotes increased use of a spatial strategy, (b) KIBRA rs17070145 T/T homozygotes superior episodic memory, (c) CHRNA4 (rs1044396) T allele carriers better ability to focus visuospatial attention.

Method: Military cadets (n = 382) genotyped for BDNF, KIBRA, and CHRNA4 SNPs used a map and compass to navigate in unmarked woods. Participants completed a morning course within 3.0 km and an afternoon course within 7.0 km. Results: Success or failure in finding each point was analyzed in a logistic regression model with KIBRA, BDNF, and CHRNA4 genotypes as fixed effects. For the morning course, the adjusted odds ratio for the effect of KIBRA T/T over KIBRA C/C was 2.58 (95% CI of 1.31, 5.06) demonstrating a statistical benefit of the KIBRA T/T genotype over individuals with KIBRA C/C genotype. BDNF did not have an independent association with navigational success. For the afternoon course, the adjusted odds ratio for the effect of CHRNA4 C/T over C/C was 1.67 (95% CI of 1.24, 2.25) demonstrating a statistical benefit of CHRNA4 T allele carriers over the C/C genotype. Conclusions: Ability to navigate in the wilderness benefits less from sense of direction (BDNF and Santa Barbara Sense of Direction) and more from episodic memory (KIBRA) in the first course and heightened ability to focus attention (CHRNA4) after experience in the 2nd course.

Keywords: BDNF, KIBRA, CHRNA4, spatial navigation, interindividual differences

The marked interindividual differences observed in ability to navigate through large-scale environments has inspired efforts to understand the source of those differences (Ishikawa & Montello, 2006; Sandstrom Kaufman, & Huettel, 1998; for a review, see Wolbers & Hegarty, 2010). Experience and knowledge have been found to influence ability to navigate (Maguire et al., 2000), as does gender (Lawton, 1994, 2001). However, interindividual differences in use of memory systems also play a specific role in spatial navigation performance. Individuals tend to select either an allocentric or an egocentric navigation style with the specific strategy used reflected in brain activation patterns. An allocentric navigation strategy (wayfinding) involves reliance on developing a spatial map of the environment, whereas an egocentric strategy (route following), involves reliance on landmarks and left and right turn directions to navigate an environment. People using a spatial (wayfinding) strategy show greater activity in the right hippocampus, whereas people using a nonspatial (route following) strategy show greater activity in the head of the caudate (Bohbot, Iaria, & Petrides, 2004; Bohbot, Lerch, Thordnyeck, Iaria, & Zijdenbos, 2007; Iaria et al., 2003). Consistent with that evidence, high performing navigators can switch flexibly between strategies, activating the hippocampus during wayfinding but the caudate during route following (Hartley, Maguire, Spiers, & Burgess, 2003; Liben, Myers, & Christensen, 2010). Although there are other functions that appear to be important for successful navigation—processing of spatial cues, computational

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This research was supported by the Office of Naval Research In-house Laboratory Independent Research (ILIR), Naval Surface Warfare Center, Dahlgren Division (N000141010198).

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http://dx.doi.org/10.1037/neu0000277

Neuropsychology In the public domain
2016, Vol. 30, No. 4, 000
mechanisms, and spatial representation (Wolbers & Hegarty, 2010)—there has been little work to date on the role of nonmemonic functions in navigation.

An approach that can broaden understanding of cognitive contributions to navigational ability examines effects of normal genetic variation on navigation performance. Comparing effects of variants in genes encoding aspects of neurotransmission in different brain systems can shed light on the neural and cognitive systems mediating navigation beyond egocentric and allocentric styles. The allelic association approach to cognitive genetics—relating normal genetic variation to cognitive performance—has been previously informative about neuronal pathways and systems important in cognitive functions (e.g., but it has also been dogged by failures to replicate (e.g., Barnett, Scoriels, & Munafo, 2008). Nevertheless, meta-analyses have confirmed genetic modulation of both specific cognitive functions (e.g., Gao et al., 2014; Kambeitz et al., 2012; Kim-Cohen et al., 2006; Milnik et al., 2012) and also of brain activity related to cognitive functions (Mier, Kirsch, & Meyer-Lindenberg, 2010). Regarding effects of normal genetic variation on navigation ability, two genes have been investigated. Both the gene encoding brain-derived neurotrophic factor (BDNF) and the gene encoding the kidney and brain expressed protein (KIBRA/WWC2) have links to hippocampus.

The KIBRA protein operates in the postsynaptic density and appears to participate in a range of neuronal functions such as cell migration, vesicle transport, transcriptional regulation, and synaptogenesis. The strongest evidence on KIBRA concerns its interaction with protein kinase Mζ (PKMζ), the latter shown in a series of studies to be critical for long-term memory maintenance in the hippocampus (Drier et al., 2002; Pastalkova, Itskov, Amarasingham, & Buzsáki, 2008; Serrano et al., 2008). KIBRA appears to stabilize PKMζ postsynaptically (Vogt-Eisele et al., 2014) in hippocampus and dentate gyrus (Yoshihama et al., 2009). These findings are consistent with arguments that KIBRA is important in memory storage (Schneider et al., 2010; Schwab et al., 2014). Allelic association studies of a SNP in the KIBRA gene (rs17070145) also suggest a role in memory. Papassotropoulos et al. (2006) were the first to report the KIBRA SNP rs17070145 was associated with episodic memory in humans. They found T allele carriers showed better memory performance than C/C homozygotes, a finding confirmed by others (Preuschhof et al., 2010; Bates et al., 2009). Although there have been some failures to replicate that finding (e.g., Franks et al., 2014), two recent meta-analysis confirmed an association between that SNP for both episodic memory (0.5% of variance explained) and working memory (0.1% of variance explained; Milnik et al., 2012). Only one study has looked at effects of this same KIBRA SNP rs17070145 SNP on navigation performance. Older adult T-allele carriers performed better on a virtual reality spatial navigation learning task compared to C/C homozygotes, a finding confirmed by others (Preuschhof et al., 2010; Bates et al., 2009). The evidence that KIBRA is important in hippocampal memory functioning led us to hypothesize that the rs17070145 SNP modulates spatial navigation ability.

The neurotrophin BDNF is critical for long-term potentiation in the hippocampus. A well-studied variant of the BDNF gene (Val66Met, rs6265) has been found to modulate memory performance and also hippocampal structure and physiology (e.g., Egan et al., 2003; Harriri et al., 2003), with memory disadvantages associated with the BDNF rs6265 Met allele confirmed in a recent meta-analysis (Kambeitz et al., 2012). Two studies have looked at BDNF in navigation. BDNF Val/Val homozygotes were more likely than Met carriers to use a spatial strategy than a nonspatial (route following) strategy and showed greater hippocampal activation during navigation (Banner, Bhat, Etchamendy, Jooher, & Bohbot, 2011). Following navigation training, Val/Val homozygotes also showed increases in brain metabolic measures while Met carriers did not ( Lövdén et al., 2011). Again, the literature is small but does support a hypothesis that BDNF modulates spatial navigation strategy.

Visuospatial attention may also play a role in navigation. Several groups have found that individuals vary substantially in how well they use spatial cues to navigate (Kelly, McNamara, Bodenheimer, Carr, & Rieser, 2009; Ishikawa & Montello, 2006; see review in Wolbers & Hegarty, 2010). Based on that evidence, we reasoned that genes which influence ability to attend to spatial cues may have a role in navigation. A well-studied variant in a cholinergic nicotinic receptor gene (CHRNA4 rs1044396) has been found to influence visuospatial attention across a range of paradigms (Espeseth et al., 2006; Greenwood, Lin et al., 2009; Greenwood, Sundararajan et al., 2009; Parasuraman et al., 2005; see also Espeseth et al., 2010, reviewed in Greenwood et al., 2012). On the basis of that evidence, the present study hypothesized that this CHRNA4 rs1044396 SNP would also influence spatial navigation but for reasons related to ability to focus attention rather than ability to maintain memory (KIBRA) or ability to navigate a route (BDNF). To assess ability to focus attention, we administered a Posner-type visuospatial attention task that required focusing and shifting of attention. As working memory has been implicated in navigation (Wolbers et al., 2007; Jones & Wilson, 2005) and as visuospatial attention and working memory have overlapping mediation (LaBar et al., 1999), we also administered a working memory task. However, neither BDNF nor KIBRA would be predicted from the literature to modulate working memory.

Visuospatial attention may be important for navigation insofar as navigation requires ability to focus attention on cues and landmarks. However, visuospatial attention may be particularly important for wilderness navigation requiring map and compass skills. Much of the previous work on navigation ability has been conducted in developed environments which have roads, buildings, and other easily identifiable constructed landmarks. In contrast, ability to navigate through a wilderness using only natural landmarks has been relatively little studied. The previous work on wilderness navigation found that both sex and prior experience in wilderness settings are modulators of navigation success (Malinowski & Gillespie, 2001). However, map and compass skills are generally needed for successful wilderness navigation unless the terrain is well known to the navigator. Map and compass skills must be learned and practiced in advance and must be applied iteratively while navigating. We reasoned that in order to follow a compass bearing accurately, the focus of visuospatial attention must be repeatedly focused and shifted between the map, the compass, and the terrain. Such repeated engaging and disengaging of visuospatial attention has much in common with laboratory tasks that require control of the focus of attention by engaging and disengaging the focus of attention, for example, Posner’s covert attention task (Greenwood, Parasuraman, & Haxby, 1993; Posner, Walker, Friederich, & Rafal, 1984). We recently argued from the relevant literature that one component of visuospatial attention—ability to focus attention in the presence of distractions—is mod-
ulated by the nicotinic cholinergic system and by a variant in the CHRNA4 gene that encodes the α4 sub-unit of α4β2 cholinergic nicotinic receptors (Greenwood, Parasuraman, & Espeseth, 2012). The CHRNA4 rs1044396 SNP is a synonymous C to T substitution, first reported by Steinleit et al. (1997). Converging evidence from several different research groups indicates that T allele carriers show preferential processing of events inside the attentional focus compared to events outside the attentional focus, interpreted as selectively greater ability of T carriers to maintain the focus of visuospatial attention in the face of distractions (reviewed in Greenwood et al., 2012).

Although a SNP in BDNF has been found to modulate navigational performance in developed environments (Banner et al., 2011) and a SNP in KIBRA has been found to modulate episodic memory (Milnik et al., 2012), we reasoned that ability to focus attention might also be important when navigating through a wilderness environment with a map and compass. On the basis of evidence that CHRNA4 rs1044396 T carriers are better able to maintain the focus of visuospatial attention in the face of distraction (Greenwood et al., 2012), we hypothesized that the CHRNA4 gene would also modulate individual differences in navigation through wilderness environments. Specifically, we predicted (a) BDNF (rs6265) Val/Val homozygotes would show better performance than the other BDNF genotypes due to use of a spatial strategy, (b) KIBRA rs17070145 T/T homozygotes would show better performance than the other KIBRA genotypes due to superior episodic memory, (c) CHRNA4 (rs1044396) T allele carriers would show better performance than the other CHRNA4 genotypes due to better ability to focus visuospatial attention, (d) self-reported preferences for wayfinding strategies over route-following strategies would result in better performance. Further, we predicted an association between CHRNA4 and visuospatial attention assessed with an information processing task.

On the other hand, while effects of BDNF and KIBRA may interact due to similar mechanisms of action (involving hippocampal long term potentiation), effects of CHRNA4 (involving the most common nicotinic cholinergic receptor in cortex, reviewed in Greenwood et al., 2012) would not be predicted to interact with BDNF and KIBRA due to different mechanisms of action.

Method

Participants

Male cadets \((N = 382)\) enrolled at the U.S. Military Academy or in Reserve Officers’ Training Corps programs volunteered, provided informed consent, and participated in this study. Ages ranged from 18 to 24, \((M = 19.26, SD = .89)\). Racial composition included 294 Whites, 31 Asians, 28 African Americans, 24 Hispanics, and 5 American Indians. (The Department of the Army departs from NIH racial/ethnic categorization and treats the Hispanic category as a race).

Task Procedures

Land navigation task. The study consisted of a large-scale orienteering task. The site, used in previous real world wayfinding studies, was a rugged and rocky glaciated wooded terrain of the Hudson Highlands with mixed deciduous and coniferous forest and some clearings (Malinowski & Gillespie, 2001). The elevation difference between the lowest and highest points was about 300 feet. The navigation sessions were conducted in unmarked woods with no trails or roads.

Each participant underwent training in preparation for the testing. On Day 1 of training, each participant received 12 hr of instruction on basic map reading, compass usage, terrain visualization, and distance estimation. Participants practiced their skills on a terrain walk in groups of 12 individuals (for 8 hr) as well as in pairs in the dark (for 4 hr). On Day 2, trained U.S. Army personnel administered the test for record. Participants completed a morning and an afternoon course. Participants were required to find two points in the morning course and three points in the afternoon course. The morning and afternoon courses are distinct not only in the number of points required to find but also in the distances each course covered, (morning: 3.0 km; afternoon: 7.0 km).

Participants were provided a standard military lensatic compass, protractor, and a 1:25,000 scale topographic map of the area. Participants were provided the coordinates of the points they were required to find. The points in the woods were marked by standard orange and white orienteering control bags, approximately 1 cubic foot in area and hung 2 m from the ground. See Figure 1 below.

The points were arranged in a three point clustered configuration. In the morning course, points within a cluster were on average 100 m apart, whereas different clusters were separated by at least 300 m. Participants navigated a course that required them to travel 3.0 km and find two clustered points within a 3-hr time limit. Similarly, for the afternoon course, points within a cluster were on average 100 m apart while different clusters were separated by at least 300 m. However, participants navigated a course that required them to travel 7.0 km and find three clustered points within a 4-hr time limit. At each point, there was a manual “punch” with the orienteering bag; participants stamped on their scorecard to indicate the point found. Upon return, participants were scored. Scoring was binary such that a participant who found the exact point within a cluster received a score of 1. If they found the wrong point within their cluster or they found a point in a wrong cluster

![Figure 1. Orienteering control bag. See the online article for the color version of this figure.](image-url)
or no point at all they received a score of 0. Results were recorded including the number of points found and the average physical speed of moving through the course measured in meters per second (referred to in the model as “average speed”).

Figure 2 depicts the area for the terrain training walk as well as the actual area used for the test of record. The pink rings indicate the points; note they are clustered in groups of three. The inner two rings represent the morning course, whereas the outer two rings contain the points participants needed to find in the afternoon course. The points participants needed to find in the afternoon were in a part of the woods not explored in the morning course.

Participant SNP genotyping (KIBRA rs17070145; CHRNA4 rs1044396; BDNF rs6265). Before participants began the long course, two buccal swabs were used to collect buccal cells for genetic analysis from each participant. All buccal swabs were immediately placed in coolers, transported to the lab and stored in ~80°C freezers for two weeks prior to genotyping. DNA was isolated from buccal swabs collected from participants using the QIAamp DNA extraction procedure (Qiagen, Hilden DE). Quality and quantity of the gDNA isolations was assessed using a NanoDrop ND-1000 spectrophotometer, and some samples were diluted prior to PCR amplification.

Genotyping of KIBRA for all participants was performed on an Applied Biosystems ABI7500 real-time PCR instrument using an allelic discrimination 5′-exonuclease assay (Reference SNP ID: rs17070145; Life Technologies, Carlsbad CA). Pre- and postread fluorescence levels for each reaction were determined and compared to determine individual SNP genotypes at the KIBRA

Figure 2. Map of area. See the online article for the color version of this figure.
rs17070145 SNP. Reactions were monitored for quality and loss of reaction volume due to evaporation by using the passive reference dye ROX. Results of the genetic analysis revealed 162 C/C homozygotes, 160 C/T heterozygotes, and 60 T/T homozygotes. The difference between the observed and expected genotypes was analyzed by applying Fisher’s exact test to determine that participants in this study were in Hardy-Weinberg equilibrium ($p = .055$ in $\chi^2$ tests).

Genotyping of CHRNA4 for all participants was performed using the same genetic DNA extractions as above on the Applied Biosystems ABI7500 real-time PCR platform. The CHRNA4 5’-exonuclease assay for allelic discrimination of CHRNA4 (Reference SNP ID: rs1044396, Life Technologies, Carlsbad CA) pre- and postread fluorescence levels for each reaction were determined and compared to determine individual SNP genotypes at the CHRNA4 rs1044396 SNP. Reactions were monitored for quality and loss of reaction volume due to evaporation by using the passive reference dye ROX. Results of the genetic analysis revealed 103 C/C homozygotes, 180 C/T heterozygotes, and 99 T/T homozygotes. The difference between the observed and expected genotypes was analyzed by applying Fisher’s exact test to determine that participants in this study were in Hardy-Weinberg equilibrium ($p > .05$ in $\chi^2$ tests).

Genotyping of BDNF for all participants was performed using the same genetic DNA extractions as above on the Applied Biosystems ABI7500 real-time PCR platform. The BDNF 5’-exonuclease assay for allelic discrimination of BDNF (Reference SNP ID: rs6265, Life Technologies, Carlsbad CA) pre- and postread fluorescence levels for each reaction were measured and compared to determine individual SNP genotypes at the BDNF rs6265 SNP. Reactions were monitored for quality and loss of reaction volume due to evaporation by using the passive reference dye ROX. Results of the genetic analysis revealed 247 G/G (Val/Val) homozygotes, 180 G/A (Val/Met) heterozygotes, and 15 A/A (Met/Met) homozygotes. The difference between the observed and expected genotypes was analyzed by applying Fisher’s exact test to determine that participants in this study were in Hardy-Weinberg equilibrium ($p > .05$ in $\chi^2$ tests).

Santa Barbara Sense of Direction (SBSOD) questionnaire. The Santa Barbara Sense of Direction (SBSOD) questionnaire (Hegarty, Richardson, Montello, Lovelace, & Subbiah, 2002) was administered to participants upon completion of the course. The SBSOD is a paper based self-report scale of environmental spatial ability. It is composed of 15 statements; for example, “I am very good at giving directions.” Participants rate their Sense of Direction on a 7-point Likert scale ranging from strongly disagree to strongly agree. We used the “reverse scoring” scheme such that a high score on the SBSOD was achieved by those who claim to have a good sense of direction.

Information Processing Tasks

In order to assess visuospatial attention and working memory directly, information processing tasks aimed at those functions were performed on a separate day from the land navigation task. Only half of the participants were asked to volunteer for these tasks. For the CHRNA4 SNP there were 39 T/T homozygotes, 58 C/C homozygotes, and 35 heterozygotes. For the BDNF SNP, there were 85 C/C (Val/Val) homozygotes. Due to the small number of Met/Met homozygotes (4% of our sample), the Met/Met homozygotes were combined with the Val/Met heterozygotes for a total of 47 combined Met/Met plus Val/Met. For the KIBRA SNP there were 60 C/C homozygotes, 54 C/T heterozygotes, and 18 T/T homozygotes.

Visuospatial attention task. A Posner-type spatially cued letter discrimination task developed by Greenwood et al. (1993, 2000) was used (See Figure 3). First, a fixation point appeared and was displayed for 500 ms, followed by a cue (an arrow pointing either left, right, or in both directions). The cue was either valid, predicting the subsequent target location on 61.5% of the trials, or invalid on 15%, or neutral on 15% of trials. The centered location cue appeared for a variable cue—target SOA of 500 or 2,000 ms. Next, a letter target appeared to the right or left of the fixation point. Participants were required to mark a speeded categorization of the target letter as either a consonant or a vowel by using their index fingers to select one of two responses on a keyboard. The figure below depicts a valid and invalid trial. Reaction time (RT) was the measure of interest.

Working memory task. A spatial working memory task (see Figure 4) described subsequently was used (Greenwood et al., 2005). A fixation cross first appeared, followed by one, two, or three black dots (.67” in diameter, each indicating a target location) appearing at randomly chosen screen locations for 500 ms. Simultaneously with dot offset, the fixation cross reappeared for a 3-s delay. At the end of the delay, a single red test dot appeared alone on the screen. This test dot appeared either at the same location as one of the target dots (match condition) or at a different location (nonmatch condition). On nonmatch trials, the distance between the correct location and the test dot was varied over three levels, being about 2°, 4°, or 8° of visual angle. Participants had to decide whether the test dot location matched one of the target dots. Accuracy and RT were the measures of interest.

Results

For each participant, results were obtained for the morning course and the afternoon course. The results for finding each point
in both land navigation course attempts were scored as either 1 (success) or 0 (failure). That data was used as the response variable for a logistic regression model. A hierarchical logistic regression model was used with one level analyzing the morning data and the second level analyzing the afternoon data conditioned on the results from the morning. The variables used in these models are listed in Table 1.

**Equation 1: Morning Land Navigation Model**

\[
Pr(z_i = 1) = \logit^{-1}(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6)
\]

**Equation 2: Afternoon Land Navigation Model**

\[
Pr(y_{ia} = 1) = \logit^{-1}(\beta_1 + \beta_2 x_8 + \beta_3 x_9 + \beta_4 z_8 + \beta_5 + \alpha_k) \sim \mathcal{N}(0, \sigma^2_k)
\]

The comparisons of interest asked whether specific genotypes of SNPs in KIBRA, BDNF, and CHRNA4 genes modulated a cadet’s ability to successfully navigate.

**Morning Results**

Navigation success was defined as finding the target point in a 3-point cluster. Each navigational point was treated as a separate trial with each participant treated as a separate experimental unit, creating a total of 764 observations from 382 participants. We analyzed the morning results with Equation 1, using a multivariable logistic regression model. In addition to the three genes, the model also accounted for the results of the Santa Barbara survey (SBSOD) as well as the average physical speed of moving through the course. The model was fit using the iteratively reweighted least squares method using standard 0/1 coding for factors. The adequacy of the model was checked by examining both likelihood ratios as well as Akaike’s information criterion (AIC). The genotype C/C was used as a baseline because C/C homozygotes had a lower probability of success than the other genotypes. Table 2 shows that KIBRA and average speed were statistically significant for the morning results, but SBSOD was nonsignificant.

As a logistic regression model with a constant term was used, the contrasts of interest were formed by comparing the differences between genotypes with the genotype having the weakest effect serving as a baseline. The adjusted odds ratio for the effect of KIBRA T/T over KIBRA C/C was 2.58 (95% CI of 1.31, 5.06). To further demonstrate the effect of the T/T genotype, it was also compared to C/T, with C/T as a baseline. This analysis showed that the effect of the T/T genotype was also statistically greater than the effect of the C/T genotype. This analysis resulted in a coefficient value of 0.793 and an adjusted odds ratio of 2.26 (95% CI of 1.15, 4.45). This demonstrates that there is a clear statistical benefit of the KIBRA T/T genotype over individuals with either KIBRA C/C and C/T genotypes. Logistic regression assumptions were checked using the Hosmer-Lemeshow tests. Within the model, all BDNF rs6265 terms (β5 and β6 terms in Equation 1) did not reach statistical significance (\(p > .56\)).

Although BDNF did not predict navigational success, we found that BDNF genotype had a very strong positive correlation with the SBSOD questionnaire. Specifically, individuals with the BDNF Val/Met and Met/Met genotypes had higher scores on the SBSOD questionnaire than BDNF Val/Val homozygotes. An analysis of variance (ANOVA) was also conducted using SBSOD as a dependent variable and the BDNF genotype as a predictor. As above, due to the small number of Met/Met carriers, Met/Met individuals were combined with Val/Val individuals. This resulted in 247 Val/Val individuals and 135 combined Val/Met plus Met/Met individuals. An ANOVA, meeting standard assumptions, was used to analyze the results of the Santa Barbara survey. BDNF genotype was found to be a significant predictor of an individual’s score on the survey (\(p = .019\)). Therefore, BDNF did not have an independent association with navigational success, but did have an effect on navigation through a relationship with SBSOD. The average speed of moving through the course was statistically significant for the morning results (\(p = .010\)) with faster movement through the course associated with better performance.

**Table 1**

| Variable | Coefficient | Standard error | \(z\) | \(P>\left|z\right|\) |
|----------|-------------|----------------|------|----------------|
| Average speed (\(\beta_1\)) | .644 | .251 | 2.56 | .010 |
| SBSOD (\(\beta_2\)) | .0177 | .009 | 1.86 | .062 |
| KIBRA C/T (\(\beta_3\)) | .132 | .237 | .56 | .576 |
| KIBRA T/T (\(\beta_4\)) | .949 | .343 | 2.76 | .0067 |
| Constant (\(\beta_0\)) | −2.75 | .849 | −3.24 | .0012 |

**Note.** SBSOD = Santa Barbara Sense of Direction questionnaire.

**Afternoon Results**

For the afternoon data, navigation success was again defined as finding the target point in a 3-point cluster. The model fit is the second level of the hierarchical model shown in Equation 2. Similar to the morning, each participant was treated as a separate experimental unit, creating a total of 1146 observations from 382 participants. The linear mixed effects model was fit using residual maximum likelihood estimation techniques with the LME4 package in the R Software. A variety of covariance matrices were...
analyzed to check the robustness of the results. However, due to the small number of trials per participant, the choice of covariance matrix was found to have negligible effects on the fixed effects. Logistic regression was used due to the nature of the data (success at finding the target). Assumptions were checked using the Hosmer-Lemeshow tests. The within-subject variance, controlled through the use of random effects in the model, was 0.16.

In the logistics regression model, the CHRNA4 rs1044396 C/C genotype was used as a baseline for the analysis as individuals with the CHRNA4 C/C genotype scored lower, on average, than individuals with other genotypes. The adequacy of the model was checked by examining both likelihood ratios as well as AIC. The results are shown in Table 3.

The adjusted odds ratio for the effect of CHRNA4 C/T over the effect of C/C was 1.67 (95% CI of 1.24, 2.25). The adjusted odds ratio for the effect of T/T over C/C was 1.43 (95% CI of 1.02, 2.01). This shows a statistical advantage of both CHRNA4 C/T and T/T genotypes over the C/C genotype for afternoon performance.

Information Processing Tasks

**Visuospatial attention task.** Based on previous findings (Greenwood et al., 1993, 2000), we predicted that CHRNA4 genotype would modulate effects of cue validity on the visuospatial attention task, most strongly with the long (2000 ms) SOA. We tested that prediction and found that CHRNA4 did not significantly modulate mean RT under the 2000 ms or the 500 ms SOA conditions. We here report the 2000 ms SOA results. A repeated-measures ANOVA analyzed mean RT with cue validity as the within-subjects factor (valid, neutral, invalid) and CHRNA4 genotype (C/C, C/T, T/T) as the between-subjects factor. Due to unequal sample sizes, the analysis used type-III SSE, examining all interactions. greenhouse-Geisser corrections were used to account for the lack of sphericity in the data. Although the RTs were fastest following valid cues and slowest following invalid cue, $F(2, 256) = 19.00, p < .0001$, CHRNA4 genotype was not found to be a significant predictor of mean RT, $F(2, 128) = 0.305, p = .737$.

**Working memory task.** On basis of previous findings (Greenwood et al., 2005), we predicted that both BDNF and KIBRA would modulate working memory performance. To test that prediction, a repeated-measures ANOVA analyzed accuracy in the WM task. BDNF and KIBRA were both treated as between-subject effects while distance and load were treated as within-subject effects. Due to unequal sample sizes among the genes, a Type-III SSE analysis was used with Greenhouse-Geisser corrections to account for the lack of sphericity in the data. Neither KIBRA, $F(2, 128) = 0.813, p = .45$ nor BDNF, $F(1, 128) = 0.595, p = .442$, were significant predictors of accuracy. Interactions were also examined which showed no significant interactions between the genes studied nor in the within-subject effects.

**Discussion**

We hypothesized that ability to navigate in a wilderness environment with map and compass relies on sense of direction, memory formation, and ability to focus visuospatial attention. To test this, we selected three candidate genes previously associated with each of these abilities: BDNF, KIBRA, CHRNA4, respectively. The BDNF rs6265 SNP was selected on the basis of evidence of association with declarative memory (Kambeitz et al., 2012) and navigation strategy (Banner et al., 2011; Lövdén et al., 2010). The KIBRA rs17070145 SNP was selected on the basis of evidence of association with episodic memory (Milnik et al., 2012). The CHRNA4 rs1044396 SNP was selected based on evidence of association with ability to focus visuospatial attention (Greenwood et al., 2005; Espeseth et al., 2006; Greenwood et al., 2009; reviewed in Greenwood et al., 2012). We found the strongest effects from the KIBRA SNP and the CHRNA4 SNP, but differentially according to whether the navigation trial was the morning session (first time navigating without assistance) or the afternoon session (following experience gained in the morning). In the initial morning course, both KIBRA and speed of moving through the course exerted significant effects on navigation success. SBSOD was a trend-level contributor. Effects of the BDNF rs6265 SNP overlapped with effects of the SBSOD, consistent with previous evidence that this SNP influenced navigation strategy (Banner et al., 2011; Lövdén et al., 2011). However, effects of BDNF on navigation were not significant. Success in the afternoon showed a different pattern. That depended on both success in the morning and the CHRNA4 genotype. These results suggest that navigating through an unknown wilderness without landmarks depended initially on ability to form episodic memories (associated with the KIBRA rs17070145 T allele). Later in learning in the afternoon, such navigation depended on ability to focus visuospatial attention (previously associated with the CHRNA4 T allele). Effects of sense of direction (measured with SBSOD) were marginally significant in the morning course.

These results also reveal that the abilities important for wilderness navigation with map and compass change with experience. Early in learning to navigate, both KIBRA genotype (associated with episodic memory) and speed of moving through the course were independent contributors to success. CHRNA4 genotype (previously associated with ability to focus visuospatial attention) was not important early in navigation performance during the morning session. However, in the afternoon session CHRNA4 genotype was important. Benefits of the CHRNA4 T allele combined with previous success at navigation such that individuals who were CHRNA4 T allele carriers and had been successful at the morning navigation exercise were the most successful in the afternoon navigation exercise. CHRNA4 C/C homozygotes who had not been successful in the morning were the least successful in the afternoon. This suggests that ability to benefit from experience was playing a role in performance.

Our hypothesis that the KIBRA rs17070145 SNP modulates spatial navigation was based on evidence that KIBRA is important in memory formation processes in hippocampus (Yoshihama et al., 2009). Our finding of better performance by KIBRA T/T homozy-
gotes during the morning navigation course also supported the one previous study reporting effects of that SNP on navigation performance (Schuck et al., 2013). Despite the limited evidence on KIBRA rs17070145 and navigation, there is a large literature linking better episodic memory to the T allele of this SNP, confirmed in meta-analyses (Milnik et al., 2012). We speculate that the superior performance of KIBRA rs17070145 T/T homozygotes was due in part to better formation of episodic memories for the terrain as they navigated.

Our hypothesis that the BDNF rs6265 SNP modulates spatial navigation was based on previous allelic association evidence (BANNER, BHAT, ETCHAMENDY, JOOBER, & BOHBOT, 2011; Lövđen et al., 2011). Consistent with that, we found evidence that the SB-SOD survey and the BDNF SNP taxed the same ability. The SB-SOD survey determines whether a spatial wayfinding or route-following navigation strategy is preferred and the BDNF rs6265 Met allele carriers have been found to prefer a route-following strategy (BANNER et al., 2011). We also found a relation between BDNF genotype and navigation strategy, but in a direction opposite to that observed by BANNER et al. (2011) in that we found Met carriers claimed a stronger sense of direction than Val/Val homozygotes. However, we found only nonsignificant effects of BDNF on wilderness navigation. While there is a large literature on effects of this BDNF SNP on declarative memory, only a few studies have looked specifically at its effects on navigation (BANNER et al., 2011; Lövđen et al., 2010). A meta-analysis of human BDNF Val66Met allelic association studies confirmed that the Met allele of the Val66Met SNP is associated with poorer declarative memory and lower hippocampal volume (KAMBEITZ et al., 2012), but a larger meta-analysis did not support the association between hippocampal volume and the BDNF Val66Met SNP (HARRISBERGER et al., 2015, 2014).

In contrast to the present study, most previous navigation research has been conducted in settings with constructed rather than with natural landmarks—for example, buildings (LAWTON, 1996), a maze, a simulated city (Gale, Golledge, Pellegrino, & DOHERTY, 1990; Golledge, Ruggles, Pellegrino, & Gale, 1993; Ishikawa, & NAKAMURA, 2012; KIRASIC, ALLEN, & SIGEL, 1984; Montello, 1991). Our findings on BDNF were weak and also inconsistent with those behavioral studies. Our findings on the SB-SOD were trend-level for the morning navigation course, suggesting only a weak effect of sense of direction on wilderness navigation with map and compass. The present work extended previous literature to land navigation in an unfamiliar real-world wilderness environment with map and compass and obtained a result regarding BDNF that was not consistent in direction or significance with previous evidence from constructed environments (BANNER, BHAT, ETCHAMENDY, JOOBER, & BOHBOT, 2011; Lövđen et al., 2011). Additionally, there has been plenty of research investigating performance in virtual environments. The literature shows that virtual and real world navigation is similar and performance across the two domains is highly correlated (RICHARDSON, MONTELLO, & HEGARTY, 1999; WALLER, 2005).

Our hypothesis that the CHRNA4 rs1044396 SNP modulates wilderness navigation with map and compass was based on previous allelic association evidence linking that SNP to ability to focus attention. We recently argued for the existence of a cognitive phenotype associated with the CHRNA4 rs1044396 SNP, such that people with the T allele (a) are slower to disengage the focus of visuospatial attention than C/C homozygotes and (b) preferentially process events within the attentional focus (GREENWOOD, PARASURAMAN, & ESPESETH, 2012). This hypothesis was based on evidence that CHRNA4 T/T homozygotes were particularly slowed on invalidly cued trials (ESPESETH et al., 2006; PARASURAMAN et al., 2005), and were less influenced by precue size in visual search in cueing paradigms (GREENWOOD et al., 2005) and load paradigms (ESPESETH et al., 2010). In the present study, the previously proposed cognitive phenotype of CHRNA4 rs1044396 predicted an effect of this SNP on wilderness navigation success, with the T allele predicted to heighten ability to focus attention iteratively on map, compass, and terrain during navigation. That prediction was supported.

There may be another factor in the effect of CHRNA4 rs1044396 on wilderness navigation. One important difference between navigation using constructed versus using natural landmarks may be the extent of visual processing required. There is evidence that rapid detection of visual stimuli is mediated by cholinergic nicotinic receptors early in processing, namely, at the level of thalamic input to monkey primary visual cortex (DISNEY, AKOI, & HAWKEN, 2007). Consistent with that is human evidence of the importance of nicotinic cholinergic receptors in early vision (KIKUNO et al., 2013). In a rapid scene categorization task, KIKUNO et al. found that categorization performance was modulated by the CHRNA4 rs1044396 SNP. The T allele carriers of that SNP were more accurate in rapid categorization of natural scenes (mountain, forest) with no effect of genotype on detection of man-made scenes (city, highway), although the latter may have had a more limited array of spatial components (KIKUNO et al., 2013). Further, there is animal and human evidence that administration of nicotine facilitates the redirection of visuospatial attention in visual tasks (PHILLIPS, McALONAN, ROBB, & BROWN, 2000; THIEL, ZILLES, & FINK, 2005; WITTE & MARROCCO, 1997). Administration of nicotine to nonsmokers modulated both the effect of cue validity on RT and on brain activation (BOLD signal) in nodes of the dorsal and ventral attention network (VOSSEL, THIEL, & FINK, 2008). Based on this evidence of a role for nicotinic receptors in early vision and in visuospatial attention, we argue that the better performance of CHRNA4 T allele carriers was due to faster visual processing and to more efficient focusing of visuospatial attention on the terrain and the map and compass as the route was followed.

Conclusions and Limitations

The present study used allelic association to extend previous work on navigation in developed environments to wilderness navigation. We found evidence that episodic memory and visuospatial attention are important during navigation using map and compass in a wilderness setting. In contrast, evidence for the importance of both BDNF and sense of direction was weak. It is not clear whether results would be similar for people navigating through a wilderness well-known to them or through a developed environment. However, it should be noted that even in developed environments, people tend to navigate while looking at maps (often on smartphones), making our study with maps closer to real-world practice than studies of navigation through virtual environments without maps.

The present results add to previous evidence of a cognitive phenotype of CHRNA4 rs1044396 by showing this SNP alters...
ability to focus visuospatial attention in a complex task in the real world. Results of the present study predict modulation by CHRNA4 rs1044396 in a range of real-world tasks possessing strong attentional demands.

As we used a candidate gene approach, we acknowledge that other SNPs likely play a role in wilderness navigation. The unbiased genome-wide association (GWA) approach is not well-suited for cognitive phenotypes as the few existing samples with such phenotypes are small. The most relevant cognitive GWA studies used IQ as a phenotype found evidence that human intelligence is due to variation in many genes, each with small effect that do not reach significance (Davies et al., 2011; Benyamin et al., 2014). Therefore, despite the known limitations, the candidate gene approach continues to have a place in investigation of human cognitive phenotypes. In the present study, that approach was informative in revealing interaction between genetics and experience in a navigation task. Further, we found both episodic memory formation and visuospatial attention to be important in wilderness navigation, and neither was previously recognized to have a role in navigation performance.

The generalizability of our results is limited by the all-male sample, in light of previously reported gender differences in navigation (Lawton, 1994, 2001). Further, our participants were undergraduates at a selective military academy.

References


Received September 5, 2014
Revision received January 8, 2016
Accepted January 31, 2016