Behavioural Brain Research 408 (2021) 113236

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

# The irrelevancy of the inter-trial interval in delay-discounting experiments on an animal model of ADHD

Espen A. Sjoberg [a,b], Sergio Ramos [c], Gabriela E. López-Tolsa [c,d], Espen Borgå Johansen [a], Ricardo Pellón [c,*]

[a] Department of Behavioral Sciences, Oslo Metropolitan University, St. Olavs Plass, P.O. Box 4, Oslo, 0130, Norway
[b] School of Health Sciences, Kristiania University College, Chr. Krohgs Gate 32A, Oslo, 0186, Norway
[c] Departamento de Psicología Básica I, Universidad Nacional de Educación a Distancia (UNED), C/ Juan del Rosal 10, Madrid, 28040, Spain
[d] Facultad de Psicología, Universidad Nacional Autónoma de México, Ciudad de México, 04510, Mexico

ARTICLE INFO

*Keywords:*
Delay discounting
Trial length
Animal testing
ADHD
Impulsivity
Patience

ABSTRACT

Delay discounting involves choosing between a small, immediate reward, and a larger but delayed one. As the delay between choice and large reward gets longer, people with ADHD tend to become impulsive faster than controls, indicated by a switch in preference from the large to the smaller reward. Choosing the smaller reward when the larger is considered reward maximizing is labeled impulsive behaviour. It is well documented that increased delays between choice and reward affects choice preference in both humans and other animals. Other variables such as the inter-trial interval or trial length are observed to have an effect on human discounting, but their effect on discounting in other animals is largely assumed rather than tested. In the current experiment, we tested this assumption. One group of rats was exposed to increasing delays between choosing the large reward and receiving it, while another group experienced longer inter-trial intervals that were equal in length to the delays in the other group. This ensured that trial length was controlled for in delay discounting, but that the delay function and inter-trial intervals could be manipulated and measured separately. Results showed that while the delay between choice and reward caused impulsive behaviour in rats, the length of the inter-trial interval (and by extension trial length) had no impact on choice behaviour. A follow-up experiment found this to be the case even if the length of the inter-trial interval was signaled with audio cues. These results suggest that rats, and possibly animals in general, are insensitive to time between trials, and therefore cannot easily represent human counterparts on the task.

## 1. Introduction

To what degree are animals sensitive to time elements occurring after receiving a reward? When conducting experiments on humans, participants can be instructed on the precise experimental parameters, such as delayed rewards and waiting between trials, thus affecting their behaviour [1]. However, this does not apply to non-human animals: they cannot be told of the experimental parameters and therefore must be trained instead. This is not to say that animals cannot be taught to understand symbols or visual instructions following training (e.g. [2]), but rather that getting them to perform the experiment is dependent on training procedures and not language. To what degree an animal understands these parameters is sometimes inferred (e.g. [3]), which can lead to anthropomorphism (explaining their behaviour through human properties: i.e. [4]). In reality, this is irrelevant: when working with animals, it is paramount to avoid making assumptions concerning their mental state and instead describe the observed effects on behaviour. The current study aims to investigate the consequences of drawing such assumptions in animal modelling, specifically whether rats used as a model for Attention-Deficit/Hyperactivity Disorder (ADHD) are sensitive to the inter-trial interval (ITI) component in delay-discounting tasks, which previous research often assumes is the case [5–9]. The inter-trial interval here is defined as the waiting period between trials, a central component in multiple-trial delay-discounting experiments.

ADHD is a mental illness that affects between 3–15 % of the population, with boys being more likely than girls to develop symptoms

*Abbreviations:* ADHD, Attention Deficit Hyperactivity Disorder.

* Corresponding author.
*E-mail address:* rpellon@psi.uned.es (R. Pellón).

https://doi.org/10.1016/j.bbr.2021.113236
Received 30 May 2020; Received in revised form 6 March 2021; Accepted 8 March 2021
Available online 13 March 2021

during childhood [10–15]. The condition comes in three subtypes: inattentive, hyperactive-impulsive, and combined subtype. In the hyperactive-impulsive subtype, a defining characteristic is the tendency to act impulsive, defined by the DSM-V [16] manual as, among other things, having difficulty waiting ones turn, blurting out answers before the question is completed, and interrupting. In the research literature, "impulsive" is a broad term that classifies a range of traits and behaviours, including impatience, restlessness, risk-seeking behaviour, spontaneous decisions, and lack of foresight [17–19].

One method of investigating impulsive behaviour is the delay-discounting task, which involves choosing between a small, immediate reward, and a larger, delayed reward [20]. This setup allows for a variety of manipulations in order to investigate aspects such as reward size or waiting time. In most setups, the large reward (abbreviated as "LL": Large, Later) is considered the optimal choice following a reward-maximizing strategy. That is, choosing LL will grant the animal the highest amount of rewards. Impulsivity is therefore defined as choosing the small reward ("SS": Small, Sooner) despite LL producing the highest amount of rewards across the session. Alternatively, one group can be classified as impulsive if it shows less resilience to waiting times than a comparison group. This is indicated by a switch in preference from LL to SS as the delay for LL increases, but that this switch happens earlier in one group compared to the other [21–23].

People with ADHD tend to act impulsively on the delay-discounting task compared to controls, designated by a tendency to choose SS more often when long delays are present for LL [22,24–27]. The implication is that impulsivity in ADHD is largely explained as an unwillingness to endure long waiting times in order to secure large rewards [25,28]. Specifically, the delay-aversion theory proposed that impulsivity is an aversion to long trial lengths, and not waiting for rewards per se [22]. This was illustrated by a delay-discounting experiment, where in one condition the session ended after a fixed amount of time, while in another condition it was after a fixed amount of trials. This means that in the time condition, LL is reward-maximizing and should be chosen more often, as session length is unaffected. By comparison, LL is also reward-maximizing in the trial condition but choosing SS instead will reduce waiting time for the participant. Results showed that in the trial condition, but not the time condition, ADHD children chose SS more often than controls, resulting in shorter sessions, indicating impulsive choice. These results were subsequently replicated (for a meta-analysis see Patros et al. [29]), but it has also been found that the most important component of the trial length affecting impulsive behaviour is the delay between choice and reward [30]. This gave rise to the dual component model of ADHD, which suggested that both trial length (overall delay) and response-reward delay combined produce impulsive behaviour in people with ADHD [30].

### 1.1. Delay discounting in animals

Since animals cannot be instructed on the parameters of the task, they undergo a rigorous training phase prior to the experiment. The actual delay-discounting experiment can be conducted in two different ways [9]. In the standard design (Fig. 1A), the delay between choice and large reward gets progressively longer for each session, followed by a fixed ITI. This effectively means that the trial length (for the large reward) also increases for each session, making it difficult to distinguish if trial length or the delay caused the impulsive behaviour. Therefore, many animal experiments employ a compensating design (Fig. 1B), where the ITI is adjusted in accordance with increasing delays in order to ensure that the trial lengths remain unchanged throughout the experiment. Unfortunately, this method is susceptible to false analogies, where assumptions are made about the animals' inner state and ability to comprehend the variables occurring in a session, particularly the ITI [31].

Hayden [32] pointed out that the use of a compensating design assumes that the animals pay attention to events happening after the delivery of a reward. While the impact of the delay component on impulsive choice in animals is well documented [32], the same cannot be said for research on post-reward temporal components, such as the ITI. Available studies show that pigeons [33], starlings [34] and rhesus monkeys [35] are almost unaffected by the length of the ITI. That is, when the duration of the ITI is adjusted, the manipulation appears to have no or minimal effect on discounting. If the time between trials is made more salient, e.g. by adding a visual cue indicating its length, or rewarding an animal before the next trial, then its length will contribute to steeper discounting [36]. This may suggest that the animal pays less attention to the ITI and underestimate its length [32]. The reason for this is likely because the choice response produces a reinforcer, meaning that

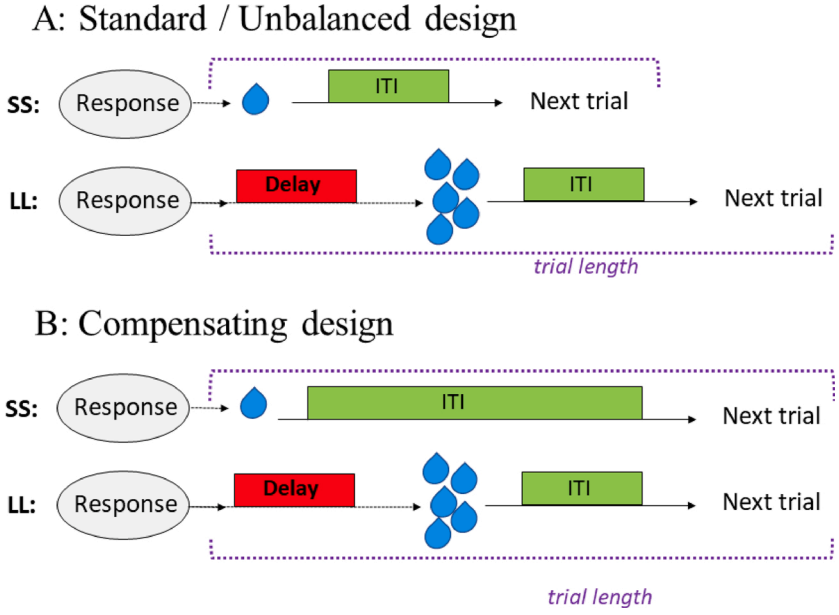


**Fig. 1.** Note: In the standard delay discounting design (A), the ITI is fixed, and thus trial length increases along with the increasing length of the delay between response and reward. In the compensating design (B), the length of the ITI for SS is usually fixed, but for LL it is adjusted so the trial length remains the same for both SS and LL, as well as when the delay increases. Setup A can also be called a non-adjusting design, with B being an adjusting design.

being rewarded for making the choice increases the likelihood of making this choice again [37], but long waiting times before the delivery of the reward decreases its effect [28]. By contrast, enduring the length of the ITI is not reinforced, and one could therefore argue that its length is largely irrelevant for the animal. It should be noted, however, that we are not talking about whether an animal "understands" or "ignores" the ITI, as this sort of inference would be a category mistake [38], but rather whether the variable has any observed effect on behaviour, regardless of any reason why.

The relevance of the ITI has profound implications when interpreting results using delay-discounting experiments in animal models of ADHD. If the choices made by the animals are largely unaffected by the ITI's duration, then this means that delay aversion (overall trial length) cannot be controlled for and that the compensating design might be an illusion, because it will be - in practical terms - identical to the standard design. That is to say, the ITI component in delay discounting would become irrelevant and should therefore not be taken into consideration, as it would not play a role in discounting. Furthermore, the length of the ITI, regardless of setup used, varies in length from study to study, and if it does have an effect then this could explain discrepancies in results. That is, if the duration of the ITI impacts discounting, then it accounts for different outcomes across studies that employed varying ITI lengths, regardless of whether these studies used fluid or fixed ITI durations. It is therefore paramount to establish whether the ITI affects choice behaviour in delay-discounting tasks, as several interpretations of data may hinge on the ITIs relevance. If it is irrelevant, then the compensating design has questionable validity and previous studies employing it need to be re-examined, but it would also mean that variations in lengths across studies is not a deciding factor in explaining differences in results. By contrast, if the ITI does have an effect on choice in animals, then animal models using delay-discounting experiments should establish a standardized length in order to make comparisons across studies more efficient. In addition, it would mean that the effect of delays and the ITI needs to be weighted in order to assess their relative impact, otherwise we are assuming that increasing one and decreasing the other has no effect, as is the case in the compensating setup. Thus, the delay-discounting procedure operates – to a certain degree – on assumptions, where the impact of the ITI on discounting is assumed rather than tested, which will impact our experimental designs and our interpretations of the data.

### 1.2. The SHR animal model of ADHD and the present study

The Spontaneously Hypertensive Rat (SHR) is an animal model of ADHD that exhibit multiple ADHD symptoms when compared to a control group [5,39–43]. On the delay-discounting task, SHRs respond more impulsively than controls, indicated by a reduced tolerance for LL delays, resulting in a switch in preference to SS [5,6,8,44–50]. Some studies, however, have failed to find any strain difference, questioning the validity of the rats as a model of the hyperactive-impulsive subtype of ADHD [4,7,51–53]. The cause of this discrepancy is an ongoing debate, with one possible reason being a varied use of the Wistar Kyoto (WKY) control strains, which have been shown to exhibit genetic and behavioural differences across vendors [54–56].

To the best of our knowledge, no previous studies have investigated the impact of the ITI on delay discounting using an animal model of ADHD. Outside of animal modelling, only a study by Smethells and Reilly [57] has investigated its role on rats. They found that the ITI had generally little effect on delay discounting, with one strange exception: short ITIs (10 s) and moderately long delay (6 s) together caused impulsive behaviour, but long ITIs or shorter delays did not, suggesting that ITI has an effect when interacting with a delay component. Unfortunately, this study had multiple limitations. First, the sample size was very small ($N = 4$). Second, the rats were exposed to an ITI of either nine or 45 s, as opposed to incremental changes that more efficiently evaluates its effect. Third, this was a within-study design, which means the rats' previous experience with delays and ITIs could compromise performance. Fourth, and most importantly, the authors used a compensating design whereby the ITI is reduced in accordance with the delay. This means that even if a 10-s ITI was reported, it would mean that its duration was actually four seconds if the delay was six seconds ($10-6 = 4$). Therefore, one can argue that Smethells and Reilly [57] were actually measuring the weighted impact of the delay function in the context of trial length. When the trial length is 45 s, delays up to six seconds form a relatively small part of the overall trial length (13 %). By contrast, a delay of six seconds in a 10-s trial occupies the majority of the trial (60 %). In this latter context, the ITI is so short that the animal may not have finished eating its reward before the next trial starts. Therefore, the function of the delay is more salient, causing a drop in the preference for the large reward. This salience is reduced with longer trials since the animal spends the majority of its time waiting for the next trial to begin.

For the present study with SHR and WKY rats, one group of each will be exposed to systematically increasing LL delays (Delay group, Fig. 2A) while different groups will be exposed to an equivalent increase in ITI for large reward (ITI group, Fig. 2B). Thus, the trial length gets systematically longer for both groups when choosing the large reward, but one group experiences this increase in the form of a delay and the other in the form of increased ITIs. In addition, we will conduct a replication with the ITI rats where the duration of the ITI is cued using a sound, in order to assess if a more salient ITI has an increased effect on choice. This setup allows for the testing of multiple theories, each of which have different predictions regarding the outcome (although they are not necessarily mutually exclusive). First, the delay-aversion theory hypothesizes that the increase in trial length will cause a preference switch in the SHR (impulsivity), and since the trial length is identical across both groups, we should observe no difference between them [22]. Second, the dual component model of impulsivity recognizes that the delay between response and reward is also a contributing variable. Therefore, this model predicts that the SHRs in both groups will express impulsive behaviour as trial length increases, but that discounting in the Delay group will be steeper than in the ITI group [30]. Third, Hayden's review of time discounting suggests a post-reward buffer hypothesis, which stipulates that the ITI has little effect on discounting and therefore the ITI group should be largely unaffected by the manipulation, but in the presence of an auditory cue the ITI will cause steeper discounting [32].

## 2. Methods

### 2.1. Experiment 1

#### 2.1.1. Subjects

Sixteen SHR/NCrl and 16 WKY/NHsd rats, all male, were used. SHRs were obtained from Janvier Laboratories (France) and WKY rats from Envigo Laboratories (United Kingdom).[i]

The rats were five weeks old upon arrival and spent the first two weeks habituating to their home cages with free access to water and food. When seven weeks old, the rats started to be gradually reduced in weight by food restriction, to be finally maintained at 85 % of their free-feeding growing curve, but had free access to water. Prior to this manipulation, the SHRs weighed on average (SEM) 191 g (±3.6) while the WKYs weighed 153 g (±3.0). Upon completion of the experiment, the rats were 11 weeks old, with the SHRs weighing an average of 208 g (±3.9) and the WKYs 194 g (±3.7). Rats were weighted daily.

The rats were housed individually in an environmentally-controlled room where temperature was held at a constant 22 °C, humidity was maintained at 55 %, and there was a 12:12 light-dark cycle (lights on at

[i] It should be noted that originally this study aimed to use SHR/NCrl from Charles River Laboratories, Germany. Unfortunately, two months prior to the start of the experiment Charles River reported that their SHRs were not free from Strep Pneumonia, forcing us to acquire SHRs elsewhere.

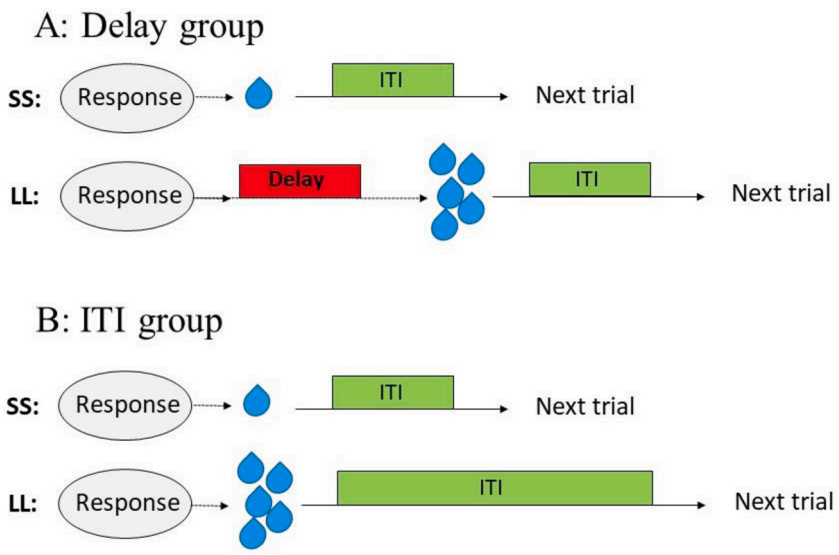


**Fig. 2.** Note: Standard delay discounting design with two groups. The Delay group (A) is exposed to delays between choice and reward delivery, which increases in length as the experiment progresses. The ITI group (B) is exposed to an identical increase in trial length expressed as a longer ITI for the LL reward. Thus, trial lengths are identical in both groups, with one group experiencing the added delay before food delivery (Delay group) and the other after (ITI group).

8:00 AM). On regular periods, a veterinarian inspected the room. The experiment was conducted during the light cycle.

*2.1.2. Apparatus and materials*

The experimental sessions employed eight Letica LI-836 conditioning chambers, housed at the Animal Learning and Behavior Laboratory, School of Psychology, UNED, Madrid, Spain. The chambers measured 29 × 24.5 × 35.5 cm and were enclosed in sound-attenuating boxes with a wall-mounted fan on one wall providing approximately 60 dB of ambient noise. The left wall was made of transparent Plexiglass, while the right and rear walls were of black Plexiglass. The front wall was equipped with two levers located at each side of a food tray. Behind the front wall was a houselight that illuminated the chamber, which remained on during the entirely of a session. The floor consisted of a 16-bars stainless metal grid, with sawdust underneath.

The food used during the experimental sessions was 45-mg pellets (Bio-Serv, Frenchtown, NJ, USA). The experimental program was compiled and executed using MED-PC-IV.

*2.1.3. Design*

This was a 2 (strain) x 2 (group) x 14 (time) mixed-subject design. Strain consisted of two levels: SHR and WKY. Group was also two levels: 1) Delay, signified by an increasing interval between choice and reward delivery, and 2) ITI, which was an equally long waiting period following reward delivery. The intervals were presented in 14 different lengths, ranging from 0 to 36 s. The dependent variable was % of large reward choices, henceforth referred to as LL (Large Later, while the small reward is SS: Small Sooner).

*2.1.4. Procedure*

Upon reaching seven weeks of age, all 32 rats were exposed to a multi-phase training program followed by the experimental manipulation. Initially, the rats were allowed one day to habituate to the conditioning chamber. Thereafter, the rats went through four days of magazine training, where food pellets were delivered at random intervals. These intervals were 20/20, 30/20, 40/20 and 60/20, referring to waiting time and margin of error, respectively (e.g. 40/20 means a pellet was delivered on average every 40 s, ±20 s).

Following this, the rats went through six days of shaping, where they were trained to press a lever in order to produce a food pellet. This was done using an automatic training procedure where a pellet was delivered every 30 s or whenever a lever was pressed, whichever came first. Rats were trained to press the left lever first, then the right lever. Rats who failed to show consistent lever pressing after three days were given manual shaping onwards, until all rats were able to obtain all food pellets by their own.

*2.1.4.1. Lever-preference test.* Following successful shaping, the rats were exposed to one session where both levers were available, and both produced one food pellet. The purpose of this session was to establish whether the rats had an individual preference for either the left or right lever, which could confound their responses when they later were exposed to large and small delays. If a rat showed a preference (indicated by 55 % or more responses) for one lever over the other, the opposite lever would be permanently assigned as LL, producing the large reward. Following this session, 15 rats preferred the right lever and were assigned the left as LL; eight rats preferred the left lever and were assigned the right lever as LL; and the remaining nine rats showed no preference and were randomly assigned a LL lever.

*2.1.4.2. Preference-for-large-reward test.* This final phase before the proper experiment aimed to establish a preference for the large reward (LL), so as to assure (rather than assume) that the rats preferred a large amount of food rather than a small one, in the absence of delays. In this phase, one lever produced one food pellet (SS) while the other produced three (LL). Following pellet delivery, a 10-s ITI occurred before the next trial began. Trials were presented in ten blocks of six trials, which were two forced and four free trials. During forced trials, only one of the levers was available during the first trial and only the other in the second trial. This order was randomized. The session lasted 30 min or when the rat had completed 40 free-choice trials, whichever came first. There was a total of five sessions.

The criterion for advancing to the experimental phase was to show a 66 % preference for LL, or higher, on two consecutive sessions. Eleven of the rats showed a 66 % preference or higher on the first day, and after three days all but five rats had passed the test. After five days all but one rat (WKY-18D) had passed the test, but this rat only marginally failed, showing a 70 % preference for LL on average across the two last days,

with an 83 % preference for LL on the last day. It was therefore decided to include the rat in the experimental phase, but its performance was closely monitored.[ii]

*2.1.4.3. Experimental phase: delay discounting.* During the experimental phase, rats were exposed to the same setup as during the preference test: one lever acted as LL and the other as SS, followed by a 10-s ITI. However, one group of rats (Delay group) was exposed to delays between response and LL delivery, which gradually increased by three seconds for each session up to a maximum of 36 s in the fourteenth and final session. The full list of delays/added ITIs were 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36 s. We also used a zero second condition, where data from the final day in the preference test were used. The 1-s condition was added to denote the difference between the presence and absence of delays. For SS, one food pellet was always delivered immediately, followed by a 10-s ITI.

The second group of rats (ITI group) was exposed to increasingly longer inter-trial intervals across sessions, of which the increased waiting time was identical to the delay in the Delay group. For example, in the 6-s condition the Delay group could choose between SS, which rewarded one pellet immediately followed by a 10-s ITI or LL, which rewarded three pellets after a six second delay, followed by a 10-s ITI. For the ITI group, however, both choices immediately produced the reward(s), but the ITI for SS was 10 s while for LL it was 16 s. Thus, the trial lengths for SS and LL were identical in both groups throughout the experiment, the only difference being that the Delay group had to endure longer waiting period before food delivery, while the ITI group had to wait longer before the next trial began. For a visual illustration of the experimental setup, see Fig. 2.

As in the preference test, the trials were presented in ten blocks of six trials, consisting of two forced and four free-choice trials. A session ended after 40 free-choices or 30 min, whichever came first. With only one exception (rat WKY-20D in the 3-s condition), the 40 free trials were completed by all rats in all sessions.

## 2.2. Experiment 2

We conducted an exploratory follow-up study using half of the sample in Experiment 1 in order to assess the impact of ITI salience, which was done by adding an audio cue to the ITI.

### 2.2.1. Subjects

The rats were 8 SHR/NCrl and 8 WKY/NHsd, who were used in Experiment 1 (the remaining 16 rats were used in a separate experiment, not recorded here, see [58]). These 16 rats had all been in the ITI condition in Experiment 1. Experiment 2 began four weeks after the conclusion of Experiment 1, and the rats were 16 weeks old. Their weights were 239 g (±7.9) for SHRs and 225 g (±4.8) for WKYs. The housing and feeding conditions were the same as outlined in Experiment 1, and upon completion of the experiment the rats were 20 weeks old, SHRs weighing 248 g (±7.8) and WKYs 246 g (±5.7).

### 2.2.2. Apparatus and materials

The equipment, setup and food were the same as outlined in Experiment 1, with one exception: the addition of an auditory cue played during the duration of the ITI. This cue was a beeping noise which systematically increased in frequency as the ITI got shorter, eventually transforming into a continuous noise. Parameters of the tone were individually calculated for each conditioning chamber to have the same salience. Average tone parameters were 70 dB and 215 Hz. There was a withe noise made by the fan of 60 dB on average.

[ii] The rat did not deviate compared to other rats in the experimental phase, and was included in the statistical analysis. The "D" in the rat's name means it was in the Delay condition.

### 2.2.3. Design

This was a 2 (strain) x 14 (interval) mixed-subject design. Strain consisted of two levels: SHR and WKY. The intervals were presented in 14 different lengths, ranging from 0 to 36 s additional time added to the ITI. All groups were subjected to the auditory cue. The dependent variable was % of large reward choices, LL.

### 2.2.4. Procedure

The training and experimental phases were largely identical to Experiment 1 (see Fig. 2), with the magazine training and shaping phase skipped due to the rats' previous experience. The rats were again subjected to a lever-preference test and assigned a permanent LL lever that was the opposite of their individual preference. Subsequently, the rats performed a preference test and had to show a 66 % preference for LL three days in a row to pass the test. Here, we also made a change in the transition between phases: in Experiment 1 all rats were subjected to an equal amount of preference sessions before the experiment began, but in Experiment 2 the experimental phase would begin whenever each individual rat passed the criterion, which could be six days at minimum. After the six days, five SHRs and five WKYs passed the test and advanced to the experimental phase. An additional SHR rat passed the test after three more days of testing, but the remaining two SHRs (I-11 and I-13) and one WKY (I-30) failed to reach the criterion after a total of eleven days of testing and were excluded from the experimental phase.

During the experimental phase, the setup was identical to the ITI setup outlined in Experiment 1, except for the addition of an audio cue. The rats could choose between one or three food pellets, both arriving immediately, with a 10-s ITI. As the experiment progressed, the ITI between choice and LL got progressively longer, beginning with adding one second, then three, six, nine and so forth in intervals of three seconds until 36 s. During the ITI, an audio cue was played consisting of a beep that increased in frequency exponentially as the ITI was nearing its completion. This beep initially occurred once every 0.8 s, progressively increasing in frequency until two-thirds of the ITI had passed, at which point the beeping occurred every 0.1 s, practically becoming a continuous noise.

## 2.3. Data analysis

The use of Linear Mixed Effects Models has been increasingly recommended in psychology and other behavioural sciences, as they account for both within- and between- subjects variance, thus providing lower Type I errors [59–62]. Linear Mixed Models were used to evaluate differences in the preference for LL between groups and strains. First, null models were constructed, and then a likelihood ratio test was used to determine which model was better to account for the data in each experiment. The best-fitting model for each experiment is described in the results section below. Statistical significance was considered as $p < .005$ to avoid Type I errors [63]. All linear mixed effects analyses were carried out using the packages *lme4* [64] and *LmerTest* [65] on *R* [66, 67].

# 3. Results

## 3.1. Rats' behaviour is sensitive to delays and insensitive to the inter-trial interval (Experiment 1)

Data from the delay-discounting experiment are presented in Fig. 3. The between-subject variables were strain (SHR vs. WKY) and group (Delay vs. ITI), with time (added delay or ITI duration for LL, ranging from zero to 36 s) being a within-subject variable. To reiterate: if the ITI component is a contributing factor in discounting, on par with the delay component, then the two conditions (Delay and ITI) should show the same results. Similarly, if overall trial length is the deciding factor (which incorporates both the Delay and ITI components), the two conditions should be treated as identical. Neither of these two results were

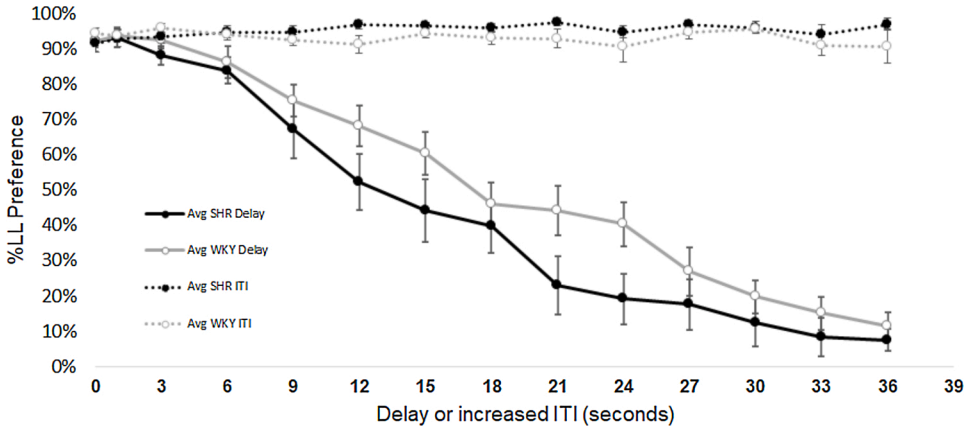


**Fig. 3.** Note: Mean choice of LL for each time condition (added delay or ITI) for each strain (SHR = black, WKY = white; solid line = Delay group, stippled line = ITI group). Error bars represent ±1 SEM.

found: the data indicate that rats exposed to increasingly long ITIs were largely unaffected by this manipulation, and do not appear to change their preference throughout the experiment. Instead, the Delay group shows the expected decline in LL preference, with SHRs becoming impulsive at 15-s delay and WKYs at 18 s, while the ITI group shows no signs of behavior change.

The Linear Mixed Model used to analyse data of Experiment 1 included strain (SHR vs. WKY) and group (Delay vs. ITI) as fixed effects, random intercepts for subjects, and by-group random slopes for delays. Preference for LL was a function of both strain and group ($\chi 2_{(2)} = 204.67, p < .001$). Preference for LL was 43.47 ± 9.01 % (slope + SEM) higher for the ITI than for the Delay group ($t = 5.56$, $p < .001$) throughout the experiment, and 3.42 ± 8.82 % higher for the WKY than for the SHR strain, although this was not statistically significant ($t = 1.07$, $p = .29$). The by-group random slopes showed that as the preference for LL decreased for the Delay group ("Intercept" column in Table 1), it remained the same for the ITI group, as confirmed by the increasing slopes (i.e. increasing differences), which showed a 1.95 % difference between groups in the 0-s delay, but an 84.7 % difference in the 36-s delay. The intercepts and by-group random slopes for all delays are specified in Table 1. Although the best-fitting model included a term for strain (compared to a model that included only group as fixed effect, and a null model that included only random intercepts for subjects), there was no significant effect of strain, so by-strain random slopes were not calculated. These results suggest that rats in the Delay condition chose LL significantly less than rats in the ITI condition as a function of time, with no significant differences between strains.

**Table 1**
By-group random slopes from Experiment 1.

| Delay | Intercept (Delay group) | Slope (ITI group) |
|---|---|---|
| 0 s | 90.27 | 1.95 |
| 1 s | 91.51 | 0.70 |
| 3 s | 88.40 | 3.83 |
| 6 s | 83.06 | 9.20 |
| 9 s | 69.43 | 22.91 |
| 12 s | 58.40 | 34.02 |
| 15 s | 50.46 | 42.00 |
| 18 s | 41.14 | 51.38 |
| 21 s | 31.81 | 60.77 |
| 24 s | 28.09 | 64.51 |
| 27 s | 20.61 | 72.03 |
| 30 s | 14.55 | 78.14 |
| 33 s | 10.21 | 82.50 |
| 36 s | 8.03 | 84.70 |

*Note.* Coefficients (intercepts and slopes) derived from the Linear Mixed Effects Model.

### 3.2. *No effect of an auditory cue on inter-trial-interval discounting (Experiment 2)*

Our data indicate that the rats, regardless of strain, did not become impulsive as the ITI increased and performed similarly to Experiment 1, despite the presence of the audio cue (Fig. 4). The best fitting model for Experiment 2 included a fixed effect of *strain* (SHR vs. WKY) and random intercepts for subjects, nevertheless, there was no evidence of a statistically significant effect of strain ($\chi 2_{(1)} = 0.09, p = .76$), as the difference between the WKY and SHR groups was only of 0.46 ± 1.63 % ($t = 0.29, p = .78$).

Additionally, in order to observe the effect of adding a cue directly, a third model included Experiment (cue vs. no cue) as a fixed effect and random intercepts for subjects. There was a small effect of adding a cue during the ITI ($\chi 2_{(1)} = 6.58, p = .01$), with rats in Experiment 2 showing a slightly lower preference for LL (1.5 ± 0.59 %, $t = -2,57, p = .01$) than rats in Experiment 1, but the results were not statistically significant [63].

Overall the present results indicate that the ITI had no effect on performance, regardless of length, strain, or whether it was cued.

## 4. Discussion

Through two experiments, we found that increasing the duration of the ITI after the choice of a large reward did not affect the preference for it in comparison to a small reward. The rats, regardless of strain, did not appear to alter their behaviour, even when the ITI for the large reward (LL) was over 4.5 times longer than for the small (SS). By contrast, adding a delay component where the rats had to wait systematically longer and longer for their reward caused them to become impulsive, indicated by a switch in preference from LL to SS. Our study also failed to find any main effects of strain differences between SHR and controls in the presence of a delay function, which is in line with several studies that reported the same [4,7,51–53]. Our results are particularly surprising considering the control group was the recommended WKY/NHsd, which is regarded as most suitable [56].

These results cannot be accounted for by the delay-aversion theory of ADHD [22], which clearly predicts a change in preference in both conditions for SHR because their LL trial lengths are identical. At the very least, this suggests that the SHR is unsuitable as a model for predicting impulsive behavior in ADHD people when the animal experiment involves trial length or ITI as a contributing variable. Furthermore, the dual component model of ADHD [30] can also not explain our results, as it predicts that SHRs in both groups would show a preference switch, with the Delay group expressing steeper discounting. While our results do show a strong effect of the response-reward delay, the trial length appears to be an irrelevant factor. This means that only the

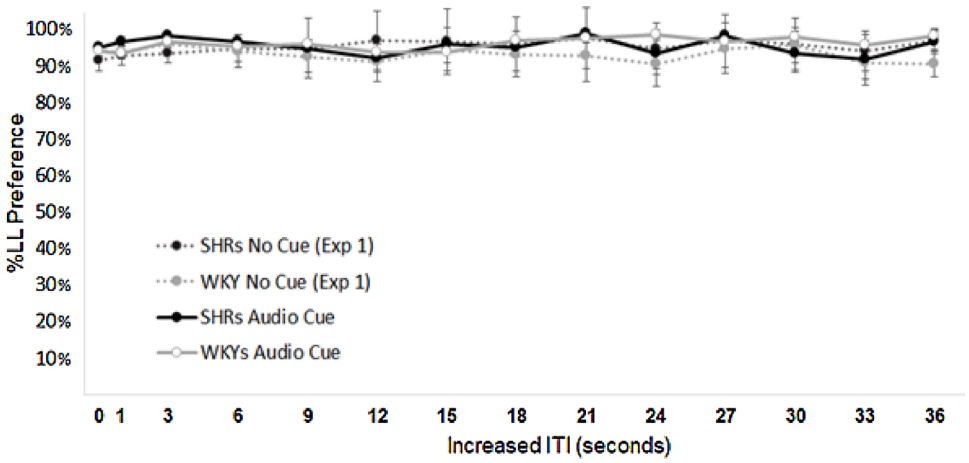


**Fig. 4.** Note: Mean choice of LL for each added ITI, for each strain across both experiments. The stipples lines show results from the first experiment (SHR = black, WKY = grey), while the solid lines are rats exposed to the ITI audio cue in Experiment 2 (SHR = black, WKY = grey with white circles). Error bars represent ±1 SEM.

impulsive drive for immediate reward component of the dual component theory, which recognizes the importance of response-reward delays, can contribute to explaining the data.

Our results are best explained through the Dynamic Development Theory (DDT), which proposes that longer delays between response and reward decrease the effect of the reinforcer [28,37,68]. In other words, there is a temporal window of reinforcement, and this window is shorter for people with ADHD [28]. In the current experiment, no reinforcer is presented at the end of the ITI and therefore its duration was arguably irrelevant for the animal. However, the delay between response and reward has a profound impact on choice, leading 100 % of rats in the Delay group to become impulsive by the end of the experiment. One inconsistency with the DDT, however, is the absence of any strain main effect. While SHRs did appear to become impulsive sooner than controls once the delay was of intermediate length (12 s), this was not statistically significant. The DDT can still account for these results, albeit that the reinforcement window is possibly longer for the SHR model of ADHD than previously anticipated, as other studies have found significant strain differences when the delays were six [5] and nine seconds [46].

Our results are in line with Hayden's [32] hypothesis that the ITI is largely irrelevant in animal discounting, and that the compensating setup (Fig. 1A) carries a risk of false results. Our study suggests that the animals endured long pauses between trials, but not long pauses between making a choice and being rewarded for that choice. These results are also in line with Smethell and Reilly's [57] study, which showed no difference in discounting between an ITI of 10 s vs. 45 s when delays were absent. Furthermore, Evenden and Ryan [9] showed that rats responding impulsively at long delays would rapidly revert back to choosing LL once the delay component is removed while the ITI remains.[iii] In the present study, none of the rats in the ITI group became impulsive even when the ITI for LL was 36 s longer than for SS.

A previous difficulty with animal discounting experiments is the inability to separate the effects of delays and ITI in the compensating design, as increasing one variable decreased the other (see Fig. 1). Similarly, in the standard setup it was not possible to isolate the delay function from trial lengths since they were positively correlated. In our study, trial length for LL becomes longer than SS as the temporal variables increase, but the impact of trial length can be inferred through our separation of delay and ITI in two independent groups (see Fig. 2). The results clearly show that neither trial length nor ITI length impacts discounting in rats, but delays between choice and reward has a profound effect. Thus, the compensating design of delay discounting is possibly unfeasible in rat experiments, if not animals in general, as controlling for trial lengths with adjusting ITIs appear to not affect performance. The compensating design has also been argued to have low ecological validity, as short ITIs would not lead to larger rewards in nature [32], nor would the choices repeat [21]. This also means that previous studies that have employed the compensating setup are only measuring the effects of reward size and delay length.

This is not to say that the ITI component may be completely irrelevant in discounting, since it has been shown to play a role when interacting with the delay component [57] or when reinforcement is given at its end [36]. The exact nature of this relationship or how it affects animal discounting is not yet completely understood. Research by Smethells and Reilly [57] suggests that ITIs may serve to amplify the effect of the delay when the trial length is short. In the present experiment, we did not investigate interactions between delays and the ITI. This could be investigated further by conducting a delay-discounting experiment with four manipulations: 1) the ITI absent; 2) a fixed ITI duration; 3) a compensating design where the ITI decreases in length as the delay increases; and 4) the ITI increases along with the increased delay. If the ITI has absolutely no effect, the results should be identical across conditions. It should also be noted that in the present experiment, the ITI only changed in one condition. One could therefore argue that the results reflect a comparison between fixed and adjusting ITI conditions. However, this is arguably irrelevant: what matters is the duration of the ITI and whether this impacts choice, and by extension discounting, which our results seem to illustrate that it does not. While the premise of the compensating design is scientifically sound (it aimed to control for third variables such as trial length), it becomes problematic when research has shown that these variables play little to no role. Theories such as delay aversion [22] hypothesize an effect of trial length on discounting, and trial length necessarily includes the ITI. In such cases, the compensating design will give a false sense of trial length control, as the ITI – and thus by extension trial length – does not appear to affect rat discounting, as suggested by the present experiment.

Our results also challenge another theory that was not explicitly evaluated *a priori* in the experiment: optimal foraging theory. This evolutionary theory suggests that animals have evolved to use reward-maximizing strategies where possible, obtaining the most amount of food while spending the least amount of energy [69]. In the current experiment, this theory has similar predictions to the delay-aversion theory, as it suggests that the rats will choose LL until a point where this option no longer produces the most rewards. The optimal choice can

[iii] In Evenden and Ryan's (1996) paper, experienced rats were exposed to a standard delay-discounting setup. On the same day, they would be exposed to both a response-reward delay session and a session without delays. This information is not entirely clear in the paper itself, but it was clarified through personal communication with John Evenden in January 2019.

be calculated for each condition by using odds ratios, obtained by calculating the food pellets obtained per second for LL trials divided by pellets per second for SS trials [21]. In the current experiment, the LL ceases to be the optimal choice at 21 s, when the LL-—SS ratio is 0.97 and SS is slightly more reward maximizing from this point onwards. The Delay group did express a preference switch point close to this prediction, switching at 15 (ratio of 1.2) and 18 (ratio of 1.07) seconds for SHRs and WKYs, respectively. However, the ITI group reliably chose LL throughout the entire experiment, which contradicts the predictions of optimality theory.

These data, combined with previous studies, suggests that the ITI is largely irrelevant in animal delay discounting, but why would post-reward delays be a unique causal factor in human impulsive choice? A likely explanation is the effect of instruction: humans can be told the precise experimental parameters, while animals cannot. Indeed, if humans are *not* told the details regarding the reward size, impulsive choice increases [1]. Using operant procedures, as in the current study, will also produce steeper discounting compared to using questionnaires with verbal information [70]. It therefore seems likely that the relevance of the ITI in humans is the result of explicit instructions given.

It should also be noted that the rats in the current experiment were also unaffected by the auditory cue meant to indicate the length of the ITI, which is contrary to what Blanchard et al. [36] found in rhesus monkeys. There are multiple possible explanations for this, one being species differences between monkeys and rats. Alternatively, auditory cues could have less salience than a visual cue, or the rats were simply not trained enough in associating the sound with time and therefore failed to relate it to the ITIs duration. A future replication could include a discrimination test to ensure that the rats can distinguish between the various tones, prior to conducting the experimental phase.

## 5. Conclusions

The current study has shown that the efficiency of the compensating design in delay discounting is limited when testing rats, and the animals appear to be unaffected by the length of the ITI. Instead, the controlling variable is the delay between response and reward, which will cause impulsivity after a certain length. Future research should be wary not to assume that the ITI is relevant when testing rats. The SHR model, while valid in other respects concerning hyperactive-impulsive behavior [38, 71], lacks predictive validity for people with ADHD in delay-discounting tasks due to an apparent inability to incorporate the ITI or trial length.

## Author contributions

E.A.S., E.B.J. and R.P. designed research; E.A.S. and S.R. performed research; E.A.S. and G.E.L-T. performed statistical analyses; G.E.L-T. and E.A.S. programmed the experiments; E.A.S. and S.R. wrote the paper, with revision from E.B.J., G.E.L-T. and R.P.

## Declaration of Competing Interest

The authors report no declarations of interest.

## Acknowledgements

The project was supported by the Ministerio de Economía, Industria y Competitividad, Secretaría de Estado de Investigación, Desarrollo e Innovación, Spanish Government [grant PSI2016-80082-P]. We would like to thank Antonio Rey for technical assistance and general help in the laboratory, along with Gianluca Calcagni and Ernesto Caballero-Garrido. Thank you to Raquel G. Wilner for her support throughout the experiment, particularly proofreading and cultural assistance. Thank you to Per Holth for article feedback. Thanks to Benjamin Hayden and John Evenden for commentary and inspiration. Thank you also to all members of Ricardo Pellón's research group at UNED and Espen B. Johansen's research group at OsloMet.

## References

[1] D.J. Navarick, Control of impulsive choice through biasing instructions, Psychol. Rec. 51 (4) (2001) 549–560.
[2] J. Hwang, S. Kim, D. Lee, Temporal discounting and inter-temporal choice in rhesus monkeys, Front. Behav. Neurosci. 3 (9) (2009) 1–13.
[3] M.C. Pardey, J. Homewood, A. Taylor, J.L. Cornish, Re-evaluation of an animal model for ADHD using a free-operant choice task, J. Neurosci. Methods 176 (2) (2009) 166–171, https://doi.org/10.1016/j.jneumeth.2008.09.009.
[4] N. Epley, A. Waytz, J.T. Cacioppo, On seeing human: a three-factor theory of anthropomorphism, Psychol. Rev. 114 (4) (2007) 864–886.
[5] A.T. Fox, D.J. Hand, M.P. Reilly, Impulsive choice in a rodent model of attention-deficit/hyperactivity disorder, Behav. Brain Res. 187 (2008) 146–152, https://doi.org/10.1016/j.bbr.2007.09.008.
[6] D.J. Hand, A.T. Fox, M.P. Reilly, Differential effects of d-amphetamine on impulsive choice in spontaneously hypertensive and Wistar–Kyoto rats, Behav. Pharmacol. 20 (5–6) (2009) 549–553, https://doi.org/10.1097/FBP.0b013e3283305ee1.
[7] E.A. Sjoberg, P. Holth, H.M. Ottåsen, R. Wilner, E. Johansen, Ascending vs. Descending delays: a delay discounting experiment on an animal model of ADHD, in: Association for Behavior Analysis International (ABAI) 44th Convention, San Diego, CA, 2018.
[8] V. Orduña, Impulsivity and sensitivity to amount and delay of reinforcement in an animal model of ADHD, Behav. Brain Res. 294 (2015) 62–71, https://doi.org/10.1016/j.bbr.2015.07.046.
[9] J. Evenden, C. Ryan, The pharmacology of impulsive behaviour in rats: the effects of drugs on response choice with varying delays of reinforcement, Psychopharmacology 128 (2) (1996) 161–170, https://doi.org/10.1007/s002130050121.
[10] S.N. Visser, et al., Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003–2011, J. Am. Acad. Child Adolesc. Psychiatry 53 (1) (2014) 34–46, https://doi.org/10.1016/j.jaac.2013.09.001, e32.
[11] R. Thomas, S. Sanders, J. Doust, E. Beller, P. Glasziou, Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis, Pediatrics 135 (4) (2015) e994–e1001, https://doi.org/10.1542/peds.2014-3482.
[12] E.G. Willcutt, The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review, Neurotherapeutics 9 (3) (2012) 490–499, https://doi.org/10.1007/s13311-012-0135-8.
[13] A.S. Rowland, et al., The prevalence of ADHD in a population-based sample, J. Atten. Disord. 19 (9) (2015) 741–754, https://doi.org/10.1177/1087054713513799.
[14] G.V. Polanczyk, E.G. Willcutt, G.A. Salum, C. Kieling, L.A. Rohde, ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis, Int. J. Epidemiol. 43 (2) (2014) 434–442, https://doi.org/10.1093/ije/dyt261.
[15] E. Taylor, et al., Clinical guidelines for hyperkinetic disorder, Eur. Child Adolesc. Psychiatry 7 (4) (1998) 184–200, https://doi.org/10.1007/s007870050067.
[16] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-5®), American Psychiatric Publishing, Artlington, VA, 2013.
[17] J.L. Evenden, Varieties of impulsivity, Psychopharmacology 146 (4) (1999) 348–361.
[18] J. Williams, Attention-deficit/hyperactivity disorder and discounting: multiple minor traits and states, in: G.J. Madden, W.K. Bickel (Eds.), Impulsivity: Theory, Science, and Neuroscience of Discounting, American Psychological Association, Washington, DC, 2010, pp. 323–358.
[19] J.W. Dalley, B.J. Everitt, T.W. Robbins, Impulsivity, compulsivity, and top-down cognitive control, Neuron 69 (4) (2011) 680–694, https://doi.org/10.1016/j.neuron.2011.01.020.
[20] J.E. Mazur, An adjusting procedure for studying delayed reinforcement, in: J. Mazur, J. Nevin, H. Rachlin (Eds.), Quantitative Analyses of Behavior Volume V: The Effect of Delay and Intervening Events on Reinforcement Value, Lawrence Erlbaum Associates Inc., New Jersey, 1987, pp. 55–73.
[21] E.A. Sjoberg, E.B. Johansen, Impulsivity or sub-optimal reward maximization in delay discounting? A critical discussion, Hum. Eth. Bull. 33 (2) (2018) 22–36, https://doi.org/10.22330/heb/332/022-036.
[22] E. Sonuga-Barke, E. Taylor, S. Sembi, J. Smith, Hyperactivity and delay aversion—I. The effect of delay on choice, J. Child Psychol. Psychiatry 33 (2) (1992) 387–398, https://doi.org/10.1111/j.1469-7610.1992.tb00874.x.
[23] G. Ainslie, Impulsive control in pigeons, J. Exp. Anal. Behav. 21 (3) (1974) 485–489, https://doi.org/10.1901/jeab.1974.21-485.
[24] E.J. Sonuga-Barke, E. Williams, M. Hall, T. Saxton, Hyperactivity and delay aversion III: the effect on cognitive style of imposing delay after errors, J. Child Psychol. Psychiatry 37 (2) (1996) 189–194, https://doi.org/10.1111/j.1469-7610.1996.tb01390.x.
[25] J. Kuntsi, J. Oosterlaan, J. Stevenson, Psychological mechanisms in hyperactivity: I response inhibition deficit, working memory impairment, delay aversion, or something else? J. Child Psychol. Psychiatry 42 (02) (2001) 199–210, https://doi.org/10.1111/1469-7610.00711.
[26] M.V. Solanto, et al., The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD, J. Abnorm. Child Psychol. 29 (3) (2001) 215–228, https://doi.org/10.1023/A:1010329714819.

[27] L. Dalen, E.J. Sonuga-Barke, M. Hall, B. Remington, Inhibitory deficits, delay aversion and preschool AD/HD: implications for the dual pathway model, Neural Plast. 11 (1–2) (2004) 1–11, https://doi.org/10.1155/NP.2004.1.

[28] T. Sagvolden, E.B. Johansen, H. Aase, V.A. Russell, A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes, Behav. Brain Sci. 28 (3) (2005) 397–418, https://doi.org/10.1017/S0140525X05000075.

[29] C.H. Patros, et al., Choice-impulsivity in children and adolescents with attention-deficit/hyperactivity disorder (ADHD): a meta-analytic review, Clin. Psychol. Rev. 43 (2016) 162–174, https://doi.org/10.1016/j.cpr.2015.11.001.

[30] R. Marco, et al., Delay and reward choice in ADHD: an experimental test of the role of delay aversion, Neuropsychology 23 (3) (2009) 367–380, https://doi.org/10.1037/a0014914.

[31] E.A. Sjoberg, Logical fallacies in animal model research, Behav. Brain Funct. 13 (1) (2017) 1, https://doi.org/10.1186/s12993-017-0121-8.

[32] B.Y. Hayden, Time discounting and time preference in animals: a critical review, Psychon. Bull. Rev. 23 (1) (2016) 1–15, https://doi.org/10.3758/s13423-015-0879-3.

[33] J.N. Goldshmidt, K.M. Lattal, E. Fantino, Context effects on choice, J. Exp. Anal. Behav. 70 (3) (1998) 301–320, https://doi.org/10.1901/jeab.1998.70-301.

[34] M. Bateson, A. Kacelnik, Rate currencies and the foraging starling: the fallacy of the averages revisited, Behav. Ecol. 7 (3) (1996) 341–352, https://doi.org/10.1093/beheco/7.3.341.

[35] J. Pearson, B. Hayden, M. Platt, Explicit information reduces discounting behavior in monkeys, Front. Psychol. 1 (237) (2010) 1–8, https://doi.org/10.3389/fpsyg.2010.00237.

[36] T.C. Blanchard, J.M. Pearson, B.Y. Hayden, Postreward delays and systematic biases in measures of animal temporal discounting, Proc. Natl. Acad. Sci. U. S. A. 110 (38) (2013) 15491–15496, https://doi.org/10.1073/pnas.1310446110.

[37] A.C. Catania, T. Sagvolden, K.J. Keller, Reinforcement schedules: Retroactive and proactive effects of reinforcers inserted into fixed-interval performances, J. Exp. Anal. Behav. 49 (1) (1988) 49–73, https://doi.org/10.1901/jeab.1988.49-49.

[38] P. Holth, The persistence of category mistakes in psychology, Behav. Philos 29 (2001) 203–219.

[39] T. Sagvolden, Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD), Neurosci. Biobehav. Rev. 24 (1) (2000) 31–39, https://doi.org/10.1016/S0149-7634(99)00058-5.

[40] B. Wultz, T. Sagvolden, The hyperactive spontaneously hypertensive rat learns to sit still, but not to stop bursts of responses with short interresponse times, Behav. Genet. 22 (4) (1992) 415–433, https://doi.org/10.1007/BF01066613.

[41] J.L. Evenden, The pharmacology of impulsive behaviour in rats IV: the effects of selective serotonergic agents on a paced fixed consecutive number schedule, Psychopharmacology 140 (3) (1998) 319–330, https://doi.org/10.1007/s002130050773.

[42] D.F. Berger, T. Sagvolden, Sex differences in operant discrimination behaviour in an animal model of attention-deficit hyperactivity disorder, Behav. Brain Res. 94 (1) (1998) 73–82, https://doi.org/10.1016/S0166-4328(97)00171-X.

[43] E.B. Johansen, P.R. Killeen, T. Sagvolden, Behavioral variability, elimination of responses, and delay-of-reinforcement gradients in SHR and WKY rats, Behav. Brain Funct. 3 (1) (2007) 1, https://doi.org/10.1186/1744-9081-3-60.

[44] J.-C. Bizot, et al., Methylphenidate reduces impulsive behaviour in juvenile Wistar rats, but not in adult Wistar, SHR and WKY rats, Psychopharmacology 193 (2) (2007) 215–223, https://doi.org/10.1007/s00213-007-0781-4.

[45] K.R. Sutherland, et al., Sensitivity to delay of reinforcement in two animal models of attention deficit hyperactivity disorder (ADHD), Behav. Brain Res. 205 (2) (2009) 372–376, https://doi.org/10.1016/j.bbr.2009.07.011.

[46] J. Íbias, R. Pellón, Schedule-induced polydipsia in the spontaneously hypertensive rat and its relation to impulsive behaviour, Behav. Brain Res. 223 (1) (2011) 58–69, https://doi.org/10.1016/j.bbr.2011.04.017.

[47] J. Íbias, R. Pellón, Different relations between schedule-induced polydipsia and impulsive behaviour in the spontaneously hypertensive rat and in high impulsive Wistar rats: questioning the role of impulsivity in adjunctive behaviour, Behav. Brain Res. 271 (2014) 184–194, https://doi.org/10.1016/j.bbr.2014.06.010.

[48] T.E. Wooters, M.T. Bardo, Methylphenidate and fluphenazine, but not amphetamine, differentially affect impulsive choice in Spontaneously Hypertensive, Wistar–Kyoto and Sprague–Dawley rats, Brain Res. 1396 (2011) 45–53, https://doi.org/10.1016/j.brainres.2011.04.040.

[49] V. Orduña, I.I.I.E. Mercado, Impulsivity in spontaneously hypertensive rats: within-subjects comparison of sensitivity to delay and to amount of reinforcement, Behav. Brain Res. 328 (2017) 178–185, https://doi.org/10.1016/j.bbr.2017.04.033.

[50] C.F. Aparicio, P.J. Hennigan, L.J. Mulligan, B. Alonso-Álvarez, Spontaneously hypertensive (SHR) rats choose more impulsively than Wistar-Kyoto (WKY) rats on a delay discounting task, Behav. Brain Res. 364 (2019) 480–493, https://doi.org/10.1016/j.bbr.2017.09.040.

[51] W. Adriani, A. Caprioli, O. Granstrem, M. Carli, G. Laviola, The spontaneously hypertensive-rat as an animal model of ADHD: evidence for impulsive and non-impulsive subpopulations, Neurosci. Biobehav. Rev. 27 (2003) 639–651, https://doi.org/10.1016/j.neubiorev.2003.08.007.

[52] A. Garcia, K. Kirkpatrick, Impulsive choice behavior in four strains of rats: evaluation of possible models of attention deficit/hyperactivity disorder, Behav. Brain Res. 238 (2013) 10–22, https://doi.org/10.1016/j.bbr.2012.10.017.

[53] C.J. Botanas, et al., Rearing in an enriched environment attenuated hyperactivity and inattention in the Spontaneously Hypertensive Rats, an animal model of Attention-Deficit Hyperactivity Disorder, Physiol. Behav. 155 (2016) 30–37, https://doi.org/10.1016/j.physbeh.2015.11.035.

[54] T. Sagvolden, T. Dasbanerjee, Y. Zhang-James, F. Middleton, S. Faraone, Behavioral and genetic evidence for a novel animal model of attention-deficit/hyperactivity disorder predominantly Inattentive Subtype, Behav. Brain Funct. 4 (56) (2008) b54, https://doi.org/10.1186/1744-9081-4-56.

[55] T. Sagvolden, E.B. Johansen, Rat models of ADHD, in: C. Stanford, R. Tannock (Eds.), Behavioral Neuroscience of Attention-deficit/Hyperactivity Disorder and Its Treatments, Springer-Verlag, Berlin, 2012, pp. 301–315, https://doi.org/10.1007/7854_2011_126.

[56] T. Sagvolden, et al., The spontaneously hypertensive rat model of ADHD–the importance of selecting the appropriate reference strain, Neuropharmacology 57 (7) (2009) 619–626, https://doi.org/10.1016/j.neuropharm.2009.08.004.

[57] J.R. Smethells, M.P. Reilly, Intertrial interval duration and impulsive choice, J. Exp. Anal. Behav. 103 (1) (2015) 153–165, https://doi.org/10.1002/jeab.131.

[58] S. Ramos, G.E. López-Tolsa, E.A. Sjoberg, R. Pellón, Effect of schedule-induced behavior on responses of spontaneously Hypertensive and Wistar-Kyoto rats in a delay-discounting task: a preliminary report, Front. Behav. Neurosci. 13 (2019) 255, https://doi.org/10.3389/fnbeh.2019.00255.

[59] M.P. Boisgontier, B. Cheval, The anova to mixed model transition, Neurosci. Biobehav. Rev. 68 (2016) 1004–1005.

[60] X.A. Harrison, L. Donaldson, M.E. Correa-Cano, J. Evans, D.N. Fisher, C.E. D. Goodwin, B.S. Robinson, D.J. Hodgson, R. Inger, A brief introduction to mixed effects modelling and multi-model inference in ecology, PeerJ (2018) E4794.

[61] M.E. Young, A place for statistics in behavior analysis, Behav. Anal.: Res. Pract. 18 (2) (2018) 193–202.

[62] B. Winter, Linear models and linear mixed effects models in R with linguistic applications, arXiv 1308 (2013) 5499.

[63] D.J. Benjamin, J.O. Berger, M. Johannesson, B. Nosek, E.J. Wagenmakers, R. Berk, K.A. Bollen, B. Brembs, L. Brown, C. Camerer, D. Cesarini, C.D. Chambers, M. Clyde, T.D. Cook, P. De Boeck, Z. Dienes, A. Dreber, K. Easwaran, C. Efferson, E. Fehr, et al., Redefine statistical significance, Nat. Hum. Behav. 2 (2018) 6–10, https://doi.org/10.1038/s41562-017-0189-z.

[64] D. Bates, M. Mächler, B. Bolker, S. Walker, Fitting linear mixed-effects models using lme4, J. Stat. Soft 67 (1) (2015) 1–48, https://doi.org/10.18637/jss.v067.i01.

[65] A. Kuznetsova, P.B. Brockhoff, R.H.B. Christensen, lmerTest package: tests in linear mixed effects models, J. Stat. Soft 82 (13) (2017) 1–26.

[66] R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2012.

[67] RStudio Team, RStudio: Integrated Development for R, URL, RStudio, PBC, Boston, MA, 2020, http://www.rstudio.com/.

[68] T. Sagvolden, H. Aase, P. Zeiner, D. Berger, Altered reinforcement mechanisms in attention-deficit/hyperactivity disorder, Behav. Brain Res. 94 (1) (1998) 61–71, https://doi.org/10.1016/S0166-4328(97)00170-8.

[69] R.H. MacArthur, E.R. Pianka, On optimal use of a patchy environment, Am. Nat. 100 (916) (1966) 603–609.

[70] D.J. Navarick, Discounting of delayed reinforcers: measurement by questionnaires versus operant choice procedures, Psychol. Rec. 54 (1) (2004) 85–94.

[71] T.A. Sontag, O. Tucha, S. Walitza, K.W. Lange, Animal models of attention deficit/hyperactivity disorder (ADHD): a critical review, ADHD Atten. Def. Hyp. Disord. 2 (1) (2010) 1–20, https://doi.org/10.1007/s12402-010-0019-x.