

Correspondence

Reduced Density of DISC1 Expressing Astrocytes in the Dentate Gyrus but not in the Subventricular Zone in Schizophrenia

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There is evidence for impaired adult neurogenesis in the hippocampal subgranular zone of schizophrenia patients (Reif *et al*, 2006; Allen *et al*, 2016 and others). Normal and compromised neurogenesis in the adult brain is influenced by a plethora of factors, one of which might be Disrupted-in-Schizophrenia 1 (DISC1) (Figure 1) expressed in astrocytes. In elegant experiments, Terrillion *et al* (2017), (this journal) have recently shown that expression of mutant DISC1 in mouse astrocytes decreased neural progenitor proliferation, produced increased anxiety and impaired hippocampus-dependent learning and memory. Chronic treatment with D-serine restored decreased adult neurogenesis in mutant DISC1 mice. This study prompted us to look for astroglial DISC1 expression in the dentate gyrus and the subventricular zone of individuals with schizophrenia, since despite growing skepticism (reviewed in Mathieson *et al*, 2012) DISC1 is regarded a risk gene in schizophrenia. We analyzed the density of DISC1-immunoreactive astrocytes in 18 patients with schizophrenia (mean age 54.5 years; nine males, nine females) and 12 matched psychiatric healthy controls (mean age 55.3 years; seven males, five females). Recruitment of cases and tissue handling were as previously described (Bernstein *et al*, 2016). To immunolocalize DISC1 we used a polyclonal rabbit DISC1 antiserum (Abcam ab 82038, IgG, immunogen affinity purified) at a dilution of 1:200. Sections were then incubated with a biotinylated goat anti-rabbit secondary antibody (Amersham) for the streptavidin-biotin technique. The chromogen 3, 3'-diaminobenzidine (DAB) and ammonium nickel sulfate were used to visualize the reaction product. DISC1 immunoreactive astrocytes were counted at 400 fold magnification. We used the optical disector method employing a counting grid as described for glutamine synthetase immunopositive hippocampal astroglia (Bernstein *et al*, 2013). Normal distribution of demographical data was demonstrated by Kolmogorov-Smirnov tests. A stepwise multiple regression

analysis was performed to control for possible influences on cell densities of age, gender, duration of disease, storage delay, whole-brain volume, and medication. Statistical analyses were performed with the SPSS package version 15.0 (Statistical Product and Service Solutions, Chicago, IL, USA). Spearman's correlation coefficients were calculated to determine the influence of variables which could have confounded the outcomes. A Bonferroni correction for multiple comparisons was used. Significance was defined as $P < 0.05$. It was revealed that unlike DISC1 immunoreactive oligodendrocytes (Bernstein *et al*, 2016), DISC1 expressing astrocytes are only few in number.

Compared with controls we found in schizophrenia patients reduced densities for DISC1 astroglia in the left (controls: 236.9 ± 47.0 cells/mm³; schizophrenia: 95.5 ± 45.3 cells/mm³; $P = 0.001$) and right (controls 189.4 ± 24.9 cells/mm³; schizophrenia: 66.8 ± 20.1 cells/mm³; $P = 0.001$) hippocampal dentate gyrus, but not in the left or right subventricular zone (left: controls: 477.2 ± 122.0 cells/mm³; schizophrenia: 434.6 ± 139.6 cells/mm³; right: controls 501.0 ± 166 cells/mm³, schizophrenia 466.5 ± 189.7 cells/mm³). Significant differences (hippocampus) survived Bonferroni correction (left $P = 0.021$; right $P = 0.030$). Our findings show that in schizophrenia there are fewer DISC1-expressing astrocytes in a brain region with established adult neurogenesis (dentate gyrus), but not in the subventricular zone, a region with questionable adult neurogenesis in humans (Comte *et al*, 2012). Pletnikov's group has shown that D-serine is able to normalize adult neurogenesis and behavioral deficits in DISC1 mutant mice (Terrillion *et al*, 2017). As astrocytic DISC1 influences D-serine production (Terrillion *et al*, 2017), a deficit of DISC1-expressing astrocytes in schizophrenia may lead to reduced local levels of D-serine, which may negatively influence neurogenesis in psychiatric patients. This pathophysiologic aspect warrants further attention in future studies.

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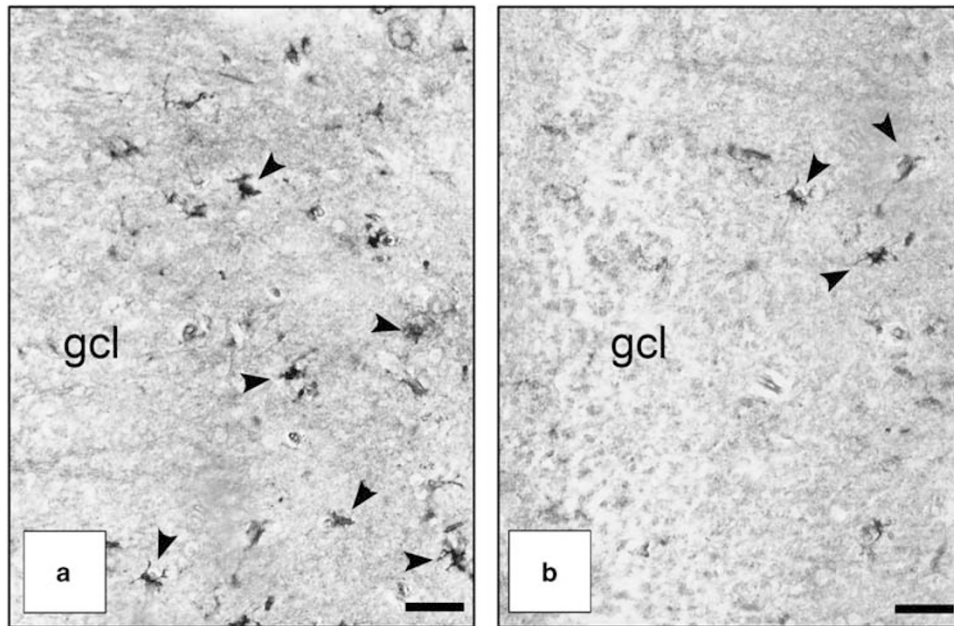


Figure 1 Immunolocalization of DISC1 in human dentate gyrus astrocytes. **(a)** DISC1 immunoreactive astrocytes (arrowheads) in the dentate gyrus of a control case. Granule cell layer (gcl) neurons are only faintly stained. Bar = 30 μ m. **(b)** Compared with controls there are fewer DISC1 immunopositive astrocytes (arrowheads) in the dentate gyrus of schizophrenia patients. Granule cell layer (gcl) neurons are only faintly stained. Bar = 30 μ m.

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