Pharmacology, Biochemistry and Behavior 179 (2019) 73–79

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Anxiogenic-like behavior and deficient attention/working memory in rats expressing the human *DISC1* gene

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ARTICLE INFO

Keywords:
Attention
Working memory
Anxiogenic behavior
Cognitive dysfunction
DISC1

ABSTRACT

In humans, mutations in the *Disrupted-in-schizophrenia 1* (*DISC1*) gene have been related to psychiatric disorders, including symptoms of abnormal cognitive and emotional behaviors. In our previous studies, overexpression of the human *DISC1* gene in rats resulted in schizophrenia-like phenotypes showing deficits in motor learning, impaired cognitive function and dysfunctions of the dopamine system. Here we asked, whether the *DISC1* overexpression affects locomotor activity in the open field (OF), anxiety in the elevated plus-maze (EPM), depression-related behavior in the forced swim test (FST), and attention-like/short-term working-memory in the spontaneous alternation behavior (SAB) in the T-maze in transgenic DISC1 (tgDISC1) rats and littermate controls (WT). TgDISC1 rats showed enhanced anxiety behavior in the EPM and an impairment in attention-like/short-term working-memory in the SAB. However, tgDISC1 animals showed no locomotor impairments or depression-like behavior in the OF and FST. These results suggest that *DISC1* overexpression leads to higher anxiety level and an attention-like/working-memory deficit. These findings may expand the causal role of DISC1 in its contribution to multiple symptom dimensions of psychiatric disorders.

1. Introduction

The *Disrupted-in-schizophrenia 1* (*DISC1*) gene was discovered in a Scottish family and linked to several psychiatric disorders, including schizophrenia, anxiety and depression (Hennah et al., 2003; Millar et al., 2000). While several genetic association studies have confirmed a DISC1 involvement in mental illnesses (Chubb et al., 2008), DISC1 has not emerged from whole genome association studies (GWAS) yet (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Li et al., 2017; Mathieson et al., 2012). Studies have shown that the *DISC1* gene influenced the structure and function in the hippocampus (Callicott et al., 2005; Kaefer et al., 2019) and mediated functions of the prefrontal cortex (Prata et al., 2008), structures critically involved in memory processes and attention (McGarrity et al., 2017; Rossi et al., 2009). Also, individuals with a balanced t(1;11) translocation in a Scottish family had less gyrification in the prefrontal cortex (Thomson et al., 2016). Various DISC1 mutant mouse models have been shown – amongst other phenotypes – to exhibit abnormal social behaviors, including the mutant human *DISC1* gene mouse model (Johnson et al., 2013; Pletnikov et al., 2008), as well as DISC1 mutant mice (Clapcote et al., 2007; Kuroda et al., 2011; Shevelkin et al., 2017). They also exhibited deficient working memory in the T-maze (Clapcote et al., 2007; Koike et al., 2006), spatial memory in the water maze (Pletnikov et al., 2008) and long-term memory in the object-place recognition test (Cui et al., 2016). They displayed hyperactivity in open field tests (Clapcote et al., 2007; Dachtler et al., 2016; Hikida et al., 2007) and were more immobile in the forced swim test (FST) (Clapcote et al., 2007; Gomez-Sintes et al., 2014; Hikida et al., 2007). The current notion of DISC1 is that, while not a major genetic risk factor as defined by GWAS studies, rare mutations may nevertheless lead to behavioral phenotypes in pedigrees. DISC1 has a definite role in neurodevelopment. Its mutation was associated with impaired information processing in the hippocampus (Kakuda et al., 2018). DISC1 is also a clear causative factor for adaptive behavior. Furthermore, the DISC1 protein

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https://doi.org/10.1016/j.pbb.2019.02.005
Received 21 January 2019; Received in revised form 13 February 2019; Accepted 15 February 2019
Available online 16 February 2019
0091-3057/

can undergo posttranslational modifications that impact on its function in behavioral control (Bradshaw and Korth, 2018).

In the current study, we investigated anxiety and cognitive behaviors in the transgenic DISC1 (tgDISC1) rat, which expresses the full-length, non-mutant human *DISC1* gene with polymorphism F607 and C704. This transgene was added with the linearized fragment of the CosSHa.tet vector, and then injected into pronuclei of Sprague Dawley rats (Hamburg et al., 2016; Trossbach et al., 2016). This rat was designed to serve as a model for sporadic schizophrenia and a subset of cases defined by the presence of insoluble DISC1 in the brain. Previous studies on this model found that tgDISC1 rats exhibited alterations in neurotransmitter systems such as a dysregulation of the brain dopamine (DA) system (Dahoun et al., 2017; Trossbach et al., 2016; Uzuneser et al., 2019) and changes in the concentrations of noradrenaline, serotonin and acetylcholine (ACh) in various brain regions (Wang et al., 2017). Furthermore, neuroanatomical changes in the DAergic system and interneuron architecture (Hamburg et al., 2016) and altered long-term memory for objects and attention-related behaviors were described (Wang et al., 2017).

Psychiatric disorders are characterized by behavioral disruption along multiple symptom dimensions (Schumann et al., 2014). As yet, there is little information on affect-related behavior in the tgDISC1 rats. Hence, we addressed the question of whether the *DISC1* gene impacts behavior in the elevated plus-maze test (EPM), which gauges anxiety-related behaviors, and the FST which measures depression-related behavior. In order to provide an independent assessment of locomotor activity and a possible confirmation of the EPM anxiety-related behaviors (Carola et al., 2002), we included the open field test (OF). Cognitive dysfunctions are concomitant with psychiatric disorders (Etkin et al., 2013). Various deficits in cognitive functions have been shown in the tgDISC1 rat, including ultra-short and long-term memory ((Wang et al., 2017). Here we also examined spontaneous alternation behavior (SAB) in the T-maze as a measure of the attention-like behavior and working memory.

Based on the evidence linking the *DISC1* gene to general psychiatric disorders, including schizophrenia, anxiety and depression (Hennah et al., 2003; Millar et al., 2000), we hypothesized that overexpression and/or aggregation of this protein rats would result in behavioral phenotypes related to depression, anxiety and deficits in attention and/or working memory.

2. Material and methods

2.1. Animals

Male Sprague Dawley rats which express the full-length non-mutant human *DISC1* gene and littermate controls (WT) were obtained from the local breeding facility (ZETT, Heinrich Heine University Düsseldorf, Düsseldorf, Germany). Each pair of tgDISC1 and WT rats was randomly selected from different parents. Animals were grouped 2–3 per cage and housed in Makrolon cages (Type IV; 60 × 38 × 20 cm) with standard temperature and humidity conditions under a reversed 12 h light-dark cycle (lights on at 19:00 h). They were allowed over two weeks to adapt to the environment and were handled for 5 min/rat/day for 10 consecutive days before performing a behavioral test, with food and water ad libitum until the end of the experiments (except for several tests described below under Behavioral Testing). The study was approved by the Landesamt für Natur, Umwelt und Verbraucherschutz (LANUV) NRW and followed the European Communities Council Directive (86/609/EEC) and the German Law on the Protection of Animals.

2.2. Apparatus

A black OF made of wood (60 × 60 × 40 cm, l × w × h) was used. Four LED lights were situated above the apparatus, providing illumination of corners and the center (~5 lx). Two geometric symbols were attached to the walls as spatial cues.

A T-maze (Start arm: 50 × 20 × 30 cm, two goal arms: 40 × 15 × 30 cm, l × w × h), made of wood and equipped with three sliding doors was used. The sliding doors were controlled by the experimenter. All surfaces were covered by black waterproof rubber. The apparatus was placed in a dimly-lit room (~3 lx). A high-contrast spatial cue was fixed on the wall facing to the start arm.

The EPM had two open arms (50 × 10 cm), two closed arms (50 × 10 cm) with surrounding walls (40 cm height) and a center platform (10 × 10 cm), and was placed 50 cm high from the floor. Two arms of each type were installed on the opposite sides. Luminous density was 11 lx on the enclosed arms and 3 lx on the open arms which was in accordance to a previous study (Petri et al., 2015).

The apparatus for the FST was a transparent Plexiglas cylinder (46 cm height, 20 cm diameter) containing 30 cm of tap water (26 ± 1 °C). The water was changed between each rat. A camera was fixed on a tripod in front of the apparatus and connected to recording DVD equipment.

The apparatuses were placed in different sound-attenuating rooms with masking noise. They were cleaned with 70% ethanol to eliminate odor cues before each rat was tested. A camera was hung 1.5–2 m above each testing apparatus and connected to a computer and a DVD player for analysis and recording. Data were calculated automatically or manually using Ethovision software 3.1 (Noldus, Wageningen, The Netherlands).

2.3. Behavioral testing

Two batches of animals were used: Batch 1 (n = 12 per group with ages of 9–11 months) was subjected to the OF, SAB test with the T-maze (SABt) and the EPM, while batch 2 (n = 15 per group with ages of 10–11 months) was subjected to the FST. To increase the activity level of the animals as previous studies suggest (Wang et al., 2017; Schulz, 2018), they were food deprived (15 g/rat/day, equivalent to 85% of the normal free-feed diet) for one week before the OF test until completion of the SABt. The animals were placed in a waiting room for about 1 h before the beginning of a behavioral test.

2.3.1. Open field

Animals were placed into the OF for 10 min for measuring locomotor activity. Distance moved (cm), velocity (cm/s), frequency and duration (s) of grooming and rearing, and center time in seconds (s) were recorded.

2.3.2. Spontaneous alternation behavior test with T-maze

Seven days after the OF test, the SABt was performed. The protocol of the SABt followed that of Spowart-Manning and van der Staay (2004) for assessing spatial working memory and attention-like behavior (Hughes, 2004; Spowart-Manning and van der Staay, 2004). The test consists of one forced-choice trial followed by 14 free-choice trials. In the first trial (forced-choice trial), either the left or right goal arm was blocked randomly by its sliding door. The animal was placed into the start arm, and after it entered the open goal arm was returned to the start arm by the experimenter. The animal stayed in the start arm for 5 s with the sliding door closed. Afterward, the “free-choice trials” were begun immediately. During the 14 free-choice trials, the animal was allowed to choose freely between the left and right goal arms after the sliding door of the start arm was opened. Once the animals entered either goal arm, the other goal arm was closed. Then, the animal was returned to the start arm, and the next free-choice trial was started after a 5-s forced stay in the start arm. This procedure was repeated until the final free-choice trial was completed or 30 min had elapsed, whichever event occurred first. A successful alternation was defined as the animal entering one goal arm on one trial, and then entering the opposite goal arm on the next trial. The percent of alternations during the 14 trials was calculated. The number of entries and the time (s) to finish the 14

trials were also recorded.

2.3.3. Elevated plus maze

The EPM is frequently used to gauge levels of anxiety in rats (Walf and Frye, 2007). Over one month after the SABt test, the animals were placed onto the center platform facing an open arm and allowed to explore the maze for 5 min. Arm entries, time spent on the open/closed arms (s), distance moved (cm), latency to an open arm (s) and time spent in the center (s) were computed.

2.3.4. Forced swim test

The FST is an assay for studying depression-like behavior in rodents (Slattery and Cryan, 2012), although this measure has been questioned (Commons et al., 2017). On the first day (pre-test session), the animal was placed in the water for 15 min. Twenty-four hours later, the animal was again placed into the cylinder for 5 min (test session). The parameters were recorded by an experienced observer, but blinded to the experimental design. The predominant behavioral marker was the duration of immobility (the animal floats in the water without struggling and keeps head/nose above the water). The duration of swimming, climbing on the rim, and diving (rat dives to the bottom of the cylinder) were also recorded. After the testing, the animal was dried by a heater.

2.3.5. Statistics

Statistical analysis was performed via IBM SPSS Statistic program (Version 19; IBM, Ehningen, Germany). For the behaviors in the OF, SABt, FST and EPM, independent-sample *t*-tests were applied. One sample *t*-tests were applied to compare the percentages in the SABt with 50% (chance level). Values represented mean ± SEM. The significant level was set as $P < 0.05$.

3. Results

3.1. Open field

There were no significant differences between the WT and tgDISC1 groups in distance moved (cm), velocity (cm/s), frequency and duration (s) of grooming and rearing, and center time ($P > 0.05$; Table 1), as determined via independent-sample *t*-tests. Hence, the WT rats and the tgDISC1 rats performed comparably in locomotor activities and open-field emotionality, as the center time reflects anxiety-related behavior in rodents (Prut and Belzung, 2003).

3.2. Spontaneous alternation behavior in the T-maze

The results from 3 animals/group were lost due to recording problems, leaving n = 9/group for analysis. The number of alternations, total entries, and time to complete the 14 free-choice trials was analyzed via independent-sample *t*-tests. The percentage of alternations after 14 free-choice trials was significantly different from chance level in the WT group, but not the tgDISC1 group (WT: $t(8) = 4.76$, $P = 0.001$; tgDISC1: $t(8) = 1.396$, $P > 0.05$; Fig. 1A). Thus, the tgDISC1 animals were deficient in spontaneous alternation, which assesses attention and working memory (Deacon and Rawlins, 2006; Richman et al., 1986).

There were no significant differences between the WT and tgDISC1 groups in number of alternations, total entries and duration to complete the 14 free-choice trials ($P > 0.05$; Table 2). Thus, both groups exhibited comparable locomotor behavior during this test.

Table 1
Results of open field test. No significant differences between groups were found for any of the parameters. Values are represented as mean ± SEM (n = 12/group).

	WT	tgDISC1
Distance moved (cm)	3251.4 ± 108.2	3057.6 ± 117.9
Velocity (cm/s)	5.4 ± 0.2	5.1 ± 0.2
Grooming frequency	5.0 ± 0.8	5.8 ± 0.6
Grooming duration (s)	48.5 ± 15.4	44.3 ± 7.0
Rearing frequency	48.8 ± 4.2	44.3 ± 3.9
Rearing duration (s)	86.1 ± 8.1	77.4 ± 9.6
Center time (s)	32.1 ± 6.5	34.3 ± 5.1

3.3. Elevated plus-maze

An anxiety-like status was gauged by the extent to which the animals avoid the open arms. The tgDISC1 group spent significantly less time on the open arms compared to the WT group ($t(22) = 2.396$, $P = 0.026$; Fig. 1B). Furthermore, the tgDISC1 group moved less distance on the open arms compared to the WT group ($t(22) = 1.778$, $P = 0.089$; Fig. 1C), although not statistically significant. There were no significant differences between groups in the measures of activities in the closed arms (entries, duration and distance moved), latency of first time into an open arm, total entries, total distance, time spent in the center ($P > 0.05$; Table 3). Hence, the difference in time spent in the open arms is unlikely to be confounded by changes in locomotor behaviors. These results suggest that the expression of the *DISC1* gene increased the anxiety/fear level of rats in the EPM test.

3.4. Forced swim test

There were no differences between groups in their behaviors during the first exposure in the FST ($P > 0.05$; Table 4). There were also no significant differences between groups during the second exposure (test session) of the FST ($P > 0.05$). A depression-like status in the animals would be expected to increase the duration of immobility. The animals exhibited comparable durations of immobility, indicating that the overexpression of *DISC1* gene is not involved in depression-related behavior in the FST, at least under the present conditions.

4. Discussion

In the current study, we provide behavioral evidence showing that overexpression and misassembly of the DISC1 protein resulted in (a) a higher anxiety level, as assessed with the EPM, and (b) an attention-related deficit, as measured by the spontaneous alternation test. This deficit can also be interpreted as a short-term working-memory deficit (Spowart-Manning and van der Staay, 2004). No evidence was found for (c) depression-like behavior in the FST, and for (d) an influence on activity measures in the OF.

The EPM is frequently used to measure levels of anxiety in rats (Walf and Frye, 2007), as, e.g., animals were found to avoid the open arms after receiving anxiogenic drug treatment (Pellow and File, 1986). In the open arms of the EPM in the present study, the tgDISC1 rats spent significantly less time and tended to move a shorter distance, suggestive of a higher anxiety level. These results are consistent with the anxiogenic phenotype found in mice with a D453G mutation in DISC1 (Dachtler et al., 2016), but not with the finding that mice, lacking exons 2 and 3 of the *DISC*1 gene, spent more time in the open arms of the EPM (Kuroda et al., 2011). It should be emphasized that while the mouse models reflect mutant DISC1 *genes*, the tgDISC1 rat was conceived to reflect aberrant DISC1 *proteostasis* in sporadic, i.e. non-mutant behavioral disorders (Trossbach et al., 2016), thus possibly explaining such differences by differences in loss-of-function as well as possible gain of function phenotypes, particularly in the case of aberrant DISC1 proteostasis. The impact of DISC1 on emotional behavior deserves further study. Nonetheless, the above evidence suggests that the DISC1 protein is associated with anxiety.

The level of anxiety can interact with practically all other possible behavioral measures. For example, high levels of anxiety can influenced

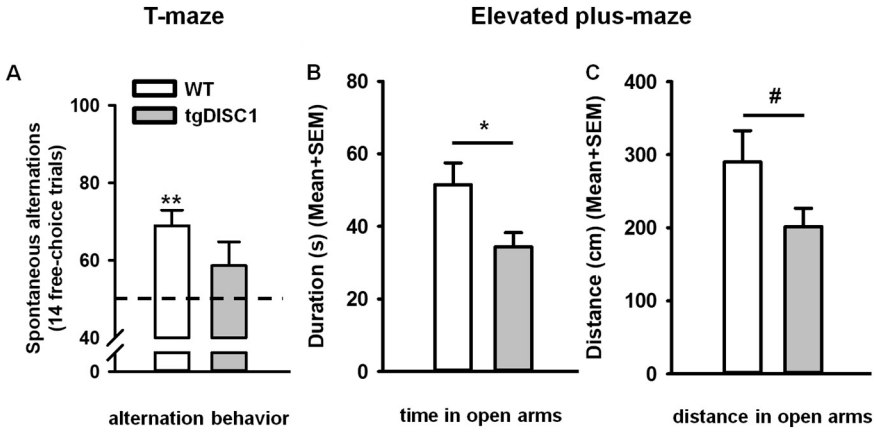

Fig. 1. TgDISC1 animals show deficits in attention/working memory and enhanced anxiety. (A) Percent of alternations during 14 free-choice trials in the T-maze compared to 50% (chance level, dashed line) (**$P < 0.01$, n = 9/group) (B) Time spent on open arms of the elevated plus maze (*$P < 0.05$, n = 12/group). (C) Distance moved on open arms (#$P = 0.089$, n = 12/group). Values presented as mean + SEM (WT, wild type).

Table 2
Results of locomotor behaviors in the spontaneous alternation behavior test in the T-maze (n = 9/group). Values are presented as mean ± SEM.

	WT	tgDISC1
Percent of alternations (14 free-choice trials)	69.0 ± 4.0**	59.0 ± 6.1
No of alternation	7.8 ± 0.7	5.8 ± 1.2
Total entries	11.3 ± 0.9	9.7 ± 1.5
Duration (s)	1459.8 ± 171.1	1570.8 ± 116.2

** $P < 0.01$.

Table 3
Results of elevated plus-maze test. Values are presented as mean ± SEM. N = 12/group.

	WT	tgDISC1
Entries into closed arms	18.3 ± 1.1	17.8 ± 1.8
Time spent in closed arms (s)	194.3 ± 9.8	208.0 ± 8.4
Distance moved in closed arms (cm)	1401.5 ± 69.1	1466.5 ± 86.5
Entries into open arms	6.7 ± 0.8	6.8 ± 1.0
Time spent in open arms (s)	51.5 ± 6.0	34.4 ± 3.9*
Distance moved in open arms (cm)	290.1 ± 42.9	201.5 ± 25.3#
Latency first entry into open arm (s)	7.2 ± 3.3	5.5 ± 2.4
Total entries	24.9 ± 1.7	24.6 ± 2.1
Total distance moved (cm)	1964.7 ± 117.0	1923.8 ± 102.8
Time spent in center (s)	54.2 ± 7.7	57.6 ± 6.9

* $P < 0.05$.
# $P = 0.089$.

Table 4
Duration of behaviors on day 1 (15 min test) and day 2 (5 min test) in the forced swim test. There were no significant differences between the WT and tgDISC1 groups in any of the parameters measured. Values are presented as mean ± SEM seconds. N = 15/group.

		WT	tgDISC1
Day 1	Swimming	187.5 ± 24.3	191.8 ± 16.3
	Climbing	86.6 ± 7.3	72.2 ± 6.9
	Immobility	604.0 ± 28.8	615.3 ± 20.8
	Diving	11.2 ± 4.1	10.6 ± 3.2
Day 2	Swimming	94.1 ± 16.1	104.9 ± 15.9
	Climbing	29.8 ± 4.7	30.1 ± 3.5
	Immobility	172.0 ± 15.6	159.3 ± 16.0
	Diving	0.1 ± 0.1	0.6 ± 0.5

the outcome of object exploration and SAB tests (Hughes, 2004). They reduce the motivation of animals to explore environmental stimuli. Thus, a higher level of anxiety could account for other behavioral deficits we have found in the tgDISC1 rat. This may include the attention-deficit/working-memory measures we report here with the SAB test, and the object-recognition measure with a very short interval between exposure and test trials, which can also be considered a deficit in ultra-short-term memory (Wang et al., 2017). It may furthermore affect measures with a long-term memory deficit in the object-recognition test when the inter-trial interval is 24 h (Wang et al., 2017), and deficits in performance on the rota-rod (Trossbach et al., 2016).

The deficient alternation behavior in the T-maze found in the tgDISC1 rat is compatible with the deficient attention-like behavior found with the novel-object preference paradigm for ultra-short-term memory (Wang et al., 2017). Over trials in the T-maze, rodents tend to choose the arm which was not recently visited and, thus, alternate between the left and right arm of the maze. This behavior is likely to be related to the tendency for rodents to prefer to explore novel places over familiar ones and may reflect a foraging strategy. In order to alternate effectively in this choice situation, the animal must establish a memory for the arm that was visited most recently, i.e. employ spatial working-memory. Depending on the interval between trials one can gauge short- or longer-term working memory with this procedure. Thus, a deficit in SAB may be a result of a failure in an aspect of establishing, consolidating or retrieving the memory for the last-chosen side of the maze. However, the deficit could just as well be due to failure to attend effectively to aspects of the task, which could either (a) preclude the required information to be available for memory to be established, consolidated, or retrieved, or (b) lead to the animal being "distracted" during the choosing or performing the behavior. Thus, a deficit in SAB (and in other working-memory tasks) cannot differentiate between attention-related vs memory-related causality. Consequently, alternation in the T-maze test has been used to gauge spatial working memory as well as attention-related behavior (Hughes, 2004; Spowart-Manning and van der Staay, 2004). Accordingly, the behavioral deficiencies we have found in the tgDISC1 rat in novel-object preference with short (zero) and long (24 h) inter-trial intervals (Wang et al., 2017) and in alternation behavior in the T-maze reported here can be interpreted either in terms of disruption of attention-related processes or of ultra-short and long-term working memory mechanisms.

The lack of significant differences between the tgDISC1 and WT groups in the measures of immobility and climbing behavior in the FST fails to confirm our hypothesis, based on the linkage between *DISC1* and general mental disorders (Hennah et al., 2003; Millar et al., 2000), that overexpression and/or aggregation of the *DISC1* gene would induce a depression-related phenotype. However, it should be noted that the FST has been questioned with regard to its validity as a model of depression (Commons et al., 2017). Further studies with different depression models are warranted to clarify the impact of overexpression/aggregation of the *DISC1* gene on depression-related behavior.

The prefrontal cortex is a key brain region involved in the processing of attention, working memory and emotion (Etkin et al., 2011; Miller and Cohen, 2001). Interestingly, substantial evidence has

indicated that the *DISC1* gene is associated with the prefrontal cortex functions. For instance, the prefrontal cortical neurons were deficient in dendrites and decreased in spine density in the DISC1 mutant mice (Lee et al., 2011) and reduced density of prefrontal GABAergic neurons was found in the DISC1 knockout mouse (Umeda et al., 2016). Hypometabolism of the prefrontal cortex was imaged in mice expressing a truncated DISC1 gene (Dawson et al., 2015). In addition, mice expressing a putative dominant-negative DISC1 performed defectively in reversal learning and reinforcement devaluation that are prefrontal cortex-related (Johnson et al., 2013). Furthermore, normal human participants who carry Ser704Cys, a common missense variant of DISC1 gene, showed less activation in the prefrontal cortex during spatial working memory processing, while in patients with anxiety disorders higher prefrontal activation was found, implicating synergic effects of states of anxiety, functions of prefrontal cortex and Ser704Cys (Opmeer et al., 2015). The overexpression of the *DISC1* gene could modulate the prefrontal cortex and its related connected circuits and underlie the behavioral phenotypes we observed here. This is also consistent with our previous findings of tgDISC1 rats displaying an impairment of attention-like behaviors or ultra-short/working memory (Wang et al., 2017).

A number of neuroanatomical and biochemical changes have been reported in the tgDISC1 rat. The most prevalent neurotransmitter-related phenotypes relate to central DA metabolism, receptors and levels. Overexpression of *DISC1* decreased the density of DAergic neurons in the substantia nigra and DAergic fibers in the striatum (Hamburg et al., 2016). It also affected presynaptic DA function by decreasing levels of DA and increasing DA transporter levels. Furthermore, it led to a postsynaptic DA dysregulation, as it increased DA D2 high-affinity receptor levels in the striatum (Trossbach et al., 2016; Uzuneser et al. submitted). However, a recent study suggested also cell-type specific interactions of DISC1 relevant to psychiatric disease endophenotypes (Winkinson et al., 2019). The DISC1-DA D2 receptor interaction has been shown to be critical in behaviors. Uncoupling this interaction ameliorated the deficits of latent inhibition in the DISC1-L100P mutant mice and facilitated latent inhibition and working memory measured in the T-maze in normal mice (Lipina et al., 2018).

The deficits in attention/working memory and higher anxiety levels in the tgDISC1 rats could be due to dysfunctioning of DAergic processes, given that DA neurotransmission is critical for learning and memory, motivation and emotion. For example, attention accuracy and working memory can be modulated by DA D1 receptors in the prefrontal cortex (Chudasama and Robbins, 2004). Fear extinction learning can be dependent on the ventral tegmental area DA circuits projecting to the prefrontal cortex and nucleus accumbens (Luo et al., 2018). Furthermore, administration of intranasal DA reverse both the ultra-short-term memory/attention-like and long-term memory deficits in the tgDISC1 rat, which suggests that the lower levels of DA found in the striatum and amygdala may be responsible for the behavioral deficits (Wang et al., 2017). Abnormal DA levels were detected in various DISC1 models (Jaaro-Peled et al., 2013; Niwa et al., 2010), together with deficit of long-term memory in the novel object recognition test (Niwa et al., 2010) and impoverished motivation in the progressive ratio test (Johnson et al., 2013).

Alternatively, the reduced ACh levels found in the hippocampus, amygdala, nucleus accumbens and dorsal striatum of the tgDISC1 rat (Wang et al., 2017) could also contribute to its behavioral phenotypes. ACh has long been known to underlie both, attention-related processes involved in orienting to novel and conditioned stimuli (Gritton et al., 2016; Pepeu and Giovannini, 2004), as well as working memory (Eckart et al., 2016; Klinkenberg et al., 2011). Furthermore, both cholinergic and DAergic processes interact closely in both attention and working memory (Klinkenberg et al., 2011; Stormer et al., 2012).

The dysregulations of DA, serotonin, noradrenalin and ACh levels in the amygdala of tgDISC1 rat (Wang et al., 2017) could be involved in the present anxiety states. The amygdala, through the type 1 neuron of the basolateral amygdala (Wang et al., 2011), is a key region to mediate anxiety. Multiple regions receive amygdala projections (Lago et al., 2017), of which two regions exhibited altered DA levels in the tgDISC1 rats (Trossbach et al., 2016; Wang et al., 2017). The striatum is incorporated in a circuit receiving information from amygdala and cortex and being interconnected with hippocampus and bed nucleus of the stria terminalis, which are regions related to the anxiety network (Lago et al., 2017). The anxiety-related behaviors exhibited by the tgDISC1 rats may have resulted from the imbalance in the DAergic system within the anxiety network. However, these results are different to those from a previous study. Mice lacking exons 2 and 3 of the *DISC1* gene spent more time in the open arms of the EPM (Kuroda et al., 2011). In the *Disc1* point mutation, L100P, mice traveled a longer distance in the light chamber and frequently transited between the chambers of the Light/Dark box (Shoji et al., 2012). As pointed out above, the tgDISC1 rat is not a model for genetic causes of aberrant behavior but one for aberrant proteostasis (Bradshaw and Korth, 2018). The difference in anxiety behaviors between those genetic studies and the present studies may result from these conceptual differences in designing the animal models and point to the variety of behavioral phenotypes that a dysfunctional DISC1 protein may lead to. Gender may also be a crucial factor, as a recent study revealed significant sex differences in DISC1 effects alone and DISC1- environmental interactions on behavior (Uzuneser et al., 2019). In that, research of the emotional involvement of DISC1 warrants further investigations.

5. Conclusions

The behavioral characterization of the tgDISC1 rat indicates that overexpression and/or aggregation of the DISC1 protein impacts a diversity of behavioral processes, including measures of emotionality and of attention and working memory. These behavioral changes can be construed to model key symptom dimensions of psychiatric disorders. However, at this point, they are difficult to reconcile with typical depression-like phenotypes.

Funding

MAdSS was supported by a Heisenberg Fellowship SO 1032/5-1, MAdSS, CK and BF were supported by EU-FP7 MC-ITN IN-SENS #607616, MAdSS, CK and ALW by a Grant of the Medical Faculty of the Heinrich Heine University Düsseldorf (#9772569).

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

Bradshaw, N.J., Korth, C., 2018. Protein misassembly and aggregation as potential convergence points for non-genetic causes of chronic mental illness. Mol. Psychiatry. https://doi.org/10.1038/s41380-018-0133-2.

Callicott, J.H., Straub, R.E., Pezawas, L., Egan, M.F., Mattay, V.S., Hariri, A.R., Verchinski, B.A., Meyer-Lindenberg, A., Balkissoon, R., Kolachana, B., Goldberg, T.E., Weinberger, D.R., 2005. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 102 (24), 8627–8632.

Carola, V., D'Olimpio, F., Brunamonti, E., Mangia, F., Renzi, P., 2002. Evaluation of the elevated plus-maze and open-field tests for the assessment of anxiety-related behaviour in inbred mice. Behav. Brain Res. 134 (1–2), 49–57.

Chubb, J.E., Bradshaw, N.J., Soares, D.C., Porteous, D.J., Millar, J.K., 2008. The DISC locus in psychiatric illness. Mol. Psychiatry 13 (1), 36–64.

Chudasama, Y., Robbins, T.W., 2004. Dopaminergic modulation of visual attention and working memory in the rodent prefrontal cortex. Neuropsychopharmacol. 29 (9), 1628–1636.

Clapcote, S.J., Lipina, T.V., Millar, J.K., Mackie, S., Christie, S., Ogawa, F., Lerch, J.P., Trimble, K., Uchiyama, M., Sakuraba, Y., Kaneda, H., Shiroishi, T., Houslay, M.D., Henkelman, R.M., Sled, J.G., Gondo, Y., Porteous, D.J., Roder, J.C., 2007. Behavioral phenotypes of Disc1 missense mutations in mice. Neuron 54 (3), 387–402.

Commons, K.G., Cholanians, A.B., Babb, J.A., Ehlinger, D.G., 2017. The rodent forced swim test measures stress-coping strategy, not depression-like behavior. ACS Chem. Neurosci. 8 (5), 955–960.

Cui, L., Sun, W., Yu, M., Li, N., Guo, L., Gu, H., Zhou, Y., 2016. Disrupted-in-schizophrenia1 (DISC1) L100P mutation alters synaptic transmission and plasticity in the hippocampus and causes recognition memory deficits. Mol. Brain 9 (1), 89.
Dachtler, J., Elliott, C., Rodgers, R.J., Baillie, G.S., Clapcote, S.J., 2016. Missense mutation in DISC1 C-terminal coiled-coil has GSK3beta signaling and sex-dependent behavioral effects in mice. Sci. Rep. 6, 18748.
Dahoun, T., Trossbach, S.V., Brandon, N.J., Korth, C., Howes, O.D., 2017. The impact of Disrupted-in-Schizophrenia 1 (DISC1) on the dopaminergic system: a systematic review. Transl. Psychiatry 7 (1), e1015.
Dawson, N., Kurihara, M., Thomson, D.M., Winchester, C.L., McVie, A., Hedde, J.R., Randall, A.D., Shen, S., Seymour, P.A., Hughes, Z.A., Dunlop, J., Brown, J.T., Brandon, N.J., Morris, B.J., Pratt, J.A., 2015. Altered functional brain network connectivity and glutamate system function in transgenic mice expressing truncated Disrupted-in-Schizophrenia 1. Transl. Psychiatry 5, e569.
Deacon, R.M., Rawlins, J.N., 2006. T-maze alternation in the rodent. Nat. Protoc. 1 (1), 7–12.
Eckart, C., Wozniak-Kwasniewska, A., Herweg, N.A., Fuentemilla, L., Bunzeck, N., 2016. Acetylcholine modulates human working memory and subsequent familiarity based recognition via alpha oscillations. NeuroImage 137, 61–69.
Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn. Sci. 15 (2), 85–93.
Etkin, A., Gyurak, A., O'Hara, R., 2013. A neurobiological approach to the cognitive deficits of psychiatric disorders. Dial. Clin. Neurosci. 15 (4), 419–429.
Gomez-Sintes, R., Kvajo, M., Gogos, J.A., Lucas, J.J., 2014. Mice with a naturally occurring DISC1 mutation display a broad spectrum of behaviors associated to psychiatric disorders. Front. Behav. Neurosci. 8, 253.
Gritton, H.J., Howe, W.M., Mallory, C.S., Hetrick, V.L., Berke, J.D., Sarter, M., 2016. Cortical cholinergic signaling controls the detection of cues. Proc. Natl. Acad. Sci. U. S. A. 113 (8), E1089–E1097.
Hamburg, H., Trossbach, S.V., Bader, V., Chwiesko, C., Kipar, A., Sauvage, M., Crum, W.R., Vernon, A.C., Bidmon, H.J., Korth, C., 2016. Simultaneous effects on parvalbumin-positive interneuron and dopaminergic system development in a transgenic rat model for sporadic schizophrenia. Sci. Rep. 6, 34946.
Hennah, W., Varilo, T., Kestila, M., Paunio, T., Arajarvi, R., Haukka, J., Parker, A., Martin, R., Levitzky, S., Partonen, T., Meyer, J., Lonnqvist, J., Peltonen, L., Ekelund, J., 2003. Haplotype transmission analysis provides evidence of association for DISC1 to schizophrenia and suggests sex-dependent effects. Hum. Mol. Genet. 12 (23), 3151–3159.
Hikida, T., Jaaro-Peled, H., Seshadri, S., Oishi, K., Hookway, C., Kong, S., Wu, D., Xue, R., Andrade, M., Tankou, S., Mori, S., Gallagher, M., Ishizuka, K., Pletnikov, M., Kida, S., Sawa, A., 2007. Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. Proc. Natl. Acad. Sci. U. S. A. 104 (36), 14501–14506.
Hughes, R.N., 2004. The value of spontaneous alternation behavior (SAB) as a test of retention in pharmacological investigations of memory. Neurosci. Biobehav. Rev. 28 (5), 497–505.
Jaaro-Peled, H., Niwa, M., Foss, C.A., Murai, R., de Los Reyes, S., Kamiya, A., Mateo, Y., O'Donnell, P., Cascella, N.G., Nabeshima, T., Guilarte, T.R., Pomper, M.G., Sawa, A., 2013. Subcortical dopaminergic deficits in a DISC1 mutant model: a study in direct reference to human molecular brain imaging. Hum. Mol. Genet. 22 (8), 1574–1580.
Johnson, A.W., Jaaro-Peled, H., Shahani, N., Sedlak, T.W., Zoubovsky, S., Burruss, D., Emiliani, F., Sawa, A., Gallagher, M., 2013. Cognitive and motivational deficits together with prefrontal oxidative stress in a mouse model for neuropsychiatric illness. Proc. Natl. Acad. Sci. U. S. A. 110 (30), 12462–12467.
Kaefer, K., Malagon-Vina, H., Dickerson, D.D., O'Neill, J., Trossbach, S.V., Korth, C., Csicsvari, J., 2019. Disrupted-in-schizophrenia 1 overexpression disrupts hippocampal coding and oscillatory synchronization. Hippocampus. https://doi.org/10.1002/hipo.23076.
Kakuda, K., Niwa, A., Honda, R., Yamaguchi, K.I., Tomita, H., Nojebuzzaman, M., Hara, A., Goto, Y., Osawa, M., Kuwata, K., 2018. A DISC1 point mutation promotes oligomerization and impairs information processing in a mouse model of schizophrenia. J. Biochem. https://doi.org/10.1093/jb/mvy116.
Klinkenberg, I., Sambeth, A., Blokland, A., 2011. Acetylcholine and attention. Behav. Brain Res. 221 (2), 430–442.
Koike, H., Arguello, P.A., Kvajo, M., Karayiorgou, M., Gogos, J.A., 2006. Disc1 is mutated in the 129S6/SvEv strain and modulates working memory in mice. Proc. Natl. Acad. Sci. U. S. A. 103 (10), 3693–3697.
Kuroda, K., Yamada, S., Tanaka, M., Iizuka, M., Yano, H., Mori, D., Tsuboi, D., Nishioka, T., Namba, T., Iizuka, Y., Kubota, S., Nagai, T., Ibi, D., Wang, R., Enomoto, A., Isotani-Sakakibara, M., Asai, N., Kimura, K., Kiyonari, H., Abe, T., Mizoguchi, A., Sokabe, M., Takahashi, M., Yamada, K., Kaibuchi, K., 2011. Behavioral alterations associated with targeted disruption of exons 2 and 3 of the Disc1 gene in the mouse. Hum. Mol. Genet. 20 (23), 4666–4683.
Lago, T., Davis, A., Grillon, C., Ernst, M., 2017. Striatum on the anxiety map: small detours into adolescence. Brain Res. 1654 (Pt B), 177–184.
Lee, F.H., Fadel, M.P., Preston-Maher, K., Cordes, S.P., Clapcote, S.J., Price, D.J., Roder, J.C., Wong, A.H., 2011. Disc1 point mutations in mice affect development of the cerebral cortex. J. Neurosci. 31 (9), 3197–3206.
Li, Z., Chen, J., Yu, H., He, L., Xu, Y., Zhang, D., Yi, Q., Li, C., Li, X., Shen, J., Song, Z., Ji, W., Wang, M., Zhou, J., Chen, B., Liu, Y., Wang, J., Wang, P., Yang, P., Wang, Q., Feng, G., Liu, B., Sun, W., Li, B., He, G., Li, W., Wan, C., Xu, Q., Wen, Z., Liu, K., Huang, F., Ji, J., Ripke, S., Yue, W., Sullivan, P.F., O'Donovan, M.C., Shi, Y., 2017. Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. Nat. Genet. 49 (11), 1576–1583.
Lipina, T.V., Beregovoy, N.A., Tkachenko, A.A., Petrova, E.S., Starostina, M.V., Zhou, Q., Li, S., 2018. Uncoupling DISC1 × D2R protein-protein interactions facilitates latent inhibition in Disc1-L100P animal model of schizophrenia and enhances synaptic plasticity via D2 receptors. Front. Synap. Neurosci. https://doi.org/10.3389/fnsyn.2018.00031.
Luo, R., Uematsu, A., Weitemier, A., Aquili, L., Koivumaa, J., McHugh, T.J., Johansen, J.P., 2018. A dopaminergic switch for fear to safety transitions. Nat. Commun. 9, 2483. https://doi.org/10.1038/s41467-018-04784-7.
Mathieson, I., Munafo, M.R., Flint, J., 2012. Meta-analysis indicates that common variants at the DISC1 locus are not associated with schizophrenia. Mol. Psychiatry 17 (6), 634–641.
McGarrity, S., Mason, R., Fone, K.C., Pezze, M., Bast, T., 2017. Hippocampal neural disinhibition causes attentional and memory deficits. Cereb. Cortex 27 (9), 4447–4462.
Millar, J.K., Wilson-Annan, J.C., Anderson, S., Christie, S., Taylor, M.S., Semple, C.A., Devon, R.S., St Clair, D.M., Muir, W.J., Blackwood, D.H., Porteous, D.J., 2000. Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum. Mol. Gen. 9 (9), 1415–1423.
Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Ann. Rev. Neurosci. 24, 167–202.
Niwa, M., Kamiya, A., Murai, R., Kubo, K., Gruber, A.J., Tomita, K., Lu, L., Tomisato, S., Jaaro-Peled, H., Seshadri, S., Hiyama, H., Huang, B., Kohda, K., Noda, Y., O'Donnell, P., Nakajima, K., Sawa, A., Nabeshima, T., 2010. Knockdown of DISC1 by in utero gene transfer disturbs postnatal dopaminergic maturation in the frontal cortex and leads to adult behavioral deficits. Neuron 65 (4), 480–489.
Opmeer, E.M., van Tol, M.J., Kortekaas, R., van der Wee, N.J., Woudstra, S., van Buchem, M.A., Penninx, B.W., Veltman, D.J., Aleman, A., 2015. DISC1 gene and affective psychopathology: a combined structural and functional MRI study. J. Psychiatr. Res. 61, 150–157.
Pellow, S., File, S.E., 1986. Anxiolytic and anxiogenic drug effects on exploratory activity in an elevated plus-maze: a novel test of anxiety in the rat. Pharmacol. Biochem. Behav. 24 (3), 525–529.
Pepeu, G., Giovannini, M.G., 2004. Changes in acetylcholine extracellular levels during cognitive processes. Learn. Mem. 11 (1), 21–27.
Petri, D., de Souza Silva, M.A., Chao, O.Y., Schnitzler, A., Huston, J.P., 2015. Serotonergic interaction between medial prefrontal cortex and mesotelencephalic DA system underlies cognitive and affective deficits in hemiparkinsonian rats. Neuroscience 307, 51–63.
Pletnikov, M.V., Ayhan, Y., Nikolskaia, O., Xu, Y., Ovanesov, M.V., Huang, H., Mori, S., Moran, T.H., Ross, C.A., 2008. Inducible expression of mutant human DISC1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. Mol. Psychiatry 13 (2), 173–186 (115).
Prata, D.P., Mechelli, A., Fu, C.H., Picchioni, M., Kane, F., Kalidindi, S., McDonald, C., Kravariti, E., Toulopoulou, T., Miorelli, A., Murray, R., Collier, D.A., McGuire, P.K., 2008. Effect of disrupted-in-schizophrenia-1 on pre-frontal cortical function. Mol. Psychiatry 13 (10), 915–917 (909).
Prut, L., Belzung, C., 2003. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. Eur. J. Pharmacol. 463 (1–3), 3–33.
Richman, C.L., Dember, W.N., Kim, P., 1986. Spontaneous alternation behavior in animals: a review. Curr. Psychol. Res. Rev. 5 (4), 358–391.
Rossi, A.F., Pessoa, L., Desimone, R., Ungerleider, L.G., 2009. The prefrontal cortex and the executive control of attention. Exp. Brain Res. 192 (3), 489–497.
Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511 (7510), 421–427.
Schulz, D., 2018. Acute food deprivation separates motor-activating from anxiolytic effects of caffeine in a rat open field test model. Behav. Pharmacol. 29 (6), 543–546.
Schumann, G., Binder, E.B., Holte, A., de Kloet, E.R., Oedegaard, K.J., Robbins, T.W., Walker-Tilley, T.R., Bitter, I., Brown, V.J., Buitelaar, J., Ciccocioppo, R., Cools, R., Escera, C., Fleischhacker, W., Flor, H., Frith, C.D., Heinz, A., Johnsen, E., Kirschbaum, C., Klingberg, T., Lesch, K.P., Lewis, S., Maier, W., Mann, K., Martinot, J.L., Meyer-Lindenberg, A., Muller, C.P., Muller, W.E., Nutt, D.J., Persico, A., Perugi, G., Pessiglione, M., Preuss, U.W., Roiser, J.P., Rossini, P.M., Rybakowski, J.K., Sandi, C., Stephan, K.E., Undurraga, J., Vieta, E., van der Wee, N., Wykes, T., Haro, J.M., Wittchen, H.U., 2014. Stratified medicine for mental disorders. Eur. Neuropsychopharmacol. 24 (1), 5–50.
Shevelkin, A.V., Terrillion, C.E., Abazyan, B.N., Kajstura, T.J., Jouroukhin, Y.A., Rudow, G.L., Troncoso, J.C., Linden, D.J., Pletnikov, M.V., 2017. Expression of mutant DISC1 in Purkinje cells increases their spontaneous activity and impairs cognitive and social behaviors in mice. Neurobiol. Dis. 103, 144–153.
Shoji, H., Toyama, K., Takamiya, Y., Wakana, S., Gondo, Y., Miyakawa, T., 2012. Comprehensive behavioral analysis of ENU-induced Disc1-Q31L and -L100P mutant mice. BMC Res. Notes 5, 108.
Slattery, D.A., Cryan, J.F., 2012. Using the rat forced swim test to assess antidepressant-like activity in rodents. Nat. Protoc. 7 (6), 1009–1014.
Spowart-Manning, L., van der Staay, F.J., 2004. The T-maze continuous alternation task for assessing the effects of putative cognition enhancers in the mouse. Behav. Brain Res. 151 (1–2), 37–46.
Stormer, V.S., Passow, S., Biesenack, J., Li, S.C., 2012. Dopaminergic and cholinergic modulations of visual-spatial attention and working memory: insights from molecular genetic research and implications for adult cognitive development. Dev. Psychol. 48 (3), 875–889.
Thomson, P.A., Duff, B., Blackwood, D.H., Romaniuk, L., Watson, A., Whalley, H.C., Li, X., Dauvermann, M.R., Moorhead, T.W., Bois, C., Ryan, N.M., Redpath, H., Hall, L., Morris, S.W., van Beek, E.J., Roberts, N., Porteous, D.J., St Clair, D., Whitcher, B., Dunlop, J., Brandon, N.J., Hughes, Z.A., Hall, J., McIntosh, A., Lawrie, S.M., 2016. Balanced translocation linked to psychiatric disorder, glutamate, and cortical structure/function. NPJ Schizophr. 2, 16024.
Trossbach, S.V., Bader, V., Hecher, L., Pum, M.E., Masoud, S.T., Prikulis, I., Schable, S., de

Souza Silva, M.A., Su, P., Boulat, B., Chwiesko, C., Poschmann, G., Stuhler, K., Lohr, K.M., Stout, K.A., Oskamp, A., Godsave, S.F., Muller-Schiffmann, A., Bilzer, T., Steiner, H., Peters, P.J., Bauer, A., Sauvage, M., Ramsey, A.J., Miller, G.W., Liu, F., Seeman, P., Brandon, N.J., Huston, J.P., Korth, C., 2016. Misassembly of full-length disrupted-in-schizophrenia 1 protein is linked to altered dopamine homeostasis and behavioral deficits. Mol. Psychiatry 21 (11), 1561–1572.

Umeda, K., Iritani, S., Fujishiro, H., Sekiguchi, H., Torii, Y., Habuchi, C., Kuroda, K., Kaibuchi, K., Ozaki, N., 2016. Immunohistochemical evaluation of the GABAergic neuronal system in the prefrontal cortex of a DISC1 knockout mouse model of schizophrenia. Synapse 70 (12), 508–518.

Uzuneser, T.C., Speidel, J., Kogias, G., Wang, A.L., de Souza Silva, M.A., Huston, J.P., von Hörsten, S., Kornhuber, J., Korth, C., Müller, C.P., 2019. Disrupted-in-schizophrenia 1 (DISC1) Mutation and Juvenile Immune Activation Cause Gender Specific Schizophrenia-like Symptoms in Rats. Submitted.

Walf, A.A., Frye, C.A., 2007. The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. Nat. Protoc. 2 (2), 322–328.

Wang, D.V., Wang, F., Liu, J., Zhang, L., Wang, Z., Lin, L., 2011. Neurons in the amygdala with response-selectivity for anxiety in two ethologically based tests. PLoS One 6 (4), e18739.

Wang, A.L., Fazari, B., Chao, O.Y., Nikolaus, S., Trossbach, S.V., Korth, C., Sialana, F.J., Lubec, G., Huston, J.P., Mattern, C., de Souza Silva, M.A., 2017. Intra-nasal dopamine alleviates cognitive deficits in tgDISC1 rats which overexpress the human DISC1 gene. Neurobiol. Learn. Mem. 146, 12–20.

Winkinson, B., Evgrafov, O.V., Zheng, D., Hartel, N., Knowless, J.A., Graham, N.A., Ichida, J.K., Coba, M.P., 2019. Endogenous cell type-specific disrupted in schizophrenia 1 interactomes reveal protein networks associated with neurodevelopmental disorders. Biol. Psychiatry 85 (4), 305–316.