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Effects of the *BDNF* Val^{66}Met Polymorphism on White Matter Microstructure in Healthy Adults

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The *BDNF* Val^{66}Met polymorphism, a possible risk variant for mental disorders, is a potent modulator of neural plasticity in humans and has been linked to deficits in gray matter structure, function, and cognition. The impact of the variant on brain white matter structure, however, is controversial and remains poorly understood. Here, we used diffusion tensor imaging to examine the effects of *BDNF* Val^{66}Met genotype on white matter microstructure in a sample of 85 healthy Caucasian adults. We demonstrate decreases of fractional anisotropy and widespread increases in radial diffusivity in Val/Val homozygotes compared with Met-allele carriers, particularly in prefrontal and occipital pathways. These data provide an independent confirmation of prior imaging genetics work, are consistent with complex effects of the *BDNF* Val^{66}Met polymorphism on human brain structure, and may serve to generate hypotheses about variation in white matter microstructure in mental disorders associated with this variant.
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INTRODUCTION

Secretory neurotrophins are abundantly expressed in the mammalian brain and are potent modulators of synaptic plasticity and neuronal survival (Lu *et al*, 2005). Specifically, brain-derived neurotrophic factor (BDNF) has been identified as a key regulator of synaptogenesis and memory formation, particularly in the medial temporal lobe (Minichiello, 2009). A frequent non-synonymous coding variant in the 5′ proregion of the *BDNF* gene (Val^{66}Met, rs6265) has been linked to abnormal activity-dependent secretion of BDNF, deficits in neural activation and cognition (Egan *et al*, 2003), the modulation of other genes (Pezawas *et al*, 2008; Tan *et al*, 2011) and the effects of environmental adversity on neural structure and function (Gatt *et al*, 2009; Gerritsen *et al*, 2011). Considering its pivotal role in neurodevelopment and adaptation, the variant has also received considerable attention as a candidate gene locus for mental disorder and treatment response (Martinowich *et al*, 2007). Among others, *BDNF* Val^{66}Met has previously been implicated as genetic risk factor for bipolar disorder (Sklar *et al*, 2002), schizophrenia (Neves-Pereira *et al*, 2005), and depression (Verhagen *et al*, 2010), although the validity of the disease associations is subject to much debate (Zhang *et al*, 2006).

On the brain structural level, *in vivo* neuroimaging has provided fairly consistent evidence for gray matter volume reductions in healthy *BDNF* Met^{66}-allele carriers, particularly in limbic areas such as hippocampus and amygdala, at least as inferred from measurements on MRI scans (Ho *et al*, 2006; Montag *et al*, 2009; Pezawas *et al*, 2004). Given that BDNF may target non-neuronal cell types (Cui *et al*, 2010) and modulates myelinogenesis (Du *et al*, 2003), it appears plausible that the variant may also impact the microstructure of white matter tracts. The *in vivo* examination of this question in healthy young volunteers has gained increasing impetus in the recent imaging genetics literature, but initial diffusion tensor imaging (DTI) studies have produced conflicting results. Specifically, one study (Soliman *et al*, 2010) conducted in 82 healthy individuals linked the *BDNF* Met^{66} allele to reductions in fractional anisotropy (FA) in the uncinate fasciculus (UF),

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a frontal-limbic fiber tract. Other investigators such as Montag *et al* (2010) (sample size: $n = 99$ subjects), however, were unable to detect significant effects of *BDNF* Val[66]Met on FA or found, like Voineskos *et al* (2011) (sample size: $n = 69$ subjects), significant interactions of FA with age in samples including elderly subjects. In the hitherto largest study on this topic ($n = 455$), Chiang *et al* (2011) reported FA reductions in Val[66] allele homozygotes in prefrontal and occipital pathways, and found significant correlations of FA with cognitive performance in Val/Val homozygotes.

Among neuroimaging methods, DTI is the most appropriate for the non-invasive quantification of white matter tract morphology and microstructure in humans. It has been demonstrated that DTI measures reflect heritable components of brain structure (Chiang *et al*, 2009; Kochunov *et al*, 2010), and are useful to delineate potential fiber tracts anomalies related to psychiatric genetic risk variants. Specifically, genetic associations of risk variants for mood disorders with FA in frontolimbic tracts relevant for emotion processing have been repeatedly described (Alexopoulos *et al*, 2009; Pacheco *et al*, 2009), as well as associations of schizophrenia risk variants linked to altered neurodevelopment with FA in prefrontal cognitive pathways (McIntosh *et al*, 2008; Zuliani *et al*, 2011). Moreover, individual differences in prefrontal white matter microstructure, as indexed by DTI, have been shown to be associated with cognitive behavior in healthy humans. This is suggested, for example, by reports on the association of FA in fronto-basal ganglia tracts and response inhibition (King *et al*, 2012), or tractography-derived estimates of tract strength of PFC-hippocampus pathways and long-term memory performance (Cohen, 2011).

In recent years, imaging genetics has emerged as a popular approach with which to explore the effects of genetic variation on measures of brain structure and function, but initial studies are often followed by inconsistent results. Consequently, and analogous to clinical and molecular genetics studies, independent replication is important to gain confidence in the validity of reported findings. In order to minimize spurious associations, we used an ethnically homogenous sample and outcome measures such as FA and radial diffusivity (RD) that are known to be heritable (Chiang *et al*, 2009; Kochunov *et al*, 2010). We also attempted to apply rigorous methodology during diffusion imaging acquisition and processing by using a cardiac gated sequence, acquiring isotropic voxels (Smith *et al*, 2007), excluding data affected by motion, correcting for image distortions caused by magnetic susceptibility (Embleton *et al*, 2010) and using methods to enhance accuracy of normalization in group analyses (Smith *et al*, 2006).

In this work, we used advanced DTI methods to examine the impact of the *BDNF* Val[66]Met variant on DTI estimates of white matter microstructure in a carefully screened sample of healthy Caucasian adults. We investigated FA because this is the index that the majority of the prior literature has focused on. In addition, we analyzed RD and axial diffusivity (AD) in order to better interpret findings with FA. Increases in RD have previously been linked to myelin defects in animal models (Song *et al*, 2002, 2005), while AD has been considered as an index of axonal integrity (Song *et al*, 2003; Sun *et al*, 2006). This dichotomy, though useful for interpretation of the underlying biology of changes in diffusion metrics in very specific contexts, should be viewed with caution in healthy brain. To date, little is known about the effects of BDNF on brain white matter per se, and prior DTI work on this variant has yielded conflicting results. Nevertheless, we expected to observe significant decreases of FA in Met-allele carriers given the results of the large sample published by Chiang *et al* (2011), but we could not clearly predict the directionality of RD and AD because the only study to assess the effect of the *BDNF* Val[66]Met variant on these quantities was negative (Montag *et al*, 2010).

MATERIALS AND METHODS

Participants

Eighty-five healthy volunteers (mean age $= 33.5 \pm 9.6$ years, 46 males) were recruited for this research as part of the NIMH Clinical Brain Disorders Branch 'Sibling Study' (Egan *et al*, 2001), an ongoing investigation of neurobiological abnormalities related to genetic risk for schizophrenia (protocol 95-M-0150, principal investigator: Daniel R Weinberger). All recruited subjects were unrelated healthy volunteers, 18–55 years of age, above 75 in IQ, and able to give informed consent. No schizophrenia patients or first-degree relatives of patients were included. To minimize the possibility of misleading associations due to ethnic stratification, only Caucasian individuals of self-identified European descent were included in this study. Structured clinical interviews for DSM-IV were acquired by a research psychiatrist to ensure the absence of a lifetime history of mental or neurological disorder. Other specific exclusion criteria included significant medical problems, history of head trauma, and prior alcohol or drug abuse. In addition, to exclude the presence of asymptomatic brain abnormalities such as subtle white matter lesions (WML), all participants were subjected to a clinical magnetic resonance imaging protocol evaluated by a trained neuroradiologist. All participants provided written informed consent for the 'sibling study' protocol approved by the NIMH Institutional Review Board.

Genotyping

We used standard methods to extract DNA from white blood cells with the Puregene DNA purification kit (Gentra Systems). The Val[66]Met single-nucleotide polymorphisms (rs6265) in the 5' proregion of *BDNF* was determined by the Taqman allelic discrimination assay as previously described (Egan *et al*, 2003). The observed genotype distribution of rs6265 did not deviate from Hardy–Weinberg equilibrium ($n = 50$ Val/Val, $n = 32$ Val/Met, $n = 3$ Met/Met; $P > 0.05$). Notably, the low frequency of the *BDNF* Met allele (0.18) and the resulting small number of Met/Met homozygotes ($n = 3$) precluded independent statistical analysis of this genotype group. Thus, analogous to previous DTI studies on this variant (Ho *et al*, 2006; Kennedy *et al*, 2009; Montag *et al*, 2010; Soliman *et al*, 2010), Val/Met and Met/Met individuals were merged in one group for all analyses. Subject demographics stratified by *BDNF* genotype are reported in Table 1. No significant group differences were observed.

Table 1 Subject Demographic Information Stratified by BDNF Genotype

Diffusion tensor imaging ($n = 85$)	**Val/Val genotype**		**Met carriers**		
Demographics	*Male*	*Female*	*Male*	*Female*	P^a
Sex	$n = 27$	$n = 23$	$n = 19$	$n = 16$	0.98
	Mean	*s.d.*	*Mean*	*s.d.*	P^b
Age (years)	33.6	9.8	33.4	9.3	0.91
Education (years)	16.5	2.6	16.6	2.6	0.76
IQ	110.2	8.5	109.7	12.2	0.82

n = number of available data points.
[a]χ^2 test.
[b]*t*-test for independent samples.

Diffusion Tensor Imaging

Magnetic resonance imaging was performed on a 1.5-T Signa scanner (General Electric, Waukesha, WI) equipped with an 8-channel radio frequency coil. Head motion was minimized with a deflatable bead filled pillow and a restraining head band. Whole-brain DTI data were acquired with an axial single shot echo planar imaging (EPI) sequence and cardiac gating for each slice (TE = 89 ms, $80 \times 2\,mm^2$ thick slices, $2 \times 2\,mm^2$ in-plane resolution). Diffusion-weighted gradients were applied in 120 non-collinear directions, acquiring 10 images at each b value of 0, 109, 327, and 545 s/mm^2, 30 directions with $b = 873$ s/mm^2, and 50 directions with $b = 1100$ s/mm^2. For the purpose of field mapping and DT image correction for EPI distortions, gradient echo (GRE) images were acquired with identical slice position and orientation as the DT images ($TE_1 = 7$ ms, $TE_2 = 11.5$ ms, TR = 1300 ms, matrix size = 256×256 pixels).

Data Processing

DTI data preprocessing was performed using the FMRIB Diffusion Toolbox (http://www.fmrib.ox.ac.uk/fsl/). The following preprocessing steps were performed: (1) correction of the diffusion images for head motion and eddy currents by affine registration to a reference (b_0) image, (2) EPI distortion correction (b_0 fieldmap unwarping), (3) extraction of non-brain tissues (Smith, 2002), and (4) linear diffusion tensor fitting. The resulting maps contained voxel-wise parameter estimates for RD, FA, and AD in individual space. Prior to further processing, all images were inspected both visually and quantitatively to confirm their quality, and volumes corrupted by head motion during slice acquisition were dropped. Additionally, no subjects with interscan rotation $> 5^\circ$ were included in this sample.

Data Analysis

Statistical analysis was carried out using tract-based spatial statistics, TBSS (Smith *et al*, 2006). First, all FA images were non-linearly registered into a common space (FMRIB58_FA template) using the FMRIB's Non-linear Registration Tool, FNIRT (Rueckert *et al*, 1999). The resulting spatial transformation matrix was subsequently applied to the other diffusion images (RD, AD). The mean FA image was calculated to create the mean FA 'skeleton', an alignment-invariant representation of the center of all tracts common to the group. A threshold of FA $\geqslant 0.25$ was chosen to minimize the effects of incidental tracts and partial voluming. Each subject's aligned FA data were then projected onto this skeleton via perpendicular search for the highest FA value. The estimated non-linear warps and projection vectors were subsequently used to register each individual's diffusion data onto the skeleton. The resulting maps were fed into voxel-wise cross-subject statistics.

The effects of genotype were examined in the context of a random-effects multiple regression model with genotype as covariate of interest, and age and sex as nuisance covariates. Statistical inference was performed using FSL Randomize, a non-parametric permutation procedure suitable for the analysis of data with unknown null distributions (5000 permutations). Threshold-free cluster enhancement (TFCE) was used to circumvent the methodological drawbacks of conventional cluster-based thresholding (Smith and Nichols, 2009). The statistical threshold was set to $P < 0.05$ family-wise error (FWE) corrected for multiple comparisons. The most probable location of voxel results was determined with the John Hopkins University (JHU) white matter atlas (http://www.dtiatlas.org).

Exploratory 'VBM-Type' Analysis of Diffusion Data in the UF

Our results (vide infra) were in the opposite direction of those reported by Soliman *et al* (2010) in the UF, but obtained with different image processing methodology. A critical difference between the two methods was the use of voxels with high FA at the center of the tracts in our study *vs* the use of the whole FA image in Soliman *et al* (2010). This raises the possibility that genetic associations in lateral portions of the UF may have gone undetected in our TBSS analysis. To address the potential impact of methodological differences on our results, additional exploratory 'voxel-based morphometry (VBM)-type' analyses of diffusion data in the UF were performed, analogous to the procedures of Soliman *et al* (2010).The effects of genotype were examined using the normalized, non-skeletonized images, and a white matter mask, which was created by thresholding the average FA image of our sample at a value >0.25. The statistical testing of these images was carried out analogous to the TBSS analysis described above.

RESULTS

Diffusion Tensor Imaging

Val/Val subjects had lower values of FA compared with Met carriers in white matter tracts such as the corpus callosum and the right posterior corona radiata ($P < 0.05$, whole-brain corrected for multiple comparisons, Figure 1; Table 2a). These effects were more diffuse and pronounced for RD, with Val/Val having higher RD than Met-allele carriers in several white matter tracts connecting the prefrontal and occipital lobes, particularly in the genu and body of the corpus callosum, bilateral posterior corona radiate (Figure 2), posterior and superior thalamic radiation,

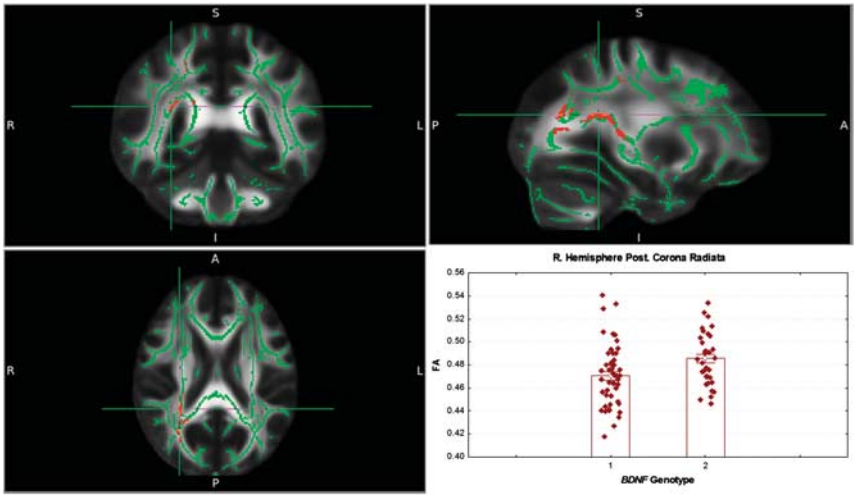

Figure 1 Effects of BDNF genotype on FA. Significant FA increases in *BDNF* Met carriers as compared with Val/Val individuals (colored in red, $P < 0.05$, corrected for multiple comparisons) overlaid on the local white matter skeleton (green) and the FA template (gray scale). The plot in the lower right-hand corner shows individual FA values in the JHU white matter atlas ROI for the right corona radiata, where the cursor is centered (MNI coordinates 30 −43 21). The whiskers on the bars represent standard error. *BDNF* genotype 1 = Val/Val, 2 = Met carriers.

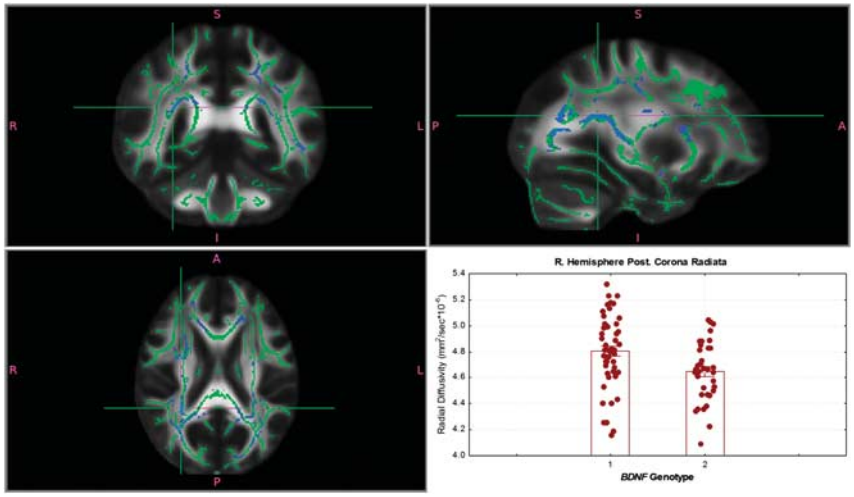

Figure 2 Effects of BDNF genotype on RD. Significant RD increases in *BDNF* Val/Val individuals as compared with Met carriers (colored in blue, $P < 0.05$, corrected for multiple comparisons) overlaid on the local white matter skeleton (green) and the FA template (gray scale). The plot in the lower right-hand corner shows individual FA values in the JHU white matter atlas ROI for the right corona radiata, where the cursor is centered (MNI coordinates 30 −43 21). The whiskers on the bars represent standard error.

and superior longitudinal fasciculus ($P < 0.05$, whole-brain corrected for multiple comparisons, Table 2b). No effects of genotype on AD were observed.

Exploratory 'VBM-Type' Analysis of Diffusion Data in the UF

Our exploratory VBM-type analysis provided evidence for a decrease in RD in the UF in Met carriers (Figure 3: $P < 0.05$, corrected; $t_{max} = 3.67$, MNI coordinates: −37, 0, −19). No effects of *BDNF* genotype on AD or FA emerged.

DISCUSSION

Using tract-based DTI methods for the *in vivo* quantification of white matter microstructure in humans, we provide evidence for a significant association of the *BDNF* Val[66]Met polymorphism with FA and RD in healthy young Caucasian adults. Significant effects of genotype were seen in several pathways subserving the prefrontal and occipital lobes, particularly the corpus callosum and the posterior corona radiata. The impact of *BDNF* genotype manifested as robust increases in RD in Val[66] homozygotes, and comparatively weaker reductions in FA, in comparison to Met-allele carriers.

In the context of prior DTI work, several aspects of our data deserve comment. Our data provide independent confirmation of the directionality of findings in at least one recent imaging genetics study, indicating reduced FA in *BDNF* Val[66]homozygotes as compared with Met carriers in prefrontal and occipital pathways (Chiang *et al*, 2011). Although our findings overlap to a great extent with those of Chiang *et al*, including many of the tracts where

Table 2 Effects of the *BDNF* Val[66]Met Polymorphism on DTI Measures of White Matter Tract Microstructure in Healthy Human Adults

	L/R	#Sign Vox	%Sign Vox	t_{max}	MNI coordinates		
					x	y	z
(a) *Fractional anisotropy (Val/Val < Met carriers)*					×	y	z
Posterior corona radiata	R	411	57.4%	2.9	30	−43	19
Posterior thalamic radiation	R	278	37.6%	3.2	35	−48	15
Internal capsule (retrolenticular)	R	229	37.2%	3.2	30	−37	18
Corpus callosum (body)	—	684	28.2%	3.3	13	−17	30
Superior corona radiata	R	143	12.6%	2.8	19	−16	37
Superior longitudinal fasciculus	R	83	7.92%	3.4	28	−25	11
Corpus callosum (splenium)	—	95	6.7%	2.9	26	−53	17
Posterior thalamic radiation	L	59	6.63%	3.3	−30	−69	13
Superior corona radiata	L	69	5.93%	3.9	−27	−13	27
Internal capsule (posterior limb)	R	35	5.6%	2.6	27	−22	17
(b) *Radial diffusivity (Val/Val > Met carriers)*							
Posterior corona radiata	R	552	73.2%	3.7	30	−46	20
Corpus callosum (genu)	—	909	54.3%	3.9	−14	35	3
Internal capsule (retrolenticular)	R	351	49.5%	3.3	32	−38	16
Posterior thalamic radiation	R	446	47.8%	3.9	34	−48	9
Corpus callosum (body)	—	1357	46.4%	4.2	−14	−18	3
Superior corona radiata	R	528	40.8%	3.5	19	−16	37
Posterior corona radiata	L	275	40.5%	2.9	−22	−35	30
Superior longitudinal fasciculus	R	536	39.8%	3.7	34	−26	36
Internal capsule (retrolenticular)	L	265	35.9%	3.1	−34	−38	10
Internal capsule (posterior limb)	R	250	31.4%	3.2	27	−22	9
Posterior thalamic radiation	L	312	30.9%	3.7	−34	−40	13
Corpus callosum (splenium)	—	572	27.7%	3.9	20	−34	30
Superior corona radiata	L	337	27.7%	3.7	−18	−18	37
Anterior corona radiata	L	468	27.6%	3.4	−15	36	7
Superior longitudinal fasciculus	L	287	24.4%	3.5	−42	−40	6
Anterior corona radiata	R	279	19.1%	3.1	25	11	10
Internal capsule (anterior limb)	R	109	15.8%	3.4	18	−46	9
External capsule	R	127	13.7%	3.9	32	0	15
Cingulum	R	33	9.6%	4.0	10	−24	34

Abbreviations: L/R, hemisphere (left or right); #Sign Vox, absolute number of significant skeleton voxels within the specified region of the JHU atlas; %Sign Vox, percent significant skeleton voxels within the specified region of the JHU atlas.
All reported voxels are significant at $P<0.05$ corrected for multiple comparisons (family-wise error, FWE).

genotype-related differences in white matter microstructure were found, there are large differences in the population assessed (Chiang *et al* assessed twins and siblings from 238 unrelated families) and the DTI acquisition and analysis methods between the two studies that prevent us from claiming a full replication of their investigation. Notably, we did not observe the reduction in FA (or an increase in RD) described by Soliman *et al* (2010) for *BDNF* Met-allele carriers in the UF; however, it is important to note that while our sample consisted only of Caucasian individuals, theirs was mixed (~40% Asian). Montag *et al* (2010) and Voineskos *et al* (2011), however, found no main effect of *BDNF* Val/Met genotype on white matter microstructure in primarily Caucasian samples. The reason for these discrepancies regarding the main effect of rs6265 genotype in the literature is unclear, but may relate in part to differences in sampling (eg, approximately half the group studied by Voineskos *et al* were over 50 years old) and methodology. In principle, many of these between-study differences in methods may contribute to the observed heterogeneity in genetic association findings. Specifically, DTI studies differ broadly in terms of acquisition parameters (eg, anisotropic voxels and large slice thickness were used by Chiang *et al* (2011), the number of independent diffusion directions varies from 6 in Kennedy *et al* (2009) to 60 in Montag *et al* (2010)), image processing pipelines (eg, no cardiac gating or correction for susceptibility induced distortion was applied in most prior work) and data analysis (our pipeline is compatible only with Montag *et al* (2010)). Moreover, prior DTI work on this genotype varies considerably regarding the definition of white matter areas of interest (eg, manually traced white matter ROI's in Kennedy *et al* (2009),

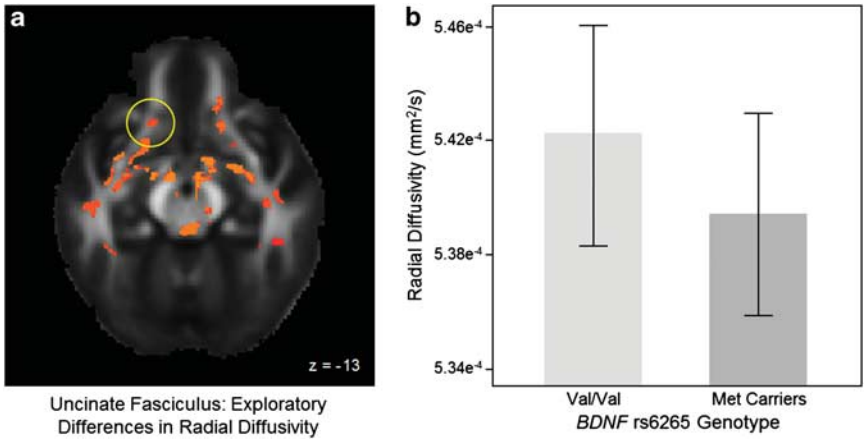

Figure 3 Exploratory 'VBM-style' ROI analysis in the UF. (a) Localization of voxels with significant RD increases in Val/Val subjects in the UF (colored in orange, $P<0.05$, corrected) overlaid on the mean FA map of the sample (gray scale). The yellow circle illustrates the region in the left UF plotted in (b). (b) Bar graph illustration of the effect of genotype on RD in the left UF; the mean and standard error in the significant voxels is plotted for both genotype groups (light gray = Val/Val subjects, dark gray = Met-allele carriers).

TBSS-based reconstruction of core white matter tracts as used here and in Montag *et al* (2010), tractography-defined regions as in Voineskos *et al* (2011), VBM-type voxel-wise analysis of normalized and thresholded FA images as in Chiang *et al* (2011) and Soliman *et al* (2010)). Other methodological differences include varying procedures for statistical inference that included parametric (Chiang *et al*, 2011; Kennedy *et al*, 2009; Voineskos *et al*, 2011) and non-parametric approaches (used here and in Montag *et al* (2010) and Soliman *et al* (2010)). Another possible explanation for the variability of findings regarding the main effect of *BDNF* Val^{66}Met on DTI measures is a possible effect of early life experience, which has been reported to interact with *BDNF* Val^{66}Met to determine other brain and behavioral phenotypes (Gatt *et al*, 2009; Gerritsen *et al*, 2011). Data on early adversity were not collected in this or in any of the other studies reporting on diffusion metrics and *BDNF*. Yet another possibility is that the various samples collected to date differ in their assortment of other genes that have been shown to interact with *BDNF* in determining some phenotypes of interest (Pezawas *et al*, 2008; Tan *et al*, 2011).

Our data indicate that the effects on measures of RD, analyzed only previously in Montag *et al* (2010) so far, may be even greater than those on FA, and may explain in large part those found for FA. Pronounced increases in RD without concomitant changes in AD are consistent with reduced myelination in several genetic and environmental models of demyelination (Song *et al*, 2002, 2005; Tyszka *et al*, 2006). Reduced BDNF signaling has been linked to altered differentiation of human fetal and adult oligodendrocyte progenitor cells (Cui *et al*, 2010) and to regional reductions of myelin-related proteins (Vondran *et al*, 2010), but these observations would be very difficult to relate to our associations with the Val allele of *BDNF*, which is the normal functional *BNDF* allele and has not been associated with reduced BDNF levels in human brain. The animal model literature is consistent in showing that the *BDNF* Met allele, which alters BDNF protein trafficking and secretion, is associated with reduced BDNF protein levels (Bath *et al*, 2012; Qin *et al*, 2011). In humans, the available post-mortem information involves only mRNA, which is not expected to be affected by the Val/Met polymorphisms (eg, http://braincloud.jhmi.edu/) and the results are consistent with this expectation (Colantuoni *et al*, 2011). The effect of the Val/Met variant on white matter biology has not been studied in animal models or in post-mortem brain tissue. Conflicting information is also present in regards to the effects of Val^{66}Met on T2 hyperintensity lesion load in multiple sclerosis, an index of prominent dysmyelination. The only investigation to examine a relatively large population ($n=209$) found that the Met allele was associated with diminished lesion load as compared with Val/Val (Zivadinov *et al*, 2007) , but this result has not been confirmed in smaller cohorts (Dinacci *et al*, 2011; Liguori *et al*, 2007). Nevertheless, T2 hyperintensities are not found in our samples and cannot explain our results.

In summary, reduced myelin in Val homozygotes is unlikely to account for the effect seen here and by others (Chiang *et al*, 2011). An alternative scenario might be suggested by a study demonstrating increased axonal branching in Met/Met mice as compared with the wild type (Val/Val) (Cao *et al*, 2007). This phenomenon was demonstrated in gray matter, and thus inferences on how this might impact on white matter are largely speculative. However, increased axonal branching might reduce extracellular space or change the distribution of axonal diameters and diminish RD in Met-allele carriers. Given the fact that our group previously demonstrated an association of the *BDNF* Val^{66}Met variant with cortical volume in the hippocampus and the prefrontal cortex (Pezawas *et al*, 2004), it is possible that our DTI measures reflect some degree of difference in intracortical development between the genotypes.

In conclusion, using rigorous DTI procedures, we provide evidence of *BDNF* Val^{66}Met genotype effects on white matter microstructure in healthy young Caucasian adults manifesting as reductions in measures of coherent spatial orientation of white matter in Val/Val homozygotes. Our results expand on prior research by suggesting that the effects of the *BDNF* Val^{66}Met

variant on human brain structure is complex, and possibly tissue-specific. In addition, our data may serve to generate hypotheses about the changes in white matter structure in disorders that have been associated with the Val allele. Finally, the Supplementary Information presents preliminary findings on the association between white matter diffusion metrics and cognition and on how *BDNF* Val[66]Met genotype modulates this association.

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DISCLOSURE

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)