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Original contribution

Exercise ameliorates deficits in neural microstructure in a Disc1 model of psychiatric illness

Brian R. Barnett[a,1], Jacqueline M. Anderson[b,1], Maribel Torres-Velázquez[c], Sue Y. Yi[a], Paul A. Rowley[b], John-Paul J. Yu[a,b,c,d,*]

[a] Neuroscience Training Program, Wisconsin Institutes for Medical Research, University of Wisconsin–Madison, Madison, WI 53705, USA
[b] Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI 53705, USA
[c] Department of Biomedical Engineering, College of Engineering, University of Wisconsin–Madison, Madison, WI 53706, USA
[d] Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison, WI 53705, USA

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ABSTRACT

Recent studies have investigated the effectiveness of aerobic exercise to improve physical and mental health outcomes in schizophrenia; however, few have explicitly explored the impact of aerobic exercise on neural microstructure, which is hypothesized to mediate the behavioral changes observed. Neural microstructure is influenced by numerous genetic factors including DISC1, which is a major molecular scaffold protein that interacts with partners like GSK3*β*, NDEL1, and PDE4. DISC1 has been shown to play a role in neurogenesis, neuronal migration, neuronal maturation, and synaptic signaling. As with other genetic variants that present an increased risk for disease, mutations of the *DISC1* gene have been implicated in the molecular intersection of schizophrenia and numerous other major psychiatric illnesses. This study investigated whether short-term exercise recovers deficits in neural microstructure in a novel genetic *Disc1* svΔ2 rat model. *Disc1* svΔ2 animals and age- and sex-matched controls were subjected to a treadmill exercise protocol. Subsequent *ex-vivo* diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) compared neural microstructure in regions of interest (ROI) between sedentary and exercise wild-type animals and between sedentary and exercise *Disc1* svΔ2 animals. Short-term exercise uncovered no significant differences in neural microstructure between sedentary and exercise control animals but did lead to significant differences between sedentary and exercise *Disc1* svΔ2 animals in neocortex, basal ganglia, corpus callosum, and external capsule, suggesting a positive benefit derived from a short-term exercise regimen. Our findings suggest that *Disc1* svΔ2 animals are more sensitive to the effects of short-term exercise and highlight the ameliorating potential of positive treatment interventions such as exercise on neural microstructure in genetic backgrounds of psychiatric disease susceptibility.

1. Introduction

The impact of exercise on brain structure and function has emerged as an area of intense interest [1–3]. To date, many of these studies exploring the effect of exercise have focused on the ameliorating effect of exercise in the setting of aging, obesity, and Alzheimer's disease [4–14]. Recent work has also turned attention to the effect of aerobic exercise as a potential treatment intervention in schizophrenia and other psychiatric illnesses. These studies, while encouraging, have returned mixed results, with some finding exercise to be a beneficial intervention for mental and physical health and others finding more inconclusive results [15–23]. Thus far, however, these studies have evaluated the impact of aerobic exercise in schizophrenic subjects using cognitive assessments, neurobiological markers, or hippocampal volume with a paucity devoted towards investigating the impact of exercise on quantitative measures of brain structure. Of these, only one study to date has explicitly examined the impact of exercise on white matter microstructure in schizophrenic subjects using diffusion tensor imaging (DTI), which demonstrated the benefit of long-term exercise on maintaining the structural integrity of motor-based white matter tracts [24]. Exercise and its effect on neurocognitive outcomes have largely focused on evaluating life-long fitness levels or the effects of a long-

* Corresponding author at: Department of Radiology, Division of Neuroradiology, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, Madison, WI 53792-3252, USA.
E-mail address: jpyu@uwhealth.org (J.-P.J. Yu).
[1] These authors contributed equally to this work.

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term exercise intervention (6 weeks-1 year). However, new evidence has emerged demonstrating the benefit of short-term and short-interval exercise on growth factors, synaptic proteins, and hippocampal plasticity [25–28] and suggests that short-term exercise interventions may have a similar effect on neurocognitive outcomes and neural microstructure.

With the initial discovery of *DISC1* in 2000 as a balanced chromosomal t(1;11)(q42.1;q14.3) translocation segregating with schizophrenia and related psychiatric disorders in a clinical population [29] *DISC1* has remained a significant and ongoing focus of wide and varying efforts towards understanding the molecular mechanisms that drive the psychiatric disease state. DISC1 has since been identified as a major molecular scaffold protein interacting with GSK3β, NDEL1, LIS1, PDE4, KAL7, TNIK, and others in multiple neuronal processes, thus placing it at the molecular intersection of schizophrenia and numerous other major psychiatric illnesses [30,31]. To better understand the role of *DISC1* in the neuropathogenesis of psychiatric illness, several groups have generated animal models of *Disc1* as an avenue towards understanding its role in the development of the psychiatric disease state. These include models with dominant-negative *Disc1* expression and models with ENU mutagen-induced point mutations [32,33]. Loss-of-function *Disc1* murine models have also been generated including a murine model lacking exons 2 and 3 of the *Disc1* gene that displays abnormalities in sensorimotor gating, impulsive behavior, and cognitive impairments centering around repetitive and compulsive-like behaviors [34,35]. We have developed a novel CRISPR/Cas9-based rat *Disc1* model to supplement this repertoire of murine genetic models [36]. The biological consequences of this early DISC1 truncation are associated with data from patients with schizophrenia [37] and several existing models that recapitulate this early truncation of the major isoform of DISC1 demonstrate evidence towards its role in neuropathophysiology [38–40]. This *Disc1* rat model enables multiple avenues of exploration in a model situated closer to human biology, including evaluation of circuit-level differences, comparison with imaging data from patients with psychiatric illness, and potential validation of biomarkers useful for diagnosis and targets for therapeutic intervention [41,42].

To better understand the role of short-term exercise and its potential impact on neural microstructure in different genetic backgrounds of psychiatric disease susceptibility, we subjected both control and *Disc1* svΔ2 animals to a four-week treadmill exercise paradigm. Age- and sex-matched sedentary animals were then compared to their matched exercise cohort with DTI and neurite orientation density and dispersion imaging (NODDI) to examine potential differences in white microstructural integrity as well as in quantitative measures of neurite density and orientation dispersion. The main advantage offered by NODDI includes the ability to sensitively capture changes in neurite density (neurite density index, NDI) and orientation (orientation dispersion index, ODI), two microstructural features representing synaptic density and organization that are not available from standard diffusion tensor imaging [43–45]. As DISC1 serves to regulate the development of synaptic growth and the organization of trans-synaptic structures and functions, we have previously reported that our *Disc1 svΔ2* model harbors decreased neurite density in numerous salient regions of the brain including the hippocampal formation, the basal ganglia, and the neocortex [36] thus making our model particularly suited to explore the impact of exercise on neural microstructure.

2. Methods

2.1. Model generation

Animals were housed and cared for in an AAALAC-accredited facility and all animal experiments were conducted in accordance with University of Wisconsin-Madison IACUC-approved protocols. Utilizing the CRISPR-Cas9 genome-editing technique, the second coding exon of the rat *Disc1* gene encoding amino acids 19-342 (RefSeq transcript ENSRNOT00000057945.4) was targeted for genome editing through the generation of non-synonymous mutations as previously described [36] Briefly, two target sequences were selected to maximize specificity with all predicted off-target sites bearing at least 3 mismatches with at least 1 mismatch in the 12 bp seed region: [1] ATGCCACGTCCGATCT CAGCGGG; [2] TCAACGGGGCCATTCGACGCCGG. An *in vitro* transcription template was generated by overlap-extension PCR with one oligo carrying a 5′ T7 adapter, the target sequence, and a portion of the common gRNA sequence, and the other oligo carrying the antisense common gRNA sequence. The *in vitro* template was column-purified and *in vitro* transcribed with the MEGAshortscript kit (ThermoFisher), and the resultant gRNA was cleaned with the MEGAclear kit (ThermoFisher). For injection-grade purification, gRNA was ammonium acetate purified, washed with 70% ethanol, and resuspended in injection buffer. One-cell fertilized Sprague Dawley (SD) embryos were microinjected with a mixture of both gRNAs (25 ng/uL each) and Cas9 protein (PNA Bio, 40 ng/uL), and then implanted into pseudopregnant female Sprague-Dawley (SD) recipients. Resultant pups were genotyped at weaning by PCR, amplifying the targeted region. Potential founders yielded an approximate 389 bp fragment indicating the successful excision between the two target sites. Putative excision fragments were gel-purified and sequenced. Those deletions causing a non-sense mutation and early termination of translation were bred to SD mates.

2.2. Subjects

24 adolescent male outbred Sprague-Dawley rats (Charles River, Worchester, MA, USA) and 16 homozygous *Disc1* svΔ2 male animals were pair housed in clear cages. All animals were maintained under a 12:12 h light:dark cycle in humidity- and temperature-controlled rooms with *ad libitum* access to water and food. All animals were acclimated to housing conditions for seven days prior to experimental manipulation.

2.3. Exercise protocol

Outbred wild-type rats were randomly assigned to either the exercise cohort (n = 15) or a control (non-exercise) cohort (n = 9). *Disc1* svΔ2 animals were also randomly assigned to either an exercise cohort (n = 10) or a control (non-exercise) cohort (n = 6). A three-lane motorized treadmill was used with a small electrified grid at the base of the treadmill with shock intensity set at 0.5-mA to provide a mild negative stimulus to encourage running [46]. All animals commenced the exercise protocol at postnatal day 45 (P45). The exercise protocol consisted of four consecutive weeks of running on the treadmill (5 times/week; 20 total exercise days) eventually reaching a maximum speed of 15 m/min and a maximum time of 40 min (Fig. 1). To acclimate the animals to the treadmill, a gradual training protocol was used. On day 1, all animals ran minutes 0–10 at a speed of 7 m/min, then minutes 10–40 at a speed of 10 m/min. On day 2, all animals ran minutes 0–10 at a speed of 7 m/min, minutes 10–20 at a speed of 10 m/min, and minutes 20–40 at a speed of 15 m/min. On day 3, all animals ran minutes 0–10 at a speed of 7 m/min and minutes 10–40 at a speed of 15 m/min. On day 4 until the completion of the experiment, all animals ran the entire 40 min at a speed of 15 m/min. One animal from the control non-exercise cohort and one animal from the *Disc1* svΔ2 exercise cohort died during the four weeks of exercise and were excluded from subsequent brain imaging. Rats were sacrificed 9–12 days after the final running session at P80-P83.

2.4. Imaging methodology

2.4.1. Data acquisition

At postnatal day 80–83, animals were deeply anesthetized with isoflurane and transcardially perfused with fresh 4% paraformaldehyde (PFA) following an initial wash with ice-cold PBS. Following dissection

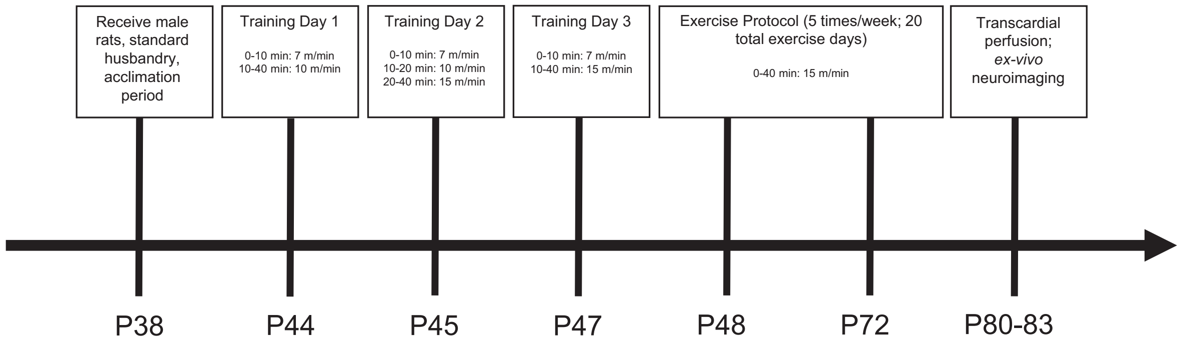

Fig. 1. Exercise protocol timeline.
Exercise protocol timeline displaying the training and data collection period and overall experimental design. P = postnatal day.

from the cranial vault, fixed brains were then stored in 4% PFA until imaging, whereupon they were serially rinsed in 0.9% saline for 48 h prior to imaging to minimize attenuating effects of fixative on the MRI signal. The brains were placed in a custom-built holder and immersed in Fluorinert (FC-3283, 3M, St. Paul, MN, USA) for image acquisition. For *ex-vivo* MR acquisition, brains were simultaneously imaged using a 4.7-T Agilent MRI system and 3.5-cm diameter quadrature volume RF coil. Multi-slice, diffusion-weighted, spin echo images were used to acquire 10 non-diffusion weighted images ($b = 0\, s{\cdot}mm^{-2}$) and 75 diffusion-weighted images (25 non-colinear diffusion-weighting directions at $b = 800\, s{\cdot}mm^{-2}$, 50 non-colinear diffusion-weighting directions at $b = 2000\, s{\cdot}mm^{-2}$). Other imaging parameters: TE/TR = 24.17/2000-ms, FOV = $30 \times 30\, mm^2$, matrix = 192×192 reconstructed to 256×256 for an isotropic voxel size of 0.25-mm over two signal averages. All animals were used in subsequent analyses.

2.4.2. Data preprocessing and region of interest analysis

Raw data files were converted to NIfTI format and FSL was used to correct for eddy current artifacts with Eddy-correct. FSL output volumes were converted to NIfTI tensor format for use with the DTI-TK software package. DTI-TK [47] was used to estimate a study-specific tensor template, to which subject tensor volumes were spatially normalized. The NODDI model was then voxel-wise fitted to the diffusion data in Matlab (The MathWorks, Inc., Natick, MA) with the NODDI toolbox (http://nitrc.org/projects/noddi_toolbox). An additional compartment of isotropic restriction was employed for *ex-vivo* studies as recommended [48].

The UNC P72 Rat Atlas was normalized to subject common space and masked with predefined regions-of-interest (ROIs) [49] (Fig. 2). Diffusion measures for all regions of interest from the atlas were extracted. Following automated volumetric segmentation of the brain, mean values of both diffusion and neurite indices were computed within six ROIs (hippocampus, external capsule, basal ganglia, internal capsule, neocortex, and corpus callosum) in each hemisphere for each individual subject. These ROIs were selected based on their relevance to mental illness for both major white matter and gray matter regions. Two-tailed, two-sample, and unequal variance Student's *t*-Test was performed comparing fractional anisotropy (FA), axial diffusion (AD), radial diffusion (RD), mean diffusivity (MD) (MD = [1/3][TR]; TR = trace diffusivity), neurite density index (NDI), and orientation dispersion index (ODI) mean values in *Disc1* svΔ2 animals against age-sex-matched controls. Raw *p*-values were reported and adjusted *p*-values were calculated using the Benjamini-Hochberg false discovery rate (FDR) correction (FDR = 0.05) to multiple comparison correction.

3. Results and discussion

In this study, we employed quantitative diffusion weighted imaging techniques to investigate the impact of short-term exercise on neural microstructure along quantitative metrics of white matter structural integrity and neurite density and orientation dispersion in both wild-type animals and in a *Disc1* svΔ2 model of psychiatric illness. Following automated volumetric segmentation of the brain into salient ROIs implicated in psychiatric illness, we demonstrate that (1) our 4-week short-term exercise paradigm imparts no significant differences in neural microstructure in age- and sex-matched control animals and (2) induces microstructural changes suggestive of microstructural amelioration in different regions of the brain in our *Disc1* svΔ2 model ($p < .05$, FDR corrected). *Disc1* svΔ2 exercise rats show increased FA values in the right neocortex and left internal capsule. Additionally, *Disc1* svΔ2 exercise rats display increased RD in the left corpus callosum and decreased RD in the left basal ganglia (Table 1). *Disc1* svΔ2 exercise rats also demonstrated increased NDI values in the right external capsule and left neocortex (Table 2). No statistically significant difference in any diffusion indices derived from DTI or NODDI were found in any of the selected ROIs in the control animals when comparing sedentary to exercised animals.

The absence of neural microstructural differences in control animals compared to the observed changes in *Disc1* svΔ2 animals suggests there exists a genetic predisposition and subsequent lability to the neurostructural effects of a short-term exercise paradigm. Previous studies on aerobic exercise and white matter microstructural change have largely focused on long-term exercise regimes in aging clinical cohorts, where exercise has been found to have a neuroprotective effect on white

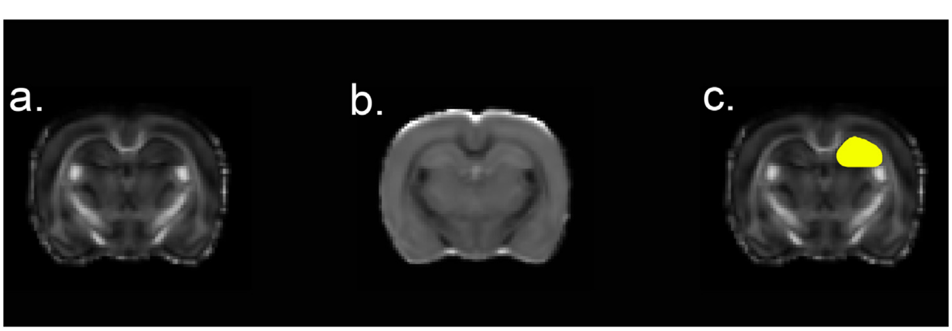

Fig. 2. Representative processed coronal (a) FA and (b) RD maps of brains from wild-type exercised animals at the level of the ventral hippocampus. (c) Coronal FA map of a wild-type exercised animal at the level of the ventral hippocampus with a yellow mask designating the region-of-interest corresponding to the left hippocampus at this slice location. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
All values are mean ± standard error of the mean. Units of measure for FA, AD, RD, and TR are [10^{-3} mm^2/s]. Bolded and italicized *p* values are statistically significant. Regions of interest (ROIs) correspond to ROIs derived from the P72 UNC Atlas. Diffusion measure abbreviations: Hemi = hemisphere; FA = fractional anisotropy; NDI = neurite density index. ROI abbreviations: HC = hippocampus; EC = external capsule; BG = basal ganglia; IC = internal capsule; NC = neocortex; CC = corpus callosum.

DTI measure	Hemi.	ROI	Control mean (± SEM)		Disc1 mean (± SEM)		*p*-Value	
			Exercise	No exercise	Exercise	No exercise	Control	Disc1
FA	Right	HC	0.31391 (± 0.00121)	0.31701 (± 0.00087)	0.31285 (± 0.00113)	0.31342 (± 0.00141)	.068	.761
		EC	0.45689 (± 0.00122)	0.45651 (± 0.00063)	0.45928 (± 0.00126)	0.45774 (± 0.00164)	.785	.476
		BG	0.29263 (± 0.00095)	0.29279 (± 0.00053)	0.29289 (± 0.00057)	0.29070 (± 0.00082)	.887	.056
		IC	0.44764 (± 0.00281)	0.44901 (± 0.00188)	0.44761 (± 0.00213)	0.44537 (± 0.00299)	.695	.557
		NC	0.28756 (± 0.00045)	0.28848 (± 0.00065)	0.28746 (± 0.00046)	0.28578 (± 0.00038)	.271	***.020****
		CC	0.52479 (± 0.00129)	0.52305 (± 0.00092)	0.52289 (± 0.00054)	0.52200 (± 0.00124)	.300	.534
	Left	HC	0.32821 (± 0.00069)	0.32814 (± 0.00044)	0.32837 (± 0.00053)	0.32893 (± 0.00102)	.935	.640
		EC	0.42266 (± 0.00127)	0.42321 (± 0.00146)	0.42053 (± 0.00087)	0.42072 (± 0.00134)	.779	.907
		BG	0.30482 (± 0.00061)	0.30618 (± 0.00075)	0.30330 (± 0.00060)	0.30143 (± 0.00104)	.189	.159
		IC	0.55799 (± 0.00224)	0.55736 (± 0.00275)	0.56602 (± 0.00230)	0.56806 (± 0.00377)	.861	.655
		NC	0.28756 (± 0.00077)	0.28777 (± 0.00064)	0.28882 (± 0.00073)	0.28718 (± 0.00089)	.834	.187
		CC	0.57708 (± 0.00029)	0.57746 (± 0.00189)	0.57403 (± 0.00090)	0.57722 (± 0.00158)	.852	.118
AD	Right	HC	0.49538 (± 0.00088)	0.49717 (± 0.00086)	0.49555 (± 0.00075)	0.49610 (± 0.00068)	.178	.598
		EC	0.43844 (± 0.00063)	0.43806 (± 0.00044)	0.43980 (± 0.00030)	0.43965 (± 0.00037)	.634	.756
		BG	0.47234 (± 0.00127)	0.47294 (± 0.00068)	0.47357 (± 0.00098)	0.47282 (± 0.00078)	.689	.756
		IC	0.45757 (± 0.00139)	0.45781 (± 0.00135)	0.45720 (± 0.00093)	0.45771 (± 0.00074)	.904	.678
		NC	0.42707 (± 0.00069)	0.42718 (± 0.00081)	0.42571 (± 0.01158)	0.42358 (± 0.00088)	.919	.177
		CC	0.43630 (± 0.00075)	0.43555 (± 0.00040)	0.43684 (± 0.00067)	0.43509 (± 0.00065)	.404	.088
	Left	HC	0.51132 (± 0.00070)	0.51224 (± 0.00023)	0.51125 (± 0.00043)	0.51111 (± 0.00044)	.258	.818
		EC	0.44450 (± 0.00065)	0.44372 (± 0.00089)	0.44322 (± 0.00063)	0.44414 (± 0.00077)	.498	.380
		BG	0.47485 (± 0.00097)	0.47643 (± 0.00063)	0.47389 (± 0.00108)	0.47541 (± 0.00050)	.205	.240
		IC	0.50003 (± 0.00114)	0.49873 (± 0.00167)	0.50311 (± 0.00170)	0.50528 (± 0.00238)	.539	.478
		NC	0.43210 (± 0.00131)	0.43095 (± 0.00025)	0.43088 (± 0.00073)	0.42860 (± 0.00072)	.428	.051
		CC	0.43429 (± 0.00040)	0.43434 (± 0.00053)	0.43421 (± 0.00073)	0.43340 (± 0.00107)	.936	.549
RD	Right	HC	0.30313 (± 0.00028)	0.30265 (± 0.00036)	0.30393 (± 0.00034)	0.30393 (± 0.00061)	.322	.990
		EC	0.21078 (± 0.00028)	0.21072 (± 0.00014)	0.21042 (± 0.00040)	0.21103 (± 0.00049)	.855	.360
		BG	0.30195 (± 0.00052)	0.30225 (± 0.00026)	0.30254 (± 0.00041)	0.30308 (± 0.00022)	.621	.281
		IC	0.22096 (± 0.00059)	0.22074 (± 0.00035)	0.22115 (± 0.00075)	0.22226 (± 0.00091)	.755	.373
		NC	0.27178 (± 0.00052)	0.27149 (± 0.00056)	0.27082 (± 0.00073)	0.27009 (± 0.00066)	.714	.471
		CC	0.18866 (± 0.00048)	0.18915 (± 0.00044)	0.18977 (± 0.00051)	0.18954 (± 0.00050)	.470	.746
	Left	HC	0.30909 (± 0.00038)	0.30942 (± 0.00040)	0.30870 (± 0.00031)	0.30835 (± 0.00081)	.567	.700
		EC	0.22714 (± 0.00037)	0.22679 (± 0.00038)	0.22799 (± 0.00037)	0.22773 (± 0.00036)	.524	.622
		BG	0.30064 (± 0.00066)	0.30106 (± 0.00023)	0.30080 (± 0.00050)	0.30256 (± 0.00019)	.564	***.015****
		IC	0.19067 (± 0.00073)	0.19068 (± 0.00065)	0.18801 (± 0.00054)	0.18770 (± 0.00101)	.990	.791
		NC	0.27638 (± 0.00072)	0.27517 (± 0.00021)	0.27487 (± 0.00024)	0.27405 (± 0.00076)	.156	.344
		CC	0.17186 (± 0.00018)	0.17192 (± 0.00079)	0.17369 (± 0.00060)	0.17187 (± 0.00052)	.941	***.046****
TR	Right	HC	0.36721 (± 0.00029)	0.36749 (± 0.00047)	0.36780 (± 0.00031)	0.36799 (± 0.00043)	.623	.727
		EC	0.28666 (± 0.00021)	0.28650 (± 0.00015)	0.28688 (± 0.00022)	0.28724 (± 0.00026)	.535	.321
		BG	0.35875 (± 0.00072)	0.35915 (± 0.00039)	0.35955 (± 0.00058)	0.35966 (± 0.00037)	.640	.882
		IC	0.29983 (± 0.00019)	0.29976 (± 0.00043)	0.29983 (± 0.00049)	0.30074 (± 0.00039)	.891	.179
		NC	0.32354 (± 0.00056)	0.32339 (± 0.00061)	0.32245 (± 0.00086)	0.32125 (± 0.00073)	.855	.312
		CC	0.27121 (± 0.00039)	0.27128 (± 0.00035)	0.27213 (± 0.00056)	0.27139 (± 0.00030)	.888	.273
	Left	HC	0.37650 (± 0.00041)	0.37702 (± 0.00032)	0.37622 (± 0.00027)	0.37594 (± 0.00061)	.341	.684
		EC	0.29960 (± 0.00020)	0.29910 (± 0.00025)	0.29973 (± 0.00034)	0.29986 (± 0.00010)	.162	.724
		BG	0.35871 (± 0.00074)	0.35952 (± 0.00031)	0.35850 (± 0.00067)	0.36018 (± 0.00015)	.350	.054
		IC	0.29379 (± 0.00032)	0.29337 (± 0.00031)	0.29305 (± 0.00037)	0.29356 (± 0.00021)	.364	.264
		NC	0.32829 (± 0.00090)	0.32709 (± 0.00015)	0.32687 (± 0.00036)	0.32557 (± 0.00070)	.246	.139
		CC	0.25933 (± 0.00020)	0.25939 (± 0.00055)	0.26053 (± 0.00059)	0.25904 (± 0.00038)	.922	.067

matter microstructural integrity [4–14]. These previous studies have contributed to the understanding of the disease process of schizophrenia wherein the integrity of white matter brain connectivity across functional networks is disrupted. Fractional anisotropy indicates the overall directionality of water diffusion with relatively higher values in organized white matter tracts and relatively lower values in disorganized fibers. Deficits to white matter integrity, as estimated by FA decreases, have been implicated in disease pathophysiology. The finding of no regions of microstructural difference in our control animals suggests that these animals are inured to the effects of our exercise paradigm and that a more long-term and strident change (*e.g.* longer more strenuous exercise) would be necessary to impart differences in observable white matter microstructure. These findings, however, stand in sharp contrast to those found in our *Disc1* svΔ2 cohort, where after being subjected to the same exercise regime, significant differences in both FA and NDI were observed. Just as our control cohort demonstrated a high degree of robustness against the potential influence of our exercise, that we see demonstrable differences in our *Disc1* svΔ2 cohort suggests genetic background significantly influences responsiveness to environmental stimuli but also that exercise can begin to partially ameliorate the deleterious effect of genetic background in a neuropsychiatric disease model. There were increased measures of white matter microstructural integrity following the short-term exercise paradigm in several regions of the *Disc1* svΔ2 rat brains, including the right and left neocortex, right external capsule, left corpus callosum, and left basal ganglia. These particular brain regions where changes were observed were part of a pool of 6 brain regions that were selected for analysis *a priori* as particular areas of interest (3 major white matter tracts, the corpus callosum, external capsule, and the internal capsule; and 3 major gray matter regions, the neocortex, basal ganglia, and hippocampus). These 6 regions have been shown in previous studies of schizophrenia to be affected in terms of white matter structural

Table 2
All values are mean ± standard error of the mean. Units of measure for NDI and ODI are [10^{-3} mm^2/s]. Bolded and italicized p values are statistically significant. Regions of interest (ROIs) correspond to ROIs derived from the P72 UNC Atlas. Diffusion measure abbreviations: Hemi = hemisphere; FA = fractional anisotropy; NDI = neurite density index. ROI abbreviations: HC = hippocampus; EC = external capsule; BG = basal ganglia; IC = internal capsule; NC = neocortex; CC = corpus callosum.

DTI measure	Hemi.	ROI	Control mean (± SEM)		Disc1 mean (± SEM)		*p*-Value	
			Exercise	No exercise	Exercise	No exercise	Control	Disc1
NDI	Right	HC	0.26760 (± 0.01295)	0.26363 (± 0.01324)	0.24721 (± 0.00298)	0.23672 (± 0.00491)	.835	.264
		EC	0.28936 (± 0.00827)	0.29606 (± 0.01317)	0.26484 (± 0.00308)	0.22979 (± 0.00596)	.678	***.005****
		BG	0.25198 (± 0.01277)	0.25025 (± 0.01891)	0.24579 (± 0.00338)	0.22542 (± 0.00614)	.941	.079
		IC	0.35350 (± 0.00458)	0.34873 (± 0.01647)	0.32301 (± 0.00523)	0.30963 (± 0.01371)	.790	.492
		NC	0.31053 (± 0.01077)	0.31405 (± 0.01147)	0.32256 (± 0.00449)	0.29987 (± 0.00827)	.827	.133
		CC	0.41389 (± 0.01305)	0.41456 (± 0.01164)	0.34162 (± 0.00295)	0.31854 (± 0.01435)	.970	.192
	Left	HC	0.26268 (± 0.01226)	0.26219 (± 0.01267)	0.25474 (± 0.00729)	0.23447 (± 0.00627)	.978	.077
		EC	0.27214 (± 0.00894)	0.26660 (± 0.00945)	0.26722 (± 0.00755)	0.24918 (± 0.00676)	.680	.084
		BG	0.25482 (± 0.01293)	0.25566 (± 0.01484)	0.24835 (± 0.00828)	0.23258 (± 0.00604)	.967	.184
		IC	0.42263 (± 0.01310)	0.42409 (± 0.01109)	0.38522 (± 0.01281)	0.33947 (± 0.01505)	.934	.143
		NC	0.32283 (± 0.00710)	0.31914 (± 0.01179)	0.35384 (± 0.01100)	0.31707 (± 0.01067)	.795	***.017****
		CC	0.42742 (± 0.01850)	0.42652 (± 0.01042)	0.36055 (± 0.00722)	0.33872 (± 0.01418)	.967	.239
ODI	Right	HC	0.19027 (± 0.01510)	0.19680 (± 0.01452)	0.18330 (± 0.01075)	0.17471 (± 0.00842)	.762	.544
		EC	0.16355 (± 0.00837)	0.17556 (± 0.01543)	0.18002 (± 0.01295)	0.15379 (± 0.01056)	.514	.149
		BG	0.21218 (± 0.01584)	0.21386 (± 0.02313)	0.20111 (± 0.01060)	0.19661 (± 0.00863)	.953	.749
		IC	0.14552 (± 0.01300)	0.15194 (± 0.01744)	0.16172 (± 0.00874)	0.15833 (± 0.02459)	.774	.901
		NC	0.23204 (± 0.00643)	0.24392 (± 0.01607)	0.23752 (± 0.01325)	0.20299 (± 0.01041)	.516	.069
		CC	0.11412 (± 0.00926)	0.12878 (± 0.01051)	0.11832 (± 0.00689)	0.15107 (± 0.02943)	.320	.323
	Left	HC	0.17526 (± 0.01575)	0.17887 (± 0.01298)	0.19140 (± 0.01150)	0.16894 (± 0.00540)	.863	.120
		EC	0.16543 (± 0.01035)	0.16493 (± 0.01750)	0.18250 (± 0.01089)	0.16750 (± 0.01510)	.981	.441
		BG	0.20624 (± 0.01796)	0.20996 (± 0.02049)	0.20729 (± 0.01328)	0.20602 (± 0.00605)	.894	.933
		IC	0.11516 (± 0.01331)	0.12510 (± 0.01942)	0.12180 (± 0.00686)	0.15535 (± 0.04076)	.683	.670
		NC	0.23468 (± 0.00673)	0.24231 (± 0.01628)	0.26036 (± 0.00874)	0.22782 (± 0.01162)	.679	.051
		CC	0.11484 (± 0.01243)	0.12857 (± 0.00947)	0.11518 (± 0.00770)	0.14353 (± 0.03751)	.401	.490

integrity as well as gray matter synaptic structure. Previous *Disc1* models have demonstrated dysmorphic and decreased dendritic density and arborization in the regions of neocortex, basal ganglia, and hippocampus [50,51]. The beneficial effects of exercise found in aging human studies may explain these differences in the schizophrenic model and shown in one study using humans with schizophrenia where patients showed improved white matter microstructure after a long-term exercise intervention [24].

We acknowledge potential limitations of our study; first, our forced exercise paradigm imparts a degree of stress, the stressful aspect being a mild shock that is delivered at the base of the treadmill. This stress may unintentionally create possible deleterious effects that might have attenuated the overall beneficial microstructural differences that we observed in our *Disc1* svΔ2 exercise cohort animals. Many studies have shown that patients with schizophrenia are more susceptible to stress and more susceptible to its negative effects [52–54]. However, this forced exercise paradigm allowed us to control the length and intensity of the exercise, which is not possible using a voluntary wheel running paradigm. Many previous studies using rat models have found beneficial neurobiological effects using voluntary wheel running, with a few using schizophrenic or depressive models [1,3,55–72]. However, none of these studies have examined white matter microstructural changes following exercise. Future studies could consider the use voluntary wheel running rather than forced treadmill exercise using *Disc1* svΔ2 animals to determine if exercise can be a purely beneficial intervention for schizophrenia. Additionally, future studies could also examine the aspect of neuroinflammation in forced *versus* voluntary exercise. Neuroinflammation has been implicated in stress and in contributing to the white matter disruptions in schizophrenia, so it could be beneficial to compare whether the number and morphology of microglia differ between *Disc1* svΔ2 rats exposed to non-stressful exercise, stressful exercise, and no exercise [73–83]. Second, the time period of the exercise paradigm (4 weeks) may not have been a long enough period to induce more dramatic differences in white matter microstructure, although previous studies on which our paradigm was modeled ranged from one week to eight weeks and demonstrated significant neurobiological changes. Finally, there remains the question of the degree of translatability between rodent and human models. We chose the *Disc1* svΔ2 rat model as our model because a rat model allows for control of factors that cannot be controlled in humans (*e.g.* the singular effect of one gene on the brain). The control of these factors is not accessible in the clinical population.

4. Conclusions

Our work provides an exciting springboard for future research on environmental effects and interventions for schizophrenia. There has been only one study examining white matter changes in schizophrenic humans following aerobic exercise, and this study focused on whether practicing an already learned activity can improve white matter structure, not specifically focusing on exercise as an intervention [24]. Our study is the first to investigate white matter differences following short-term exercise in a novel genetic *Disc1* svΔ2 model combining NODDI, DTI, and ROI analysis. These data can serve as a springboard for future investigations examining exercise as a promising intervention for schizophrenia and to stimulate further investigations underlying the neurobiological effects of exercise in psychiatric disorders.

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Declaration Competing Interest

The authors declare no competing or conflict of interest.

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