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Research report

Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: Specific deficits in 'waiting' versus 'stopping'

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ABSTRACT

Impulsivity is a core deficit of a number of neuropsychiatric disorders including attention-deficit hyperactivity disorder (ADHD), anti-social conduct disorder and drug addiction. Recent research has highlighted the multifaceted nature of impulsivity and the myriad of putative neural and psychological mechanisms thought to underpin behavioural syndromes of impaired self-control. Here we report a novel conceptualisation of impulsivity based on 'waiting' and 'stopping' efficiency with explanatory value in defining the psychological and neural basis of impulsivity and the high co-morbidity of brain disorders such as ADHD and drug addiction. Rats selected for high levels of impulsivity on a reaction time task analogous to the continuous performance test in humans exhibited correspondingly high levels of impulsive decision-making on a delay-of-reward task. The same rats, however, were unimpaired on a stop-signal task requiring inhibition of an already initiated motor response. The specific nature of this deficit in 'waiting impulsivity' was confirmed by unimpaired acquisition of appetitive Pavlovian conditioning, a putative ancillary measure of impulsive behaviour. These findings are significant in light of recent evidence linking impulsivity in rats to high levels of cocaine self-administration and development of compulsive cocaine seeking behaviour. We thus suggest that an inability to bridge delays to future rewards and reward-related stimuli is a candidate behavioural endophenotype that pre-disposes to clinical psychopathology.

1. Introduction

Impulsivity, the tendency to respond prematurely, without foresight, is a characteristic of normal human behaviour but can also contribute to psychopathology in a number of different neuropsychiatric conditions including attention-deficit hyperactivity disorder (ADHD) and drug addiction [1–6]. However, impulsivity is unlikely to represent a unitary construct and 'varieties of impulsivity' exist, probably with distinct neurobiological substrates [1,7–9]. Evidence to support this notion arises from both clinical and pre-clinical studies where different neuropsychological tests and animal models of impulsive responding have been used to characterise different forms of impulsive behaviour with distinct neural substrates [7,9].

We recently identified a sub-population of Lister-hooded rats with a high level of premature responding in the 5-choice serial reaction time test (5-CSRTT) of sustained visual attention [10,11]. These high impulsive animals were shown to exhibit enhanced cocaine self-administration and a decrease in dopamine (DA) $D_{2/3}$ receptor availability in the ventral striatum quantified using micro positron emission tomography (PET) [10]. Notably, high impulsivity in rats also predicts the transition to compulsively seek and take cocaine, a hallmark feature of addiction [12].

However, premature responding in the 5-CSRTT may only reflect a specific form of impulsivity [1,7,8]. It is thus important to better characterise this phenotype using other measures of the impulsivity construct, including the temporal discounting of reward [13,14], the stop-signal reaction time task (SSRTT) [15], and Pavlovian autoshaping [16]. Delay discounting is an impulsive choice paradigm in which the rat is given a choice between a small, immediate reward and a large delayed reward, with increasing impulsivity being reflected in the choice of the temporally more proximal reward. The stop-signal reaction time task requires the cancellation of a speeded response in a reaction time task, and

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can be used to measure the speed at which this inhibition of an initiated motor response occurs [15]. The autoshaping procedure indexes the elicitation of a Pavlovian response directed generally to stimuli predicting food delivery [16]. Such Pavlovian responses have long been known to interact, often detrimentally, with instrumental behaviour—for example, as described by Breland and Breland [17].

In the present study we first characterised rats exhibiting high impulsivity on the 5-CSRTT, and then subjected them to these three ancillary procedures for quantifying impulsivity, in order to determine whether they could be described as impulsive according to different measures. Thus, we employed a delay-discounting procedure to measure 'impulsive choice' [18]. We also measured the capacity for motor inhibition in both low and high impulsive rats using a SSRTT procedure [15,19]. Finally, we tested some rats in an autoshaping procedure with an omission schedule [16,20] in order to test the hypothesis that high impulsivity in the 5-CSRTT might derive from the elicitation of responses governed by Pavlovian appetitive processes.

2. Materials and methods

2.1. Subjects

The subjects were male Lister-hooded rats weighing approximately 250 g at the start of training and 350–450 g at the end of training (Charles River, UK), housed in pairs or groups of four under temperature-controlled conditions and a 12-h:12-h light–dark cycle (lights off at 0700 h). They were maintained at approximately 90% of their free feeding weight by restricting access to laboratory chow (Purina, UK) to approximately 18 g/day per rat. Water was provided *ad libitum*. All procedures were conducted in accordance with the requirements of the UK Animals (Scientific Procedures) Act 1986 and in accordance with local institutional guidelines. All behavioural testing was carried out between 0800 h and 1800 h during the animals' active phase.

Subjects included in this study were first trained on the 5-CSRTT and then subsequently screened for impulsivity as described below (and see Fig. 1). At the end of this period animals were allocated to a single subsequent testing procedure. As such, no animal was used in more than one task in addition to the 5-CSRTT. Training on the second task commenced at least 2 weeks after screening for impulsivity. It is unlikely the different tasks interfered with one another as only the 5-CSRTT involved a nose-poke operant response for food reward.

2.2. 5-choice serial reaction time task training

A detailed description of the nine-hole apparatus and procedures has been provided previously [21–23]. The boxes were controlled by Whisker software (Cardinal RN, Aitken MRF, 2001; version 2.2. http://www.whiskercontrol.com). Groups of animals were trained to criterion (>80% accuracy, <20% omissions at stimulus duration 0.5 s) using the standard training schedule described recently [23]. Screening for impulsivity was carried out over a 3-week period with an identical testing procedure for each week [10]. Animals were first tested under baseline conditions (0.5 s stimulus duration; 5 s inter-trial interval (ITI); 5 s limited hold (LH)) on two consecutive days (days 1 and 2). On day 3, animals were challenged with a long ITI where the delay from trial onset to stimulus presentation was increased to 7 s, a manipulation which increases the frequency of premature responses and which helps to differentiate between high and low impulsive rats on the 5-CSRTT [10]. On days 4 and 5 animals were again tested at baseline (0.5 s stimulus duration; 5 s ITI; 5 s limited hold). This procedure was repeated on two further occasions as summarised in Fig. 1.

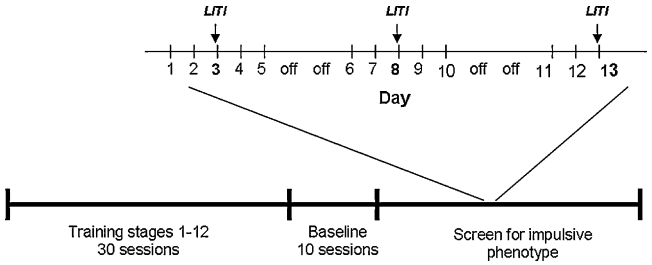

Fig. 1. Illustration showing the schedule used for training rats and screening for high impulsivity on the 5-CSRTT (see [23] for details of the training procedure); LITI = long inter-trial interval.

At the end of the screen the results were analysed and animals meeting criterion for high impulsive (mean absolute number of premature responses/session ≥50 on each of the three individual LITI challenge sessions) or low impulsive animals (mean absolute number of premature responses/session ≤30 on each long LITI challenge session) were selected.

2.3. Stop-signal reaction time (SSRT) task

The stop-signal reaction time task was derived from the task of Logan and Cowan [24]. This task provides an estimate of the time taken to stop a response, the stop-signal reaction time (SSRT) from measurable task parameters, the go trial reaction time distribution, and the accuracy of stopping on stop trials. SSRT cannot be measured directly as there is no observable endpoint to the response inhibition. Logan and Cowan [24] proposed that the 'stop' and 'go' processes are independent of one another, that a 'race' occurs between the two processes for completion, and that whichever process finishes first wins the race. If the go process wins, a response occurs, and if the stop process wins, a response is inhibited. The finishing times of these processes are assumed to vary randomly, so the outcome of the race is a matter of probability. The race model assumes the stop process to be faster than the go process, and the placement of the stop-signal during the go process biases the race in favor of one process or the other. For example, if the stop-signal occurs early in the trial, the response will usually be inhibited. Conversely, if the stop-signal occurs late enough, the response will rarely be inhibited.

All sessions were performed in six operant chambers (Med Associates, VT, USA), as described previously [15]. In all sessions, trials were initiated with a nose-poke to the central food well after which the left lever and left light were presented. A press on the left lever resulted in the right lever and right light being presented, and the left lever and left light being withdrawn. If a rat failed to press the left lever within 30 s, the left lever was withdrawn, rats received a 5 s timeout, and the trial was recorded as an omission trial. Rats were trained to perform a rapid reaction time (RT) response from left lever to right lever—the go response. Response speed was maintained by limiting the time for which the right lever was presented—the limited hold, LH), maintained at a constant value for each rat throughout the study. Study groups were matched for LH. During go trials, rats were rewarded with a pellet delivered to the central food well for pressing the right lever but received a timeout of 5 s in darkness if they failed to press the right lever within the LH period.

On 20% of the trials, the stop trials, a tone (40 ms, 4500 Hz) was presented at a predetermined time between the left- and right-lever presses. Stop trials were presented randomly within the session to discourage the rats from anticipating the presentation of the stop trials. On stop trials, the rats were required to initiate the same response as on go trials, but after the presentation of the stop-signal, the rat was required to stop the completion of the go response, i.e. to refrain from pressing the right lever. The rat was required to withhold from responding for the LH period, after which it was rewarded with a pellet. An incorrect response, which was a press on the right lever, resulted in a timeout of 5 s of darkness. On a few trials designated as stop trials, the rat responded on the right lever before the onset of the tone (more common for late tone presentations), and these trials were reclassified as go trials to maintain the overall proportion of valid stop trials in each session at 20%.

To apply Logan's race model to the behavioural data rats must perform go trials as quickly as possible while attempting to stop on all stop trials after the stop-signal is detected. Failure to perform the task in this way may be reflected in the form of the inhibition function and go reaction time (GoRT) across different SSDs. Therefore, rats were excluded from further analysis if they showed inverted inhibition functions (accuracy of stopping improved as the stop-signal was played closer to the go signal), if go accuracy was inversely correlated with stop accuracy or if GoRT systematically increased with SSD (more usually presented as a change in go trial accuracy in the rat SSRT task). Such behavioural patterns reflect strategic changes in performance that cannot be accommodated by the race model. All rats were tested across a full range of SSDs, their inhibition functions were plotted and SSRT calculated.

Rats were initially trained in a no-delay condition (where the stop-signal on stop-signal trials was presented as the left lever was pressed, i.e. with no delay between the onset of the go response and the presentation of the stop-signal) until both stop and go trials were maintained at a stable and high level of accuracy. Following training, rats received 3 × 20-min no-delay sessions from which mean GoRT and SSDs for each rat were calculated. Over the following five sessions (20 min, 200 trials), individual rat inhibition functions were generated with SSDs presented in a randomised order from the following set: SSD = GoRT – 600 ms; GoRT – 500 ms; GoRT – 400 ms; GoRT – 300 ms; GoRT – 200 ms. SSRT was calculated from data for all of the delay sessions, and mean GoRT is shown for the same sessions (see Fig. 4).

2.4. Delay-discounting paradigm

Testing was performed in six standard modular operant chambers (Med Associates, VT, USA; 30.5 cm L × 24.1 cm W × 21.0 cm H) with identical dimensions and configuration to those used in the SSRT task. Lever training and the main delay-