Increased exploratory activity in rats with deficient sensorimotor gating: a study of schizophrenia-relevant symptoms with genetically heterogeneous NIH-HS and Roman rat strains

Carles Tapias-Espinosa *, Cristóbal Río-Álamos, Daniel Sampedro-Viana, Cristina Gerbolés, Ignasi Oliveras, Ana Sánchez-González, Adolf Tobeña, Alberto Fernández-Teruel *

Department of Psychiatry & Forensic Medicine, Institute of Neurosciences, Autonomous University of Barcelona, 08193-Bellaterra, Barcelona, Spain

*Corresponding authors:

Carles Tapias-Espinosa; carles.tapias@uab.cat

Alberto Fernández-Teruel; albert.fernandez.teruel@uab.cat

Abstract

Schizophrenia involves positive, negative and cognitive symptoms, as well as comorbidity with anxiety and obsessive-compulsive disorder. Prepulse inhibition (PPI) of the startle response is a measure of sensorimotor gating that is impaired in schizophrenia and animal models of the disease. Remarkably, impaired PPI has been related to other schizophrenia-like features in rodent models, such as cognitive deficits and hyperactivity. However, it remains to be investigated whether deficient PPI and increased exploratory activity are associated in genetically heterogeneous (outbred) naïve animals. This study was undertaken to evaluate the relationships among PPI and other schizophrenia-related symptoms, such as augmented exploratory activity, anxiety and compulsivity in the genetically heterogeneous (outbred) NIH-HS rat stock (HS) and in the genetically-selected inbred Roman High-Avoidance (RHA) and Low avoidance (RLA) rats. Animals underwent the following tests: open-field (exploratory activity), elevated zero-maze (anxiety-like behavior), marble burying (compulsive-like behavior), and PPI. Three groups of HS rats were formed according to their PPI scores, i.e. Low-, Medium- and High-PPI. The HS Low-PPI group displayed higher exploratory activity in the open-field than the HS Medium-PPI and HS High-PPI groups. Likewise, compared with their RLA counterparts, RHA rats exhibited lower PPI and more intense exploratory activity in the open-field test. Correlational and factorial analyses of the whole HS sample and the RHA/RLA data globally corroborated the results of the PPI-stratified HS subgroups. These data suggest that such a consistent association between impaired PPI and increased exploratory activity in outbred HS and inbred RHA/RLA rats is a relevant parameter that must be taken into account when modeling clusters of schizophrenia-relevant symptoms.

Keywords: Prepulse inhibition, schizophrenia, exploratory activity, compulsive-like behavior, genetically heterogeneous rats, Roman rats

1. Introduction

Schizophrenia is mainly characterized by the presence of three groups of symptoms: positive (hallucinations, delusions and disorganized behavior), negative (anhedonia, apathy, reduced affect display) and cognitive (impaired sensorimotor gating, attention and executive functions). Moreover, schizophrenia also shows comorbidity with anxiety and obsessive-compulsive symptoms (Braga et al., 2013; Buckley et al., 2009). The complexity and diversity of schizophrenia hinders the full modelling of the entire constellation of symptoms in rodents, although it is desirable to evaluate all putative animal models with the broadest range possible of disease-related phenotypes.

Prepulse inhibition (PPI) of the startle response is a measure of sensorimotor gating, in which the magnitude of the startle is attenuated by the presence of a pre-stimulus of lower intensity (Graham, 1975). Impaired PPI has been proposed as an endophenotype for schizophrenia (Braff et al., 2008), although such an alteration is also present in other psychiatric disorders. Interestingly, the administration of amphetamine, which is known to cause psychotic-like symptoms in humans (Kokkinidis and Anisman, 1981; Snyder, 1973), disrupts PPI in humans (Hutchison and Swift, 1999; Kumari et al., 1998) and rodents (Kinney et al., 1999; Swerdlow et al., 2007). Apart from PPI deficits, amphetamine also induces hyperactivity in rodents, in line with the disorganized behavior of schizophrenia (Alsene et al., 2010; Blanc et al., 1994; Dickinson et al., 1988; Ott and Mandel, 1995; Powell and Miyakawa, 2006; Swerdlow et al., 2002). The association between increased activity and impaired PPI has also been found in other well-established animal models of schizophrenia, such as ventral hippocampal neonatal lesion (Tseng et al., 2009), NMDA infusion (Peleg-Raibstein and Feldon, 2006; Wang et al., 2015), NMDA-antagonist administration (Maple et al., 2017), genetic alterations in mice (Kulikov et al., 2016; Miyakawa et al., 2003; Munesue et al., 2010; Powell and Miyakawa, 2006; Takao et al., 2013; Young et al., 2014) and social isolation (Domeney and Feldon, 1998; Lukkes et al., 2009; Oliveras et al., 2016). Thus, as these studies

suggest, impaired PPI and excessive motor/exploratory activity may constitute relevant parameters that must be taken into account when modeling clusters of schizophrenia-relevant symptoms. On the other hand, as mentioned above, compulsive and anxious behaviors have also been associated with schizophrenia, although research with rodent models has shown controversial evidence in that respect (Lindemann et al., 2008; McAuley et al., 2009).

This study was undertaken to evaluate the relationships among PPI and other schizophrenia-related symptoms, such as augmented exploratory activity, anxiety, and compulsivity in the genetically heterogeneous NIH-HS outbred rat stock (HS) and in the genetically-selected inbred Roman High-Avoidance (RHA) and Low avoidance (RLA) rats. The RHA and RLA rats were bidirectionally selected and bred for their very good (RHA) vs. extremely poor (RLA) ability to acquire the two-way active avoidance task (Driscoll et al., 1998; Escorihuela et al., 1999; Río-Álamos et al., 2017; Steimer and Driscoll, 2005). Compared with their RLA counterparts, RHA rats show deficient PPI, impaired working memory (Oliveras et al., 2015) and reduced latent inhibition (Esnal et al., 2016; Fernández-Teruel et al., 2006). These divergent behavioral profiles, together with the reported between-strain differences in dopaminergic (Giorgi et al., 2007; Guitart-Masip et al., 2008; Tournier et al., 2013), serotoninergic (Fomsgaard et al., 2017; Klein et al., 2014) and glutamatergic (Wood et al., 2017) systems, suggest that RHA rats may be a valid model for schizophrenia-related features. On the other hand, the HS rats were developed to obtain a stock of rats as genetically heterogeneous as possible (Hansen and Spuhler, 1984). To this aim, a crossing of eight parental inbred strains was carried out, generating a higher genetic recombination pattern and phenotypic variability than those shown by the most commonly used laboratory rat strains (Hansen and Spuhler, 1984). Since HS rats appear to show genetic variabilities more similar to human population, they constitute an excellent tool to study the neurobiological and genetic basis of both normal and abnormal (illness-related) complex traits (Baud et al., 2013;

Díaz-Morán et al., 2013). Furthermore, similar to findings with the Roman rats, studies with the HS rats have shown tight associations among impaired PPI and other schizophrenia-related symptoms, such as deficient working memory (Oliveras et al., 2015) or reduced latent inhibition (Sánchez-González et al., 2016). These behavioral data suggest that HS rats stratified by low PPI may constitute a putative model of some schizophrenia-relevant features. It remains to be stablished whether exploratory activity in response to novelty, which is another schizophrenia-associated feature (Powell and Miyakawa, 2006), is also associated with PPI impairment in HS rats.

In this study, HS rats underwent the following tests: (i) open-field (to assess exploratory activity), (ii) elevated zero-maze (to evaluate anxiety-like behavior), (iii) marble burying (to examine compulsive-like behavior), and PPI. The data obtained from HS rats were analyzed both in the whole sample and in three groups of rats stratified by Low-, Medium- and High-PPI. Moreover, the same procedures were used with inbred RHA vs. RLA rats, so that we would be able to see the generalizability of the association among PPI and the other phenotypes from the Roman rat strains to the outbred HS stock.

2. Materials and methods

2.1. Subjects

Naïve male HS (n=92), and inbred RHA (n=12) and RLA (n=12) rats, from the permanent colonies maintained at our laboratory (Medical Psychology Unit, Dept. Psychiatry and Forensic Medicine, School of Medicine, Autonomous University of Barcelona) since 1996 (RHA, RLA) and 2004 (HS), were used in this study. They were aged 3-4 months, having a weight range of 250-350 g. They were housed in pairs of the same strain in macrolon cages (50 x 25 x 14 cm) and maintained with food and water *ad libitum* (standard animal chow). These animals were bred and reared in our laboratory at Autonomous University of Barcelona. They were maintained under a 12:12 h light-dark cycle (lights on at 08:00 a.m.), with controlled temperature (22 ± 2 °C) and humidity (50-70%).

The HS rat stock was derived from eight inbred rat strains by Hansen and Spuhler (Hansen and Spuhler, 1984). These eight parental strains were the MR/N, WN/N and WKY/N (whose ancestors trace back to the original Wistar stock), the M520/N and F344/N (established in the 1920s with an unknown origin), the M520/N and the ACI/N (hybrids between the August and Copenhagen stocks), the BN/SsN (derived from a color mutant from a stock of wild rats kept at the Wistar Institute), and the BUF/N strain. To establish our colony, we received 40 pairs of NIH-HS rats from Dr. Eva Redei (Center for Comparative Medicine, Northwestern University, Chicago, USA) in 2004.

2.2. Experimental procedures

All behavioral testing was carried out during the light cycle between 09:00-14:00 h. Apart from the PPI test (see below), all the other test measures were taken by an expert observer, who was blind to group condition. After testing each rat, the corresponding apparatus was thoroughly wiped clean with 70% ethanol solution. In the marble burying test, new bedding was used for each animal and marbles were cleaned with a 70% ethanol solution between animals.

Experiments were performed in accordance with the Spanish legislation on "Protection of Animals Used for Experimental and Other Scientific Purposes" and the European Communities Council Directive (2010/63/EU) on this subject. Every effort was made to minimize any suffering of the animals used in this study.

Figure 1 shows the experimental timeline.

2.2.1. Open-Field

The apparatus was a circular arena (diameter, 83 cm) walled by white walls (height, 34 cm) and divided into 19 equal sectors by lines drawn on the floor. The test was carried out in a black-painted testing room, dimly illuminated with white fluorescent light (65 lx at the level of the apparatus). Each rat was individually placed in the periphery of the open-field, and behavior was videotaped and measured outside the testing room for 5 min. Total number of "exploratory activity" episodes (crossings + rearings), and "self-grooming" time were measured. The lower decile of the "grooming time" variable conformed the Low-Grooming (Low-Groom) group, the higher decile was for the H-Grooming (High-Groom) group, while a Medium-Grooming (Medium-Groom) group was randomly drawn from the intermediate deciles.

2.2.2. Elevated Zero-Maze

The maze comprised a circular corridor (105 cm diameter; 10 cm width) made of black plywood, elevated to 65 cm above the ground, having two open sections and two enclosed ones (walls 40 cm height). It was situated in a black-painted testing room, dimly illuminated with red fluorescent light (50 lx at the level of the apparatus). Each rat was placed in an enclosed section of the zero-maze facing the wall and behavior was videotaped and measured outside the testing room for 5 min. Measures taken were "time spent in open sections" and "number of head-dips" through the edge of the maze, as anxiety-related variables, as both parameters have previously been reported to be highly and positively correlated ($r = 0.76$; e.g. see (Martínez-Membrives et al., 2015)). Moreover, both measures have also been shown to be sensitive to anxiolytic and

anxiogenic pharmacological and non-pharmacological treatments, in a manner that is independent of their effects on locomotor activity (Braun et al., 2011; Oliveras et al., 2016; Río-Àlamos et al., 2015; Shepherd et al., 1994).

2.2.3. Marble Burying Test

Four white polyethylene box cages measuring 40 x 40 x 40, containing 5 cm depth bedding were used. Above the bedding were placed 16 translucent, light-green glass marbles, 20 mm in diameter arranged in 4 rows of 4 marbles each. The boxes were situated in a black-painted testing room, dimly illuminated with white fluorescent light (65 lx at the level of the apparatus). Each rat was placed in the center of the cage test for a 15-min period of observation. The "% of buried marbles" (i.e. marbles covered at least two-thirds by bedding) were counted.

2.2.4. Prepulse Inhibition Test

Four sound attenuated boxes (SR-Lab Startle Response System, San Diego Instruments, USA) were used. Each box consists of a Plexiglas cylinder situated on the top of a platform with a sensor that detects the strength made by the rat in each trial. Two speakers situated 15 cm from each side of the cylinder deliver the acoustic stimuli and a white noise generator provides the background noise. Each box was constantly lit by a 10 W lamp. The data were transduced by an accelerometer into a voltage which is amplified, digitized and saved into a computer for analysis. The session started with a 5 min habituation period in the startle chambers. Then, 10 "pulse-alone" trials (105 dB, 40 ms) were delivered in order to obtain a stable baseline of startle. After this, each one of the six different types of trials are randomly administered 10 times (60 trials in total):

1. Pulse-alone trials (105 dB 40ms, "startle response", which was the variable used to calculate the percentage of prepulse inhibition (% PPI); see the formula below).
2. Prepulses of 65/70/75/80 dB (20 ms) followed by the startle stimulus (105 dB, 40 ms) with an inter-stimulus interval of 100 ms.
3. No stimulus trials (background noise at 55 dB).

The interval between trials was 10–20 s with a mean of 15 s. The startle magnitude was recorded during 200 ms after the onset of the pulse. The %PPI for each prepulse intensity was calculated by applying the following formula:

$$\%PPI = 100 - \left(\frac{startle\ response\ amplitude\ on\ prepulse\ trials}{startle\ response\ amplitude\ on\ pulse\ trials}\ x\ 100\right)$$

Subgroups of PPI were stratified according to their mean value between the two lower intensities of the PPI session (i.e. mean between the 65dB and 70dB). Lower pre-pulse intensities, which are closer to the lowest threshold, are known to elicit lower levels of PPI (Swerdlow et al., 2001). Therefore, these pre-pulse intensities may be more sensitive to detect differences in information-filtering. The lower PPI decile conformed the Low-PPI group, the higher decile was for the High-PPI group, while a Medium-PPI group was randomly drawn from the intermediate deciles.

2.3. Statistics

All the analyses were performed employing the "Statistics Package for Social Sciences" (SPSS, version 17).

For the analyses of the whole HS rat sample (n=92), Pearson's correlation coefficients were performed among all the variables. Significance level was set at $p < 0.05$. Factorial analysis (direct oblimin; oblique rotation) was also performed on data from the whole HS rat sample.

For the assessment of PPI-stratified HS subgroups, One-Way ANOVAs were performed on all variables from the open-field, elevated zero-maze and marble burying tests, followed by Duncan's multiple range tests. Significance level was set at $p < 0.05$.

For the analyses of RHA vs. RLA rat groups, Student's t-tests were applied to the variables from the open-field, elevated zero-maze and marble burying tests. Significance level was set at $p < 0.05$.

3. Results

3.1. Deficient PPI is associated with increased exploratory activity in the open-field in HS and Roman rats

Pearson's correlations among variables from the 92 HS rats (Table 1) showed a significant negative moderate correlation between PPI and locomotor activity in the open-field test ($r = -.32$, $p<0.05$). Accordingly, obliquely-rotated factor analysis (direct oblimin), which grouped the main behavioral variables of this study in 3 main factors, revealed a third factor comprising "OF_Activity" and "PPI" with loadings of -.76 and .77, respectively (Table 2). Otherwise, neither the anxiety- nor the compulsivity-like variables were associated with PPI in the correlational and factorial analyses. The first and the second factors will be dealt with in the following sections.

After correlational and factorial studies, comparisons among the three PPI subgroups of HS rats and between both Roman strains were performed to further investigate the relationships among deficient PPI and other behavioral responses. As expected, the division of HS rats in three subgroups according to PPI scores led to a significant *GROUP* effect on PPI [One-Way ANOVA; $F_{(2,24)} = 66.021$, $p = <.001$; and Duncan's test confirmed the expected trend, High-PPI > Medium-PPI > Low-PPI; Figure 2a]. Furthermore, RHA showed poorer PPI than RLA rats [Student's t-test; $t_{(1,22)} = 3.897$, $p = .001$] (Figure 2b). With regard to exploratory activity in HS rats, one-way ANOVA revealed a significant *GROUP* effect on the "OF_Activity" variable [$F_{(2,24)} = 7.927$, $p = .002$]. Duncan's test confirmed that the Low-PPI group showed greater exploratory activity in the open-field test (Figure 3a) than both the Medium-PPI and High-PPI groups, while no differences were observed between the Medium-PPI and the High-PPI group. Similarly, RHA rats displayed a higher number of exploratory activity episodes in the open–field test than the RLAs [$t_{(1,22)} = -5.138$, $p = <.001$] (Figure 3c).

3.2. Reduced PPI is related to a higher number of head-dips in the elevated zero maze in HS and Roman rats

Correlational and factorial analyses showed no associations among PPI and anxiety-like behaviors measured in the elevated zero-maze, such as time spent in the open sections or number of head-dips (Table 1 and Table 2). On the other hand, the three subgroups of PPI-stratified HS rats did not differ in time spent in open sections of the elevated zero-maze [one-way ANOVA, $F_{(2,24)} = 1.882$, $p = .174$] (Figure 4a), but there was a significant difference in the number of head dips [one-way ANOVA, $F_{(2,24)} = 3.441$, $p = .049$]. Duncan's test confirmed that the Low-PPI group showed a higher number of head dips in the zero-maze than the High-PPI group, while no differences were observed with the Medium-PPI and between the Medium-PPI and the High-PPI groups (Figure 4b). Likewise, and partly supporting these results, RHA rats (which are PPI-impaired) exhibited greater number of head dips [$t_{(1,22)} = -2.997$, $p = .009$] and spent more time in the open sections of the elevated zero-maze than their RLA counterparts [$t_{(1,22)} = -2.428$, $p = .027$] (Figure 4c,d).

3.3. Impaired PPI is not linked to compulsive-like behaviors in HS and Roman rats

As shown in Table 1, neither of the behavioral traits supposed to measure compulsive-like behaviors, i.e. "Time Spent Grooming" and "%Marbles", were associated with PPI. Moreover, the PPI-stratified HS subgroups did not show significant differences either in the time spent self-grooming in the open-field [$F_{(2,24)} = 1.552$, $p = .232$] (Figure 3b) or in the percentage of buried marbles in the marble burying test [$F_{(2,24)} = 2.000$, $p = .157$] (%Marbles, Low-PPI: 3.5 ±2.4; Medium-PPI: 22.9 ±10.7; High-PPI: 9.7 ±5.2). Regarding the Roman rats, RLAs showed longer time spent grooming in the open-field than their RHA counterparts [$t_{(1,22)} = 7.089$, $p = .010$] (Figure 3d), while no between-strain differences were observed in the percentage of buried marbles [$t_{(1,22)} = 1.433$, $p = .171$] (%Marbles, RHA: 11.5 ±3.7; RLA: 7.3 ±3.1).

3.4. Analysis of anxious-like and compulsive-like behaviors among HS rats

The main aim of this study was to investigate the association among PPI and some possibly co-selected behavioral features. However, additional analyses of the anxiety and compulsivity-relevant variables were needed to confirm their meaning in this study. As depicted in Table 1, positive high correlations were found between time in open sections and head-dips (r = .74) in the elevated zero-maze test (see Table 1). Accordingly, obliquely-rotated factor analysis (direct oblimin) grouped these two variables in a first factor of "anxiety-related behaviors" with loading of .92 and .93, respectively (Table 2). Regarding the compulsive-like behaviors, a significant positive mild correlation between the time spent grooming and the percentage of marbles buried was found (r = .46; Table 1). Additionally, the second component of the factorial analysis included these two variables related to "compulsivity-like responses" with loadings of .83 and .87, respectively (Table 2). The "baseline startle response" variable was not related to any of the three components of the factorial analysis (Table 2). The very low correlations observed among the three components of the factor analysis indicate that these three factors are essentially independent.

Interestingly, confirming the results from the factor analysis (see the second factor in Table 2), one-way ANOVA of Grooming-stratified HS subgroups yielded a significant *GROUP* effect in the percentage of buried marbles [$F_{(2,24)}$ = 6.896, p = .004]. Duncan's test revealed higher marble-burying behavior in the H-Groom rats than in the Medium-Groom and the Low-Groom groups, while no significant differences were found between the Medium-Groom and the High-Groom groups (%Marbles, Low-Groom: 2.8 ±1.8; Medium-Groom: 6.3 ±2.9; High-Groom: 36.8 ±11.9).

4. Discussion

The purpose of this study was to evaluate, in naïve outbred (HS) and inbred (Roman) rats, the relationships among PPI and other behavioral traits that are relevant in schizophrenia, such as altered exploratory/locomotor activity, anxiety and compulsive-like behavior. The present data suggest that augmented exploration is associated with deficient PPI in the genetically heterogeneous HS rats and the Roman rat strains.

The HS Low-PPI group displayed higher exploratory behavior in the open-field test than the Medium-PPI and High-PPI groups. The negative relationship between PPI and open-field exploratory activity was also supported by the following findings: (i) a significant negative correlation (-0.32) between both measures in the whole HS rat sample (n=92); (ii) the fact that both variables grouped (with opposite sign) in the third factor of the factorial analysis; (iii) the fact that, compared with their RLA counterparts, RHA rats exhibited low PPI and increased exploratory behavior in the open-field test. The “low PPI – high exploratory activity” association has also been observed in rodent models of schizophrenia involving different manipulations or treatments. Examples of this are the social isolation syndrome (Domeney and Feldon, 1998; Lukkes et al., 2009; Oliveras et al., 2016), the ventral hippocampal syndrome (Peleg-Raibstein and Feldon, 2006; Tseng et al., 2009; Wang et al., 2015), genetic mouse models (Kulikov et al., 2016; Miyakawa et al., 2003; Munesue et al., 2010; Powell and Miyakawa, 2006; Takao et al., 2013; Young et al., 2014) or amphetamine administration (Alsene et al., 2010; Blanc et al., 1994; Dickinson et al., 1988; Ott and Mandel, 1995; Swerdlow et al., 2002). All of these models are characterized by an impairment of PPI and an increase of exploratory activity. However, to our knowledge, the present is the first study in which the “low PPI – high exploratory activity” association is reported in untreated rats (i.e. at baseline) derived from different sources and strains (i.e. HS rats derived from 8 inbred strains and inbred Roman rats, derived from Wistar rats). In this context, it is worth to mention that studies with HS rats stratified by their PPI levels have revealed positive associations

among PPI and spatial working memory (Oliveras et al., 2015) and latent inhibition (Sánchez-González et al., 2016). Thus, these clusters among PPI and other attentional/cognitive and exploratory activity traits, and their consistency across different rat strains (i.e. HS and Roman rats), suggest that PPI may be a suitable predictor of other behavioral phenotypes related to schizophrenia.

No significant associations among PPI and anxiety-like behaviors were found in the correlational and factorial analyses. However, compared with the High-PPI group, the Low-PPI group showed an increased number of head dips in the elevated zero-maze, which may be indicative of lowered anxiety (Braun et al., 2011; Oliveras et al., 2016; Río-Ålamos et al., 2015; Shepherd et al., 1994). Remarkably, similar to the Low-PPI group, RHA rats showed a greater number of head dips and spent more time in the open sections of the elevated zero-maze than RLA rats. These results agree with some previous studies reporting that deficient PPI is found in animals with low anxiety (Lindemann et al., 2008; McAuley et al., 2009).

Regarding measures of compulsive-like behavior, i.e. self-grooming (Kalueff et al., 2015) and marble burying (Andersen et al., 2010), they did not show significant associations with PPI. Furthermore, self-grooming was increased in RLA vs. RHA rats but did not differ between the PPI-stratified HS subgroups. Thus, contrary to the finding that schizophrenic patients –characterized by PPI deficits– often present obsessive-compulsive symptoms, in our HS rat sample compulsive-like behaviors were not associated with PPI levels (see Table 2). Remarkably, factor analysis of HS data revealed a strong positive relationship between self-grooming and marble burying, and this was confirmed by the comparison among grooming-stratified HS subgroups. Hence, these results suggest that both compulsive-like parameters are part of a common trait in the HS rats. This evidence agrees with previous studies using genetically-altered models of compulsivity in mice (Sungur et al., 2014) and rats (Bahi, 2016), which have also reported positive associations between both compulsive-like parameters.

As mentioned above, the evidence supporting the “low PPI – high exploratory activity” association is mostly derived from animals submitted to a variety of pharmacological and genetic manipulations, whereas there is a relative paucity of data derived from genetically heterogeneous (i.e. outbred) naïve animals, which has better translational value in view of the high genetic heterogeneity of the human population. Therefore, the present experiments performed in HS rats provide novel information that may be used to detect, in animal models, phenotypic traits (or clusters of them) that are reminiscent of schizophrenia-relevant symptoms.

Acknowledgements

This work was supported by grants PSI2013-41872-P and PSI2017-82257-P (MINECO), 2014SGR-1587 (DGR), “ICREA-Academia 2013” (to A.F-T). C.T-E. is recipient of a Ph.D. FPU fellowship (MECD, FPU15/06307), I.O. is recipient of a Ph.D. FI fellowship (DGR 2014) and A.S-G. is recipient of a Ph.D. FPI fellowship.

References

Alsene, K.M., Fallace, K., Bakshi, V.P., 2010. Ventral Striatal Noradrenergic Mechanisms Contribute to Sensorimotor Gating Deficits Induced by Amphetamine. Neuropsychopharmacology 35, 2346–2356. https://doi.org/10.1038/npp.2010.106

Andersen, S.L., Greene-Colozzi, E.A., Sonntag, K.C., 2010. A novel, multiple symptom model of obsessive-compulsive-like behaviors in animals. Biol. Psychiatry 68, 741–7. https://doi.org/10.1016/j.biopsych.2010.05.011

Bahi, A., 2016. Sustained lentiviral-mediated overexpression of microRNA124a in the dentate gyrus exacerbates anxiety- and autism-like behaviors associated with neonatal isolation in rats. Behav. Brain Res. 311, 298–308. https://doi.org/10.1016/j.bbr.2016.05.033

Baud, A., Hermsen, R., Guryev, V., Stridh, P., Graham, D., McBride, M.W., Foroud, T., Calderari, S., Diez, M., Ockinger, J., Beyeen, A.D., Gillett, A., Abdelmagid, N., Guerreiro-Cacais, A.O., Jagodic, M., Tuncel, J., Norin, U., Beattie, E., Huynh, N., Miller, W.H., Koller, D.L., Alam, I., Falak, S., Osborne-Pellegrin, M., Martinez-Membrives, E., Canete, T., Blazquez, G., Vicens-Costa, E., Mont-Cardona, C., Diaz-Moran, S., Tobena, A., Hummel, O., Zelenika, D., Saar, K., Patone, G., Bauerfeind, A., Bihoreau, M.-T., Heinig, M., Lee, Y.-A., Rintisch, C., Schulz, H., Wheeler, D.A., Worley, K.C., Muzny, D.M., Gibbs, R.A., Lathrop, M., Lansu, N., Toonen, P., Ruzius, F.P., de Bruijn, E., Hauser, H., Adams, D.J., Keane, T., Atanur, S.S., Aitman, T.J., Flicek, P., Malinauskas, T., Jones, E.Y., Ekman, D., Lopez-Aumatell, R., Dominiczak, A.F., Johannesson, M., Holmdahl, R., Olsson, T., Gauguier, D., Hubner, N., Fernandez-Teruel, A., Cuppen, E., Mott, R., Flint, J., 2013. Combined sequence-based and genetic mapping analysis of complex traits in outbred rats. Nat. Genet. 45, 767–75. https://doi.org/10.1038/ng.2644

Blanc, G., Trovero, F., Vezina, P., Hervé, D., Godeheu, A.M., Glowinski, J., Tassin, J.P., 1994. Blockade of prefronto-cortical alpha 1-adrenergic receptors prevents locomotor hyperactivity induced by subcortical D-amphetamine injection. Eur. J. Neurosci. 6, 293–298. https://doi.org/10.1111/j.1460-9568.1994.tb00272.x

Bortolato, M., Godar, S.C., Davarian, S., Chen, K., Shih, J.C., 2009. Behavioral Disinhibition and Reduced Anxiety-like Behaviors in Monoamine Oxidase B-Deficient Mice. Neuropsychopharmacology 34, 2746–2757. https://doi.org/10.1038/npp.2009.118

Braff, D.L., Greenwood, T.A., Swerdlow, N.R., Light, G.A., Schork, N.J., 2008. Advances in endophenotyping schizophrenia. World Psychiatry 7, 11–18. https://doi.org/10.1002/j.2051-5545.2008.tb00140.x

Braga, R.J., Reynolds, G.P., Siris, S.G., 2013. Anxiety comorbidity in schizophrenia. Psychiatry Res. 210, 1–7. https://doi.org/10.1016/j.psychres.2013.07.030

Braun, A.A., Skelton, M.R., Vorhees, C. V, Williams, M.T., 2011. Comparison of the elevated plus and elevated zero mazes in treated and untreated male Sprague-Dawley rats: effects of anxiolytic and anxiogenic agents. Pharmacol. Biochem. Behav. 97, 406–15. https://doi.org/10.1016/j.pbb.2010.09.013

Brisch, R., Saniotis, A., Wolf, R., Bielau, H., Bernstein, H.-G., Steiner, J., Bogerts, B., Braun, A.K., Jankowski, Z., Kumaritlake, J., Henneberg, M., Gos, T., Henneberg, M., Gos, T., 2014. The Role of Dopamine in Schizophrenia from a Neurobiological and Evolutionary Perspective: Old Fashioned, but Still in Vogue. Front. Psychiatry 5, 47. https://doi.org/10.3389/fpsyt.2014.00047

Buckley, P.F., Miller, B.J., Lehrer, D.S., Castle, D.J., 2009. Psychiatric comorbidities and schizophrenia. Schizophr. Bull. 35, 383–402. https://doi.org/10.1093/schbul/sbn135

Díaz-Morán, S., Palència, M., Mont-Cardona, C., Cañete, T., Blázquez, G., Martínez-Membrives, E., López-Aumatell, R., Sabariego, M., Donaire, R., Morón, I., Torres, C., Martínez-Conejero, J.A., Tobeña, A., Esteban, F.J., Fernández-Teruel, A., 2013. Gene expression in amygdala as a function of differential trait anxiety levels in genetically heterogeneous NIH-HS rats. Behav. Brain Res. 252, 422–31. https://doi.org/10.1016/j.bbr.2013.05.066

Dickinson, S.L., Gadie, B., Tulloch, I.F., 1988. α1- and α2-Adrenoreceptor antagonists differentially influence locomotor and stereotyped behaviour induced by d-amphetamine and apomorphine in the rat. Psychopharmacology (Berl). 96, 521–527. https://doi.org/10.1007/BF02180034

Domeney, A., Feldon, J., 1998. The disruption of prepulse inhibition by social isolation in the wistar rat: How robust is the effect? Pharmacol. Biochem. Behav. 59, 883–890. https://doi.org/10.1016/S0091-3057(97)00534-0

Driscoll, P., Escorihuela, R.M., Fernandez-Teruel, A., Giorgi, O., Schwegler, H., Steimer, T., Wiersma, A., Corda, M.G., Flint, J., Koolhaas, J.M., Langhans, W., Schulz, P.E., Siegel, J., Tobeña, A., 1998. Genetic Selection and Differential Stress Responses: The Roman Lines/Strains of Rats. Ann. N. Y. Acad. Sci. 851, 501–510. https://doi.org/10.1111/j.1749-6632.1998.tb09029.x

Escorihuela, R.M., Fernández-Teruel, A., Gil, L., Aguilar, R., Tobeña, A., Driscoll, P., 1999. Inbred roman high- and low-avoidance rats: Differences in anxiety, novelty-seeking, and shuttlebox behaviors. Physiol. Behav. 67, 19–26. https://doi.org/10.1016/S0031-9384(99)00064-5

Esnal, A., Sánchez-González, A., Río-Álamos, C., Oliveras, I., Cañete, T., Blázquez, G., Tobeña, A., Fernández-Teruel, A., 2016. Prepulse inhibition and latent inhibition deficits in Roman high-avoidance vs. Roman low-avoidance rats: Modeling schizophrenia-related features. Physiol. Behav. 163, 267–273. https://doi.org/10.1016/j.physbeh.2016.05.020

Fernández-Teruel, A., Blázquez, G., Pérez, M., Aguilar, R., Cañete, T., Guitart, M., Giménez-Llort, L., Tobeña, A., 2006. Latent inhibition threshold in Roman high-avoidance rats: A psychogenetic model of abnormalities in attentional filter? Actas Esp. Psiquiatr. 34, 257–263.

Fomsgaard, L., Moreno, J.L., de la Fuente Revenga, M., Brudek, T., Adamsen, D., Rio-Alamos, C., Saunders, J., Klein, A.B., Oliveras, I., Cañete, T., Blazquez, G., Tobeña, A., Fernandez-Teruel, A., Gonzalez-Maeso, J., Aznar, S., 2017. Differences in 5-HT2A and mGlu2 Receptor Expression Levels and Repressive Epigenetic Modifications at the 5-HT2A Promoter Region in the Roman Low- (RLA-I) and High- (RHA-I) Avoidance Rat Strains. Mol. Neurobiol. https://doi.org/10.1007/s12035-017-0457-y

Giorgi, O., Piras, G., Corda, M.G., 2007. The psychogenetically selected Roman high- and low-avoidance rat lines: a model to study the individual vulnerability to drug addiction. Neurosci. Biobehav. Rev. 31, 148–63. https://doi.org/10.1016/j.neubiorev.2006.07.008

Glausier, J.R., Fish, K.N., Lewis, D.A., 2014. Altered parvalbumin basket cell inputs in the dorsolateral prefrontal cortex of schizophrenia subjects. Mol. Psychiatry 19, 30–36. https://doi.org/10.1038/mp.2013.152

González-Maeso, J., Ang, R.L., Yuen, T., Chan, P., Weisstaub, N. V, López-Giménez,

J.F., Zhou, M., Okawa, Y., Callado, L.F., Milligan, G., Gingrich, J.A., Filizola, M., Meana, J.J., Sealfon, S.C., 2008. Identification of a serotonin/glutamate receptor complex implicated in psychosis. Nature 452, 93–7. https://doi.org/10.1038/nature06612

Graham, F.K., 1975. The more or less startling effects of weak prestimulation. Psychophysiology. https://doi.org/10.1111/j.1469-8986.1975.tb01284.x

Guitart-Masip, M., Johansson, B., Cañete, T., Fernández-Teruel, A., Tobeña, A., Terenius, L., Giménez-Llort, L., 2008. Regional adaptations in PSD-95, NGFI-A and secretogranin gene transcripts related to vulnerability to behavioral sensitization to amphetamine in the Roman rat strains. Neuroscience 151, 195–208. https://doi.org/10.1016/j.neuroscience.2007.09.072

Hansen, C., Spuhler, K., 1984. Development of the National Institutes of Health Genetically Heterogeneous Rat Stock. Alcohol. Clin. Exp. Res. 8, 477–479. https://doi.org/10.1111/j.1530-0277.1984.tb05706.x

Hutchison, K.E., Swift, R., 1999. Effect of d-amphetamine on prepulse inhibition of the startle reflex in humans. Psychopharmacology (Berl). 143, 394–400. https://doi.org/10.1007/s002130050964

Kalueff, A. V., Stewart, A.M., Song, C., Berridge, K.C., Graybiel, A.M., Fentress, J.C., 2015. Neurobiology of rodent self-grooming and its value for translational neuroscience. Nat. Rev. Neurosci. 17, 45–59. https://doi.org/10.1038/nrn.2015.8

Kinney, G.G., Wilkinson, L.O., Saywell, K.L., Tricklebank, M.D., 1999. Rat strain differences in the ability to disrupt sensorimotor gating are limited to the dopaminergic system, specific to prepulse inhibition, and unrelated to changes in startle amplitude or nucleus accumbens dopamine receptor sensitivity. J. Neurosci. 19, 5644–5653.

Klein, A.B., Ultved, L., Adamsen, D., Santini, M.A., Tobeña, A., Fernandez-Teruel, A., Flores, P., Moreno, M., Cardona, D., Knudsen, G.M., Aznar, S., Mikkelsen, J.D., 2014. 5-HT2A and mGlu2 receptor binding levels are related to differences in impulsive behavior in the Roman Low- (RLA) and High- (RHA) avoidance rat strains. Neuroscience 263, 36–45. https://doi.org/10.1016/j.neuroscience.2013.12.063

Kokkinidis, L., Anisman, H., 1981. Amphetamine psychosis and schizophrenia: A dual model. Neurosci. Biobehav. Rev. 5, 449–461. https://doi.org/10.1016/0149-7634(81)90015-4

Kulikov, A. V., Korostina, V.S., Kulikova, E.A., Fursenko, D. V., Akulov, A.E., Moshkin, M.P., Prokhortchouk, E.B., 2016. Knockout Zbtb33 gene results in an increased locomotion, exploration and pre-pulse inhibition in mice. Behav. Brain Res. 297, 76–83. https://doi.org/10.1016/j.bbr.2015.10.003

Kumari, V., Mulligan, O.F., Cotter, P.A., Poon, L., Toone, B.K., Checkley, S.A., Gray, J.A., 1998. Effects of single oral administrations of haloperidol and d-amphetamine on prepulse inhibition of the acoustic startle reflex in healthy male volunteers. Behav. Pharmacol. 9, 567–576. https://doi.org/10.1097/00008877-199811000-00012

Lindemann, S., Gernert, M., Bennay, M., Koch, M., Löscher, W., 2008. Comparative analysis of anxiety-like behaviors and sensorimotor functions in two rat mutants, ci2 and ci3, with lateralized rotational behavior. Physiol. Behav. 93, 417–426. https://doi.org/10.1016/j.physbeh.2007.11.034

Lukkes, J.L., Watt, M.J., Lowry, C.A., Forster, G.L., 2009. Consequences of post-

weaning social isolation on anxiety behavior and related neural circuits in rodents. Front. Behav. Neurosci. 3, 18. https://doi.org/10.3389/neuro.08.018.2009

Maple, A.M., Call, T., Kimmel, P.C., Hammer, R.P., 2017. Effects of Repeated Ropinirole Treatment on Phencyclidine-Induced Hyperlocomotion, Prepulse Inhibition Deficits, and Social Avoidance in Rats. J. Pharmacol. Exp. Ther. 361, 109–114. https://doi.org/10.1124/jpet.116.238634

Martínez-Membrives, E., López-Aumatell, R., Blázquez, G., Cañete, T., Tobeña, A., Fernández-Teruel, A., 2015. Spatial learning in the genetically heterogeneous NIH-HS rat stock and RLA-I/RHA-I rats: Revisiting the relationship with unconditioned and conditioned anxiety. Physiol. Behav. 144, 15–25. https://doi.org/10.1016/j.physbeh.2015.03.003

McAuley, J.D., Stewart, A.L., Webber, E.S., Cromwell, H.C., Servatius, R.J., Pang, K.C.H., 2009. Wistar–Kyoto rats as an animal model of anxiety vulnerability: Support for a hypervigilance hypothesis. Behav. Brain Res. 204, 162–168. https://doi.org/10.1016/j.bbr.2009.05.036

Miyakawa, T., Leiter, L.M., Gerber, D.J., Gainetdinov, R.R., Sotnikova, T.D., Zeng, H., Caron, M.G., Tonegawa, S., 2003. Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. Proc. Natl. Acad. Sci. 100, 8987–8992. https://doi.org/10.1073/pnas.1432926100

Moreno, M., Cardona, D., Gómez, M.J., Sánchez-Santed, F., Tobeña, A., Fernández-Teruel, A., Campa, L., Suñol, C., Escarabajal, M.D., Torres, C., Flores, P., 2010. Impulsivity Characterization in the Roman High- and Low-Avoidance Rat Strains: Behavioral and Neurochemical Differences. Neuropsychopharmacology 35, 1198–1208. https://doi.org/10.1038/npp.2009.224

Munesue, T., Yokoyama, S., Nakamura, K., Anitha, A., Yamada, K., Hayashi, K., Asaka, T., Liu, H.-X., Jin, D., Koizumi, K., Islam, M.S., Huang, J.-J., Ma, W.-J., Kim, U.-H., Kim, S.-J., Park, K., Kim, D., Kikuchi, M., Ono, Y., Nakatani, H., Suda, S., Miyachi, T., Hirai, H., Salmina, A., Pichugina, Y.A., Soumarokov, A.A., Takei, N., Mori, N., Tsujii, M., Sugiyama, T., Yagi, K., Yamagishi, M., Sasaki, T., Yamasue, H., Kato, N., Hashimoto, R., Taniike, M., Hayashi, Y., Hamada, J., Suzuki, S., Ooi, A., Noda, M., Kamiyama, Y., Kido, M.A., Lopatina, O., Hashii, M., Amina, S., Malavasi, F., Huang, E.J., Zhang, J., Shimizu, N., Yoshikawa, T., Matsushima, A., Minabe, Y., Higashida, H., 2010. Two genetic variants of CD38 in subjects with autism spectrum disorder and controls. Neurosci. Res. 67, 181–91. https://doi.org/10.1016/j.neures.2010.03.004

Oliveras, I., Río-Álamos, C., Cañete, T., Blázquez, G., Martínez-Membrives, E., Giorgi, O., Corda, M.G., Tobeña, A., Fernández-Teruel, A., 2015. Prepulse inhibition predicts spatial working memory performance in the inbred Roman high- and low-avoidance rats and in genetically heterogeneous NIH-HS rats: relevance for studying pre-attentive and cognitive anomalies in schizophrenia. Front. Behav. Neurosci. 9, 213. https://doi.org/10.3389/fnbeh.2015.00213

Oliveras, I., Sánchez-González, A., Piludu, M.A., Gerboles, C., Río-Álamos, C., Tobeña, A., Fernández-Teruel, A., 2016. Divergent effects of isolation rearing on prepulse inhibition, activity, anxiety and hippocampal-dependent memory in Roman high- and low-avoidance rats: A putative model of schizophrenia-relevant features. Behav. Brain Res. 314, 6–15. https://doi.org/10.1016/j.bbr.2016.07.047

Ott, D.A., Mandel, R.J., 1995. Amphetamine sensitivity in open-field activity vs. the prepulse inhibition paradigm. Brain Res. Bull. 37, 219–22. https://doi.org/10.1016/0361-9230(94)00276-7

Peleg-Raibstein, D., Feldon, J., 2006. Effects of dorsal and ventral hippocampal NMDA stimulation on nucleus accumbens core and shell dopamine release. Neuropharmacology 51, 947–957. https://doi.org/10.1016/j.neuropharm.2006.06.002

Powell, C.M., Miyakawa, T., 2006. Schizophrenia-Relevant Behavioral Testing in Rodent Models: A Uniquely Human Disorder? Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2006.05.008

Río-Álamos, C., Gerbolés, C., Tapias-Espinosa, C., Sampedro-Viana, D., Oliveras, I., Sánchez-González, A., Cañete, T., Blázquez, G., del Mar López, M., Baldellou, C., Otaegui, P.J., Tobeña, A., Fernández-Teruel, A., 2017. Conservation of Phenotypes in the Roman High- and Low-Avoidance Rat Strains After Embryo Transfer. Behav. Genet. 47, 537–551. https://doi.org/10.1007/s10519-017-9854-2

Río-Álamos, C., Oliveras, I., Cañete, T., Blázquez, G., Martínez-Membrives, E., Tobeña, A., Fernández-Teruel, A., 2015. Neonatal handling decreases unconditioned anxiety, conditioned fear, and improves two-way avoidance acquisition: a study with the inbred Roman high (RHA-I)- and low-avoidance (RLA-I) rats of both sexes. Front. Behav. Neurosci. 9, 174. https://doi.org/10.3389/fnbeh.2015.00174

Sánchez-González, A., Esnal, A., Río-Álamos, C., Oliveras, I., Cañete, T., Blázquez, G., Tobeña, A., Fernández-Teruel, A., 2016. Association between prepulse inhibition of the startle response and latent inhibition of two-way avoidance acquisition: A study with heterogeneous NIH-HS rats. Physiol. Behav. 155, 195–201. https://doi.org/10.1016/j.physbeh.2015.12.011

Shepherd, J.K., Grewal, S.S., Fletcher, A., Bill, D.J., Dourish, C.T., 1994. Behavioural and pharmacological characterisation of the elevated "zero-maze" as an animal model of anxiety. Psychopharmacology (Berl). 116, 56–64.

Snyder, S.H., 1973. Amphetamine psychosis: a “model” schizophrenia mediated by catecholamines. Am. J. Psychiatry 130, 61–67. https://doi.org/10.1176/ajp.130.1.61

Steimer, T., Driscoll, P., 2005. Inter-individual vs line/strain differences in psychogenetically selected Roman High-(RHA) and Low-(RLA) Avoidance rats: Neuroendocrine and behavioural aspects. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2004.07.002

Sungur, A.Ö., Vörckel, K.J., Schwarting, R.K.W., Wöhr, M., 2014. Repetitive behaviors in the Shank1 knockout mouse model for autism spectrum disorder: Developmental aspects and effects of social context. J. Neurosci. Methods 234, 92–100. https://doi.org/10.1016/j.jneumeth.2014.05.003

Swerdlow, N.R., Geyer, M.A., Braff, D.L., 2001. Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. Psychopharmacology (Berl). 156, 194–215. https://doi.org/10.1007/s002130100799

Swerdlow, N.R., Shoemaker, J.M., Bongiovanni, M.J., Neary, A.C., Tochen, L.S., Saint Marie, R.L., 2007. Strain differences in the disruption of prepulse inhibition of startle after systemic and intra-accumbens amphetamine administration. Pharmacol. Biochem. Behav. 87, 1–10. https://doi.org/10.1016/j.pbb.2007.03.014

Swerdlow, N.R., Stephany, N., Wasserman, L.C., Talledo, J., Shoemaker, J., Auerbach, P.P., 2002. Amphetamine Effects on Prepulse Inhibition Across-Species: Replication and Parametric Extension. Neuropsychopharmacology 28, 640–650. https://doi.org/10.1038/sj.npp.1300086

Takao, K., Kobayashi, K., Hagihara, H., Ohira, K., Shoji, H., Hattori, S., Koshimizu, H., Umemori, J., Toyama, K., Nakamura, H.K., Kuroiwa, M., Maeda, J., Atsuzawa, K., Esaki, K., Yamaguchi, S., Furuya, S., Takagi, T., Walton, N.M., Hayashi, N., Suzuki, H., Higuchi, M., Usuda, N., Suhara, T., Nishi, A., Matsumoto, M., Ishii, S., Miyakawa, T., 2013. Deficiency of Schnurri-2, an MHC Enhancer Binding Protein, Induces Mild Chronic Inflammation in the Brain and Confers Molecular, Neuronal, and Behavioral Phenotypes Related to Schizophrenia. Neuropsychopharmacology 38, 1409–1425. https://doi.org/10.1038/npp.2013.38

Tournier, B.B., Steimer, T., Millet, P., Moulin-Sallanon, M., Vallet, P., Ibañez, V., Ginovart, N., 2013. Innately low D2 receptor availability is associated with high novelty-seeking and enhanced behavioural sensitization to amphetamine. Int. J. Neuropsychopharmacol. 16, 1819–34. https://doi.org/10.1017/S1461145713000205

Tseng, K.Y., Chambers, R.A., Lipska, B.K., 2009. The neonatal ventral hippocampal lesion as a heuristic neurodevelopmental model of schizophrenia. Behav. Brain Res. 204, 295–305. https://doi.org/10.1016/j.bbr.2008.11.039

Wang, J., Li, G., Xu, Y., Zhang, W.-N., 2015. Hyperactivity and disruption of prepulse inhibition induced by NMDA infusion of the rat ventral hippocampus: Comparison of uni- and bilateral stimulation. Neurosci. Lett. 594, 150–154. https://doi.org/10.1016/j.neulet.2015.03.066

Wood, C.M., Nicolas, C.S., Choi, S.L., Roman, E., Nylander, I., Fernandez-Teruel, A., Kiianmaa, K., Bienkowski, P., de Jong, T.R., Colombo, G., Chastagnier, D., Wafford, K.A., Collingridge, G.L., Wildt, S.J., Conway-Campbell, B.L., Robinson, E.S.J., Lodge, D., 2017. Prevalence and influence of cys407* Grm2 mutation in Hannover-derived Wistar rats: mGlu2 receptor loss links to alcohol intake, risk taking and emotional behaviour. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2016.03.020

Young, J.W., Ratty, A., Dawe, G.S., Geyer, M.A., 2014. Altered exploration and sensorimotor gating of the chakragati mouse model of schizophrenia. Behav. Neurosci. 128, 460–467. https://doi.org/10.1037/a0036425

Table legends

Table 1. **Pearson's correlations among the main variables in the HS rats (n=92).** "OF_Activity" refers to the number of activity episodes (crossings + rearings) in the open field. "OF_Grooming" corresponds to time spent self-grooming in the open field. "ZM_Osections", time spent in the open sections of the elevated zero maze. "ZM_Hdips", number of head dips in the elevated zero maze. "%MBT", percentage of buried marbles in the marble burying test. "%PPI", mean of the percentatge of pre-pulse inhibition at pre-pulse intensities of 65 and 70 dB. "StartleR", baseline startle response. *, $p<0.05$; ** $p<0.01$ (2-tailed).

Table 2. Factorial analysis of the performance of HS rats (n=92). Oblique three-factor solution (direct oblimin) with the main selected behavioral variables (2 from each test except for the marble burying test) and correlations between factors. Only factors with eigenvalues greater than 1 are considered. Loadings $\geq$.40 are shown. Symbols/abbreviations as in Table 1.

Figure legends

Figure 1. Experimental timeline. HS, RHA and RLA rats underwent three consecutive tests of exploratory activity (open field, elevated zero maze and marble burying test) before being tested for sensorimotor gating in the prepulse inhibition test (PPI). Each test was separated by a 7-day interval. The main variables of each test are indicated. As it is shown in the last arrows, HS rats were divided into Low-PPI, Medium-PPI and High-PPI to analyze their previous performance in the exploratory activity tests**.**

Figure 2. Prepulse Inhibition Test. Mean ± SEM of the "% of PPI" averaged for the 65 and 70 dB prepulse intensities in **a)** HS rats with Low-PPI (n=9), Medium-PPI (n=9) and High-PPI (n=9) and **b)** RHA (n=12) and RLA (n=12) rats. *: $p < 0.05$ between the indicated groups (Duncan's tests for "a" and Student's t-test for "b").

Figure 3. Open Field. Mean ± SEM of **a)** number of exploratory activity episodes (crossings + rearings) and **b)** time spent self-grooming in HS rats with Low-PPI (n=9), Medium-PPI (n=9) and High-PPI (n=9). Mean ± SEM of **c)** number of exploratory activity episodes (crossings + rearings) and **d)** time spent self-grooming in RHA (n=12) and RLA (n=12) rats. *: $p < 0.05$ between the indicated groups (Duncan's tests for "a" and Student's t-test for "c" and "d"), *ns*: not significant.

Figure 4. Elevated Zero Maze. Mean ± SEM of **a)** time spent in the open sections, **b)** number of head dips in HS rats with Low-PPI (n=9), Medium-PPI (n=9) and High-PPI (n=9). Mean ± SEM of **c)** time spent in the open sections, **d)** number of head dips in RHA (n=12) and RLA (n=12) rats. *: $p < 0.05$ between the indicated groups (Duncan's tests for "b" and "c", and Student's t-test for "d" and "e"), *ns*: not significant.

Table 1. Pearson's correlations of the main behavioral variables in the HS rat sample (n=92).

Variables	*1*	*2*	*3*	*4*	*5*	*6*	*7*
OF_Activity	1						
OF_Grooming	-.13	1					
ZM_Osections	**.31****	.06	1				
ZM_Hdips	**.26***	.18	**.74****	1			
%MBT	.07	**.46****	-.07	-.03	1		
%PPI	**-.32****	.11	.09	-.12	.04	1	
StartleR	-.08	.08	-.11	-.17	.08	.09	1

Table 2. Factorial analysis of the main behavioral variables in the HS rat sample (n=92).

	Factors		
Variables	1	2	3
OF_Activity	-	-	.-76
OF_Grooming	-	.83	-
ZM_Osections	.92	-	-
ZM_Hdips	.93	-	-
%MBT	-	.87	-
%PPI	-	-	.77
StartleR	-	-	-
% of cumulative variance	28.61%	50.35%	66.56%
Factor correlations	1		
	.05	1	
	.16	.08	1

Figure 1

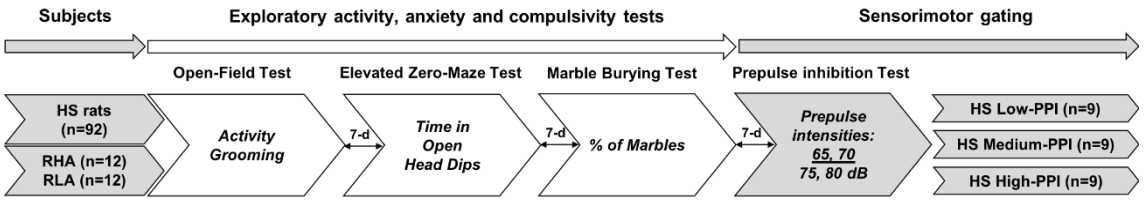

Subjects
Exploratory activity, anxiety and compulsivity tests
Sensorimotor gating
Open-Field Test
Elevated Zero-Maze Test
Marble Burying Test
Prepulse inhibition Test
HS rats (n=92)
RHA (n=12)
RLA (n=12)
Activity
Grooming
7-d
Time in Open Head Dips
7-d
% of Marbles
7-d
Prepulse intensities:
65, 70
75, 80 dB
HS Low-PPI (n=9)
HS Medium-PPI (n=9)
HS High-PPI (n=9)

Figure 2

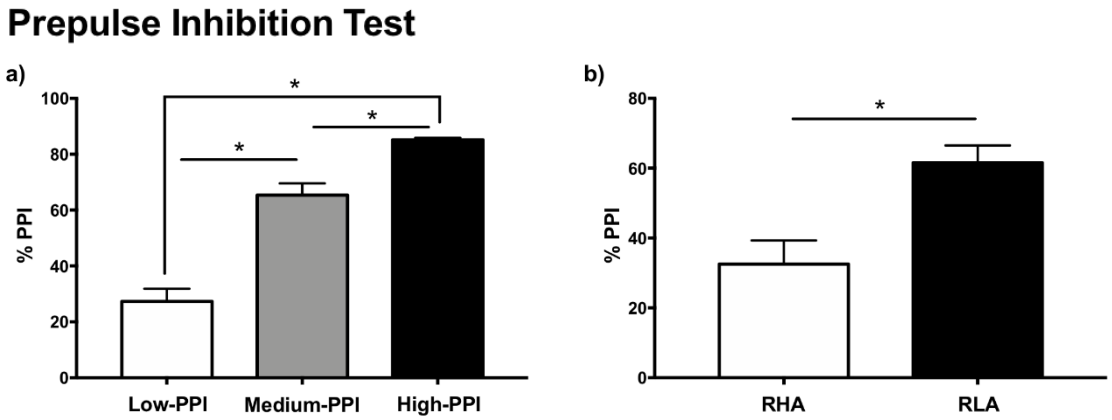

Prepulse Inhibition Test
a)
% PPI
100
80
60
40
20
0
*
*
*
Low-PPI
Medium-PPI
High-PPI
b)
% PPI
80
60
40
20
0
*
RHA
RLA

Figure 3

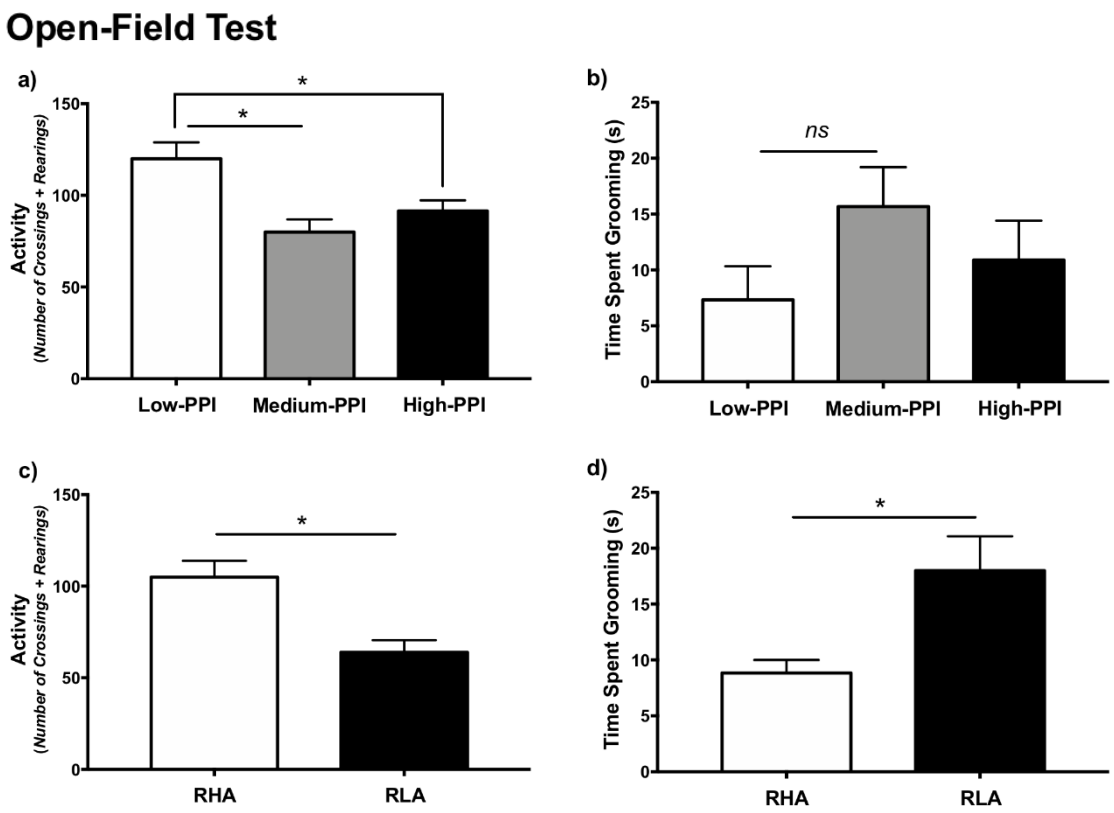
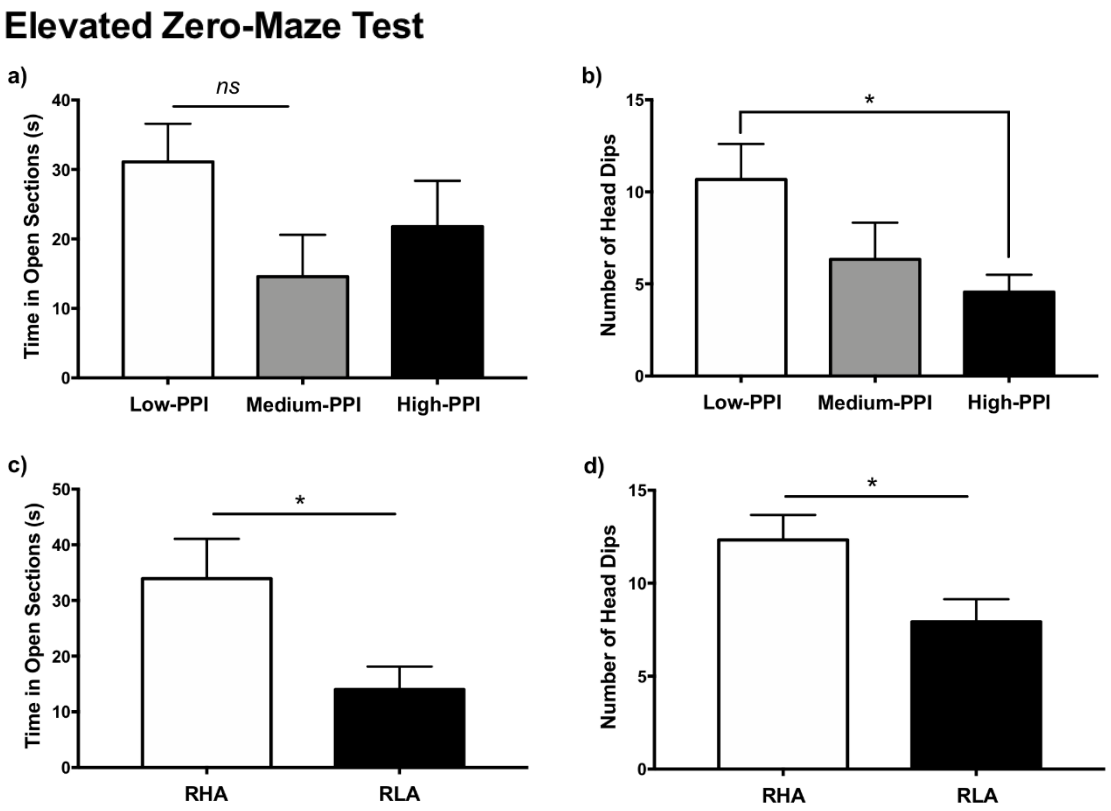

Open-Field Test
a)
Activity
(Number of Crossings + Rearings)
150
100
50
0
*
*
Low-PPI
Medium-PPI
High-PPI
b)
Time Spent Grooming (s)
25
20
15
10
5
0
ns
Low-PPI
Medium-PPI
High-PPI
c)
Activity
(Number of Crossings + Rearings)
150
100
50
0
*
RHA
RLA
d)
Time Spent Grooming (s)
25
20
15
10
5
0
*
RHA
RLA

Figure 4


Elevated Zero-Maze Test
a)
ns
Time in Open Sections (s)
0
10
20
30
40
Low-PPI
Medium-PPI
High-PPI
b)
*
Number of Head Dips
0
5
10
15
Low-PPI
Medium-PPI
High-PPI
c)
*
Time in Open Sections (s)
0
10
20
30
40
50
RHA
RLA
d)
*
Number of Head Dips
0
5
10
15
RHA
RLA