Cerebral Cortex September 2014;24:2249–2257
doi:10.1093/cercor/bht089
Advance Access publication April 12, 2013

FEATURE ARTICLE
Influence of the BDNF Genotype on Amygdalo-Prefrontal White Matter Microstructure is Linked to Nonconscious Attention Bias to Threat

Joshua M. Carlson[1,], Jiook Cha[2], Eddie Harmon-Jones[4], Lilianne R. Mujica-Parodi[1] and Greg Hajcak[3]

[1]Department of Biomedical Engineering, [2]Program in Neuroscience and [3]Department of Psychology, State University of New York at Stony Brook, Stony Brook, NY 11794, USA and [4]School of Psychology, University of New South Wales, Sydney, NSW 2052, Australia

J.M.C. and J.C. contributed equally to this work.

Address correspondence to Dr Joshua M. Carlson, Department of Biomedical Engineering, Bioengineering Building Room 117, SUNY Stony Brook, NY 11794, USA. Email: carlsonjm79@gmail.com

Cognitive processing biases, such as increased attention to threat, are gaining recognition as causal factors in anxiety. Yet, little is known about the anatomical pathway by which threat biases cognition and how genetic factors might influence the integrity of this pathway, and thus, behavior. For 40 normative adults, we reconstructed the entire amygdalo-prefrontal white matter tract (uncinate fasciculus) using diffusion tensor weighted MRI and probabilistic tractography to test the hypothesis that greater fiber integrity correlates with greater nonconscious attention bias to threat as measured by a backward masked dot-probe task. We used path analysis to investigate the relationship between brain-derived nerve growth factor genotype, uncinate fasciculus integrity, and attention bias behavior. Greater structural integrity of the amygdalo-prefrontal tract correlates with facilitated attention bias to nonconscious threat. Genetic variability associated with brain-derived nerve growth factor appears to influence the microstructure of this pathway and, in turn, attention bias to nonconscious threat. These results suggest that the integrity of amygdalo-prefrontal projections underlie nonconscious attention bias to threat and mediate genetic influence on attention bias behavior. Prefrontal cognition and attentional processing in high bias individuals appear to be heavily influenced by nonconscious threat signals relayed via the uncinate fasciculus.

Keywords: amygdala, anterior cingulate, DTI, dot-probe, uncinate fasciculus

Introduction

Humans have evolved to rapidly respond to signals of potential threat (Ohman et al. 2001), even when these signals are nonconsciously processed (Beaver et al. 2005; Carlson, Fee et al. 2009). This response includes an automatic allocation of attentional resources to the location of potential threat, which serves to prioritize visual cortical processing within this retinotopic location (Carlson et al. 2011). Although affective processing biases are an adaptive aspect of the human fear response (Ohman et al. 2001), vulnerability to anxiety is linked to excessive attention bias to nonconscious threat (Fox 2002; Mogg and Bradley 2002). Furthermore, individual differences in nonconscious attention bias to threat prospectively predict cortisol release during laboratory-based and real-world stress (Fox et al. 2010). Critically, attention bias to threat is not only correlated with anxiety, but appears to play a casual role in its development (MacLeod et al. 2002). Given that attention bias is strongly and causally associated with stress reactivity and anxiety vulnerability, it is important to understand the anatomical pathway by which threat biases cognition and how structural variability in this pathway may relate to variability in attention bias behavior.

Models of cognitive processing biases claim that such biases only occur when multiple stimulus representations compete for attention (Mathews and Mackintosh 1998; Mathews and MacLeod 2002). Under this model, the anterior cingulate cortex (ACC) is thought to serve as a conflict monitor and resolver, while the amygdala is thought to nonconsciously evaluate threat and "bias" the monitoring system (i.e., ACC) in favor of threat. Similarly, Gray and McNaughton's (2000) model states that fear-related or "active avoidance" type behaviors such as increased attention to threat are mediated by the amygdala–ACC system, while during states of uncertainty and anxiety septo-hippocampal activity accompanies the amygdala response to threat. Consistent with these models, accumulating evidence suggests that the amygdala detects and evaluates nonconscious representations of visual threat (Morris et al. 1998; Whalen et al. 1998; Liddell et al. 2005), which are likely relayed via the pulvinar nucleus of the thalamus and the superior colliculus (Morris et al. 1999, 2001; Liddell et al. 2005). Furthermore, amygdala reactivity to nonconscious threat is elevated in a variety of negative affect-related dispositions such as anxiety (Etkin et al. 2004), depression (Sheline et al. 2001), anger (Carlson et al. 2010), and post-traumatic stress disorder (Rauch et al. 2000; Armony et al. 2005). More recent research has linked the facilitation of spatial attention by nonconscious threats to an amygdala–ACC network (Carlson, Reinke et al. 2009), in which amygdala reactivity is positively coupled with ACC activity. Additionally, amygdala activation during nonconscious attention bias to threat is elevated among anxious individuals (Monk et al. 2008). Anatomically, attention bias to threat is correlated with greater ACC gray matter volumes (Carlson, Beacher et al. 2012). Within the prefrontal cortex, the ACC is one of the most densely and reciprocally connected with the amygdala (Porrino et al. 1981; Amaral and Price 1984) and the uncinate fasciculus is the primary white matter tract connecting these structures. Thus, the uncinate fasciculus directly connects the "threat evaluating" amygdala to the "conflict resolving" ACC, and we would therefore expect that the integrity of this tract should positively correlated with attention bias behavior. Yet, this relationship has not been tested.

The extent to which genetic factors influence the integrity of the uncinate fasciculus pathway and, in turn, attention bias behavior is currently unknown. Growth factors such as brain-derived neurotrophic factor (*BDNF*) are critical in regulating neural development, connectivity, and plasticity (Poo 2001; Martinowich and Lu 2008) and, for precisely this reason, genetic variability affecting these growth factors may contribute to variability in white matter integrity across individuals. Here, we turn our attention to a single nucleotide polymorphism in the *BDNF* gene, which results in the substitution of valine (Val) to methionine (Met) at codon 66—the *BDNF* Val66Met polymorphism (Egan et al. 2003). The frequency of the Met/Met (4.5%, 15.9%), Met/Val (27.1%, 50.3%), and Val/Val (68.4%, 33%) genotypes has been shown to differ across ethnic backgrounds (United States [a primarily Caucasian sample] and Japan, respectively; Shimizu et al. 2004). The substitution of Met for Val reduces a number of factors associated with synaptic plasticity and memory such as memory performance, hippocampal activity, synaptic activity, BDNF dendritic expression, and activity-dependent secretion of BDNF (Egan et al. 2003). Additionally, Met/Met mice manifest less neuronal BDNF secretion and display increased fear-related behaviors such as freezing (Chen et al. 2006). Similar to the mouse model, Met/Met humans are at increased risk for mood disorders (Montag, Basten et al. 2010) and Met+ (i.e., Met/Met and Met/Val) adults display heightened rumination (Hilt et al. 2007; Beevers et al. 2009) and disrupted fear conditioning (Hajcak et al. 2009). Additionally, the Met-*BDNF* genetic variant has been linked to increased depression in women across ethnic backgrounds (Verhagen et al. 2010). In human functional neuroimaging research, Met+ individuals show a hyperactive amygdala response to emotional stimuli (Montag et al. 2008)—an effect exaggerated in anxious individuals (Lau et al. 2010). Human structural neuroimaging research indicates that Met allele carriers show smaller amygdala, hippocampus, caudate, and dorsolateral prefrontal volumes, compared with Val/Val individuals (Pezawas et al. 2004). However, in terms of white matter, greater fiber integrity has been linked to the Met-*BDNF* genetic variant in a number of the major fiber tracts (Chiang et al. 2011) and in particular the uncinate fasciculus (Tost et al. 2013). Given the prevalent impacts of *BDNF* Val66Met on neural structure including white matter (Chiang et al. 2011; Tost et al. 2013) and fear-related behavior (Chen et al. 2006), we hypothesized that Met+ individuals would display greater uncinate fasciculus fiber integrity and increased attentional bias to nonconscious threat.

The primary goal of this study was to test the relationship between amygdalo-prefrontal tract integrity and attention bias behavior. Based on the models (Mathews and Mackintosh 1998; McNaughton and Gray 2000; Mathews and MacLeod 2002) and research (Carlson, Reinke et al. 2009; Carlson, Beacher et al. 2012) outlined above, we hypothesized that greater amygdalo-prefrontal tract integrity predicts greater levels of nonconscious attention bias to threat. To test this hypothesis, we used a recently designed global tractography method (Yendiki et al. 2011) to reconstruct the entire uncinate fasciculus tract and measured nonconscious attention bias to threat with a backward masked fearful face dot-probe task. Further, we examined the role of the *BDNF* Val66Met polymorphism on this brain–behavior relationship (Martinowich and Lu 2008; Montag et al. 2008; Montag, Basten et al. 2010; Tost et al. 2013). Specifically, we used path analysis to test the hypothesis that differences in *BDNF* genotype would influence fiber integrity and in turn attention bias behavior.

Materials and Methods

Participants

Forty (16 females) consenting adults 19–25 years old participated. Our sample contained 18 Caucasians, 3 African Americans, 15 Asians, 0 Hispanic, and 4 individuals of other ethnicities (Ethnicity was neither associated with attention bias to threat [$F_{3,36} = 1.82$, $P = 0.16$] nor uncinate fasciculus integrity, $F_{3,36} = 1.27$, $P = 0.3$.). Thirty-five reported being right handed. Potential participants were screened for metal in their bodies. The Institutional Review Board of Stony Brook University approved this study. Participants were compensated for their time.

Dot-Probe Task

The task was performed in a small testing room outside the scanner. Stimuli were presented on a 60-Hz PC monitor and stimulus presentation was controlled by E-Prime (Psychology Software Tools, Pittsburg, PA, USA). Facial stimuli were from a standardized database (Gur et al. 2002). Four individual identities (2 males) of fearful and neutral grayscale faces were used for the initial (i.e., masked) faces and a different female identity with an open-mouthed happy facial expression was used as a mask. As depicted in Figure 1*a*, trials started with a white fixation cue (+) centered on a black background for 1000 ms. Afterward, 2 faces were then simultaneously presented to the left and right of fixation (33 ms). Each face subtended ~$5 \times 7°$ of visual angle. Faces were separated by 14°. To limit the potential influence of perceptual inconsistencies, these initial faces were instantly masked with an open-mouth happy face (100 ms) offset by 1° on the vertical axis (Carlson and Reinke 2008). A target dot immediately followed in either the location of the left or the right face and remained on the screen until a response was made. Participants responded to the location of the dot using the numeric pad on a keyboard: pressing the "1" key with their right index finger for left-sided targets and the "2" key with their right middle finger for right-sided targets. The fixation cue remained in the center of the screen throughout the entirety of each trial. Participants were instructed to always fixate on this cue.

Trials used to calculate attention bias scores contained one fearful and one neutral face. For half of these trials, the target dot was presented in a spatially congruent location to the fearful face, while for the other half the target dot was spatially incongruent (i.e., appeared behind the neutral face). The facilitation of spatial attention by backward masked fearful faces is marked by faster reaction times on congruent compared with incongruent trials. Thus, attention bias scores were calculated as the mean difference between congruent and incongruent reaction times. More negative values are indicative of an attention-related reduction of reaction time on congruent compared with incongruent trials. The task contained 40 congruent and 40 incongruent trials equally presented in each visual field plus 40 neutral-neutral trials.

Participants also completed a task designed to assess awareness of the backward masked faces. Participants were instructed that each trial would contain 2 sets of faces presented in rapid succession and that they should identify the facial expressions of the first set of faces. Stimulus presentation for this task was identical to the dot-probe task with the exception that following the masked faces participants were prompted to use a keyboard to indicate whether they saw a fearful face on the left, a fearful face on the right, or 2 neutral faces. The task included 60 trials: 20 of each type.

Genotyping Procedure

Participants were genotyped for Val66Met *BNDF* polymorphism (Participants were also genotyped for the *5-HTTLPR*. Given the very small number of $\text{long}_A\text{long}_A$ individuals [$n = 4$] and the homogenous effects of short-short [$n = 19$] and short-long [$n = 17$] individuals, we were unable to explore the effects of the *5-HTTLPR*. However, it should be noted that *BDNF* and *5-HTTLPR* genotypes are believed to have interacting influences on brain morphometry (Pezawas et al. 2008) and the interpretation of the current *BDNF* genotype effects should consider our large portion of S-allele carriers.). The genotyping

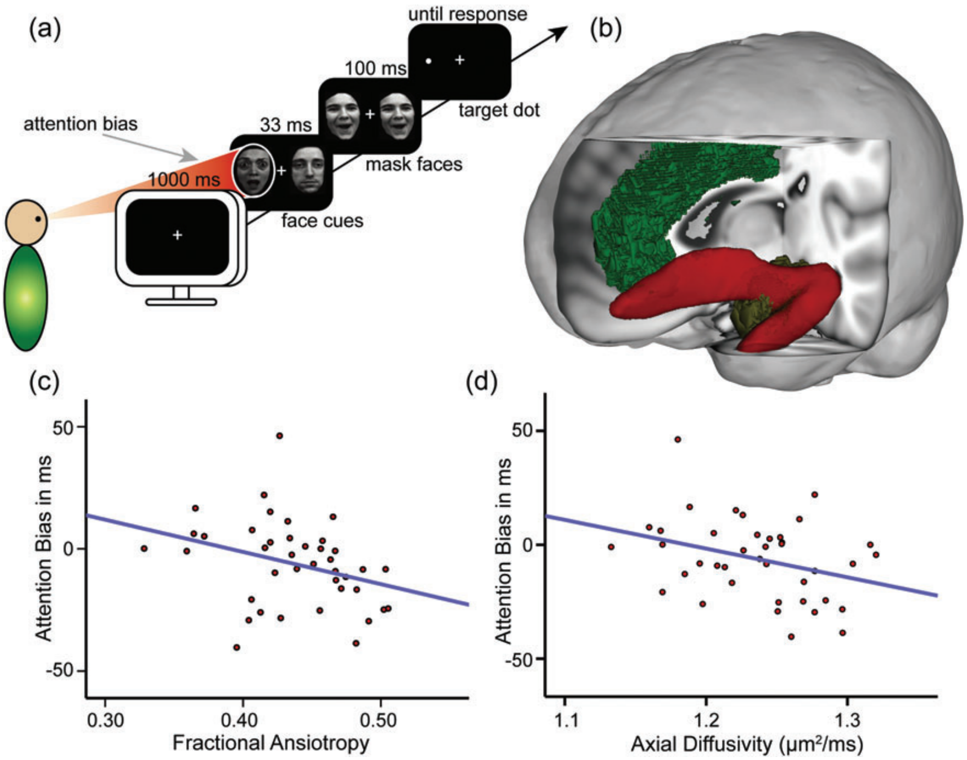

Figure 1. (*a*) An example of a congruent trial. Attention bias is calculated as the difference between masked fear congruent and incongruent dot-probes, where greater attention to threat is reflected by a more negative value. (*b*) Posterior distribution of the reconstructed uncinate fasciculus averaged across 40 subjects and thresholded at 20% maximum. The uncinate fasciculus (red) connects the amygdala (brown) to ventral prefrontal and anterior cingulate (green) cortices. (*c*) Scatter plots depicting correlations between attention bias and left uncinate fasciculus fractional anisotropy and (*d*) axial diffusivity.

procedures for BDNF have previously been described (Hajcak et al. 2009). Briefly, we used the QuickExtract DNA Extraction Solution (Epicentre Technologies, Madison, WI, USA) to extract DNA from buccal cells, and a high-resolution melt analysis for genotype analysis. Our sample contained 18 Met carriers (Met/Met = 6 & Met/Val = 12) and 22 homozygous Val/Val individuals. Using the Hardy–Weinberg equilibrium calculator (Rodriguez et al. 2009) our *BDNF* genotype distribution did not deviate from the expected distribution ($\chi^2(1) = 3.27$, $P > 0.05$).

Image Acquisition

Participants were scanned at the Stony Brook University Social, Cognitive, and Affective Neuroscience center with a 3-Tesla Siemens Trio whole-body magnetic resonance image scanner. DTIs were collected using the following parameters: repetition time (TR) = 5500 ms, echo time (TE) = 93 ms, field of view (FOV) = 220 × 220 mm, matrix = 120 × 220 × 220, voxel size = 1.7 × 1.7 × 3.0 mm, echo planar imaging factor = 128, slices = 40, slice thickness = 3 mm, Bandwidth = 1396 Hz/pixel, GRAPPA acceleration factor = 2. The series included 2 initial images acquired without diffusion weighting and with diffusion weighting along 40 noncollinear directions ($b = 800\ \mathrm{sm}^{-2}$). T_1-weighted images were acquired in the same session with the following parameters: TR = 1900 ms, TE = 2.53, flip angle = 9°, FOV = 176 × 250 × 250 mm, matrix = 176 × 256 × 256, and voxel size = 1 × 0.98 × 0.98 mm.

Image Processing

We corrected eddy current distortions for each subject, and registered individual images without diffusion weighting to T_1 images. We used FDT (FMRIB software library's Diffusion Toolbox 2.0) for DTI preprocessing. We performed cortical parcellation and subcortical segmentation from individual's T_1-weighted image employing an automated cortical reconstruction and volumetric segmentation tool, Freesurfer 5.1 (http://surfer.nmr.mgh.harvard.edu/).

Global Tractography: TRACULA

We performed a recently developed global tractography method, TRActs Constrained bv UnderLying Anatomy (TRACULA; Yendiki et al. 2011), to reconstruct our a priori white matter tract of interest, the uncinate fasciculus. Global tractography parameterizes a connection between 2 regions at a global level, instead of tracking through a local orientation field. This global approach has several advantages over local tractography in that it eschews local uncertainty issues due to noise or partial volume effects, and it can increase the sensitivity and robustness of the tractography solutions by informing tractography process of a known connection between 2 regions (Jbabdi et al. 2007). Furthermore, TRACULA minimizes bias due to the need of manual intervention, for example, to set arbitrary angle or length for tractography or to draw anatomical boundaries for tracts, which potentially lead to spurious results. TRACULA uses a Bayesian framework for global tractography with anatomical priors (Yendiki et al. 2011). Prior information on the surrounding anatomy of the pathway are derived from training datasets of 33 healthy adults, of which major pathways including the uncinate fasciculus are identified by a neuroanatomist (for detailed manual labeling procedures, see Yendiki et al. 2011). Notably in TRACULA, 2 end regions for the tractography algorithm are obtained by intersection of the pre-labeled tract atlas, and the brain areas of a test subject, parcellated and segmented in Freesurfer. Based on this prior knowledge, posterior distributions of tracts are estimated via a Markov Chain Monte Carlo algorithm (see individual tracts in Fig. 2). Statistics on standard diffusion measures (i.e., fractional anisotropy [FA], axial diffusivity [AD], radial diffusivity, and mean diffusivity) are then extracted from the estimated posterior pathway distribution.

DTI Metrics and Statistical Analysis

Based on earlier work (Carlson, Reinke et al. 2009; Carlson, Beacher et al. 2012), we tested the directional hypothesis that greater attention bias would be associated with greater uncinate fasciculus fiber

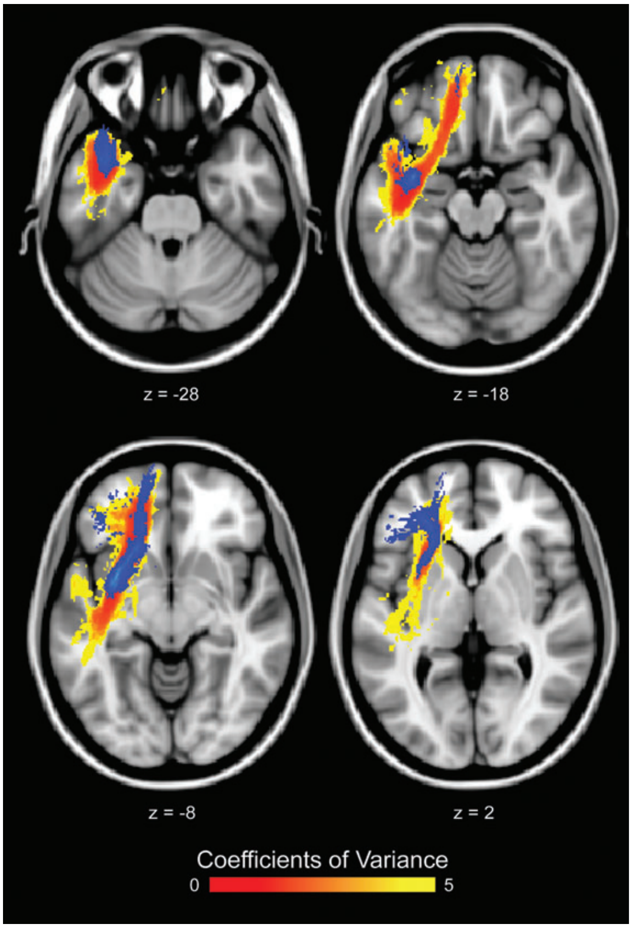

Figure 2. Variability map of the reconstructed UF. The voxelwise coefficients of variance map (shown in red-yellow) of the reconstructed uncinate fasciculus showed shared inmost region and highly variable outmost region. A probabilistic uncinate fasciculus atlas (shown in blue; JHU White-Matter Tractography Atlas; http://fsl.fmrib.ox.ac.uk/fsl/fslview/) was overlapped. The voxelwise CV map was derived from posterior distribution map in each subject.

integrity. Based on the reports that the Met-*BDNF* variant of Val66Met single nucleotide polymorphism (SNP) is associated with greater white matter integrity (Chiang et al. 2011) and increased fear-related behaviors (Chen et al. 2006), we tested the directional hypotheses that Met allele carriers would show greater fiber integrity in the uncinate fasciculus and greater attention to threat. Our primary measure of interest was FA, which is an indicator of fiber integrity and degree of myelination (Le Bihan 2003). Radial and axial diffusivity (RD and AD), which, respectively, measure the degree of myelination and axonal integrity (Song et al. 2003), were also assessed. FA was positively correlated with AD (left: $r = 0.62$, $P = 0.00004$ right: $r = 0.52$, $P = 0.0003$), but negatively with radial diffusivity (left: $r = -0.90$, $P < 0.00001$; right: $r = -0.90$, $P < 0.00001$). Thus, we tested an inverse relationship with radial diffusivity. Given our directional tests, we used 1-tailed *P*-values.

We diagnosed potential outliers for every test at a threshold of Cook's distance of $4/n$ (i.e., 0.1). When potential outliers were detected, robust linear regression was used. Robust regression in Stata 12 used a stepwise weighting estimation (i.e., Huber weighting and biweights) and a biweight tuning constant of 6 was used (Goodall 1983).

Path Analysis

We combined path analysis and a model comparison method in AMOS 18 (SPSS, Inc.) to test the serial relationship of *BDNF* SNP, FA of the left uncinate fasciculus, and attention bias. We chose path analysis because it can effectively differentiate direct and indirect effects, and with aid of structural equation model functionality (e.g., bootstrap model comparison method), it provides a useful approach for hypothesis testing. We first built the most intuitive model (Model 1), which assumed serial effects of *BDNF* genotype onto FA and FA onto attention bias. We then constructed 5 variations and compared model fit to choose the best one. Confounding variables in the model included age, sex, and ethnicity for the effects of BDNF on the FA in addition to awareness level and information processing speed for attention bias.

Given our sample size of forty and the numbers of parameters included in the model, our degrees of freedom (*df*) were only 18 for the intuitive model. Thus, a goodness of model fit could be driven by only a few outliers. Our data indeed contained one potential outlier whose attention bias index is more than 2 SD + average (Fig. 1*c*), and this outlier has a significant impact on the goodness of model fit: in case of the intuitive model (Model 1), χ^2/df changed from 1.108 (without the outlier) to 0.696 (with the outlier). We thus excluded this outlier from the path analyses. No outliers were found in FA. For model comparison, we employed a bootstrapping method following the Linhart and Zucchini's approach (Linhart and Zucchini 1986) in addition to comparison of standard goodness of fit statistics. The bootstrapping approach involves 4 steps. First, we generated bootstrap samples considering the original data as the population for the purpose of sampling. Second, the 5 models were fitted to every 10 000 bootstrap samples using the maximum likelihood function. For each iteration, the discrepancy between each bootstrap sample and the bootstrap population was calculated. Third, the average discrepancy across bootstrap samples for each model was calculated. Fourth, the best model among the 5 was selected based on the mean discrepancy. We additionally considered standard goodness of fit measures, such as Akaike's Information Criterion (AIC), the root mean square error of approximation (RMSEA), and the comparative fit index (CFI). Cutoff criteria for RMSEA (<0.06) and CFI (0.95) were considered (Hu and Bentler 1999).

Results

Behavior

Reaction time data were restricted to correct responses occurring within 150–750 ms (Carlson and Reinke 2008), which resulted in 2.5% of the data being discarded for incorrect responses and another 2% discarded for premature or delayed responses. Thus, 95.5% of the reaction time data were used for analysis. Overall, participants responded faster on congruent compared with incongruent trials (mean congruent-incongruent difference = −6.20 ms, SD = 17.50, $t_{39} = -2.24$, $P = 0.02$) suggesting that at the group-level, attention was captured by backward masked fearful faces (It should be noted that age [$r = -0.16$, $P = 0.34$], gender [$t_{38} = 0.07$], handedness [$t_{38} = 0.97$], and ethnicity [$F_{3,36} = 1.82$, $P = 0.16$] were not associated with attention bias scores.). For correlation analyses, "Attention Bias" scores were calculated as the congruent-incongruent difference, where more negative values are indicative of faster responses on congruent trials and thus, greater attentional bias to threat. Participants' performance on a post-task assessment of awareness was at chance ($t_{39} = 0.82$, $P = 0.21$).

Reconstructed Uncinate Fasciculus

We reconstructed the uncinate fasciculus in each subject (Supplementary Fig. 1). In order to quantify variability of the reconstructed tracts, we examined voxelwise coefficients of variance (Fig. 2). The tracts showed shared configuration in the inmost region (i.e., low coefficients of variance) and highly variable configuration in the outmost region (i.e., high coefficients of variance). Each posterior distribution of the uncinate fasciculus had on average 13 715 voxels (±495; mean standard error [SEM]), and an average of 38.6% (±1.3; SEM) of them were nonoverlapping with the probabilistic atlas of the uncinate fasciculus (JHU White-Matter Tractography Atlas; http://fsl.fmrib.ox.ac.uk/fsl/fslview/; Supplementary Table). An average of 79.9% (±0.7; SEM) of the atlas was nonoverlapped with the posterior distribution map. These results indicate a high degree of uncinate fasciculus variability across individuals and highlight the problem of solely using a standardized atlas for DTI analysis without consideration of this large degree of individual variability.

Correlations with Attention Bias

As predicted, greater left uncinate fasciculus FA ($r_{\text{partial}} = -0.36$, $P = 0.01$; Fig. 1*c*) and AD ($r_{\text{partial}} = -0.35$, $P = 0.02$; Fig. 1*d*) were correlated with greater attention bias to threat with a trend observed for the right uncinate fasciculus (FA: $r_{\text{partial}} = -0.20$, $P = 0.11$; AD: $r_{\text{partial}} = -0.25$, $P = 0.07$), after controlling for participants' level of awareness and speed of information processing (Wiens 2006; Turken et al. 2008). These effects were robust to potential outliers (FA: $t_{36} = -2.33$, $P = 0.01$; AD: $t_{36} = -1.67$, $P = 0.053$, robust linear regression; see Materials and Methods section for outlier diagnosis). The overall effect was in an uncinate-fasciculus-specific manner as we did not observe a correlation with the mean FA of the entire brain ($r = -0.07$, $P = 0.32$).

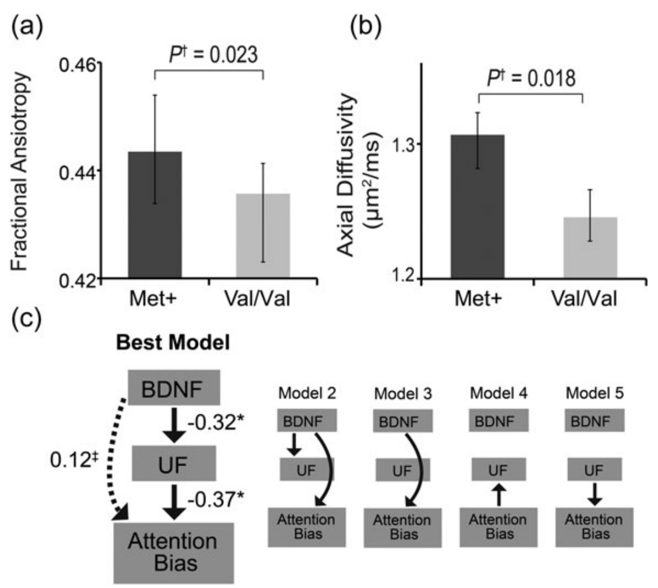

Figure 3. The Met + BDNF variant (Met/Met and Met/Val) as compared to Val/Val, resulted in greater fractional anisotropy (*a*) and axial diffusivity (*b*) in the left uncinate fasciculus. Effects controlled for age, sex, and ethnicity. (*c*) Five regression models containing BNDF Val66Met, FA of uncinate fasciculus, and attention bias were compared. The best model selected based on multiple model fit criteria suggests that BDNF Val66Met influences uncinate fasciculus integrity, which in turn influences attention bias to threat. Bold arrows denote estimated direct effects. A dotted arrow in the best model indicates an indirect effect. BDNF, BDNF Val66Met polymorphism; UF, fractional anisotropy of the left uncinate fasciculus. †Significance of coefficients in robust linear regression. $^{*}P < 0.05$; $^{\ddagger}P = 0.066$.

Impacts of BDNF SNP Variant on Fiber Integrity and Attention Bias

We then explored a link between uncinate fasciculus fiber integrity and genetic factors. As predicted, we found a significant effect of the Met allele (both Met/Val and Met/Met) on FA ($t_{35} = -2.08$, $P = 0.02$, robust linear regression) and AD ($t_{35} = -2.18$, $P = 0.02$) in the left uncinate fasciculus (Fig. 3*a*, *b*). These effects controlled for ethnicity, sex, and age. We observed a trend-level effect of Met-*BDNF* variant on attention bias ($P = 0.13$, robust linear regression) when controlling for awareness and speed of information processing. Thus, the results suggest that the Met-*BDNF* variant is associated with greater uncinate fasciculus integrity, which is associated with attention bias to threat. This may suggest a serial impact of the genetic variant to white matter structure to attention bias behavior.

To test such a relationship directly, we performed a path analysis between the *BDNF* SNP, FA of the uncinate fasciculus and attention bias. We built a model accounting for the serial relationship and 4 alternatives, and compared them. Confounding variables were included (see Materials and Methods section). As predicted, the model of the serial influences showed the best goodness of model fit: lowest AIC (55.9) and mean discrepancy of bootstrap samples versus population (49.3), highest Comparative Fit Index (0.93), and root mean square error of approximation (0.053) (Fig. 3*c*, Table 1). In this model, the total effect of *BDNF* SNP on FA was $\beta = -0.32$, $P = 0.043$ (Bias-corrected using Bootstrap estimation) and the total effect of FA on attention bias was $\beta = -0.37$, $P = 0.03$. The indirect effect of the *BDNF* SNP on attention bias via FA was $\beta = 0.12$, $P = 0.066$). Overall, the model accounted for 35.3% of variance in the FA and 20.6% of AI variance (squared multiple correlations). These results strongly support the serial relationship of gene to white matter structure to behavior.

Discussion

We provide evidence linking uncinate fasciculus microstructure to elevated attention bias to nonconscious threat. The direction of this correlation suggests that for hyperthreat attentive individuals, the ACC and amygdala together play a role in potentiating the nonconscious threat response. Our results further suggest that the Met allele of the *BDNF* Val66Met polymorphism elevates attention bias to threat through its influence on amygdalo-prefrontal connectivity.

Table 1
Comparison of linear regression models

Model	*Df*	χ^2/df	Discrepancy of bootstrap samples and population	AIC	CFI	RMSEA	Squared multiple correlations
Model 1	18	1.11*	49.3*	55.9*	0.93*	0.053*	UF, 0.353; AI, 0.206
Model 2	18	1.32	53.0	59.8	0.79	0.092	UF, 0.353; AI, 0.101
Model 3	19	1.49	55.4	62.3	0.67	0.113	UF, 0.216; AI, 0.101
Model 4	19	1.18	50.6	56.3	0.88	0.068	UF, 0.383; AI, 0.060
Model 5	19	1.28	51.7	58.4	0.81	0.086	UF, 0.216; AI, 0.198
Independent model	28	2.00	–	72.2		0.163	

Note: *Indicating best goodness of model fit in each criterion. AI, attention bias; UF, FA of the uncinate fasciculus.

Amygdala–Prefrontal Integrity and Attention Bias to Threat

Similar to the amygdala (Morris et al. 1998; Whalen et al. 1998; Liddell et al. 2005), the ACC is activated in response to nonconscious threat signals (Liddell et al. 2005; Williams, Liddell et al. 2006). Both the amygdala and ACC are hyperactive in response to nonconscious threats in anxiety disorders such as post-traumatic stress disorder (Bryant et al. 2008; Kemp et al. 2009) and are positively coupled during nonconscious threat processing (Williams, Das et al. 2006). Given evidence that the amygdala receives representations of nonconscious threat through a subcortical route (Morris et al. 1999; Morris et al. 2001; Liddell et al. 2005), the logical flow of information processing would be that the amygdala first detects these nonconscious fear representations and then relays this threat signal to the ACC via the uncinate fasciculus. The existence of such forward projections is supported by anatomical studies in monkeys (Porrino et al. 1981; Amaral and Price 1984). The ACC is thought to contain cognitive (dorsal) and affective (ventral) subdivisions (Bush et al. 2000), both of which appear to play a role in conflict monitoring and resolution (Botvinick et al. 1999; Etkin et al. 2006). We recently identified attention bias-related morphological variability in an ACC region at the conjunction of the traditional cognitive and emotion subdivisions (Carlson, Beacher et al. 2012). Greater attentional bias to threat was correlated with greater gray matter volume. Taken together, the data support the model purported by Mathews and Mackintosh (1998). Consistent with this model, we speculate that nonconscious threat-related information, detected in the amygdala, is relayed via the uncinate fasciculus to the ACC and during conditions of conflict (i.e., 2 facial expressions competing for attention), this threat signal "biases" the ACC to resolve conflict by favoring threat (at least for high bias individuals). Furthermore, it appears that for high bias individuals, the integrity of the fibers connecting the amygdala to the ACC are strengthened, which presumably results in a greater amygdala-driven threat bias.

There is increasing focus on cognitive processing biases, such as increased attention to threat, as causal factors in the development and maintenance of anxiety disorders (MacLeod et al. 2002). As such, attention bias modification (ABM) was conceived as a treatment option where anxiety is alleviated through a training regiment that reduces an individual's attention bias to negative information. After a decade of ABM research, it appears that this treatment option has an efficacy comparable to selective serotonin reuptake inhibitors and cognitive behavioral therapy (Hakamata et al. 2010). Additional research suggests that training, on the order of hours to weeks, in both motor and cognitive domains leads to structural changes in gray and white matter observable in MRI (Scholz et al. 2009). Given the current results and earlier reports linking gray matter volume to attention bias behavior (Carlson, Beacher et al. 2012), one direction for future research would be to assess the impact of ABM treatment in reorganizing the amygdalo-prefrontal system. We hypothesize that greater treatment efficacy should coincide with a "reprogramming" of the underlying brain mechanisms. If this is true, structural biomarkers such as amygdala-prefrontal integrity may provide a definitive and stable measurement to tract the recovery of anxiety following ABM treatment. Although our initial evidence that neuroanatomical white matter structure correlates with attention bias to threat shows promise for measuring the efficacy of ABM treatment, further research is needed. As we did not screen participants for mental health status, it is particularly important that the relationship between attentional bias and amygdala-prefrontal integrity is studied in clinically anxious samples.

Attentional bias to threat is an important fear-related behavior that has been linked to increased anxiety (Fox 2002; Mathews and MacLeod 2002; Mogg and Bradley 2002). However, fear and anxiety are not synonymous. Anxiety refers to a prolonged state of worry characterized by uncertainty in the risk assessment of potential (future) danger, while fear refers to a brief "fight or flight" response to a specific threat (Gray and McNaughton 2000; Sylvers et al. 2011). In Gray and McNaughton's (2000) model, anxiety arises from the activation of the septo-hippocampal "Behavioral Inhibition System" in conjunction with the amygdala threat response. With this distinction in mind, it is worth noting that previous DTI studies on trait or group level anxiety have produced mixed results in terms of the direction of the relationship (for review, see Ayling et al. 2012). Although a recent study with a large sample found that high trait anxious males have greater structural integrity of the left hemisphere uncinate fasciculus (Montag et al. 2012), a majority of studies (Kim and Whalen 2009; Pacheco et al. 2009; Phan et al. 2009; McIntosh et al. 2012; Tromp et al. 2012) have reported lower fiber integrity (e.g., FA) of the uncinate fasciculus for high anxious individuals (or those at genetic risk for anxiety; *5-HTTLPR* short allele). Given that anxiety is associated with the apprehension or worry about a potentially threatening future event, we would expect this response to be initiated by a top-down mechanism (i.e., prefrontal to amygdala). Alternatively, fear responses such as increases in attention to threat are immediate bottom-up stimulus-driven events (i.e., amygdala to prefrontal). Thus, given that amygdalo-prefrontal communication is reciprocal (Porrino et al. 1981; Amaral and Price 1984), it is likely that fear-related behaviors are linked to heightened "bottom-up" cognitive bias, whereas anxiety is linked to deficits in "top-down" signals. Additionally, question–answer type measures of anxiety, which are used in trait anxiety questionnaires and the structured clinical interview, are more likely to tap into reflective higher order top-down mechanisms. Regardless, it is likely that different aspects of fear and anxiety are differentially influenced by amygdala-prefrontal communication, and it may therefore be more meaningful to relate variation in brain structure to specific symptom-relevant behavioral measures, rather than broadly defined traits or disorders. Thus, further DTI research on a variety of fear- and anxiety-related behaviors is needed to better understand how fiber integrity relates to different aspects of fear and anxiety.

Amygdala–Prefrontal Integrity and the BDNF Polymorphism

BDNF is associated with synaptic plasticity and Met/Met individuals are at increased risk for mood disorders (Martinowich and Lu 2008; Montag, Basten et al. 2010). Here, we extend these effects to attention bias to threat via uncinate fasciculus tract integrity. Our results complement earlier research suggesting that Met+ individuals have a hyperactive amygdala response to emotional stimuli (Montag et al. 2008), especially in anxious individuals (Lau et al. 2010), and are more likely to display anxiety- and fear-related behaviors such as rumination (Hilt et al. 2007; Beevers et al. 2009) and the generalization of fear conditioning (Hajcak et al. 2009). Furthermore, our results add to a growing body of research linking variability in attentional bias to threat to an underlying genetic component (Beevers et al. 2007; Osinsky et al. 2008; Fox et al. 2009; Elam et al. 2010; Kwang et al. 2010; Perez-Edgar et al. 2010; Carlson, Mujica-Parodi et al. 2012). Our results are particularly informative in that they suggest that the *BDNF* gene first influences the integrity of the uncinate fasciculus and this influence contributes to variability in one's allocation of attentional resources toward potential threats. Specifically, we found the Met allele carriers have greater levels of uncinate fasciculus FA and AD. In animal models, FA is an indicator of fiber integrity and degree of myelination (Le Bihan 2003), while AD is thought to measure axonal integrity (Song et al. 2003). Thus, if these models apply to the human brain, our results may suggest that the *BDNF* gene influences the mechanisms regulating the degree of myelination, axonal integrity, and general fiber integrity of the uncinate fasciculus, which ultimately contributes to variability in nonconscious attention bias across individuals.

Although BDNF is known to affect synaptic plasticity, it is still unclear how the *BDNF* Val66Met polymorphism influences white matter integrity in the human brain, and the neuroimaging literature in this area has produced conflicting results. For example, in one study, there was no association between the *BDNF* Val66Met polymorphism and white matter integrity (Montag, Schoene-Bake et al. 2010), while in other research, the Met-*BDNF* genetic variant was linked to greater fiber integrity (e.g., increase FA or decreased radial diffusivity) in various major fibers, such as the cingulum bundle, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and uncinate fasciculus (Chiang et al. 2011; Voineskos et al. 2011; Tost et al. 2013). It should be noted that the majority of the fiber integrity research on the *BDNF* Val66Met polymorphism used voxelwise approaches (except for Voineskos et al. 2011). While statistically stringent and suitable for exploratory analyses, this method may over look smaller, yet meaningful, effects. On the other hand, the present study focused on the global integrity of an a priori white matter pathway and revealed a localized effect of the *BDNF* Val66Met polymorphism on uncinate fasciculus FA and AD. Thus, future hypothesis-driven research may benefit from similarly focused analyses. We should note that our sample was of mixed ethnicity (see Materials and Methods section for details). Although ethnicity was not associated with attentional bias to threat or uncinate fasciculus integrity in our sample and prior work has shown that ethnicity does not impact the relationship between BDNF and depression (Verhagen et al. 2010), future research should directly assess the effects of ethnicity on uncinate fasciculus integrity in a larger sample. Nevertheless, our results suggest that the *BDNF* genotype influences uncinate fasciculus fiber integrity, which is in turn linked to facilitated attention to nonconscious threat.

In conclusion, our results link individual differences in amygdalo-prefrontal white matter integrity to nonconscious attention bias to threat and the *BDNF* genotype. These results provide evidence for the notion that some individuals may be "hard-wired" to focus on the negative side of life.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Funding

Research was supported by the National Science Foundation: BCS-0643348 (E.H.J.), BCS-0921565 (E.H.J.), and CBET-0954643 (L.R.M.P.); Office of Naval Research: N0014-04-1-005 (L.R.M.P.); and the Army Research Office: W911NF1110246 (L.R.M.P. and J.M.C.).

Notes

Conflict of Interest: None declared.

References

Amaral DG, Price JL. 1984. Amygdalo-cortical projections in the monkey (Macaca-Fascicularis). J Comp Neurol. 230:465–496.

Armony JL, Corbo V, Clement MH, Brunet A. 2005. Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. Am J Psychiatry. 162:1961–1963.

Ayling E, Aghajani M, Fouche JP, van der Wee N. 2012. Diffusion tensor imaging in anxiety disorders. Curr Psychiatry Rep. 14:197–202.

Beaver JD, Mogg K, Bradley BP. 2005. Emotional conditioning to masked stimuli and modulation of visuospatial attention. Emotion. 5:67–79.

Beevers CG, Gibb BE, McGeary JE, Miller IW. 2007. Serotonin transporter genetic variation and biased attention for emotional word stimuli among psychiatric inpatients. J Abnorm Psychol. 116:208–212.

Beevers CG, Wells TT, McGeary JE. 2009. The BDNF Val66Met polymorphism is associated with rumination in healthy adults. Emotion. 9:579–584.

Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature. 402:179–181.

Bryant RA, Kemp AH, Felmingham KL, Liddell B, Olivieri G, Peduto A, Gordon E, Williams LM. 2008. Enhanced amygdala and medial prefrontal activation during nonconscious processing of fear in posttraumatic stress disorder: an fMRI study. Hum Brain Mapp. 29:517–523.

Bush G, Luu P, Posner MI. 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci. 4:215–222.

Carlson JM, Beacher F, Reinke KS, Habib R, Harmon-Jones E, Mujica-Parodi LR, Hajcak G. 2012. Nonconscious attention bias to threat is correlated with anterior cingulate cortex gray matter volume: a voxel-based morphometry result and replication. Neuroimage. 59:1713–1718.

Carlson JM, Fee AL, Reinke KS. 2009. Backward masked snakes and guns modulate spatial attention. Evol Psychol. 7:527–537.

Carlson JM, Greenberg T, Mujica-Parodi LR. 2010. Blind rage? Heightened anger is associated with altered amygdala responses to masked and unmasked fearful faces. Psychiatry Res. 182:281–283.

Carlson JM, Mujica-Parodi LR, Harmon-Jones E, Hajcak G. 2012. The orienting of spatial attention to backward masked fearful faces is associated with variation in the serotonin transporter gene. Emotion. 12:203–207.

Carlson JM, Reinke KS. 2008. Masked fearful faces modulate the orienting of covert spatial attention. Emotion. 8:522–529.

Carlson JM, Reinke KS, Habib R. 2009. A left amygdala mediated network for rapid orienting to masked fearful faces. Neuropsychologia. 47:1386–1389.

Carlson JM, Reinke KS, LaMontagne PJ, Habib R. 2011. Backward masked fearful faces enhance contralateral occipital cortical activity for visual targets within the spotlight of attention. Soc Cogn Affect Neur. 6:639–645.

Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, Herrera DG, Toth M, Yang C, McEwen BS et al. 2006. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science. 314:140–143.

Chiang MC, Barysheva M, Toga AW, Medland SE, Hansell NK, James MR, McMahon KL, de Zubicaray GI, Martin NG, Wright MJ et al. 2011. BDNF gene effects on brain circuitry replicated in 455 twins. Neuroimage. 55:448–454.

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M et al. 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 112:257–269.

Elam KK, Carlson JM, DiLalla LF, Reinke KS. 2010. Emotional faces capture spatial attention in 5-year-old children. Evol Psychol. 8:754–767.

Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. 2006. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron. 51:871–882.

Etkin A, Klemenhagen KC, Dudman JT, Rogan MT, Hen R, Kandel ER, Hirsch J. 2004. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron. 44:1043–1055.

Fox E. 2002. Processing emotional facial expressions: the role of anxiety and awareness. Cogn Affect Behav Neurosci. 2:52–63.

Fox E, Cahill S, Zougkou K. 2010. Preconscious processing biases predict emotional reactivity to stress. Biol Psychiatry. 67:371–377.

Fox E, Ridgewell A, Ashwin C. 2009. Looking on the bright side: biased attention and the human serotonin transporter gene. Proc Biol Sci. 276:1747–1751.

Goodall C. 1983. M-estimators of location: an outline of the theory. In: Hoaglin DC, Mosteller F, Tukey JW, editors. Understaning robust and exploratory data analysis. New York: Wiley. p. 339–431.

Gray JA, McNaughton N. 2000. The neuropsychology of anxiety: an enquiry into the functions of the septo-hippocampal system. Oxford: Oxford University Press.

Gur RC, Sara R, Hagendoorn M, Marom O, Hughett P, Macy L, Turner T, Bajcsy R, Posner A, Gur RE. 2002. A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. J Neurosci Methods. 115:137–143.

Hajcak G, Castille C, Olvet DM, Dunning JP, Roohi J, Hatchwell E. 2009. Genetic variation in brain-derived neurotrophic factor and human fear conditioning. Genes Brain Behav. 8:80–85.

Hakamata Y, Lissek S, Bar-Haim Y, Britton JC, Fox NA, Leibenluft E, Ernst M, Pine DS. 2010. Attention bias modification treatment: a meta-analysis toward the establishment of novel treatment for anxiety. Biol Psychiat. 68:982–990.

Hilt LM, Sander LC, Nolen-Hoeksema S, Simen AA. 2007. The BDNF Val66Met polymorphism predicts rumination and depression differently in young adolescent girls and their mothers. Neurosci Lett. 429:12–16.

Hu LT, Bentler PM. 1999. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Modeling. 6:1–55.

Jbabdi S, Woolrich MW, Andersson JL, Behrens TE. 2007. A Bayesian framework for global tractography. Neuroimage. 37:116–129.

Kemp AH, Felmingham KL, Falconer E, Liddell BJ, Bryant RA, Williams LM. 2009. Heterogeneity of non-conscious fear perception in posttraumatic stress disorder as a function of physiological arousal: an fMRI study. Psychiat Res-Neuroim. 174:158–161.

Kim MJ, Whalen PJ. 2009. The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. J Neurosci. 29: 11614–11618.

Kwang T, Wells TT, McGeary JE, Swann WB Jr, Beevers CG. 2010. Association of the serotonin transporter promoter region polymorphism with biased attention for negative word stimuli. Depress Anxiety. 27:746–751.

Lau JYF, Goldman D, Buzas B, Hodgkinson C, Leibenluft E, Nelson E, Sankin L, Pine DS, Ernst M. 2010. BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents. Neuroimage. 53:952–961.

Le Bihan D. 2003. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci. 4:469–480.

Liddell BJ, Brown KJ, Kemp AH, Barton MJ, Das P, Peduto A, Gordon E, Williams LM. 2005. A direct brainstem-amygdala-cortical "alarm" system for subliminal signals of fear. Neuroimage. 24:235–243.

Linhart H, Zucchini W. 1986. Model selection. Wiley series in probability and mathematical statistics. Oxford, England: John Wiley & Sons.

MacLeod C, Rutherford E, Campbell L, Ebsworthy G, Holker L. 2002. Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. J Abnorm Psychol. 111:107–123.

Martinowich K, Lu B. 2008. Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacology. 33:73–83.

Mathews A, Mackintosh B. 1998. A cognitive model of selective processing in anxiety. Cogn Ther Res. 22:539–560.

Mathews A, MacLeod C. 2002. Induced processing biases have causal effects on anxiety. Cogn Emotion. 16:331–354.

McIntosh AM, Bastin ME, Luciano M, Munoz Maniega S, del C. Valdes Hernandez M, Royle NA, Hall J, Murray C, Lawrie SM, Starr JM et al. 2012. Neuroticism, depressive symptoms and whitematter integrity in the Lothian Birth Cohort 1936. Psychol Med. doi: 10.1017/S003329171200150X: 1–10.

McNaughton N, Gray JA. 2000. Anxiolytic action on the behavioural inhibition system implies multiple types of arousal contribute to anxiety. J Affect Disorders. 61:161–176.

Mogg K, Bradley BP. 2002. Selective orienting of attention to masked threat faces in social anxiety. Behav Res Ther. 40:1403–1414.

Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HM, Chen G, McClure-Tone EB, Ernst M, Pine DS. 2008. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen Psychiatry. 65:568–576.

Montag C, Basten U, Stelzel C, Fiebach CJ, Reuter M. 2010. The BDNF Val66Met polymorphism and anxiety: support for animal knock-in studies from a genetic association study in humans. Psychiatry Res. 179:86–90.

Montag C, Reuter M, Newport B, Elger C, Weber B. 2008. The BDNF Val66Met polymorphism affects amygdala activity in response to emotional stimuli: evidence from a genetic imaging study. Neuroimage. 42:1554–1559.

Montag C, Reuter M, Weber B, Markett S, Schoene-Bake JC. 2012. Individual differences in trait anxiety are associated with white matter tract integrity in the left temporal lobe in healthy males but not females. Neuroscience. 217:77–83.

Montag C, Schoene-Bake JC, Faber J, Reuter M, Weber B. 2010. Genetic variation on the BDNF gene is not associated with differences in white matter tracts in healthy humans measured by tract-based spatial statistics. Genes Brain Behav. 9:886–891.

Morris JS, DeGelder B, Weiskrantz L, Dolan RJ. 2001. Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. Brain. 124:1241–1252.

Morris JS, Ohman A, Dolan RJ. 1999. A subcortical pathway to the right amygdala mediating "unseen" fear. Proc Natl Acad Sci USA. 96:1680–1685.

Morris JS, Ohman A, Dolan RJ. 1998. Conscious and unconscious emotional learning in the human amygdala. Nature. 393: 467–470.

Ohman A, Flykt A, Esteves F. 2001. Emotion drives attention: detecting the snake in the grass. J Exp Psychol Gen. 130:466–478.

Osinsky R, Reuter M, Kupper Y, Schmitz A, Kozyra E, Alexander N, Hennig J. 2008. Variation in the serotonin transporter gene modulates selective attention to threat. Emotion. 8:584–588.

Pacheco J, Beevers CG, Benavides C, McGeary J, Stice E, Schnyer DM. 2009. Frontal-limbic white matter pathway associations with the serotonin transporter gene promoter region (5-HTTLPR) polymorphism. J Neurosci. 29:6229–6233.

Perez-Edgar K, Bar-Haim Y, McDermott JM, Gorodetsky E, Hodgkinson CA, Goldman D, Ernst M, Pine DS, Fox NA. 2010. Variations in the serotonin-transporter gene are associated with attention bias patterns to positive and negative emotion faces. Biol Psychol. 83:269–271.

Pezawas L, Meyer-Lindenberg A, Goldman AL, Verchinski BA, Chen G, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 2008. Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. Mol Psychiatry. 13:709–716.

Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR. 2004. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci. 24:10099–10102.

Phan KL, Orlichenko A, Boyd E, Angstadt M, Coccaro EF, Liberzon I, Arfanakis K. 2009. Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. Biol Psychiatry. 66:691–694.

Poo MM. 2001. Neurotrophins as synaptic modulators. Nat Rev Neurosci. 2:24–32.

Porrino LJ, Crane AM, Goldmanrakic PS. 1981. Direct and indirect pathways from the amygdala to the frontal-lobe in rhesus-monkeys. J Comp Neurol. 198:121–136.

Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, Orr SP, Pitman RK. 2000. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biol Psychiat. 47:769–776.

Rodriguez S, Gaunt TR, Day IN. 2009. Hardy-Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies. Am J Epidemiol. 169:505–514.

Scholz J, Klein MC, Behrens TEJ, Johansen-Berg H. 2009. Training induces changes in white-matter architecture. Nat Neurosci. 12:1370–1371.

Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry. 50:651–658.

Shimizu E, Hashimoto K, Iyo M. 2004. Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: the possibility to explain ethnic mental traits. Am J Med Genet B. 126B:122–123.

Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage. 20:1714–1722.

Sylvers P, Lilienfeld SO, LaPrairie JL. 2011. Differences between trait fear and trait anxiety: implications for psychopathology. Clin Psychol Rev. 31:122–137.

Tost H, Alam T, Geramita M, Rebsch C, Kolachana B, Dickinson D, Verchinski BA, Lemaitre H, Barnett AS, Trampush JW et al. 2013. Effects of the BDNF val(66)met polymorphism on white matter microstructure in healthy adults. Neuropsychopharmacology. 38:525–532.

Tromp DPM, Grupe DW, Oathes DJ, McFarlin DR, Hernandez PJ, Kral TRA, Lee JE, Adams M, Alexander AL, Nitschke JB. 2012. Reduced structural connectivity of a major frontolimbic pathway in generalized anxiety disorder. Arch Gen Psychiat. 69:925–934.

Turken AU, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JDE. 2008. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. Neuroimage. 42: 1032–1044.

Verhagen M, van der Meij A, van Deurzen PAM, Janzing JGE, Arias-Vasquez A, Buitelaar JK, Franke B. 2010. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. Mol Psychiatr. 15:260–271.

Voineskos AN, Lerch JP, Felsky D, Shaikh S, Rajji TK, Miranda D, Lobaugh NJ, Mulsant BH, Pollock BG, Kennedy JL. 2011. The brain-derived neurotrophic factor Val66Met polymorphism and prediction of neural risk for Alzheimer disease. Arch Gen Psychiatry. 68:198–206.

Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA. 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci. 18:411–418.

Wiens S. 2006. Current concerns in visual masking. Emotion. 6:675–680.

Williams LM, Das P, Liddell BJ, Kemp AH, Rennie CJ, Gordon E. 2006. Mode of functional connectivity in amygdala pathways dissociates level of awareness for signals of fear. J Neurosci. 26: 9264–9271.

Williams LM, Liddell BJ, Kemp AH, Bryant RA, Meares RA, Peduto AS, Gordon E. 2006. Amygdala-prefrontal dissociation of subliminal and supraliminal fear. Hum Brain Mapp. 27:652–661.

Yendiki A, Panneck P, Srinivasan P, Stevens A, Zöllei L, Augustinack J, Wang R, Salat D, Ehrlich S, Behrens T et al. 2011. Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. Front Neuroinform. 5:23.