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Wisket rat model of schizophrenia: Impaired motivation and, altered brain structure, but no anhedonia

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ABSTRACT

It is well-known that the poor cognition in schizophrenia is strongly linked to negative symptoms, including motivational deficit, which due to, at least partially, anhedonia. The goal of this study was to explore whether the schizophrenia-like Wisket animals with impaired motivation (obtained in the reward-based hole-board test), also show decreased hedonic behavior (investigated with the sucrose preference test). While neurochemical alterations of different neurotransmitter systems have been detected in the Wisket rats, no research has been performed on structural changes. Therefore, our additional aim was to reveal potential neuroanatomical and structural alterations in different brain regions in these rats.

The rats showed decreased general motor activity (locomotion, rearing and exploration) and impaired task performance in the hole-board test compared to the controls, whereas no significant difference was observed in the sucrose preference test between the groups. The Wisket rats exhibited a significant decrease in the frontal cortical thickness and the hippocampal area, and moderate increases in the lateral ventricles and cell disarray in the CA3 subfield of hippocampus.

To our knowledge, this is the first study to investigate the hedonic behavior and neuroanatomical alterations in a multi-hit animal model of schizophrenia. The results obtained in the sucrose preference test suggest that anhedonic behavior might not be involved in the impaired motivation obtained in the hole-board test. The neuropathological changes agree with findings obtained in patients with schizophrenia, which refine the high face validity of the Wisket model.

1. Introduction

Schizophrenia is a chronic neurodevelopmental disorder, that affects approximately 1% of the world population. The symptoms can be categorized into three major groups: the positive, negative and cognitive signs [1]. The negative symptoms of schizophrenia, particularly the lack of motivation, have been linked to poor cognition and represent an unmet therapeutic target [2–5]. In patients with schizophrenia patients, the motivation to look for pleasurable experiences and make appropriate decisions is disturbed [6–9]. The inability to experience pleasure is called anhedonia and is a core feature of reward deficits [10–12]. To actively obtain a reward a motivational drive is required, which is influenced by the hedonic value of the reward [10,11,13,14]. The consumption of a reward (e.g., palatable food) produces hedonic consequences, which initiate learning processes [15]. Although some data suggest the presence of anhedonia in patients with schizophrenia [16–19], a growing body of evidence proposes that patients have deficits in motivational drive without altered hedonic components [12,17,20–23].

Translational research depends on the relevance of animal models replicating the human disease and investigations of the action mechanism of different potentially beneficial drugs for the treatment of schizophrenia. We developed a chronic, three-hit rat model (named Wisket) from the **W**istar strain by combining developmental, pharmacological, and genetic factors. Post-weaning **IS**olation rearing for 4 weeks (1st hit), subchronic **KET**amine treatment (2nd hit; intraperitoneally: 30 mg/kg, 4 ml/kg body weight, daily, 5 times/week, 15 injections in total) and selective breeding (3rd hit; based on behavioral phenotype obtained with tail-flick, prepulse inhibition and cognitive

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Abbreviations

CA1,3	cornu ammunis
CG	cingular cortex
fmi	forceps minor
HB	hole-board
IL	infralimbic cortex
LV	lateral ventricles
M	motor cortex
PRh	perirhinal cortex
PRL	prelimbic cortex
S	somatosensory cortex

tests for >30 generations) were applied [24,25]. Wisket rats show several disturbances, including sensory gating, pain sensitivity and autonomic changes [25–27]. Furthermore, decreased exploratory activity and learning functions (decreased differentiation index, learning capacity, impaired working and reference memory) were detected in model rats using novel object recognition and food-reward-based (Ambitus and hole-board [HB]) tests [24,25,28–30]. However, it cannot be excluded from these data whether an altered hedonic behavior has any role in this phenomenon. The hedonic component of reward-seeking behavior can be tested in rodents with the widely used sucrose preference test, in which the animals can choose between a sweet solution and water [31–34]. Therefore, the first goal of this study was to explore whether the Wisket animals with impaired motivation also show decreased hedonic behavior [25,28].

Multiple morphological differences in several brain regions have been confirmed between patients with schizophrenia and healthy individuals by volumetric and histological studies. Among others, the altered structures of the cortical, striatal, and hippocampal areas as well as, white matter and the enlargement of the brain lateral ventricles (LVs) have been reported in human and in a few schizophrenia animal models, but not in this type of multiple-hit rat model [35–42]. Therefore, our second aim was to reveal the potential neuroanatomical alterations in different brain regions in Wisket rats.

2. Materials and methods

2.1. Subjects

Male Wistar (control) and Wisket rats (weight: 350–450 g) were involved in the study. All experiments were performed with the approval of the Hungarian Ethics Committee for Animal Research (registration number: XIV/1248/2018) and in accordance with the guidelines set by the Government of Hungary and EU Directive 2010/63EU for animal experiments. The rats were kept with a 12-h light/dark cycle under controlled temperature (22 °C ± 1 °C) with ad libitum water and food access, except for the experiment in the HB test, for which they were food deprived for 2 days (see below), however, water was always freely available. Their body weight was carefully controlled during the whole experiment.

2.2. Experimental paradigm

The paradigm for selective breeding of Wisket rats was sustained and the basal behavioral tests were performed according to our previous studies Table 1 [24,25]. The rats (n = 8 in both groups) were subjected to the simplified HB test at 10 weeks of age and to the sucrose preference test at the age of 11 weeks. At 22 weeks of age, histological analysis was performed (n = 6 per group)

2.2.1. Simplified HB test

The appetitively motivated HB task is able to assess the behavior related to motivation and cognitive performance in animals [25,30]. As the three-phase (habituation, learning and trial phase) version of HB task requires a long-time food restriction for the animals to maintain their motivation, it cannot effectively be used as an easy and fast test of high number of animals, which is required in preclinical studies. Our previous data suggested that a simplified HB (see-below) could be suited to predict the cognitive performance of rats [25,30].

The floor of the arena (an 80 × 80 cm square arena with 40 cm high black walls) contained 16 cylinders (5 × 5 cm diameter) in a 4 × 4 array. The task was to collect all food rewards from the 16 cylinders within 600 s. The rats were placed into the center of the arena, and their behavior was recorded using an infrared video device (WCM-21VF; CNB, China). In agreement with previous reports, food reward (puffed rice) was used as a positive motivation after 48 h of total food deprivation and additional food restriction throughout the experiment (approximately the 50% of the daily nutritional requirement) [25,43,44]. The simplified version of HB test was performed twice over a 3-day period (between 8:00 a.m. and 3:00 p.m.) to detect improvement in the performance by repetition: Trial 1 on day 1, Trial 2 on day 3. On day 2, no test was executed.

The task was conducted only once in both trials. The apparatus was cleaned with 70% alcohol after each animal. Two, trained investigators blinded to the group scored the different behaviors was performed offline by. The durations of the general activities, i.e., locomotion, rearing and grooming (stereotypy) were registered. The count of sniffing events towards the reward containing cylinders was considered to reflect exploratory activity, and the time spent in the center of the arena (within the outer line of the holes) and with the grooming activity were considered to be a sign of anxiety [45,46]. The motivation index of the rats was determined according to the number of eaten rewards and the task completion time [25,28] as follows:

$$\textit{Motivation index}\,(\%) = \left[\frac{\text{number of collected food rewards} \times \text{cutoff time of the learning phase (600 s)}}{\text{number of food rewards (16)} \times \text{time required to complete the task (s)}}\right] \times 100$$

2.2.2. Sucrose preference test

After 4 days of finishing the HB task, the rats were housed individually with two pre-weighed bottles containing tap water or 1% sucrose solution. The test consisted of three sessions: one sucrose and two water sessions. During the first water session, the rats were provided with two water-containing bottles for 6 days; in the sucrose session, one of the bottles was replaced with a 1% sucrose solution for 3 days. It was followed by the second water session for 4 days. The positions of the bottles (sucrose left or right) were randomly assigned by cage every day to account for the possible side preferences. Following each session, the rats' body weight was recorded, bottles were reweighed, and total fluid intake was calculated. Furthermore, sucrose preference was determined as the ratio of sucrose intake to total fluid intake and the values

Table 1
Experimental paradigm.

Age	Week 3	Weeks 4–7	Weeks 5–7	Week 8	Week 9	Week 10	Weeks 11–12	Weeks 22
Wistar	Weaning, TF test 1	Social rearing			TF test 2, PPI test			
Wisket		Isolation rearing	Ketamine treatment (30 mg/kg i.p. daily)	Resocialization		HB test	Sucrose preference test	Histology

Abbreviations: HB: hole-board, i.p.: intraperitoneally, PPI: prepulse inhibition, TF: tail-flick.Procedures.

converted to percentages. In the case of water sessions, the ratio of the right sides to the total consumption was determined.

2.2.3. Neuroanatomical examinations

2.2.3.1. Tissue preparation and staining. After the animals were deeply anesthetized with 4% chloral hydrate (400 mg/kg; intraperitoneally, they were perfused via the ascending aorta with 0.1 M phosphate-buffered saline, followed by 4% paraformaldehyde in 0.1 M phosphate-buffered saline. The whole brain was removed and postfixed overnight in the same fixative and cryoprotected in ascending sucrose solutions up to 30%. The whole brain was cryosectioned in 30-μm serial coronal sections; every 10th section was mounted on a gelatin-coated slide. Sections were stained with 1% cresyl violet mixture, covered with a cover slip, and then viewed under a light microscope. Sections were captured with a Zeiss AxioImager M2 light microscope with a 20 × objective (Carl Zeiss, Jena, Germany) and analyzed using the Image Tool 3.0 software.

2.2.3.2. Histological analysis. The images were analyzed using ImageJ (National Institutes of Health, Version 1.53, USA) and the levels of the sections with respect to Bregma were determined using a rat brain stereotaxic atlas [47]. All measurements were performed bilaterally. Cortical thickness was defined as the length of the line perpendicular to the pial surface extended to the white matter (Fig. 1). To determine the location of cortical regions, shape, cytoarchitectonics, and position relative to subcortical structures were used across the controls and Wisket rats [36,47]. The sections of the prefrontal cortex were taken at the Bregma 3.3 mm coordinate, and the thicknesses of the anterior cingular cortex 1 (CG1), infralimbic (IL), motor (M), prelimbic (PRL) and somatosensory (S1) regions were measured. At this level, the forceps minor of the corpus callosum (fmi) is a clearly recognizable closed structure, which allows a precise measurement of the cortical thickness [48–51] (Fig. 1A). The frontoparietal cortex was sampled at the level of the anterior commissure (Bregma, −0.12), and the thicknesses of CG1, CG2, M, and S1 regions were defined (Fig. 1B). For the parietal cortex, the thickness was measured at the Bregma -3.3 mm coordinate in the M, S2 and perirhinal (PRh) areas [36] (Fig. 1C).

To estimate changes in the white matter of the brain, the length of the fmi was determined at the Bregma 3.3 mm coordinate based on the method of Biro *et al.* [51]. Thus, from the upper and lower end of the fmi, two perpendicular lines were drawn to the medial longitudinal fissure,

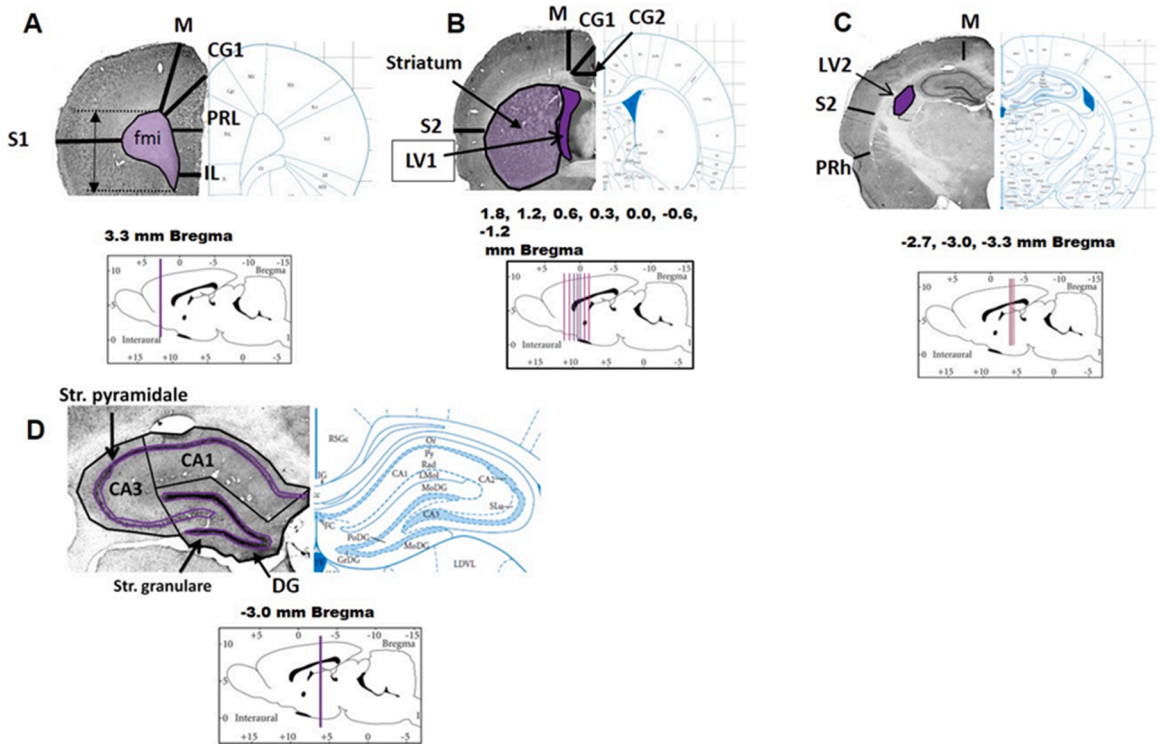

Fig. 1. Coronal sections of the brain of a control rat showing the levels where cortical thicknesses and subcortical regional areas were measured. (A) The prefrontal cortex at the level of the forceps minor, where it is a clearly recognizable closed structure and the thicknesses of the M, S1, CG1, PRL and IL cortices as well as the length of the fmi were measured. (B) At the level of the anterior commissure, the M, S2, CG1 and CG2 as well as the areas of the LV and striatum were analyzed. (C) At the levels of the rostral hippocampus, M, S2, perirhinal (PRh) cortices, and area of the LV, (D) the hippocampus and its subfields and cellular layer were measured [47]. *Abbreviations*: CA1,3: cornu ammunis 1,3; CG: cingular cortex; fmi: forceps minor; IL: infralimbic cortex; LV: lateral ventricle; M: motor cortex; PRL: prelimbic cortex; PRh: perirhinal cortex; S: somatosensory cortex.

and the distance between them characterized the length of the fmi (Fig. 1A).

Sections were sampled posterior to Bregma -3.0 mm at the level of the medial habenula and dorsal hippocampal commissure to analyze the morphology and extent of the dorsolateral hippocampus. The structures of the dorsal hippocampus subfields were observed and compared with control brains by referring to the rat brain stereotaxic atlas [47]. The whole hippocampus and its subfields (CA1, CA3 and dentate gyrus [DG]) and cellular layers (str. pyramidale and str. granulare) were manually delineated according to the rat brain stereotaxic atlas, and the area was measured from micrographs [36,52] (Fig. 1D).

The volumes of the LVs and striatum were estimated by multiplying the delineated surface area, thickness (30 μm) of the section, and distance between two slices (300 μm) according to the principles of the Cavalieri volume estimator [53]. The anterior part of the LV (LV1) was determined between Bregma 0.6 and -0.12 mm and the posterior horn between Bregma -2.7 and -3.3 mm (LV2) (Fig. 1B, C). Striatum sections were selected from levels at Bregma 1.8 and -1.2 mm at every 600 μm (Fig. 1B).

2.3. Statistical analysis

For the analyses, STATISTICA 14.00 (TIBCO Software Inc., Palo Alto, CA, USA) was used. Behavioral data were analyzed using one-way, factorial (group, session, or trial), or repeated-measures analysis of variance (ANOVA). One-way ANOVA was used to analyze histological data. For post-hoc comparisons LSD test was used. Only probabilities of (p-values) < 0.05 were considered significant. In all graphs, data are presented as means ± standard errors of the mean.

3. Results

3.1. Body weight

The detection of body weight revealed that there were no significant differences between the groups during the testing period. ANOVA revealed significant effect of time ($F_{7,98} = 402.49$, $p < 0.0001$). The two-days food deprivation before HB test significantly reduced the body weight in both groups (Fig. 2). The post hoc analysis also revealed significant weight gain in both groups 1 week after the cessation of food restriction. Thus, there were no significant differences in body weight between the groups when assigned to treatment conditions in sucrose preference test. During this test, body weight increased with time similarly in both groups.

3.2. Simplified HB test

Regarding the locomotor activities, ANOVA analysis showed significant effects of group ($F_{1,28} = 7.57$; $p < 0.05$), trial ($F_{1,28} = 5.76$; $p < 0.05$) and their interactions ($F_{1,28} = 4.54$; $p < 0.05$). In Trial 2, the locomotor activity remained unchanged in the Wistar rats, but decreased significantly in the Wisket rats relative to Trial 1 and the Wistar group (Fig. 3A).

Regarding the rearing activity, ANOVA analysis showed significant effects of group and trial interaction ($F_{1,28} = 7.4$; $p < 0.05$). Post-hoc analysis revealed that the rearing activity significantly increased in Trial 2 compared to Trial 1 in the Wistar rats, but not in the Wisket rats (Fig. B). Furthermore, significantly lower duration was detected in Wisket rats compared to Wistar animals in Trial 2.

ANOVA analysis showed significant effects of group ($F_{1,28} = 28.09$; $p < 0.001$) and group and trial interaction ($F_{1,28} = 4.5$; $p < 0.05$) in the sniffing count. Compared with the Wistar rats, the Wisket rats sniffed the holes significantly less often in both trials (Fig. 3C).

The ANOVA analysis of motivation index showed significant effects

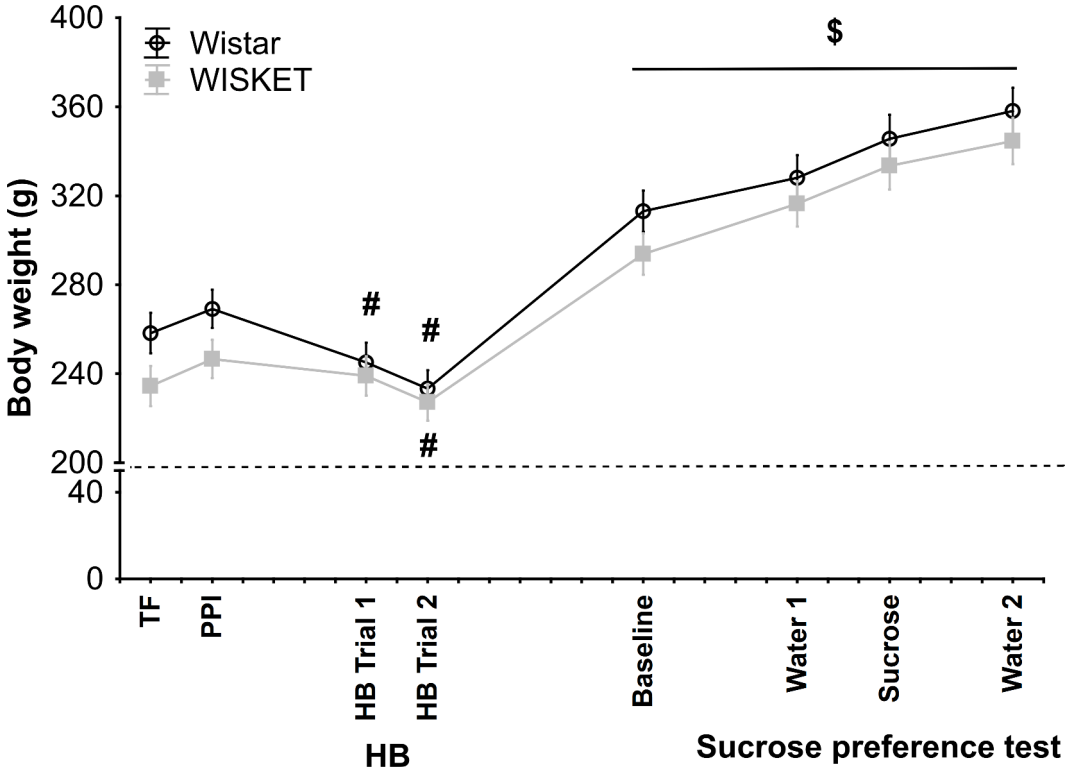

Fig. 2. Body weight of the rats during the testing period. The symbols # and $ indicate significant differences ($p < 0.05$) compared to body weight before food restriction period (PPI) and compared to the body weight in HB Trial 2, respectively.

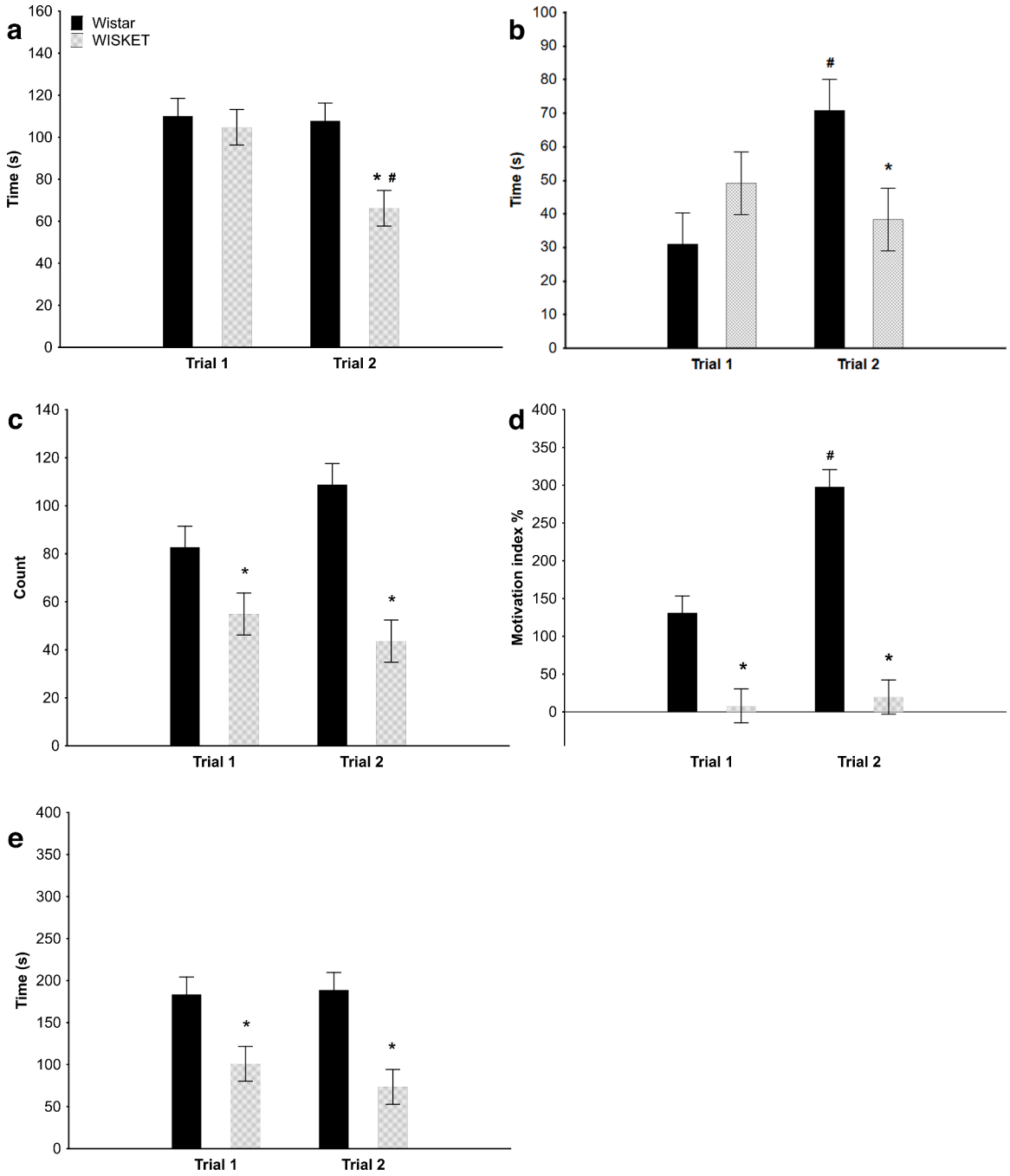

Fig. 3. Results of the HB test: time spent with locomotion (A), rearing (B), exploratory activity: hole-sniffing count (C), motivation index (D) and time spent in the center area of the arena (E). The symbols (*, #) indicate significant differences ($p < 0.05$) between the corresponding Wistar and Wisket groups or between trials, respectively.

of group ($F_{1,28} = 79.90$; $p < 0.001$), trial ($F_{1,28} = 15.80$; $p < 0.001$) and their interaction ($F_{1,28} = 11.92$; $p < 0.005$). Post-hoc analysis revealed that it was significantly lower in both trials for the Wisket rats than for the Wistar rats (Fig. 3D). Furthermore, the motivation index significantly increased in Trial 2 relative to Trial 1 in the Wistar rats, but not in the Wisket rats.

ANOVA analysis of the time spent in the center of the arena revealed a significant effect of the group ($F_{1,28} = 22.77$; $p < 0.001$). The Wisket rats spent significantly shorter time in the center of the arena during both trials than the controls (Fig. 3E). Regarding the grooming activity, ANOVA analysis showed no significant effects of the factors (Trial 1: Wistar: 8.63 ± 2.77 s and Wisket: 27.01 ± 15.94 s, Trial 2: Wistar 16.79 ± 4.51 s; and Wisket: 39.48 ± 15.65 s; group: $p = 0.08$, series: $p = 0.37$, interaction of factors: $p = 0.85$), however, the level of this activity showed tendency to be higher during both trials in the Wisket rats than in the Wistar rats.

3.3. Sucrose preference test

ANOVA analysis of the daily fluid consumption showed a significant effect of session ($F_{1,42} = 21.32$; $p < 0.001$); thus, the introduction of 1% sucrose solution significantly increased the total consumption in both groups compared to that of the water sessions (Wistar: $p < 0.0001$; Wisket: $p < 0.05$, Fig. 4A). The total fluid consumption was similar during the two water sessions in both groups. There were no significant differences in the total daily consumption in any sessions between the

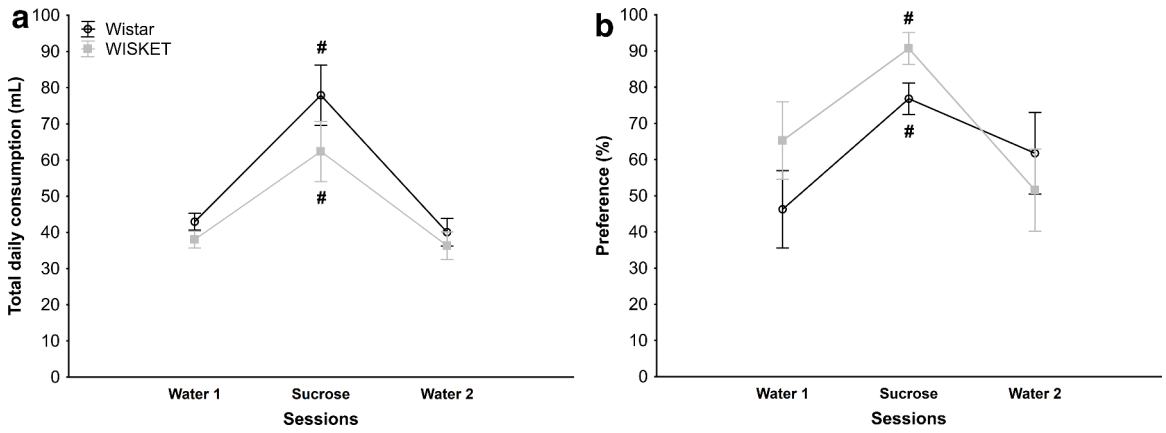

Fig. 4. Results of the sucrose preference test. Changes in total daily fluid consumption (A) and preference (B) of the animals during the water and sucrose drive. The symbol (#) indicates significant differences ($p < 0.05$) compared to Water 1 session.

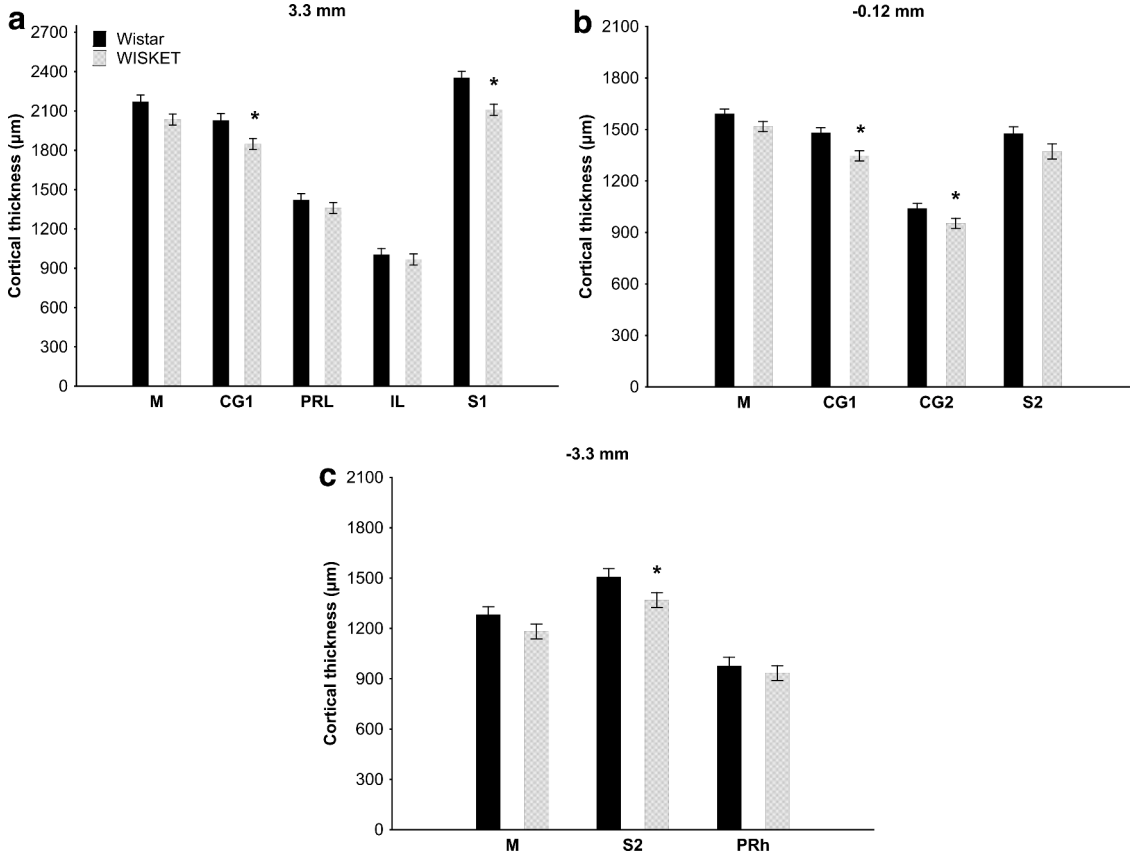

Fig. 5. Cortical thicknesses from different anatomical levels; Bregma: 3.3 mm (A), -0.12 mm (B) and -3.3 mm (C). The symbol (*) indicates significant differences between the Wistar and Wisket groups. *Abbreviations*: CG: cingular cortex, IL: infralimbic cortex, M: motor cortex, PRL: prelimbic cortex, PRh: perirhinal cortex, S: somatosensory cortex.

two groups (Fig. 4A). Regarding the preference toward sucrose solution, ANOVA analysis showed significant effects of session ($F_{1,42} = 5.82$; $p < 0.01$); and a slightly higher tendency toward the preference for sucrose solution was observed in the Wisket rats (Fig. 4B).

3.4. Histological analysis

ANOVA analysis of the cortical thickness at the Bregma 3.3 mm coordinate revealed significantly thinner CG1 and S1 cortices in the Wisket rats than in the control brain samples (CG1: $F_{1,13} = 6.2$; $p < 0.05$; S1: $F_{1,14} = 12.87$, $p < 0.01$; Fig. 5A). The CG1 and CG2 cortices obtained from the Bregma −0.12 mm regions were also significantly thinner in the Wisket rats (CG1: $F_{1,17} = 11.18$; $p < 0.01$; CG2: $F_{1,17} = 5.10$, $p < 0.05$, Fig. 5B). In the parietal region, only the S2 cortical region showed reduced thickness in the Wisket vs. Wistar rats (S2: $F_{1,13} = 7.37$, $p < 0.05$, Fig. 5C).

Regarding the white matter, a trend toward a decreased fmi length was observed in the Wisket rats (Wistar: 1917.47 ± 128.92 µm; Wisket: 1665.84 ± 89.4 µm, $p = 0.15$). The hippocampal area was significantly smaller in the Wisket rats than in the controls ($F_{1,6} = 10.51$, $p < 0.05$) (Fig. 6A). Further analysis of the subfields revealed a shrinkage of the CA3 and CA1 regions (CA3: $F_{1,8} = 11.69$, $p < 0.01$; CA1: $F_{1,7} = 11.23$, p

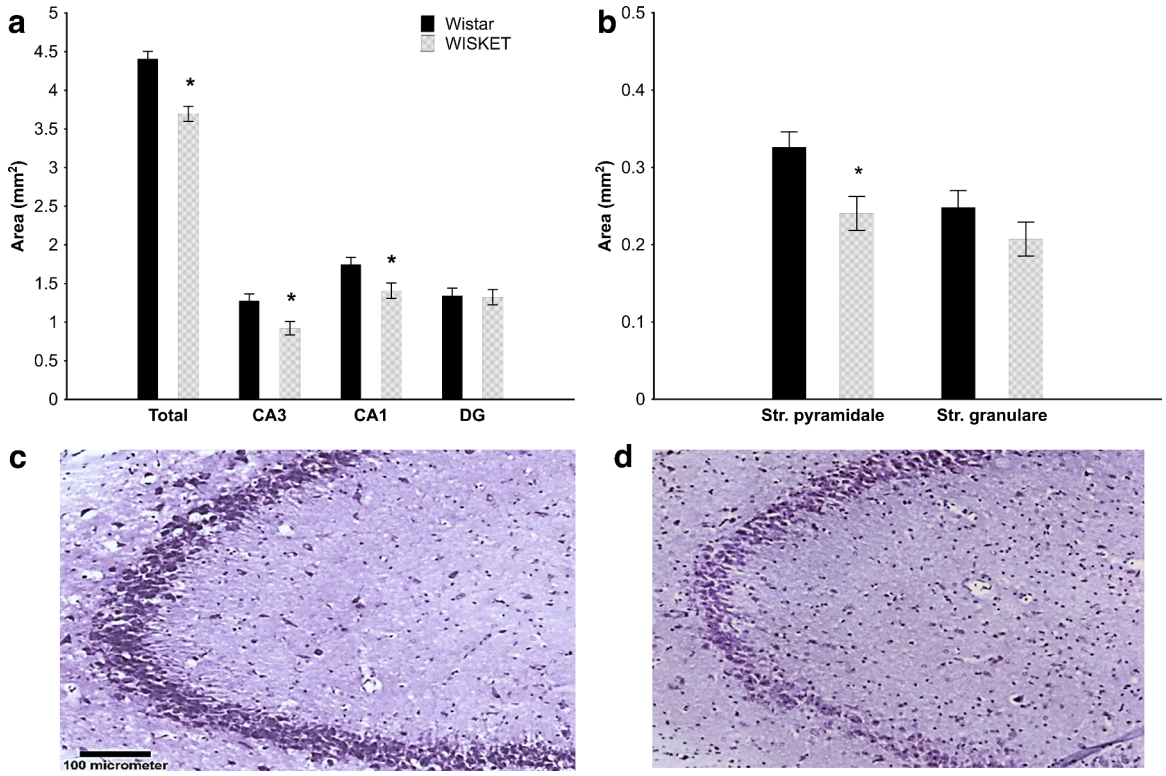

Fig. 6. Areas of the hippocampus, its subfields (A) and its cellular layers (B). Histological staining of the CA3 region in the dorsal hippocampus at Bregma -3.00 mm in Wistar (C) and Wisket (D) rats. The symbol (*) indicates significant differences ($p < 0.05$) between the Wistar and Wisket groups.

< 0.05), however, the DG area remained unchanged. Regarding the two investigated layers in the hippocampus, the str. pyramidale area was significantly smaller in the Wisket rats ($F_{1,7} = 6.28$, $p < 0.05$), but there was no significant difference in the str. granulare areas between the groups (Fig. 6B). Morphological analysis of the hippocampal region revealed disarray of the pyramidal cells in the CA3 subfield; thus, instead of the integrated compact structure, a dispersed cell location was observed between the groups (Figs. 6C and D).

In the Wisket rats, a tendency toward enlargement was observed in both investigated parts of the LVs. The differences in LV1 vol were close to significant based on group (LV1: Wistar: 1.67 ± 0.27 μm^3; Wisket: 3.24 ± 0.63 μm^3, $p = 0.06$; LV2: Wistar: 0.9 ± 0.16 μm^3; Wisket: 1.44 ± 0.39 μm^3, $p = 0.25$). Moderate shrinkage of the striatal volume relative to that in the Wistar rats was observed in the Wisket rats (Wistar: 12.72 ± 0.39 μm^3; Wisket: 11.78 ± 0.15 μm^3, $p = 0.067$).

4. Discussion

In harmony with recent human data, this study revealed that the anhedonic phenotype might have no significant role in the impaired reward-seeking behavior of Wisket rats shown in simplified HB test. Furthermore, also in agreement with human data, these rats showed several schizophrenia-related neuropathological changes in the brain. Similar to earlier results obtained in schizophrenic patients or animal models, the Wisket rats showed decreased exploratory activity (decreased sniffing count) towards reward containing cylinders, which were also accompanied by signs of enhanced anxiety compared to control animals [24,25,28–30,54–60]. It is well known that the HB test is sensitive to several interventions used to induce schizophrenia-related alterations; e.g., cognitive deficiencies and impaired acquisition indicated by memory deficits [61–66]. In reward-based behavioral tests, it is difficult to identify which functional impairments cause exactly the decreased performance. It can be due to altered reward valuation and/or impaired motivational processes, among others, leading to signs of cognitive dysfunction [67,68].

Motivational deficits have been shown to play important roles in predicting cross-sectional and longitudinal functional outcomes in schizophrenia [3,69–74]. It has been found that motivation is significantly related to global cognitive performance, specifically verbal fluency, verbal and working memory, attention and processing speed and reasoning and problem solving [3]. Furthermore, primarily motivational deficits mediate the relationship between cognition and functional outcome [8,75–77].

Several schizophrenia rat models have shown increased locomotor activity in response to a novel environment [61,78–84], while, in agreement with our observations, other studies have found no change or decreased motor activity [85–89]. These controversies between the studies might be due to, at least partially, the different animal model types and/or the test circumstances. Stress-related behavior, including anxiety, can also negatively affect cognitive performance [90]. The HB test is also appropriate for determining increased anxiety-like behaviors (less time spent in center of the arena or enhanced self-grooming) [80,91,92]. In agreement with our previous studies, Wisket rats avoided the central area of the testing arena, and had moderate increase in grooming activity, which suggests their anxiety-like behavior [25,30].

Anhedonia, broadly defined as loss of interest and/or an inability to experience pleasure, should be viewed as a complex phenomenon, given the identified components of reward-related behavior, such as motivation, learning, response to reward and the experience of pleasure [10,11,13,14]. Thus, anhedonia may reduce cognitive performance in tasks motivated by pleasurable outcomes (rewards) [93–97]. It is considered as one of the negative symptoms of schizophrenia and an important feature of several psychiatric disorders, however, the data are controversial [6,22,98–102]. Gard *et al.* found that patients with schizophrenia reported significantly more anhedonia only in relation to motivational items [103], however, it has also been suggested that schizophrenia patients have normal or nearly normal experiences of positive emotions when presented with emotionally evocative stimuli [104–107].

Therefore, it might be supposed that cognitive deficits, especially memory impairments (which are prominent in schizophrenia), could contribute to motivation, but sparing consummatory pleasure [68]. It seems that deficits in motivational processes that decrease performance is not due to an inability to experience pleasure given that hedonic reaction appears intact in these patients [108].

In animal models of schizophrenia, the results are also controversial in this respect, and only one-hit animal model results are available. Thus, acute, but not subchronic or chronic, phencyclidine treatment has been shown to decrease sucrose intake [109]. Other models, including neonatal or adult lesions of the ventral hippocampus or prenatal polyinosinic:polycytidylic acid (poly I:C)-induced immune activation, have led to decreased preference for sweetened fluids [110,111]. In agreement with some human results [12,17,20–23], our results obtained in this complex schizophrenia model suggest that, the motivational deficit in HB-test might not be due to the rats' anhedonic behavior. Even no significant correlation was detected between the motivation index and the sucrose preference values (r = -0.384; p = 0.347).

In our previous studies numerous neurochemical impairments were detected in different brain regions of Wisket animals, including dopaminergic, opioid, cannabinoid, GABAergic and oxytocinergic systems, but this is the first study, which examined the potential gross neuroanatomical changes in this model [112–116]. The results of the histological analysis revealed several structural changes in the Wisket rats' brain samples, including decreased frontal cortical thicknesses and hippocampal area, cell disarray of CA3 subfields and moderate changes in the volumes of the LVs and striatum, however, further investigations are required to define more precise structural or cellular alterations in these animals. These observations are comparable to clinical and preclinical findings [35–38,117–123]. The most dramatic change observed in brain imaging studies is the reduction of cortical thickness in the prefrontal region in schizophrenia patients [120,124,125]. The integrity of prefrontal cortex is vital for attention, working memory, motivation, volition and various related executive functions, therefore, the impairment in function might potentially underlie the pathophysiology of various features of negative symptoms [126,127]. Besides the frontal lobe, the hippocampus is also an important region in learning and memory processes. Controverting data suggest reductions or no differences in the volume of hippocampus in schizophrenia [122,128–132]. Furthermore, meta-analyses have confirmed that schizophrenic patients often have larger LVs and consequently decreased gray matter and whole-brain volumes [132–134].

Some one-hit schizophrenia animal models have found similar structural brain impairments; thus, poly I:C- or methylazoxymethanol acetate-treated or socially isolated rodents have shown smaller hippocampal volumes and ventricular enlargement [36,42,54,118,135–137]. However, in a recent study, Sánchez-González and colleagues have found an increment in volume of medial prefrontal cortex after long-lasting social isolation of Roman rats [138]. All these human and preclinical data suggest that the structural changes might be linked to functional impairments. However, with this low number of animals, no significant correlation was found between the motivation index and the different anatomical parameters. Further studies are required to uncover and support behavioral consequences of structural abnormalities in our rat model.

5. Conclusion

The results of this study suggest that anhedonia may not be involved in the low performance of Wisket rats in their reward-seeking behavior obtained in HB test, and further tests are required to define these disturbances related to motivation. The histological analysis, performed in multiple brain regions, revealed decreased cortical thickness, hippocampal and striatal regions, and LVs enlargement in these rats. All these changes can be observed in patients with schizophrenia, which suggest that the Wisket rat model has reliable face validity in both behavioral and neuropathological aspects. However, these gross neuroanatomical results must be replicated in more detailed and sophisticated histological analyses in the future for confirmation.

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Declarations of Competing Interest

The authors declare no competing interest.

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