Environmental enrichment improves cognitive deficits in Spontaneously Hypertensive Rats (SHR): Relevance for Attention Deficit/Hyperactivity Disorder (ADHD)

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**Abstract**

The interaction between genes and environment seems to be relevant for the development of Attention Deficit/Hyperactivity Disorder (ADHD), one of the most prevalent childhood psychiatric diseases. The occurrence of ADHD is typically associated with poor academic performance, probably reflecting learning difficulties and/or cognitive impulsiveness. The inbred Spontaneously Hypertensive Rats (SHR) strain has often been considered as an animal model of ADHD, since they ‘naturally’ display the main ADHD symptomatology. Although pharmacological agents improve SHR’s cognitive deficits, little is known about the involvement of environmental factors in SHR disabilities and to what extent ‘protective’ non-pharmacological factors may be considered as strategy for ADHD prevention. Here we investigated whether the rearing environment during neurodevelopment may counteract later cognitive deficits presented by adult SHR. Wistar (WIS) rats were also used to investigate whether the putative effects of environmental enrichment depend on a specific genetic background. The animals were reared in enriched environment (EE) or standard environment (SE) from the post-natal day 21 until 3 months of age (adulthood) and tested for maze spatial reference, social and object recognition tasks, while non-cognitive traits, such as nociception and hypertension, were not affected by EE. Response of WIS rats was generally not affected by the present EE. These results show that the general low cognitive performance presented by SHR rats strongly depends on the rearing environment and they may suggest modifications of the familial environment as a putative preventive strategy to cope with ADHD.

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**1. Introduction**

The interaction between environmental and genetic factors seems to be relevant for the development of one of the most prevalent childhood psychiatric diseases, namely Attention Deficit/Hyperactivity Disorder (ADHD) (Brookes et al., 2006; Thapar et al., 2005). ADHD affects approximately 5–10% of school-aged children in U.S.A. and other countries (American-Academy-of-Pediatrics, 2000; Faraone et al., 2003) and its core symptoms are motor overactivity and inattention, although the clinical presentation of the disease is much more heterogeneous and involves complex motor and cognitive processes, such as impulsivity and social impairments (Barkley and Biederman, 1997; Himelstein et al., 2000; Taylor et al., 2004; Wilens and Dodson, 2004). The occurrence of ADHD is typically associated with poor academic performance, probably reflecting learning difficulties and/or cognitive impulsiveness (Mannuzza et al., 1993; Wilens and Dodson, 2004). Pharmacotherapy using psychostimulant medications, such as methylphenidate, is rigorously the most accepted pharmacological treatment for ADHD patients (Krause et al., 2002). The diagnosis and treatment of ADHD patients normally occur during childhood/adolescence (Wilens and Dodson, 2004), but little is known about the persistent effects of treatment with psychostimulants during childhood (Wilens and Dodson, 2004). Arguably, early post-natal treatment with psychotropic drugs exposes individuals to the threat of long-term neurodevelopmental consequences, which may override the drug’s therapeutic effects (Andersen and Navalta, 2004). In face of this risk, the search for alternative/complementary non-pharmacological therapeutic approaches for ADHD is a field of high interest.

Among the several genetic and drug-induced animal models of ADHD available, the inbred Spontaneously Hypertensive Rats (SHR) strain has often been considered the most validated model, since they ‘naturally’ display the main ADHD symptomatology, including
hyperactivity, impulsivity and poorly sustained attention (Russell, 2007; Sagvolden et al., 2005). Although SHR's hyperactivity has been questioned – and almost exclusively appears in response to novelty and in comparison to Wistar–Kyoto rats (Ferguson and Cada, 2003) – the cognitive deficits of SHR have been extensively reported in several behavioral paradigms by our group (Pires et al., 2009; Prediger et al., 2005a,b) and others (De Bruin et al., 2003; Kantak et al., 2008; Nakamura-Palacios et al., 1996; Sagvolden and Xu, 2008). For this reason, the SHR strain is of interest in the study of neurobiological changes involved in ADHD and for testing of new therapeutic interventions for cognitive dysfunctions (Takahashi et al., 2008). Although different pharmacological approaches have been successfully tested in SHR, and therefore suggested as alternatives for ADHD therapy, relatively little is known about the involvement of environmental factors in ADHD-like symptomatology presented by this rat strain and to what extent ‘protective’ non-pharmacological factors may be considered as preventive strategies for such behavioral abnormalities.

One potential non-pharmacological approach to neurological disorders is environmental enrichment, which induces beneficial effects against cognitive dysfunctions (Kempermann et al., 1997; van Praag et al., 2000). In a broad sense, environmental enrichment is an experimental paradigm in animals which supposedly parallel physical, social and intellectual activity of humans. These include encouragements to perform physical exercise (e.g., running wheels), exposure to a variety of active and passive sensorial stimuli (e.g., toys and colored objects), opportunity to forage for food and water (e.g. changing the location of eating and drinking places) and increased social contact. Long-term exposure to an enriched environment (EE) stimulates neurogenesis, elicits neuroprotective responses and induces synaptic structural changes that enhance learning and memory (Kempermann et al., 1997; van Praag et al., 2000). However, little is known about the effects of EE in the symptomatology of ADHD.

Therefore, the aim of the present study was to investigate whether the exposure to EE during neurodevelopment may prevent later cognitive deficits presented by adult SHR. The animals have been also tested for a non-cognitive behavioral trait (nociception) and a physiological measure (arterial pressure). Wistar (WIS) rats were also included in the present study as a ‘normal’ heterogenic outbred strain, to investigate whether the effects of EE depend on a specific genetic background.

2. Methods

2.1. Subjects

WIS and SHR rats from our own colony were separated from their mother at the age of 21 days and the male pups were reared in EE or in standard conditions (see below). They were maintained under controlled temperature (23 ± 1 °C), with a 12 h light cycle (lights on 7:00 a.m.) and free access to food and water. Male rats of both strains were tested during adulthood (3 months old), weighing about 280–340 g (WIS) or 250–300 g (SHR). Juvenile male rats of these strains (approximately 1 month old, 100–150 g) were kept in groups of 10 per cage and served as social stimuli for the adult rats of the correspondent strain in the social recognition task. The procedures used in the present study follow the rules of the UFSC Ethics Committee on the Use of Animals and respect international guidelines on animal care. The authors further attest that all efforts were made to minimize the number of animals used and their suffering.

2.2. Environmental enrichment

From the post-natal day 21 until the age of 3 months (and throughout behavioral testing), WIS and SHR rats were maintained in groups of 7–10 animals in an enriched environment (EE) or in groups of 4–5 animals in each of two cages of standard environment (SE). The EE consisted of two specially designed plastic cages (46 × 33 × 23 cm) with a wire mesh cover and connected to each other by a plastic tube (10 cm diameter, 20 cm long). These EE cages were equipped with a set of plastic tubes, a running wheel, wood shelter and small colorful toys, providing multimodality stimulation (Nithianantharajah and Hannan, 2006; van Praag et al., 2000). Twice a week the EE was cleaned and the objects inside were rearranged to enhance novelty. The SE consisted of a standard plastic cage (42 × 34 × 17 cm) with a wire mesh cover. Rats in EE and SE groups were subjected to the same cleaning and handling procedures and reared in parallel in two cage setups. EE rats were transferred to a clean collective cage right after testing and back to the EE by the end of a given experimental session.

2.3. Behavioral tests

The behavioral tests were conducted in three independent cohorts of WIS and SHR rats, reared at the same time in two sets of standard (SE) and enriched (EE) cages. One group was tested in the open field habituation and water maze tasks, the second group in the object recognition and hot-plate tests and the third one was used for social recognition task and arterial pressure measurements. Tests were run in the order listed, from the least aversive to the most aversive, to minimize the chance that behavioral responses were markedly altered by prior test history (Mclwain et al., 2001). Behavior was monitored through a video camera positioned above the apparatuses and the images were analyzed online, in an adjacent room, by an experienced experimenter who was unaware of the strain and experimental group of the animals tested.

2.3.1. Open field habituation task

The open field was made of white-painted wood, with a white floor of 100 × 100 cm (divided by black lines into 25 squares of 20 × 20 cm) and 40 cm–high white walls. The experiments were conducted in a sound-attenuated room under low-intensity light (10 lx). In the habituation task, the animals were allowed to explore the open field for 10 min in two consecutive days. The number of squares crossed was registered as an index of general activity (Rodgers, 1997). The apparatus was cleaned with ethanol solution (10% v/v) and dried with paper towels after each trial in order to avoid odor impregnation.

2.3.2. Water maze spatial reference task

The water maze was made of black painted fiberglass, 1.70 m inside diameter, 0.8 m high, and filled to a depth of 0.6 m with water maintained at 25 °C. The target platform (10 × 10 cm) was made of transparent Plexiglas and submerged 1–1.5 cm beneath the surface of the water in the center of one quadrant (approximately 35 cm from the wall). The animals were subjected to a spatial reference task of the water maze following a protocol previously established in our laboratory (Takahashi et al., 2008). The training session consisted of six consecutive trials during which the animals were left in a starting point in the tank and allowed to swim freely to the submerged platform. The animal was allowed to remain on the platform for 10 s after escaping to it and was then removed from the tank for 20 s before being placed at the starting point for the next trial. The platform was located in a fixed position throughout the training session, whereas the starting point was different for each trial. The time necessary to reach the platform (escape latency) was registered for each training trial and animals that did not find the platform during a period of 60 s were gently guided to it. The test session was carried out 24 h later and consisted of a single probe trial where the platform was removed from the pool and each animal was allowed to swim for 60 s in the maze. The time spent in the correct quadrant (i.e. where the platform was located on the training session) was recorded and analyzed as percentage of the total time.
2.3.3. Social recognition task

The social memory was assessed with the social recognition task originally described by Dantzer et al. (1987) and previously used in our laboratory (Prediger et al., 2005a). Adult rats from both the SE and EE groups were individually housed for 7 days in standard plastic cages and the juvenile rats used as social stimuli were isolated for 20 min before the experiment. The social recognition task consisted of two consecutive 5-min presentations to the same juvenile rat, separated by an interval of 30 min, during which the juvenile rats were kept in individual cages. The experimental adult animals remained in the home cage, where they were isolated beforehand. The time spent by the adult rat investigating the juvenile (sniffing, grooming or touching) was recorded during each exposure. The short-term social recognition memory is expressed as a reduction in the investigation time during the second exposure compared to the first.

2.3.4. Object recognition task

The object recognition task was conducted in the open field in three distinct phases: habituation, sample and discrimination (Ennaceur and Delacour, 1988). The habituation phase consisted of...
exploration of the open field for 10 min in two consecutive days. In the sample phase, 24 h later, two identical objects (A1 and A2, cubes) were placed in opposite corners of the open field for 3 min of free exploration. The rats stayed for 30 min in the home cages before start of the discrimination phase. Then, objects A1 and A2 were replaced by an identical copy of the familiar object (A3) and a novel object (B) for 3 min of exploration. Object locations were counterbalanced. Exploration of an object was defined as directing the nose to the object at a distance of less than 2 cm and/or touching it with the nose (Ennaceur and Delacour, 1988). The following measures were considered: total exploration time (A1 + A2) in the sample phase and discrimination index (B – A3 / B + A3) in the discrimination phase.

2.3.5. Hot-plate

The hot-plate test was performed as previously established in our laboratory (Vendruscolo et al., 2004). Briefly, the hot-plate (Insight, Brazil) was maintained at 52.2 ± 0.5 °C and the rats were placed in an acrylic cylinder on the heated metal surface. Time between placement and hind paw licking or jumping (whatever occurred first) was recorded as nociceptive latency (s).

2.4. Blood pressure measure

The arterial blood pressure (mm Hg) was measured using a protocol previously described (Prediger et al., 2005b). Briefly, under

![Graphs](image)

**Fig. 2.** Effects of environmental enrichment on short-term recognition memory abilities of Wistar (WIS) and Spontaneously Hypertensive Rats (SHR). WIS and SHR rats were reared from the post-natal day 21 to 3 months of age (adulthood) in standard environment (SE) or enriched environment (EE) and tested in cognitive tasks. (A, B) The social recognition (SR) task was performed in 2 consecutive 5-min presentations of a juvenile rat, with 30 min interval. The investigation time was used as an index of recognition memory. The object recognition (OR) task was performed in 2 consecutive phases, with 30 min interval. (C, D) In the sample phase 2 identical objects (A1, A2) were presented to the animals and the total investigation time was recorded (A1 + A2). (E, F) In the discrimination phase, another identical object (A3) and one novel object (B) were presented and the discrimination index was calculated as the percentage of investigation time of (B – A3) / (B + A3). A–B: [WIS SE n = 9; WIS EE n = 10, SHR SE n = 9, SHR EE n = 8], and C–F: [WIS SE n = 7; WIS EE n = 7, SHR SE n = 7, SHR EE n = 7]. Data are presented as mean ± S.E.M. +p < 0.05 compared to the 1st SR session, *p < 0.05 compared to the SE group (Duncan's post-hoc test).
deep ketamine/xylazine anesthesia a polyethylene catheter was inserted into the right carotid artery for recording of arterial pressure. After 30 min of stabilization, systolic and diastolic arterial blood pressures were recorded for 60 min. Data were recorded at a 10 s sampling rate with a Digit-Med BP Analyser system (Model 190) connected to a Digit-Med System Integrator (Model 200; Louisville, KY).

2.5. Statistical analysis

All data were checked for normality of frequency distribution with the Kolmogorov–Smirnov test. The statistical comparison of results was carried out using one- or two-way ANOVA with environment, objects and trial/session/juvenile presentation (repeated measures) as independent variables. Following significant ANOVAs, differences between groups were evaluated by the Duncan’s post-hoc test. All values are expressed as means±S.E.M. and the accepted level of significance for the tests was \( p<0.05 \). All tests were performed using the Statistica 6.0 software package.

3. Results

Data of each strain were individually analyzed because our objective was to investigate the effects of environmental enrichment in one strain and the other. A direct comparison between the present control groups (SE) of each strain replicated the response pattern previously observed in our experimental settings (Pamplona et al., 2007; Pandolfo et al., 2007; Pires et al., 2009; Prediger et al., 2005a,b; Takahashi et al., 2008; Vendruscolo et al., 2004), indicating overall hyperlocomotion in the open field \( [F(1,12)=10.22, p<0.01 \) for strain; \( F(1,12)=8.12, p<0.01 \) for session], deficit of long-term memory in the water maze (\% time in platform quadrant; \( t=2.24, p<0.05 \)), increased investigation in the first session (\( t=4.59, p<0.001 \) and short-term memory deficit (\( F(1,16)=49.49, p<0.0001 \) for strain; \( F(1,16)=11.88, p<0.01 \) for session] in the social recognition test, increased investigation (\( t=3.68, p<0.01 \) and a trend towards short-term memory deficit (\( t=1.89, p=0.08 \) in the object recognition test, as well as hyponociception in the hot-plate test (\( t=3.19, p<0.01 \) and hypertension (\( t=2.81, p<0.05 \) for SHR compared to WIS rats.

3.1. Effects of environmental enrichment in the performance of WIS and SHR rats in learning and memory tasks

**Fig. 1(A, B)** shows the number of squares crossed (locomotor activity) exhibited in the open field habituation task. Two-way ANOVA (session vs. environment) of the total locomotion revealed significant effects of session \( [F(1,13)=9.21, p=0.01 \) and environment \( [F(1,13)=10.13, p<0.05 \] for WIS rats (Fig.1A) and significant effects of session \( [F(1,12)=26.98, p<0.001 \], environment \( [F(1,12)=40.36, p<0.0001 \] and session vs. environment interaction \( [F(1,12)=5.09, p<0.05 \] for SHR (Fig. 1B). Post-hoc comparisons indicated that EE reduced the locomotor activity of WIS and SHR in the 1st open field session.
revealed that EE reduced the investigation time for both WIS ANOVA (environment) of the investigation time in the sample phase and SHR rats strongly depended on the rearing environment vs. juvenile presentation compared to WIS SE group, with no evidence for SHR F(1,12)=47.62, p<0.0001, but not for WIS F(1,113)=3.51, p=0.10. There was no significant effect of environment vs. trials interaction for WIS F(5,65)=0.11, p=0.99 or SHR F(5,60)=2.04, p=0.09. Post-hoc comparisons indicated that the EE improved the performance of SHR during the training trials of the water maze task, as indicated by a significant reduction in the escape latency to find the platform across the trials in comparison to SE group (Fig. 1D).

Fig. 1 (C, D) shows the escape latencies exhibited during the training session of the water maze spatial reference task. Two-way ANOVA (environment vs. trials) revealed significant effect of trial for both WIS F(6,78)=17.77, p<0.0001) and SHR F(5,60)=12.20, p<0.0001. However, it indicated a significant effect of environment for SHR F(1,112)=47.62, p<0.0001, but not for WIS F(1,113)=3.51, p=0.10. There was no significant effect of environment vs. trials interaction for WIS F(5,65)=0.11, p=0.99 or SHR F(5,60)=2.04, p=0.09. Post-hoc comparisons indicated that the EE improved the spatial memory of SHR, promoting an increase in the percentage of time spent in the platform quadrants, with no significant difference between environments. One-way ANOVA (environment) revealed significant effect of environment for SHR F(1,112)=5.12, p<0.05, but not for WIS F(1,113)=1.62, p=0.22. Subsequent post-hoc comparisons indicated that EE selectively improved the spatial memory of SHR, promoting an increase in the percentage of time spent in the platform quadrants where the platform was located during the training session (Fig. 1F).

Fig. 2 (A, B) shows the investigation time exhibited in the social recognition task. Two-way ANOVA (environment vs. juvenile presentation) revealed significant effect of juvenile presentation for WIS F(1,17)=25.57, p<0.0001, but not of environment F(1,17)=0.87, p=0.36 for WIS. Moreover, it revealed a significant effect of presentation F(1,15)=55.47, p<0.0001, environment F(1,15)=63.19, p<0.0001 and of the environment vs. juvenile presentation interaction for SHR F(1,15)=4.36, p<0.05. Subsequent comparisons indicated that the SHR SE group presented a significantly higher investigation time in the first juvenile presentation compared to WIS SE group, with no significant reduction during the second exposure. Moreover, post-hoc comparisons indicated that the WIS SE animals showed a reduction on investigation time during the second juvenile exposure (Fig. 2B).

Fig. 2 (C–F) illustrates the performance of rats during the sample and discrimination phases of the object recognition task. One-way ANOVA (environment) of the investigation time in the sample phase revealed that EE reduced the investigation time for both WIS F(1,12)=6.20, p<0.05) and SHR F(1,12)=29.60, p<0.0001 (Fig. 2C, D). Moreover, one-way ANOVA (environment) of the discrimination phase revealed that EE improved the discrimination index for SHR F(1,12)=4.97, p<0.05, but not for WIS F(1,12)=0.46, p=0.51 (Fig. 2E, F).

3.2. Effects of environmental enrichment in non-cognitive traits of WIS and SHR

Fig. 3(A, B) shows the nociceptive latencies exhibited in the hot-plate test. One-way ANOVA (environment) revealed no significant effects of environment for WIS F(1,12)=0.05, p=0.83) or SHR F(1,12)=0.00, p=0.99) in the pain sensitivity. Additionally, Fig. 3 (C, D) shows that EE did not alter the mean arterial pressure of WIS F(1,7)=3.47, p=0.10) or SHR F(1,8)=0.31, p=0.59.

4. Discussion

The present results show that the general low cognitive performance presented by SHR rats strongly depends on the rearing environment. SHR rats reared from the post-weaning period to adulthood in a stimulating environment, full of novelty, physical exercise and social contact (i.e., EE) displayed a remarkable better performance in short- and long-term cognitive tasks, despite no change in non-cognitive characteristics, such as pain sensitivity and blood pressure. The pro-cognitive effects of EE were observed in the SHR rats, but not in the WIS rats, suggesting that impoverished non-stimulating rearing conditions is detrimental to cognitive functions on individuals with a specific (yet undetermined) genetic background, but maybe not on a general heterogeneous population. One limitation of the present study is that our analysis was restricted to learning and memory abilities, whereas the investigation must be expanded to other ADHD-like symptoms presented by SHR.

The fact that EE did not alter the cognitive performance of WIS rats in the present results might be interpreted as if the rearing environment played little role on the formation of ‘normal’ cognitive abilities. In fact, although the benefits that EE can produce on the brain plasticity are well documented, most of the literature showing unequivocal behavioral benefits of EE in rodents has been obtained in cognitively-impaired animals (e.g. aging rodents and experimental models of neurodegenerative diseases) (for review see Nithianantharajah and Hannan, 2006; van Praag et al., 2000). However, it must be conceded that some authors reported cognitive enhancement in WIS rats exposed to EE (Leggio et al., 2005). In the present experiments, we intentionally used task settings in which we knew by experience that WIS rats would present a reasonable performance, as opposed to SHR rats, which reduced the possibility of further mnemonic improvement for WIS due to ceiling effect. This question would likely be addressed by using more demanding cognitive tasks, such as more elaborated maze tasks (radial arm mazes, water maze reversal task), complex operant schedules of reinforcement or longer delays between training and test (Leggio et al., 2005). Another possibility might be that a more intense enrichment protocol (for instance, by increasing novelty even more by changing objects on a daily basis) would be necessary to induce positive cognitive effect in WIS rats. Nevertheless, as EE affected the impact of novelty on rat’s behavior, irrespective of the genetic background – as already reported (Bezard et al., 2003) – this may be taken as an evidence that our enrichment protocol induced neurodevelopmental alterations in WIS rats as well, turning unlikely that a more intense enrichment protocol was required. The mentioned reduced response to novelty was consistently observed as reduced locomotion on the open field and reduced investigation on the 1st trial of the social and object recognition tests.

In the recent decades, many efforts have been made to understand the genetic and pharmacological factors contributing to brain function and dysfunction, while the detailed exploration of environmental factors has been kept relatively aside. Although the classic studies already suggested that animals living in a complex and stimulating environment present improved cognition (Hebb, 1947) accompanied by neurochemical and anatomical changes (Bennett et al., 1964), the interaction of environmental factors with genetics and pharmacology deserves a more profound investigation. One of the most popular strategies to depict the role of environment on animal behavior is the so-called environmental enrichment. This term refers to housing conditions, either home cages or exploratory chambers, that provide higher sensory, cognitive and motor stimulation compared to standard laboratory housing conditions (Nithianantharajah and Hannan, 2006). This leads to a way more stimulating rearing environment, often with increased social contact through enhanced number of individuals sharing the cages and the inherent challenges of ever-changing social hierarchy networks. Enrichment objects generally vary in composition, shape, size, texture, smell, color, etc. and are constantly re-positioned inside the cage, either by the animals or experimenters: novelty is one important component to keep EE being stimulating. Another important aspect is whether or not the EE provides access to running wheels (for rodents), since voluntary physical exercise has alone beneficial effects on the brain (for comprehensive reviews, van Praag et al., 2000; Will et al., 2004). The time the animals spent in the EE is another variable and there are studies exposing the animals for long periods (days, weeks) to such environments, while others provide short (hours) repeated exposures. Finally, the age when
the animals are exposed to enriched housing conditions plays another important role. If EE starts early in life, it may have additional effects compared to EE starting during adulthood. There might hypothetically be neurodevelopmental critical periods of maturation during which environmental enrichment would exert its maximum effects.

It is interesting to observe that our ‘life-long’ environmental enrichment improved the performance of SHR rats on both short- and long-term memory tasks. EE groups displayed consistent better performance than SE groups in the open field habituation task, water maze spatial reference task, social recognition task and object recognition tasks, each one of them with particular sensorial characteristics and physical demands. The better performance of SHR on these distinct mnemonic tasks suggests a functional improvement in multiple brain sites, as the interaction among distinct neural systems, as well as cellular changes within specific regions supports memory formation (McGaugh, 2000). One may highlight the likely participation of the prefrontal cortex – whose function is somewhat deficient in the SHR strain (Heal et al., 2008; Li et al., 2007) – and hippocampus, which are highly involved in working memory and in the formation of long-term spatial memories (open field habituation, water maze reference task) and in the discrimination using short-term sampling (object and social recognition) (Dalley et al., 2004; Izquierdo et al., 2006). The perirhinal and entorhinal cortices are also important brain sites for stimuli discrimination, while the perirhinal cortex is involved in object recognition (Norman and Eacott, 2004) the entorhinal cortex is important in the social recognition task (Sanchez-Andrade et al., 2005). The amygdala complex might have played a role, especially in the consolidation of mnemonic tasks with higher emotional content (McGaugh, 2000). Moreover, it is important to emphasize that hippocampus and entorhinal cortex may play different roles during the dynamic stages of memory formation, which involves parallel processing of short- and long-term memory (Izquierdo et al., 1998). As we did not quantify the rats’ swim speed in the water maze, the possible influence of EE on this parameter cannot be ruled out. Rats from both groups displayed comparable results in other non-cognitive traits expressed under genetic influences, such as hot-plate pain sensitivity and mean arterial blood pressure. Arguably, this means that the present environmental modifications specifically affected certain behavioral characteristics linked to cognitive performance in the SHR strain, rather than modifying the phenotype of these animals as a whole. It could be hypothesized that EE maintained the original ‘genetic’ characteristics of the strain, while improved the ability of these animals to change the synaptic function depending on experience (i.e. better synaptic plasticity), which constitutes a very interesting field that requires additional research. For instance, there are reports that EE enhances learning and memory, which relates to a variety of effects on neuronal synaptic plasticity at certain brain sites (Moser et al., 1997; Rampon et al., 2000; Tang et al., 2001). This is in line with the concept that higher cognitive performance may be one predictive factor of protection against the development of psychiatric diseases, as depicted in the Theory of Cognitive Reserve (Barnett et al., 2006). The idea is that the higher the neuronal/synaptic density, the higher will be the number of healthy synapses prior to a given pathology. If this ‘synaptic reserve’ is sufficient, little or no loss of cognitive function will be observed; conversely, if the reserve is low, the threshold at which clinical manifestations occur will be easily reached (Barnett et al., 2006). In summary, the term refers to the ability of an individual to cope or compensate a given brain insult by recruitment of an alternative set of neurons to function. This perspective is somewhat pioneering in ADHD research and the clinical relevance of it may be assessed by examining epidemiological indices of education grade, or psychological indices of cognitive functionality in association with the severity of ADHD symptoms.

5. Conclusion

To the best of our knowledge, this is the first report showing the relationship between exposure to environmental factors during neurodevelopment and occurrence of ADHD-like symptomatology in laboratory animals, as far as SHR rats are concerned as an animal model. We hope that these preliminary positive results encourage further studies in the field and foster the translation of these findings into clinical practice. Thus, modifications of the familial environment could be considered as a putative preventive strategy to ADHD. This approach may (or not) be used in combination with conventional drugs. Additional studies should also investigate whether such non-pharmacological manipulations may prove of therapeutic utility once ADHD symptoms appear.

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