Disorders of the Nervous System

Parvalbumin Interneuron Dysfunction in a Thalamo-Prefrontal Cortical Circuit in Disc1 Locus Impairment Mice

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Abstract

Altered cortical excitation-inhibition (E-I) balance resulting from abnormal parvalbumin interneuron (PV IN) function is a proposed pathophysiological mechanism of schizophrenia and other major psychiatric disorders. Preclinical studies have indicated that disrupted-in-schizophrenia-1 (Disc1) is a useful molecular lead to address the biology of prefrontal cortex (PFC)-dependent cognition and PV IN function. To date, PFC inhibitory circuit function has not been investigated in depth in Disc1 locus impairment (LI) mouse models. Therefore, we used a Disc1 LI mouse model to investigate E-I balance in medial PFC (mPFC) circuits. We found that inhibition onto layer 2/3 excitatory pyramidal neurons in the mPFC was significantly reduced in Disc1 LI mice. This reduced inhibition was accompanied by decreased GABA release from local PV, but not somatostatin (SOM) INs, and by impaired feedforward inhibition (FFI) in the mediodorsal thalamus (MD) to mPFC circuit. Our mechanistic findings of abnormal PV IN function in a Disc1 LI model provide insight into biology that may be relevant to neuropsychiatric disorders including schizophrenia.

Key words: disrupted-in-schizophrenia-1; feedforward inhibition; mediodorsal thalamus; parvalbumin interneurons; prefrontal cortex

Significance Statement

A popular theory suggests that dysregulation of fast-spiking parvalbumin interneurons (PV INs) and elevated excitation-inhibition (E-I) balance contribute to the pathophysiology of various psychiatric disorders. Previous studies suggest that genetic perturbations of the disrupted-in-schizophrenia-1 (Disc1) gene affect prefrontal cortex (PFC)-dependent cognition and PV IN function, but synaptic and circuit physiology data are lacking. Here, we provide evidence that the presynaptic function of PV INs in the medial PFC (mPFC) is altered in Disc1 LI mice and that E-I balance is elevated within a thalamofrontal circuit known to be important for cognition. These findings may contribute to our understanding of the biology that gives rise to cognitive symptoms in a range of neuropsychiatric disorders.

Introduction

Parvalbumin interneurons (PV INs) provide powerful somatic inhibition to excitatory pyramidal neurons and regulate excitation-inhibition (E-I) balance (Isaacson and Scanziani, 2011). Prefrontal PV INs are implicated in working memory (WM) function (Cardin et al., 2009; Fries, 2009; Sohal et al., 2009; Murray et al., 2015; Ferguson and Gao, 2018b) and have emerged from human post-mortem studies as a key node of interest in the pathophysiology of schizophrenia (Beasley and Reynolds, 2011).
circuits of mice heterozygous for the Disc1 locus impairment (LI allele, in which the majority of Disc1 isoforms are abolished (Seshadri et al., 2015; Shahani et al., 2015). We found that Disc1 LI was associated with elevated E-I balance and altered PV IN function in mPFC circuits relevant to cognition.

Materials and Methods

Animals

Mice were group housed under a 12/12 h light/dark cycle (9 A.M. to 9 P.M. light), with food and water freely available. Both male and female mice were used. All procedures involving animals were approved by the Institutional Animal Care and Use Committee of Cold Spring Harbor Laboratory and conducted in accordance with the National Institutes of Health guidelines. The PV-Cre (http://jaxmice.jax.org/strain/008069.html), SOM-Cre (http://jaxmice.jax.org/strain/013044.html), and Ai14 (https://www.jax.org/strain/007914) mice were described previously (Hippemeyer et al., 2005; Madsen et al., 2010; Taniguchi et al., 2011). We previously generated the Disc1 LI mice, which harbor a deletion (6.9 kb) encompassing the first three exons of the Disc1 gene (Seshadri et al., 2015). The majority of Disc1 isoforms are abolished in mice homozygous for the Disc1 LI allele (Seshadri et al., 2015), and in the current study we used mice that harbored one Disc1 LI allele (+/−). All mice were bred onto C57BL/6 background for at least five generations.

Viral vectors

Adeno-associated virus (AAV) vectors AAV-CAG-ChR2 (H134R)-YFP and AAV-eF1a-DIO-ChR2(H134R)-YFP were produced as AAV2/9 serotype by the University of North Carolina Vector Core and have been previously described (Zhang et al., 2007; Delevich et al., 2015). All viral vectors were stored in aliquots at −80°C until use.

Stereotaxic surgery

Mice aged postnatal day (P)40–56 were used for all surgeries. Unilateral viral injections were performed using previously described procedures (Li et al., 2013) at the following stereotaxic coordinates: MD: −1.58 mm from bregma, 0.44 mm lateral from midline, and 3.20 mm ventral from cortical surface; dorsal mPFC: 1.94 mm from bregma, 0.34 mm lateral from midline, and 0.70 mm ventral from cortical surface. Surgical procedures were standardized to minimize the variability of AAV injections. To ensure minimal leak into surrounding brain areas, injection pipettes remained in the brain for ~5 min after injection before being slowly withdrawn. The final volume for AAV-CAG-ChR2(H134R)-YFP injected into MD was 0.3–0.35 μl, and for AAV-eF1a-DIO-ChR2(H134R)-YFP injected into dorsal mPFC was 0.5 μl. The titer for the viruses was ~10^{12} viral particles/ml. For experiments in which mPFC inhibitory INs were optogenetically stimulated (Fig. 2) mice were injected at P56 and approximately two weeks were allowed for viral expression before recording. For experiments in which MD axons within mPFC were optogenetically stimulated (Figs. 3, 5) mice

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were injected at P40–45 and approximately four weeks were allowed for viral expression before recording. For each of these experiments, littermates were injected and recorded at the same age to control for expression duration between genotypes.

**Electrophysiology**

Mice were anaesthetized with isoflurane and decapitated, whereupon brains were quickly removed and immersed in ice-cold dissection buffer (110.0 mM choline chloride, 25.0 mM NaHCO3, 1.25 mM NaH2PO4, 2.5 mM KCl, 0.5 mM CaCl2, 7.0 mM MgCl2, 25.0 mM glucose, 11.6 mM ascorbic acid, and 3.1 mM pyruvic acid, gassed with 95% O2 and 5% CO2). Coronal slices (300 μm in thickness) containing mPFC were cut in dissection buffer using a HM650 Vibrating Microtome (Thermo Fisher Scientific), and were subsequently transferred to a chamber containing artificial CSF (ACSF; 118 mM NaCl, 2.5 mM KCl, 26.2 mM NaHCO3, 1 mM NaH2PO4, 20 mM glucose, 2 mM MgCl2, and 2 mM CaCl2, at 34°C, pH 7.4, gassed with 95% O2 and 5% CO2). After ~30 min of recovery time, slices were transferred to room temperature and were constantly perfused with ACSF.

The internal solution for voltage-clamp experiments contained 140 mM potassium gluconate, 10 mM HEPES, 2 mM MgCl2, 0.05 mM CaCl2, 4 mM MgATP, 0.4 mM Na3GTP, 10 mM Na2-phosphocreatine, 10 mM BAPTA, and 2 mM MgATP, 0.4 mM Na2-phosphocreatine, 10 mM BAPTA, and 2 mM MgCl2, and 2 mM CaCl2, at 34°C, pH 7.4, gassed with 95% O2 and 5% CO2. After ~30 min of recovery time, slices were transferred to room temperature and were constantly perfused with ACSF.

To measure the kinetics of the IPSCs, averaged sweeps collected at the 150-ms interval were normalized, and the decay time constant and half-width were measured using automated procedures in the AxoGraph X 1.5.4 software.

To determine IPSC reversal potential (EIPSC), IPSCs were recorded at varying holding potentials (20-mV steps) in the presence of CNQX (5 μM) and AP-5 (100 μM) to block AMPA receptors and NMDA receptors, respectively. IPSC amplitude was measured, and a linear regression was used to calculate the best-fit line, and the x-intercept was used as the EIPSC. Under our recording conditions, the EIPSC was ~−60 mV. Therefore, in the excitation/inhibition ratio (E/I) experiments, we recorded EPSCs at −60 mV and IPSCs at 0 mV holding potential. The only drug used for the E/I experiments was AP-5 (100 μM). In these experiments we used the same light intensity for evoking both IPSCs and EPSCs. In addition, we used similar stimulation regime for WT and Disc1 LI mice, such that the peak amplitudes of IPSCs were comparable between genotypes.

For the experiments in which we optogenetically stimulated the MD axons in the mPFC, mice were excluded if the extent of infection in the MD was too large and leaked into surrounding brain regions. Rodent MD lacks INs; therefore all ChR2-infected neurons are expected to be relay projection neurons (Kuroda et al., 1998).

The latency and 10–90% rise time of EPSCs and IPSCs were calculated from either the averaged trace or individual sweeps for each cell using automated procedures in the AxoGraph X 1.5.4 software. ESPC and IPSC onset latency was calculated as the time from stimulation onset to 10% rise time, with EPSC-IPSC lag calculated as the difference. The 10% rise time has been reported to be a more reliable measure of delay to onset, as it minimizes the contribution of EPSC and IPSC rise time differences that are reflected in the time to peak (Mittmann et al., 2005). Some of the control data from WT mice used for comparing with Disc1 LI mice (appearing in Figs. 3, 4) were previously reported in Delevich et al., 2015, (Figs. 1, 2, and 4).

**Data analysis and statistics**

All statistical tests were performed using Origin 9.0 (Origin-Lab) or GraphPad Prism 6.0 (GraphPad Software) software. All data were tested for normality using the Agostino–Pearson omnibus normality test to guide the selection of parametric or non-parametric statistical tests. Data are presented as mean ± SEM or median ± interquartile range as indicated. For parametric data, a two-tailed t test or two-way ANOVA was used, with a post hoc Sidak’s test for multiple comparisons. For non-parametric data, a two-tailed Mann–Whitney U test was used; p < 0.05 was considered significant. A summary of the statistical analyses performed can be found in Table 1.

**Results**

Inhibitory synaptic transmission is reduced in adult Disc1 LI mice

As a first estimation of inhibitory drive in the mPFC, we recorded mIPSCs onto L2/3 PNs in the dorsal anterior
Figure 1. Reduced inhibitory synaptic transmission onto L2/3 pyramidal neurons in the mPFC of adult and juvenile Disc1 LI mice. 
A, Recording configuration and sample miPSC traces recorded from L2/3 PNs in the mPFC of WT (upper) and Disc1 LI (lower) mice at P70. B, miPSC amplitude (WT, n = 27 cells; Disc1 LI, n = 29 cells). C, miPSC frequency (WT, n = 27 cells; Disc1 LI, n = 29 cells; **p < 0.01, Mann–Whitney U test). D, Recording configuration and sample mEPSC traces recorded from L2/3 PNs in the mPFC of WT (upper) and Disc1 LI (lower) mice at P70. E, mEPSC amplitude (WT, n = 23 cells; Disc1 LI, n = 20 cells). F, mEPSC frequency (WT, n = 23 cells; Disc1 LI, n = 20 cells). G, Recording configuration and sample miPSC traces recorded from L2/3 PNs in the mPFC of WT (upper) and Disc1 LI (lower) mice at P15. H, miPSC amplitude (WT, n = 44 cells; Disc1 LI, n = 26 cells). I, miPSC frequency (WT, n = 44 cells; Disc1 LI, n = 26 cells).
cingulate cortex (dACC) subregion of the mPFC in adult mice (P70). We found that compared with wild-type (WT) littersmates, Disc1 LI mice had significantly reduced mIPSC frequency (WT, 3.75 ± 0.25 Hz, n = 27 cells, N = 6; Disc1 LI, 2.27 ± 0.27 Hz, n = 29 cells, N = 5; U = 217.0, \( p < 0.01 \), Mann–Whitney U test), but not amplitude (WT, 12.5 ± 2.48 pA, n = 29 cells, N = 6; Disc1 LI, 12.52 ± 1.51 pA, n = 27 cells, N = 5; U = 351.0, \( p = 0.51 \), Mann–Whitney U test; Fig. 1A–C). The two groups did not differ in measures of mEPSCs (frequency: WT, 3.47 ± 1.97 Hz, n = 23 cells, N = 4; Disc1 LI, 2.79 ± 2.4 Hz, n = 20 cells, N = 5; U = 173.0, \( p = 0.17 \), Mann–Whitney U test; amplitude: WT, 8.91 ± 0.18 pA; Disc1 LI, 8.99 ± 0.37 pA, \( t_{(41)} = 0.18 \), \( p = 0.86 \), t test; Fig. 1D–F). Notably, we found that the frequency (but not amplitude) of mIPSCs recorded from dACC L2/3 PNs in Disc1 LI mice was lower compared to their WT littersmates at preweanling (−P15) age (amplitude: WT, n = 44 cells; Disc1 LI, n = 26 cells; \( p = 0.12 \), t test; frequency: WT, n = 44 cells; Disc1 LI, n = 26 cells; \( p = 0.05 \), Mann–Whitney U test; Fig. 1G–I). These data indicate that the inhibitory synaptic transmission is selectively impaired in the mPFC of Disc1 LI mice, and that this impairment manifests early in postnatal development.

Altered presynaptic function of PV INs in Disc1 LI mice

A reduction in mIPSC frequency could result from a decrease in synaptic transmission from one or more inhibitory IN populations. To investigate the source of reduced inhibitory drive onto L2/3 PNs in the mPFC of Disc1 LI mice, we sought to examine the IPSCs originating from either PV or somatostatin (SOM) INs. To this end, we selectively expressed ChR2, the light-gated cation channel (Zhang et al., 2006), in PV or SOM INs by injecting the mPFC of Disc1 LI; PV-Cre or Disc1 LI; SOM-Cre mice, as well as their WT littersmates, with an AAV expressing ChR2 in a Cre-dependent manner (AAV-DIO-ChR2 (H134R)-YFP). After viral expression had reached sufficient levels, we prepared acute brain slices and recorded light-evoked IPSCs onto L2/3 PNs in mPFC (Fig. 2A,D). We delivered paired light pulses (pulse duration 1 ms) with an interpulse interval of 50, 100, or 150 ms, and measured the ratio of the peak amplitude of the second IPSC over that of the first (IPSC2/IPSC1), also known as paired-pulse ratio (PPR; Fig. 2B,E). A similar technique was previously used to interrogate presynaptic GABA release from PV INs (Chu et al., 2012).

We found that the PPR of GABAergic transmission between PV INs and L2/3 PNs was significantly increased in the Disc1 LI mice compared to their WT littersmates at the 50- and 100-ms interpulse intervals (WT, n = 13 cells; Disc1 LI, n = 10 cells; interval: \( F_{(2,42)} = 6.77, \ p < 0.01 \); genotype: \( F_{(1,21)} = 10.77, \ p < 0.01 \); interaction: \( F_{(2,42)} = 3.92, \ p < 0.05 \); two-way repeated-measures (RM) ANOVA followed by Sidak’s tests; Fig. 2C), suggesting that GABA release from PV INs is impaired. In contrast, the PPR of GABAergic synaptic transmission from SOM INs to L2/3 PNs did not differ between genotypes (WT, n = 15 cells; Disc1 LI, n = 12 cells; interval: \( F_{(2,50)} = 24.88, \ p < 0.0001 \); genotype: \( F_{(1,25)} = 1.64, \ p = 0.21 \); interaction \( F_{(2,50)} = 0.47, \ p = 0.63 \), two-way RM ANOVA; Fig. 2F). SOM-evoked IPSCs displayed significantly slower decay kinetics than PV-evoked IPSCs (Fig. 2G,H), consistent with previous reports (Koyanagi et al., 2010; Ma et al., 2012). No differences in IPSC kinetics were observed between Disc1 LI mice and their WT littersmates (cell type: \( F_{(1,46)} = 90.82, \ p < 0.0001 \); genotype: \( F_{(1,46)} = 0.678, \ p = 0.41 \); two-way ANOVA; Fig. 2G,H). In light of the observed reduction in mIPSC frequency, the increased PPR of PV-mediated IPSCs suggests that there is a presynaptic deficit in GABA release from PV cells to L2/3 PNs in the mPFC of Disc1 LI mice.

Reduced feedforward inhibition (FFI) in a thalamus–mPFC circuit in Disc1 LI mice

The mediiodorsal nucleus of the thalamus (MD) sends major projections to the mPFC. This MD–mPFC circuit has been implicated in cognitive processes such as WM (Parnaudeau et al., 2013, 2018; Bolkan et al., 2017; Ferguson and Gao, 2018b) and cognitive flexibility (Parnaudeau et al., 2015; Rikhye et al., 2018) that are impaired in schizophrenia (Lesh et al., 2011; Parnaudeau et al., 2013, 2015). We and others have shown that excitatory inputs from the MD drive mPFC FFI (Miller et al., 2017; Collins et al., 2018; Meda et al., 2019) that is primarily mediated by mPFC PV INs (Delevich et al., 2015). Given the deficit in GABA release from PV INs to PNs in the mPFC of Disc1 LI mice (Fig. 2), we reasoned that FFI in the MD–mPFC circuit may be affected in these mice. To test this hypothesis, we injected the MD of Disc1 LI mice and their WT littersmates with AAV-ChR2(H134R)-YFP. After viral expression reached sufficient levels, we used these mice to prepare acute brain slices, in which we recorded both excitatory and inhibitory synaptic transmission onto dACC L3 PNs in response to optogenetic stimulation of MD axons (Fig. 3A,B).

Brief (0.5 ms) light stimulation evoked monosynaptic EPSCs and disynaptic IPSCs onto L3 PNs in the dorsal mPFC (Fig. 3C; and see Delevich et al., 2015). We found that the contribution of inhibitory synaptic transmission to total synaptic inputs, measured as IPSCpeak/IPSCpeak1 + EPSPpeak, or \( \text{IPSC}_{\text{peak}}/\text{EPSP}_{\text{peak}} \), was significantly lower in Disc1 LI mice than in WT mice when comparing the means of the two groups of animals (Disc1 LI, 0.52 ± 0.03, N = 11 mice; WT, 0.70 ± 0.02, N = 14 mice; \( t_{(23)} = 5.73, \ p < 0.0001 \), t test; Fig. 3D), or the means of the two groups of neurons (Disc1 LI, 0.60 ± 0.03; N = 30 cells, WT, 0.70 ± 0.02, n = 40 cells; \( t_{(68)} = 3.17, \ p < 0.01 \),
Figure 2. Altered presynaptic function of PV but not SOM INs in the mPFC of Disc1 LI mice. A, Schematic of the experimental configuration. B, Sample traces of PV IN-mediated IPSCs recorded from WT (left panel) or Disc1 LI (right panel) mice. Paired light pulses (1-ms duration; blue bars) were delivered at an interval of 50 ms (top), 100 ms (middle), or 150 ms (bottom). C, Quantification of PPR for each genotype (WT, n = 13 cells; Disc1 LI, n = 10 cells); *p < 0.05, ***p < 0.001, two-way RM ANOVA followed by Sidak’s test.

D, Schematic of the experimental configuration. E, Sample traces of SOM IN-mediated IPSCs recorded from WT (left panel) or Disc1 LI (right panel) mice. Paired light pulses (1-ms duration; blue bars) were delivered at an interval of 50 ms (top), 100 ms (middle), or 150 ms (bottom). F, Quantification of PPR for each genotype (WT, n = 15 cells; Disc1 LI, n = 12 cells). G, Sample IPSC traces evoked by optogenetic stimulation of PV or SOM INs. Colored lines indicate exponential fits to the decays of the IPSCs. H, Quantification of IPSC decay tau; ****p < 0.0001, t test. Data in C, F, H are presented as mean ± SEM.
**Figure 3.** Reduced FFI in the MD–mPFC circuit in Disc1 LI mice. **A, B,** Schematics of the experimental configuration. The right panel of **A** is an image of a brain section from a mouse used in electrophysiological recording, showing MD infected with AAV-CAG-ChR2-YFP. **C,** Representative traces of evoked EPSC (recorded at −60 mV) and IPSC (recorded at 0 mV) from L3 PNs. **D,** To estimate the relative recruitment of disynaptic FFI versus monosynaptic excitation, we divided peak IPSC (Ipeak) by the sum of peak IPSC and peak EPSC (Ipeak/Epeak). WT, N = 14 mice, Disc1 LI, N = 11 mice; ***p < 0.001, t test. **E,** Same as in **D,** except that the cumulative probability distributions of the values for individual neurons are shown. WT, n = 40 cells, Disc1 LI, n = 30 cells; **p < 0.01, Kolmogorov–Smirnov test. **F,** Scatter plot showing the peak amplitudes of IPSC and EPSC for individual neurons. Each circle represents one neuron (WT, n = 30 cells; Disc1 LI, n = 40 cells). Dashed lines are linear regression lines for neurons in WT mice and Disc1 LI mice. The slopes of the regression lines significantly differed at the 0.95 confidence level (**p < 0.05). **G,** Sample traces of IPSC (recorded at 0 mV) and EPSC (recorded at −60 mV) recorded from L2/3 PNs in response to light-stimulation (blue bars) of MD axons. The latency to onset was measured from the time the light stimulus was triggered to the 10% EPSC (blue arrow) or IPSC (red arrow) rise time. Note that IPSC rise time was calculated from the peak of the inward current recorded at 0 mV. **H,** Cumulative probability distributions for EPSC latency to onset (left) and IPSC latency to onset (right; EPSC, WT, n = 40 cells, Disc1 LI, n = 30 cells, p = 0.40; IPSC, WT, n = 40 cells, Disc1 LI, n = 30 cells, p = 0.56; Kolmogorov–Smirnov test). **I,** Quantification of IPSC–EPSC lag,
calculated as the difference in the latency to onset between the IPSC and the EPSC of each neuron (see also G; WT, n = 40 cells, Disc1 LI, n = 30 cells; p > 0.05, t test). J. Quantification of the 10–90% EPSC rise time and decay tau (K; WT, n = 40 cells, Disc1 LI, n = 30 cells; p > 0.05, Mann–Whitney U test). L. Quantification of the 10–90% IPSC rise time and decay tau (M; WT, n = 40 cells, Disc1 LI, n = 28 cells; p > 0.05, t test). Data are presented as median ± interquartile range (J, K) or mean ± SEM (D, L, M).

$ t $ test; Fig. 3E). In addition, the slope of a linear regression describing the relationship between IPSC and EPSC peak amplitudes of individual neurons in the Disc1 LI mice was significantly lower than that in WT (Fig. 3F). The latencies (Fig. 3G–J) and kinetics of the EPSCs (Fig. 3J,K) and IPSCs (Fig. 3L,M) in Disc1 LI mice were similar to those in WT mice. These results together indicate that Disc1 LI is associated with reduced MD-driven FFI in the mPFC.

Spontaneous excitatory synaptic transmission onto PV INs and their intrinsic properties are unchanged in Disc1 LI mice

The decrease in FFI in the MD–mPFC pathway in Disc1 LI mice could result from the impairment in GABA release from PV INs in the mPFC (Fig. 2), or reduced recruitment of mPFC PV INs by MD. Thalamically-driven FFI relies on the ability of PV INs to reach threshold in response to thalamic inputs, a process dependent on both synaptic and intrinsic properties of PV INs. DISC1 is expressed in MGE-derived inhibitory INs including PV INs (Schurov et al., 2004; Meyer and Morris, 2008; Steinecke et al., 2012; Seshadri et al., 2015) raising the possibility that DISC1 could alter excitatory synaptic transmission onto PV INs and/or their intrinsic properties. We crossed the Disc1 LI mouse line onto the PV-Cre::tdTomato lines, allowing us to assess the synaptic and intrinsic properties of visually identified PV INs in the context of Disc1 LI. We found that mEPSC amplitude and frequency onto mPFC PV INs was consistent between genotypes (amplitude: WT, 12.39 ± 0.4.0 pA; Disc1 LI, 13.46 ± 0.45 pA, n = 20, 23 cells/genotype, N = 4 mice/genotype; t(41) = 1.78, p = 0.08; frequency: WT, 6.99 ± 0.74 Hz; Disc1 LI, 6.55 ± 0.69 Hz, t(41) = 0.53, p = 0.60; Fig. 4A,B). Next, we examined the intrinsic properties of PV INs in WT and Disc1 LI mice and found no significant differences between genotypes (Fig. 4C–H), including minimum current injection required to elicit spiking (WT, 142.3 ± 12.67 pA; Disc1 LI, 119.2 ± 14.3 pA, t(24) = 1.21, 9p = 0.24; Fig. 4G) or maximum firing rate (WT, 88.92 ± 3.9 Hz; Disc1 LI, 88.92 ± 6.78 Hz, t(24) = 0, 9p > 0.99; Fig. 4H). These results suggest that neither intrinsic excitability of prefrontal PV INs nor spontaneous glutamatergic transmission onto them is grossly perturbed in Disc1 LI mice.

Enhanced input but reduced output of PV INs in Disc1 LI mice

We next examined recruitment of mPFC PV INs specifically within the MD–mPFC circuit to determine if reduced excitatory drive could account for the observed reduction in FFI in Disc1 LI mice. We recorded evoked EPSCs onto PV IN and PN pairs in the mPFC in response to optogenetic stimulation of MD axons (Fig. 5A). We found that in WT mice, amplitudes of thalamocortical EPSCs were similar between PV INs and neighboring PNs (PV, −109.3 ± 109.7 pA, PN, −129.1 ± 103.2 pA, n = 15 pairs, W = 0, $ p = 1.0 $, Wilcoxon matched-pairs signed rank test; Fig. 5B,C). By contrast, in Disc1 LI mice, thalamocortical EPSCs onto PV INs were much larger than those onto neighboring PNs (PV, −153.4 ± 211.9 pA; PN, −73.74 ± 104.6 pA; n = 14 pairs, W = −83, $ p < 0.01 $ Wilcoxon matched-pairs signed rank test; Fig. 5B,C). These data suggest that MD excitatory drive onto PV INs is enhanced relative to L2/3 PNs in the mPFC of Disc1 LI mice. Therefore, reduced excitatory synaptic strength onto PV INs does not account for the decrease in FFI in the MD–mPFC circuit in Disc1 LI mice compared with WT (Fig. 3).

Next, we probed presynaptic GABA release from PV cells within the MD–mPFC circuit, by optogenetically stimulating the MD axons (see the recording configuration in 3A, B) and measuring the PPR of MD-driven FFI onto mPFC PNs (Fig. 5D). Notably, we found that PPR of was significantly higher in Disc1 LI mice than in WT mice (WT: 0.0 ± 0.1, n = 24 cells, N = 10; Disc1 LI: 0.24 ± 0.34, n = 17 cells, N = 6; U = 62, 9p = 0.0001, two-tailed Mann–Whitney U test; Fig. 5D,E), mirroring the increase in PPR we observed when directly activating PV INs (Fig. 2C). In order to reduce variability in measuring the PPR, we set the light-stimulation such that there was no difference between genotypes in the average amplitude of the first evoked IPSCs (WT, 493.3 ± 41.31 pA, n = 24 cells, N = 10; Disc1 LI, 367.1 ± 46.26 pA, n = 17 cells, N = 6; t(39) = 1.152, 9p = 0.256, unpaired t test; Fig. 5F). Finally, we examined the relationship between PPR of MD-driven FFI and E-I ratio of MD-driven synaptic currents onto PNs. We found that there was a significant inverse correlation between FFI PPR and $ I_{\text{peak}}/(I_{\text{peak}}+I_{\text{Epeak}}) $ within PNs from Disc1 LI mice but not WT mice (Fig. 5G). Together, our data suggest that in Disc1 LI mice, GABA release from prefrontal PV INs is reduced, leading to decreased FFI in the MD–mPFC circuit.

Discussion

Perturbation of the multifunctional scaffolding protein DISC1 is linked to a range of behavioral phenotypes that are associated with major psychiatric disorders (Brandon and Sawa, 2011). These findings highlight DISC1 as a promising molecular lead to investigate the molecular pathways and neural circuits that underlie major mental illnesses (Niwa et al., 2016). Here, we used the Disc1 LI mouse model to investigate the function of mPFC circuits that may be particularly relevant to the cognitive symptoms of psychiatric disorders. We found that Disc1 LI mice exhibited elevated E-I ratio, measured as a reduction of spontaneous inhibitory transmission onto L2/3 PNs in mPFC and decreased FFI onto L2/3 PNs in the MD–mPFC circuit. Several lines of evidence suggest that this effect can be accounted for by a reduction in GABA
Figure 4. mEPSCs and intrinsic properties of PV INs are not altered in Disc1 LI mice. A, Recording configuration and sample mEPSC traces recorded from PV INs in WT (upper) and Disc1 LI mice (lower). B, Mean mEPSC amplitude (left) and median frequency (right; n = 20, 23 cells/genotype; N = 4 mice/genotype). C, Sample traces from whole-cell current clamp recording of L2/3 PV IN in WT (left) and Disc1 LI mouse in response to current injections. D, Input-output curve showing average firing rate of PV INs in response to current injection in WT versus Disc1 LI. E, Resting membrane potential. F, Input resistance. G, Current threshold required to elicit spiking. H, Maximum firing rate. Data in D, E, H shown as mean ± SEM. Data in F, G shown as median ± interquartile range.
Multiple mouse models of DISC1 perturbation exhibit cognitive impairments (Koike et al., 2006; Clapcote et al., 2007; Li et al., 2007; Kvajo et al., 2008; Lipina et al., 2010; Niwa et al., 2010; Brandon and Sawa, 2011; Lee et al., 2013), strengthening the mechanistic link between DISC1 and cognition. Here we provide evidence of cell type-specific alterations within mPFC circuits implicated in multiple aspects of cognition. While we did not examine cognition in the Disc1 LI mice, Disc1 LI (–/–) mice are reported to exhibit blunted startle response and prepulse inhibition (PPI; Jaaro-Peled et al., 2018), a behavior that is regulated by the mPFC (Swerdlow et al., 2001; Schwabe and Koch, 2004). Future experiments interrogating mPFC-dependent cognition in Disc1 LI mice will be critical for relating the circuit-level changes we observed in E-I balance and PV IN function to behavior.

While our study is the first to specifically detect a presynaptic deficit in PV INs in a DISC1 genetic deficiency model, previous studies using different transgenic models have reported that DISC1 influences inhibitory IN function or development: spontaneous IPSC frequency is reduced in the frontal cortex of male mice expressing truncated mouse DISC1 (Holley et al., 2013); PV IN function is impaired in the mPFC of mice overexpressing a truncated form of DISC1 (Sauer et al., 2015); PV expression is reduced in the PFC of several Disc1 mouse models (Hikida et al., 2007; Shen et al., 2008; Niwa et al., 2010; Ayhan et al., 2011; Lee et al., 2013); and tangential migration of MGE-derived neurons is impaired by Disc1 mutation or RNA interference (Steinecke et al., 2012; Lee et al., 2013). These findings provide converging evidence that DISC1 perturbation alters PFC inhibition. Our current findings more specifically implicate the presynapse of PV INs as a site of impairment in mice harboring a Disc1 LI allele, which is the most extensively perturbed form of the gene reported to date (Shahani et al., 2015).

Several important caveats should be considered when interpreting our electrophysiology results. First, a reduction

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Table 1: Statistical tests and significance threshold used for each comparison

| Data structure | Statistical test, post hoc | Significance threshold |
|----------------|---------------------------|------------------------|
| aNon-normal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| bNon-normal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| cNon-normal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| dNormal distribution | Two-tailed unpaired t test | $p < 0.05$ |
| eNormal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| fNon-normal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| gNon-normal distribution | Two-way ANOVA | $p < 0.05$ |
| hNormal distribution | Two-way ANOVA | $p < 0.05$ |
| iNormal distribution | Two-tailed unpaired t test | $p < 0.05$ |
| jNon-normal distribution | Two-tailed unpaired t test | $p < 0.05$ |
| kNormal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| lNon-normal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| mNon-normal distribution | Wilcoxon matched-pairs signed ranks test | $p < 0.05$ |
| nNon-normal distribution | Wilcoxon matched-pairs signed ranks test | $p < 0.05$ |
| oNon-normal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| pNon-normal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| qNon-normal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |
| rNon-normal distribution | Two-tailed Mann-Whitney U test | $p < 0.05$ |

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release from PV INs in the mPFC: 1) mIPSC frequency was significantly reduced onto L2/3 PNs in Disc1 LI mice, consistent with a reduction in presynaptic release probability; 2) the PPR of IPSCs directly evoked by optogenetic stimulation of PV INs but not SOM INs was significantly increased in Disc1 LI mice compared with WT; and 3) the PPR of MD-evoked FFI, which is almost exclusively driven by PV INs under the experimental conditions used (Delevich et al., 2015), was increased in Disc1 LI mice compared with WT. Together, our findings suggest that PV → PN synapses are the primary site of impairment in the MD–mPFC circuit in Disc1 LI mice.

It has been hypothesized that the cognitive deficits in psychiatric diseases may be the consequence of imbalances between excitatory and inhibitory INs (E-I) in key neural circuits (Kehrer et al., 2008; Lisman, 2012; Marin, 2012; Krystal et al., 2017; Ferguson and Gao, 2018a). Consistent with this hypothesis, several studies have shown that experimentally imposing elevated E-I within the mPFC impairs cognitive processing in rodents (Yizhar et al., 2011; Cho et al., 2015; Murray et al., 2015; Ferguson and Gao, 2018b). In addition to evidence of altered PV IN mediated inhibition, we observed that excitatory synaptic transmission onto PV cells driven by MD inputs was enhanced in Disc1 LI mice, which could compensate for presynaptic deficits in PV IN function. Indeed, a recent study that examined multiple autism genetic mouse models found that increased E-I ratio did not drive network hyperexcitability but in fact led to homeostatic stabilization of excitability (Antoine et al., 2019). Therefore, potential network effects arising from altered E-I conductance ratios should not be overinterpreted, and it remains unclear how the changes we observed in the Disc1 LI mice affect network activity in vivo and resulting behavior.

In humans, Disc1 polymorphisms are associated with measures of cognitive performance and frontal lobe structure among some ethnic groups (Burkitt et al., 2005; Cannon et al., 2005; Hennah et al., 2005; Liu et al., 2006; Palo et al., 2007; Carless et al., 2011; Nicodemus et al., 2014).
in mIPSC frequency is also consistent with a reduced number of inhibitory synapses. A recent study investigating Disc1 LI mice reported no change in the number of PV INs themselves within the mPFC (Seshadri et al., 2015). In addition, we focused on PV and SOM IN function, which together comprise ~70% of cortical INs (Rudy et al., 2011). It is therefore possible that the remaining 30% of IN cell types, e.g., 5HT3a receptor-expressing neurons, also contribute to the reduced mIPSC frequency observed in Disc1 LI mice. Next, IPSCs directly evoked by optogenetic stimulation significantly overlapped at short interstimulus intervals; therefore, changes in the input resistance due to open channels likely influenced the size of the second signal and hence the PPR measurement. More detailed analysis such as multiple probability-compound binomial analysis or direct analysis of failure rate is necessary to conclude that GABA release probability from PV INs is reduced in Disc1 LI mice. We observed that PV IN evoked IPSC PPR was significantly increased at the 50- and 100-ms intervals but not at the 150-ms interval. The time dependence of this effect may suggest a postsynaptic mechanism, such as GABA-mediated regulation of PPR (Kirischuk et al., 2002). Alternatively, GABAergic presynaptic regulation may play a role in influencing PPR. Interestingly, a reduction in GABAergic receptor expression in PNs has been observed in postmortem brain tissue of individuals with schizophrenia.

Figure 5. Altered presynaptic function of PV INs underlies the deficit of FFI in Disc1 LI mice. A, left, schematic of the experimental configuration. Right: schematic of the recording configuration in the mPFC acute slices. A TdTomato+ PV IN (red) and an adjacent PN (gray) in L3 of the mPFC were recorded simultaneously or sequentially. EPSCs onto these neurons were evoked by optogenetic stimulation (0.5-ms light pulses; blue bars) of MD axons. B, Sample EPSC traces recorded from PV IN and PN pairs are superimposed and color-coded. C, Quantification of the EPSC peak amplitude. n.s., not significant (p = 1.0); **p < 0.01; Wilcoxon matched-pairs signed ranks test. D, Sample traces of FFI currents recorded from L3 PNs in response to optogenetic stimulation of MD axons. E, Quantification of PPR of the MD-driven FFI onto L3 PNs; ***p < 0.001, Mann–Whitney U test. F, The mean amplitude of the first IPSC was consistent between genotypes. G, FFI PPR plotted against (Ipeak)/(Ipeak + Epeak), as seen in Fig. 3D) within cells shows that for Disc1 LI mice but not WT mice, FFI PPR inversely correlated with (Ipeak)/(Ipeak + Epeak), suggesting that synapses with high FFI PPR also exhibit higher E/I ratio; **p < 0.01. Data in E presented as median ± interquartile range data in F presented as mean ± SEM.
(Mizukami et al., 2002). These caveats considered, we provide multiple lines of evidence that are consistent with elevated E-I balance and abnormal PV IN function in mPFC circuits in Disc1 Li mice.

The coordinated activity between the MD and the PFC is important for WM, attention, and flexible goal-oriented behavior (Mitchell and Chakraborty, 2013; Parnaudeau et al., 2013, 2015; Schmitt et al., 2017; Alcaraz et al., 2018), faculties that are impaired in a variety of psychiatric disorders. Meanwhile, studies have found that MD–mPFC synaptic strength is modulated by social interaction, perhaps relevant to negative symptoms of schizophrenia and depression (Northoff and Sibille, 2014; Franklin et al., 2017; Zhou et al., 2017). In relation to DISC1, one study found that a common missense variant of Disc1 was associated with altered thalamofrontal functional connectivity (Liu et al., 2015). Notably, patients with schizophrenia and bipolar disorder exhibit reduced MD–PFC functional connectivity relative to healthy controls (Welsh et al., 2010; Woodward et al., 2012; Anticevic et al., 2014). An emerging hypothesis posits that local disinhibition of PFC may destabilize the flow of information through the thalamofrontal loop and contribute to cognitive and negative symptoms in schizophrenia and related disorders (Anticevic et al., 2012; Murray and Anticevic, 2017). Structural alterations within thalamofrontal circuits have also been linked to cognitive deficits associated with aging (Hughes et al., 2012) and epilepsy (Pulsipher et al., 2009). However, until recently there was a paucity of data describing how the MD and frontal cortex interact at the neural circuit level. Recent studies have demonstrated that the MD thalamus recruits FFI in the rostral mPFC (Delevich et al., 2015; Miller et al., 2017; Collins et al., 2018; Meda et al., 2019) that is primarily mediated by PV INs (Delevich et al., 2015). Interestingly, chemogenetic excitation of mPFC PV INs has been shown to rescue cognitive deficits induced by chemogenetic inhibition of MD (Ferguson and Gao, 2018b).

Our findings extend data suggesting that MD, via its projections to PV INs, is a key regulator of E-I balance that underpins PFC circuit function. We demonstrate that reduced DISC1 expression, a key molecular candidate to study biology relevant to behavioral constructs related to several psychiatric disorders, leads to elevated E-I balance in the MD–mPFC thalamofrontal circuit. Given that few treatment options exist to address the cognitive symptoms of psychiatric disorders, efforts towards understanding the cellular and molecular mechanisms underlying abnormal thalamofrontal functional connectivity may yield therapies that will improve patient outcomes.

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