Neuropsychobiology

Review Article

Neuropsychobiology 2022;81:418–437
DOI: 10.1159/000525579

Received: September 1, 2021
Accepted: May 13, 2022
Published online: July 15, 2022

Pavlovian-to-Instrumental Transfer across Mental Disorders: A Review

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Keywords
Pavlovian-to-instrumental transfer · Dimensional psychopathology · Mental disorders · Reliability

Abstract
A mechanism known as Pavlovian-to-instrumental transfer (PIT) describes a phenomenon by which the values of environmental cues acquired through Pavlovian conditioning can motivate instrumental behavior. PIT may be one basic mechanism of action control that can characterize mental disorders on a dimensional level beyond current classification systems. Therefore, we review human PIT studies investigating subclinical and clinical mental syndromes. The literature prevails an inhomogeneous picture concerning PIT. While enhanced PIT effects seem to be present in non-substance-related disorders, overweight people, and most studies with AUD patients, no altered PIT effects were reported in tobacco use disorder and obesity. Regarding AUD and relapsing alcohol-dependent patients, there is mixed evidence of enhanced or no PIT effects. Additionally, there is evidence for aberrant corticostriatal activation and genetic risk, e.g., in association with high-risk alcohol consumption and relapse after alcohol detoxification. In patients with anorexia nervosa, stronger PIT effects elicited by low caloric stimuli were associated with increased disease severity. In patients with depression, enhanced aversive PIT effects and a loss of action-specificity associated with poorer treatment outcomes were reported. Schizophrenic patients showed disrupted specific but intact general PIT effects. Patients with chronic back pain showed reduced PIT effects. We provide possible reasons to understand heterogeneity in PIT effects within and across mental disorders. Further, we strengthen the importance of reliable experimental tasks and provide test-retest data of a PIT task showing moderate to good reliability. Finally, we point toward stress as a possible underlying factor that may explain stronger PIT effects in mental disorders, as there is some evidence that stress per se interacts with the impact of environmental cues on behavior by selectively increasing cue-triggered wanting. To conclude, we discuss the results of the literature review in the light of Research Domain Criteria, suggesting future studies that comprehensively assess PIT across psychopathological dimensions.

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Introduction

Pavlovian-to-instrumental transfer (PIT) is a naturally occurring phenomenon: individuals integrate environmental information to act and make decisions [1]. PIT effects describe the impact of environmental cues in guiding behavior – more specifically, PIT is a measure of the effect of Pavlovian conditioned cues (CSs) on independent instrumental responses to obtain a certain reward or avoid a certain punishment. Thus, it is a phenomenon relevant for understanding decision-making, instrumental choice behavior, putative irrational behavior, and, finally, the psychopathology of behavior. Consequently, PIT effects can be measured in healthy individuals, such as in consumer shopping behavior or marketing studies [2, 3], and are not exclusively a phenomenon of dysfunctional decisions, aberrant behavior, or psychopathology per se.

PIT paradigms usually consist of three or four parts. The first two parts comprise instrumental and Pavlovian conditioning and the third part is the transfer phase. Here, Pavlovian CSs occur in the environment (e.g., a certain cage in animal studies or background cues on the computer screen in human studies) while the individual is asked for the instrumental behavior again, such as lever presses in animal studies or button presses in human studies. The fourth part can test explicit or implicit knowledge of the Pavlovian CSs to gage learning success (mainly in human studies). The third part is the most relevant as it provides the influence of Pavlovian cues on independent instrumental behavior, which constitutes the PIT effect. Appetitive Pavlovian cues usually intensify instrumental approach behavior and reduce instrumental avoidance behavior, while vice versa for aversive Pavlovian cues [4]. To avoid further learning, this part is usually performed under (nominal) extinction. Importantly, the outcomes associated with instrumental behavior (i.e., successfully obtaining a reward with response 1 vs. unsuccessfully with response 2) do not depend on the presence of Pavlovian cues. Hence, the success of instrumental behavior is independent of the presence of Pavlovian cues (e.g., in the background of a visual task presentation), and any biasing of instrumental behavior by Pavlovian cues toward a certain response (e.g., in the example above, the unsuccessful response 2) does not lead to a different outcome of the respective instrumental response. PIT paradigms can distinguish between general and specific forms of transfer (see also Belanger et al., this issue). In general PIT (gPIT), Pavlovian cues exert control over behavior in general, i.e., irrespective of the specific rewards associated with the Pavlovian cue versus the respective instrumental response, while in specific PIT (sPIT) tasks, Pavlovian cues associated with a certain reward especially motivate independent instrumental behavior that is related to the same reward [5]. PIT paradigms can occur in different experimental setups [1]: single-lever PIT (presumably gPIT according to animal studies [see 1], but missing studies in humans [see 6]), sPIT, and full transfer PIT (measures gPIT and sPIT effects both in one paradigm).

When investigating mental disorders, e.g., addictions, habit formation (i.e., a shift from goal-directed to habitual behavior) is a key mechanism that could be elucidated in PIT paradigms. Several competing explanations try to describe how gPIT and sPIT may be associated with goal-directed versus habitual decision-making (for review, see [1, 6]). Habitual versus goal-directed decisions can best be distinguished with revaluation (satiation/devaluation) paradigms. Here, habitual decisions are reflected by insensitivity to revaluation, while goal-directed decisions are sensitive to revaluation [6, 7]. In animal studies, gPIT is evidenced to be sensitive to revaluation procedures (e.g., [8]); however, the issue appears to be more complex for gPIT in humans, as studies on this regard are limited to date, and humans may generally display an increased impact of explicit knowledge compared to rodents when performing PIT tasks [1]. On the other hand, sPIT has often been described to be insensitive to devaluation (e.g., [8]). In this context, effects of Pavlovian cues on specific responses may be mediated by sensory aspects of the outcome associated with a specific Pavlovian cue, so the cues activates an outcome expectancy that triggers the specific response previously associated with this outcome [7]. Other accounts questioned the insensitivity of sPIT to devaluation, particularly in humans, and suggested that explicit knowledge may guide response selection [6]. Moreover, the specific and general effects of Pavlovian CSs on instrumental behavior may change over time: during the development of addictive behavior, Everitt and Robbins [9] suggested that with extended exposure to drugs, Pavlovian CSs fail to retrieve the specific identity of the drug and instead only facilitate the retrieval of affectively positive drug effects, thus promoting a shift from sPIT to gPIT. Altogether, the heterogeneity of results could be caused by the high variability of PIT procedures per se, as well as by conceptual differences between animal and human studies [6]. Thus, the evaluation of sPIT versus gPIT and its relation to goal-directed versus habitual behavior require a closer look on procedures and measurements used in each study.

Finally, PIT paradigms differ with respect to types of rewards used for instrumental and Pavlovian conditioning: primary (e.g., food) or secondary reinforcers (e.g., money in human studies), or in the context of disease-related or unrelated reinforcers (e.g., beer points vs. chocolate points for investigating PIT effects in alcohol consumers, see [10]). For an example of single- and full-transfer PIT task designs using different types of reinforcers, see Belanger et al. (this issue).

PIT has been assessed in animal and human studies on behavioral and neural levels (for reviews see e.g., [1, 3, 6, 11–13]). Taken together, there is a long research tradition in investigating PIT effects in animals; however, assessing PIT in humans is a rather young field of research, especially in consideration of subclinical or clinical mental phenomena. Despite this, PIT might help to better explain clinical phenomena, such as the loss of control over drinking in patients with alcohol dependence, avoidance behavior in patients with anxiety disorders, overeating in obesity, food restriction in anorexia nervosa (AN), or social withdrawal in patients with depression. The aims of this review were (i) to summarize findings from previous PIT studies with a focus on human psychopathology, (ii) to assess the reliability of the PIT paradigm as a key element for the evaluation of past and future research in the clinical sector, and (iii) integrate these findings into a dimensional view of mental disorders.

PIT across Mental Disorders

Addictions

According to the *incentive-sensitization theory*, environmental cues associated with the experience of drug consumption can have a strong motivational impact on cue-triggered *wanting* of a drug reward [14–16]. A stronger *wanting* of the drug itself – in contrast to *liking* – has been shown in addicted animals and in human studies with patients suffering from addiction [17]. Consequently, stimuli previously associated with drug rewards potentially influence craving, promote approach behavior, and enhance relapse probability, as indirectly investigated in so-called cue-reactivity studies. In these studies, patients are confronted with drug-related cues. It has been observed that patients with addiction compared to healthy controls (HC) show stronger physiological, behavioral, and neurobiological responses to such cues (e.g., [18, 19]). Such responses are further predictive of treatment outcomes, such that stronger responses predict worse treatment outcomes (e.g., [20, 21]). With respect to alcohol addiction, environmental CSs (e.g., clinking of glasses [22]) can trigger instrumental behavior such as alcohol seeking and intake. Moreover, the *incentive-sensitization theory* has also been adapted to non-substance-related disorders as well as the phenomenon of overeating [15]. However, cue-reactivity studies only represent the result of a learning process that has already taken place, thereby providing only indirect information on how drug-associated CSs can influence behavior (e.g., via measures of prospective relapse). There is evidence how instrumental and Pavlovian mechanisms are involved in substance use disorders (SUDs), including AUD [23]. However, by assessing the impact of environmental Pavlovian cues on instrumental behavior, PIT paradigms provide the possibility to measure the direct influence of both mechanisms in one task in the laboratory.

In addition to the *incentive-sensitization theory*, habit formation could play an important role in the development and maintenance of addiction [9]. It is assumed that formerly goal-directed recreational drug use shifts toward habitual drug seeking behavior [24]. As mentioned above, PIT procedures are potentially capable to explain habit formation.

Alcohol Use Disorder

In connection with AUD, PIT has been investigated in several social drinking and clinical samples. In the context of this review, a social drinker is considered someone who regularly drinks alcohol in a variety of social settings. However, drinking does not disrupt their lives or create health problems. Martinovic et al. [10] investigated a sPIT task using alcohol and chocolate rewards; social drinkers were assessed with the alcohol use disorder identification test (AUDIT). They observed that instrumental responding increased for congruous trials when images of alcohol were combined with alcohol reward associated instrumental behavior, indicating evidence for sPIT with alcohol-related cues in humans. However, this alcohol sPIT effect did not correlate with AUDIT scores, suggesting that alcohol sPIT is not a measure for hazardous drinking [10]. Hardy et al. [25] wanted to understand the mechanisms of how cue-reactivity can potentially influence drug-seeking responses, i.e., how stimuli (S) influence a response (R) associated with a respective outcome (O), by using a biconditional sPIT task with alcohol and food rewards in social drinkers. In the instrumental phase, two discriminative stimuli conditions were learned. In one condition, pressing the left button would lead to an alcohol O, while pressing the right button would lead to a food O; in the other condition, these connections

were reversed. In the transfer phase, instrumental behavior had to be shown while alcohol or food pictures were presented. The biconditional approach allowed the discrimination between congruous and incongruous choices. They [25] found evidence that Pavlovian CSs primed congruous outcome choices; hence, alcohol pictures specifically primed alcohol-associated choices, while pictures of food specifically primed food-associated choices, respectively. These results emphasize a hierarchical S:R-O knowledge [26], meaning that S (here alcohol cues) causes the expectancy of an O (here alcohol) and therefore primes the R (here the behavioral choice in favor of alcohol approaching). The authors conclude that the results speak against an S-O-R account of cue reactivity, which assumes that binary connections between S-O and O-R are built in the instrumental and Pavlovian phases, which lead to an associative chain (S-O-R) [27]. Therefore, the presentation of a specific S evokes the specific O and leads to the specific R, irrespective of contingency knowledge [25]. Rose et al. [28] examined the impact of alcohol cues on alcohol-associated instrumental behavior in social drinkers. In a sPIT task, participants had to choose between receiving points for a soft drink or an alcoholic drink. Prior to the transfer phase, a devaluation task was performed, where one group of participants received an alcoholic drink infused with a bitter solution (devaluation group), while another group of participants received an unadulterated alcoholic drink (control group). While alcohol-seeking behavior per se was reduced in the devaluation group, sPIT was not. Thus, the choice behavior toward alcohol appears to be driven by the present value of the drink and hence is reduced if the taste is aversive (as in the devaluation procedure), while the specific impact of the presented cue does not depend upon the associated reward value [28]. Mahlberg et al. [98] investigated cue-elicited craving in a sPIT task with alcohol and chocolate cues. Young male beer drinkers were assessed with the AUDIT. They showed that alcohol cues enhanced craving and a sPIT effect was demonstrated by increased key presses during the transfer phase, which is in line with results from the above-mentioned studies [10, 25]. Contrary to initial expectations, PIT measures and craving were not correlated. However, alcohol sPIT and the belief in the expectancy of alcohol were positively correlated.

In a previous study by our work group, we examined how the strength of instrumental responding is influenced by background Pavlovian CSs, predicting action-independent rewards and losses in a sample of young healthy male social drinkers. During the transfer phase, participants performed a previously learned money-related instrumental response under nominal extinction during the presentation of appetitive (previously associated with monetary reward), aversive (previously associated with monetary loss), or neutral Pavlovian stimuli. We observed that gPIT (i.e., a higher/lower instrumental response rate with positively/negatively valued background stimuli) was enhanced in high-compared to low-risk social drinkers. Moreover, the PIT effect was associated with an increased polygenic risk for alcohol consumption and, on a neurofunctional level, with enhanced amygdala activation [29]. We suggest a non-drug-related PIT effect to be a predisposing factor for developing problematic alcohol use with genetic and neurofunctional biomarkers that might further point to habitual processes. Besides, our work group used the same task to compute instrumental error rates and further investigated neurofunctional underpinnings of congruent and incongruent conditions in the same cohort. The sample was again separated into groups of high-risk and low-risk social drinking men. On average, both groups showed a significant gPIT effect, reflected by higher error rates when Pavlovian cues and instrumental stimuli were in conflict compared with congruent trials. The strength of behavioral gPIT correlated with neural activation in the ventral striatum and the dorsomedial and lateral prefrontal cortices (dmPFC and lPFC, respectively). Additionally, connectivity between the ventral striatum and the lPFC was decreased in the high-risk group during the incongruent condition [30]. Taken together, PIT studies in samples of social drinkers showed evidence of alcohol PIT effects, while there was no association with craving or AUDIT. However, using a non-drug-related PIT task, there is evidence of enhanced gPIT effects in people exhibiting risky alcohol consumption along with neural and genetic underpinnings.

In addition to subclinical samples, several studies investigated the links between AUD and PIT in patient samples. In 2014, our group observed the first evidence for PIT effects in recently detoxified alcohol-dependent (AD) patients and matched controls in a single-lever alcohol- and money-related PIT task. Moreover, we reported moderate-to-good robustness and temporal stability of our PIT effects [31]. AD patients more frequently showed PIT effects. Moreover, the PIT effect was stronger in AD patients in response to aversive CSs (conditioned suppression), but there was no group difference in response to appetitive CSs. The findings support an association between AD and an increased propensity toward PIT [31]. Additionally, we could show that gPIT-related

BOLD signals predict prospective alcohol intake and relapse in AD patients after detoxification [32]. Further, Sommer et al. [33] reported that positively-valenced background CSs can provoke dysfunctional instrumental approach behavior in AD patients and matched controls using, again, a single-lever alcohol- and money-related PIT task; this result was found to be especially pronounced in impulsive AD patients. AD patients showed stronger monetary PIT and a reduced alcohol PIT effect [33]. Notably, further investigations with group comparison between matched controls and AD patients, where relapsers and abstainers were distinguished, showed that prospective relapsers particularly failed to correctly perform in trials where the instrumental stimulus required inhibition while a Pavlovian background CS indicated a monetary gain [34]. Under that condition, relapsers approached the instrumental stimulus independently of the expected punishment. In contrast, no difference in PIT was found between relapsers and abstainers when alcohol-related background stimuli were presented. Sommer et al. [34] argue that the failures in inhibiting an aversive stimulus in favor of approaching an appetitive non-alcohol-related context cue might reflect dysfunctional aberrant learning mechanisms in patients that relapse. Adding to the picture, Schad et al. [16] found (in a single-lever PIT task) inhibitory effects of alcohol-related backgrounds on approach behavior in detoxified AD patients but not in HC. Interestingly, this gPIT effect was stronger in prospective abstaining compared to relapsing patients. The behavioral PIT effect was also reflected in associated activation patterns in the nucleus accumbens. These effects were only present in abstinent patients and in individuals with a mild symptom severity but no severe dependence, suggesting that reduced instrumental approach behavior in an alcohol-related environment is a protective factor for relapse. An fMRI study by Sekutowicz et al. [35] examined whether or not neural activation clusters during the transfer phase of an alcohol-related single-lever PIT task can predict relapse in AD patients within the first year after detoxification. Using a machine learning classification scheme, they showed that relapsing and abstinent AD patients can be detected with an overall accuracy of 71.2%. Additional analysis revealed that the classification was predominantly based on voxel clusters in the medial PFC. Further, they applied the established classifier in a sample of young adult men to see if the algorithm generalizes. It was demonstrated that the classifier was able to predict if the young men were able to reduce their alcohol consumption at a 12-month follow-up. Sekutowicz et al. [35] suggest that brain response during PIT could be a useful marker for the prediction of future alcohol consumption in AUD, and the results emphasize the role of the medial PFC as important region to distinguish differences in instrumental behavior.

Sebold et al. [36] further investigated potential biomarkers for the wanting of drug-related cues according to the *incentive-sensitization theory* [14]. They investigated the A118G polymorphism of the OPRM1 gene, money-related PIT, and relapse rates in recently detoxified AD patients, as well as two independent HC samples. They observed increased PIT effects in carriers of the minor OPRM1 G-allele (G+) gene expression in all groups, independently. They reported significant interactions between OPRM1 polymorphism and PIT in relapsing AD patients but not in abstinent ones. These results point toward connections between OPRM1 polymorphisms and PIT effects.

Van Timmeren et al. [37] investigated PIT effects and outcome devaluation. In their fMRI study, AD patients and matched HC, participated in a PIT task with food outcomes and a devaluation test. In comparison to the reported stronger PIT effects in AD patients and prognostic values of PIT for relapse measures as mentioned above, they did not find connections between sPIT and gPIT, AUD severity or duration, and no deficits in corticostriatal regions in the AD group. Regardless, sPIT and gPIT were strongly present in both groups and outcome devaluation successfully reduced instrumental behavior. Additionally, fMRI analysis revealed mediations between both PIT measures and neural activity in areas like the amygdala, the pallidum, and subcortical parts of the striatum. The results intend normal functioning in goal-directed learning in AD and capability to integrate action-outcome relations. Nevertheless, the authors outline, that deficits in the used PIT paradigm and a small sample size could explain the lack of group differences in their findings [37].

Tobacco Use Disorder

In addition to AD and high-risk drinking behaviors, PIT has been investigated in several studies concerning tobacco use disorder (TUD) including clinical and subclinical tobacco consumption (i.e., heavy and occasional smokers). Although there is a declining trend concerning the global use of tobacco and prevalence rates for TUD [38], smoking remains one of the most serious risk factors to human health, especially considering that nicotine is a highly addictive substance [38, 39]. Therefore, it is of high interest to investigate and understand potential mechanisms underlying tobacco consumption as well as potential treatment options for smoking behaviors in humans.

Several studies investigated the PIT effect in smoking individuals (for an overview see studies included in [1]). In the first study concerning the underlying mechanisms of smoking behaviors, Hogarth et al. [26] found a sPIT effect in humans with regular tobacco consumption patterns (i.e., at least five cigarettes per day) regarding stimuli related to tobacco and money. Importantly, this PIT effect was only present in participants that reported to be aware of the outcome in consequence of the specific stimulus. Furthermore, the cigarette-associated stimulus enhanced the tobacco-seeking response compared to the money-seeking response during the transfer phase. Hogarth et al. [26] hypothesized that this sPIT effect is mediated by the participants' awareness of the relationship between a certain stimulus and associated outcome, suggesting that a substantial mediator in the drug-seeking behavior of regular smokers may be drug expectancy rather than habitual learning processes. A further experiment by Hogarth et al. [40] concerned differences in sPIT effect between daily and non-daily smokers. Both groups showed sPIT PIT effects (tobacco- and chocolate-related cues) respectively but did not differ significantly in their sensitivity to the transfer of stimulus-control over goal seeking. Therefore, the authors conclude that tobacco dependence could be explained by an increased drug appraisal shown by a more frequent instrumental choice for the drug. Nevertheless, the possibility that habitual processes may play a role in later clinical stages of tobacco dependence was mentioned [40].

A more recent study by Manglani et al. [41] tested for sPIT effect in smokers who were asked to remain abstinent for 12 h before the experiment. Participants learned specific associations between stimuli preceding either cigarette or food outcomes. The cigarette-cues exceeded the food-cues concerning drug-seeking behaviors in the sPIT task during deprivation, and thus, had a stronger effect over reward-seeking responses. While the lack of a control group limits the impact of the result, the authors conclude that this might be informative for abstinence treatment as there is evidence in deprived smokers (but here without the aim of abstinence) for stronger impact of smoking cues on drug-seeking behavior compared to alternative nondrug-associated food cues.

In a further study, focusing not only on underlying drug-seeking mechanisms of smoking behavior but also on potential influences on this behavior, Hogarth et al. [42], investigated the transition from goal-directed to habitual control over tobacco seeking in smokers. More precisely, a nominal PIT task was assessed including tobacco- or chocolate-related outcomes, followed by a revaluation procedure. Afterward, participants were instructed that they could drink either water or alcohol after the session. Results showed that alcohol expectancy, as an alternative reinforcer, eradicated goal-directed control of tobacco seeking during the extinction phase. However, it did not affect stimulus-control and thus did not impact sPIT effects. These findings suggest phasic transitions from goal-directed to habitual control over tobacco seeking by means that they can co-occur and that phasic transitions can be accelerated by alternative rewards like alcohol [42].

Next to the influence of alternative rewards, Steins-Loeber et al. [43] tested the potential effect of subjective stress (induced by the Socially Evaluated Cold Pressure Test) on sPIT effects in moderate smokers. The specific stimuli in the study were either chocolate- or cigarette-associated. Findings confirmed a sPIT effect in contingency-aware participants for both stimuli, respectively. However, stress neither increased nor diminished the sPIT effects and, therefore, showed no influence on tobacco- or chocolate-related instrumental responding.

Finally, three studies addressed the PIT effect in smokers regarding its potential implications for treatment. The first of these studies investigated the effect of nicotine replacement therapy (NRT) nasal spray on the PIT effect in daily and non-daily smokers [44]. The specific stimuli within the paradigm were related to either a chocolate or a tobacco reward. The study is based on contemporary learning theory assuming that two separate controllers add up to the behavior of drug-seeking [45]. The NRT procedure weakened merely one of the two controlling components of drug-seeking which is participants' goal-directed behavior (i.e., tobacco choice during extinction). However, it did not affect the second controlling factor which is stimulus-elicited drug-seeking (i.e., transfer-cue-triggered tobacco choice in the PIT task). The dual controller theory further suggests that goal-directed tobacco choice is determined by expected drug-value whereas stimulus-elicited tobacco-seeking is determined by the possible probability of the drug, independent of its value [46]. In a later study, Hogarth et al. [47] addressed the question of potential treatment options that may affect cue-evoked tobacco seeking. In one of their experiments that tested smoking participants, they administered a Pavlovian extinction training after a PIT procedure that included either chocolate- or tobacco-related cues. The results showed no elimination of the learned PIT effect (i.e., stimulus control over goal-directed behavior) by Pavlovian extinction in smokers, compared to its effective abolishment in two further experiments by

discriminative extinction training and propositional hierarchical instructions in a sample of social drinkers. Thus, the authors suggested that drug therapy should rather include the diminishment of response-drug expectancy by cues than Pavlovian cue-exposure therapies [47]. The third study concerning sPIT and treatment for smoking behaviors by Hogarth et al. [48] investigated whether plain versus branded cigarette packs would differently evoke instrumental tobacco seeking and chocolate seeking in a nominal PIT task in smokers. Accordingly, branded packs did prime a higher rate of tobacco seeking in smokers, compared to the plain packs and the no-stimulus condition. Authors hypothesized that this effect may be due to branded cigarette packs eliciting a greater expectation of the tobacco-specific outcome and, therefore, the use of plain packing may reduce smoking in current consumers [48].

Substance Use Disorder

The PIT effect, in the context of (illegal) substance consumption and clinical SUD, has been explored in several animal studies (for an overview, see [22]). To our knowledge, the PIT task in human substance users has only been applied in one study so far investigating a mixed sample of patients suffering from SUD currently in treatment for the use of heroin, alcohol, amphetamines, prescription opiates, and prescription benzodiazepines, as well as a group of HCs [49]. In their research, Hogarth et al. [49] conducted two experiments to examine sPIT effects and outcome devaluation in SUD. In experiment 1, subjects performed a sPIT task with water- or chips-related outcomes. Besides, a water devaluation procedure was performed. In experiment 2, participants completed a more complex task with chocolate and cola outcomes, a cola devaluation procedure, and a sPIT task (i.e., R-O contingencies were randomly switched in each trial and signaled by two specific stimuli). In both experiments, overall significant sPIT effects were reported, but no group differences between the SUD and HC groups were found. Besides, in both experiments devaluation procedures successfully reduced instrumental responding during the transfer phase. The authors discuss the results in context of habit formation and mention that a differentiated study of the various substance groups would be useful because of marked differences in psychotropic effects [49].

Non-Substance-Related Disorders

Non-substance-related disorders suit well to investigate the role of endogenous cognitive changes involved in addiction, such as learning since they do not involve any substance that might interfere with neurocognitive functioning [50]. However, so far only one study has investigated the role of PIT in non-substance-related disorders. Vogel et al. [51] focused on the problematic use of Internet gaming and shopping applications. They used a PIT paradigm to investigate the association between the magnitude of problematic use patterns and sPIT toward gaming and shopping rewards. The paradigm incorporated instrumental learning in the form of repeated button presses by selecting one out of two buttons to obtain either gaming or shopping points (free choice). During the PIT phase, abstract pictures, which were formerly paired with different gaming or shopping pictures, respectively, were shown in the background while the participants once again performed the instrumental task. A sPIT effect was observed for gaming as well as shopping rewards shown by increased response rates and choice preferences. Awareness of experimental contingencies and the strength of expectancy of the Pavlovian reward outcomes, which might be also interpreted as a measure for the strength of associative learning, were found to be positively associated with the gaming sPIT effect as well as the severity of problematic use of Internet gaming. Thus, the authors hypothesized that extensive Internet gaming might specifically strengthen problematic use of such applications by increasing the association between gaming-related stimuli and its reward expectancies. No such interactions were observed between the shopping sPIT and the severity of problematic use of shopping applications.

Eating Disorders

Over-eating, as a major cause of obesity, may be well-explained by the excessive *wanting* as proposed within the *incentive-sensitization theory* for addictions mentioned above [14]. Once highly palatable food becomes excessively *wanted*, it could be highly attention-grabbing and lead to overconsumption [15]. This hypothesis could be tested in the context of the PIT paradigm. Lehner et al. [52] examined differences in sPIT effects between three groups: normal-weight, over-weight, and obese subjects. Interestingly, while the PIT effect was stronger for the over-weight group, this effect was comparable between the normal-weight and obese groups. Consistent with the sPIT effect, the eye-tracking during the Pavlovian conditioning phase indicated that the over-weight group directed more attention to the reward location, regardless of the experimental conditions (reward or neutral condition). The enhanced reactivity to food cues of the over-weight group fits well to *incentive-sensitization theory*,

which indicates that this might be an important intermediate state toward developing obesity. During this stage, people tend to be more sensitive to food cues. However, when these behaviors become habitual, the sensitivity to the environmental cues may decrease. Exploring this intermediate stage or the developmental process may have important implications for intervention. Another view is that the intensity in which people react toward food cues may be dependent on the cue type. Watson et al. [53] assumed that obese individuals, in contrast to normal-weight individuals, may be more susceptible to high-calorie than low-calorie food rewards. A response-prime test showed that the instrumental outcome and the Pavlovian CSs together primed more instrumental responses for the high-calorie food than the low-calorie food in the obese group but not for the normal-weight group. This difference was primarily driven by the lower response toward low-calorie food in the obese group as compared to the normal-weight group. This result thus suggests that obese individuals may find it particularly difficult to make healthy food choices.

Meemken and Horstmann [54] tested gPIT and sPIT within a full PIT paradigm that offered immediate gustatory rewards during the instrumental and Pavlovian training phases instead of food pictures. Overall, a sPIT effect was observed, but a gPIT effect was missing. As pointed out by the authors, the missing gPIT effect could be explained by the setup of the task that drives the participants into responding according to the cue-button combinations instead of responding naturally as in real-world settings. This may call for the development of a full PIT paradigm to test how immediate food rewards influence instrumental behaviors with higher ecological validity. In addition, there was a trend for a less sPIT effect in the obese group. These null results may be explained by less attention directed to low-calorie food and decreased sensitivity to environmental cues once the over-eating behavior had become compulsive. Overall, these mixed findings suggest that it is not as straightforward as one might hypothesize when it comes to examining how food cues influence the ongoing instrumental behavior in obese individuals as assessed with the PIT task, especially when other cognitive mechanisms in addition to the susceptibility of the food cues also play important roles. For example, it was found that the restraint scores, which indicate cognitive efforts to restrict food intake, could predict BMI change after 3 years [54].

Intriguingly, not only high-calorie food can acquire incentive-sensitization, low-calorie food or physical activities could also do and trigger *wanting*, which has been suggested to be the underlying mechanism of AN [55, 56]. Vogel et al. [57] tested this hypothesis in patients with AN and HCs with a sPIT paradigm that offered high- and low-calorie food outcomes. Although participants increased in their responses for both high- and low-calorie food when the corresponding stimuli were presented, this effect was not different between AN and HC groups. Nevertheless, evidence was found supporting the notion that individuals with AN may favor low-calorie food to maintain their weight loss goals; the severity of the eating disorder-related psychopathology was associated with the instrumental responding rate to low-calorie food in the AN group. Another interesting finding from the study indicated that fewer participants with AN were aware of the Pavlovian contingencies as compared to the control group, indicating deficits in the Pavlovian learning in the AN group. However, this result may need replication in a larger study sample.

Obsessive-Compulsive Disorder

One key component of obsessive-compulsive disorder (OCD) is excessive compulsions on the behavioral level, which can be operationalized with instrumental responses to avoid aversive outcomes. Further, environmental cues might have an irrationally high impact on the instrumental behavior, such as intensive, repeated checking behavior (e.g., checking that the stove or lights are off). With the cornerstone of PIT stating that instrumental behavior can be influenced by Pavlovian stimuli due to independent pairings of behavior and stimuli with a common outcome, PIT could help to better explain the nature of OCD. Krypotos and Engelhard [58] conducted the first study on PIT effects in subjects with subclinical levels of OCD separated into two groups, one with low and one with high OCD traits using the Obsessive Compulsivity Inventory – Revised [59]. An avoidance-based PIT task was utilized, in which videos of buildings were presented and button presses could prevent collapsing or exploding of the buildings. Results showed that participants with higher OCD traits displayed weaker sPIT effects relative to those with low OCD traits. No group differences regarding the gPIT effect were observed. This could be linked with decreased model-based behavior associated with higher OCD traits [60].

In another study, adolescents with OCD were compared to HCs [61]. A different avoidance-based PIT task was employed, in which participants had to move a joystick left or right to avoid aversive noises. Based on the findings from Krypotos and Engelhard [58], the author predicted a weaker sPIT effect and intact gPIT. However,

results showed no group differences, but both groups showed comparable sPIT specific and gPIT general PIT effects. The different findings may partly be explained by a small difference in sample size, as the study that observed a group difference investigated a slightly larger sample with OCD (trait). The studies used different aversive outcomes. In Krypotos and Engelhard [58], videos of buildings collapsing/exploding were used as unconditioned stimuli, while in Aziz Marzuki [61], aversive noises were used as unconditioned stimuli. The harm avoidance in OCD may be limited to certain circumstances [61]. Further, we speculate that intermediate states of the disease (subclinical OCD traits) versus patients that fulfill criteria for OCD might have a different impact on PIT effects, as seen in obesity already.

Depression

A key aspect of depressive disorders is impairments in the motivational domain, such as a loss of hedonic pleasure, difficulties in learning from rewarding outcomes, and psychomotor retardation. Major depressive disorder (MDD) is usually characterized by hyposensitivity to rewarding events and hypersensitivity to aversive events. However, despite extensive research, the precise mechanisms associated with impairments in reward processing in MDD are still largely unclear. Moreover, the research on reward processing in MDD is plagued by several challenges that call into question whether such impairments can serve as useful clinical predictors [62].

In this context, PIT promises to be a useful tool as it can contribute to a better understanding of how reflexive Pavlovian responses may bias decision-making and thereby help to characterize affective and behavioral impairments and capture ecologically relevant learning and decision-making processes in MDD [63]. So far, though, PIT effects have only very rarely been studied in MDD. In one study, Huys et al. [60] observed the absence of action-specific effects of Pavlovian stimuli on instrumental responses in depression. While appetitive Pavlovian stimuli boosted approach behavior and aversive Pavlovian stimuli promoted withdrawal in HC (see also [4]), Pavlovian stimuli did not exhibit valence-specific effects on instrumental responses of participants with depression. Interestingly, the degree of action-specificity during PIT in depression was predictive of the improvement of depressive symptoms at a follow-up measurement 4–6 months after the initial assessment. This means that the preservation of action-specific PIT effects was associated with better recovery from depressive symptoms. However, these promising findings conflict with a more recent study by Nord et al. [64]. In this case, HC did not show action-sPIT effects. Responses of participants with depression, in contrast, demonstrated action specificity during PIT, which was especially driven by aversive Pavlovian stimuli. In the presence of aversive Pavlovian stimuli, participants with depression showed a reduced approach but increased withdrawal behavior in comparison to HC. This could indicate an exaggerated influence of environmental cues that are associated with previous negative experiences and thus lead to an excessive avoidance of certain situations by patients with MDD. This notion is supported by similar behavioral tendencies in individuals with subclinical symptoms of depression [65].

However, since the studies by Huys et al. [60] and Nord et al. [64] obtained markedly different findings, the precise nature of depression-related biases in decision-making during PIT remains unclear. These conflicting results may reflect a general heterogeneity regarding the cognitive mechanisms in individuals with depression. Robinson and Chase [66] further point out that the assessment of PIT effects rests on the assumption of successful previous instrumental learning. In some individuals with depression, however, instrumental learning might be delayed even though these individuals eventually show intact learning at the end of the instrumental learning phase. Thus, differences in the speed of instrumental learning between groups may contribute to the presence of group differences during PIT. Furthermore, it is important to consider that the reliable detection of group differences hinges on the size of measurement error, which can, for instance, be quantified in terms of the test-retest reliability [62] (see also the section on Reliability of PIT in this article). In this context, higher degrees of measurement error require larger sample sizes to obtain sufficiently strong levels of statistical power.

Another line of research that could contribute to a better understanding of depression-related impairments during PIT, albeit less directly, pertains to the investigation of the involvement of specific neurotransmitter systems. In this regard, dopamine and serotonin are often seen as two interacting systems modifying in motivational responses [67]. For PIT, dopamine is selectively involved in appetitive PIT [1]. For a deeper understanding of altered PIT effects in depression, insights into the function of serotonin are particularly relevant. The specific role of serotonin in PIT, however, is less clear. According to one account, serotonin enhances the inhibiting effects of aversive Pavlovian stimuli on instrumental behavior [68, 69]. Findings from other studies are inconsistent with this view, however, and rather suggest that reduc-

tions in serotonin increase the motivational influence of aversive stimuli on instrumental responses [70] and another study found no effect of serotonin transporter blockade or deletion on PIT but reduced operant responding for natural rewards [71]. Despite these conflicting results and the need to further elucidate the role of serotonin in PIT, the understanding of the involvement of this neurotransmitter can possibly help to resolve some of the discrepancies found in the literature [60, 64]. While individuals with depression that were currently taking psychotropic medication were excluded in Nord et al. [64], current medication may have biased participants' responses in Huys et al. [60], especially since most antidepressants alter serotonergic processing.

Schizophrenia

PIT can be a useful tool to investigate how individuals can integrate the consequences of their action in a certain environment associated with the action-related outcome (sPIT). This might modify future goal-directed action selection. Although there is a debate about how gPIT and sPIT relate to habitual versus goal-directed behavior (e.g., see [6]), PIT might also give insights into psychopathology beyond addiction, addiction-associated behavior, compulsive behavior and depression. Thus, gPIT and sPIT effects have also been investigated in a sample of medicated patients with schizophrenia/schizoaffective disorder [72]. In their task, the instrumental response consisted of left and right button presses to release two different snacks from a vending machine. Colored lights in front of the machine served as CSs during Pavlovian training, predicting either the action-associated snacks (specific condition), a third new snack (general condition) or nothing (control condition), respectively. The transfer part was completed during an fMRI procedure. While patients and controls did not differ in their ability to acquire both instrumental and Pavlovian contingencies, patients showed impaired sPIT as well as gPIT, whereby the latter was due to higher responses in face of the non-reward-predicting cue (CS-). Morris et al. [72], interpret this with impaired goal-directed actions in schizophrenic patients, more precisely a deficit to integrate predictive stimuli from the environment to modify action selection. On a neural level, decreased sPIT in patients with schizophrenia was accompanied by reduced amygdala BOLD responses, while increased responses toward the CS- in the transfer phase of the gPIT correlated with heightened medial OFC activity. Furthermore, medial OFC activity was positively correlated with positive symptoms, such as delusions, in accordance with previous studies suggesting that frontocortical activation is related to delusion formation in schizophrenia [73, 74]. Taken together, this finding suggests an amygdala-mediated impairment of reward-related cues to guide choice behavior, combined with a generalized response to task-irrelevant cues (CS-) might be related to positive symptoms.

Chronic Pain

Shifting the focus to what could be considered a more universal experience among humans and other animals, pain and the learning processes associated with it have some notable intersections with Pavlovian learning and sPIT effects. From an evolutionary perspective, pain is considered a vital, protective response to injury or threat thereof. Physical manifestations of pain frequently accompany feelings of fear or escape, increased arousal, and more emotionally charged facial expressions. Safety-seeking behavior or the urge to alleviate discomfort generally follows suit [75]. Following this model, one must recognize the crucial role that learning plays in the experience of pain. In some situations, such as the classic example of touching a hot stovetop, it could be advantageous to quickly learn the association between an action and a painful outcome; committing it to memory would ensure that one would be unlikely to repeat harmful actions. For this reason, pain can be considered an effective motivator for learning through the mechanism of Pavlovian conditioning [76]. However, one must differentiate between acute and chronic pain to understand if and how PIT mechanisms diverge based on the pathophysiology of both. From a clinical standpoint, chronic pain can be considered a disease state; its treatment is multifaceted and often requires a different therapeutic approach compared to that of acute pain [77]. It is posited that the onset of some physical manifestations of chronic pain may be linked to one's psychological state, indicating that instrumental or Pavlovian learning processes play an important modulatory role.

There are relatively few studies that incorporate acute pain as primary or secondary reinforcers, and even fewer studies that involve clinical populations with chronic pain. Some researchers found contradictory results across multiple studies, at one point concluding that pain avoidance behavior increased in the presence of pain-related Pavlovian cues in HC [78]. However, they were unable to reach the same conclusion concerning intrinsic pain avoidance behavior in a later study [79]. The authors speculated that several factors could have contributed to this unexpected result, including potential confounders

introduced by the sample, task design, or wording of the task instructions. It is suggested that these results are interpreted cautiously until a more profound understanding of the involved mechanisms is developed through further research. Despite the contradictory results that exist in the literature, these studies critically demonstrate that pain-related cues can potentially modulate instrumental behavior, fear responding, and decision-making behavior; however, further studies must be performed.

In assessing these learning processes and how they relate to chronic pain, researchers in the clinical sector compared control participants and patients with chronic back pain using an appetitive PIT paradigm. They determined that patients with chronic back pain displayed reduced transfer effects compared to the control group, which might be explained by the focus of pain-related stimuli to the cost of positive stimuli used in this PIT paradigm. Critically, imaging results indicated that those with chronic back pain had increased BOLD signal in the hippocampus, which was associated with a failure to incorporate the learned contingencies into instrumental behavior for appetitive stimuli [80]. This finding is contrary to the literature, which identifies parallels between hippocampal activation and learning-related behaviors [81]. Considering that the sample is drawn from a clinical population, however, Nees et al. [80] identify critical brain-behavior pathways relating to chronic pain, motivational salience, habituation, and symptomatology. It is suggested that reduced transfer effects in chronic pain patients could be due to difficulties translating learned contingencies to behavioral outcomes, explained by memory processes hindered by hyperfixation on pain-related stimuli, compared to other (positive) reinforcers. It was later established that this identified behavioral bias was somewhat modulated by the participants' levels of depression, anxiety, and the duration of their pain symptoms. The association between the displayed maladaptive habitual learning and clinical symptom modulators can be used to inform future pain-related PIT studies within this clinical population.

Summary and Conclusion

According to the presented subclinical and clinical human studies, PIT seems to be a promising candidate to further understand how contextual cues influence behavior throughout different psychopathologies. Across different mental disorders, there is evidence that PIT effects are altered between control subjects and patients with a respective mental disorder or that PIT relates to the severity level of a psychopathological phenomenon in subclinical or healthy samples (see Table 1).

Nevertheless, a heterogenous picture prevails. For example, higher PIT effects have been demonstrated in social drinkers [29, 30], AD patients [31–34, 82], and non-substance-related disorders [50], while no difference was present in studies in the field of TUD and SUD (including some AUD studies) [6, 10, 25, 26, 49]. This could be explained by the heterogeneity of PIT studies – regarding (i) the mixed availability of human PIT studies investigating mental disorders, (ii) the heterogeneity in PIT tasks used and (iii) other possible influencing factors – and this might lead to mixed results.

Mixed Availability of PIT Studies across Mental Disorders

First, the number of studies across the respective disorders varies considerably, e.g., there is only one study each in patients with non-SUD, schizophrenia, OCD, and chronic pain, but several studies in patients with addiction (especially for AUD and TUD). PIT studies are not available for all mental disorders or in patient cohorts with comorbidities. To elaborate, i.e., there are no PIT studies in clinical samples of patients with specific anxiety disorders (but see e.g., [60], they included general anxiety disorder in the MDD sample). The PIT phenomenon can give insights into the mechanisms of the mentioned diseases. To give one example, the pathology of anxiety is an irrational generalization of fear to safe Pavlovian stimuli and the associated avoidance behavior [83, 84]. However, there are only two studies in humans that investigated associations between PIT and combined scores of anxiety and stress in student samples [85, 86]. Quail et al. [84] measured the PIT effect using a vending machine task in which junk food snacks were used as rewards. Decreased expression of gPIT was observed along with increased combined levels of anxiety and stress. Further analysis indicated that this effect may be driven by enhanced responding to Pavlovian stimuli that were associated with non-rewarding outcomes in participants with higher levels of stress and anxiety. The findings suggest that deficits in motivational effects of reward-paired cues are associated with increased stress and anxiety in students [85]. However, this study needs replication and since stress and anxiety levels are combined, the effect of only anxiety is not clear; in contrast Metts et al. [85] did find a reward related gPIT effect, but no associations to anxiety and depression scores. Using a PIT-like paradigm (Pavlovian-instrumental generalization [PIG] paradigm) [84], the

Table 1. Summary of the PIT studies across mental disorders in humans

Authors	Year	Sample	Group size	PIT task	Reinforcers	Main results: PIT effects
Alcohol use disorder						
Social drinkers						
Martinovic et al. [10]	2014	social drinkers	*n* = 31	sPIT	beer and chocolate points	sPIT for alcohol-associated cues, no correlation with AUDIT
Hardy et al. [25]	2017	social drinkers	*n* = 128	sPIT	alcoholic drinks, food	alcohol and food sPIT, PIT correlated with effectiveness belief, no association between alcohol sPIT and AUDIT, positive association between food sPIT and AUDIT
Rose et al. [28]	2018	social drinkers	*n* = 30 (alcohol devaluation), *n* = 32 (no devaluation)	sPIT	alcoholic drinks, soft drinks	↑ sPIT for alcohol-associated cues, no group differences
Mahlberg et al. [98]	2019	social drinkers	*n* = 38	sPIT	alcohol cues, chocolate cues	↑ sPIT for alcohol-associated cues, no correlation between alcohol sPIT and craving
Garbusow et al. [31]	2019	social drinkers	*n* = 94 low-risk, *n* = 97 high-risk	sl PIT	monetary win or loss (appetitive PIT)	gPIT (higher/lower instrumental response rate with positive/negative Pavlovian cues): ↑ in high-risk group, positive correlation with polygenetic risk for alcohol consumption, ↑ amygdala activation
Chen et al. [30]	2021	social drinkers	*n* = 94 low-risk, *n* = 97 high-risk	sl PIT	monetary win or loss (appetitive PIT)	gPIT (higher instrumental error rate in incongruent trials), high-risk group: ↑ behavioral PIT, ↑ activation in VS, ↓ activation in lPFC, ↓ connectivity from VS to lPFC for incongruent trials
AD patients						
Garbusow et al. [31]	2014	AD patients	*n* = 31	sl PIT	alcohol cues, monetary win or loss (appetitive PIT)	↑ PIT in AD patients: for aversive CSs (conditioned suppression), moderate to good temporal stability and robustness of PIT effects
		controls	*n* = 24			
Garbusow et al. [32]	2016	AD patients	*n* = 31 (*n* = 13 rel. and *n* = 11 abs.)	sl PIT	monetary win or loss (appetitive PIT)	gPIT (higher/lower instrumental response rate with positive/negative Pavlovian cues): ↑ in AD patients, ↑ Nacc PIT BOLD in AD patients, Nacc PIT BOLD predicted relapse
		controls	*n* = 24			
Sommer et al. [33]	2017	AD patients	*n* = 116	sl PIT	alcohol cues, monetary win or loss (appetitive PIT)	↑ PIT in AD patient: ↑ in impulsive patients, ↑ for instrumental inhibition with positive background stimuli, ↑ avoidance behavior for alcohol CSs
		controls	*n* = 91			
Schad et al. [16]	2019	AD patients	*n* = 31 (*n* = 16 rel. and *n* = 13 abs.)	sl PIT	alcohol cues, water cues	gPIT (higher/lower instrumental response rate with water/alcohol cues): ↑ in abstaining patients, ↑ Nacc PIT activation in AD patients (abs. and with mild symptom severity)
		controls	*n* = 24			
Sekutowicz et al. [35]	2019	AD patients	*n* = 52 (*n* = 30 rel. and *n* = 22 abs.)	sl PIT	alcohol cues, water cues	alcohol PIT in mPFC: predicting relapse in AD patients (accuracy 71.2%), predicting drinking of social drinkers
		social drinkers	*n* = 136			

Table 1 (continued)

Authors	Year	Sample	Group size	PIT task	Reinforcers	Main results: PIT effects
Sommer et al. [34]	2020	AD patients	$n = 109$ ($n = 70$ rel. and $n = 39$ abs.)	sl PIT	alcohol cues, monetary win or loss (appetitive PIT)	↑ money PIT in rel: ↑ for instrumental inhibition with positive background stimuli, no group differences (rel. vs. abs.) for alcohol PIT
		controls	$n = 93$			
van Timmeren et al. [37]	2020	AD patients	$n = 38$ ($n = 22$ abs., $n = 12$ rel.)	sl PIT	appetitive food	gPIT and sPIT: mOFC, ACC (gPIT); caudate, putamen, Thalamus, pallidum, hippocampus, indusla, middle cingulate, SMA, lmOFC, rpOFC (sPIT); no group differences (behavioral or neural), no relapse prediction
		controls	$n = 22$			
Sebold et al. [36]	2021	AD patients	$n = 186$	sl PIT	monetary win or loss (appetitive PIT)	↑ PIT in minor OPRM1 G-allele carriers in all three samples
		controls	$n = 105$			
		social drinkers	$n = 161$			
Tobacco use disorder						
Hogarth et al. [26]	2007	regular tobacco users	$n = 16$	sPIT	tobacco, money	tobacco sPIT: only in outcome "aware" subjects
Hogarth and Chase [40]	2012	daily versus non-daily smokers	Exp. 1: $n = 44$, Exp. 2: $n = 26$	sPIT	tobacco, chocolate	tobacco and chocolate sPIT: no group differences
Hogarth [44]	2012	daily versus non-daily smokers	$n = 91$	sPIT	tobacco, chocolate	tobacco and chocolate sPIT: no effect of nicotine replacement therapy on tobacco sPIT
Hogarth et al. [43]	2013	smokers	$n = 80$	sPIT	tobacco, chocolate	tobacco sPIT: vanished by alcohol expectancies
Hogarth et al. [47]	2014	smokers, social drinkers	Exp. 1: $n = 33$, Exp. 2: $n = 40$	sPIT	tobacco, chocolate	tobacco and chocolate sPIT: no effect of Pavlovian cue-exposure therapy on tobacco sPIT
Hogarth et al. [48]	2015	smokers	Exp. 1: $n = 23$, Exp. 2: $n = 121$	sPIT	tobacco, chocolate	stronger tobacco sPIT with branded versus plain cigarette packs
Manglani et al. [41]	2017	12 h abstinent smokers	$n = 23$	sPIT	tobacco, food	stronger tobacco sPIT compared to food sPIT
Steins-Loeber et al. [43]	2020	moderate smokers	$n = 59$	sPIT	tobacco, chocolate	tobacco and chocolate sPIT: no effect of acute stress induction (SECPT)
Substance use disorder						
Hogarth et al. [49]	2019	treatment-seeking substance users, controls	Exp. 1: $n = 61$, Exp. 2: $n = 27$	sPIT	water, appetitive food	sPIT in both groups, no group differences
Non-substance-related disorders						
Vogel et al. [51]	2018	problematic internet gaming and internet shopping users	$n = 66$	sPIT	gaming points, shopping points	gaming and shopping sPIT: ↑ for outcome "aware" subjects, ↑ with higher associative learning rates
Eating disorders						
Over-eating/obesity						
Lehner et al. [52]	2017	normal-weight individuals	$n = 20$	sPIT	appetitive food pictures	↑ food sPIT in overweight group, ↔ food sPIT in normal-weight versus obese groups
		overweight individuals	$n = 17$			
		obese individuals	$n = 17$			

Table 1 (continued)

Authors	Year	Sample	Group size	PIT task	Reinforcers	Main results: PIT effects
Watson et al. [53]	2017	normal-weight individuals	*n* = 19	sPIT (response-priming test)	low-calorie food pictures, high-calorie food pictures	↑ high- versus low-calorie sPIT in obese individuals
		obese individuals	*n* = 19			
Meemken and Horstmann [54]	2019	normal-weight individuals	*n* = 26	ft PIT	immediate gustatory rewards (palatable and neutral)	sPIT but no gPIT, no group differences in food sPIT
		obese individuals	*n* = 25			
Anorexia nervosa						
Vogel et al. [57]	2020	anorexia nervosa patients	*n* = 39	sPIT	low-calorie food pictures, high-calorie food pictures (earning points)	sPIT: no group differences, higher low-calorie food PIT with higher AN disorder severity
		controls	*n* = 41			
OCD						
Krypotos and Engelhard [58]	2020	low subclinical OCD level subjects	*n* = 20	ft PIT	videos of collapsing versus exploding buildings (avoidance-based PIT)	sPIT: ↓ in high OCD group, gPIT: no group differences
		high subclinical OCD level subjects	*n* = 28			
Aziz Marzuki [61]	2021	adolescent OCD patients	*n* = 20	ft PIT	aversive noises (avoidance-based PIT)	
		controls	*n* = 19			
Depression						
Huys et al. [60]	2016	MDD patients	*n* = 40	sl PIT	money wins and losses (appetitive and avoidance PIT)	valence- sPIT: in controls, absent in MDD patients; predicted better treatment outcome in MDD patients
		controls	*n* = 40			
Nord et al. [64]	2018	MDD patients (unmedicated)	*n* = 26	sl PIT	money wins and losses (appetitive and avoidance PIT)	action- sPIT: absent in controls, in MDD patients (esp. for aversive CSs)
		controls	*n* = 28			
Schizophrenia						
Morris et al. [72]	2015	Schizophrenic patients (medicated)	*n* = 18	ft PIT	appetitive food to eat	sPIT and gPIT: intact in controls, reduced in patients (with reduced AMY activity and hightened mOFC activity)
		controls	*n* = 18			
Chronic pain						
Nees et al. [80]	2020	patients with chronic back pain	*n* = 30	ft PIT	appetitive food pictures	reduced sPIT in patients versus controls, increased hippocampal activity with reduced sPIT in patients
		controls	*n* = 30			

AD, alcohol-dependent; CSs, conditioned stimuli; Exp, experiment; ft PIT, full transfer PIT; gPIT, general PIT; lPFC, lateral prefrontal cortex; MDD, major depression; mPFC, medial prefrontal cortex; OCD, obsessive compulsive disorder; sl PIT, single-lever PIT; sPIT, specific PIT.

Pavlovian generalization for fear-associated stimuli (electric shocks) and the related overgeneralization of avoidance-based decisions has been proven [84]. Interestingly, this effect was enhanced with higher levels of anxiety sensitivity and intolerance of uncertainty in a student sample [83]. While this evidence needs further proof in clinical

anxiety samples, one could also speculate that avoidance-based PIT effects measuring conditioned suppression might be aberrant in patients with anxiety. The notion that PIG and PIT might measure overlapping constructs is supported by similar neural underpinnings of the PIG [86] and PIT (REFs) paradigms. Using a PIT paradigm in HCs, Gerlicher et al. [87] found no association between conditioned suppression and trait anxiety as well as anxiety sensitivity (preprint, unpublished work) [88]. The authors explain the lack of evidence by not being able to measure conditioned suppression with their PIT task is possibly due to a too weak intensity of the aversive Pavlovian stimulus [87]. Consequently, this null finding needs to be proven with a PIT task that produces conditioned suppression and in a clinical sample of patients with anxiety disorder. Consequently, our knowledge of PIT across mental disorders is fragmentary due to the varying number of PIT studies and the lack of human PIT studies for some mental disorders.

Heterogeneity of PIT Tasks

Second, the design of the PIT task varies across studies: first, there are different types of PIT tasks and second, PIT can be operationalized in different ways. Regarding the types of PIT task, there are appetitive and avoidance-based (or a mixture of both) versions of PIT, which addresses the kind of instrumental behavior investigated in the PIT task. Further, PIT tasks differ with respect to measuring gPIT, sPIT, or both PIT effects (see [1]). Overall, each PIT study operationalizes the respective research question in a different way, leading to even more variation in PIT tasks, e.g., if different types of rewards are used. Rewards could differ, e.g., with respect to (i) being primary or secondary reinforcers, (ii) being disease-specific or not, (iii) the question of outcome delivery: is the subject receiving the outcome at all, delayed, or immediate, and (iv) stimuli used. Finally, some technical issues might have an impact on the PIT effect, such as how the transfer phase is instructed to the subjects, the number of stimuli used (which makes the task more or less complex), uncertainty during learning, and the probabilistic nature of learning parts. To elaborate, the instructions given during the transfer phase can affect the strategy of the subject: whether the subject is aware of the experimental contingencies and how the participants expect environmental cues and their behavior to relate to one another (see Belanger et al., this issue, and [48]). Overall, poor psychometric properties of the PIT task have been criticized, which is of relevance when assessing psychopathology and treatment interventions of mental disorders [89]. All these factors might have an influence on the strength of the PIT effect and consequently the sensitivity to detect group effects within one study and it makes it very difficult to compare between different studies.

Other Influencing Factors

Besides the already mentioned factors that lead to heterogeneity of PIT studies, more broad factors might influence PIT effects. This could be treatment status (e.g., abstinence status in addiction), current craving, priming, and acute or chronic stress. These are all factors that can differ systematically between groups when comparing across studies or when comparing patients with a mental disorder to controls within one study and that can systematically influence PIT effects. Exposure to stressors, e.g., was proposed to be related to the deficits in reward-seeking. A study in rats showed that rats exposed to chronic stress were impaired in sPIT [89]. Also, Quail et al. [84], showed the association of stress and PIT effects in humans; however, Steins-Loeber et al. [43] did not find effects of acute stress induction on PIT. Thus, the impact of acute and chronic stress on PIT effects and the potential link between mental disorders is not yet clear.

What to Do Next?

Reliability of PIT

First, we would like to address the above-mentioned technical issue that relates to the PIT task: psychometric properties. Good psychometric properties are of special relevance, as they are needed for investigating traits, such as, clinical studies, treatment outcomes, experimental manipulations of PIT effects (e.g., the influence of acute stress on PIT), the determinants of therapeutic interventions, or for tracking individual development. However, it has been shown that the temporal stability of Pavlovian influence during the reinforcement learning can be rather low [89], although this was a PIT-like task only, measuring Pavlovian influences in a Go-No go task. However, developing PIT paradigms with good psychometric properties is of high relevance [88]. We already showed moderate to high reliability and validity measures of our PIT task variant [31], however, this was split-half reliability only. Here, we investigated test-retest reliability for an adapted version of our original 2014 PIT task [31] as shown in Figure 1, to further specify its psychometric properties. We used a single-lever PIT task in a 2-day study design. We invited $n = 20$ subjects without known neurological or psychiatric conditions for 2 consecutive days to conduct two parallel versions of the task in a crossover randomized study design. On the first day, sub-

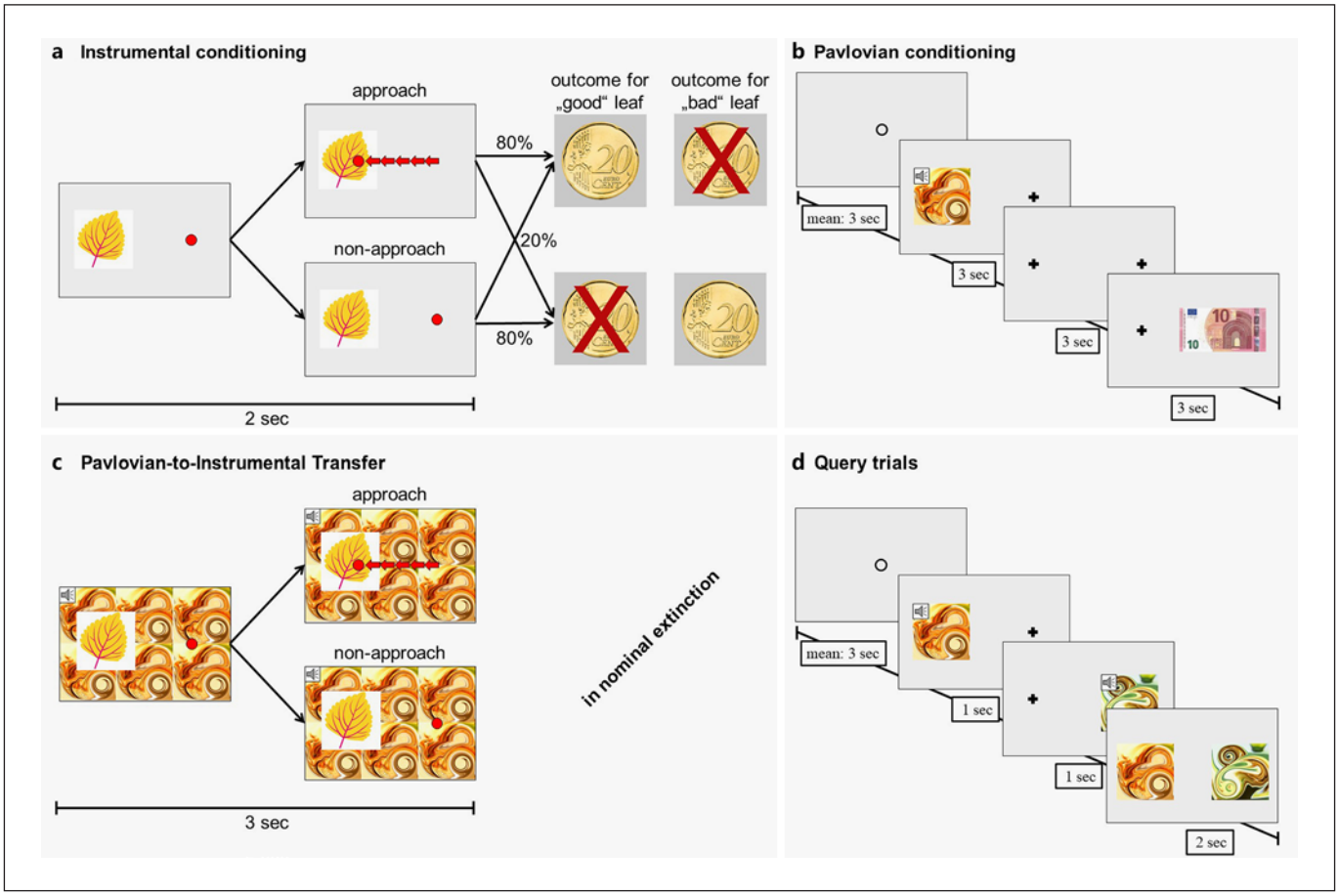

Fig. 1. PIT paradigm, leaf version. **a** Instrumental conditioning: Subjects were asked to collect an instrumental stimulus (here a leaf) by repeated button presses or to not collect by withholding button presses. Via trial and error, subjects learned by probabilistic feedback (win or loss of 20 cents) which instrumental stimulus leads to a win or loss of money. Per version, we used a set of six instrumental stimuli (three go, three no-go). **b** Pavlovian conditioning: subjects passively observed associations between a compound audio-visual fractal-like image with a musical tone deterministically associated with monetary win (here +10 EUR) or loss. Per version, we used a set of three Pavlovian stimuli (associated with +10 EUR, 0 EUR, −10 EUR). **c** Pavlovian-to-instrumental transfer: subjects were asked to collect or to not collect instrumental stimuli again (as learned during **a**). Additionally, Pavlovian stimuli were shown tiled in the background in a mosaic-style pattern. **d** Query trials: subjects were asked to choose between the better of two Pavlovian stimuli to ensure successful Pavlovian learning.

jects were asked to do the "shell" version, on the second day the "leaf" version of the task (see Fig. 1) or vice versa. The transfer phase consisted of 162 trials. Outside of the two parallel versions of stimulus sets for instrumental and Pavlovian conditioning, all other task conditions were kept constant (e.g., instructions, timing, rewards). Subjects were healthy volunteers, recruited from internet advertisements (13 female, age mean = 33.7, SD = 12.52). They provided written, informed consent, received a monetary inconvenience allowance (~10 EUR/h), and the study was approved by Charité – Universitätsmedizin Berlin Ethics Committee (EA2/239/18).

We computed intra-class correlation coefficients (ICC) [91] for individual PIT effects capturing the influence of Pavlovian cues on the number of button presses during the transfer phase. Therefore, random regression slopes from a linear mixed-effects model (GLMM) were calculated (for model details, see [29]). The paradigm's test-retest reliability between the (i) two testing days (day 1 and day 2) and (ii) two versions (leaves and shells) was estimated using the *ICC* function built in the *psych* package in R [92]. We report absolute agreement, ICC(2,1), and consistency, ICC(3,1). For testing day, the estimated agreement was 54, 95% confidence interval (CI) = [0.23,

Table 2. Results table for test-retest reliability of the PIT task (by day)

Number	Type	ICC	F	df1	df2	*p* value	Lower bound	Upper bound
1	ICC1	0.53	3.2	19	20	0.006	0.21	0.75
2	ICC2	0.54	3.7	19	19	0.0033	0.23	0.76
3	ICC3	0.57	3.7	19	19	0.0033	0.26	0.78
4	ICC1k	0.69	3.2	19	20	0.006	0.34	0.86
5	ICC2k	0.7	3.7	19	19	0.0033	0.37	0.86
6	ICC3k	0.73	3.7	19	19	0.0033	0.41	0.87

Table 3. Results table for test-retest reliability of the PIT task (by version)

Number	Type	ICC	F	df1	df2	*p* value	Lower bound	Upper bound
1	ICC1	0.61	4.1	19	20	0.0015	0.31	0.8
2	ICC2	0.61	4.1	19	19	0.0018	0.31	0.8
3	ICC3	0.61	4.1	19	19	0.0018	0.31	0.8
4	ICC1k	0.75	4.1	19	20	0.0015	0.48	0.89
5	ICC2k	0.75	4.1	19	19	0.0018	0.48	0.89
6	ICC3k	0.75	4.1	19	19	0.0018	0.47	0.89

0.76], and the estimated consistency was 57, 95% CI = [0.26, 0.78]. For version, the estimated agreement was 61, 95% CI = [0.31, 0.80], and the estimated consistency was 61, 95% CI = [0.31, 0.80] (as shown in Table 2 and Table 3). Together this speaks for a moderate temporal stability (test-retest reliability for day) and a moderate to good internal consistency (test-retest reliability for version) [93].

Outlook

Finally, we would like to give an outlook of future studies: For true comparison of PIT effects, it would be indispensable to use one similar PIT task across mental disorders. This PIT task ideally should capture different types of PIT effects (e.g., a full transfer PIT task with appetitive and avoidance-based parts) and should use different kinds of reinforcers (e.g., primary, secondary, and disease-specific reinforcers). A suggestion for such a task you can find in Belanger et al. (this issue). Another promising approach could be investigating (with one PIT task) a comprehensive cohort including a broad spectrum of severity in different psychopathological domains, as studies so far showed that PIT might have the ability to detect severity, as shown in the cases of AUD, OCD, obesity, and AN severity. This would also go along with the emerging claim in the field of psychiatry to overcome disease categories [94] and support the idea of transdiagnostic dimensions (Research Domain Criteria, https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc). This would not only make it possible to compare PIT effects across psychopathology but also to observe specific mechanisms that are relevant for different disorders. For example, one could speculate from the literature that appetitive PIT effects are more relevant to understand addictive disorders while avoidance PIT effects might be more relevant for OCD or MDD. Further transdiagnostic interactions may emerge. Hogarth et al. [95] observed that in subjects drinking alcohol, acutely depressed mood statements prime alcohol over food-seeking behavior to cope with negative effects. This effect was further associated with depression symptoms [96].

On a conceptual level, it turned out to be relevant to understand how gPIT and sPIT match habitual and goal-directed decisions, as habit formation is a mechanism that contributes to the understanding of mental disorders. Potentially, it can be targeted in PIT paradigms but to date, human PIT studies that include revaluation procedures are scarce [1]. In case of AUD, devaluation reduced alcohol seeking, but had no effect on sPIT in a sample of social drinkers, which may reflect habitual behavior [28]. In contrast, outcome devaluation was associated with weaker instrumental responding in a sample of HC

and individuals with AUD in sPIT, suggesting goal directed behavior [37]. Similar evidence was found in a study that investigated SUD (including AUD) [49]. In TUD, nicotine devaluation procedures altered instrumental choice behavior [44] but did not affect drug-expectancy; other results showed that revaluation altered instrumental choice behavior, intending goal-directed behavior [40]. For OCD, it has been suggested that weaker sPIT in individuals with higher OCD traits is associated with lower goal-directed behavior [61]. Even though this data provides interesting evidence, the concept of how habit formation applies to the two forms of PIT is an own line of research and current discussion (for an overview, see Mahlberg et al. [6]) and thus cannot finally be answered in this review. A better understanding of the specific mechanisms and transdiagnostic interactions using a PIT task can thus be fruitful for future clinical studies when considering precision medicine [97].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Funded in part by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy – EXC-2049 – 390688087. Funded in part by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project numbers 402170461 [TRR 265, 97] and 186318919 (FOR 1617).

Author Contributions

Maria Garbusow, Andreas Heinz, Michael A. Rapp, and Maximilian Pilhatsch outlined the concept of the review. Maria Garbusow, Andreas Heinz, Michael A. Rapp, Maximilian Pilhatsch, Marcus Rotkirch, Claudia Ebrahimi, and Michael N. Smolka contributed to the study design (to prove test-retest reliability). Maria Garbusow, Claudia Ebrahimi, and Marcus Rotkirch conducted the analyses of the test-retest reliability. Luisa Daldrup conducted the primary literature research. Maria Garbusow wrote the review. Claudia Ebrahimi, Carlotta Riemerschmid, Luisa Daldrup, Angela Hentschel, Ke Chen, Marcus Rotkirch, Matthew J. Belanger, and Hao Chen supported writing (subchapters of "PIT across mental disorders", respectively). Maria Garbusow, Claudia Ebrahimi, Carlotta Riemerschmid, Luisa Daldrup, Marcus Rothkirch, Ke Chen, Hao Chen, Matthew J. Belanger, Angela Hentschel, Michael N. Smolka, Andreas Heinz, Maximilan Pilhatsch, and Michael A. Rapp conducted intensive proof reading, critical revisions, and gave their final approval.

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