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Research report

Acoustic noise improves motor learning in spontaneously hypertensive rats, a rat model of attention deficit hyperactivity disorder

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HIGHLIGHTS

- SH rats, an ADHD model, display acoustic noise benefit in motor learning.
- SH rats learn the Montoya staircase and rotarod running slower than controls.
- 75 dBA noise improved SH rotarod learning as much as methylphenidate.
- Impaired skilled reach learning was ameliorated by noise but not methylphenidate.
- SH rats share the acoustic noise benefit previously reported in children.

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ABSTRACT

The spontaneously hypertensive (SH) rat model of ADHD displays impaired motor learning. We used this characteristic to study if the recently described acoustic noise benefit in learning in children with ADHD is also observed in the SH rat model. SH rats and a Wistar control strain were trained in skilled reach and rotarod running under either ambient noise or in 75 dBA white noise. In other animals the effect of methylphenidate (MPH) on motor learning was assessed with the same paradigms. To determine if acoustic noise influenced spontaneous motor activity, the effect of acoustic noise was also determined in the open field activity paradigm.

We confirm impaired motor learning in the SH rat compared to Wistar SCA controls. Acoustic noise restored motor learning in SH rats learning the Montoya reach test and the rotarod test, but had no influence on learning in Wistar rats. Noise had no effect on open field activity in SH rats, but increased corner time in Wistar. MPH completely restored rotarod learning and performance but did not improve skilled reach in the SH rat.

It is suggested that the acoustic noise benefit previously reported in children with ADHD is shared by the SH rat model of ADHD, and the effect is in the same range as that of stimulant treatment. Acoustic noise may be useful as a non-pharmacological alternative to stimulant medication in the treatment of ADHD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders worldwide [1] and is often associated with school failures and academic under-achievement [2–4]. Stimulant treatment with e.g. methylphenidate (MPH) can be used to treat behavioural problems in ADHD, like attention deficits and hyperactivity, and can improve school performance [5,6]. Stimulant treatment is however associated with adverse effects like risk of abuse, and the long-term developmental effects are not known [7,8].

The effects of acoustic noise on learning have often been investigated in relation to hearing in difficult conditions, where noise is usually an obstacle [9]. Indeed, even low levels of continuous or intermittent noise impair the learning and reproduction of texts in healthy control subjects [10]. However, in individuals with poor attention, loud acoustic noise (80 dBA) improves

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cognitive performance [11,12]. The phenomenon is typical for persons with low attention and its mechanism is unknown but may involve masking, general arousal [13–15] or possibly resonance mechanisms like stochastic resonance [16]. The moderate brain arousal model is based on the stochastic resonance phenomenon and was designed to explain the benefit of noise specifically in hypodopaminergic states, like ADHD [17], assuming that sensory noise either regulates dopamine transmission or substitutes its effects.

To the best of our knowledge, the effect of sensory noise on motor learning has not been investigated previously. The spontaneously hypertensive (SH) rat is one of the most used and validated animal models of ADHD [18,19] and it was recently shown that the SH rat displays impaired learning and performance of skilled reach [20]. In ADHD, motor learning is important because in addition to attention deficits and hyperactivity, children with ADHD often display impaired fine and gross motor skills [21,22], which is an additional handicap during education. Recent findings indicate that motor skills of ADHD children can be improved by MPH [23–26], but that this effect is attention-driven and reversed by drug withdrawal [24]. Furthermore, improvement in handwriting is only partial [27].

To investigate if acoustic noise benefit improves learning in an animal model of ADHD we used a skilled reach learning paradigm and learning of the rotarod balance and locomotion task in the SH (SH NCrl, Charles River, Germany) ADHD model. Animals were trained in either in loud noise (75 dBA) or in ambient "silence". Outbred Wistar rats (Wistar SCA, Scanbur, Denmark) were used as controls. In parallel experiments, the effect of MPH (i.p) was compared to that of saline injections in ambient noise conditions. Furthermore, the effect of noise on spontaneous open field activity was investigated. We report a powerful positive effect of acoustic noise on the learning of skilled reach and on rotarod balance/locomotion performance in SH rats, but not in Wistar rats, indicating that noise benefit may be a general phenomenon associated with the ADHD phenotype. The effect of loud noise on the acquisition of these two motor tasks was at least as large as the effect of MPH, but it did not alter the spontaneous motor activity of SH rats.

2. Materials and methods

The experiments were conducted in accordance with Swedish animal welfare legislation and the European Union Directive 2010/63/EU on the protection of animals used for scientific purposes. The experimental design was approved by the Gothenburg Animal Research Ethics Committee.

2.1. Animals and housing conditions

Male spontaneously hypertensive rats ($n = 55$, SH/NCrl, Charles River, Germany) and male Wistar SCA ($n = 48$, WIS/SCA, Scanbur AB, Sweden) were used in the project. The animals were 4 weeks of age on arrival. The animals were housed four per cage ($55 \times 35 \times 20$ cm) and kept on a 12/12 h light/dark cycle. Two days before testing started the animals were handled daily and fasted over night with free access to water to achieve 90 to 95% of initial weight to motivate food seeking behaviour. Throughout the training phase the animals' food intake was restricted during night-time. Food was administered directly after the Montoya session in the morning and adjusted so that a desired bodyweight gain of 3% was achieved each day. A figure of weight gain for all rats can be found in the supplemental section (Suppl. Fig. S1). All training took place during the light time cycle.

2.2. Experimental design

The animals were divided into eight different groups based on strain and treatment: SH white noise ($n = 15$), SH ambient silence ($n = 16$), SH MPH ($n = 12$), SH NaCl ($n = 12$), Wistar white noise ($n = 12$), Wistar ambient silence ($n = 16$), Wistar MPH ($n = 8$) and Wistar NaCl ($n = 12$). Each animal group received the same treatment throughout training.

Animals were trained in batches of 8 to 16 individuals as they arrived and in most cases SH and Wistar rats were trained in parallel to ensure as similar conditions as possible. A schematic overview of the training protocol can be found as supplement (Suppl. Fig. S2)

2.3. Montoya staircase test

The Montoya staircase test is a skilled reaching task designed to measure independent reaching and grasping using the forelimbs as described previously [28]. Each staircase can only be reached with the ipsilateral forelimb.

Three sugar pellets (45 mg; BioServ, Frenchtown, NJ, U.S.A.) were placed at each level of the staircases. The Montoya box was placed inside a sound attenuating polyurethane box and each rat was left in the box to forage for 15 min. Montoya training took place in the AM session and continued for 10 days. The main outcome was the number of pellets consumed per session and the observed success rate (ratio of consumed pellets/(consumed + dropped pellets)) in pellet retrieval. Prior to the experiment an exclusion criterion was decided so that animals that retrieved only one or no pellets over the entire learning period were excluded from the final analysis, as they were non-learners. The proportion of learners is reported as a result and the full data set prior to exclusion is available as supplemental data (Suppl. Figs. S3, S5 and S7).

2.4. Rotarod

Animals were trained using an accelerating rotarod device (LE-8500, Panlab S.L.U., Spain) placed in a ventilated and sound attenuating cupboard. Training consisted of four successive trials per day where the animals were trained to stay on the rotating rod as it accelerated from 4 to 40 rpm in 5 min. Rotarod training was performed in the afternoon session after Montoya training and continued for 10 days. Groups were trained in such a way that the time between the end of the Montoya session and the start of the rotarod were equally distributed. Care was taken not to influence the animal behaviour on the rod. When an animal managed to stay on the rod for more than 6 min the test was terminated and the trial was assigned the maximum performance of 360 s. The mean latency to fall for the four trials was used as one data point. Prior to the experiment an inclusion criterion of learning to run for at least 100 s and an exclusion criterion of displaying progressive worsening of performance was set up. Data from animals complying with these criteria and the proportion of learners are presented. The full data set is available as supplement (Suppl. Figs. S4, S6 and S8).

2.5. Open field motor activity

Motor activity (locomotion, rearing activity and corner time) was measured over 60 min in injection naïve Wistar and SH rats that had already completed the 10 days of Montoya and rotarod training. The apparatus used was a standard open field activity box (48×48 cm) with light beams that registered animal movements in 5-min bins under dimmed light conditions. Each rat was tested on two consecutive days and noise (75 dBA) or silence (20 dBA) conditions were applied in a balanced order.

Table 1
The ratio of animals that learned the tasks in each treatment group are given.

Learning ratios	Montoya	Rotarod
SH silent	14/16[a]	8/8
SH noise	14/15[b]	5/7
SH MPH	4/12	7/8
SH NaCl	8/12	6/8
Wistar silent	7/16	6/8
Wistar noise	4/12	–
Wistar MPH	7/8	5/8
Wistar NaCl	4/12	5/8

[a] Significantly fewer excluded SH than Wistar trained in ambient silence.
[b] Significantly fewer excluded SH than Wistar trained in acoustic white noise.

2.6. Acoustic noise and ambient silence in the motor learning tasks

A white noise sound file with equally distributed frequencies (0–8 kHz) was played back in a continuous loop through strategically placed loudspeakers (SBA1600/00, Philips, Amsterdam, Netherlands). In the Montoya test the loudspeakers were placed speaker side up above the extension containing the staircase and secured with surgical tape. In the rotarod test the loudspeaker were mounted on a ring stand and placed 20 centimetres from the rotor. The volume was adjusted to 75 dBA at a point near the head level of the rats and the level was confirmed regularly with a sound pressure meter. In the skilled reach apparatus ambient sound levels were on average 38 dBA, and in the rotarod cabinet they varied between 50 and 68 dBA depending on the speed of the rotarod.

2.7. Drug preparation and treatment

10 mg methylphenidate hydrochloride (immediate release Ritalin® tablet) was dissolved in 0.9% NaCl solution (2 mg/ml). The solution was centrifuged at 4400 rpm for 5 min, and the supernatant was removed and acidified to pH 4 with HCl.

Groups treated with MPH were injected with 4 mg/kg MPH (2 mg/ml in 0.9% NaCl) i.p. and vehicle treated groups were administered the same volume of 0.9% NaCl i.p according to body weight 30 min before each training session.

2.8. Statistical analysis

Two-way repeated measures analysis of variance with Bonferroni multiple comparisons and nonlinear regression was performed using GraphPad Prism version 5.00 for Windows, (GraphPad Software, San Diego, USA).

Data are given as mean ± SEM and were analysed both in an intention to train analysis including all animals and in the *per protocol* analysis after applying inclusion and exclusion criteria. The *per protocol* analysis is reported on the result section and the intention to train results can be found in Suppl. Figs. S3–S8. Mann–Whitney *U*-test was used to determine if the ratio of animals that managed to learn the tasks differed between the groups.

3. Results

3.1. Strain differences in motor learning

In the Montoya skilled reach task, significantly more SH rats than Wistar were learners (Mann–Whitney *U*-test, $p = 0.026$ in silent condition and $p = 0.0046$ in noise, Table 1). In rats that could be evaluated for speed of learning (per protocol analysis), repeated measure two-way ANOVA did not indicate a significant main effect of strain, only of trial day, and there was no interaction (Fig. 1A). As the learning curves were roughly sigmoidal, the number of training days needed to achieve 50% of full performance was analyzed. Non-linear best fit to a sigmoidal dose response curve assuming constant Hill slope, top and bottom performance indicated a significant difference in the number of training days needed to achieve 50% of best performance. SH rats needed 2.2 more training days than Wistar ($F(1, 205) = 8.127$, $p = 0.0048$).

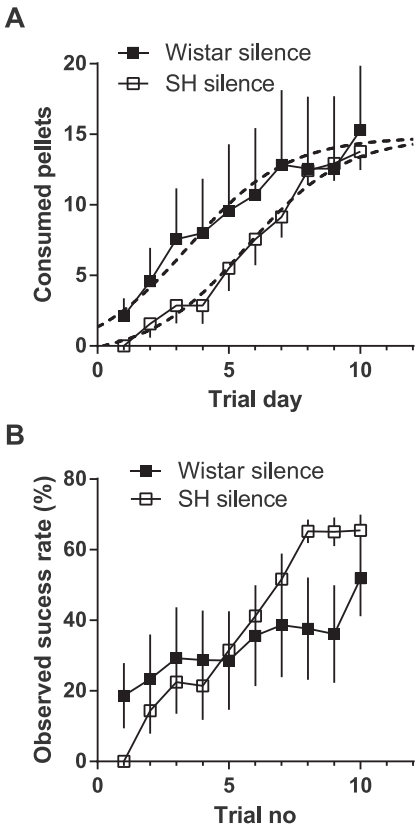

Fig. 1. (A) Pellet retrieval learning in SH rats (open squares, $n = 14$) and Wistar rats (open squares, $n = 7$) trained in ambient silence in the Montoya staircase test. Non-linear best fits to sigmoidal dose response curves assuming the same Hill slope, top and bottom performance is indicated with dashed lines. (B) Observed success rate of pellet retrieval of SHR and Wistar rats trained in ambient silence. Values are presented as mean ± S.E.M.

The observed success rate in pellet retrieval (proportion of pellets that were not dropped) developed differently in learning in SH rats and Wistar rats, as indicated by a significant interaction strain × trial day ($F(9, 180) = 3.00$, $p = 0.0023$, Fig. 1B). A large number of Wistar rats failed to pick more than one pellet over the entire training period and when all non-learners were included in the analysis (intention to train), the SH rat group therefore achieved higher performance than Wistar rats (Suppl. Fig S3).

When trained on the rotarod in ambient silence, SH animals performed significantly worse than Wistar (main effect of strain $F(1, 108) = 12.19$, $p = 0.0045$, Fig. 2). However, the actual learning phase was short in both strains, and plateau performance was achieved within the first three days. The difference in performance developed early in training as there was significant effect of strain ($F(1, 132) = 5.66$, $p = 0.0348$) but no interaction ($F(11, 132) = 1.37$, $p = 0.1944$), when repeated measure two-way ANOVA was performed on the first 12 trials in training day 1–3 (Fig. 2).

3.2. Effect of noise and MPH on the motor learning of SH rats

SH rats that trained in 75 dBA white noise demonstrated faster development of skilled reach than SH rats trained in ambient silence as indicated by interaction noise × trial day ($F(9, 234) = 2.13$,

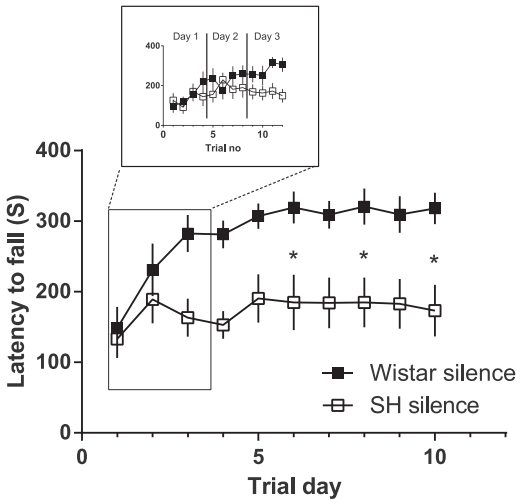

Fig. 2. Rotarod learning curves of SH rats (open squares, $n = 8$) and Wistar rats (filled squares, $n = 6$) trained in ambient silence (* indicates Bonferroni corrected $p < 0.05$ for individual times). The insert shows the individual trials in the first three days. Values are presented as mean ± S.E.M.

$p = 0.0282$, Fig. 3A), and a left shift in time to 50% of final achieved skill ($F(1, 275) = 25.05$, $p < 0.0001$). SH rats trained in noise learned the skilled reach task as fast as Wistar control rats, and improved success rate earlier than SH rats trained in ambient silence as indicated by significant interaction between noise and trial day ($F(9, 234) = 3.21$, $p = 0.0011$, Fig. 3B). In comparison with vehicle treated animals, MPH did not alter skilled forelimb reach ($F(1, 99) = 0.08$, $p = 0.7814$, Fig. 3C).

SH rats that learned the rotarod task in 75 dBA white noise performed better than SH trained in ambient silence (main effect of noise $F(1, 99) = 11.98$, $p = 0.0053$, Fig. 4A). MPH treated SH rats learned the rotarod task better than vehicle treated animals (interaction treatment × time $F(9, 99) = 2.51$, $p = 0.0124$, Fig. 4B).

3.3. Effect of noise and MPH on the motor learning of Wistar rats

Seven out of eight Wistar rats treated with MPH learned the Montoya skilled reach task per protocol, as compared to four out of twelve vehicle treated rats (Mann–Whitney U, $p = 0.0509$). The learners in the vehicle group learned the task nominally better than MPH treated animals but there was no main effect of treatment ($F(1, 81) = 0.62$, $p = 0.4497$ and no interaction $F(9, 81) = 0.372$, $p = 0.945$, Fig. 5A). Wistar rats trained in noise learned the skilled reach similarly to Wistar rats trained in ambient silence (no main effect of treatment ($F(1, 81) = 0.003$, $p = 0.958$ and no interaction treatment × trial day ($F(9, 81) = 0.16$, $p = 0.997$, Fig. 5B). On the rotarod, repeated measure two-way ANOVA indicated no main effect of treatment ($F(1, 72) = 0.63$, $p = 0.4510$) and no interaction treatment × trial day ($F(9, 72) = 1.22$, $p = 0.294$), but a ceiling effect is likely as five of the seven included animals in the MPH group regularly achieved maximum performance in the trials (Fig. 4C).

3.4. Strain differences in spontaneous motor activity

The initial exploratory behaviour of SH and Wistar rats in ambient silence was similar, but SH rats habituated less easily. After the first 30 min residual (habituated) locomotor activity levelled out at 48 (39–56, $CI_{95\%}$) counts/5 min as compared to 7 (0–16, $CI_{95\%}$) counts/5 min (non-linear fit with exponential decay, Fig. 6A). SH rats also displayed significantly more rearing in the last 30 min (18 counts/5 min vs. 0 counts/5 min in Wistar, Fig. 6B). There was a

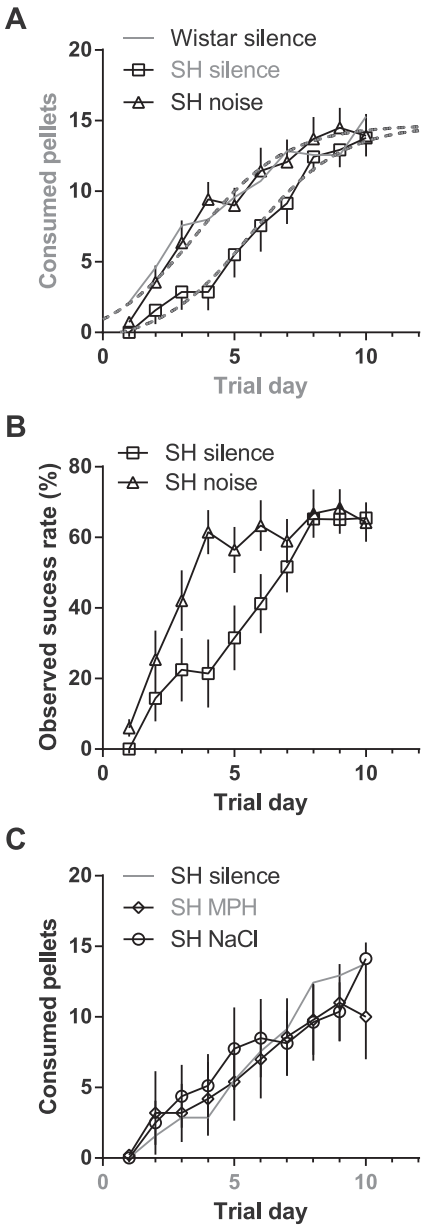

Fig. 3. (A) Pellet retrieval learning in SH rats trained in 75 dBA acoustic white noise (open triangles, $n = 14$) and SH rats trained in ambient silence (open squares, $n = 14$). Wistar controls trained in ambient silence are shown for comparison (grey solid line, $n = 7$). (B) Observed success rate of SH rats trained in acoustic white noise and SH rats trained in ambient silence. (C) Pellets consumed by SH rats treated with methylphenidate 4 mg/kg (open diamonds, $n = 5$) compared to SH rats treated with NaCl (open circles, $n = 8$). Performance of SH rats trained in ambient silence is shown for comparison (grey solid line). Values are presented as mean ± S.E.M.

prominent difference in time spent in corners, where SH rats, in contrast to Wistar rats, did not develop a corner preference at all (Fig. 6C).

3.5. The effects of noise on spontaneous motor activity in SH and Wistar rats

Noise had no significant effect on the spontaneous motor activity in SH rats compared to ambient silence when the best fit non-linear regression functions were compared ($F(3, 186) = 0.549$, $p = 0.65$). Wistar rats subjected to 75 dBA white noise displayed a somewhat different best non-linear fit of locomotion when

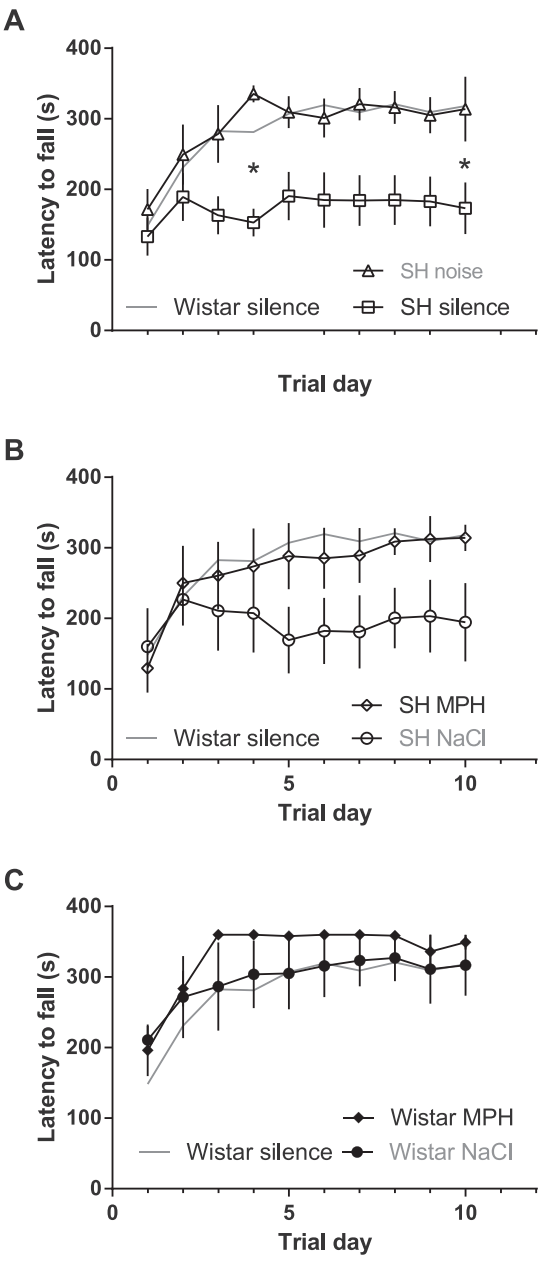

Fig. 4. (A) Rotarod learning curves of SH rats trained in noise (open triangles, $n = 5$) and in ambient silence (open squares, $n = 8$). Wistar control are shown for comparison (solid grey line, * indicates $p < 0.05$ in Bonferroni post hoc tests at individual trial days). (B) Rotarod learning curves of SH rats treated with methylphenidate (open diamonds, $n = 7$) and SH rats treated with NaCl (open circles, $n = 6$). (C) Rotarod learning curves of Wistar rats treated with methylphenidate 4 mg/kg (solid diamonds, $n = 5$) and Wistar rats treated with NaCl (solid circles, $n = 5$). Wistar control rats trained in ambient silence is shown for comparison (solid grey line). Values are presented as mean ± S.E.M.

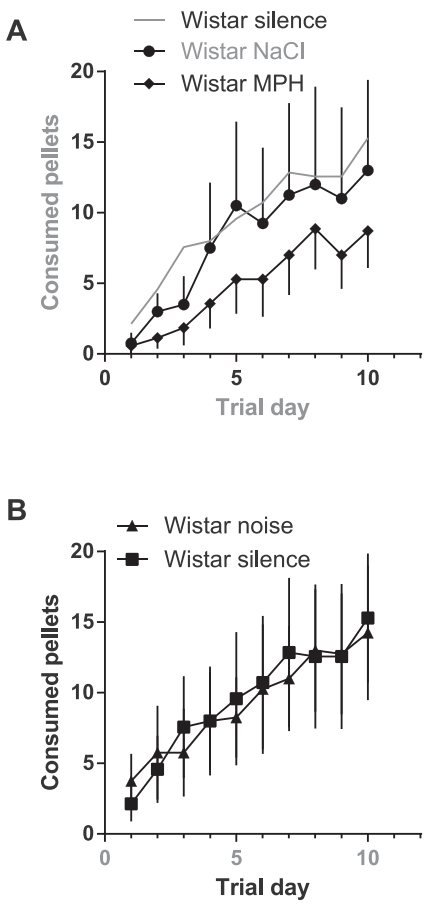

Fig. 5. (A) Pellet retrieval learning in Wistar rats treated with methylphenidate (solid diamonds, $n = 7$) and Wistar rats treated with NaCl (solid circles, $n = 4$). Wistar trained in silence is shown for comparison (solid grey line). (B) Pellet retrieval learning in Wistar rats trained in white noise (solid triangle, $n = 4$) and Wistar rats trained in ambient silence (solid squares, $n = 7$). Values are presented as mean ± S.E.M.

compared to ambient silence ($F(3, 186) = 2.755$, $p = 0.044$) and habituated at 17 counts/5 min (7–27, CI95%, Fig. 6A).

SH rats displayed significantly more rearing activity in ambient silence over the last 30 min (18 (14–23, CI95%) counts/5 min) compared to Wistar rats (0 (−7 to 7, CI95%) counts/5 min). In noise, SH rats leveled out at 16 (11–22, CI95%) counts/5 min (Fig. 6B).

Wistar rats spent more time in corners in ambient silence than SH rats. Noise did not influence the time SH rats spent in corners, however Wistar rats exposed to noise tended to spend more time in corners than Wistar rats in ambient silence as demonstrated by a higher plateau value in a significantly different best nonlinear fit ($F(3, 186) = 5.258$, $p = 0.0017$, Fig. 6C).

4. Discussion

To the best of our knowledge this is the first demonstration of the benefit of acoustic noise in the acquisition of fine and gross motor skills in a rodent ADHD model. Just like in children [11], the noise benefit in rats was specific to the animals with ADHD-like phenotype and was not found in control animals. We propose that benefit of acoustic noise is associated with aspects of the ADHD phenotype that are common to children and the SH rat ADHD model. It is known from previous studies of children that noise benefit is strongly associated with poor attention [12]. Like children with ADHD, SH rats have impaired sustained attention [18], suggesting that a common mechanism of ADHD-phenotype specific noise benefit may involve improved attention. In the SH model of ADHD, acoustic noise was as efficacious for improving motor learning and performance as MPH.

4.1. Strain differences in open field activity and motor learning

SH rats habituate less to locomotion over time, spend much less time in the corners of the box and rear more compared to Wistar (Fig. 6). These findings are consistent with low anxiety levels in the SH rat [29–31] and with previous work [20,32,33] where habituation to spontaneous behaviour was studied in a similar fashion. It

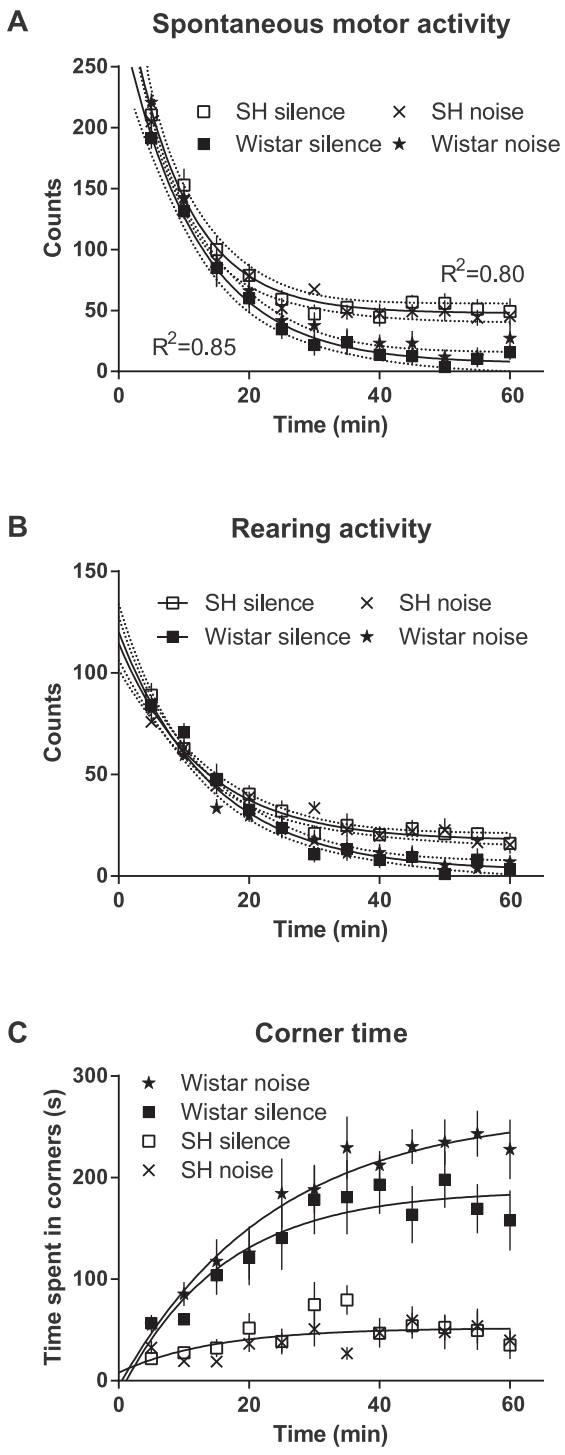

Fig. 6. (A) Spontaneous motor activity, (B) rearing activity and (C) corner time of SH rats ($n = 8$) and Wistar rats ($n = 8$) in ambient silence and 75 dBA acoustic white noise. The best fit regression curves for Wistar and SH in ambient silence are indicated as solid lines (95% confidence interval given by dashed lines). Values are presented as mean ± S.E.M.

should be stressed that the Montoya staircase task involves an initial exploratory phase where the rat must voluntarily venture onto the staircase platform to get access to sugar pellets. The actively exploring behaviour of SH rats may therefore partly explain why a larger proportion of SH rats learned the skilled reach task, as exploration is necessary for receiving any positive feedback in the first sessions in the Montoya box. When we previously observed non-learners in the Montoya test, they demonstrated no or very little exploratory behaviour inside the box. We therefore argue that explorative behaviour rather than the ability to learn per se can explain why more SH rats were learners in the Montoya test.

Although it can be argued that many tests of memory and attention in animal models also contain an element of motor learning, there are few previous examples where motor learning per se is studied in the SH rat. Qian et al. [20] reported poorer end performance in skilled reach in SH (SH/NCrl) rats compared to Wistar (WIS/Furth/Sca) and no difference in rotarod learning. In the Montoya test, we found that SH rats and Wistar performed similarly when training started and did not differ in end performance. The learning curves for the two strains were however significantly different, and although the variability was larger for Wistar rats they also displayed earlier acquisition of skilled reach compared to SH rats, where skilled reach learning is slower and delayed. The somewhat different outcomes compared to Qian et al. [20] may be related to: (i) the use of a different reach task, (ii) somewhat different outcome measures, and (iii) a different control strain. Although the rotarod protocol used in that study was similar to ours, we found a considerable difference in rod performance between SH and controls. Qian et al. [20] did not report the background noise during the rotarod task. This may be important as we only found different rotarod learning between strains in low ambient noise. Other diverging findings regarding rotarod performance in SH rats [34,35] may be related to age and differences in the training protocol.

4.2. Noise and MPH effects on motor learning

On the rotarod, both noise and MPH medication improved learning in the SH rat to the levels of Wistar controls. The MPH rotarod improvement was strain specific and validates the SH model in relation to known effects of MPH on motor function in ADHD children [23,25,26]. We have previously found no effect of acoustic noise on extracellular dopamine [36], so it is remarkable that the effect of noise was as large as with MPH. Although we have not observed altered dopamine release in response to acoustic noise [36] the noradrenaline system may influence behavioural responses to noise [37] and could also be important for learning. In the Montoya test, noise more or less restored learning to the level of Wistar controls, but MPH was not efficacious. A likely explanation for the lack of MPH effect in the reach task is that MPH decreases appetite [38]. Attenuation of appetite is a major obstacle for studying the effects of stimulant treatment on fine motor skills in animals, as fine motor skills in laboratory animals are usually learned using food as reinforcement. Another important confounder in this study is the route of MPH administration. Animals that received i.p. injections had poorer development of skilled reach also when NaCl was injected. Tentatively the i.p. injection is associated with some discomfort that has a detrimental effect on the motivation to feed but that does not restrict locomotion on the rotarod.

We have previously found compelling evidence of differential effects of noise on humans and in animal models. In humans the predictive factors for noise benefit are low self- or teacher-rated attention ability [12], or an ADHD diagnosis [11]. Similarly, the effect of stimulant treatment in ADHD is baseline dependent [39,40]. Sensory noise benefit has been demonstrated in the SH rat model of ADHD [36] and in the 6-OHDA hemilesioned rat model of Parkinson's disease [41], but does not occur in the corresponding control animals. To the best of our knowledge, dose–response effects of noise on rat behaviour have only been assessed in the pre-pulse inhibition of startle paradigm [37]. The present study only evaluates one level of noise and one dose of MPH, so it is possible that lower levels of noise e.g. would have improved learning in the Wistar rat as well. The noise level was chosen based on

previous data from pre-pulse inhibition and studies of word recall in children where a similar noise level displayed different effects in the ADHD phenotype compared to controls. The mechanism of noise benefit in humans is unknown, but data from animal models do not indicate that vestibular or acoustic white noise alters dopamine transmission [36,41]. It is possible that sensory noise benefit involves stochastic resonance phenomena on neural system levels leading to improved attention. The occurrence of stochastic resonance reveals little about the specific mechanisms involved in acoustic noise benefit, but altered arousal and masking of distracting stimuli can tentatively contribute.

In clinical ADHD, arousal may be either decreased or increased [42], but 24 h heart rate is overall increased [43]. The common assumption is nevertheless that hypoarousal is a core feature of ADHD that in part explains positive effects of stimulant treatment. Furthermore, EEG and skin conductance recordings seem to support hypoarousal [44], although low anxiety is a possible confounder. An alternative view is that regulation of arousal is a central deficit in ADHD [14,45–48] and this could account for findings that seem inconsistent with hypoarousal (like hyperactivity). In the available animal models of ADHD there is to our knowledge no evidence of hypoarousal. SH rats, for example, display sympathetic over-activity and hyper-arousal during sleep [49], increased spontaneous motor activity, and small acoustic startle responses [36], in agreement with high constitutive arousal. Although it is possible to measure arousal in rats with EEG, heart rates or sniffing responses [50], no such assessments were made in this study, so that it remains to be determined whether noise influences arousal. Although the absence of noise effects on open field activity in SH rats is an argument against arousal as an important explanation of the observed noise benefit in motor learning, we cannot rule out some stressor-induced change in arousal, as higher levels of acoustic noise can influence spontaneous behaviour and stress hormones [37,51].

Acoustic white noise is often used as a masker in behavioural animal experiments as the noise signal is assumed to quench external sounds that may disturb the animals. Animals that are easily distracted or impulsive could perform better in an environment with auditory masking. SH rats display increased impulsivity in some but not all tests [52] so they are likely to be more easily distracted in a goal directed task. We tried to minimize external auditory information by using sound attenuating enclosures in all experiments. The masking effect of 75 dBA white noise is evidently not large enough to alter spontaneous motor activity in SH rats, but it did increase corner time slightly in Wistar rats, possibly as a result of increased habituation. To determine the importance of masking it would be useful to investigate the effects of sensory noise without sound masking properties, like for example vestibular noise [41].

It remains to be determined to what extent arousal and masking contribute to improved motor learning behaviour of SH rats during acoustic noise exposure. An additional possibility is that acoustic noise induces stochastic resonance phenomena in the SH rats, as has previously been proposed as an explanation for acoustic noise effects in children with low attention [17]. It is currently only hypothetical whether acoustic noise exposure alters neuronal noise in areas of the brain that are important for motor learning, but a role for random neuronal activation in basal ganglia function/learning has been proposed [53]. As discussed by McDonnel and Abbott [54], it is probably more meaningful to see improved learning during noise exposure as a "noise benefit" than as stochastic resonance. One effect of improved noradrenaline and dopamine is increased signal/noise ratios for salient stimuli [55,56] and the similarity this has to attentional selectivity in response to noise [15] may explain why noise and stimulant treatment have similar effects in the ADHD rat model.

5. Conclusion

Acoustic noise improves the conditions for learning in the ADHD rat model, as it does in ADHD children, and the effects are in parity with MPH treatment. The possible clinical benefit of sensory noise in ADHD should be further explored.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2014.11.032.

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