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The impact of a Dysbindin schizophrenia susceptibility variant on fiber tract integrity in healthy individuals: A TBSS-based diffusion tensor imaging study

Thomas Nickl-Jockschat [a,b,*], Tony Stöcker [b,c], Valentin Markov [a], Axel Krug [d], Ruihuang Huang [b,c], Frank Schneider [a,b], Ute Habel [a,b], Klaus Zerres [e], Markus M. Nöthen [f], Jens Treutlein [g], Marcella Rietschel [g], N. Jon Shah [b,c,h], Tilo Kircher [d]

[a] Department of Psychiatry and Psychotherapy, RWTH Aachen University, Aachen, Germany
[b] Juelich Aachen Research Alliance - Translational Brain Medicine, Germany
[c] Institute of Neurosciences and Medicine-4, Juelich Research Center, Juelich, Germany
[d] Department of Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany
[e] Institute of Human Genetics, RWTH Aachen University, Aachen, Germany
[f] Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany
[g] Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany
[h] Department of Neurology, RWTH Aachen University, Aachen, Germany

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ABSTRACT

Schizophrenia is a severe neuropsychiatric disorder with high heritability, though its exact etiopathogenesis is yet unknown. An increasing number of studies point to the importance of white matter anomalies in the pathophysiology of schizophrenia. While several studies have identified the impact of schizophrenia susceptibility gene variants on gray matter anatomy in both schizophrenia patients and healthy risk variant carriers, studies dealing with the impact of these gene variants on white matter integrity are still scarce. We here present a study on the effects of a Dysbindin schizophrenia susceptibility gene variant on fiber tract integrity in healthy young subjects.

101 subjects genotyped for Dysbindin-gene variant rs1018381, though without personal or first degree relative history of psychiatric disorders underwent diffusion tensor imaging (DTI), 83 of them were included in the final analysis. We used Tract-Based Spatial Statistics (TBSS) analysis to delineate the major fiber tracts. Carriers of the minor allele T of the rs1018381 in the Dysbindin gene showed two clusters of reduced fractional anisotropy (FA) values in the perihippocampal region of the right temporal lobe compared to homozygote carriers of the major allele C. Clusters of increased FA values in T-allele carriers were found in the left prefrontal white matter, the right fornix, the right midbrain area, the left callosal body, the left cerebellum and in proximity of the right superior medial gyrus.

Dysbindin has been implicated in neurite outgrowth and morphology. Impairments in anatomic connectivity as found associated with the minor Dysbindin allele in our study may result in increased risk for schizophrenia due to altered fiber tracts.

Introduction

While the exact etiopathogenesis of schizophrenias is still unknown, the view of a largely genetically determined disorder associated with anomalies in brain structure and function is widely accepted (Harrison and Weinberger, 2005). Findings of structural MRI studies have generally demonstrated enlarged lateral ventricles and subtle pathological changes in frontal and temporal regions, especially volume reductions of the hippocampus, the superior temporal gyrus (STG) and the dorsolateral prefrontal cortex (DLPFC) in patients (Shenton et al., 2001). Since hypotheses on the underlying pathophysiology of schizophrenia have repeatedly taken dysfunctional connectivity into focus (Harrison and Weinberger, 2005; Stephan et al., 2006), a growing number of studies has aimed at identifying abnormalities of white matter and structural connectivity in schizophrenia. Several MRI studies have demonstrated white matter anomalies in schizophrenia patients, mainly in frontal and temporal white matter (Ashtari et al., 2007; Buchsbaum et al., 2006; Cheung et al., 2008; Ellison-Wright and Bullmore, 2009; Stephan et al., 2009; Szeszko et al., 2008).

As well as pathological associations with brain structure there have been a number of successful studies combining genetic data with neuroimaging data. Genetic imaging studies were able to identify correlations

* Corresponding author at: Department of Psychiatry and Psychotherapy, RWTH Aachen University, Aachen, Germany.
E-mail address: tnickl-jockschat@ukaachen.de (T. Nickl-Jockschat).

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between schizophrenia risk gene variants and brain structure anomalies (Nickl-Jockschat et al., 2009). Most of these studies, however, have focused on structural changes within the gray matter. Conversely only three studies have yet been published dealing with the correlation of white matter anomalies and schizophrenia risk gene variants (Konrad et al., 2009; McIntosh et al., 2008; Winterer et al., 2008).

The dystrobrevin-binding protein 1 (*DTNBP1*) is of special interest for such a neuroimaging study. In addition, Dysbindin has been ranked as one of the most important candidates for schizophrenia identified to date (Sun et al., 2008).

The single nucleotide polymorphism (SNP) rs1018381 located in the Dysbindin gene has been found to be associated with schizophrenia and general cognitive abilities.

In a recent metaanalysis, using an approach based on the EM algorithm that detects allelic heterogeneity and assigns studies to subpopulations of analyzed markers, Maher et al. (2010) identified four SNPs to be most significantly associated with schizophrenia (Woolf test $p<0.0001$) in genetic association studies in Caucasians. Among these four SNPs, rs1018381 is the strongest tagging SNP (HapMap2 CEU). The study of Burdick et al. (2006) found the minor T allele to be associated with general cognitive ability. The allele associated with schizophrenia is not consistent. In 10 studies the T allele was found to be associated with the disorder and in seven studies it was the C allele (Maher et al., 2010). This phenomenon, which was also reported for the other markers in the *DTNBP1* locus and for other genes in complex genetic diseases, was termed the 'Flip-Flop' phenomenon (Lin et al., 2007) which can occur even without varying linkage disequilibrium between markers, e.g., due to haplotypic heterogeneity (Zaykin and Shibata, 2008).

The Dysbindin protein is a coiled-coil containing protein initially found in the muscle and the brain of mice to interact with alpha- and beta dystrobrevin (DTNA and DTNB) (Benson et al., 2001). DTNA and DTNB have been identified as members of the Dystrophin-associated protein complex (DPC) in the neuromuscular junction and the brain, which links the cytoskeleton to the extracellular matrix and scaffolds signaling protein (Benson et al., 2001; Veroni et al., 2007). While Dystrophin mutations cause several forms of X-linked muscular dystrophy, it seems important that Duchenne's muscular dystrophy in humans goes along with neuropsychological and neuropathological features reminiscent of schizophrenia (Harrison and Weinberger, 2005). More recently, in a *Drosophila* model that used an electrophysiology-based genetic screen to test the function of neuronal genes for a role in the homeostatic modulation of synaptic transmission, Dysbindin turned out to be essential for adaptive neural plasticity (Dickman and Davis, 2009). The authors concluded that Dysbindin may influence complex neurological diseases by alteration of homeostatic signaling (Dickman and Davis, 2009).

Recent data (Kubota et al., 2009) suggests an involvement of Dysbindin in the cytoskeletal organization of growth cones of hippocampal neurons. Reduced Dysbindin expression by RNA interference led to impaired neurite outgrowth and abnormal neurite morphology (Kubota et al., 2009). An impaired Dysbindin function seems to result in a failure of normal axon guidance by the disruption of growth cones during embryonic development, and therefore, in abnormal anatomical connectivity. Moreover, as shown by Kubota et al. (2009), Dysbindin hypofunctionality results in an aberrant organization of the actin cytoskeleton. These disturbances of cytoskeletal organization might lead not only to an abnormal thinning of neurites, but also to an abnormal enlargement.

The Dysbindin interactome has been shown to be complex and to involve a variety of proteins engaged in cytoskeletal anchoring and synaptic plasticity (Guo et al., 2009). Due to the different molecular environment in distinct neurons, Dysbindin hypofunctionality might lead to diverse effects on neurite morphology. Thus, the finding of both increased and decreased anatomic connectivity due to Dysbindin hypofunctionality seems plausible.

Given these biological functions of Dysbindin and the fact that Dysbindin variants have been shown to be associated with schizophrenia and cognitive function, it is plausible that genetic variation in Dysbindin might be involved in the pathogenesis of white matter alterations.

Diffusion tensor imaging (DTI) is an MRI-based imaging technique to assess white matter structures in a more detailed manner than conventional MRI (Beaulieu, 2002). DTI utilizes MR sequences sensitive to the diffusion movements of water molecules. Since the diffusion of water in brain tissue is limited by the coherence of the fiber tracts (Ono et al., 1995), structural fiber integrity, their diameter and packing density (Ono et al., 1995), and as well as by myelination (Gulani et al., 2001; Sakuma et al., 1991), proxy conclusions about white matter microstructure can be drawn from a DTI index called fractional anisotropy (FA) that quantitates how strongly directional the local tract structure is.

Whereas ROI-based or tractography analysis of DTI data sets requires an a priori-hypothesis, conventional VBM-style whole-brain approaches for multi-subject FA images have been criticized for alignment problems (Simon et al., 2005; Vangberg et al., 2006) and smoothing issues (Jones et al., 2005). The Tract-Based Spatial Statistics (TBSS) approach, however, tries to address both these problems by application of an initial approximate non-linear registration, followed by the projection of the FA values onto an alignment invariant tract representation, the "mean FA skeleton" (Smith et al., 2006). The mean FA skeleton is generated in a fully automatized procedure, in which first the voxels with the regionally highest FA values are identified and then the centers of the tracts are determined by local center-of-gravity (CofG) calculation.

Despite its obvious viability/optimization to studies of group difference in white matter structures there have only been four TBSS studies published in schizophrenia (Douaud et al., 2007; Karlsgodt et al., 2008; Miyata et al., 2009; Smith et al., 2006) and only two dealing with bipolar disorder (Benedetti et al., 2011; Versace et al., 2008). In general, studies dealing with schizophrenia found FA reductions in the callosal body and in the prefrontal regions in schizophrenia patients compared to healthy subjects.

In the current study we used TBSS in a genetic imaging study to correlate the rs1018381 variant in the Dysbindin gene with white matter changes in 83 healthy young individuals. MRI scans were performed and diffusion weighted image sequences were obtained. We hypothesized alterations of white matter tracts in carriers of the T-allele compared to C/C homozygotes in core regions of schizophrenia pathology such as the medial and superior temporal and the frontal lobes.

Methods

Subjects

The study protocol was approved by the local ethics committee of the University Hospital Aachen. Subjects were recruited from RWTH Aachen University students and by advertisements in local newspapers. The inclusion criteria were: age 18–55 years old, no psychiatric disorder according to ICD-10, and an absence of a family history for psychiatric disorders in first degree relatives. All subjects were of Western- or Middle European descent. 101 Subjects (74 men, 27 women) initially underwent diffusion tensor imaging. 18 subjects had to be excluded due to head movement and anatomic abnormalities, leaving 83 (62 males, 21 females) for the final analysis. The final sample did not differ in sociodemographic characteristics from the whole group. The subjects had a mean age of 23.3 years (SD = 2.9), were right handed (as tested with the Edinburgh Laterality Scale) and had 15.7 (2.6) years of education. Their fathers were educated for 15.4 (4.5) and their mothers for 13.9 (4.1) years on average. Mean IQ was 112.3 (13.4). After a complete description of the procedure, subjects provided written informed consent to participate in the

study. Cognitive tests were administered as described previously. For both a description of the tests and the results of the same sample see Krug et al. (2008) and Kircher et al. (2009). Blood was taken from a vein of each subject's arm.

Genotyping

DNA from peripheral leucocytes was isolated by a simple salting out procedure. The SNP rs1018381 (P1578 by (Straub et al., 2002)) was genotyped by using Applied Biosystems 7900HT Fast Real-Time PCR System and TaqMan-probes designed by Applied Biosystems (Foster City, California). Primers and VIC/FAM-probe sequences for rs1018381 detection were: Forward-5′- GAGTTACAAGTAAATGAAACGTCATGCA-3′; Reverse-5′-GCTGAGATCTGCCGGTGATTC-3′; 5′-VIC-ACAGC**G**TGCGGAAC-3′; 5′-FAM-AACAGC**A**TGCGGAAC-3′. Thus, the common C-allele reported in previous studies is equivalent to our G-allele and the T-allele is equivalent to our A-allele. For differences between actual and expected frequencies of the SNP rs1018381, we employed Hardy–Weinberg equilibrium (HWE) equation as implemented in the DeFinetti program (Strom and Wienker 2005, program online at http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl). Genotype distribution of the initial larger cohort (Kircher et al., 2009; Markov et al., 2009a,b) did not significantly deviate from HWE ($p = .43$). We replicated more than 15% of genotypes with 100% identical results.

Image acquisition

Imaging was performed on a 3 Tesla Trio MR scanner (Siemens Medical Systems) in the Institute of Neuroscience and Biophysics — Medicine, Research Center Jülich. Head movements were minimized by immobilizing the head with cushions during the scanning procedure. Further, an anatomical T1-weighted MP-RAGE sequence was acquired (scan time 9:15 min, 1 mm isotropic resolution). The images were acquired with a diffusion weighted (DW) double spin-echo EPI sequence (echo time 89 ms; 1.8 mm isotropic resolution). A twelve-channel phased-array coil was used and the sequence utilized twofold acceleration with the Grappa parallel imaging technique. Sixty different gradient directions distributed over the unit sphere according to the Jones-scheme were acquired with a b-value of 800 s/mm^2, in addition seven interleaved acquisitions of non-DW images ($b = 0$) for improved retrospective motion correction. The protocol was acquired twice and, after individual motion correction, the DW images were averaged to increase the signal-to-noise-ratio. The total acquisition time was 35 min.

Image preprocessing

We followed the standard protocol by Smith et al. (2007). First, data sets were corrected for head motion and eddy currents. Then a diffusion tensor model was fit to the set of diffusion-weighted images, before calculating FA maps for each subject. All FA images were visually checked for artifacts, intensity range problems and general data quality.

TBSS analysis

After visual assessment, we used the FSL TBSS scripts (http://www.fmrib.ox.ac.uk/fsl/tbss) on the individual FA maps (Smith et al., 2006, 2007). All individual FA maps were non-linearly registered to each other to determine the “most typical” subject of each group. After identification of the “most typical” subject as the target, all other FA images were aligned to it and then transformed into $1*1*1$ mm^3 MNI152 space. All subsequent processing was carried out using this space and resolution. The transformed images were then averaged to create a mean FA image. This mean FA image was then fed into the tract skeleton generation, resulting in an FA skeleton aiming to represent all fiber tracts common to all subjects included in the study. To restrict further analysis to points which are within white matter, a skeleton threshold of $FA > 0.2$ was applied (Smith et al., 2007). Then the nearest local FA maximums of each individual FA image were projected onto the mean FA skeleton.

This process of registration helps to increase sensitivity and interpretability of results yielded by DT imaging. For example, ventricular enlargement caused by a pathophysiological process can notably mislead the interpretation of the results of a voxel-based VBM-style DTI analysis. In their paper introducing TBSS, Smith and colleagues refer to a scenario, in which a patient group has a larger ventricular volume than a control group, while both groups however have the same basic white matter integrity. Because of differences in ventricular configuration, conventional (low to medium degrees-of-freedom) registration approaches are likely to shift the anterior section of the corpus callosum anteriorly in the patient group relative to the controls. Data registration and subsequent smoothing might not be capable to fully remove this group difference in alignment. Thus, when voxel-wise statistics is carried out, this alignment problem might show up as a group difference in FA with artificially elevated FA values at the anterior front of the corpus callosum, while at the back, the reverse is implied (Smith et al., 2007). The step of projecting individual FA maps onto a mean FA skeleton therefore helps to confine the effect of cross-spatial subject variability that remains after the non-linear registration. Especially in studies, in which group differences are expected to be small such as genomic imaging approaches, TBSS is valuable to limit artifacts and provide more precise results.

Statistical analysis

Comparison between the minor T allele carrier group and the homozygote wild-type C-allele carriers was performed by means of a two-sample non-parametric *t*-test on the FA values along the tract skeleton. Statistical inference was determined using a permutation-based approach (Nichols and Holmes, 2002) with 6400 permutations to establish a null-distribution of differences and derive non-parametric *p*-values for the group comparison. To control for gender effects, subjects' sex was included as a covariate of no interest into the statistical model ($T_{df = 2,80}$). The t-maps were then thresholded at $p < 0.001$ and projected onto the mean FA skeleton for visualization.

For a more detailed anatomical analysis, we used the Anatomy Toolbox (Eickhoff et al., 2005, 2007) to compare the localization of the obtained significant effects to myeloarchitectonical probability maps derived from the histological analysis of ten human post-mortem brains (Bürgel et al., 2006), spatially normalized into the MNI reference space. These maps quantify how often a particular tract has been found at each position of the white matter in the reference space. They were then combined into a Maximum Probability Map, which is a summary map of the probabilistic information. It is based on the idea of attributing each voxel of the reference space to the most likely myeloarchitectonically defined fiber-tract at this position. MPMs thus allow the definition of non-overlapping representations of all areas from a set of inevitably overlapping probabilistic maps (Eickhoff et al., 2006).

Results

Demographics

The images of 83 subjects (62 males, 21 females) were included in our final TBSS analysis. The T allele carrier group consisted of 37 subjects (31 male, 6 female), the wild type group of 46 subjects (31 male, 15 female). Mean age in the T allele carrier group was 22.5 yrs (standard deviation: 2.2 yrs), in the wild type group 23.4 (standard

deviation: 3.0 yrs). Both groups did not differ significantly in mean age ($p = .18$) or gender ($p = .11$).

Impact of the Dysbindin genotype on fiber tract integrity

We found two clusters of reduced FA values in Dysbindin rs1018381 T allele carriers. Both were located in the right temporal lobe with maxima at (18, −11, −20) and (38, −3, −27) (Fig. 1).

T allele carriers showed six clusters of elevated fiber tract integrity compared to homozygous wild type carriers. These clusters were located in the left frontal lobe (−24, −5, 44), the right fornix (6, −30, 22), the right midbrain area (3, −30, 0), the left callosal body (−16, −44, 36), the left cerebellum (−33, −58, −23) and close to the right superior medial gyrus (12, 52, 19). (See Fig. 2).

Discussion

In this study, we investigated the effects of the Dysbindin rs1018381 risk variant on fiber tract integrity of young healthy subjects without history of psychiatric disorders in first degree relatives. T-allele carriers showed two clusters of reduced FA values in the right perihippocampal region, and further exhibited six clusters of elevated FA values in the left frontal lobe, the right fornix, the right midbrain area, the left callosal body, the left cerebellum and in proximity of the right superior medial gyrus.

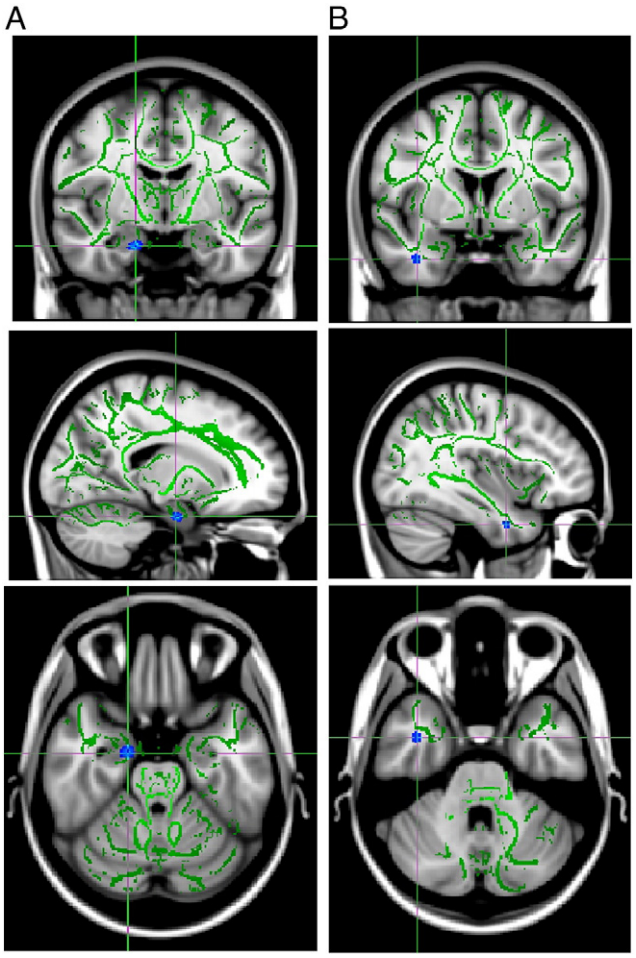

Fig. 1. Clusters of reduced FA values in the right temporal lobe in Dysbindin risk allele carriers. The clusters show maxima at (18, −11, −20) (Fig. 1a) and (38, −3, −27) (Fig. 1b). Major fiber tracts as determined by TBSS are shown in green, while the blue clusters indicate reduced FA values in Dysbindin risk allele carriers.

The Dysbindin interactome has recently been described (Guo et al., 2009). Since the Dysbindin protein has been shown to interact with several protein networks involved in cytoskeletal anchoring and synaptic plasticity, Dysbindin seems to be a plausible candidate to impact on structural connectivity in the brain. Dysbindin interacts with various other signaling pathways including the Calmodulin signaling cascade, involved in long-term potentiation (LTP) of synaptic transmission (Blitzer et al., 2005). Recent data suggests an involvement of Dysbindin in the cytoskeletal organization of growth cones of hippocampal neurons (Kubota et al., 2009). Although these functional results focus primarily on the effects of Dysbindin on medial temporal lobe structures, the protein form of Dysbindin can be found not only throughout wide areas of the developing and the mature brain, but also in the neuromuscular junction (Benson et al., 2001).

In the brains of schizophrenia patients, Dysbindin mRNA and protein levels were reported to be reduced in the dorsolateral prefrontal cortex (Weickert et al., 2004) and in the hippocampus (Talbot et al., 2004).

Although no direct evidence of functional effects of rs1018381 exists to date, the T allele of rs1018381 is in complete linkage disequilibrium with the A-allele of rs1047631. In postmortem samples, carriers of the A allele showed significant under-expression of *DTNBP1* mRNA ($p<0.0001$) in the cerebral cortex (Bray et al., 2005). Thus, although on a molecular level a more detailed characterization of the rs1018381 variant remains yet to be given, alterations of Dysbindin functioning are likely to cause changes in neurite outgrowth and morphology that – over a certain threshold – will be detectable by diffusion tensor imaging.

We detected two clusters of reduced FA values in the right temporal lobe of T-allele allele carriers. We interpret these FA value reductions as correlates of reduced anatomic connectivity, most likely due to an impaired Dysbindin functionality.

Serendipitously, in another study of ours using fMRI, Dysbindin rs1018381 T allele status went along with stronger brain activation in the right superior (BA 22, BA 38) and medial temporal gyrus (BA21) and in the anterior cingulate gyrus (BA24) in a subset of the current subjects during a semantic verbal fluency task (Markov et al., 2009a,b). The changes now found in anatomical connectivity in the right temporal lobe might well reflect the anatomical basis of these hyperactivations. Other studies on this Dysbindin variant enrolling the same collective found changes in brain activation during working memory (Markov et al., 2009a,b) and episodic memory encoding and retrieval tasks (Thimm et al., 2010).

A variety of studies indicates structural and functional changes of the temporal lobe in schizophrenia patients. A recent meta-analysis of DTI studies was able to confirm reports of decreased FA values in the left, but not in the right temporal lobe of schizophrenia patients (Ellison-Wright and Bullmore, 2009). However, it has to be noted that the number of studies enrolled (n = 15) in this meta-analysis based on anatomic likelihood estimation (ALE) was comparatively low (Eickhoff et al., 2009), so that changes in the right perihippocampal region might not have reached the threshold for statistical significance. In contrast, several DTI-based studies report reduced FA values to be pronounced in the right medial temporal lobe in schizophrenia patients (Phillips et al., 2009; Schlösser et al., 2007).

There is also evidence for anatomic short-range anatomic hypoconnectivity in the temporal lobes of schizophrenia patients. A recent study on cortico-cortical structural integrity in schizophrenia patients and their first-degree relatives found reduced superficial FA values in the left temporal and bilaterally in the occipital lobes of schizophrenia patients. In patient relatives, fractional anisotropy was shown to vary in accordance with relatedness to a patient in both hemispheres and in the temporal and occipital lobes (Phillips et al., 2011). The latter finding suggests a genetic contribution also to temporal cortico-corical dysconnectivity in schizophrenia.

A variety of functional imaging data emphasize the pathophysiological relevance of these structural anomalies. A decreased functional

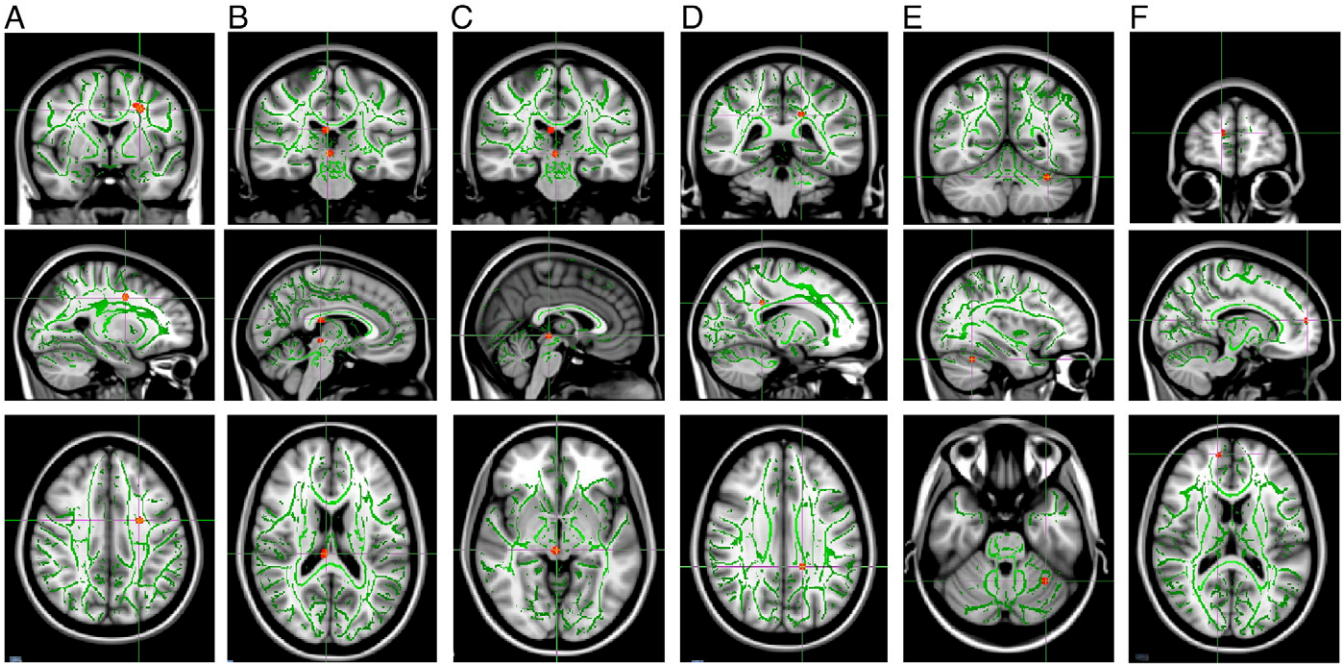

Fig. 2. Clusters of elevated FA values in Dysbindin risk allele carriers were located in the left frontal lobe (−24, −5, 44) (2a), the right fornix (6, −30, 22) (2b), the right midbrain area (3, −30, 0) (2c), the left callosal body (−16, −44, 36) (2d), the left cerebellum (−33, −58, −23) (2e) and close to the right superior medial gyrus (12, 52, 19) (2f). Major fiber tracts as determined by TBSS are shown in green, while red clusters indicate increased FA values in Dysbindin risk allele carriers.

lateralization in the temporal lobes has been described in schizophrenia patients (Sommer et al., 2001, 2003). A reversal of brain activity in the temporal lobes during continuous overt speech has also been reported in schizophrenia patients (Kircher et al., 2002) and it has been implicated in some of the core symptoms of schizophrenia such as formal thought disorder (Kircher et al., 2001) and hallucinations (Dierks et al., 1999; McGuire et al., 1996; Shergill et al., 2000). The fact that a decreased functional lateralization is present in non-affected monozygotic twins of schizophrenia patients (Sommer et al., 2004) further highlights the importance of the genetic contribution to these anomalies. Moreover, it is a well established fact that also structural anomalies of the temporal lobe, e.g. volume reductions of the superior temporal gyrus (Gur et al., 2000; Hajek et al., 1997; Sanfilipo et al., 2000) and of the hippocampus (DeLisi et al., 1991; Niemann et al., 2000) were found to be lateralized.

Healthy Dysbindin rs1018381 T-allele carriers display anomalies of anatomic connectivity in the right temporal lobe and compensatory hyperactivation in this brain region during a semantic verbal fluency task. Moreover, T-allele carriers were shown to reach significantly lower scores on the SPQ-B and the Interpersonal Deficit subscale (Kircher et al., 2009). Under the assumption that – at least in a large number of cases – vulnerability for schizophrenia might be conferred by a polygenic inheritance (Harrison and Weinberger, 2005), we interpret these findings that Dysbindin T-allele carriers without a sufficiently large number of risk variants in other genes actually display structural and functional alterations in the temporal lobe, thus reflecting the anatomical basis of these changes.

Besides the discussed FA reductions in the temporal lobe, we also found six clusters of elevated FA values in Dysbindin T-allele allele carriers. One cluster of increased FA values was located in the midbrain area. A variety of functionally diverse fiber tracts, such as e.g. the pyramidal tract, the ascending sensory tracts, etc., are closely located in this comparatively small cerebral region. Hence, it is challenging to attribute these changes to a specific tract.

A variety of DTI-based studies reported reductions of FA values in the corpus callosum (Gasparotti et al., 2009; Kubicki et al., 2008; Michael et al., 2008) and the fornix (Fitzsimmons et al., 2009; Rametti et al., 2009; Takei et al., 2008) in patients with schizophrenia. Several studies reported associations between FA changes in these fiber tracts and symptom severity (Rametti et al., 2009; Takei et al., 2008). One recent study yielded evidence for an irregularly turbulent or inhomogeneously distributed fiber trajectories especially of the frontotemporal and temporoparietal fibers of the corpus callosum as potential cause for the reported FA changes (Whitford et al., 2011).

The same holds true for the FA changes we detected in the frontal lobe. T-allele allele carriers showed changes in fiber tracts of the left frontal lobe and the frontal lobe proximate to the superior medial gyrus. FA reductions in frontal white matter tracts have been repeatedly reported in schizophrenia patients (Kyriakopoulos et al., 2008), while a meta-analysis proves that findings were lateralized to the left side (Ellison-Wright and Bullmore, 2009).

It has been proposed that lateral cerebellar dysfunction may lead to impairment of higher cognitive functions (Schmahmann and Sherman, 1998) and that cerebellar dysfunction might be involved in the pathogenesis of schizophrenia (Andreasen et al., 1998). Indeed, DTI studies in schizophrenia patients found FA changes in the cerebellum (Kyriakopoulos et al., 2008; Okugawa et al., 2006). In this context, elevated FA values in the cerebellum fit well into that picture, although, again, these studies found reduced, not elevated FA values in schizophrenia patients.

Although most studies find evidence for reduced both anatomical and functional connectivity in schizophrenia patients, it has to be pointed out that several studies also found evidence for increased connectivity as a potential pathomechanism. In a recent study using structural equation model e.g. patients exhibited a stronger thalamic-insular connection than healthy controls (Corradi-Dell'acqua et al., 2011).Thus, it is tempting to speculate that also our results indicating increased anatomical connectivity in some brain regions in Dysbindin risk allele carriers might hint at a potential pathomechanism.

There are several limitations in our study. Although there is quite a robust body of evidence for the involvement of the Dysbindin rs1018381 variant in the etiology of schizophrenia (Schwab et al., 2003; Straub et al., 2002; Tang et al., 2003; van den Bogaert et al., 2003), there are inconsistencies about which allele is actually associated with an increased

risk for schizophrenia (Schwab et al., 2003; Straub et al., 2002; Tang et al., 2003; van den Bogaert et al., 2003). Thus, our interpretations here have to be read with care, concerning the assignment of the T allele – and therefore the structural changes that go along with it – to an increased risk of schizophrenia.

Moreover, fractional anisotropy is a parameter that measures changes not only in fiber tract coherence (Ono et al., 1995) and structural integrity of the fibers, their diameter and packing density (Beaulieu, 2002), but also the degree of myelination (Gulani et al., 2001). Thus, due to the lack of pathophysiological specificity, it will be a challenge for future studies to give a better characterization by using related parameters such as axial and radial diffusivity.

The changes in brain structure we found were of course rather discrete. It has to be considered however that we examined healthy young subjects with a high level of intellectual functioning and without a history of psychiatric disorder in first degree relatives. Thus, more pronounced brain structure alterations cannot reasonably be expected.

Moreover, we included both male and female subjects in this study. Although gender was used as a covariate, a direct comparison between male and female T allele carriers would be interesting. However, the number of subjects included does not allow such a comparison. Future studies enrolling larger populations should also focus on gender-specific effects.

In summary, we found clusters of elevated and reduced FA values in healthy Dysbindin T allele carriers with their location in line with structural and functional alterations in schizophrenia patients. The structural alterations found might well in part represent the anatomical basis of changes on a behavioral (Kircher et al., 2009) and functional imaging (Markov et al., 2009a,b; Thimm et al., 2010) level found in the same collective.

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