Development of Novel Tasks to Assess Outcome-Specific and General Pavlovian-to-Instrumental Transfer in Humans

Belanger, Matthew J.; Chen, Hao; Hentschel, Angela; Garbusow, Maria; Ebrahimi, Claudia; Knorr, Felix G.

DOI:
10.1159/000526774

Publication date:
2022

Neuropsychobiology

Research Article

Neuropsychobiology
DOI: 10.1159/000526774

Received: September 3, 2021
Accepted: August 14, 2022
Published online: November 14, 2022

Development of Novel Tasks to Assess Outcome-Specific and General Pavlovian-to-Instrumental Transfer in Humans

Matthew J. Belanger[a] Hao Chen[a] Angela Hentschel[a] Maria Garbusow[b] Claudia Ebrahimi[b] Felix G. Knorr[a] Hilmar G. Zech[a] Maximilian Pilhatsch[a, c] Andreas Heinz[b] Michael N. Smolka[a]

[a]Department of Psychiatry and Psychotherapy, Technische Universität Dresden, Dresden, Germany; [b]Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany; [c]Department of Psychiatry and Psychotherapy, Elblandklinikum Radebeul, Radebeul, Germany

Keywords

Pavlovian-to-instrumental transfer · Specific Pavlovian-to-instrumental transfer · General Pavlovian-to-instrumental transfer · Appetitive conditioning · Approach-avoidance · Reward · Gustatory reward · Full transfer

Abstract

Introduction: The emergence of Pavlovian-to-instrumental transfer (PIT) research in the human neurobehavioral domain has been met with increased interest over the past two decades. A variety of PIT tasks were developed during this time; while successful in demonstrating transfer phenomena, existing tasks have limitations that should be addressed. Herein, we introduce two PIT paradigms designed to assess outcome-specific and general PIT within the context of addiction. ***Materials and Methods:*** The single-lever PIT task, based on an established paradigm, replaced button presses with joystick motion to better assess avoidance behavior. The full transfer task uses alcohol and nonalcohol rewards associated with Pavlovian cues and instrumental responses, along with other gustatory and monetary rewards. We constructed mixed-effects models with the addition of other statistical analyses as needed to interpret various behavioral measures. ***Results:*** Single-lever PIT: both versions were successful in eliciting a PIT effect (joystick: $p < 0.001$, $\eta_p^2 = 0.36$, button-box: $p < 0.001$, $\eta_p^2 = 0.30$). Full transfer task: it was determined that the alcohol and nonalcoholic reward cues selectively primed their respective reward-associated responses (gustatory version: $p < 0.001$, $r = 0.59$, and monetary version: $p < 0.001$, $r = 0.84$). The appetitive/aversive cues resulted in a general transfer effect (gustatory: $p < 0.001$, $\eta_p^2 = 0.09$, and monetary: $p < 0.001$, $\eta_p^2 = 0.17$). ***Discussion/Conclusion:*** Single-lever PIT: PIT was observed in both task versions. We posit that the use of a joystick is more advantageous for the analysis of avoidance behavior. It evenly distributes movement between approach and avoid trials, which is relevant to analyzing fMRI data. Full transfer task: While gustatory conditioning has been used in the past to elicit transfer effects, we present the first paradigm that successfully elicits both specific and general transfers in humans with gustatory alcohol rewards.

Introduction

An impaired ability to control one's alcohol intake constitutes one of the fundamental characterizations of alcohol use disorder (AUD). There is a considerable

Karger@karger.com
www.karger.com/nps

Karger
OPEN ACCESS

Correspondence to:
Matthew J. Belanger, matthew.belanger@tu-dresden.de
Michael N. Smolka, michael.smolka@tu-dresden.de

amount of evidence outlining the detrimental effects that chronic, excessive drinking has on an individual and societal level. Such effects include increased social harm costs and evitable burden on global healthcare systems [1]. Researchers have previously identified links between AUD and Pavlovian-to-instrumental transfer (PIT), establishing it as a promising mechanism that can lead to a better understanding of the development and maintenance of substance use disorders [2–4]. PIT describes a phenomenon by which a classically conditioned stimulus (CS) influences instrumental responding, or in a broader sense, how one's operant behavior is modulated by environmental cues [5–7]. Appetitive and aversive CSs are frequently utilized to elicit PIT effects [8–11], which can be quantified by various behavioral and motivational measures. Appetitive cues have previously been shown to induce approach behavior, while aversive cues tend to induce withdrawal behavior. Beyond animal studies, this effect was also found in humans [10, 12, 13]. Conceptually, PIT is also connected to cognitive control as it is regulated by specific cognitive and motivational processes [14, 15]. Interference control may also play a role in PIT regulation, as goal-directed instrumental approach and avoidance behavior were found to be more susceptible to Pavlovian cues associated with incongruent rather than congruent motivational states in high-risk drinkers [16]. From an associative learning perspective, PIT processes can help explain changes in ongoing behavior in the presence of environmental cues. The influence of environmental cues on ongoing instrumental behaviors can be viewed as adaptive and at times necessary to promote survival. For instance, if one were to encounter an environmental cue that reliably predicts the receipt of food, it is likely that one would change ongoing behavior in response to that cue and pursue the food [17]. However, in some circumstances PIT may lead to maladaptive behaviors, such as in the presence of drug-related stimuli that elicit drug seeking. This leads researchers to believe that PIT is a sensitive and powerful metric for assessing key mechanisms related to addictive behaviors [18].

PIT was first conceptualized in the 1940s [5]; however, current literature reflects a surge of both human and animal PIT studies over the past two decades as the interplay between PIT and its respective intersections becomes increasingly recognized [9, 19]. There are two forms of PIT: specific and general transfer. Specific PIT, or outcome-specific PIT, occurs when an instrumental response associated with a rewarding stimulus is selectively primed or augmented by a Pavlovian cue associated with the same stimulus (for an example of an early, well-functioning example task in humans, see Allman and colleagues [20]). General transfer, however, is reflected by an unspecific augmentation of instrumental response rates by a Pavlovian cue associated with a different reward. As far as naming conventions go, PIT experiments can be categorized based on the type of instrumental response that is required. If the instrumental device has only one button, one lever, or comprises a singular unit in and of itself (i.e., one reward available), the PIT task can be categorized as "single lever." We chose to use this terminology in a general sense for the purposes of this paper as our first task only has one reward available. Some "specific transfer" PIT designs incorporate two response buttons, levers, or devices (i.e., the choice between two different rewards), thus enabling the assessment of specific transfer if one unconditioned stimulus (US) is assigned to each response option. In the first case, one measures the vigor of the response to obtain the reward, and in the second case, one assesses the preference for each of the two rewards. Lastly, PIT tasks that assess both general and specific transfer can be referred to as "full transfer" tasks, as they encompass and assess both forms of PIT [9]. Such full transfer tasks have been previously used to assess the effects of appetitive food-associated cues in healthy [21] and disordered eating [17].

An existing task previously used to assess PIT in our research has limitations that we now plan to address in this paper. Concerning negatively valenced cues, our previous task does not distinguish whether such cues only inhibit approach behavior or also boost avoidance in an economic design that was also accessible in clinical populations in an fMRI environment [22]. Due to time constraints, the task we previously used in our research (described in Chen et al. [16]) is a shortened version of the task used by Geurts et al. [10] in their previously mentioned study (withdrawal-go condition removed). Shortening the task allowed us to assess PIT in an fMRI environment, but the task design was not balanced. As appetitive and aversive cues have previously been explored with respect to PIT [10, 12, 13], we wished to further elucidate the complex relationship between appetitive and aversive Pavlovian cues, response inhibition, and avoidance behavior. To achieve this, we implemented a joystick as a response device, which allowed us to intuitively assess approach and avoidance behavior with the extra advantage of a balanced task design to model future fMRI analyses. Therefore, we introduce our new task design and demonstrate the facets of PIT that can be reflected with the joystick. To further disentangle the nuances of appetitive and aversive PIT, we also compare the joystick PIT task

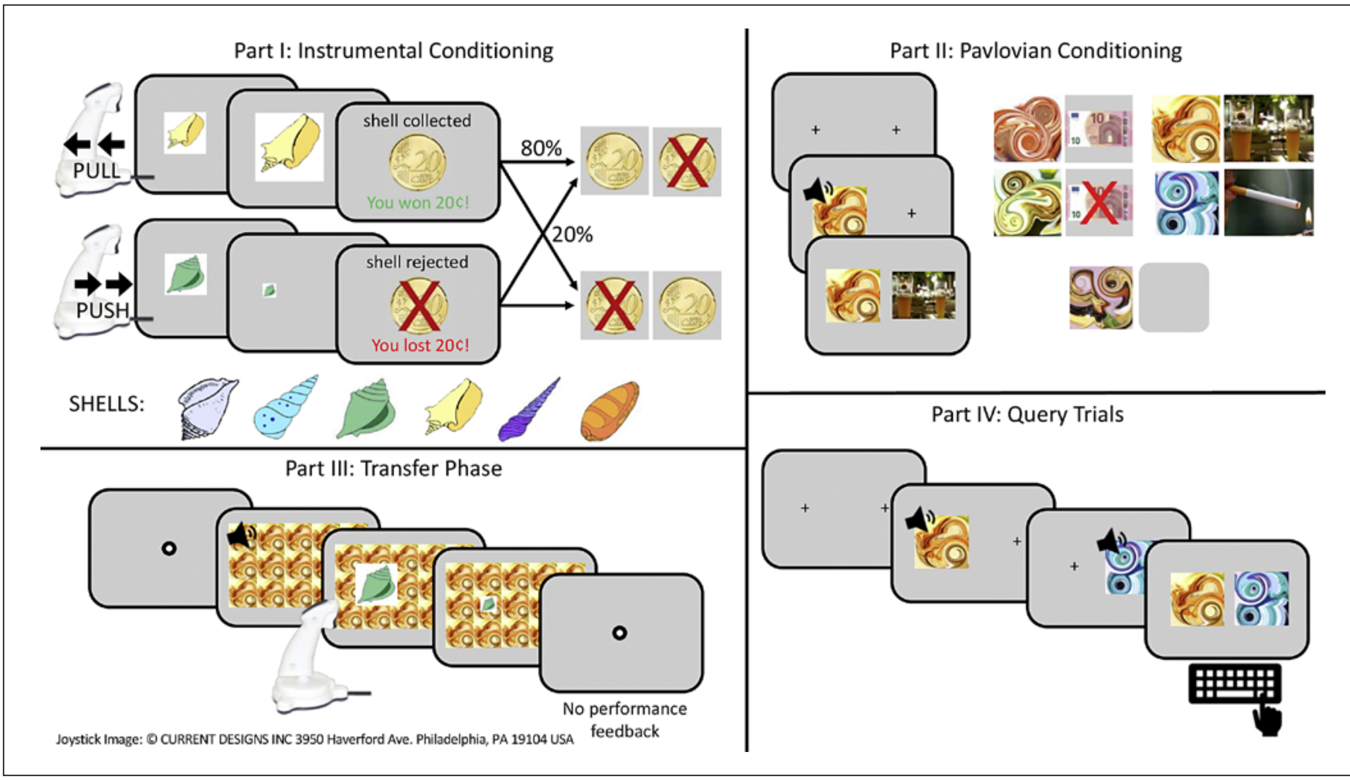

Fig. 1. Experimental design of the single-lever PIT task. Each part of the experiment is detailed in a respective quadrant. The "speaker" symbol indicates audio presented to the participant, and it does not appear on-screen.

to the established button press PIT task and discuss what these paradigms can offer to future research.

We first present a single-lever PIT paradigm based around a goal-oriented task. As mentioned, this single-lever PIT paradigm is an improved version of an established task used in our past studies [2, 16, 23]. The first part of the task is an instrumental discrimination learning phase during which the participant will use their response device to complete the goal-directed approach-avoidance task of collecting and rejecting "good" and "bad" shells with probabilistic monetary contingency feedback. The second part consists of a Pavlovian conditioning protocol, during which the participant must learn the associations between compound fractal-like audiovisual stimuli (CSs) and their respective outcomes (USs; see Fig. 1). To investigate PIT, the participant must then perform the same approach-avoidance task as found in part one, but now in the presence of the CSs from part two. Our main objective was to optimize our existing task by incrementally changing certain components of the task design to address the previously mentioned limitations. The original button press design element of the original task created several challenges when it came to data analysis and interpretation, especially concerning fMRI data. Repeatedly pressing the button during the PIT phase to collect rewarding objects and then inhibiting a response to reject aversive objects resulted in a movement imbalance; this was now improved by using a joystick as a response device so that the movements needed to approach and avoid are balanced. Since the joystick allows for balanced movements in the scanner and also allows us to assess the invigoration of avoidance behavior, the question remained as to whether the effects are comparable to the old version.

Another limitation that we experienced with our previous design concerned the inability to discern whether observed effects represent specific or general transfer. Since we used monetary outcomes (albeit of differing amounts) in both the instrumental and Pavlovian conditioning phases, we are unable to discern whether increases in instrumental responding elicited by the appetitive monetary CS + reflect specific or general transfer. If the PIT effect we observed in the past is specific, then we would not see such an increase with respect to a nonmonetary outcome. However, if the task reflects an unspecific augmentation of response rates by the appetitive monetary Pavlovian cue, it would also increase responding for a nonmonetary outcome and thus would be representative of general PIT. In response to this limitation, we conceptualized a second paradigm that more concretely distinguishes between the two types of PIT. The full transfer task follows a similar procedure as the single-lever PIT task; however, a key difference is that it utilizes direct, gustatory rewards delivered into the mouth of the participant. We incorporated alcohol and nonalcoholic (juice) rewards along with a second juice reward and aversive bitter solution. To investigate specific PIT, the same alcohol and juice rewards were used during both the instrumental and Pavlovian conditioning phases; meanwhile, the second juice reward and aversive bitter solution were introduced during the Pavlovian phase to assess general PIT. We were additionally interested in comparing general transfer between gustatory USs and monetary USs, so we piloted a version that replaces the second juice and bitter solution with monetary outcomes. This task is presented to the participant under the guise of a cover story about the development of a drink machine that requires button presses to operate. As traditional appetitive PIT tasks use images of food and drinks to visually condition participants [17, 21], the main objectives in the development of this task were to (1) determine if specific PIT effects could be detected through gustatory conditioning with alcohol and nonalcohol rewards in humans, and (2) determine whether or not we could successfully elicit both specific and general PIT within a single paradigm, which enables us to analyze and compare both processes simultaneously within an individual. Beyond more concretely distinguishing between specific and general transfers, we were especially interested in the direct, immediate gustatory reward aspect of this task design. There is strong evidence in support of direct gustatory (or intravenous) conditioning of drug rewards and PIT in animal studies [24, 25]; therefore, we were interested in translating this aspect to human studies, rather than using delayed rewards or visual cues, as is typically done. Further, using gustatory stimuli holds the advantage of closely matching the naturalistic stimuli consumed by the participant in their daily life.

Achieving these objectives and incorporating these new design elements into our tasks will allow us to explore PIT effects more thoroughly in clinical populations. With the single-lever joystick task, we will be able to test whether – compared to controls – participants with risky alcohol consumption or moderate to severe AUD show increased PIT effects not only with respect to approach but also regarding avoidance behavior. Our full transfer task will allow us to investigate the degree by which the motivation to obtain alcohol rewards can be enhanced by Pavlovian cues experimentally paired with alcohol (specific PIT) and/or appetitive cues (general PIT). Before studies in AUD participants can occur, though, it was first necessary to determine whether the design of the paradigms successfully elicited PIT effects by testing control populations. Hence, both paradigms were piloted to ensure that the relevant aspects of PIT were evoked.

Materials and Methods

Participant Characteristics

Single-Lever PIT Task

Sixty-six participants were invited from a local participant pool of the Technische Universität Dresden, Germany. Half of the participants performed the task with a Thrustmaster® T16000M FCS Flightstick USB joystick, hereafter referred to as the "joystick version," while the other half performed the task using a standard computer mouse, now referred to as "button-box version."

Full Transfer Task

For the full transfer study, 116 additional participants were recruited from the same participant pool. All participants received alcohol and juice rewards. Sixty-one of the participants performed a version in which they received a second juice reward and aversive bitter solution (referred to as the "gustatory version"), and the other 55 performed a version in which they viewed images of positive and negative monetary outcomes (referred to as the "monetary version"). More information about the participant characteristics and exclusion criteria can be found in the online supplementary information Section 1, in addition to Table 1 (for all online supplementary material, see www.karger.com/doi/10.1159/000526774).

Questionnaires

In addition to basic sociodemographic data, all participants responded to the Alcohol Use Disorders Identification Test (AUDIT) [26] and the Fagerström Test for Nicotine Dependence (FTND) [27] (Table 1).

Single-Lever PIT Task Description

The first change to the established task incorporated the introduction of new USs and reflected the inclusion of fewer USs in total. To elaborate, the monetary stimuli were changed such that instead of 5 outcomes, the current version only has 2 monetary outcomes: a positive and a negative. The "0 Euro" condition, previously used to represent a neutral outcome, was replaced with no outcome. Furthermore, the established task included pictures of alcohol and water as conditioned cues. We now replaced these with an image representing tobacco consumption, allowing us to include populations with tobacco use disorder (TUD) in future studies. For details about the set-up and training session, please refer to the online supplementary material.

Table 1. Summary of participant characteristics for each version of the two PIT tasks

Version	Single-lever PIT		Full transfer PIT	
	joystick ($N = 32$)	button-box ($N = 33$)	gustatory ($N = 51$)	monetary ($N = 46$)
Mean age ± SD, years	28±8.34	29±9.87	26±7.12	27±6.21
Range of ages, years	21–67	21–65	19–55	19–45
Gender distribution	40.63% male (13 participants)	39.39% male (13 participants)	35.29% male (18 participants)	41.30% male (19 participants)
Mean AUDIT score[a] ± SD	7.06±6.06	6.27±5.34	6.66±4.75	6.96±4.41
AUDIT range	0–26	0–22	1–25	0–21
Recent cigarette smokers	6	8	16	13
Mean FTND score[b] ± SD	2.67±2.16	1.88±2.17	0.69±1.20	1.38±2.06
FTND range	0–5	0–5	0–4	0–6

In addition to basic sociodemographic data, all participants provided responses to the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993 [26]) and the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991 [27]). Participants were only required to fill out the FTND if they had smoked a cigarette within the last 30 days (i.e., "recent smokers"). SD, standard deviation. [a] Maximum AUDIT score is equal to 40. [b] Maximum FTND score is equal to 10.

Part 1: Instrumental Conditioning

This experiment was coded in MATLAB using the Psychophysics Toolbox Version 3 [28–30]. As mentioned above, the instrumental stimuli in this paradigm consisted of six differently colored clipart-like shells that were randomly assigned an affective quality (three good and three bad). The participants had to learn the qualities of the shells through trial-and-error by collecting and rejecting them. After each collection or rejection, they saw an outcome message for 1,100 ms indicating whether they successfully collected or rejected the shell (see Fig. 1). They then saw probabilistic visual feedback for 1,500 ms indicating a monetary gain or loss of 20 cents (EUR). For correct responses, the visual feedback showed a picture of the 20-cent coin with a sentence saying "You win 20 cents!" For incorrect responses, the participant saw a picture of the 20-cent coin with a bright red "X" through it, with the words "You lose 20 cents!" The probabilistic feedback followed an 80 × 20% reinforcement ratio to introduce a modest amount of uncertainty. This phase consisted of a minimum of 60 and a maximum of 120 trials. To complete the instrumental conditioning, it was required that the participant maintains 80% correct responses over the last 16 trials within said range. In the joystick version, the size of the shell image increased or decreased depending on the movement of the joystick (i.e., shell size increased for collections and decreased for rejections). This feature was not present in the button-box version, where instead the participant saw a small blue dot moving across the screen toward the shell after each button press. The response time for both versions of the paradigm was 2,000 ms.

Part 2: Pavlovian Conditioning

After the instrumental conditioning, the participants performed a Pavlovian conditioning phase that consisted of committing some stimulus-outcome associations to memory. In this phase, compound audiovisual stimuli were randomly paired with one of five outcomes. The audiovisual stimuli consisted of abstract, colorful, fractal-like images paired with a musical instrument tone. The fractals' main differentiating colors were red, yellow/orange, blue, pink/black/yellow, and green. The musical instruments included a grand piano, a koto, and a vibraphone. Two of the USs that were randomly assigned to a fractal and tone pairing were the alcohol and smoking images selected during the set-up (please refer to the online suppl. material for more information). The remaining outcomes were monetary based, one showing an image indicating a gain of 10 Euro and the other showing a loss of 10 Euro, as indicated by a bright red "X" through the image. For the neutral condition, no outcome was presented. At the onset of each trial, a CS appeared in the left center for 2,500 ms with a 1,000-ms musical tone, to which the participant listened with Sony® MDR-ZX310B headphones set at a reasonable volume (~40/100%). After 2,500 ms, the CSs associated US appeared in the right center of the screen. The participant then viewed the stimulus-outcome juxtaposition on the screen for 500 ms, after which the CS disappeared, leaving the participants to view the US for an additional 2,500 ms. The US then disappeared, and there was a blank screen for a 2,000-ms intertrial interval. This part of the experiment had 80 trials.

Part 3: PIT Phase

During part three, the participants were asked to once again perform the approach-avoidance task found in part one by collecting and rejecting the shells. The shell images and their randomly assigned intrinsic qualities remained constant throughout the entire experiment. At the onset of each trial, the participant saw and heard one of the CSs tiled in the background of the screen. The CSs were presented for 600 ms before the shell appeared on the screen, after which the participant had 2,000 ms to respond. The intertrial interval was randomly determined from an exponential distribution, ranging from 2,000 to 6,000 ms with an overall mean of 3,000 ms. Each CS was presented in the background 36 times, equaling 180 trials. The instructions informed the participants that they should focus their attention on the shells and that the CSs in the background did not influence on the previously learned qualities of the shells. Part three was performed under nominal extinction to avoid further learning; however, to maintain motivation, the participants were told that the monetary win/loss calculations were happening off-screen, and that correctness of their responses would count toward the amount of their final inconvenience allowance. In reality, their performance during the PIT phase did not influence on the final amount they received; the participants received some extra compensation (a maximum of 5 Euro) calculated with an algorithm that analyzed how well they performed during the instrumental learning phase.

Part 4: Query Trials

The last part of the experiment, barring any final questionnaires, required the participants to choose between a comparison of two of the CSs. The instructions informed the participant they were to choose the CS that was most appealing to them, in whatever way. During each trial, the participant would see the CSs on the left-center and right-center positions on the screen as in the Pavlovian conditioning phase. On the left side, one of the CSs appeared, and the musical instrument tone played through the headphones. The CS disappeared after 1,000 ms. On the right side, a different CS appeared along with its corresponding musical tone. It was also displayed for 1,000 ms. Both CSs then appeared on the screen, and the participant was instructed to use the left or right arrow keys on a standard keyboard to indicate their choice. They had 2,000 ms to respond. There were 60 total comparisons, meaning each CS pairing appeared 6 times. The pairings were randomly presented, and the sides on which each CS appeared were randomized.

Full Transfer Task Description

For details about the set-up, US selection, and training session, please refer to the online supplementary material.

Part 1: Instrumental Conditioning

This paradigm was coded in Python using the PyParadigm library [31]. The instrumental conditioning procedure was the same in both versions of the paradigm. At the beginning of the trial, the participants saw a white circle with a black outline appear in the center of the screen on a light gray background. Inside the circle, there was a red exclamation mark (!). The participants were instructed to choose a button upon seeing the graphic on the screen and repeatedly press the button during the 2,000-ms response window. If they did not surpass the threshold of five button presses, the screen would display a message instructing the participant to choose a button and press it repeatedly. If the threshold was achieved, the paradigm then determined whether the trial in question passes a 50% reinforcement ratio. If the trial was not successful, the screen displayed a message asking the participant to try again, explaining that there was a pump failure. A limit of three consecutive pump failures in a row was set, as to not frustrate or discourage the participant. If the trial was deemed successful, the participant was rewarded with the drink associated with the button they selected in 80% of the cases. To introduce uncertainty, the participants received the opposite drink 20% of the time. The maximum number of consecutive switches was set to 3. To encourage even learning throughout the instrumental conditioning, the paradigm detected whether the participant was choosing one button much more often than the other. If this was the case, or if the participant had already received all of the rewards for one of the drinks, the paradigm displayed a message informing the participant that their selected beverage had run out and that they must choose the other one. The volume of each drink reward delivered to the participant during each successful trial equaled 1 mL. After receiving a drink reward, the participants saw an instruction on the screen telling them to taste it and swallow. After, the participants received 3 mL of artificial saliva to neutralize the flavor. They were instructed to swallow the saliva after swishing it around their mouth. The overall goal of the participant during the instrumental conditioning phase was to find out which button was associated with which drink “most of the time” and commit the assignments to memory. Part one was completed upon the receipt of 24 total rewards: 12 of the alcohol and 12 of the juice. According to these specifications, the instrumental conditioning phase took approximately 50–60 trials to complete for the majority of the participants. After completing the instrumental conditioning, the participants answered 25 questions to check their explicit knowledge about which button dispensed which drink.

Part 2: Pavlovian Conditioning

As in the experiment described above, a Pavlovian conditioning procedure was then performed. The participants were asked to learn the outcomes associated with 5 novel compound audiovisual stimuli. These CSs consisted of 5 more colorful fractals (blue, green, red, light blue/tan, and pink/green) paired with a musical instrument sound playing the same middle C note (banjo, piano, clarinet, cello, and tuba). In both versions of the experiment (i.e., gustatory and monetary versions), the same alcohol and juice rewards from part one were used as outcomes during part two, along with no outcome to serve as a neutral condition.

In the *gustatory* version of the experiment, the participants received a second juice reward and a 3% bitter solution, delivered into their mouth via tubes connected to two additional AL-4000 syringe pumps. The bitter solution was prepared by the study administrator by mixing magnesium sulfate crystals and tap water. The selection procedure of the second juice reward followed the protocol described in the online supplementary material referencing the drink rating questionnaire.

The second reward and punishment were different in the *monetary* version of the paradigm, instead replacing the juice with a picture indicating a monetary gain of 10 Euro and replacing the bitter solution punishment with a picture indicating a monetary loss of 10 Euro. There were 80 total trials, meaning each CS and US were presented 16 times. At the beginning of the experiment, a pseudo-randomized mapping was generated which determined the assignment of the tones, fractals, and associated USs. At the beginning of a trial, the participants saw a fixation cross in the center of the screen for 500 ms, after which they would view and hear the CS for 2,500 ms. During this time, the syringe pump then dispensed the corresponding US. The participants had 1,000 ms to taste the drink and then 2,000 ms to swallow. There was a jittered 7,000-ms intertrial interval, during which the participant received 3 mL of artificial saliva to neutralize any remaining flavors and rinse out their mouth. In the monetary version of the paradigm, the participants viewed the US indicating a monetary gain/loss for 1,000 ms after viewing the CS.

Part 3: Pavlovian-to-Instrumental Transfer

The transfer phase was again performed under nominal extinction to avoid further learning. The cover story in this part of the experiment informed the participants that their data and input had been calculated by the company and the drink machine was fixed and ready to be tested one last time. During part three, it was

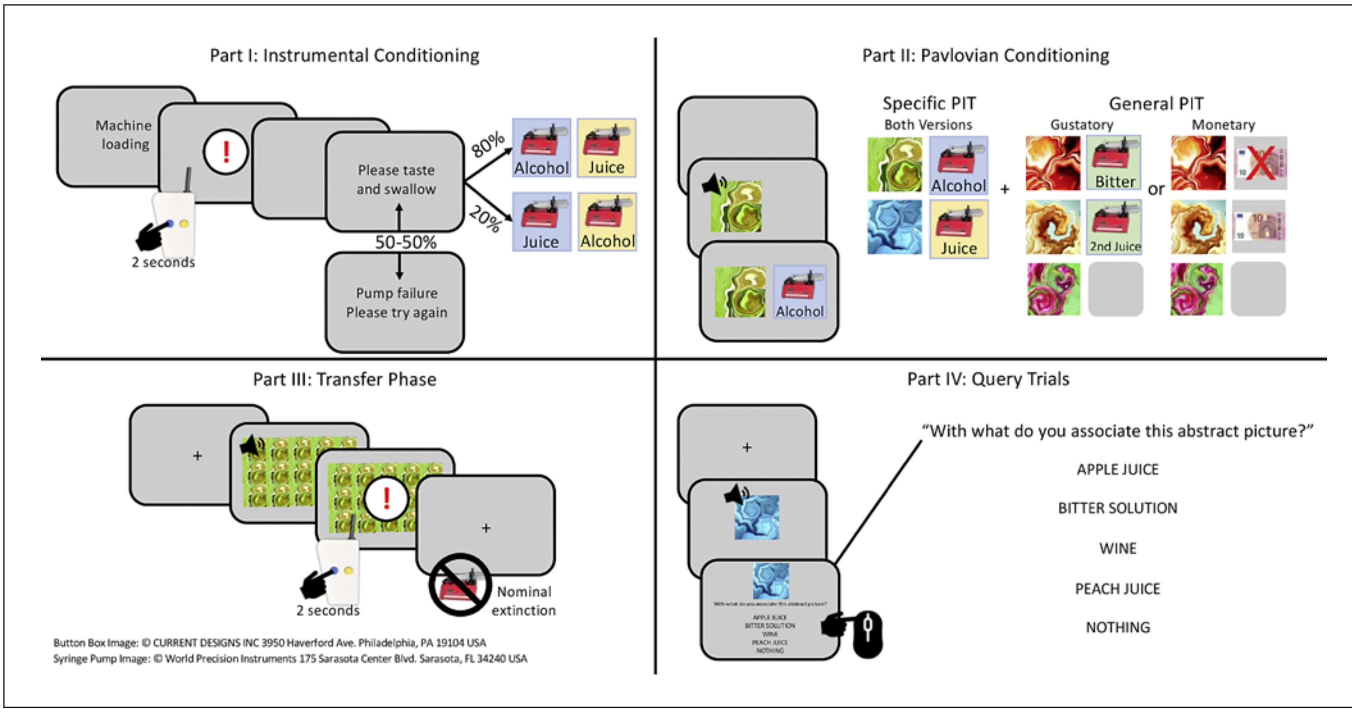

Fig. 2. Experimental design of the full transfer task. Each part of the experiment is detailed in its respective quadrant. The "speaker" symbol indicates audio presented to the participant, and this symbol does not appear on-screen. In the Instrumental Conditioning section, the colors of the alcohol and juice rewards correspond to the color of the buttons on the button-box. To elaborate, the figure indicates that out of all reward trials, the blue button dispensed alcohol 80% of the time and juice 20% of the time. In the Pavlovian conditioning quadrant, the USs for the gustatory and monetary versions are shown.

required that the participants choose a button and repeatedly press it at the onset of every trial to receive a drink. As in the single-lever PIT study, the CSs were tiled in the background and the corresponding musical instrument tones were played through the headphones. Since the USs were no longer immediately given, the instructions indicated that their choices and drink samples would be collected for them and presented at the end of the study. The participants were informed that the button associations they had learned during the instrumental conditioning remained constant and that the background CSs associated with the alcohol and juice rewards had no influence on their receipt of the respective drinks. In the monetary version, they were informed that if a CS associated with a monetary outcome was shown, the computer would randomly credit/deduct the 10 Euro half of the time. The participant had a free choice as to which button to choose and how often to press, and since they were informed that the machine had been fixed by the company, the instructions indicated that the supply of the beverages was now unlimited. At the beginning of each trial, the participants saw a fixation cross in the center of the screen for 500 ms. The tiled CSs then appeared for a 600-ms primer before the exclamation point graphic appeared for the 2,000 ms response window, during which time the respective CS remained tiled in the background. There was a jittered intertrial interval of 2,000 ms, and there were a total of 240 trials during the transfer phase.

Part 4: Query Trials

The last part of the experiment served to determine how successful the Pavlovian conditioning from part two was. At the beginning of the trial, we presented a fixation cross for 500 ms. A randomly presented CS appeared on the screen, and the corresponding tone was played through the headphones. Below the CS, there was a question asking the participant to identify the US that was associated with the CS. Below the question, there was a list of the five possible answers. The participant was given an unlimited amount of time to respond to each question using a standard computer mouse. Each CS appeared 5 times during part four; therefore, the participants responded to 25 questions asking for their explicit knowledge of the associations. For a visualization of the experimental design of the full transfer task, please reference Figure 2.

Hypotheses and Analyses

Analysis of the Single-Lever PIT Task

In the past, our group and collaborators characterized behavioral PIT effects through individual regression slopes [23] representing the motivational effects of Pavlovian background cues on instrumental approach and avoidance, and calculated error rates to assess interference control [16]. From the interference PIT perspective, we characterized the influence of the CSs on instrumental responding in consideration of congruent and incongruent trials (i.e., congruent: the act of collecting a shell with a positively va-

Neuropsychobiology
DOI: 10.1159/000526774

Table 2. Results of the linear mixed-effects models of the error rate as predicted by congruity

Predictor(s)	Joystick version						Button-box version					
	estimates	SE	conf. int (95%)	*T*	*p* value	df	estimates	SE	conf. int (95%)	*t*	*p* value	df
Intercept	1.02	0.05	0.93–1.11	21.82	**<0.001**	3,400.00	0.97	0.05	0.88–1.07	19.84	**<0.001**	3,558.00
Congruity	−0.14	0.03	−0.20 to −0.07	−4.17	**<0.001**	3,400.00	−0.11	0.03	−0.17 to −0.05	−3.72	**<0.001**	3,558.00
Random effects												
Mean squared error	0.12						0.14					
Between-subject variance	0.06 $_{Participant}$						0.07 $_{Participant}$					
Random slope variance	0.03 $_{Participant.Congruity}$						0.03 $_{Participant.Congruity}$					
Random slope intercept correlation	−0.87 $_{Participant}$						−0.90 $_{Participant}$					
ICC	0.32						0.23					
N	32 $_{Participant}$						33 $_{Participant}$					
Observations	3,406						3,564					
Marginal R^2/conditional R^2	0.065/0.366						0.045/0.267					

Visual inspection of residual plots did not reveal heteroscedasticity or other deviations from normality. To examine the differences in correctness as predicted by congruity, our model was constructed with the congruity as a main predictor in addition to participant-specific random intercepts and slopes.

lenced fractal/rejecting a shell with a negatively valenced fractal vs. incongruent: collecting a shell with a negatively valenced fractal or rejecting a shell with a positively valenced fractal). Interference PIT scores were calculated by subtracting the mean error rates between the two congruity conditions. As the aforementioned studies have previously established that the error rate is lower in congruent choice trials compared to incongruent trials, our main goal in piloting this task was to determine if these observed effects would be present using the joystick.

We additionally analyzed the motivational components of both versions. To characterize motivation in the joystick version, we examined the peak velocity of the collect/reject movements of the joystick shaft. For the button-box version, the motivational aspect was represented by the number of button presses variable. Like in all previous versions of the PIT paradigm, it has been established that positively valenced Pavlovian cues enhance instrumental responding, while the negatively valenced Pavlovian cue hinders instrumental responding. Our aim, in the case of the joystick version, was to investigate whether or not avoidance behavior would be enhanced by the negative cues.

Ultimately exploring the differences between the joystick and button-box versions of the paradigm, we investigated whether or not the joystick and button-box versions yielded different results or effect sizes with respect to interference control and motivation. Mixed-effects models were performed where appropriate to model the effects of Pavlovian-conditioned cues and other factors on instrumental behavior. The random-effects structures for each model are outlined in the online supplementary material. RStudio and the "lme4" package were used to construct the models of these behavioral relationships [32, 33].

Analysis of the Full Transfer Task

A button-box was selected as the response device for this task, as it easily captured both of our areas of interest: motivation and choice preference. The choice proportion was of key interest for the specific PIT analysis, as this reflects the degree to which the alcohol and juice cues selectively primed their respective choice outcomes during the PIT phase. Comparisons regarding the choice proportion were made by means of a specific PIT score. The specific PIT score was calculated by dividing the difference between the number of congruent (i.e., choosing the alcohol button when seeing the alcohol-associated CS) and incongruent choice outcomes by the total number of choices. A score of 0 represents an even number of congruent and incongruent outcomes, indicating no evidence of a specific PIT effect. This would occur, for example, if only one button was chosen throughout the entire PIT phase. A positive score indicates some degree of specific PIT; the strength of the effect is reflected in how close the score is to 1. Intuitively, the calculated specific PIT scores would be positive if more choice outcomes aligned with the CS (i.e., choosing the juice button upon seeing the juice-associated CS or choosing the alcohol button upon seeing the alcohol-associated CS). Lastly, a negative score would represent choice behavior that resulted in more incongruent than congruent choice outcomes (i.e., choosing the alcohol button upon seeing the juice-associated CS). We hypothesized that the alcohol and juice Pavlovian-conditioned cues would selectively prime their respective choices during the transfer phase. Regarding the motivational aspect (i.e., general transfer), we additionally hypothesized that the stimuli associated with the second juice reward (positively valenced) would result in more button presses whereas

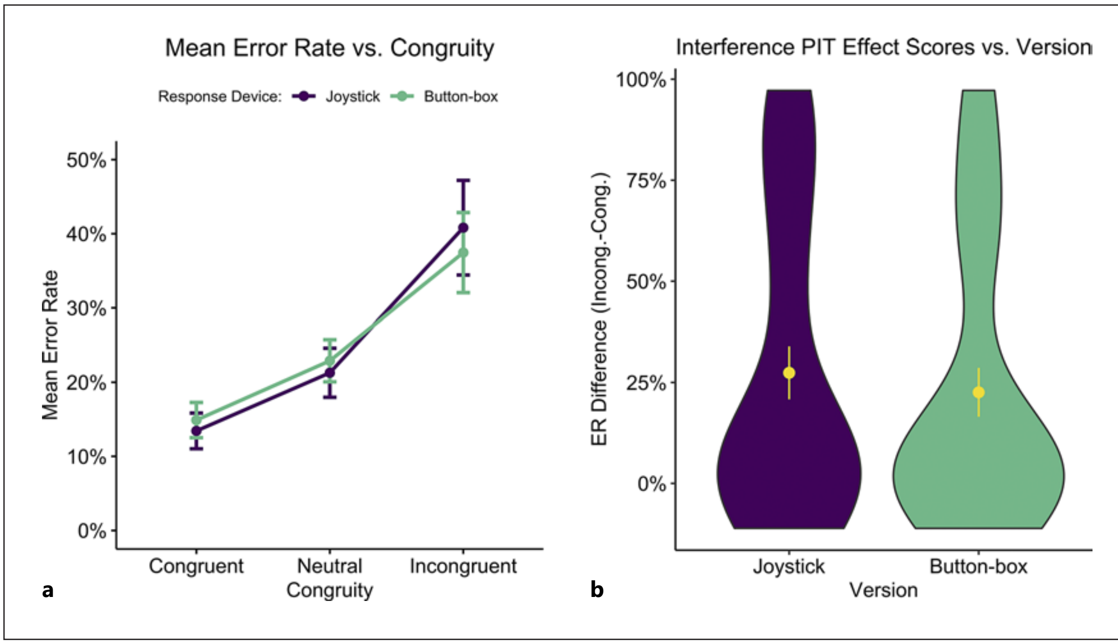

Fig. 3. a Comparison of the error rate variable within each of the congruity conditions for both versions of the task. **b** Interference PIT effect scores for both versions calculated by subtracting the congruent error rate from the incongruent error rate. The point in the middle of each violin indicates the mean interference PIT effect score with the standard error indicated by the vertical lines.

the stimuli associated with the bitter solution (negatively valenced) would inhibit instrumental responding, resulting in fewer button presses. We expected the same outcome for the Pavlovian-conditioned cues representing gain/loss in the monetary version of the task. As in the task above, we model the influence of several factors on instrumental responding.

Results

Single-Lever PIT Task Results

It was found in both versions that the error rate was higher in the incongruent condition ($mean_{joystick} = 40.8\%$, $mean_{button\text{-}box} = 37.5\%$) compared to the congruent condition ($mean_{joystick} = 13.4\%$, $mean_{button\text{-}box} = 14.9\%$). Subtracting these values results in an overall mean interference PIT effect score of 27.4% in the joystick version and 22.6% in the button-box version. Including the neutral condition in a mixed-model-based analysis determined that the correctness incrementally decreased by an approximate value of 11–14% between the congruent, neutral, and incongruent conditions (joystick: $\beta = -0.14$, $p < 0.001$, $\eta_p^2 = 0.36$, button-box: $\beta = -0.11$, $p < 0.001$, $\eta_p^2 = 0.30$; model details can be found in Table 2). Figure 3a outlines the main findings, while an in-depth look at the distribution of error rates and individual participant trajectories can be found in the online supplementary material Figure S1. Figure 3b indexes the participants' susceptibility to the influence of the Pavlovian-conditioned cues. Individual interference PIT effect scores (i.e., incongruent-congruent error rates) can also be found in the online supplementary material Figure S1. Comparing the scores between the two versions, there was no difference in the mean scores as determined by the Wilcoxon test ($W = 583$, $p = 0.47$, $r = 0.08$). A nonparametric test was chosen due to the abnormal distribution of interference PIT effect scores.

Examining the peak velocity within the monetary conditions, it was found that the valence of the CS influenced instrumental responding. In the joystick version, the peak velocity of the push and pull movement of the joystick shaft served to represent the implicit motivation to collect or reject. Given our model, we report that the CSs presented to the participant influenced the peak velocity by a factor of approximately 110°/s between the –10 Euro, neutral, and +10 Euro conditions ($\beta = 109.56$, $p < 0.001$, $\eta_p^2 = 0.31$; see Table 3). Separating the trials by shell quality, the influence of the CSs remained evident. To expand upon this, the joystick version demonstrates that avoidance behavior was boosted by the negatively valenced cues while

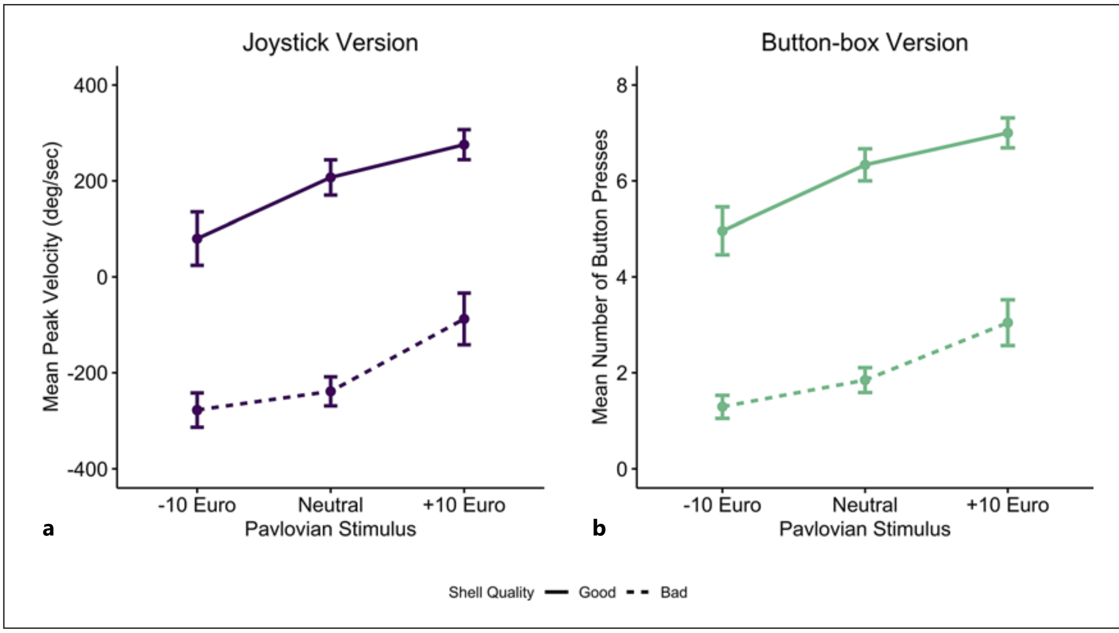

Fig. 4. Comparison of the motivational variables between the joystick and button-box versions. **a** Motivational salience within the "good shell" trials (solid line) and "bad shell" trials (dashed line) as measured by the peak velocity (deg/sec). Positive velocity values indicate a collection (pull), and negative values indicate a rejection (push). **b** Motivational salience as measured by the mean number of button presses within all "good shell" (solid line) and "bad shell" (dashed line) trials. Both: Data are separated according to the intrinsic qualities of the shells, which reflect the influence of the CSs in each condition, regardless of shell quality.

approach behavior was enhanced by the positively valenced cues in terms of response vigor. There was no interaction between the Pavlovian cue and the quality of the shell ($\beta = 3.26$, $p = 0.75$, $\eta_p^2 = 3.08e{-}05$); thus, the Pavlovian influence was equivalent in both conditions, regardless of shell quality. Figure 4b shows similar implicit motivation when responding with the button-box. The mean number of button presses was influenced by the CSs, which reflected an increase of just under 1 button press between the negatively, neutral, and positively conditioned cues ($\beta = 0.88$, $p < 0.001$, $\eta_p^2 = 0.29$), indicating that there was increased response vigor in the +10 Euro condition and a decrease in button presses in the −10 Euro condition. There was also no interaction between the Pavlovian cue and the quality of the shell ($\beta = 0.14$, $p = 0.19$, $\eta_p^2 = 5.07e{-}04$). The individual trajectories, found in the online supplementary material Figure S2, reveal similar response patterns as found in the joystick version. With respect to the implicit motivational measures, nonparametric Friedman tests determined that the response vigor appears to not have been influenced by the alcohol- or smoking-associated CSs in either version of the paradigm (joystick good shells: $\chi^2(2) = 3.06$, $p = 0.22$, joystick bad shells: $\chi^2(2) = 0.75$, $p = 0.69$, button-box good shells: $\chi^2(2) = 3.80$, $p = 0.15$, button-box bad shells: $\chi^2(2) = 4.66$, $p = 0.10$; see Figure 5 and the online suppl. material Fig. S5).

Full Transfer Task Results

Specific PIT

In the presence of the juice-associated Pavlovian cue, participants more often chose to press the juice-associated button. Additionally, more participants chose the alcohol-associated button in the presence of the alcohol-associated cue. Therefore, an outcome-specific PIT effect was found in both versions of the task. The slopes of the lines and the degree of crossover (or lack thereof) in Figure 6a, b reflect the strength of the effect; the monetary version appeared to result in a stronger specific PIT effect compared to the gustatory version. This is evidenced by the higher proportion of button choices that aligned with its respective Pavlovian cue. We compared versions by means of a specific PIT score, as the total proportion of choices was not evenly distributed between the two buttons. The specific PIT scores were abnormally distributed; therefore, analysis was performed using the nonparametric Wilcoxon test. The Wilcoxon test determined that the specific PIT score median

DOI: 10.1159/000526774

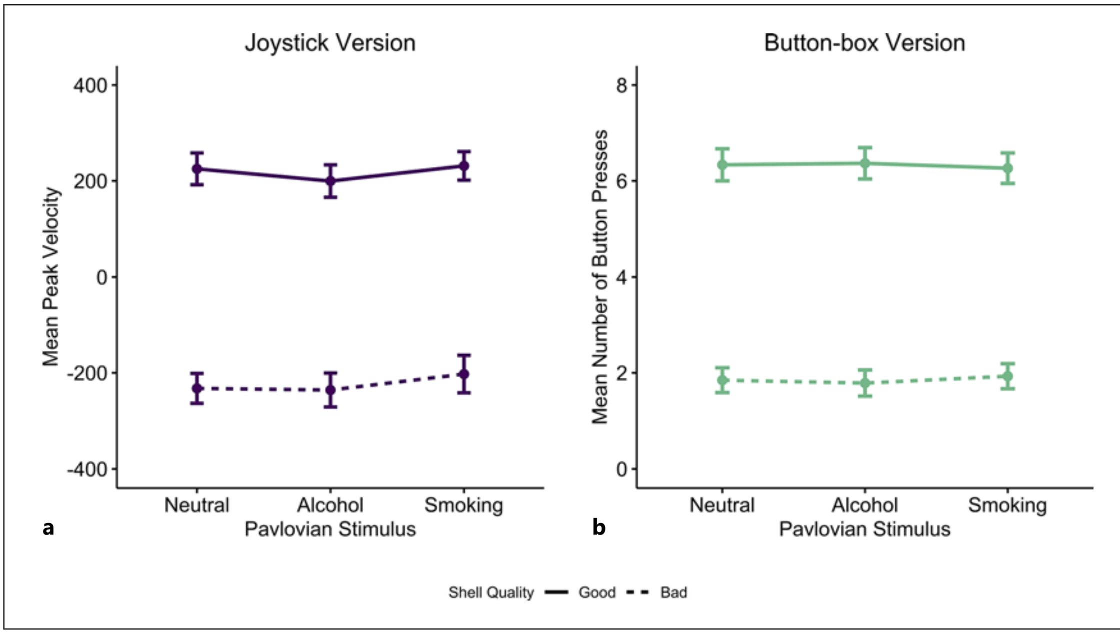

Fig. 5. a, **b** Comparison of the motivational aspect between the joystick and button-box versions within the trials that contained an alcohol or smoking Pavlovian cue.

Table 3. Results of the linear mixed-effects model for the motivational variables

Predictor(s)	Joystick version						Button-box version					
	estimates	SE	conf. int (95%)	*t*	*p* value	df	estimates	SE	conf. int (95%)	*t*	*p* value	df
Intercept	−423.10	52.28	−525.57 to −320.63	−8.09	<0.001	3,395.00	0.31	0.47	−0.61–1.23	0.65	0.513	3,553.00
Pavlovian cue	109.56	30.19	50.39–168.74	3.63	<0.001	3,395.00	0.88	0.27	0.35–1.41	3.24	0.001	3,553.00
Shell quality (good)	395.51	61.48	275.00–516.02	6.43	<0.001	3,395.00	3.75	0.51	2.76–4.74	7.41	<0.001	3,553.00
Pavlovian cue:shell quality (Good)	3.26	10.22	−16.76–23.28	0.32	0.750	3,395.00	0.14	0.11	−0.07–0.36	1.33	0.185	3,553.00
Random effects												
Mean squared error	58,886.53						7.00					
Between-subject variance	79,661.65 Participant						6.37 Participant					
Random slope variance	27,482.05 Participant.Pavlovian Cue						2.22 Participant.Pavlovian Cue					
Random slope intercept correlation	105,484.76 Participant.Shell Quality (Good)						6.6 Participant.Shell Quality (Good)					
Mean squared error	−0.84						−0.89					
Between-subject variance	0.12						0.12					
ICC	0.45						0.35					
N	32 Participant						33 Participant					
Observations	3,406						3,564					
Marginal R^2/conditional R^2	0.314/0.620						0.303/0.547					

Visual inspection of residual plots did not reveal heteroscedasticity or other deviations from normality. To investigate the peak velocity (joystick) and number of button presses (button-box) as predicted by several different factors, linear mixed-effects models were constructed with the Pavlovian cue and shell quality as fixed effects with an interaction term between the two and participant-specific random intercepts and slopes for the fixed predictors.

was significantly shifted compared to 0 in both the gustatory (mean = 0.27, $V = 858$, $p < 0.001$, $r = 0.59$) and monetary (mean = 0.53, $V = 977$, $p < 0.001$, $r = 0.84$) versions with large effect sizes. Comparing both versions directly, the median specific PIT score in the monetary version was significantly higher than in the gustatory version with a moderate effect size ($W = 706$, $p < 0.001$, $r = 0.34$), which indicates that observed specific transfer was stronger in the monetary version. As shown in Figure 6c (and online suppl. material Fig. S3), there were more participants in the gustatory version that did not show evidence of specific PIT compared to the monetary version. Notably, the number of participants that

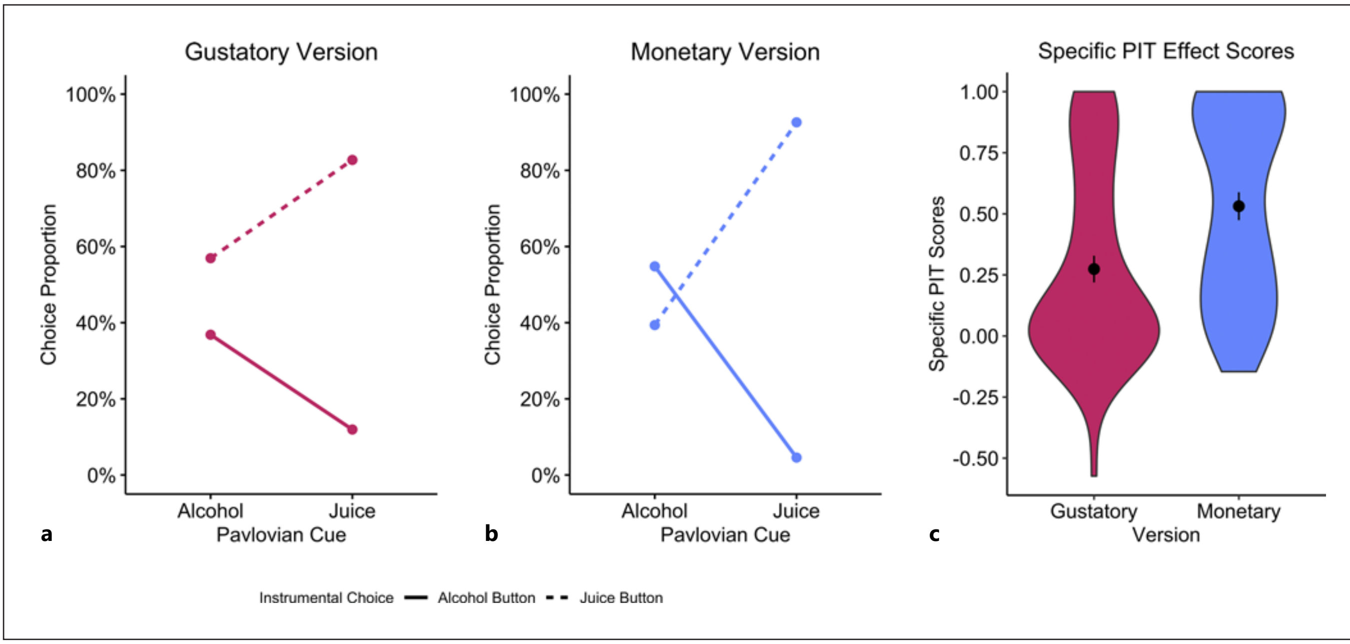

Fig. 6. Comparison of specific PIT effects between the gustatory and monetary versions. **a**, **b** Comparing the proportion of instrumental choices during the PIT phase of the gustatory and monetary versions within the alcohol and juice reward conditions. The dashed line represents the button associated with the juice reward, while the solid line represents the button with the alcohol reward. **c** A comparison of specific PIT scores of both versions, serving as an index of participants' susceptibility to specific transfer effects. The mean specific PIT scores and standard error are represented by the points located in the center of the violins.

showed an "opposite" specific PIT effect (i.e., a negative specific PIT score) was higher in the gustatory version, which contributed to the lower mean specific PIT score of 0.27, comparatively. The majority of the participants in the monetary version demonstrated a specific PIT effect, resulting in a mean specific PIT score of 0.53.

General PIT

Through the incorporation of a second reward and a negative outcome, we investigated whether and to what extent general PIT occurred during the transfer phase by modeling Pavlovian influence on instrumental responding. Participants in both samples showed evidence of a general PIT effect. According to the model of the gustatory version, there was an upward trend in the number of button presses during the presentation of a CS associated with the alternative juice reward compared to the bitter solution condition ($\beta = 0.31$, $p < 0.001$, $\eta_p^2 = 0.09$; see Table 4 for more details). Assuming the same model for the monetary version, a larger incremental increase in the number of button presses is predicted by the different CSs, resulting in effects that follow a similar pattern ($\beta = 0.36$, $p < 0.001$, $\eta_p^2 = 0.17$). Full distributions and individual trajectories can be found in the online supplementary material Figure S4. Although the effect size of the monetary version was numerically larger, the mean difference score between the second reward and negative outcome in both versions of the task does not differ statistically (Fig. 7c, $W = 1{,}098.5$, $p = 0.59$, $r = 0.05$).

Additional Results

Details about the query trials of both tasks can be found in the online supplementary material Figure S6 for the single-lever PIT task and S7 for the full transfer task.

Discussion

Discussion of the Single-Lever PIT Task

Both versions of the single-lever PIT task induced substantial PIT effects within the motivational and interference control aspects. Additionally, the respective effect sizes were comparable between the joystick and button-box versions, which substantiates the notion that single-lever PIT effects can be evoked with the joystick.

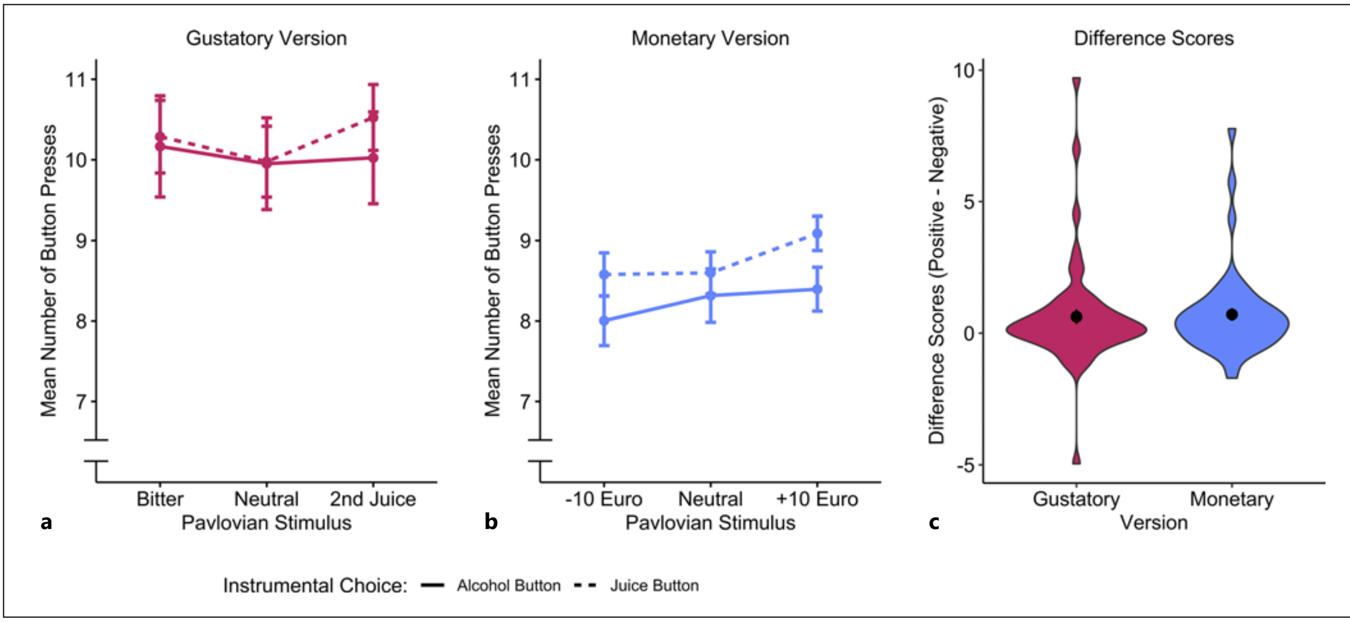

Fig. 7. Comparison of general PIT effects between the gustatory and monetary versions. **a**, **b** Comparison of the mean number of button presses within the second reward and negative outcome conditions (left: gustatory, right: monetary). The left sides of these graphs represent the negatively conditioned Pavlovian cue (bitter solution or monetary loss), while the right side represents the positively conditioned Pavlovian cue (second juice or monetary gain). The neutral condition is shown in the middle. An exploratory analysis did not reveal a significant interaction between the Pavlovian stimuli and the instrumental choice (gustatory: $p = 0.19$, monetary: $p = 0.20$). **c** A comparison of the overall difference in the mean number of button presses (positive-negative) for both versions (instrumental choice collapsed).

Table 4. Results of the linear mixed-effects models of the general PIT components of the full transfer task

Predictor(s)	Gustatory version						Monetary version					
	estimates	SE	conf. int (95%)	*t*	*p* value	df	estimates	SE	conf. int (95%)	*t*	*p* value	df
Intercept	8.80	0.53	7.77–9.84	16.67	<0.001	7,340.00	7.50	0.26	6.99–8.01	28.75	<0.001	6,620.00
Pavlovian cue	0.31	0.04	0.23–0.40	7.38	<0.001	7,340.00	0.36	0.04	0.28–0.44	8.75	<0.001	6,620.00
Random effects												
Mean squared error	8.84						7.30					
Between-subject variance	13.79 Participant						2.77 Participant					
ICC	0.61						0.28					
N	51 Participant						46 Participant					
Observations	7,344						6,624					
Marginal R^2/conditional R^2	0.003/0.610						0.008/0.281					

Visual inspection of residual plots did not reveal heteroscedasticity or other deviations from normality. Mixed-effects models were constructed with the Pavlovian cue listed as a fixed effect predicting the number of button presses. Participant-specific random intercepts and slopes were also included in the models.

Regarding the motivational aspect of the single-lever PIT task, the positively valenced CSs enhanced instrumental responding in both versions. As anticipated, the negatively valenced CSs of the button-box version hindered instrumental responding in the sense of approach behavior. With respect to the joystick version, we observed that avoidance behavior was enhanced by the negatively valenced CSs, as reflected by increased response vigor in the negative direction [13]. The results illustrate the nuanced differences in instrumental responding between the two response devices and further support established notions surrounding the influence of motivation on the vigor of instrumental responding [7]. Critically, both CSs associated with a monetary gain and loss inspired a behavioral change in some participants that is consistent with the valence of the associated outcome. In the joystick version, there appears to be a symmetrical effect, such that the avoidance behavior was enhanced by the negative cues to a similar degree that the approach behavior was enhanced by the positive cues.

Avoidance behavior was better assessed having used a joystick as a response device; this type of behavior was previously unable to be assessed in the button-box version. While the motor inhibition aspect of the button-box version may be of interest in some spheres, our goal of assessing avoidance behavior required an alternative approach, as response inhibition and avoidance behavior are fundamentally distinct concepts [34]. In addition, the previously described movement imbalance between the approach and avoid trials was improved with the joystick. Optimizing the experimental design such that the same type of movement is required for both choice outcomes allows for a balanced reduction in movement artifacts during fMRI data processing. Zech and colleagues [35] showed a similar vigor (or force)-based effect in an approach-avoidance task, later concluding that the observed force-based effects were driven by independent (perhaps more motivational) processes. The joystick ultimately provides a more intuitive interface for collecting and rejecting the shells, as the push and pull movements correspond well to physical movements of approach and avoidance (i.e., the direction of motivation). We, therefore, establish the joystick as a promising response device for approach-avoidance PIT studies by yielding comparable, if not, more informative results across multiple variables.

Regarding the alcohol and smoking cues, there was no observed group-level effect in these conditions in our control-like population. If we included AUD or TUD subpopulations in our sample, we suspect that we would have observed stronger PIT effects within these two conditions. An analysis of the AUDIT and FTND questionnaires revealed that there were some hazardous drinkers and smokers in our sample, so it is plausible that these participants found the alcohol and smoking cues to be rewarding due to their associative history of alcohol and tobacco consumption. However, there were not enough hazardous drinkers or smokers in our sample to perform any meaningful correlation analyses. It is possible that these cues could affect ongoing instrumental behavior in light- or nonconsuming individuals (i.e., smoking cues could be aversive to nonsmokers). However, the question of whether our alcohol and smoking cues would elicit stronger PIT effects in individuals with AUD/TUD must be tested in a clinical sample, as we suspect that dependent populations may exhibit more pronounced reactivity to these cues.

Shifting to the interference control perspective of the single-lever PIT task, we confirmed previously established results that state the error rate was lower in congruent choice trials compared to incongruent trials. Sensitivity to this conflict was previously found to be especially pronounced in high-risk alcohol drinkers [16]. Ultimately, since our PIT task involves a conflict between an instrumentally learned response and a motivational cue, the mechanisms between interference control during PIT and conflict at the stimulus and/or response levels, such as those seen in Stroop or Simon tasks, remain ambiguous [36]. Conceptually, our PIT task differs from these traditional interference tasks as there is an instrumental learning component rooted in a reward-punishment dichotomy. As a result, Pavlovian cues in conflict with instrumental responding could inspire changes in both motivation and interference control when responding, which could involve more complex mechanisms than those employed by the Stroop or Simon tasks.

In conclusion, both versions of the single-lever PIT task encompass the motivational and interference control perspectives of PIT. However, susceptibility to Pavlovian influence is not always strong at the individual level [16]. It remains unclear whether or not transfer effects (motivational and/or interference-related) occur in all individuals. Speculatively, some people may experience more subtle degrees of susceptibility to Pavlovian interference not measurable by our task. Alternatively, some individuals may easily overcome interference effects by employing more pronounced top-down control than others. As such, further research is warranted to address the parallels between motivation and PIT interference as well as avoidance behavior and response inhibition. The latter could begin to be rectified by creating a task version that only embodies response inhibition as the rejection criterion.

Discussion of the Full Transfer Task

We introduce two versions of a novel "full transfer" PIT task utilizing gustatory conditioning with alcohol and nonalcohol rewards. We successfully designed a task that elicits specific PIT, such that the alcohol- and juice-associated cues selectively primed their respective choice outcomes during the PIT phase. The immediate, gustatory rewards delivered into the mouth of the participant are a facet of the task design that is unique so far with respect to PIT tasks in humans. The monetary version resulted in what appear to be stronger specific PIT effects, as evidenced by the higher specific PIT scores (Fig. 6c and online suppl. Fig. S3C) despite having the same specific PIT components in both versions. Examining the specific PIT scores, one can see that 66.6% of the gustatory sample and 91.3% of the monetary sample engaged in specific PIT (i.e., a positive score). The main difference between the two versions lies in the Pavlovian conditioning, as there were 4 different flavors to consume in the gustatory version and only 2 in the monetary version. The consumption of the additional gustatory stimuli (to test general PIT) could have led to overgeneralization, disrupting these associations enough to have weakened the specific PIT effects at the group level.

There was an overall preference for the juice reward across both versions. In the gustatory version, the juice button represented 70.8% of all choice outcomes, whereas the alcohol button represented 20.9%. In the monetary version, the juice versus alcohol proportions were 67.7% and 26.5%, respectively. This could be due to the perceived valence of the alcohol and juice rewards. Even though the pleasantness of both gustatory rewards was matched at the beginning of the study, many participants reported that the alcohol reward (for example, wine) acquired a negative valence throughout the study due to the continuous juxtaposition of flavors, citing instances of amplified unpleasantness in stark contrast to the sweetness of the juice despite flavor neutralizations between trials. As outlined in Table 1, most participants in our sample had low AUDIT scores, so it remains to be tested whether or not the preference for the alcohol reward would be higher in an AUD population.

Regarding the mechanisms of general PIT, the second juice reward cues enhanced instrumental responding compared to the neutral condition in the gustatory version. Similar results were observed in the monetary version concerning the Pavlovian cues representing monetary gain and loss. It is important to note that the general PIT effect sizes vary (gustatory: $\eta_p^2 = 0.09$, monetary: $\eta_p^2 = 0.17$), although they do not differ statistically. It is possible that the gustatory rewards were not as salient as monetary outcomes and may not have been rewarding enough or worth the expenditure of effort to receive them. To identify the role that subjective value plays in PIT and reward type, one study compared monetary, food, and social approval rewards and determined that the strength of the PIT effect was not dependent on reward type, but rather, it was modulated by the subjective value of the reward [37]. As both monetary and food cues are established appetitive reinforcers, it is likely that the subjective value modulated the PIT effects we observed. Since the mean difference scores did not differ statistically, we believe that the observed differences in effect size can be explained by the tasks; however, due to the between-subject design, we also cannot exclude that observed differences are at least partly explained by the sampling.

Moreover, it is difficult to interpret the general PIT results of the gustatory version. When taking the instrumental choice into account, it appears as though the juice-associated cue selectively motivates responding via the juice button, but an exploratory analysis did not reveal an interaction. As both cues are associated with juice, the interpretation of these general transfer effects is not very straightforward; one could argue that there is some degree of selective transfer.

In Meemken and Horstmann's [11] appetitive full transfer PIT task, they were unable to elicit a general PIT effect, citing various reasons including participant confusion and the complexities of testing both transfer types at once. While the results of our monetary task version reflect a successful elicitation of both types of transfer under nominal extinction, we cautiously interpret the general PIT results. As shown in Figure 7c (and online suppl. Fig. S4C), there are some participants in both samples that are profoundly affected by the CSs (6 in the gustatory version and 3 in the monetary version); however, 65.2% (monetary) and 66.6% (gustatory) showed an effect in the expected direction. This is a known and ongoing issue regarding the assessment of general PIT effects at the group level. When general PIT effects are observed, they have either small effect sizes [17, 21] or high variance. As some people are profoundly affected by Pavlovian cues, it is worth discussing the role of general PIT in individual difference research in the addiction field and beyond. The question remains as to whether traditional behavioral PIT tasks are sensitive enough to assess individuals that are not profoundly affected by the Pavlovian cues. The field would additionally benefit from further exploration of the role or relevance of general PIT (other than specific PIT) in addiction research.

Directly comparing the effect sizes between our single-lever PIT and the general PIT component of our full transfer task, it becomes evident that the single-lever task elicited much stronger effects ($\eta_p^2{}_{gustatory} = 0.09$ and $\eta_p^2{}_{monetary} = 0.17$ vs. $\eta_p^2{}_{button\text{-}box} = 0.29$ and $\eta_p^2{}_{joystick} = 0.31$). One reason might be that our single-lever PIT design does not only capture general PIT, as there were monetary rewards and losses during both the instrumental and Pavlovian phases [9]. Our single-lever PIT task may also have specific components that work in synergy with the general components, which results in the high effect sizes we observed.

Limitations and Conclusion

A limitation upon which future studies can improve is related to the alcohol rewards in the full transfer paradigm, as there were difficulties in translating this aspect from animal studies. While we offered a range of alcoholic rewards, our sample found them to be generally aversive. Future studies could improve the alcoholic drink offerings to be more representative of the variety of tastes or offer an alternative nonalcoholic reward that does not contrast so much in flavor.

Another minor limitation of the full transfer paradigm is that the experimental design does not control for no-response trials, which invites the opportunity for an unmotivated participant to withhold all responses during the transfer phase; this renders their dataset useless for the purpose of analyzing transfer effects. Some participants in our sample (14 people or 12% of the original sample) displayed this behavior, resulting in excluded datasets. Future studies could mitigate this limitation by incorporating a more engaging goal-directed task in the instrumental learning phase.

In conclusion, we establish two different PIT tasks that were designed to address limitations of our past work. With our single-lever PIT task, we established the joystick as a promising response device and addressed our inability to assess avoidance behavior. In our full transfer task, we explored observed differences based on the type of reward received, while successfully demonstrating specific and general transfer using gustatory alcohol rewards. In the future, we will be able to incorporate this task when investigating whether motivation to obtain alcohol rewards is enhanced by Pavlovian cues experimentally paired with alcohol and/or other appetitive cues in clinical populations. These two tasks, therefore, provide a foundation for us to further explore PIT and understand its underpinning mechanisms and connections to addiction.

Acknowledgments

We are grateful to Dorothee Scheuermann, Linda Engelhardt, Esther Preuschhof, Anne Maria Dörfler, Miriam Schmitz, and Mariana Plumbohm for their assistance in data collection.

Statement of Ethics

Ethical approval was obtained by the Ethics Commission of the Technische Universität Dresden (Application: EK512122018). Written informed consent was obtained prior to participation in this study. All participants were informed of their right to withdraw from the study at any time, and all relevant information about data protection, security, and anonymization was provided. As the full transfer task involved alcohol consumption, participants under the age of 18 were barred from participation.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

This study was supported by the German Research Foundation (DFG: Deutsche Forschungsgemeinschaft project numbers 402170461 [TRR 265: Losing and Regaining Control over Drug Intake: Trajectories, Mechanisms, and Interventions], 186318919 [FOR 1617: Learning and Habitization as Predictors of the Development and Maintenance of Alcoholism], and 178833530 [SFB 940: Volition and Cognitive Control: Mechanisms, Modulators and Dysfunctions]).

Author Contributions

Matthew J. Belanger drafted the manuscript, collected data, aided in study design and implementation, performed the data analysis, and read, reviewed, and approved the final manuscript. Hao Chen collected data, aided in study design and implementation, provided IT support, helped code the single-lever task, aided in the analysis, and read, reviewed, and approved the final manuscript. Angela Hentschel collected data, aided in study design and implementation, and read, reviewed, and approved the final manuscript. Maria Garbusow conceptualized the study and tasks, aided in the design and implementation, and read, reviewed, and approved the final manuscript. Claudia Ebrahimi and Hilmar G. Zech aided in the study design and implementation, and read, reviewed, and approved the final manuscript. Felix G. Knorr provided IT support, coded the full transfer task, and read, reviewed, and approved the final manuscript. Maximilian Pilhatsch and Andreas Heinz helped to conceptualize the study and tasks, and read, reviewed, and approved the final manuscript. Michael N. Smolka conceptualized the study, aided in the study design, obtained ethical approval, aided in the interpretation of the results, and read, reviewed, and approved the final manuscript.

Data Availability Statement

The data reported in this article are available for download via the following link: https://osf.io/5yja4/.

References

1 Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet. 2009 Jun;373(9682):2223–33.
2 Garbusow M, Schad DJ, Sommer C, Jünger E, Sebold M, Friedel E, et al. Pavlovian-to-instrumental transfer in alcohol dependence: a pilot study. Neuropsychobiology. 2014;70(2):111–21.
3 Robbins TW, Everitt BJ. Drug addiction: bad habits add up. Nature. 1999 Apr;398(6728):567–70.
4 Sekutowicz M, Guggenmos M, Kuitunen-Paul S, Garbusow M, Sebold M, Pelz P, et al. Neural response patterns during Pavlovian-to-instrumental transfer predict alcohol relapse and young adult drinking. Biol Psychiatry. 2019 Dec;86(11):857–63.
5 Estes WK. Discriminative conditioning. I. A discriminative property of conditioned anticipation. J Exp Psychol. 1943;32(2):150–5.
6 Rescorla RA, Solomon RL. Two-process learning theory: relationships between Pavlovian conditioning and instrumental learning. Psychol Rev. 1967;74(3):151–82.
7 Talmi D, Seymour B, Dayan P, Dolan RJ. Human Pavlovian instrumental transfer. J Neurosci. 2008 Jan;28(2):360–8.
8 Campese VD, Kim IT, Kurpas B, Branigan L, Draus C, LeDoux JE. Motivational factors underlying aversive Pavlovian-instrumental transfer. Learn Mem. 2020 Nov;27(11):477–82.
9 Cartoni E, Balleine B, Baldassarre G. Appetitive Pavlovian-instrumental transfer: a review. Neurosci Biobehav Rev. 2016 Dec;71:829–48.
10 Geurts DE, Huys QJ, den Ouden HE, Cools R. Aversive Pavlovian control of instrumental behavior in humans. J Cogn Neurosci. 2013 Sep;25(9):1428–41.
11 Meemken MT, Horstmann A. Appetitive Pavlovian-to-instrumental transfer in participants with ormal-weight and obesity. Nutrients. 2019 May;11(5):1037.
12 Hebart MN, Gläscher J. Serotonin and dopamine differentially affect appetitive and aversive general Pavlovian-to-instrumental transfer. Psychopharmacology. 2015 Jan;232(2):437–51.
13 Huys QJM, Cools R, Gölzer M, Friedel E, Heinz A, Dolan RJ, et al. Disentangling the roles of approach, activation and valence in instrumental and pavlovian responding. PLoS Comput Biol. 2011 Apr;7(4):e1002028.
14 Ostlund SB, Marshall AT. Probing the role of reward expectancy in Pavlovian-instrumental transfer. Curr Opin Behav Sci. 2021 Oct;41:106–13.
15 Balleine BW. The cognitive control of goal-directed action: how predictive learning affects Choice. In: Wang R, Pan X, editors. Advances in cognitive neurodynamics (V). Singapore: Springer Singapore; 2016. p. 27–33.
16 Chen H, Nebe S, Mojtahedzadeh N, Kuitunen-Paul S, Garbusow M, Schad DJ, et al. Susceptibility to interference between Pavlovian and instrumental control is associated with early hazardous alcohol use. Addict Biol. 2021 Jul;26(4):e12983.
17 Watson P, Wiers RW, Hommel B, de Wit S. Working for food you don't desire. Cues interfere with goal-directed food-seeking. Appetite. 2014 Aug;79:139–48.
18 Everitt BJ, Robbins TW. Drug addiction: updating actions to habits to compulsions ten years on. Annu Rev Psychol. 2016 Jan;67(1):23–50.
19 Holmes NM, Marchand AR, Coutureau E. Pavlovian to instrumental transfer: a neurobehavioural perspective. Neurosci Biobehav Rev. 2010 Jul;34(8):1277–95.
20 Allman MJ, DeLeon IG, Cataldo MF, Holland PC, Johnson AW. Learning processes affecting human decision making: an assessment of reinforcer-selective Pavlovian-to-instrumental transfer following reinforcer devaluation. J Exp Psychol Anim Behav Process. 2010;36(3):402–8.
21 Quail SL, Morris RW, Balleine BW. Stress associated changes in Pavlovian-instrumental transfer in humans. Q J Exp Psychol. 2017 Apr;70(4):675–85.
22 Huys QJM, Gölzer M, Friedel E, Heinz A, Cools R, Dayan P, et al. The specificity of Pavlovian regulation is associated with recovery from depression. Psychol Med. 2016 Apr;46(5):1027–35.
23 Garbusow M, Schad DJ, Sebold M, Friedel E, Bernhardt N, Koch SP, et al. Pavlovian-to-instrumental transfer effects in the nucleus accumbens relate to relapse in alcohol dependence: PIT and alcohol relapse. Addict Biol. 2016 May;21(3):719–31.
24 Alarcón DE, Delamater AR. Outcome-specific Pavlovian-to-instrumental transfer (PIT) with alcohol cues and its extinction. Alcohol. 2019 May;76:131–46.
25 LeBlanc KH, Ostlund SB, Maidment NT. Pavlovian-to-instrumental transfer in cocaine seeking rats. Behav Neurosci. 2012;126(5):681–9.
26 Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction. 1993 Jun;88(6):791–804.
27 Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Addiction. 1991 Sep;86(9):1119–27.
28 Brainard DH, Vision S. The psychophysics toolbox. Spat Vis. 1997;10(4):433–6.
29 Kleiner M, Brainard D, Pelli D. What's new in Psychtoolbox-3? 2007.
30 Pelli DG, Vision S. The VideoToolbox software for visual psychophysics: transforming numbers into movies. Spat Vis. 1997;10(4):437–42.
31 Knorr FG, Petzold J, Marxen M. PyParadigm: a Python library to build screens in a declarative way. Front Neuroinformatics. 2019 Aug;13:59.
32 RStudio Team. RStudio: integrated development for R. Boston, MA: RStudio, Inc.; 2020. Available from: http://www.rstudio.com/.
33 Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015;67(1).
34 Driscoll RL, de Launay KQ, Fenske MJ. Less approach, more avoidance: response inhibition has motivational consequences for sexual stimuli that reflect changes in affective value not a lingering global brake on behavior. Psychon Bull Rev. 2018 Feb;25(1):463–71.
35 Zech HG, Rotteveel M, van Dijk WW, van Dillen LF. A mobile approach-avoidance task. Behav Res Methods. 2020 Oct;52(5):2085–97.
36 Hommel B. The Simon effect as tool and heuristic. Acta Psychol. 2011 Feb;136(2):189–202.
37 Lehner R, Balsters JH, Herger A, Hare TA, Wenderoth N. Monetary, food, and social rewards induce similar pavlovian-to-instrumental transfer effects. Front Behav Neurosci. 2017;10:247. Available from: https://www.frontiersin.org/article/10.3389/fnbeh.2016.00247.