RESEARCH ARTICLE

Effects of a Balanced Translocation between Chromosomes 1 and 11 Disrupting the DISC1 Locus on White Matter Integrity

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Abstract

Objective

Individuals carrying rare, but biologically informative genetic variants provide a unique opportunity to model major mental illness and inform understanding of disease mechanisms. The rarity of such variations means that their study involves small group numbers, however they are amongst the strongest known genetic risk factors for major mental illness and are likely to have large neural effects. DISC1 (Disrupted in Schizophrenia 1) is a gene containing one such risk variant, identified in a single Scottish family through its disruption by a balanced translocation of chromosomes 1 and 11; t(1;11) (q42.1;q14.3).

Method

Within the original pedigree, we examined the effects of the t(1;11) translocation on white matter integrity, measured by fractional anisotropy (FA). This included family members with (n = 7) and without (n = 13) the translocation, along with a clinical control sample of patients with psychosis (n = 34), and a group of healthy controls (n = 33).

Results

We report decreased white matter integrity in five clusters in the genu of the corpus callosum, the right inferior fronto-occipital fasciculus, acoustic radiation and fornix. Analysis of the mixed psychosis group also demonstrated decreased white matter integrity in the above regions. FA values within the corpus callosum correlated significantly with positive psychotic symptom severity.

Conclusions

We demonstrate that the t(1;11) translocation is associated with reduced white matter integrity in frontal commissural and association fibre tracts. These findings overlap with those shown in affected patients with psychosis and in DISC1 animal models and highlight the value of rare but biologically informative mutations in modeling psychosis.

Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are severe neurodevelopmental disorders with a combined lifetime prevalence of around 2% [1]. Together with major depressive disorder (MDD) they are amongst the top ten leading causes of disability worldwide [1]. Although the aetiologies of these disorders are incompletely understood, they are known to be highly heritable with complex genetic architectures [2,3]. Genetic risk variants for these disorders are proposed to lie along a spectrum of effect sizes: from rare monogenic variants of large effect, to common but relatively weak variants that, in aggregate, result in disorder. Rare variants affect small numbers of individuals but can be particularly informative in that they have a large effect on underlying biology and studying them in multiply-affected families may substantially reduce heterogeneity associated with clinically-defined cases. Studies of rare variants can therefore inform understanding of disease mechanisms relevant not only for individuals carrying such mutations, but also for wider patient populations [4,5].

One such rare highly penetrant mutation occurs in the Disrupted-in-Schizophrenia 1 gene (*DISC1*). *DISC1* was first implicated in psychopathology after the identification of a balanced chromosomal t(1;11) (q42.1;q14.3) translocation in an adolescent with conduct disorder. Follow-up of this Scottish pedigree indicated the translocation co-segregated with multiple cases of SZ, MDD and BD [6]. Further studies demonstrated that family members who carried the translocation also showed deficits in attention and information processing [6]. Subsequently, independent genetic evidence for the involvement of the *DISC1* locus in SZ and affective disorders has emerged [7–9] suggesting a role for *DISC1* variants as risk factors in major mental illness [4,10]. Examination of the effects of this translocation could therefore bring insights into how *DISC1* mediates its effects on psychopathology through intermediate phenotypes such as brain structure and function.

DISC1 functions as a molecular scaffold protein interacting with other proteins contributing to multiple neurodevelopmental processes [4,11–15]. Expression of DISC1 is highest in the central nervous system, and is reported in both neurons and glial cells [4,16–18]. Although the complex molecular consequences of the t(1;11) translocation are incompletely understood, given roles of DISC1 in neurodevelopment, the translocation is likely to contribute to abnormal brain development, including white matter. This is particularly relevant for major psychiatric disorders where multiple lines of evidence implicate disruption of white matter connections in

SZ, BD and MDD particularly in fronto-temporal and callosal tracts [19–21]. Further, animal models of altered DISC1 expression are reported to result in a range of abnormalities including partial agenesis of the corpus callosum (CC) [7,22–24]. Effects of common variants within DISC1 have also been shown to affect white matter integrity and cognitive function, involving the prefrontal cortex and inter-connecting regions [9,25–34]. The specific effects of the t(1;11) translocation on white matter pathology in humans has, however, not previously been reported.

Given that DISC1 is known to be involved in white matter formation [18,35], that white matter integrity is highly heritable [36–38] and related to familial risk, as well as to illness [39–41], we sought to compare white matter integrity in individuals from the original DISC1 Scottish pedigree with and without the chromosomal translocation. We hypothesised that the t(1;11) translocation would lead to reduced white matter integrity in multiple neural networks that have been shown to be both heritable and genetically correlated with SZ and demonstrated in animal models of DISC1 biology, including the corpus callosum, and tracts connecting with prefrontal regions especially fronto-temporal connections. In order to relate the effect of the translocation to the effect of major mental illness, we also compared a clinical control group (of individuals with SZ or BD) to a matched control group.

Methods

Study population

The current analysis involved four study groups, (i) family members with and (ii) without the t(1;11) translocation, (iii) a clinical control group of patients with a range of psychotic illness and (iv) healthy controls. Family members were recruited from a previously reported Scottish family known to carry the t(1;11) translocation [42,43]. Twenty five family members known to carry the translocation were approached to participate. Through these individuals other members of the family were also invited. All family members willing to participate were recruited and, after informed consent obtained, translocation status determined.

Patients with clinical diagnosis of SZ or BD were identified across Scotland as part of the Scottish Family Mental Health Study. Healthy controls were recruited from the same geographical areas as the patient groups. For all groups exclusion criteria included any major medical or neurological conditions, any personal history of harmful substance abuse in the last year or substance dependence, and for the control group any personal or familial history of psychiatric disorders. Subjects were excluded where there were MRI safety considerations.

Ethics Statement

A detail description of the study was given to all individuals and all participants gave written informed consent. The study was approved by the Multicentre Research Ethics Committee for Scotland.

Seven family members with, and 13 without the t(1;11) translocation provided usable diffusion tensor imaging (DTI) data, along with the clinical control group of patients with a range of psychotic illness (n = 34; comprising n = 23 with SZ, and n = 11 with BD) and a group of healthy controls (n = 33). Of those family members with the t(1;11) translocation, all had a psychiatric diagnosis (1 had a diagnosis of SZ, 3 of cyclothymia and 3 of MDD; 1 recurrent, 2 single episode). For the non-carrier group 2 individuals met criteria for MDD (1 recurrent, 1 single episode). One individual from the carrier group was taking clozapine, valproate and lithium, and one taking fluoxetine. One family member from the non-carrier group was taking amytriptyline. Medication for the patient group is contained in S1 Table.

Inclusion of the patient group was to provide a clinical group to relate the effects of the t (1:11) translocation to the effect of generalized psychotic illness. The analysis plan was to examine the effects of the translocation (carriers versus non-carriers), and then to relate any differences to those seen in the comparison of the clinical psychosis group versus controls. We did not consider a direct comparison between the psychosis patient group and translocation carriers justified given differences in degrees of relatedness and shared environmental effects between groups.

The diagnosis of all affected subjects was confirmed using the structured clinical interview for DSM IV (SCID) administered by one of two trained psychiatrists (DB, AW) [44]. Symptom severity was assessed using the Young Mania Rating Scale (YMRS) [45], the Hamilton Depression Rating Scale (HRSD) [46], Positive and Negative Symptoms Scale (PANSS) [47] and the Scale for the Assessment of Negative Symptoms (SANS) [48]. Symptom rating took place within one week of the MRI scan. All participants IQ levels were assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Psychological Corporation, San Antonio TX).

PCR typing of translocation breakpoint

The translocation status of all participants was tested on new blood samplesusing polymerase chain reaction (PCR) based methods. Primers were designed to span the t(1;11) breakpoint of *DISC1* exon9 using the Primer 3 design program [49,50], further details in S1 Text.

Scan Acquisition and Preprocessing

Whole brain DTI scans were acquired with a prototype single-shot pulsed gradient spin-echo echo-planar imaging (EPI) sequence with diffusion gradients (b = 1000 s/mm^2) applied in 56 non-collinear directions, further details in S1 Text. Standard pre-processing procedures were employed involving conversion to NifTI format, eddy current correction, linear motion correction and brain extraction using tools in FSL (http://www.fmrib.ox.ac.uk/fsl). Water diffusion tensor parameters, specifically fractional anisotropy (FA), were estimated by fitting the tensor model to the data. Absolute motion was extracted for each subject using the 'avscale' tool and averaged to produce a measure of mean displacement to the first EPI volume for each subject. All subjects with average motion estimates exceeding two-times the voxel size were excluded (3 controls; 4 SZ; 1 BD and 1 t(1;11) carrier diagnosed with MDD). Group numbers given above refer to individuals with usable imaging data.

Tract Based Spatial Statistics

Tract-Based Spatial Statistics (TBSS) [51,52] was performed using the standard FSL procedure, see S1 Text. Voxel-wise statistics were performed using threshold-free cluster enhancement (TFCE) in FSL's randomise [53]. P-values were corrected using family-wise error rate (p_{FWE}) over 5000 permutations, TFCE-corrected p-values were considered significant at $p_{FWE} < 0.05$. All analyses were corrected for age and sex.

Additional analyses were conducted in ASReml-R (www.vsni.co.uk/software/asreml) to determine whether the main clusters of difference for the comparison of translocation carriers versus non-carriers remained significant while accounting for relatedness between individuals (as well as controlling for age and sex), see S1 Text. Statistical analysis of demographic and clinical data was conducted using one-way ANOVAs, Mann-Whitney U tests or chi-squared tests where appropriate.

Table 1. Demographics and clinical measures.

	t(1;11) non-carriers	t(1;11) carriers	Statistics (T/ χ²)	p-value
N	13	7	-	-
Age (mean, std dev)	34.54 (20.38)	54.57 (9.88)	2.96	**0.008**
Gender (F:M)	5:8 (38%:62%)	2:5 (29%:71%)	0.120	0.658
Current IQ	87.75 (9.24)	92.43 (19.56)	0.61	0.555
		Clinical measures#		
PANSS +	7 (0.00)	7 (11.00)	2.49	**0.013**
PANSS -	7 (0.00)	7 (3.00)	1.98	**0.048**
PANSS gen	16 (5.00)	26 (16.00)	2.42	**0.016**
PANSS tot	30 (5.00)	40 (29.00)	2.46	**0.014**
HDRS	0 (1.00)	2 (6.00)	2.15	**0.032**
YMRS	0 (0.00)	1 (5.00)	2.95	**0.003**
SANS tot	0 (0.00)	0 (0.00)	0.53	0.594
	Controls	**Psychosis**	Statistics	p-value
N	33	34	-	-
Age (mean, std dev)	37.15 (15.30)	40.21(11.40)	0.93	0.356
Gender (F:M)	15:18 (45%:55%)	14:20 (41%:59%)	0.13	0.724
Current IQ	116.58 (10.88)	106.58 (15.98)	2.73	**0.009**
		Clinical measures#		
PANSS +	7 (0.00)	10.5 (6.00)	5.40	**<0.001**
PANSS -	7 (0.00)	10 (5.00)	5.71	**<0.001**
PANSS gen	16 (0.00)	24.5 (10.00)	6.18	**<0.001**
PANSS tot	30 (0.50)	45 (19.25)	6.49	**<0.001**
HDRS	0 (1.00)	8 (13.50)	5.26	**<0.001**
YMRS	0 (0.00)	1 (3.00)	4.23	**<0.001**
SANS tot	0 (0.00)	18.50 (23.25)	6.04	**<0.001**

median and interquartile range and non-parametric Mann-Whitney U statistics applied.

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Results

Demographic and clinical measures

Comparison of the translocation carrier versus non-carrier groups demonstrated significant differences in age (Table 1). Although we had controlled for age, we additionally performed a post-hoc analysis to maximize the age overlap in the familial samples (see below). There were no significant differences in gender between groups. For the majority of clinical assessments the translocation carriers had significantly higher scores than the non-carriers (Table 1). For the comparison of patients versus controls, the groups were not significantly different in terms of age or gender however there were significant differences in all clinical measures.

Effects of Translocation

Whole-brain voxel-wise comparison indicated that t(1;11) translocation carriers had reduced FA in five clusters versus the non-carriers (p_{FWE} = 0.05, Fig 1, Table 2, and contained within S1 Data). These included the genu of corpus callosum (cluster 1, size = 921 voxels and cluster 3, size = 55 voxels, left and right respectively), right inferior fronto-occipital fasciculus (cluster 2 size = 63 voxels), right acoustic radiation (cluster 4 size = 38 voxels), and right fornix (cluster 5
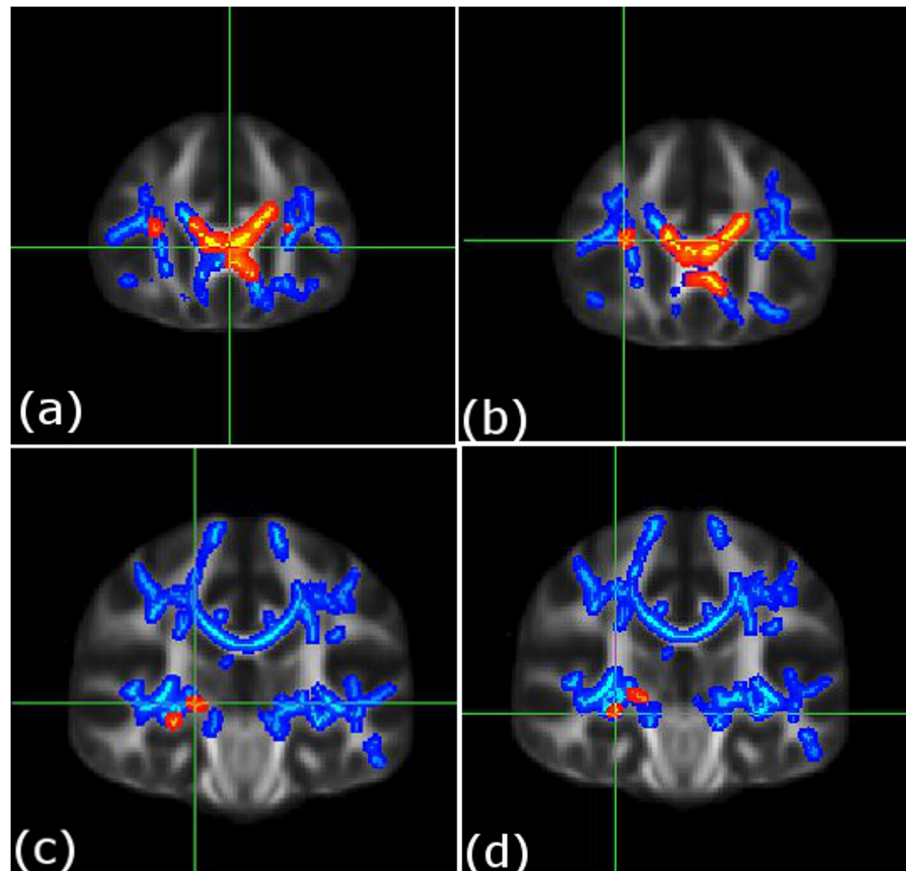
Fig 1. Decreases in white matter integrity in t(1;11) translocation carriers (n = 7) versus non-carriers (n = 13) and in patients (n = 34) versus controls (n = 33). Deceased white matter integrity in translocation carriers versus non-carriers (shown in red), and in the patient group versus the control group (shown in blue). Individual figures (a-d) present the main cluster peak co-ordinates for the translocation carrier versus non-carrier comparison; (a) left genu of corpus callosum [–3, 28, 6], (b) right inferior fronto-occiptal fasciculus [29, 26, 15], (c) right acoustic radiation [20, 25, 0], and (d) right fornix [28, –24, –8]. For further details see Table 2. To aid visualization the results (pfwe < 0.05) are thickened using the "tbss-fill" command. Statistics for FA decreases in the patient group versus controls for these peaks; cluster 1: p = 0.023 at [-3, 28, 6; left genu of corpus callosum], cluster 2: p = 0.032 at [29, 26, 15; right fronto-occipital fasciculus], cluster 3: p = 0.012 at [11, 26, 14; right genu of corpus callosum], cluster 4: p = 0.033 at [20, 25, 0; right acoustic radiation], and cluster 5: p = 0.031 at [28, -24, -8; right fornix] i.e. for clusters 1–5 respectively, see, Table 2).

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size = 23 voxels). There were no regions where FA was significantly increased in t(1;11) carriers in comparison to t(1;11) non-carriers.

We repeated the analysis to determine whether differences in age could be confounding the results. This was based on removing eight individuals aged 17–24 years from the non-carrier group (leaving five subjects aged > 40, mean = 57.6 years, mean difference non-significant, p = 0.647). White matter integrity remained significantly lower in translocation carriers in all of the above clusters with the exception of the cluster in the left inferior fronto-occipital fasciculus (p = 0.056, Table 2). Similarly, all clusters with the exception of the cluster in the inferior fronto-occipital fasciculus, remained significantly different between carriers versus non-carriers while controlling for relatedness between individuals (p = 0.048, p = 0.016, p = 0.003, p = 0.015 for the left and right corpus callosum, acoustic radiation and fornix respectively).

Table 2. TBSS findings.

Cluster size	P_{FWE}	Co-ord	Peak region
Effects of translocation (family members without (n = 13) > with (n = 7) translocation)			
Effects of translocation (family members without (n = 13) > with (n = 7) translocation)			
Non-carriers (n = 13) **> carriers** (n = 7)			
1) 921	0.042#(0.039)*	-3 28 6	L genu of corpus callosum
2) 63	0.049#(0.056)*	29 26 15	R inferior fronto-occipital fasciculus
3) 55	0.049#(0.046)*	11 26 14	R genu of corpus callosum
4) 38	0.040#(0.037)*	20–25 0	R acoustic radiation
5) 23	0.049#(0.035)*	28–24–8	R fornix
Effects of psychosis (controls (n = 33) > psychosis patients (n = 34))			
1) 31818	0.008	-6–31 22	R/L splenium body and genu of corpus callosum
2) 437	0.047	29 16–6	R external capsule, inferior fronto-occip fasciculus, uncinate fasciculus
3) 294	0.047	-1–5 13	R/L fornix

reverse contrasts of carriers > non-carriers and psychosis patients > controls: not significant.

#peak also significant for the controls > patient analysis, see text for further details.

*number in brackets represents p values for at the same co-ordinate for the analysis removing the younger individuals from the non-carrier group.

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Effects of Psychosis

Whole-brain comparison indicated that patients with psychotic illness exhibited reduced FA in three clusters extending over much of the white matter skeleton (see Fig 1, Table 2). These clusters included the body and splenium of corpus callosum (cluster 1, size = 31,818 voxels), right external capsule, inferior fronto-occipital fasciculus and uncinate fasciculus (cluster 2; size = 437 voxels), and bilateral fornix (cluster 3 size = 294 voxels). There were no regions where FA was increased in the patient group relative to controls.

Fig 1 illustrates the peak co-ordinates of the clusters reported in the translocation analyses to facilitate comparison with effects seen in the mixed psychosis group (versus controls). This indicates an overlap of findings for all clusters reported in the comparison of translocation carriers versus non-carriers in the patient versus control comparison (see Fig 1 and Fig 1 legend for more details). The extracted FA values across these main clusters for all four groups are plotted in Fig 2.

Relation to positive symptom severity

We also examined the relationship between FA values from the five clusters of interest corresponding to the above analysis (effects of translocation), with positive symptom severity as determined by the PANSS positive total score across all individuals whilst controlling for group. This indicated significant negative correlations for the two clusters in the genu of corpus callosum (Spearman's rho ρ = -0.366, p = 0.001; ρ = -0.233, p = 0.030). Other regions also demonstrated negative correlations but were not significant (inferior fronto-occipital fasciculus ρ = -0.197, p = 0.068; acoustic radiation ρ = -0.199, p = 0.065, fornix ρ = -0.190, p = 0.077). These
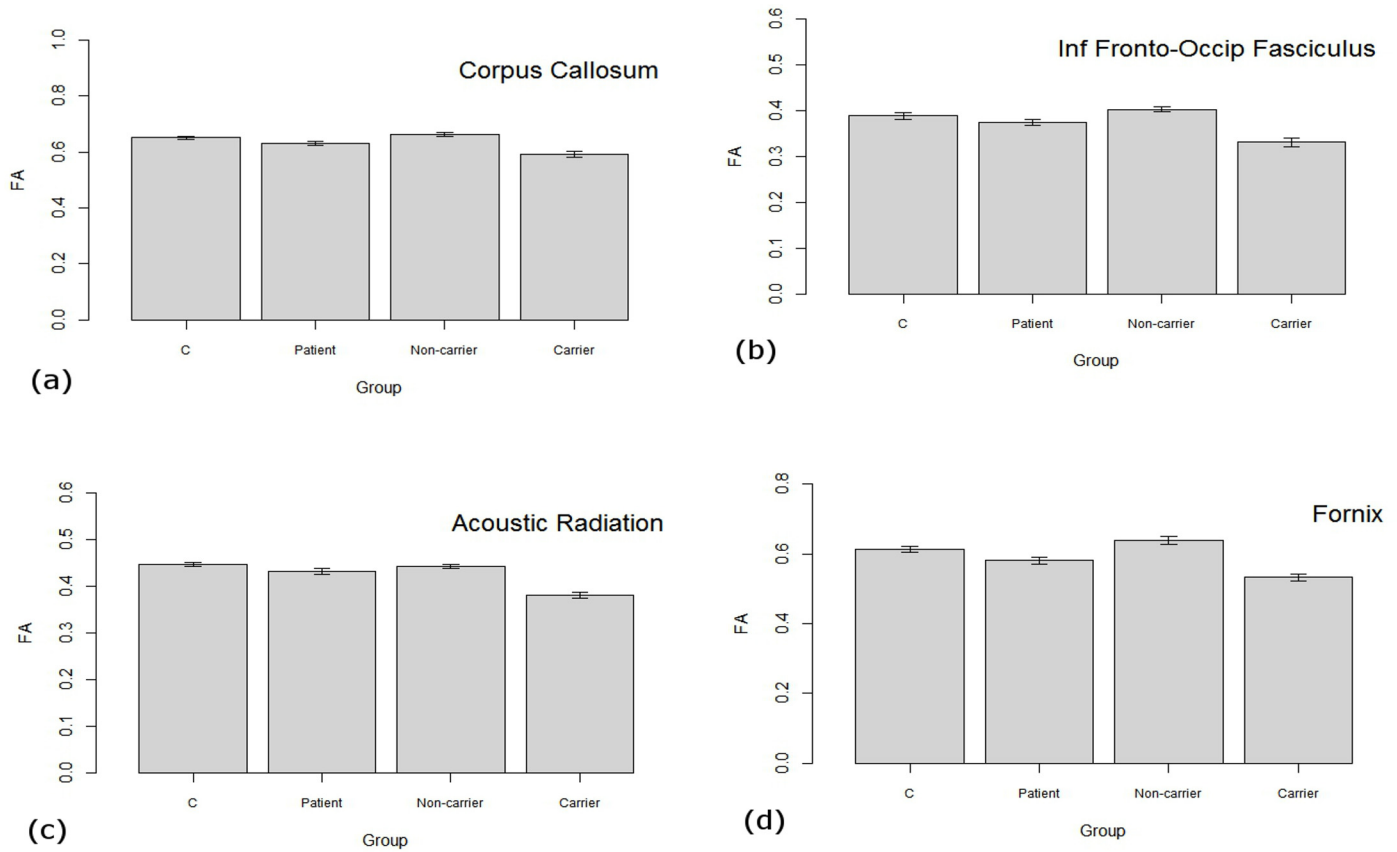
Fig 2. FA values extracted from clusters of differences between carrier and non-carrier groups. Individual figures represent FA values across the main clusters of differences from the comparison of translocation carrier versus non-carrier comparison; (a) cluster 1: genu of corpus callosum, (b) cluster 2: right inferior fronto-occiptal fasciculus, (c) right acoustic radiation, and (d) cluster 4: right fornix. C = control group, Patient = group with mixed psychoses, Non-carrier = family members not carrying translocation, Carrier = family members with the translocation.

findings therefore indicated that greater positive symptomatology was related to decreases in callosal white matter integrity whilst controlling for group status in these regions.

Discussion

We examined the effects of the t(1;11) (q42.1;q14.3) chromosomal translocation on white matter integrity using DTI in individuals from the family where original linkage was first reported [42,43]. As predicted, the translocation had a significant effect on multiple neural pathways including callosal fibers and tracts connecting frontal regions. In addition, FA in the corpus callosum was significantly negatively correlated with positive psychotic symptomatology. With the exception of the inferior fronto-occipital fasciculus, these findings remained significant after removing non-age matched individuals from the non-carrier group and controlling for relatedness. In addition, all cluster effects were evident in the comparison of mixed psychosis patients versus controls. We interpret the findings therefore as supporting a core role for aberrant white matter connectivity in these tracts in the risk-conferring effects of the DISC1 translocation.

DISC1 functions as a molecular scaffold protein interacting with other proteins and contributes to multiple neural processes including proliferation, migration, and differentiation [4]. Most literature has focused on the role of DISC1 in neuronal function and development,

however recently attention has moved to its effects on glial cells [17,18]. These studies suggest that DISC1 is expressed in glia and has a fundamental role in white matter development. In particular, it has been reported that dysfunction of DISC1 or its interactors may result in impaired oligodendrocyte differentiation resulting in deficits in axonal myelination, defective neuronal communication, altered structural connectivity and altered white matter integrity [18,54]. This is also highly compatible with other lines of evidence for the involvement of DISC1 in white matter development from studies in both animals and humans [34], in particular in association with agenesis of the corpus callosum [24,35].

Overall these findings are consistent with hypotheses that aberrant fronto-temporal and callosal connectivity underlie deficits seen in SZ and BD; through a loss of frontal executive control over temporal and limbic regions [55], and though reduced inter-hemispheric connectivity and the impact on co-ordination of information processing [56]. One of the main findings was decreased white matter integrity of callosal fibers, specifically in anterior regions, in translocation versus non-translocation carriers. This was also seen in patients versus healthy controls, and was related to severity of symptoms, indicating a potential role for DISC1 in the genesis of positive symptomatology. This finding is also consistent with reports of callosal abnormalities in patients with psychosis and in unaffected relatives, particularly in anterior sections [57–63]. The corpus callosum contributes the bulk of axonal transmission between the cerebral hemispheres hence sub-serves inter-hemispheric information transfer. Topographical organisation means that anterior regions carry connections between frontal regions and are responsible for transfer and co-ordination of cognitive information [64]. Animal literature also confirms a specific role for DISC1 in corpus callosum development [18,24,35]. In terms of human studies, one report investigated three family members with complete agenesis of the corpus callosum and reported that all three shared deletions in chromosome 1q24, including the DISC1 region [35,65]. A larger study of 144 individuals with partial or complete agenesis of corpus callosum also identified multiple rare variants and deletions involving DISC1 [35,65]. Further, in humans, agenesis of the corpus callosum is typically associated with impaired higher-order cognitive functioning similar to that found in patients with psychosis [66]. Taken together these findings strengthen evidence that DISC1 maintains a critical role in corpus callosum development and indicate that its involvement in the pathogenesis of psychiatric disorders may indeed be mediated through these structural white matter abnormalities.

This study also reported structural connectivity deficits in prefrontal association fibers, including those connecting the frontal cortex with temporal and limbic regions. These findings were also replicated in the comparison between patients and healthy controls. While the direct effects of DISC1 on these tracts remain largely underexplored in animals and humans, deficits have been reported in these tracts, or in the functional connections between regions concerned, in both SZ and BD and in unaffected relatives [41,67–70]. Neurobiological models proposed to underlie these disorders suggest either a loss or reduction of higher order cognitive control from the prefrontal cortex over temporal and limbic regions. Disconnection between these regions is proposed to underpin executive impairments in SZ and BD and is central to cognitive models of psychotic disorders. In such models deficits in self-monitoring and corollary discharge across a range of emotional and cognitive domains are proposed to result in characteristic neuropsychological and clinical features seen in the disorders [71]. Here, evidence suggests involvement of DISC1 in disconnectivity within these circuits.

Studying rare genetic events in multi-affected families carries several inherent disadvantages, unavoidable given the challenges of recruiting from a single pedigree. These include small group numbers, difficulties in age-matching, and a potential lack of generalisability of findings. Here, all analyses were corrected for age, and findings were replicated in an age-matched sub-group. Also, all clusters reported in the translocation carriers were seen in the

patient-control comparison. Further, although all members of the family with the t(1;11) translocation who participated in the study had a psychiatric disorder, the severity of this ranged from cyclothymia to chronic SZ. Notably however, phenotypic pleiotropy of DISC1 has been evident since the first description of the family [43] and is consistent with emerging genetic findings from large genome-wide association studies [72], showing a significant degree of overlap in the genetic associations of different psychiatric disorders. Regarding possible confounding effects of anti-psychotic medication, it should be noted that only one individual from either of the familial groups was taking psychotropic medication (a translocation carrier). Further, examination of the correlation between FA values from the clusters of interest and chlorpromazine equivalents across the entire study sample, or within the patient sample alone, did not indicate any significant relationship with FA. Other studies have also reported decreased FA in anti-psychotic naïve cohorts [73]. The decreases in FA reported here are therefore unlikely to be attributable to medication effects.

It should also be noted that although DTI is an established method of indexing white matter integrity, deficits in FA could be due to a number of factors, including differences in axonal density, myelination, diameter, membrane permeability, or in the orientational coherence of axons within voxels [74]. Hence we are unable to interpret findings as providing evidence of a particular cellular pathology [74]. Also, FA cannot accurately describe multifiber architecture and might be influenced by motion, eddy currents, misregistration, and partial volume effects [75].

In summary, rare, causal and family-specific mutations may usefully model the neurobiology of SZ both *in vitro* and *in vivo* in the presence of greatly reduced genetic complexity and greater penetrance at the level of both clinical diagnosis and biological intermediates. The t(1;11) translocation involving DISC1 is one of the few such rare mutations implicated in psychiatric disorders. Our results suggest that the t(1;11) translocation is associated with reduced white matter integrity in frontal commissural and association pathways, also seen in the comparison of the patient group to healthy controls. The replication of corpus callosum abnormalities previously seen in animal studies in humans also indicates an exciting translational opportunity. These findings are consistent with the notion that white matter integrity could mediate the effects of the t(1;11) translocation on risk for major psychiatric disorders. Further investigation through molecular and cellular studies may bring new insights into biological pathways and mechanisms of the DISC1 gene and may have an important impact on identification of new interventions.

Supporting Information

S1 Data. Supplementary data. Extracted FA data from main clusters of difference between the translocation carriers and non-carriers. Group abbreviations, Co = controls, Pt = patient group, FN = family member negative for translocation, FP = family member positive for translocation.
(CSV)

S1 Table. Medication details of patient group.
(DOCX)

S1 Text. Supplementary methods.
(DOCX)

Acknowledgments

Author Contributions

Conceived and designed the experiments: MD BM NB BW JD ZH JH DHRB AMM SML. Performed the experiments: HCW RD ES MD BD BM MB JH AW PT ZH NJB JD BW DHRB AMM SML. Analyzed the data: HCW RD ES. Contributed reagents/materials/analysis tools: ES MB SIS PT LR NR SG. Wrote the paper: HCW RD ES MRD LR BD ARW BM MB SIS SG JH PT NR ZAH NJB JD BW DHRB AMM SML.

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