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BRIEF REPORT

Dominant negative DISC1 mutant mice display specific social behaviour deficits and aberration in BDNF and cannabinoid receptor expression

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Abstract

Objectives. Disrupted in schizophrenia 1 (DISC1) is considered the most prominent candidate gene for schizophrenia. In this study, we aimed to characterize behavioural and brain biochemical traits in a mouse expressing a dominant negative DISC1mutant (DN-DISC1). *Methods.* DN-DISC1 mice underwent behavioural tests to evaluate object recognition, social preference and social novelty seeking. ELISA was conducted on brain tissue to evaluate BDNF levels. Western blot was employed to measure BDNF receptor (TrkB) and cannabinoid receptor CB1. *Results.* The mutant DISC1 mice displayed deficits in preference to social novelty while both social preference and object recognition were intact. Biochemical analysis of prefrontal cortex and hippocampus revealed a modest reduction in cortical TrkB protein levels of male mice while no differences in BDNF levels were observed. We found sex dependent differences in the expression of cannabinoid-1 receptors. *Conclusions.* We describe novel behavioural and biochemical abnormalities in the DN-DISC1 mouse model of schizophrenia. The data shows for the first time a possible link between DISC1 mutation and the cannabinoid system.

Key words: *DISC1, animal model, schizophrenia, BDNF, CB1*

Abbreviations: *DISC1, disrupted in schizophrenia 1; BDNF, brain-derived neurotrophic factor*

Introduction

Disrupted in schizophrenia gene 1 (DISC1) is considered a top candidate gene for schizophrenia (Ayalew et al. 2012). The gene was originally identified in a Scottish family in which a balanced translocation (1;11) segregated with major psychiatric illness (Millar et al. 2000). The DISC1 gene is located at the translocation site in chromosome 1. More recently, basic research studies have shown its role in neuronal differentiation, neurogenesis, synaptic strength and other key processes in the development and homeostasis of the brain (Brandon and Sawa 2011). Importantly, though originally linked to schizophrenia, DISC1 was shown to be involved in the pathophysiology of other neurodevelopmental disorders affecting social behaviour, including autism (Kilpinen et al. 2007).

Various labs have generated mouse models harbouring DISC1 mutations (Jaaro-Peled 2009). These mice were characterized for distinct abnormal behavioural endophenotypes including deficits in prepulse inhibition, hypersensitivity to stimulants, depressive-like behaviour, and impaired social behaviour. Importantly, studies have shown that expression of mutant DISC1 in forebrain restricted manner (under the control of the CamKII promoter) is sufficient to produce such behavioural abnormalities (Hikida et al. 2007; Pletnikov et al. 2007).

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In the current study, we aimed to further characterize the mice harbouring a DISC1 mutant in specific forebrain areas, which results in dominant negative DISC1 (DN-DISC1) mouse model (Pletnikov et al. 2007). Specifically, we aimed to analyze the impact of DN-DISC1 mutation on BDNF and cannabinoid pathways, which were reported to play a role in the pathophysiology of schizophrenia (Muller-Vahl and Emrich 2008; Favalli et al. 2012).

Methods

Animals

DN-DISC1 mice were generated from breeding tetracycline-responsive element mutant DISC1 mice (kindly donated by Mikhail Pletnikov and Akira Sawa from Johns Hopkins University, USA) and transgenic mice expressing tetracycline-controlled transactivator protein (tTA) under regulatory control of the forebrain-specific calcium-calmodulin-dependent kinase II (Camk2a), established and maintained on a mixed B6;CBA genetic background (Jackson Laboratory, Sacramento, CA, USA). Mice were genotyped and expression of both mutant DISC1 and CamK2 was verified. Mice from the same litters harbouring only the TRE-mutant DISC1 were used as controls. For all behavioural experiments, male mice aged 8–10 weeks were used. Thereafter, mice were sacrificed and brains were dissected for future tissue analysis. All animal experiments and protocols were approved by the Committee for Animal Research at Tel Aviv University.

Behavioural tests

Analysis of all tests was conducted using the Ethovision 8 platform (Noldus, Wageningen, The Netherlands) for the analysis of animal behaviour from video files.

Open field

Mice were put in the arena (50 cm^2) and videotaped for 20 min.

Novel object recognition test

Test was conducted according to known protocols (Ibi et al. 2009). Briefly, after two consecutive days of habituation to the arena (50 cm^2) for 20 min, mice were put in an arena harbouring two identical objects (object A + A) for 10 min. Three hours later, one object was replaced (object A + B) and animals were put in the arena again for 5 min. After 24 h, B object was changed again and animals were put in the arena for another 5 min (object A + C).

Social preference and social recognition (preference to social novelty) test

Social behaviour was evaluated as previously reported using the three chamber paradigm (Nadler et al. 2004). Briefly, after two consecutive days of habituation, the test mouse was put in the arena for 10 min limited to the central zone; thereafter, an unfamiliar mouse was introduced into one chamber of the arena, and the test mouse was free to explore all of the arena chambers for another 10 min to evaluate social preference. Lastly, another unfamiliar mouse was introduced to the vacant chamber, allowing the test mouse to explore the arena for another 10 min in which preference to social novelty was evaluated.

Tissue processing

After sacrifice, brains were removed and dissected for prefrontal cortex and hippocampus. Thereafter, tissue was cryopreserved in −80°C. Consequently, protein was extracted as previously reported (Barzilay et al. 2011).

Enzyme-linked immunosorbent assay (ELISA)

Quantification of total BDNF levels in the protein extract was conducted as previously described (Barzilay et al. 2011) using BDNF ELISA kit (Millipore, Billerica, MA, USA).

Western blot

Protein expression levels were assessed as previously described (Barzilay et al. 2011). The following antibodies were employed: anti-TrkB (Santa Cruz, CA, USA, cat. Num. sc-8316) 1:1000 in blocking buffer, anti-CB1 (Proteintech, Chicago, IL, USA, cat. num. 17978-1-AP) and anti-actin (Biomeda, Burlingame, USA). Expression was normalized to actin.

Statistic analysis

Mann–Whitney *U*-test was used to determine if there were significant differences between experimental and control groups. The significance level of $P < 0.05$ was used for all statistical analyses.

Results

Performance of DN-DISC1 male mice in behavioural tests

In the open field arena, DN-DISC1 mice did not differ in their total locomotor activity from control mice, as observed by total distance moved (Figure 1A). No difference was observed in total

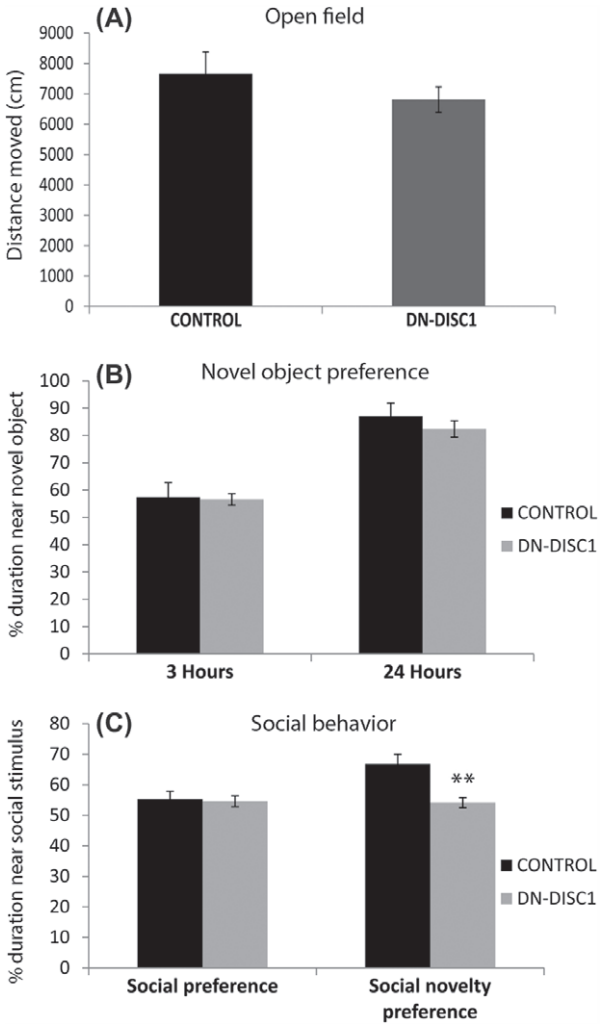

Figure 1. Behavioural tests of male DN-DISC1 ($n = 13$) and control ($n = 8$) mice. (A) Open field: total distance moved (in cm) in the open field arena over 20 min. (B) Novel object recognition test: ratio of the time spent investigating a novel object divided by total time spent investigating familiar and novel object. Test was conducted after 3 and 24 h from the training session. Results represent % of time spent near novel object out of total time spent either near novel or familiar object. (C) Three chamber social test: ratio of the time spent investigating a mouse divided by total time spent investigating a social and an inanimate stimulus (social preference), or ratio of the time spent investigating an unfamiliar mouse divided by the time spent investigating a familiar and an unfamiliar mouse (social novelty preference), $^{**}P < 0.005$.

time spent in the centre of the arena during the open field test, 6.76 ± 3.9 in DN-DISC1 mice and 7.76 ± 2.36 in control mice (% of time spent in centre $\pm$ STD, *P*-value = 0.5898). In the novel object recognition test, DN-DISC1 mice displayed similar preference towards the novel object both after 3- or 24-h retention (Figure 1B), as observed by the ratio between time spent in proximity to the novel object and the total time spent in proximity either to the familiar or novel object.

In the social preference test, analysis of the duration of time spent in each chamber revealed that DN-DISC1 mice displayed similar preference pattern towards the social stimulus versus the inanimate object. However, when confronted with the option to explore a novel mouse over a now familiar mouse (which the test mouse was allowed to explore for the previous part of the test), DN-DISC1 mice showed significantly reduced preference towards the novel mouse compared to control mice (Figure 1C, DN-DISC1 mice spent $66.75 \pm 3.21\%$ of time exploring novel mouse versus $54.11 \pm 1.66\%$ in controls, $P < 0.005$).

Evaluation of BDNF and TrkB levels

No differences in total BDNF levels were detected in the prefrontal cortex (Figure 2A) or in the hippocampus (Figure 2B) of DN-DISC1 mice compared with control. Analysis of the BDNF receptor TrkB revealed significantly decreased levels in the cortex of DN-DISC1 mice (Figure 2C, $64.1 \pm 6.67\%$ compared to controls, $P < 0.005$), while no difference in TrkB was found in the hippocampus between the two groups (Figure 2D).

Evaluation of CB1 expression

CB1 receptor expression was evaluated in the prefrontal cortex and hippocampus of mice using Western blot. Since reports were made suggesting specific sex effect in the cannabinoid system in rodents (Fattore and Fratta 2010), we evaluated the brains of females as well.

In the cortex, we found that CB1 expression was significantly decreased in females (Figure 3B, $58.27 \pm 8.2\%$ compared to controls, $P < 0.005$), while no statistically significant difference was observed in the cortex of males (Figure 3A, $84.85 \pm 4.81\%$ compared to controls, $P = 0.056$). In the hippocampus, CB1 expression was significantly lower in males (Figure 3C, $78.89 \pm 3.26\%$ compared to controls, $P < 0.05$), while not significantly different in females (Figure 3D $80.06 \pm 9.66\%$ compared to controls).

Discussion

DISC1 is the most investigated candidate gene for susceptibility to severe neuropsychiatric disorders, specifically schizophrenia (Millar et al. 2000; Jaaro-Peled 2009; Brandon and Sawa 2011; Ayalew et al. 2012). Mouse models expressing mutant DISC1 are a useful tool to analyse gene–environment interaction in the generation of schizophrenia-like endophenotypes (Abazyan et al. 2010, 2013; Nagai et al. 2011; Haque et al. 2012; Lipina et al. 2013; Niwa et al.

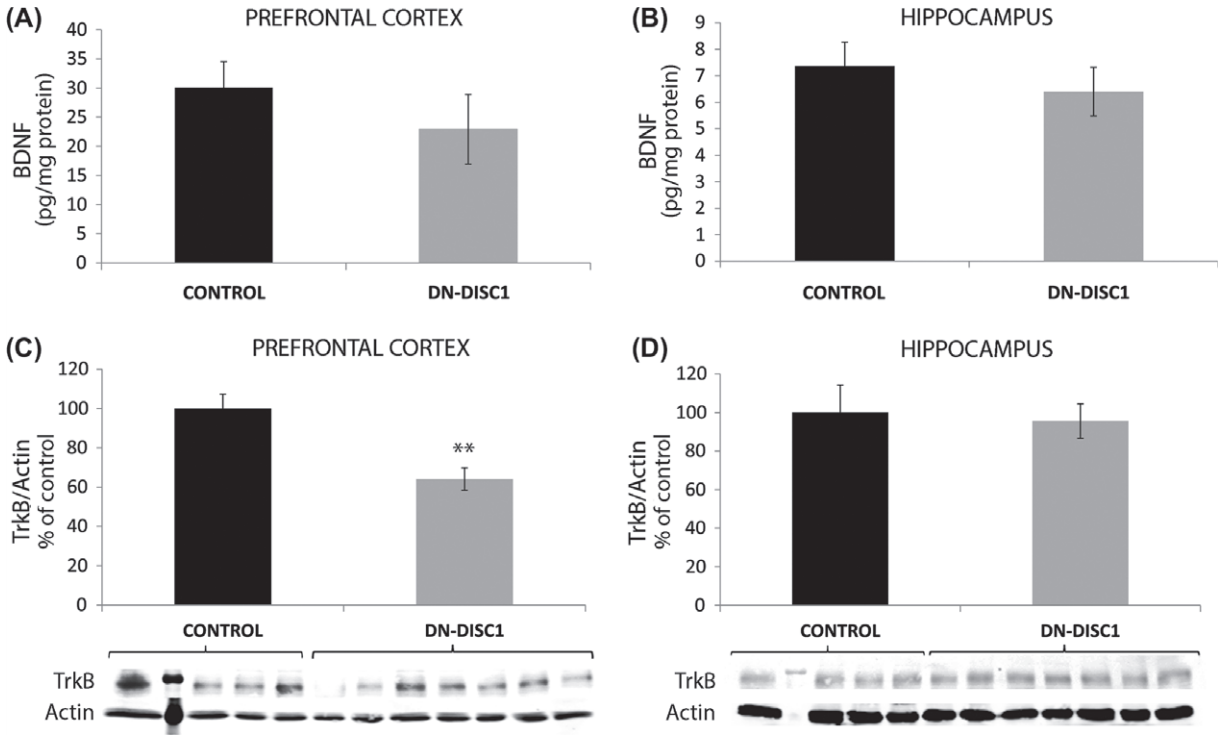

Figure 2. BDNF and TrkB protein levels in the brains of male DN-DISC1 ($n = 10$) and control ($n = 8$) mice. (A, B) BDNF levels as measured using ELISA in the prefrontal cortex and hippocampus, respectively (results are presented as mean ± SEM pg BDNF/mg total protein). (C, D) TrkB levels as measured using Western blot in the prefrontal cortex and hippocampus, respectively. The intensity of the bands was standardized to actin. The results are presented as a percentage of the levels of expression measured in control mice. Results are displayed as mean ± SEM. $^{**}P < 0.005$.

2013). In this study, we describe distinct behavioural and biochemical endophenotypes of the DN-DISC1 mouse model. Our study is the first to directly link an animal model of DISC1 mutation with aberrant sex-dependent expression of CB1 receptors.

In the current study, we chose to focus on social behaviour since social deficits represent core negative symptoms in schizophrenia, and are specifically refractory to drug treatment. Methodologically, we included the open field test and the object recognition test in order to show that motor function and object recognition are intact, thus enabling assessment of preference to social novelty. Indeed, only the complete battery of tests allows us to conclude that DN-DISC1 display impaired social recognition, manifested by specific decrease in preference towards a novel social stimulus versus a familiar social stimulus.

When designing our study, we sought to focus on molecular pathways that are relevant for the pathophysiology of schizophrenia and that have been reported to mediate some of the environmental insults that confer a risk for the emergence of schizophrenia (Le Strat et al. 2009). BDNF/TrkB (Weickert et al. 2003; Green et al. 2011; Favalli et al. 2012) and endocannabinoid signalling (Muller-Vahl and Emrich 2008; Fernandez-Espejo et al. 2009; Bossong and Niesink 2010) are known to be involved in the underlying pathophysiology of schizophrenia. Cannabis abuse is among the most prominent independent risk factors for the development of psychosis and schizophrenia (Moore et al. 2007). Importantly, a recent report has pointed to a possible interaction of the Val66Met BDNF genotype, cannabis abuse and gender in the context of the age of schizophrenia onset (Decoster et al. 2011), emphasizing the need to investigate the relationship between these factors in appropriate animal models.

Little is known about the interplay between BDNF and cannabinoid signalling in the context of schizophrenia. Of note, data from mouse (Butovsky et al. 2005) and human (D'Souza et al. 2009) studies suggests that cannabis administration directly affects BDNF levels. Mechanistically, a few studies which investigated the interplay between BDNF and cannabinoid system have shown that BDNF controls brain striatal CB1 function (De Chiara et al. 2010), and that the lack of CB1 receptor in mice (Aso et al. 2008) or chronic antagonism of CB1 receptors in rats (Beyer et al. 2010), induces a decrease in hippocampal BDNF levels and manifestation of abnormal neuropsychiatric behavioural phenotypes.

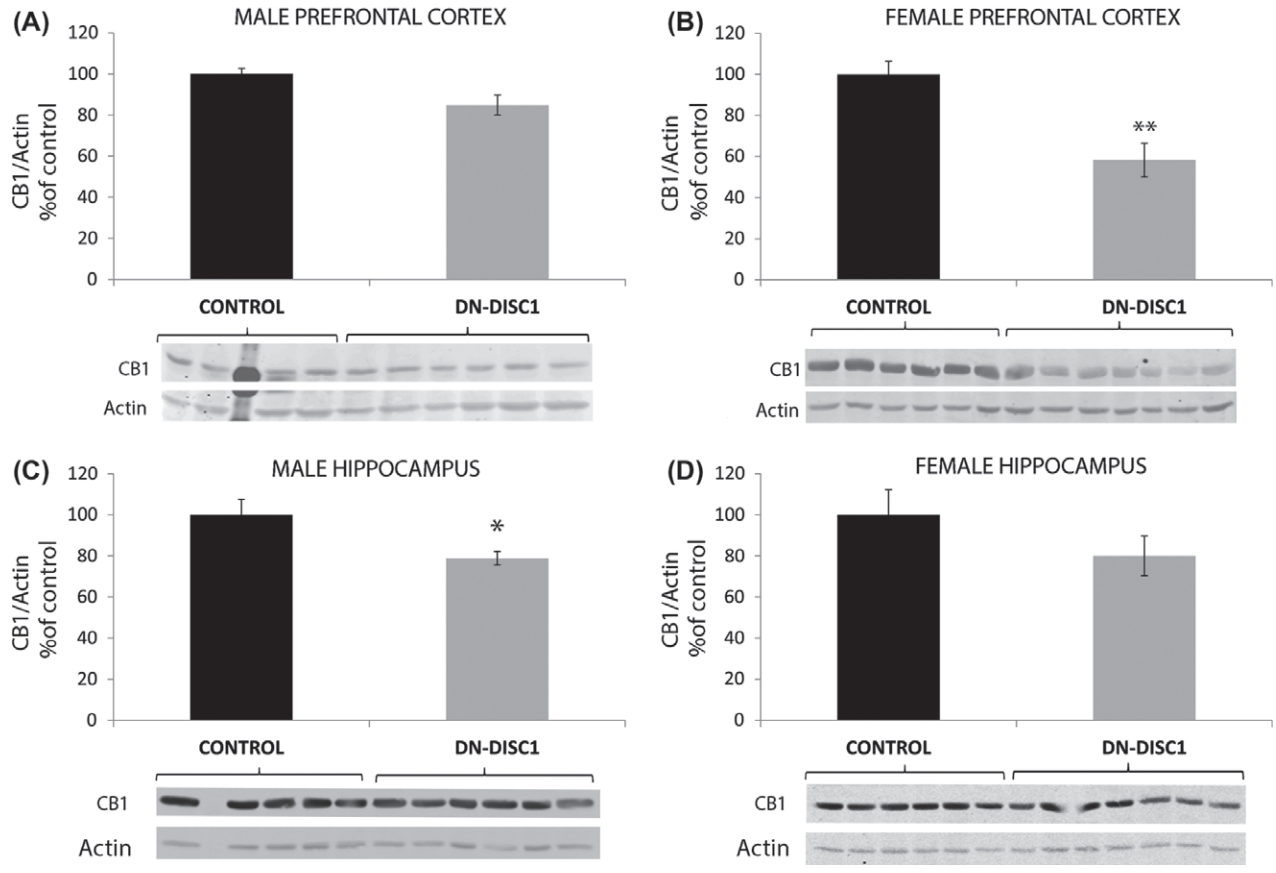

Figure 3. CB1 protein levels in the brains of male DN-DISC1 ($n = 10$) and control ($n = 8$) mice, and of female DN-DISC1 ($n = 10$) and control ($n = 10$) mice (A, B) CB1 levels as measured using Western blot in the prefrontal cortex of males and females, respectively. (C, D) CB1 levels as measured using Western blot in the hippocampus of males and females, respectively. The intensity of the bands was standardized to actin. The results are presented as a percentage of the levels of expression measured in control mice. Results are displayed as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.005$.

Aberrant brain BDNF levels were previously linked to schizophrenia both in the clinical context (Weickert et al. 2003; Thompson Ray et al. 2011) and in relevant animal models (Lipska et al. 2001; Guo et al. 2010). In the current study, we found no significant differences in BDNF levels in the cortex or hippocampus of DN-DISC1 mice, neither in males nor females (data not shown). However, we did detect significant reduction in TrkB expression in the cortex of male mice compared to controls, which suggests that the expression of DISC1 mutant in the cortex indeed affects BDNF signalling.

Cortical levels of CB1 mRNA and protein are reduced in schizophrenia patients (Eggan 2008). In animal models, CB1 knockout mice are used to model specific endophenotypes of schizophrenia (Marongiu et al. 2012). In our study, we found decreased CB1 levels in the hippocampus (in males) and in the cortex (in females) compared to controls. These result are consistent with the known sex effect on the cannabinoid system (Fattore and Fratta 2010). Importantly, sex-dependent differences were already reported in DN-DISC1 mice manifested in differences in monoamine levels (Ayhan et al. 2011) and in sensitization by methamphetamine (Pogorelov et al. 2012).

Since BDNF and the cannabinoid system were reported to mediate distinct aspects of schizophrenia pathophysiology, we suggest that evaluation of these pathways in the DN-DISC1 animal model is crucial for future sex, gene and environment interaction studies in these mice. Future studies may include early exposure to stress, which is known to affect BDNF signalling (Smith et al. 1995), or administration of tetrahydrocannabiol (THC), which is used as a tool to investigate psychotic disorders in genetically susceptible animal models (Arnold et al. 2012). To our view, our findings are important in establishing the DN-DISC1 mouse as a platform to explore this gene × sex × environment interactions in animal models, as an instrument to identify novel mechanisms and targets in schizophrenia research.

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Statement of Interest

None to declare.

References

Abazyan B, Nomura J, Kannan G, Ishizuka K, Tamashiro KL, Nucifora F, et al. 2010. Prenatal interaction of mutant DISC1 and immune activation produces adult psychopathology. Biol Psychiatry 68:1172–1181.

Abazyan B, Dziedzic J, Hua K, Abazyan S, Yang C, Mori S, et al. 2013. Chronic exposure of mutant DISC1 mice to lead produces sex-dependent abnormalities consistent with schizophrenia and related mental disorders: a gene-environment interaction study. Schizophr Bull. In press.

Arnold JC, Boucher AA, Karl T. 2012. The yin and yang of cannabis-induced psychosis: the actions of Δ(9)-tetrahydrocannabinol and cannabidiol in rodent models of schizophrenia. Curr Pharm Des 18:5113–5130.

Aso E, Ozaita A, Valdizán EM, Ledent C, Pazos A, Maldonado R, et al. 2008. BDNF impairment in the hippocampus is related to enhanced despair behavior in CB1 knockout mice. J Neurochem 105:565–572.

Ayalew M, Le-Niculescu H, Levey DF, Jain N, Changala B, Patel SD, et al. 2012. Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. Mol Psychiatry 17:887–905.

Ayhan Y, Abazyan B, Nomura J, Kim R, Ladenheim B, Krasnova IN, et al. 2011. Differential effects of prenatal and postnatal expressions of mutant human DISC1 on neurobehavioral phenotypes in transgenic mice: evidence for neurodevelopmental origin of major psychiatric disorders. Mol Psychiatry 16:293–306.

Barzilay R, Ben-Zur T, Sadan O, Bren Z, Taler M, Lev N, et al. 2011. Intracerebral adult stem cells transplantation increases brain-derived neurotrophic factor levels and protects against phencyclidine-induced social deficit in mice. Transl Psychiatry 1:e61.

Beyer CE, Dwyer JM, Piesla MJ, Platt BJ, Shen R, Rahman Z, et al. 2010. Depression-like phenotype following chronic CB1 receptor antagonism. Neurobiol Dis 39:148–155.

Bossong MG, Niesink RJM. 2010. Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. Prog Neurobiol 92:370–385.

Brandon NJ, Sawa A. 2011. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. Nat Rev Neurosci 12:707–722.

Butovsky E, Juknat A, Goncharov I, Elbaz J, Eilam R, Zangen A, et al. 2005. In vivo up-regulation of brain-derived neurotrophic factor in specific brain areas by chronic exposure to Delta-tetrahydrocannabiol. J Neurochem 93:802–811.

De Chiara V, Angelucci F, Rossi S, Musella A, Cavasinni F, Cantarella C, et al. 2010. Brain-derived neurotrophic factor controls cannabinoid CB1 receptor function in the striatum. J Neurosci 20:8127–8137.

Decoster J, Van Os J, Kenis G, Henquet C, Peuskens J, De Hert M, et al. 2011. Age at onset of psychotic disorder: Cannabis, BDNF Val66Met, and sex-specific models of gene environment interaction. Am J Med Genet B Neuropsychiatr Gene 156:363–369.

D'Souza DC, Pittman B, Perry E, Simen A. 2009. Preliminary evidence of cannabinoid effects on brain-derived neurotrophic factor (BDNF) levels in humans. Psychopharmacology (Berlin) 202:569–578.

Eggan SM, Hashimoto T, Lewis DA. 2008. Reduced cortical cannabinoid 1 receptor messenger rna and protein expression in schizophrenia. Arch Gen Psychiatry 65:772–784.

Fattore L, Fratta W. 2010. How important are sex differences in cannabinoid action? Br J Pharmacol 160:544–548.

Favalli G, Li J, Belmonte-de-Abreu P, Wong AHC, Daskalakis ZJ. 2012. The role of BDNF in the pathophysiology and treatment of schizophrenia. J Psychiatr Res 46:1–11.

Fernandez-Espejo E, Viveros MP, Nunez L, Ellenbroek BA, Rodriguez de Fonseca F. 2009. Role of cannabis and endocannabinoids in the genesis of schizophrenia. Psychopharmacology (Berlin) 206:531–549.

Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. 2011. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol Psychiatry 16:960–972.

Guo C, Yang Y, Su Y, Si T. 2010. Postnatal BDNF expression profiles in prefrontal cortex and hippocampus of a rat schizophrenia model induced by MK-801 administration. J Biomed Biotechnol 2010:783297.

Haque FN, Lipina TV, Roder JC, Wong AHC. 2012. Social defeat interacts with Disc1 mutations in the mouse to affect behavior. Behav Brain Res 233:337–344.

Hikida T, Jaaro-Peled H, Seshadri S, Oishi K, Hookway C, Kong S, et al. 2007. Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. Proc Natl Acad Sci USA 104:14501–14506.

Ibi D, Nagai T, Kitahara Y, Mizoguchi H, Koike H, Shiraki A, et al. 2009. Neonatal polyI:C treatment in mice results in schizophrenia-like behavioral and neurochemical abnormalities in adulthood. Neurosci Res 64:297–305.

Jaaro-Peled H. 2009. Gene models of schizophrenia: DISC1 mouse models. Prog Brain Res 179:75–86.

Kilpinen H, Ylisaukko-oja T, Hennah W, Palo OM, Varilo T, Vanhala R, et al. 2007. Association of DISC1 with autism and Asperger syndrome. Mol Psychiatry 13:187–196.

Le Strat Y, Ramoz N, Gorwood P. 2009. The role of genes involved in neuroplasticity and neurogenesis in the observation of a gene-environment interaction (GxE) in schizophrenia. Curr Mol Med 9:506–518.

Lipina TV, Zai C, Hlousek D, Roder JC, Wong AH. 2013. Maternal immune activation during gestation interacts with Disc1 point mutation to exacerbate schizophrenia-related behaviors in mice. J Neurosci 33:7654–7666.

Lipska BK, Khaing ZZ, Weickert CS, Weinberger DR. 2001. BDNF mRNA expression in rat hippocampus and prefrontal cortex: effects of neonatal ventral hippocampal damage and antipsychotic drugs. Eur J Neurosci 14:135–144.

Marongiu MF, Poddie D, Porcu S, Manchinu MF, Castelli MP, Sogos V, et al. 2012. Reversible disruption of pre-pulse inhibition in hypomorphic-inducible and reversible CB1–/– mice. PLoS ONE 7:e35013.

Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CAM, et al. 2000. Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum Mol Genet 9:1415–1423.

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 370:319–328.

Muller-Vahl KR, Emrich HM. 2008. Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia. Expert Rev Neurother 8:1037–1048.

Nadler JJ, Moy SS, Dold G, Simmons N, Perez A, Young NB, et al. 2004. Automated apparatus for quantitation of social approach behaviors in mice. Genes Brain Behav 3:303–314.

Nagai T, Ibi D, Yamada K. 2011. Animal model for schizophrenia that reflects gene-environment interactions. Biol Pharm Bull 34:1364–1368.

Niwa M, Jaaro-Peled H, Tankou S, Seshadri S, Hikida T, Matsumoto Y, et al. 2013. Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids. Science 339:335–339.

Pletnikov MV, Ayhan Y, Nikolskaia O, Xu Y, Ovanesov MV, Huang H, et al. 2007. Inducible expression of mutant human DISC1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. Mol Psychiatry 13:173–186.

Pogorelov VM, Nomura J, Kim J, Kannan G, Ayhan Y, Yang C, et al. 2012. Mutant DISC1 affects methamphetamine-induced sensitization and conditioned place preference: a comorbidity model. Neuropharmacology 62:1242–1251.

Smith MA, Makino S, Kim SY, Kvetnansky R. 1995. Stress increases brain-derived neurotropic factor messenger ribonucleic acid in the hypothalamus and pituitary. Endocrinology 136:3743–3750.

Thompson Ray M, Weickert CS, Wyatt E, Webster MJ. 2011. Decreased BDNF, trkB-TK+ and GAD67 mRNA expression in the hippocampus of individuals with schizophrenia and mood disorders. J Psychiatry Neurosci 36:195–203.

Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. 2003. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. Mol Psychiatry 8:592–610.