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Research report

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

Göran B.W. Söderlund [a,1], Daniel Eckernäs [b,*,1], Olof Holmblad [b], Filip Bergquist [b]

[a] Sogn og Fjordane University College, Sogndal, Norway
[b] Department of Pharmacology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

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

* Corresponding author. Tel.: +46 317863425; fax: +46 317863164.
E-mail address: daniel.eckernas@neuro.gu.se (D. Eckernäs).
[1] Shared first authorship.

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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 × 35 × 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.