
Article:
Overton, P. orcid.org/0000-0003-4334-261X, Dommett, E., Dinu, L. et al. (4 more authors) (2024) Sign-tracking and goal-tracking in humans: utilising eye-tracking in clinical and non-clinical populations. Behavioural Brain Research, 461. 114846. ISSN 0166-4328

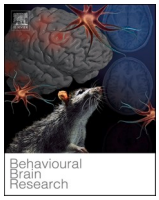
https://doi.org/10.1016/j.bbr.2024.114846

Behavioural Brain Research 461 (2024) 114846

Contents lists available at ScienceDirect

Behavioural Brain Research

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



Research report

Sign-tracking and goal-tracking in humans: Utilising eye-tracking in clinical and non-clinical populations

Larisa-Maria Dinu [a,*], Alexandra-Livia Georgescu [a], Samriddhi N. Singh [a], Nicola C. Byrom [a], Paul G. Overton [b], Bryan F. Singer [c], Eleanor J. Dommett [a]

[a] Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, UK
[b] Department of Psychology, The University of Sheffield, Cathedral Court, Sheffield S1 2LT, UK
[c] School of Psychology, Sussex Addiction Research & Intervention Centre, Sussex Neuroscience, University of Sussex, Brighton BN1 9RH, UK

ARTICLE INFO

Keywords:
Sign-tracking
Goal-tracking
Eye-tracking
Externalising behaviour
ADHD

ABSTRACT

Background: In Pavlovian conditioning, learned behaviour varies according to the perceived value of environmental cues. For goal-trackers (GT), the cue merely predicts a reward, whilst for sign-trackers (ST), the cue holds incentive value. The sign-tracking/goal-tracking model is well-validated in animals, but translational work is lacking. Despite the model's relevance to several conditions, including attention deficit hyperactivity disorder (ADHD), we are unaware of any studies that have examined the model in clinical populations.

Methods: The current study used an eye-tracking Pavlovian conditioning paradigm to identify ST and GT in non-clinical (N = 54) and ADHD (N = 57) participants. Eye movements were recorded whilst performing the task. Dwell time was measured for two areas of interest: sign (i.e., cue) and goal (i.e., reward), and an eye-gaze index (EGI) was computed based on the dwell time sign-to-goal ratio. Higher EGI values indicate sign-tracking behaviour. ST and GT were determined using median and tertiary split approaches in both samples.

Results: Despite greater propensity for sign-tracking in those with ADHD, there was no significant difference between groups. The oculomotor conditioned response was reward-specific (CS+) and present, at least partly, from the start of the task indicating dispositional and learned components. There were no differences in externalising behaviours between ST and GT for either sample.

Conclusions: Sign-tracking is associated with CS+ trials only. There may be both dispositional and learned components to sign-tracking, potentially more common in those with ADHD. This holds translational potential for understanding individual differences in reward-learning.

1. Introduction

Sign-tracking refers to the tendency to engage with a cue, or conditioned stimulus (CS), that has been paired with a reward, or unconditioned stimulus (US) [14]. Sign-tracking develops even though the presence of the reward is not contingent on a response to the cue, as exemplified in Pavlovian conditioning. To date, much of our understanding of sign-tracking has come from animal studies using Pavlovian conditioning paradigms which consist of a lever (CS) paired with food (US). The CS and US are presented in different locations and, following their presentation, two different conditioned responses (CR) can be elicited: (1) sign-tracking, where the animal approaches the lever (the sign) and, after its termination, engages with the location of the food (the goal); or (2) goal-tracking, where the animal approaches the location of the food, even before food is available. Importantly, in rodent studies, the extent to which a cue can become attractive and bias behaviour is influenced by individual differences with some rats displaying sign-tracking and others displaying goal-tracking, creating a so-called sign-tracking/goal-tracking model where sign-trackers (ST) attribute more motivational value (incentive salience) to cues paired with rewards, whilst goal-trackers (GT) are more influenced by contextual cues [31].

Despite much of the research to date being conducted in rodents, sign-tracking is thought to be found across species and is linked to externalising behaviours, including impulsivity, inattention, defiance, and aggression [4]. It has been proposed that sign-tracking can result in

Abbreviations: ST, sign-trackers; GT, goal-trackers; CR, conditioned response; EGI, eye-gaze index.

* Corresponding author.
E-mail address: larisa.dinu@kcl.ac.uk (L.-M. Dinu).

https://doi.org/10.1016/j.bbr.2024.114846
Received 22 September 2023; Received in revised form 18 December 2023; Accepted 2 January 2024
Available online 5 January 2024

continued engagement with a maladaptive cue in the absence of rewards or even in the presence of undesirable effects [31], which can be a powerful, albeit inappropriate, motivator of behaviour [15]. Subsequently, sign-tracking could capture a neurobehavioral endophenotype important in psychiatric and neurodevelopment disorders, particularly those relating to externalising behaviours [25,31,33,6], and it is believed that understanding sign-tracking could aid screening and early interventions for these conditions. In rats, responses to the incentive salience of stimuli in ST and GT phenotypes has been suggested to be driven by different neural circuitry and to be modulated by attentional processes [36]. Perhaps unsurprising then, translational efforts to capture sign-tracking in humans are increasing [16,34,6]. For example, Garofalo & di Pellegrino [16] demonstrated that cue-controlled behaviour in healthy adults can be predicted from individual differences in the tendency to engage with a sign (cue predictive of reward) or a goal (reward) in humans using an eye-tracking paradigm. Using eye-tracking and functional magnetic resonance imaging, Schad et al. [34] showed that ST displayed neural reward prediction error signals not detectable in GT in a sample of male, healthy adults. They further proposed that ST base their decision-making process on model-free learning, characterised by habitual control and inflexible thinking patterns, in contrast to GT, who engage in model-based learning, characterised by goal-directed or cognitive control [10]. Colaizzi et al. [6] investigated, for the first time, sign-tracking in healthy children using a real-life Pavlovian paradigm mimicking the animal paradigm. They found that sign-tracking was associated with attentional and inhibitory control deficits and that ST overly relied on subcortical cue-reactive brain systems. Despite not investigating ST/GT per se, Serrano-Barroso et al. [37] used an gamified autoshaping task in a sample of 103 young children, and found a relationship between high and low respondents on the task and level of attention, indicating that the tool might help evaluate endophenotypes and link them to attentional problems.

These studies have made a significant contribution to advancing our understanding of sign-tracking in humans and provide an important foundation for future research. However, despite promising translational potential, the assessment of human sign-tracking research is still in its infancy. For example, the Pavlovian conditioning paradigm developed by Garofalo & di Pellegrino [16] has not yet been replicated. Considering its ease of administration, replicability, and potential scalability, this is a missed opportunity, especially in light of the debated replicability crisis in psychology and neuroscience [22]. Additionally, the median split method of categorising ST and GT in this previous work did not consider the presence of those showing intermediate responses, commonly reported in rodent studies, which results in ST and GT consisting of more extreme responses than would be found for a median split approach, after intermediate responders are excluded from analysis [13,44]. The previous work also did not attempt to link ST and GT to externalising behaviours. Both of these additions would offer helpful extensions to the paradigm. Moreover, and arguably the biggest limitation of existing research, is that we are unaware of any studies that have investigated sign-tracking in clinical populations, despite evidence that it is relevant to psychopathology and/or atypical behaviour and cognition [25,31,33,6].

Sign-tracking is hypothesised to be linked to conditions associated with externalising behaviours, including addiction [31], binge eating and impulse control disorders [25,33], attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder [6]. Within these, ADHD is arguably one of the more prevalent conditions, impacting 5.3–7.2% of children and adolescents, and 2.5%−4.4% of adults [21,30,39,42]. Importantly, a diagnosis of ADHD has been hypothesised to represent the extreme end of a spectrum of ADHD-like symptoms in the general population [23], with nearly 60% of non-clinical samples across several cultures displaying symptoms of inattention and hyperactivity-impulsivity [2]. This continuum perspective of ADHD-like symptoms has important implications for prevention and early intervention, as it suggests that ADHD symptoms in the general population have similar relationships with other phenotypes as the clinical extreme (i.e., an ADHD diagnosis) [23]. Given the hope that a greater understanding of sign-tracking could aid screening and early interventions, ADHD is an ideal condition in which to study sign-tracking. Therefore, building on previous research, the current study aims to i) Replicate the work of Garofalo & di Pellegrino [16] by using a Pavlovian conditioning paradigm in a non-clinical sample to identify ST and GT utilising the original categorisation methods, and extend this work by also using categorisation methods found in animal studies, which account for intermediate responses, and examining how sign-tracking relates to externalising behaviours in this population, ii) Determine whether sign-tracking can be demonstrated in those with ADHD and how it relates to externalising behaviours in this sample, and iii) Compare participants with and without ADHD who are classified as ST and GT, where we hypothesise that those with ADHD will show greater sign-tracking behaviour since externalising tendencies, and explicitly attention deficit/hyperactivity problems, have previously been linked to sign-tracking, at least in healthy children [6].

2. Methods

2.1. Participants

Data were collected as part of a larger randomised controlled trial (ISRCTN registry: ID ISRCTN39271564). Full details of the trial recruitment and inclusion criteria are reported elsewhere [11] but briefly, participants were recruited from the community through posters, social media, and institutional recruitment emails. Participants provided written informed consent and were compensated £ 22 in vouchers for the two hours spent participating in the trial. Ethical approval for the study was obtained from the ethics committee of King's College London (REF: MOD-19/20–13264). An a priori power analysis was conducted for the wider trial only (see [11]). However, based on two previous studies using similar paradigms in human participants [16,5], a sample of 40 is sufficient to detect a large effect ($d = 0.91$) with 80% power and therefore, we aimed to collect data from 40 individuals without a psychiatric diagnosis and 40 individuals with ADHD, given the two groups are analysed separately in line with our research aims.

To be eligible to participate, all individuals had to be aged 18–35 years. Those making up the non-clinical group had to be free from any psychiatric or neurological condition and any learning differences, in line with previous work [6]. To ensure that the sample did not overlap with our clinical sample, they also had to score < 14 on the Adult ADHD Self-Report Scale (ASRS) Screener items, indicating they are below the clinical threshold for ADHD [19]. In contrast those within the ADHD group had to declare a diagnosis of ADHD made by a clinician on the screening survey (see below), and score ≥ 14 i.e., above the clinical threshold, on the ASRS Screener.

Most ADHD participants were not receiving pharmacological treatment at the time of testing (56.1%), and the rest (43.9%) were receiving stimulant medication. To be eligible to participate, those with ADHD taking medication had to have at least 70% adherence, measured using an existing adherence scale [32]. On average, medication adherence in the current sample was 87.39%.

2.2. Measurement and procedure

2.2.1. Externalising behaviours

Externalising behaviours were measured as part of the screening for the study, in which participants were required to complete the 18-item, Adult ADHD Self-Report Scale (ASRS) which takes approximately 5 min to complete [20]. Items are scored on a 5-point Likert scale (0 = never, 4 = very often). The ASRS can be used in several ways. Firstly, it can be used as a screener, using items 1–6, and it is these items that can provide a score with reference to a clinical threshold of 14 [19]. Secondly, the whole scale can be used to give an indication of the severity of the

externalising behaviours within ADHD, divided into inattention (IA) or hyperactivity-impulsivity (HI), each consisting of nine items [9]. The ASRS has good reliability and validity in clinical and non-clinical samples [11]. In the present study, the internal consistency for the non-clinical sample, as indicated by Cronbach's alpha, was deemed acceptable for all item combinations (Screener items 1–6 $\alpha = 0.74$; Total ASRS $\alpha = 0.89$, IA subscale $\alpha = 0.83$, HI subscale $\alpha = 0.83$). For the clinical sample, i.e., those with ADHD, Cronbach's alpha indicated acceptable reliability for most item combinations (Total ASRS $\alpha = 0.78$, IA subscale $\alpha = 0.69$, HI subscale $\alpha = 0.69$). However, the screener items for this cohort were deemed to have low reliability ($\alpha = 0.45$).

2.2.2. Pavlovian conditioning task

The task (Fig. 1) was adapted from the Pavlovian conditioning task designed by Garofalo and di Pellegrino [16] and programmed using Experiment Builder version 2.3.38 (SR Research). Participants were presented with on-screen instructions and with four practice trials. During the task itself, participants were presented with one of two cues in the form of fractal images within a square in the upper part of the screen. The cue appeared on the screen for 5000 ms. After that, a grey patch appeared in a square in the bottom part of the screen. Participants were instructed to press the space bar as soon as the grey patch appeared on the screen to reveal the outcome underneath it. The outcome was presented for 1000 ms. Importantly, participants were told that the outcome would be revealed regardless of whether they pressed the space bar when seeing the grey patch, but that their task was to press the space bar anyway. This was added to avoid any possible instrumental influences on the task [16]. However, due to an error in the programming of the task, the latency of participants' responses (pressing the space bar) was not recorded, and this is therefore not included in any further analyses. One fractal cue was associated with the reward outcome (a fractal image resembling a banknote) on 80% trials (CS+ trials) and the other fractal cue was associated with a no reward outcome (a fractal image of the same shading and dimension but not money) on all trials (CS- trials). The task had 40 trials in total and took approximately 6 min to complete.

For analysis purposes, the task was divided into two hemiblocks of 20 trials each, and the second hemiblock (the last 20 trials) were used in all analyses to characterise individuals as ST or GT as previous research indicated that this is the point when contingencies had been learned [16]. Two versions of the task were used to counterbalance the association between the fractal cues and the different outcomes between participants. At the end, participants were asked to indicate which of the two outcomes represented the monetary one to check that they understood the task.

2.2.3. Eye-tracking

An EyeLink 1000 Plus eye-tracker (SR Research; recording the right eye at 1000 Hz) head-mounted system was used to record eye gaze during the Pavlovian conditioning paradigm. Participants were seated at a desk in a dark, silent room for the duration of the task. Their position was centred relative to the screen (1920 ×1080 pixels), at a viewing distance of 51 cm from the screen. The EyeLink head-mount was used to restrict head movement, with participants being instructed to position their chin on a chinrest for the duration of the task. Calibration was performed prior to starting the task using a nine-point system, followed by validation, as many times as necessary to collect satisfactory data. Data from a pre-defined interest period were analysed, corresponding to the time between CS presentation and the presentation of the grey response patch before the US was revealed. The length of the interest period was 5000 ms. Data from two specific areas of interest (AOI) were analysed: the upper square location where the conditioned stimulus (CS, the sign) appears with the following coordinates: 885 pixels (left), 296 pixels (top), 1035 pixels (right), 446 pixels (bottom) and 960,371 pixels (centre) and the lower square location where the unconditioned stimulus (US, the goal) appears with the following coordinates: 885 pixels (left), 612 pixels (top), 1035 pixels (right), 762 pixels (bottom) and 960,687 pixels (centre). The number of fixations was calculated for each trial for each area of interest. EyeLink is a saccade-based software, and fixations are defined as any events that do not qualify as a saccade nor as a blink. Because smooth pursuits can be incorrectly classified as fixations, we only included in the analysis fixations with a duration of at least 100 ms.

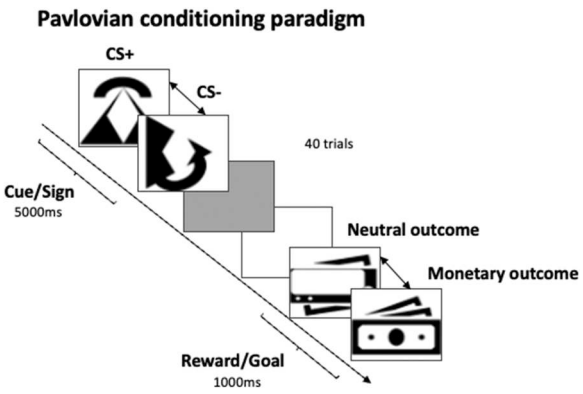


Fig. 1. Pavlovian conditioning paradigm. CS = conditioned stimulus.

2.3. Data processing

Data acquired during the task were processed offline using Data Viewer 3.1.1 (SR Research) and R Studio (Version 2022.12.0 +353). Participants who had > 50% eye-tracking trials missing were excluded from the analysis (non-clinical, N = 11; ADHD, N = 14), together with participants who spent > 80% of the interest period gazing at neither the top nor the bottom areas of interest (non-clinical, N = 2; ADHD, N = 2). Furthermore, we excluded data from participants who failed to distinguish the monetary reward from the neutral reward at the end of the task (non-clinical, N = 2; ADHD, N = 2). These steps were taken to remove from analysis individuals who did not sufficiently engage with or understand the task. After exclusions, the non-clinical sample consisted of 54 participants aged 18–35 years, including 32 females (59.3%) and 22 males (40.7%), who completed a Pavlovian conditioning task (M_{age} = 24.31, SD = 4.45). The ADHD sample consisted of 57 participants (M_{age} = 25.95, SD = 5.04), including 48 females (84.2%) and 9 males (15.8%).

To check if there were any differences between those excluded and those included, we ran independent t-tests for age and ASRS scores, and chi-square tests for sex. In the ADHD sample, the two groups did not differ in terms of age (t = 1.61, df=65, $p = .11$, M_{age} included: 26.06, SD_{age} included: 5.06; M_{age} excluded: 28.42, SD_{age} excluded=4.27), nor ASRS scores (t = −1.37, df=65, $p = .17$, M_{ASRS} included: 19.08, SD_{ASRS} included: 2.81, M_{ASRS} excluded: 17.79, SD_{ASRS} excluded: 4.15). The difference between the groups was not statistically significant in terms of sex ($\chi2 = 3.82$, df=1, $p = .051$), but more males were excluded (included: 7, excluded: 5) than females (included: 46, excluded: 9). In the non-clinical sample, the two groups did not differ in terms of age (t = −.53, df=63, p = .60, M_{age} included: 24.31, SD_{age} included: 4.45; M_{age} excluded: 23.55, SD_{age} excluded=4.27). However, there were significant differences in terms of ASRS scores, with those excluded having lower scores (M=5.36, SD=2.87) than those included (M=8.19, SD=4.01), t = −2.21, df= 63, $p = .03$. The difference between the groups was not statistically significant in terms of sex ($\chi2 = 3.76$, df=1, $p = .052$), though more males were excluded (included: 22, excluded: 8) than females (included: 32, excluded: 3).

2.4. Defining sign-trackers and goal-trackers

Participants were categorised as ST or GT based on their oculomotor CR in the second hemiblock of the task. In animal studies, the number of

contacts with the sign (lever) and the goal (food tray) are compared to characterise behaviour and divide the sample into those with a high probability of engaging with the location of the lever (ST) and those with a high probability of engaging with the location of the food tray (GT). This approach has been adapted in human studies investigating reward learning using eye-tracking [16,34]. To define STs and GTs, Data Viewer (SR Research) was used to extract and calculate a dwell time, defined as the sum of durations for all fixations which remained within the same AOI. Dwell time for each AOI was calculated for each trial and then averaged for each participant. Then, we computed an eye-gaze index (EGI) as the difference between the dwell time on the sign and the dwell time on the goal over the total dwell time, so that a higher value corresponded to more time spent on the sign and a lower value corresponded to more time spent on the goal:

$$EGI = \frac{DwelltimeSign - DwelltimeGoal}{Dwelltimetotal}$$

Using this approach, the EGI could theoretically range from + 1 to −1. We took two approaches to dividing the sample into ST and GT based on the EGI. Firstly, using a median split, those falling above the median were classified as ST and those falling below the median were classified as GT, in line with Garofalo & di Pellegrino [16]. Secondly, using a tertiary split, those in the upper third were classified as ST and those in the lower third were classified as GT. This aligns more closely with rodent work, which typically includes a central band referred to as intermediates [13] that are removed from analyses in consideration of individual differences, allowing only those clearly showing sign- and goal-tracking to be analysed [44]. An alternative method for dividing the sample used in animal research, where values below −0.5 were classified as GT and those with values above 0.5 as ST [46] was considered, but could not be used because no ADHD participants had a score above 0.5 and only one non-clinical participant had a value above 0.5 (0.62) meaning only one individual could be classified as an ST according to this approach. Similarly, there were no non-clinical participants with values below −0.5 and only one with ADHD scored below −0.5 (−0.50), meaning only one GT would have been identified with this method.

2.5. Data analysis

Each sample was categorised with descriptive statistics for gender, age and ASRS scores. Dwell time were compared for the sign and goal AOI in the second hemiblock of CS+ trials. For these comparisons data was checked for normality, and a paired sample t-tests used. After categorising individuals as ST or GT, and checking data for normality, several analyses were run for both the median and tertiary split groupings. To examine whether the sign-tracking and goal-tracking was a learned response, EGI was analysed using a repeated-measures ANOVA with hemiblock in CS+ trials as the within-subjects variable, and the group (ST/GT) as the between-subjects variable. A learned response would be indicated by a significant interaction between hemiblock and group. Where significant, this was explored with t-tests. To evaluate if this was specific to CS+ trials, the same analysis was repeated for CS- trials. To examine the relationship with externalising behaviours, scores on the IA and HI subscales of the ASRS were compared for ST and GT. Where data was normally distributed, a t-test was used, but where data did not have a normal distribution, a Mann-Whitney test was used.

In addition, further analysis was conducted to compare the non-clinical and ADHD samples. The groups were compared for age, IA, HI and Total ASRS score using independent sample t-tests and chi-square analysis for gender. Following identification of differences in age and gender between the two groups, ANCOVA was used to examine group differences in dwell time and EGI in the second hemiblock of CS+ and CS- trials. The combined sample was also analysed using an ANOVA to examine whether the CR was a learned effect, as outlined for the individual samples.

3. Results

3.1. Sample characteristics

Participants in the non-clinical group had a mean score of 8.19 (SD = 4.01) on the ASRS screener items, lower than the clinical cut-off of 14 [19], and aligning with their declaration of having no psychiatric, neurological condition or learning difference. Low scores on the total ASRS (M = 22.02, SD = 9.77) and the individual subscales for inattention (IA; M = 12.65, SD = 5.45) and hyperactive-impulsive (HI; M = 9.88, SD = 5.51) symptoms support the non-clinical nature of the sample. These participants spent a similar amount of time gazing at the sign (M = 1569.26 ms, SD = 851.79) and the goal (M = 1539.98 ms, SD = 969.48; $t(53) = .31$, $p = .78$).

Participants in the ADHD group scored 19.16 (SD = 4.09) on the ASRS screener, meeting the recommended clinical cut-off of ≥ 14 [19]. Given the low reliability of these combined items for this sample, it is noteworthy that scores on the total scale (M = 54.42, SD = 7.44), the IA subscale (M = 29.02, SD = 4.62) and HI subscale (M = 24.11, SD = 5.06) were also in line with a diagnosis of ADHD. The medicated and unmediated groups did not differ in terms of age (t(55) = −.92, $p = .36$) or gender (χ^2 (1) = 1.07, $p = .47$). They also did not differ on measures of the ASRS (Total $t(50) = 1.21$, $p = .23$; IA $t(51) = 0.10$, $p = .92$; HI $t(51) = 1.10$, $p = .28$). Finally, the medicated and unmedicated groups did not differ in terms of the EGI from CS+ trials in the second hemiblock (t(55) = .22. $p = .826$), or categorisation to ST or GT using either the median split approach ($\chi^2(1) = .84$, $p = .36$) or the tertiary split approach ($\chi^2(1) = .00$, $p = 1.00$). Given the similarities between medicated and unmedicated participants, they were considered as a single group for analysis. As with the non-clinical sample, the ADHD group spent a comparable amount of time gazing at the sign (M = 1851.54, SD = 938.88) and goal (M = 1768.78, SD = 891.01; $t(56) = .78$, $p = .44$) areas in the second hemiblock of CS+ trials.

3.2. Median split analysis

For the non-clinical sample, the distribution of the EGI in the second hemiblock did not indicate a strong preference for either the cue or the reward, with most data close to the theoretical midpoint of zero rather than the extreme values (+1 or −1), although the median value (−.003) does indicate a slight skew towards goal-tracking (Fig. 2a). Similarly, within the ADHD sample, there was not a strong preference. However, where the non-clinical group showed a slight skew towards goal tracking, the median value (.033) in the ADHD sample indicates a slight skew towards sign-tracking (Fig. 2b).

Within the non-clinical sample, a significant hemiblock x group interaction ($F(1, 52) = 9.78$, $p = .003$) was found for EGI indicating that the response changed over time. Simple effects were then explored using independent t-tests for CS+ trials in the first and second hemiblock. The two groups (ST vs. GT) differed significantly in the first hemiblock ($t = 2.06$, $p = .05$, $d = .26$, 95% CI[.01, 1.10]; ST: $M = .05$, $SD = .29$, GT: $M = -.09$, $SD = .23$). The mean difference was greater in the second hemiblock and the difference was more significant (ST: $M = .20$, $SD = .16$, GT: $M = -.17$, $SD = .13$, $t(52) = 9.61$, $p < .001$, $d = .14$, 95% CI [1.88, 3.34]) suggesting that preferences towards the cue or the reward were present from the beginning to some extent and appeared to have increased throughout the task. The same ANOVA was run for CS- trials to check if learning was specific to CS+ trials. The interaction between time and ST/GT categorisation was not significant ($F(1,52) = .003$, $p = .96$), indicating the learning was specific to trials with the reward (Fig. 3a, b).

For the ADHD sample, the same analysis was run to examine whether the oculomotor response used to categorise ST and GT was a learned CR, a repeated-measures ANOVA was run and revealed a significant hemiblock x group interaction ($F(1,55) = 9.60$, $p = .003$). Simple effects were then explored using independent t-tests for CS+ trials in the first and

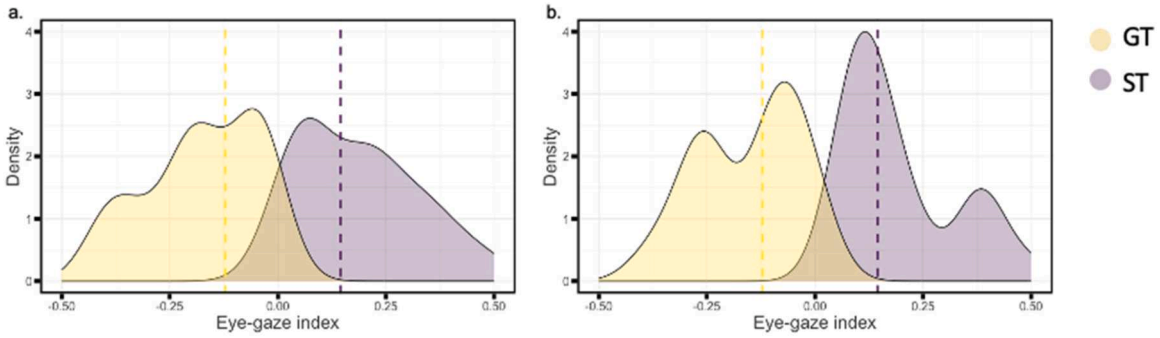


Fig. 2. Distribution of EGI (eye-gaze index) scores averaged across the second hemiblock of the paradigm in CS+ trials for the non-clinical (a) and ADHD sample (b). Dashed lines represent the median values within each phenotype. The sign-tracking phenotype were characterised by an EGI score above the sample's median (non-clinical = −.003; ADHD = 0.033) and the goal-tracking phenotype by an EGI score below the sample's median.

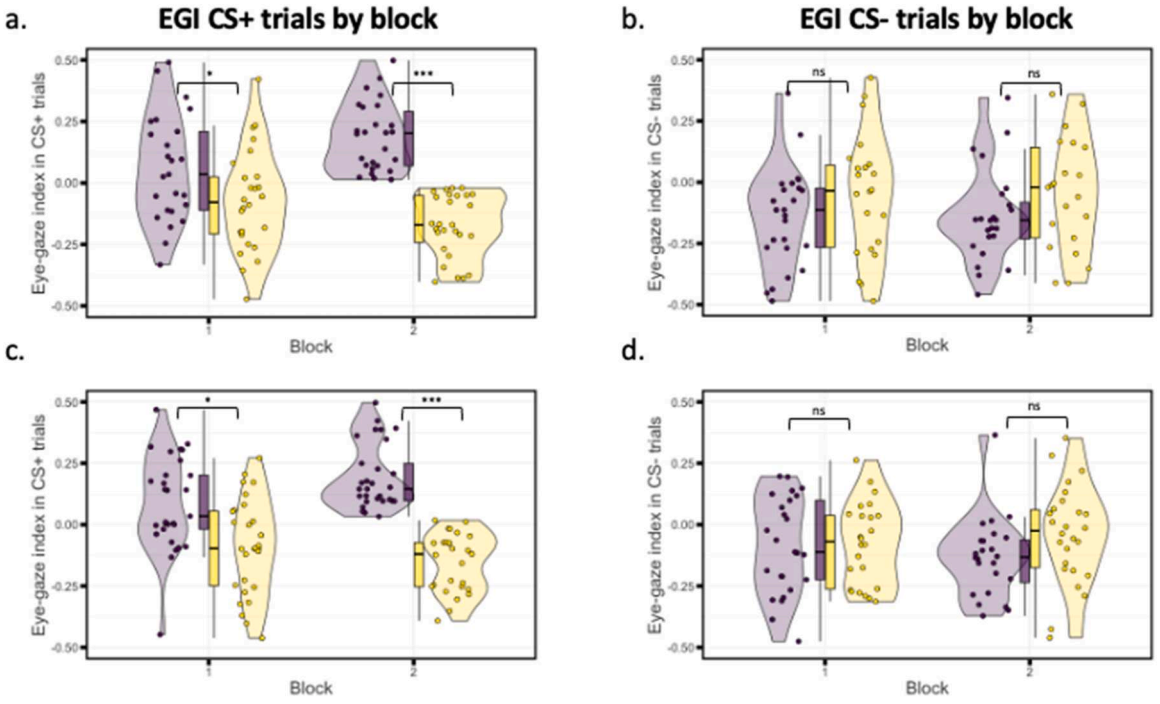


Fig. 3. For the non-clinical sample: a. Eye-gaze index in CS+ trials shown by block (block 1 – 1–20 trials; block 2 – 21–40 trials) and ST/GT categorisation using the median split approach (purple = ST, yellow = GT). b. Eye-gaze index in CS- trials shown by block (block 1 – 1–20 trials; block 2 – 21–40 trials) and ST/GT categorisation using the median split approach (purple = ST, yellow = GT). For the ADHD sample: c. Eye-gaze index in CS+ trials shown by block (block 1 – 1–20 trials; block 2 – 21–40 trials) and ST/GT categorisation using the median split approach (purple = ST, yellow = GT). d. Eye-gaze index in CS- trials shown by block (block 1 – 1–20 trials; block 2 – 21–40 trials) and ST/GT categorisation using the median split approach (purple = ST, yellow = GT). * ** $p < .001$, ns = not significant.

second hemiblock. The two groups differed significantly in the first hemiblock ($t(55) = 3.42$, $p < .001$, $d = .19$, 95% CI[.36, 1.45]; ST: $M = .09$, $SD = .19$, GT: $M = -.09$, $SD = .20$). The mean difference was larger in the second hemiblock (ST: $M = .19$, $SD = .13$, GT: $M = -.17$, $SD = .13$, ($t(55) = 10.26$, $p < .001$, $d = .13$, 95% CI[1.99, 3.44]) suggesting again that preferences towards the cue or the reward were present from the beginning and appeared to increase throughout the task. The same analysis for CS- trials did not have a significant interaction ($F(1, 55) = .02$, $p = .89$) (Fig. 3c, d), indicating learning was specific to CS+ trials.

To further understand preferences towards the cue or the reward in the first half of the task (trials 1–20), the trials were binned into blocks of 4 trials and linear mixed models were run independently for the non-clinical and the ADHD samples. The results are reported in the Supplementary material (Fig. S1, Tables S1 and S2), but briefly – in the ADHD group, there were no main effects of ST/GT categorisation, block or type of trial (CS+ or CS-) on the EGI in the first 20 trials, nor any interaction effects, and in the non-clinical sample there was a main effect of block 2 (trials 5–8) on EGI, indicating that there were slightly higher EGI scores in the second (trials 5–8) compared to the first block of the task (trials 1–4). There were no significant main effects of ST/GT categorisation, trial type, nor any interaction effects.

3.3. Tertiary split analysis

In the non-clinical sample, based on the EGI in the second hemiblock, the sample was divided into thirds, resulting in 18 individuals classed as GT (33.3%) and 18 individuals classed as ST (33.3%). Intermediates were not included in this analysis in-keeping with the approach from animal studies of the sign-tracking/goal-tracking model. As with the median split analysis, to check if the oculomotor response used to categorise ST and GT was a learned CR, a repeated-measures ANOVA was run and there was a significant hemiblock x group interaction ($F(1, 34) = 11.15$, $p = .002$). Independent t-tests revealed that there was a

significant difference for the first hemiblock (t(34) = −2.26, p = .03, d = .27, 95% CI[− 1.43, −.07]) in the EGI for GT (M = −.13, SD =.19) compared with ST (M =.08, SD =.33). There was also a significant difference between ST (M =.28, SD =.14) and GT (M = −.24, SD = 10) in the second hemiblock (t(34) = −12.92, p < .001, d = .12, 95% CI [−5.51, −3.09]), with a greater mean difference and more significant finding, suggesting that sign- and goal-tracking, as with the median split approach, were present from the outset but increased throughout the task. The same ANOVA was run for CS- trials did not reveal a significant interaction (F(1, 34) = .01, p = .92) (Fig. 4a, b) suggesting that this is specific to reward-related or CS+ trials.

For the ADHD sample, based on the EGI in the second hemiblock, the sample was divided into thirds, resulting in 19 individuals classed as GT (33.3%) and 19 individuals classed as GT (33.3%). As with the median split, to check if the oculomotor response used to categorise ST and GT was learned CR, a repeated-measures ANOVA was run. There was a significant interaction hemiblock x group interaction (F(1, 36) = 22.83, p < .001). Independent t-tests for CS+ trials in the first and second hemiblock revealed that there was a significant difference between ST and GT in both the first (t(36) = −2.41, p = .02, d = .20, 95% CI[−1.44, −.12] ST: M = .06, SD = .20, GT: M = −.10, SD = .20) and the second hemiblock (t(36) = −12.39, p < .001, d = .12, 95% CI[−5.13, −2.89] ST: M = .25, SD = .12, GT: M = −.22, SD = .11), although the mean difference and significance increased in the second hemiblock. Again, this suggests that sign-tracking and goal-tracking was present from the start but may have strengthened during the task. An ANOVA was run for CS- trials to check if learning was specific to CS+ trials. The interaction was not significant (F(1, 36) = .25, p = .62) (Fig. 4c, d).

3.4. Externalising behaviours by phenotype

The data presented so far provides evidence ST and GT can be differentiated on reward-paired or CS+ trials only and that these differences are found from early in the task but do increase during the task for both the non-clinical and ADHD sample. Here we examine how ST and GT differ in terms of externalising behaviours (IA and HI) in both samples. Within the non-clinical sample HI scores were normally distributed, and an independent t-test was used to compare GT and ST based on median split as the grouping variable and the EGI in the second hemiblock in CS+ trials as the independent variable. IA scores were non-normally distributed, and comparisons were carried out using the Mann-Whitney U test. Although ST scored slightly higher on the HI subscale (M = 10.65, SD = 5.91) than GT (M = 9.12, SD = 5.09) the difference was not statistically significant (t(45) = 1.01, p = .32, d = 5.51, 95% CI [−.27,.82]). The same was found for the IA subscale (ST: M = 13.31, SD = 6.50; GT: M = 12.00, SD = 4.18; U = 256.5, p = .13) (Fig. 5a, b). The same analyses were repeated using the tertiary split and similar null differences were found (HI: t(28) = −1.10, p = .28, d = 5.77, 95% CI [−1.05,.30]; IA: U = 106, p = .18).

For the ADHD sample, both IA and HI measures were non-normally distributed and so analysed using Mann-Whitney tests. Using the median split grouping, no significant differences were found between ST and GT on the IA (ST: M = 28.93, SD = 5.06; GT: M = 29.13, SD = 4.13; U = 323, p = .65) or HI subscale (ST: M = 24.03, SD = 5.10; GT: M = 24.21, SD = 5.12; U = 324, p = .66) (Fig. 5c, d). The same analyses were repeated using the tertiary split and similar null results were found (HI: U = 145.50, p = .832; IA: U = 139.50 p = .69).

To further check potential links between externalising behaviours and behavioural data, we ran two linear regression models with EGI in the second hemiblock in CS+ trials as the dependent variable, and externalising behaviour (IA and HI scores) as predictors. Inattentive and hyperactive-impulsive scores derived from the ASRS were not statistically significant predictors of the eye-gaze index in the second hemiblock in CS+ trials in the ADHD group (R^2 =.00, p = .96), nor in the non-clinical group (R^2 =.02, p = .70).

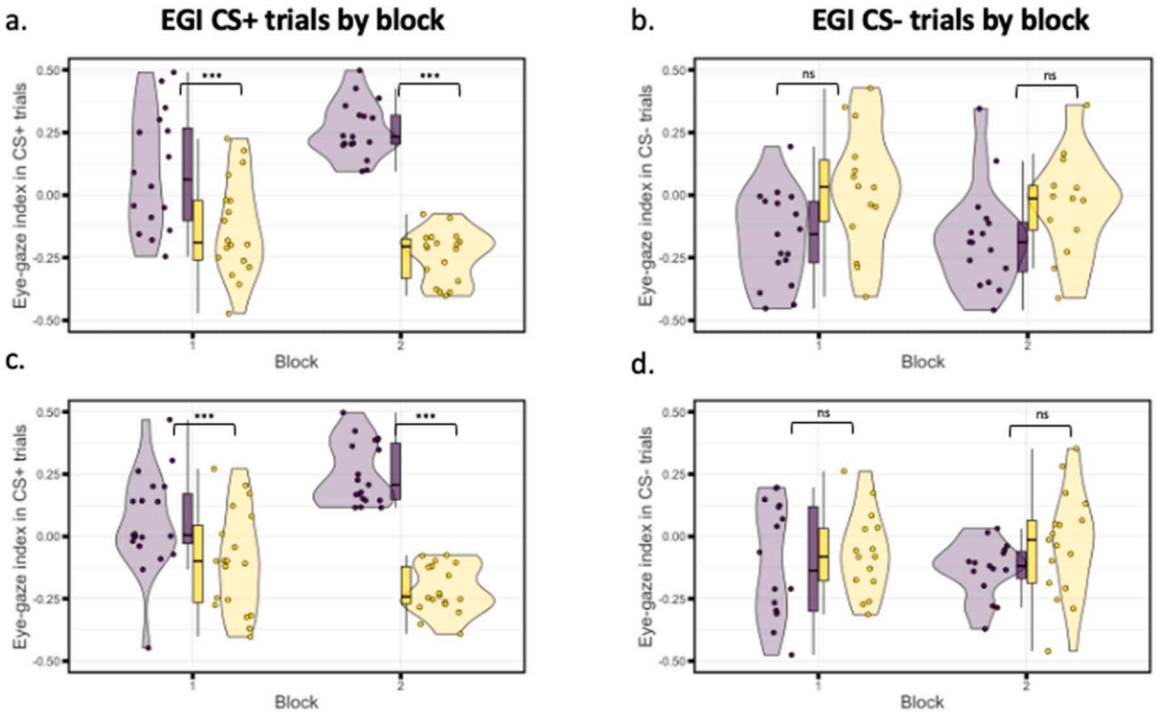


Fig. 4. For the non-clinical sample: a. Eye-gaze index in CS+ trials shown by block (block 1 – 1–20 trials; block 2 – 21–40 trials) and ST/GT categorisation using the tertiary split approach (purple = ST, yellow = GT). b. Eye-gaze index in CS- trials shown by block (block 1 – 1–20 trials; block 2 – 21–40 trials) and ST/GT categorisation using the tertiary split approach (purple = ST, yellow = GT). For the ADHD sample: c. Eye-gaze index in CS+ trials shown by block (block 1 – 1–20 trials; block 2 – 21–40 trials) and ST/GT categorisation using the tertiary split approach (purple = ST, yellow = GT). d. Eye-gaze index in CS- trials shown by block (block 1 – 1–20 trials; block 2 – 21–40 trials) and ST/GT categorisation using the tertiary split approach (purple = ST, yellow = GT). * p = .05, * ** p < .001, ns = not significant.

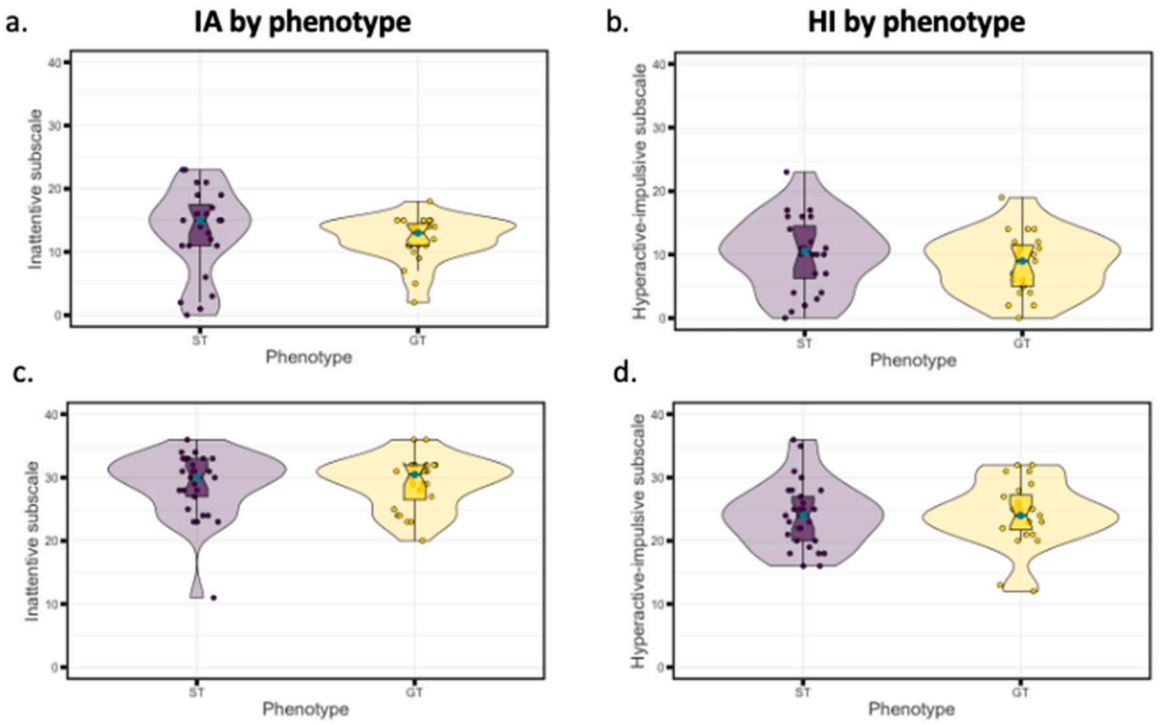


Fig. 5. For the non-clinical sample: a. IA subscale score is calculated by summing nine items of the ASRS scale relating to inattention, and the distribution is shown by phenotype. b. HI subscale score is calculated by summing the remaining nine items of the ASRS scale that relate to symptoms of impulsivity and hyperactivity, and the distribution is shown by phenotype. For the ADHD sample: c. IA subscale score is calculated by summing items nine items of the ASRS scale relating to inattention, and the distribution is shown by phenotype. d. HI subscale score is calculated by summing the remaining items of the scale relating to hyperactivity-impulsivity, and the distribution is shown by phenotype. GT/ST are based on the median split.

3.5. Comparing non-clinical and ADHD samples

The two groups differed with respect to age ($t(109) = -1.81$, $p = .04$), with the ADHD group being slightly older ($M = 25.95$, $SD = 5.04$) than the non-clinical sample ($M = 24.31$, $SD = 4.45$). Additionally, there was a significant association between gender and group ($\chi^2(1) = 8.56$, $p = 0.003$) with a higher proportion of females in the ADHD group. Unsurprisingly, the ADHD group scored higher than the non-clinical samples on all ASRS measures (IA: $t(98) = 16.26$, $p < .001$; HI: $t(98)$ 14.22, $p < .001$; Total: $t(98) = 17.28$, $p < .001$).

Dwell time for sign and goal were compared for the two groups. To ensure significant differences were not masked by gender and age differences, the analysis was conducted with an ANCOVA where these variables could be included as covariates. Null effects were found here (Sign dwell time: $F(1107) = 3.22$, $p = .075$, Goal dwell time: $F(1, 107) = 2.59$, $p = .11$), although in both cases, the ADHD group had longer dwell times (Sign: $M = 1851.54$, $SD = 938.88$; Goal: $M = 1768.78$, $SD = 891.01$) than the non-clinical sample (Sign: $M = 1569.26$ ms, $SD = 851.79$; Goal: $M = 1539.98$ ms, $SD = 969.48$). Although the two groups showed slightly different propensities for sign-tracking and goal tracking, as indicated by the median EGI from hemiblock 2 of CS+ trials, Mood's Median Test revealed no significant difference between the group medians (χ^2 (1) = .01, $p = .92$).

The EGI in the second hemiblock for CS+ trial for those categorised as ST and GT was compared for the two groups using an ANCOVA with gender and age as covariates. There was no significant difference between the two groups for ST ($F(1, 52) = .17$, $p = .68$) or GT ($F(1, 51) = .01$, $p = .93$) when using the median split approach. This was also the case for CS- trials (ST: $F(1, 52) = .04$, $p = .84$, GT: $F(1, 51) = .30$, $p = .59$). The same analysis using the tertiary split also revealed no significant group differences for CS+ trials (ST: $F(1, 33) = .60$, $p = .45$, GT: $F(1, 33) = .20$, $p = .66$) and CS- trials (ST: $F(1, 33) = .00$, $p = .97$, GT: $F(1, 33) = .46$, $p = .50$).

4. Discussion

The present work set out to better understand sign-tracking behaviour in non-clinical and clinical (ADHD) samples and revealed four key findings. Firstly, we demonstrated both samples could be categorised as ST or GT using median and tertiary split approaches. Although there was no significant difference between the median EGI for both groups, the median for the non-clinical sample indicated a slight preference for goal-tracking, whilst the ADHD sample showed a slight preference for sign-tracking. Secondly, we found that the oculomotor CR in both the ADHD and non-clinical samples is reward specific in that it was only present in CS+ and not CS- trials. Thirdly, our data suggest that there was a preference towards the sign or goal from early in the task in both groups and that this behaviour grew during the task, suggesting there may be both dispositional and learned components to sign-tracking and goal-tracking. Finally, our data indicated no significant differences between ST and GT in terms of externalising behaviours of inattention and hyperactivity impulsivity.

The results of the current study extend previous work by examining sign-tracking and goal-tracking in an adult clinical sample with ADHD for the first time. Whilst the results do show that the non-clinical sample were slightly more prone to goal-tracking and the ADHD sample slightly more prone to sign-tracking, the difference between the median EGI of the two groups was not statistically significant. Given that sign-tracking has been associated with externalising behaviours, including those seen in ADHD, this is surprising. One possible explanation for the lack of difference between the non-clinical and clinical groups is that a significant proportion of the ADHD sample was receiving stimulant medication and had therefore likely seen some normalisation of their behaviour. Prior studies have suggested that medications used to manage ADHD can impact sign- and goal-tracking behaviour in rats [12,17,18,28,39]. This is perhaps unsurprising considering the proposed role of dopamine in reward, the pathophysiology of ADHD, and findings

suggesting that sign-tracking is linked to the dopamine transporter, which is a key target of amphetamine (e.g., [3,38,40]). Doremus-Fitzwater & Spear [12] found that rats exposed to a sensitising regimen of amphetamine over four days expressed higher incentive motivation for cues predicting food reward (sign-tracking), but not goal-tracking behaviour. Similar results were reported by Nordquist et al. [28] and Berridge [3]. Other studies investigating amphetamine sensitisation have reported mixed results, for example that prior sensitisation increases goal-tracking, but not sign-tracking using an autoshaping procedure [39]. Acute amphetamine administration has been shown to enhance sign-tracking behaviours [40] in ST but have no impact on goal-tracking. Although another study reported shifting responses in the direction of goal-tracking behaviour [18], further work using quinpirole, a dopaminergic agonist, found decreases in sign-tracking after the drug was administered [24]. Therefore, the direction of the effect is not entirely clear, and it is not possible at this stage to conclude as to what the effects of dopaminergic drugs, and specifically ADHD medications, are on incentive sensitisation in animal models. However, it is also important to consider that dose regimes used in animal studies are different from ADHD medication, and therapeutically relevant doses have previously been shown to lead to tolerance rather than sensitisation [43]. Additionally, whilst the presence of medication could have impacted on the current findings, it is notable that there were no significant differences between the unmedicated and medication individuals with ADHD in terms of the measures used to categorise sign-tracking and goal-tracking, suggesting that the presence of medicated individuals cannot explain this finding entirely. Although the two groups did differ in terms of their ASRS scores as would be expected, it is noteworthy that controls who were excluded had lower ASRS scores, which could indicate that the exclusions effectively brought the two groups closer together. Furthermore, it is also worth noting that the ADHD group in the current study was not required to identify their subtype, and that a structured clinical interview was not conducted to confirm self-reported diagnoses. However, we did report scores for the inattentive and hyperactive-impulsive subscales derived from the ASRS. Future studies should consider the heterogeneity of ADHD and collect information on the inattentive and hyperactive-impulsive subtypes.

The remaining findings of the study partially align with previous research. Our finding that the CR is only found in CS+ trials is consistent with the study by Garofalo & di Pellegrino [16], that also showed that the CR could only be found on trials where the reward-related cue (CS+) was present and not in the neutral cue trials (CS-). However, our finding that the preference for the cue or the goal was not purely a learned behaviour and is present, to some extent, from the start in adults with and without ADHD, is at odds with previous work. Garofalo & di Pellegrino [16] reported that the oculomotor CR in their sample emerged throughout the task rather than being present from the beginning, and therefore concluded that the behaviour was learned. Schad et al. [34] also reported an increase in ST behaviour throughout the task, indicating it was learned, but only in trials associated with wins and not in those associated with loses. There are several explanations for the difference in findings between this study and previous work. Firstly, it is possible that sign-tracking was a learned behaviour in the current study but that the initial learning was rapid, such that it might not be possible to observe differences between blocks of 20 trials and a more nuanced analysis may be needed. However, this seems unlikely, given the similarity of the task with Garofalo & di Pellegrino [16] including the same number of trials and blocks. Secondly, the nature of the reward may have impacted the findings. Both previous studies used illustrations resembling coins as rewards, rather than a monetary fractal like in the current study, which could have impacted the incentive value. Additionally, Schad et al. [34] used several amounts for the rewards which could have led to a higher incentive value being attributed to the CS+ trials and influenced the progressive increase in maladaptive cue-elicited tendency throughout the task, in a way that was not found with our monetary fractal. Finally, it is noteworthy that in the study by Garofalo & di Pellegrino [16] participants were advised they would receive and actual payment actual payment corresponding to the amount they collected in the task and in Schad et al. [34] participants received a flat rate payment, as in the current study, and a performance related payment. It is therefore possible that the differences stem from the performance-related payment.

Consistent with ADHD being an externalising disorder, scores on inattention and hyperactivity-impulsive scales were higher in those with ADHD compared to the non-clinical sample but in neither group were scores different between ST and GT. These findings depart from results reported in previous translational studies investigating sign- and goal-tracking behaviour in humans. Cope et al. [7] measured behavioural impulsivity using the Barratt Impulsivity Scale and found that higher scores were associated with sign-tracking behaviour in young adults, in accordance with Garofalo & di Pellegrino [16]. Using an experience sampling design to investigate real-life attribution of high incentive salience to reward-related cues, Schettino et al. [35] found that high levels of impulsivity, obsessive-compulsive tendencies and addiction-prone tendencies predicted higher attractiveness of the sign, compared with the goal. Colaizzi et al. [6] measured externalising tendencies using parent-report questionnaires (Child Behaviour Checklist and Early Adolescent Temperament Questionnaire), and reported increased ADHD-like symptoms, increased fear, and lower inhibitory control in ST, though they found no group differences in self-reported or behavioural measures of inhibition and impulsivity. The lack of association between sign-tracking and externalising behaviours in the present study was therefore surprising. It is possible that other externalising behaviours are more closely associated with sign- and goal-tracking, although this seems unlikely given Colaizzi et al. [6] measured the same behaviours as in the current study, albeit with a different scale. Another explanation is that the measures used in the previous studies (Barratt Impulsivity Scale, Child Behaviour Checklist) tap into slightly different constructs to the current measure (ASRS), although this also seems unlikely given previous studies indicating correlations between the measures [8]. It is possible that the sample size of the present study was too small to detect any difference, but the effect sizes reported do not indicate this. Finally, it may be that differences would be apparent if we could better distinguish between dispositional, rather than learned, behaviour, which we could not unpick any more than the two hemi-block divisions in the current study. Future research should further examine the relationship between sign-tracking and externalising behaviours employing larger samples, using a more comprehensive battery of self-report and behavioural tests, and by trying to tease apart trait and state characteristics, since most studies to date are limited to laboratory assessments that might lack external validity [27].

Whilst the current study adds to the valuable translational research into sign-tracking, it also highlights the work that still needs to be carried out to advance our understanding of incentive motivation in reward processing in humans. Firstly, we recognise that different CS values might produce different out comes in terms of categorising ST and GT. One analysis approach that future studies could consider is latent profile analysis (LPA). LPA can be used to identify potential subgroups of individuals in a heterogeneous sample in the absence of established known variables [41,45]. However, LPA is sensitive to sample size, and a rule of thumb from a previous simulation study recommends that a minimum sample size of 500 is needed to ensure sufficient accuracy in identifying the correct latent profiles [29], which was not possible in the current studies. Another analysis approach could be the calculation of a Pavlovian conditioning approach (PCA) index [26], which would facilitate the comparison of results in translational studies to those reported in animal research. Secondly, the task used in the current study associated a fractal cue with the reward outcome on 80% trials (CS+ trials). Reward uncertainty has been shown to increase the propensity to sign-track in animal studies [1]. Despite that our aim was to replicate the task used by Garofalo and & di Pellegrino [16] and that studies showing

an association between sign-tracking and reward uncertainty typically use higher proportions of uncertainty (e.g., 50%), future studies should consider the implications of information seeking through exploration when adapting or designing such tasks. Thirdly, it is important that the stability and plasticity of these phenotypes is established in humans. Future research could investigate the developmental trajectories of sign-tracking behaviour from a transdiagnostic perspective. Finally, future studies might use this experimental paradigm to investigate sign-tracking/goal-tracking in other clinical groups or investigate more externalising disorders from a transdiagnostic angle. Nonetheless, the results presented here are promising for identifying sign- and goal-tracking behaviour in humans and help advance our understanding of individual differences in reward-learning, implicated in several psychiatric disorders.

Pre-registration

The studies presented here were not pre-registered.

Funding

This research was funded by The Rosetrees Trust, grant number M875.

CRediT authorship contribution statement

Dinu Larisa-Maria: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Georgescu Alexandra-Livia:** Formal analysis, Methodology, Software, Supervision. **Singh Samriddhi N.:** Investigation, Project administration. **Byrom Nicola C.:** Conceptualization, Funding acquisition. **Overton Paul G.:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Singer Bryan F.:** Funding acquisition, Methodology, Writing – review & editing. **Dommett Eleanor J.:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Data availability

The data for all experiments are available at https://osf.io/v8myu/.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2024.114846.

References

[1] P. Anselme, M.J.F. Robinson, K.C. Berridge, Reward uncertainty enhances incentive salience attribution as sign-tracking, Behav. Brain Res. 238 (2013) 53–61, https://doi.org/10.1016/j.bbr.2012.10.006.
[2] M. Arcos-Burgos, M.T. Acosta, Tuning major gene variants conditioning human behavior: the anachronism of ADHD, Curr. Opin. Genet. Dev. 17 (3) (2007) 234–238, https://doi.org/10.1016/j.gde.2007.04.011.
[3] K.C. Berridge, The debate over dopamine's role in reward: the case for incentive salience, Psychopharmacology 191 (3) (2007) 391–431, https://doi.org/10.1007/s00213-006-0578-x.
[4] J.M. Colaizzi, S.B. Flagel, M.A. Joyner, A.N. Gearhardt, J.L. Stewart, M.P. Paulus, Mapping sign-tracking and goal-tracking onto human behaviors, Neurosci. Biobehav. Rev. 111 (2020) 84–94, https://doi.org/10.1016/j.neubiorev.2020.01.018.
[5] J.M. Colaizzi, S.B. Flagel, A.N. Gearhardt, M.A. Borowitz, R. Kuplicki, V. Zotev, G. Clark, J. Coronado, T. Abbott, M.P. Paulus, The propensity to sign-track is associated with externalizing behaviour and distinct patterns of reward-related brain activation in youth [Prepr.], Neuroscience. (2022), https://doi.org/10.1101/2022.01.29.477945.
[6] J.M. Colaizzi, S.B. Flagel, A.N. Gearhardt, M.A. Borowitz, R. Kuplicki, V. Zotev, G. Clark, J. Coronado, T. Abbott, M.P. Paulus, The propensity to sign-track is associated with externalizing behavior and distinct patterns of reward-related brain activation in youth, Sci. Rep. 13 (1) (2023) 1, https://doi.org/10.1038/s41598-023-30906-3.
[7] L.M. Cope, A. Gheidi, M.E. Martz, E.R. Duval, H. Khalil, T. Allerton, J.D. Morrow, A mechanical task for measuring sign- and goal-tracking in humans: a proof-of-concept study, Behav. Brain Res. 436 (2023) 114112, https://doi.org/10.1016/j.bbr.2022.114112.
[8] A. Costa, C. la Fougère, O. Pogarell, H.-J. Möller, M. Riedel, U. Ettinger, Impulsivity is related to striatal dopamine transporter availability in healthy males, Psychiatry Res. 211 (3) (2013) 251–256, https://doi.org/10.1016/j.pscychresns.2012.07.011.
[9] D. Das, N. Cherbuin, P. Butterworth, K.J. Anstey, S. Easteal, A population-based study of attention deficit/hyperactivity disorder symptoms and associated impairment in middle-aged adults, PLos One 7 (2) (2012) e31500, https://doi.org/10.1371/journal.pone.0031500.
[10] N.D. Daw, S.J. Gershman, B. Seymour, P. Dayan, R.J. Dolan, Model-based influences on humans' choices and striatal prediction errors, Neuron 69 (6) (2011) 1204–1215, https://doi.org/10.1016/j.neuron.2011.02.027.
[11] L.M. Dinu, S.N. Singh, N.S. Baker, A.L. Georgescu, B.F. Singer, P.G. Overton, E. J. Dommett, The effects of different exercise approaches on attention deficit hyperactivity disorder in adults: a randomised controlled trial, Behav. Sci. 13 (2) (2023) 129, https://doi.org/10.3390/bs13020129.
[12] T.L. Doremus-Fitzwater, L.P. Spear, Amphetamine-induced incentive sensitization of sign-tracking behavior in adolescent and adult female rats, Behav. Neurosci. 125 (4) (2011) 661–667, https://doi.org/10.1037/a0023763.
[13] C.J. Fitzpatrick, J.D. Morrow, Pavlovian conditioned approach training in rats, JoVE (J. Vis. Exp.) 108 (2016) e53580, https://doi.org/10.3791/53580.
[14] S.B. Flagel, Sign-tracking, in: I.P. Stolerman, L.H. Price (Eds.), Encyclopedia of Psychopharmacology, Springer, 2010, pp. 1–7, https://doi.org/10.1007/978-3-642-27772-6_7020-1.
[15] S.B. Flagel, J.J. Clark, T.E. Robinson, L. Mayo, A. Czuj, I. Willuhn, C.A. Akers, S. M. Clinton, P.E.M. Phillips, H. Akil, A selective role for dopamine in stimulus–reward learning, Nature 469 (7328) (2011) 7328, https://doi.org/10.1038/nature09588.
[16] S. Garofalo, G. di Pellegrino, Individual differences in the influence of task-irrelevant Pavlovian cues on human behavior, Front. Behav. Neurosci. 9 (2015) 163, https://doi.org/10.3389/fnbeh.2015.00163.
[17] J.M. Holden, Effects of two kinds of noradrenergic ADHD medicines on sign-tracking and goal-tracking in male rats, Exp. Clin. Psychopharmacol. 30 (2022) 760–773, https://doi.org/10.1037/pha0000538.
[18] J.M. Holden, L.L. Peoples, Effects of acute amphetamine exposure on two kinds of pavlovian approach behavior, Behav. Brain Res. 208 (1) (2010) 270, https://doi.org/10.1016/j.bbr.2009.11.014.
[19] R.C. Kessler, L.A. Adler, M.J. Gruber, C.A. Sarawate, T. Spencer, D.L. Van Brunt, Validity of the World Health Organization adult ADHD self-report scale (ASRS) Screener in a representative sample of health plan members, Int. J. Methods Psychiatr. Res. 16 (2) (2007) 52–65, https://doi.org/10.1002/mpr.208.
[20] R.C. Kessler, L. Adler, M. Ames, O. Demler, S. Faraone, E. Hiripi, M.J. Howes, R. Jin, K. Secnik, T. Spencer, T.B. Ustun, E.E. Walters, The World Health Organization adult ADHD self-report scale (ASRS): a short screening scale for use in the general population, Psychol. Med. 35 (2) (2005) 245–256, https://doi.org/10.1017/S0033291704002892.
[21] R.C. Kessler, L. Adler, R. Barkley, J. Biederman, C.K. Conners, O. Demler, S. V. Faraone, L.L. Greenhill, M.J. Howes, K. Secnik, T. Spencer, T.B. Ustun, E. E. Walters, A.M. Zaslavsky, The prevalence and correlates of adult ADHD in the United States: results from the national comorbidity survey replication, Am. J. Psychiatry 163 (4) (2006) 716–723, https://doi.org/10.1176/ajp.2006.163.4.716.
[22] S. Lewandowsky, K. Oberauer, Low replicability can support robust and efficient science, Nat. Commun. 11 (1) (2020) 1, https://doi.org/10.1038/s41467-019-14203-0.
[23] T. Li, N.R. Mota, T.E. Galesloot, J. Bralten, J.K. Buitelaar, J. IntHout, A. AriasVasquez, B. Franke, ADHD symptoms in the adult general population are associated with factors linked to ADHD in adult patients, Eur. Neuropsychopharmacol. 29 (10) (2019) 1117–1126, https://doi.org/10.1016/j.euroneuro.2019.07.136.
[24] J.C. Lopez, R.-M. Karlsson, P. O'Donnell, Dopamine D2 modulation of sign and goal tracking in rats, Neuropsychopharmacol. 40 (9) (2015) 9, https://doi.org/10.1038/npp.2015.68.
[25] V. Lovic, B.T. Saunders, L.M. Yager, T.E. Robinson, Rats prone to attribute incentive salience to reward cues are also prone to impulsive action, Behav. Brain Res. 223 (2) (2011) 255–261, https://doi.org/10.1016/j.bbr.2011.04.006.
[26] P.J. Meyer, V. Lovic, B.T. Saunders, L.M. Yager, S.B. Flagel, J.D. Morrow, T. E. Robinson, Quantifying individual variation in the propensity to attribute incentive salience to reward cues, PLos One 7 (6) (2012) e38987, https://doi.org/10.1371/journal.pone.0038987.
[27] I. Myin-Germeys, Z. Kasanova, T. Vaessen, H. Vachon, O. Kirtley, W. Viechtbauer, U. Reininghaus, Experience sampling methodology in mental health research: new insights and technical developments, World Psychiatry 17 (2) (2018) 123–132, https://doi.org/10.1002/wps.20513.
[28] R.E. Nordquist, P. Voorn, J.G. de Mooij-van Malsen, R.N.J.M.A. Joosten, C.M. A. Pennartz, L.J.M.J. Vanderschuren, Augmented reinforcer value and accelerated habit formation after repeated amphetamine treatment, Eur.

Neuropsychopharmacol. 17 (8) (2007) 532–540, https://doi.org/10.1016/j.euroneuro.2006.12.005.
[29] K.L. Nylund, T. Asparouhov, B.O. Muthén, Deciding on the number of classes in latent class analysis and growth mixture modeling: a Monte Carlo simulation study, Struct. Equ. Model. A Multidiscip. J. 14 (4) (2007) 535–569, https://doi.org/10.1080/10705510701575396.
[30] G. Polanczyk, M.S. de Lima, B.L. Horta, J. Biederman, L.A. Rohde, The worldwide prevalence of ADHD: a systematic review and metaregression analysis, Am. J. Psychiatry 164 (6) (2007) 942–948, https://doi.org/10.1176/ajp.2007.164.6.942.
[31] T.E. Robinson, L.M. Yager, E.S. Cogan, B.T. Saunders, On the motivational properties of reward cues: individual differences, Neuropharmacology 76 (2014) 450–459, https://doi.org/10.1016/j.neuropharm.2013.05.040.
[32] S.A. Safren, P. Duran, I. Yovel, C.A. Perlman, S. Sprich, Medication adherence in psychopharmacologically treated adults with ADHD, J. Atten. Disord. 10 (3) (2007) 257–260, https://doi.org/10.1177/1087054706292165.
[33] B.T. Saunders, T.E. Robinson, Individual variation in resisting temptation: implications for addiction, Neurosci. Biobehav. Rev. 37 (9, Part A) (2013) 1955–1975, https://doi.org/10.1016/j.neubiorev.2013.02.008.
[34] D.J. Schad, M.A. Rapp, M. Garbusow, S. Nebe, M. Sebold, E. Obst, C. Sommer, L. Deserno, M. Rabovsky, E. Friedel, N. Romanczuk-Seiferth, H.-U. Wittchen, U. S. Zimmermann, H. Walter, P. Sterzer, M.N. Smolka, F. Schlagenhauf, A. Heinz, P. Dayan, Q.J.M. Huys, Dissociating neural learning signals in human sign- and goal-trackers, Nat. Hum. Behav. 4 (2) (2019) 201–214, https://doi.org/10.1038/s41562-019-0765-5.
[35] M. Schettino, I. Ceccarelli, M. Tarvainen, M. Martelli, C. Orsini, C. Ottaviani, From skinner box to daily life: sign-tracker phenotype co-segregates with impulsivity, compulsivity, and addiction tendencies in humans, Cogn. Affect. Behav. Neurosci. 22 (6) (2022) 1358–1369, https://doi.org/10.3758/s13415-022-01014-y.
[36] A. Serrano-Barroso, J.P. Vargas, E. Diaz, P. O'Donnell, J.C. López, Sign and goal tracker rats process differently the incentive salience of a conditioned stimulus, PLos One 14 (9) (2019) e0223109, https://doi.org/10.1371/journal.pone.0223109.
[37] A. Serrano-Barroso, J.P. Vargas, E. Diaz, I.M. Gómez-González, G. Ruiz, J.C. López, A videogame as a tool for clinical screening of possible vulnerability to impulsivity and attention disturbances in children, Child. 9 (11) (2022) 11, https://doi.org/10.3390/children9111652.
[38] P. Shaw, M. Gornick, J. Lerch, A. Addington, J. Seal, D. Greenstein, W. Sharp, A. Evans, J.N. Giedd, F.X. Castellanos, J.L. Rapoport, Polymorphisms of the dopamine D4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder, Arch. Gen. Psychiatry 64 (8) (2007) 921–931, https://doi.org/10.1001/archpsyc.64.8.921.
[39] V. Simon, P. Czobor, S. Bálint, Á. Mészáros, I. Bitter, Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis, Br. J. Psychiatry 194 (3) (2009) 204–211, https://doi.org/10.1192/bjp.bp.107.048827.
[40] B.F. Singer, B. Guptaroy, C.J. Austin, I. Wohl, V. Lovic, J.L. Seiler, R.A. Vaughan, M.E. Gnegy, T.E. Robinson, B.J. Aragona, Individual variation in incentive salience attribution and accumbens dopamine transporter expression and function, Eur. J. Neurosci. 43 (5) (2016) 662–670, https://doi.org/10.1111/ejn.13134.
[41] S.K. Sterba, Understanding linkages among mixture models, Multivar. Behav. Res. 48 (2013) 775–815, https://doi.org/10.1080/00273171.2013.827564.
[42] 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.
[43] D. Turner, C. Laier, M. Brand, T. Bockshammer, R. Welsch, M. Rettenberger, Response inhibition and impulsive decision-making in sexual offenders against children, J. Abnorm. Psychol. 127 (5) (2018) 471–481, https://doi.org/10.1037/abn0000359.
[44] F.R. Villaruel, N. Chaudhri, Individual differences in the attribution of incentive salience to a pavlovian alcohol cue, Front. Behav. Neurosci. 10 (2016) https://www.frontiersin.org/articles/10.3389/fnbeh.2016.00238.
[45] K. Wardenaar, Latent profile analysis in R: a tutorial and comparison to Mplus, PsyArXiv (2021), https://doi.org/10.31234/osf.io/wzftr.
[46] L.M. Yager, K.K. Pitchers, S.B. Flagel, T.E. Robinson, Individual variation in the motivational and neurobiological effects of an opioid cue, Neuropsychopharmacology 40 (5) (2015) 1269–1277, https://doi.org/10.1038/npp.2014.314.