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Review article

Appetitive Pavlovian-instrumental Transfer: A review

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ABSTRACT

Reward-related cues are an important part of our daily life as they often influence and guide our actions. This paper reviews one of the experimental paradigms used to study the effects of cues, the Pavlovian to Instrumental Transfer paradigm. In this paradigm, cues associated with rewards through Pavlovian conditioning alter motivation and choice of instrumental actions. The first transfer experiments date back to the 1940s, but only in the last decade has it been fully recognised that there are two types of transfer, specific and general. This paper presents a systematic review of both the neural substrates and the behavioral factors affecting both types of transfer. It also examines the recent application of the paradigm to study the effect of cues on human participants, both in normal and pathological conditions, and the interactions of transfer with drugs of abuse. Finally, the paper analyses the theoretical aspects of transfer to build an overall picture of the phenomenon, from early theories to recent hierarchical accounts.

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Glossary

Pavlovian conditioning: During Pavlovian conditioning a neutral stimulus, such as a sound, becomes a conditioned stimulus (CS) by pairing its occurrence with an unconditioned stimulus (US) that naturally elicits some response. For example, a sound (CS) might be paired with food (US) by delivering food only when the sound is present. At the end of training, the animal/participant will have learned that the CS predicts the US and so it will approach the site of food delivery when it hears the sounds.

Instrumental conditioning: During instrumental conditioning an animal/participant is trained to make a response by delivering an attractive outcome. For example, a hungry rat might be trained to press a lever that delivers food. This training can lead to two kinds of instrumental behavior: habits, controlled by antecedent stimuli through the formation of stimulus-response (S-R) associations or goal-directed actions, controlled by the consequences of the action through the formation of action-outcome (A-O) associations.

Devaluation: Outcome devaluation is a procedure where the US or the outcome (O) value is altered. For example, the value of a certain food might be altered by feeding it to satiation or by pairing it with illness (the latter induced by lithium-cloride injections).

Extinction: A training session where the US predicted by a CS or the outcome (O) predicted by an action is no longer delivered, thus promoting the extinction of the Pavlovian conditioned response or the instrumental action.

1. Introduction

Predictive cues are an important part of our life that continuously influence and guide our actions. Hearing the sound of a horn makes us stop before we attempt to cross the street. Seeing an advertisement for fast food might make us hungry and lead us to seek out a specific type and source of food. In general, cues can both prompt us towards or stop us from engaging in a certain course of action. They can be adaptive (saving our life in crossing the street) or maladaptive, leading to suboptimal choices, e.g. making us eat when we are not really hungry (Colagiuri and Lovibond, 2015). In extreme cases they can even play a part in pathologies such as in addiction, where drug associated cues produce craving and provoke relapse (Belin et al., 2009).

One particular paradigm used to study the effect of such cues is the Pavlovian to Instrumental Transfer paradigm. In this paradigm, Pavlovian predictions and instrumental actions are first trained in separate experimental phases. The instrumental actions are then tested in both the presence and the absence of the Pavlovian cues to assess the effect of the latter on the former.

The first Pavlovian to instrumental transfer studies date back to the 1940s, reporting that stimuli paired with food were able to augment instrumental actions directed towards food (Estes and Skinner, 1941; Walker, 1942; Estes, 1943). Transfer effects can either promote or discourage actions, with the presence of cues increasing/decreasing the frequency of an action or biasing choice in favour of certain actions. Amongst other factors, the type of effect obtained depends on the valence of the Pavlovian US, i.e., whether it is appetitive or aversive. For example, a Pavlovian cue associated with an aversive shock might promote actions leading to shock avoidance but decrease actions leading to food (Rescorla and Solomon, 1967).

Our understanding of transfer has naturally developed with our understanding of Pavlovian and instrumental conditioning. At the same time, studying the interaction of Pavlovian and instrumental conditioning has often yielded new insights into these individual processes. At the time of the earliest studies, for example, it was not clear if Pavlovian and instrumental conditioning constituted different forms of learning. Gradually, however, two-process theories emerged that separated Pavlovian and instrumental processes (see Rescorla and Solomon (1967) for a review). Transfer effects were, at that stage, understood as the result of Pavlovian cues generating general appetitive or aversive emotional states and, indeed, the transfer paradigm was typically used to study the influence of conditioned emotional responses (Rescorla and Solomon, 1967). Subsequent studies refined this general emotional state finding that, in many conditions, transfer was better characterised as controlled by primary motivational processes than emotional states. So, for example, Dickinson and colleagues demonstrated in studies of the so called irrelevant incentive effect that a cue predicting sugar solution would enhance instrumental actions both when rats were hungry and when they were thirsty whereas a cue associated with dry food pellets would only elevate performance when hungry. These effects were generally interpreted as suggesting that primary motivational processes could modulate the production of conditioned emotional states, much as suggested by Bindra (Dickinson and Dawson, 1987; Balleine, 1994; Bindra, 1974). However, none of these accounts explained the influences of Pavlovian cues on choice: i.e., how Pavlovian cues could sometimes be found to enhance actions tied to a specific outcome, e.g. how a CS associated with grain pellets enhanced lever pressing for grain pellets but not for other food outcomes (such as sugar). One possibility is that both Pavlovian and instrumental conditioning lead to the formation of associations: stimulus-outcome associations (S-O) in one case and response-outcome associations in the other case (R-O), and that the common outcome mediates the interaction (Trapold and Overmier, 1972). In the 1980s and 90s much experimental work was devoted to establishing that instrumental conditioning could be subdivided into two types: habitual actions, controlled by stimulus-response (S-R) associations, and goal-directed actions, controlled by response-outcome (R-O) associations (Balleine and Dickinson, 1998). In parallel, a series of articles examined the ability of Pavlovian cues tied to a specific outcome to bias choice between specific actions (Colwill and Rescorla, 1988; Colwill and Motzkin, 1994; Rescorla, 1991, 1994a,b; Delamater, 1995, 1996). At the beginning of the century, investigation of the neural substrates of transfer began: some initially contrasting results led at that stage to the realisation that transfer effects come in two different forms and so had to be subdivided as well. These studies divided the phenomenon into specific and general transfer, each characterized by a different neural substrate (Corbit and Balleine, 2005, 2011, see Section 4). Specific transfer refers to the ability of cues to enhance specific actions associated with the same outcome as the cue, whereas general transfer refers to the ability of cues to enhance also actions paired with different outcomes.

Most data on transfer come from animal studies,[1] however in recent years the transfer paradigm has also been adapted for human participants. In general, human studies have produced similar results to animal studies both in terms of the behavioral factors

[1] Studies mostly involved rats, however other species have been used as well, such as mice (see Lederle et al., 2011 in different mice strains), monkeys (Stebbins and Smith, 1964), dogs (Rescorla and LoLordo, 1965), pigeons (Morse and Skinner, 1958) and even horses (Lansade et al., 2013).

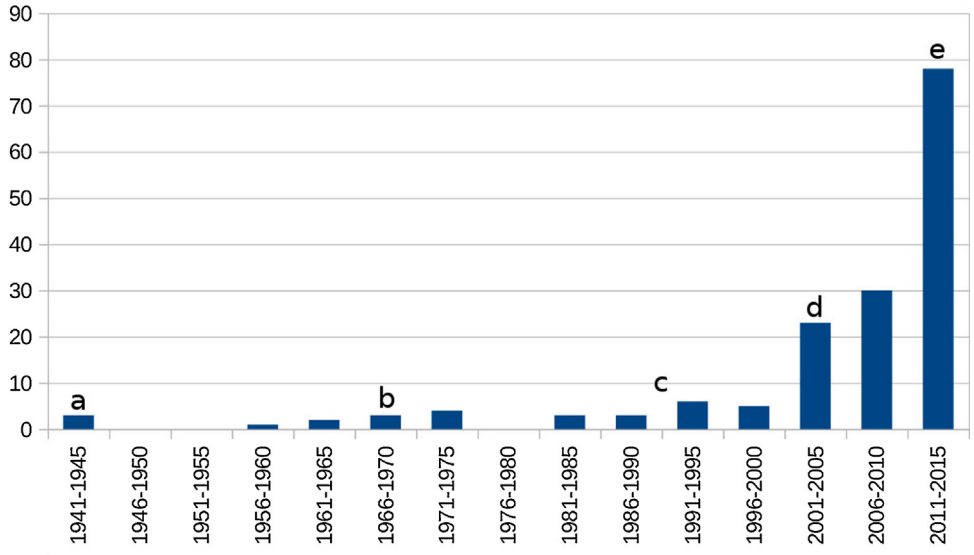

Fig. 1. Articles referenced in this review, grouped in 5 years bins. Letters indicate landmark events in transfer research. The last decade has seen a marked increase in the investigation of transfer. (a) First experiments in the 1940s. (b) Rescorla and Solomon (1967) review theories of Pavlovian and instrumental conditioning and their interaction, advocating a two-process theory. (c) During the 1980s and 90s instrumental conditioning was clearly subdivided into habitual (S-R) and goal-directed (A-O) actions. Around 1990, Rescorla and colleagues produce a series of studies examining how Pavlovian cues affect instrumental responding in an outcome-specific manner. (d) At the turn of the century investigation of the neural substrates of transfer begins, leading to the subdivision of general and specific transfer each with its separate neural substrate. (e) The transfer paradigm is adapted to human participants and neural substrates are investigated using fMRI.

and the neural substrates (e.g., Bray et al., 2008; Talmi et al., 2008; Watson et al., 2014, see Section 6) controlling transfer effects.

1.1. Scope and purpose of the review

In the last decade there has been an increasing number and range of studies on transfer, both in animals and humans, examining transfer under both normal and pathological conditions (Corbit et al., 2007; Corbit and Balleine, 2011; Laurent et al., 2015; Ostlund et al., 2014b; Nadler et al., 2011; Morris et al., 2015; Colagiuri and Lovibond, 2015; Garbusow et al., 2016). Although there has been a relatively recent review on the topic (Holmes et al., 2010) the literature on transfer has essentially doubled in size over the last 5 years providing considerable new information on models and the neural bases of the transfer effect across species. In particular, we will focus on appetitive transfer which is the subject of the large majority of these recent studies. Fig. 1 summarises our coverage of research and shows some landmarks in the investigation of the transfer effect. In our review we included only articles which follow the standard transfer paradigms: i.e. where the Pavlovian conditioning and instrumental conditioning are conducted in separate sessions.

The review is structured as follows: Section 2 describes the transfer paradigm and its variants; Section 3 then reviews behavioral factors influencing the transfer effect; Section 4 describes the neural mechanisms underlying transfer; Section 5 reviews studies of the interaction between transfer and drugs of abuse; Section 6 reviews transfer studies with human participants; Section 7 reviews theoretical aspects of transfer; Section 8 then draws overall conclusions. Where possible we will separate experimental findings from their theoretical interpretation using procedural rather than theoretical descriptions or definitions. In this regard, we clarify here our use of what may be seen as a theoretically laden term 'action'. We use 'instrumental action' or just 'action' to refer to measures in the instrumental conditioning phase of transfer studies, whether the experiments were designed to encourage the development of goal-directed instrumental actions or of habitual instrumental actions. Measures taken from Pavlovian conditioning instead will always be referred to as 'Pavlovian conditioned responses', 'conditioned responses' or simply as 'responses'.

2. The transfer paradigm

There are many variations of the transfer paradigm but it is always composed of three phases: Pavlovian training, instrumental training and the transfer test. The two training phases can be conducted in any order (either Pavlovian or instrumental first) with no change in the effect (but see Holmes et al., 2010, where lengthening the first or second phase varied the amount of transfer). In the Pavlovian phase one or more stimuli (usually auditory cues) are paired with the delivery of rewards such as food pellets or sucrose (see Fig. 2). Pairing stimuli with an aversive event to develop an aversive transfer paradigm has also been conducted (e.g., Lewis et al., 2013; Rigoli et al., 2012; Campese et al., 2013).

During the instrumental training, a contingency is established between one or more actions and the delivery of one or more outcomes – usually involving pairing lever pressing with food delivery. Using one or more actions (e.g. one or two levers paired with different foods) leads to critical differences in what is measured in the final test (see below).

In the last phase, the animal/participant can again perform the instrumental actions, but this time the conditioned stimuli (CS) trained in the Pavlovian phase are presented during the session. The effect of presenting the CS on the instrumental response (the transfer effect) is then assessed by comparing instrumental responding during periods when no CS is presented (baseline) with periods when a CS is presented, or, if two CS's are presented, by comparing responding during the presentation of the different CSs (e.g., one paired with the same food as the lever and another one paired with a different food). The CSs are never presented in the presence of the instrumental manipulanda before the test, so no explicit training of a relationship between the CS and the instrumental action takes place. When multiple actions are used, the test may involve a choice between two levers presented at the same time (e.g., Ostlund and Balleine, 2008) or separate tests of each instrumental action (e.g., Corbit et al., 2001). Test sessions are usually conducted in

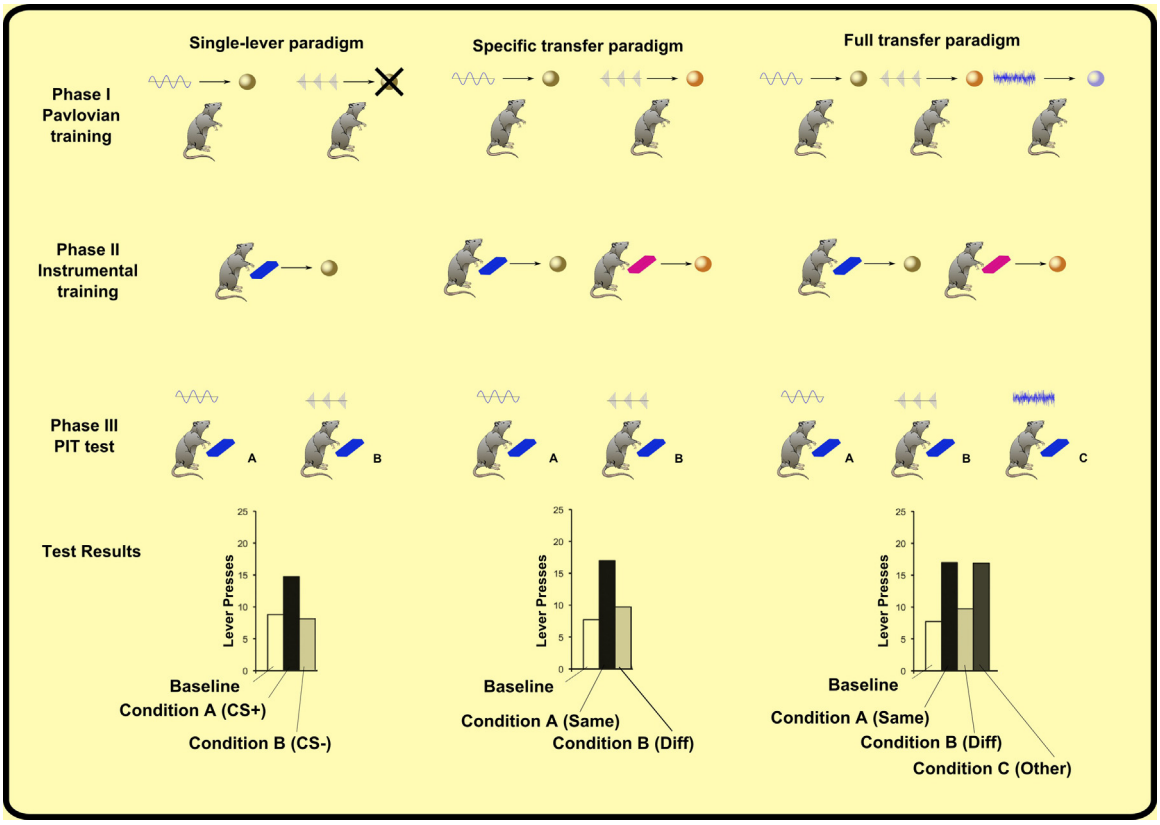

Fig. 2. Transfer paradigms. We illustrate three possible experimental setups ("Transfer paradigms") that have been used to test the transfer effect. On the left ("Single-lever paradigm"), only one CS and one lever are trained with a reward and an unpaired CS is used as control. This first paradigm usually leads to the expression of general transfer. In the centre ("Specific transfer paradigm"), two CS+ and two levers are trained, using two rewards. Each CS+ is associated with a reward used for only one lever, thus enabling the expression of specific transfer. On the right ("Full transfer paradigm"), the specific paradigm is enhanced by adding an additional CS+. This last CS+ is associated with a third outcome that is not used for instrumental training. Using this third CS+ during the test phase provides a test of general transfer. The paradigm on the right is thus a "full transfer paradigm" in the sense that it can test both specific and general transfer. The bottom row provides schematic graphs that exemplify typical results obtained in the three paradigms.

extinction, i.e., no outcomes are delivered either after the stimuli or after the actions, to avoid changes in performance due to new learning.

In all cases, what is generally found is that a CS paired with an appetitive outcome (CS+) enhances instrumental responding compared to an unpaired CS (CS−). Usually the CS+ also increases instrumental responses compared to the baseline (CS-free period), however, in some cases, differences between the CS+ and CS− have emerged but with no difference between the CS+ and baseline, producing instead a reduction of CS-induced response suppression. Furthermore, in the two action case, although typically the 'same' CS elevates performance of the action delivering the outcome predicted by the CS relative to both the other action and to baseline performance, it has sometimes been found that both CSs reduce lever pressing compared to the baseline but that the CS sharing the same outcome as the instrumental action reduces performance less than a CS associated with a different outcome. This reduction with respect to the baseline could be due to response competition between instrumental and Pavlovian responses. For example, if the CS prompts considerable magazine approach, it will reduce the time spent pressing the lever (see also next section).

As we mentioned in the introduction, there are two kinds of transfer: specific transfer and general transfer. In specific transfer, the CS enhances actions associated with the same outcome as that paired with the CS whereas, in general transfer, a CS can enhance actions directed to other outcomes as well. Studies using a single lever paired with food usually also use one single paired CS in the Pavlovian phase and in the test phase cannot behaviorally distinguish between the specific and general transfer effects. This is because both general and specific transfer effects enhance instrumental performance, something that could be because the action shares the same outcome as the CS or through a general effect of the cue (e.g. motivational). For simplicity, throughout this review we will call these studies "single lever studies" (see Fig. 2). It must be noted that while it is not possible to behaviorally distinguish between specific and general transfer in a "single lever study", lesions experiments suggest that using a single lever usually elicits only general transfer. As we will see in Section 4, studies investigating the neural basis of transfer have found distinct neural substrates for specific and general transfer (Corbit and Balleine, 2005, 2011), and transfer in "single lever" studies is impaired by lesions targeting general transfer substrates and spared by those targeting specific transfer substrates (Hall et al., 2001; Holland and Gallagher, 2003). It is not known why the "single lever" studies elicit general transfer and not specific transfer (as multiple lever studies do). It has been suggested that the different type of transfer elicited by single and double lever procedures might be caused by the more or less detailed representation of the outcome (Holland, 2004). Procedures with multiple levers (and reinforcers) favour the creation of a more detailed and sensory-specific representation of the reinforcers used, which in turn may lead to the transfer effect being specific. A single-lever lever procedure does not need a detailed representation of the outcome, so in this case the transfer effect might be conveyed by the more "general" appetitive characteristics of the outcome.

Another category of studies uses two levers, each paired with different outcomes (e.g. food pellet vs. sucrose) and usually two CSs each paired with one of these outcomes. In this case, during the test phase, each CS usually only enhances lever pressing associated with the same outcome as the CS. We will call this variant the "specific transfer paradigm" (see Fig. 2). In this paradigm, when testing transfer one lever at a time, the CS presentations can be divided into two conditions: in the *same* condition the CS and the lever share the same outcome whereas in the *different* or *diff* condition the CS predicts a different food compared to the one associated with the lever. Usually the different CS does not enhance lever pressing relative to the baseline or it does so to a lesser extent than the specific transfer effect in the *same* condition (see Fig. 2, bottom graphs). It is still unclear why the different lever is not equally enhanced through a general transfer effect, especially when, in experimental situations able to express both the specific and general transfer effects, the two effects tend to have a comparable size (see Fig. 2).

This last category of experiments is usually conducted using two levers, each delivering a different outcome, and with three CSs, two paired with the outcomes delivered by the levers and one paired with a third outcome. During the test, this paradigm has been reported to show both the specific and the general transfer effects. The two CSs paired with the same outcomes as the levers enhance responding on the lever sharing the same outcome (specific transfer). Again we note that the CS+ paired with the food associated with one lever does not enhance responding on the other lever although the third CS, paired with an outcome that was not used in the instrumental training, enhances pressing on both levers (general transfer). We will call this the "full transfer paradigm".

3. Behavioral results – variables influencing transfer

There are many behavioral factors affecting transfer effects. These are analysed in detail in this section.

3.1. Pavlovian factors

Response competition between Pavlovian responses and instrumental responding can make transfer effects harder to detect (Lovibond, 1983). As we noted in the previous section, a CS+ usually enhances instrumental responding compared to the baseline. However, the Pavlovian responses elicited by the CS, such as magazine approach, can compete with lever pressing and lead to a reduction of lever pressing compared to the baseline. Using discrete (e.g. a light cue) vs. diffuse (a sound) cues as the CS can favour the development of competing sign-tracking responses (e.g. approaching the CS) which can compete with instrumental responses, or favour them if the cue is located near the manipulanda (Tomie, 1996). The degree of similarity between Pavlovian and instrumental responses might also help or hinder the transfer effect (Baxter and Zamble, 1982). Holmes et al. (2010) showed that extinguishing Pavlovian responses can enhance transfer in a subsequent test. This result might be seen to conflict with previous experiments by Delamater (1996) in which the transfer effect was shown to be unaltered after various types of CS extinction such as nonreinforcement, pairing with an alternative outcome and exposure to random or explicitly unpaired S-O contingencies. The difference might lie in the length of previous CS training, which in the case of Holmes et al. (2010) was deliberately extended to create strong Pavlovian approach responses. In other words, Pavlovian extinction might be beneficial to the transfer effect only when the Pavlovian training is sufficiently strong that it interferes with instrumental responding (in the ways described above) but has no effect otherwise. On the relationship between transfer and Pavlovian extinction, we also note that in a single-lever human transfer paradigm Lovibond et al. (2015) found, in contrast to the animal studies, that Pavlovian extinction of the CS affected transfer. Although the Pavlovian extinction did not completely eliminate the transfer effect, its efficacy contrasted with the results obtained in animals by Delamater (1996). Lovibond et al. (2015) suggested that one of the critical differences might lie in the fact that they focused on absolute response rate (using a single-lever paradigm) whereas in Delamater's (1996) study the transfer test involved a response choice (specific-transfer paradigm). This suggestion predicts that Delamater's extinction procedure would have been effective if he had tested his actions individually rather than in a choice test. However, given that single-lever paradigms seem to evoke general transfer, it remains possible that CS extinction differentially affects specific and general transfer. And, of course, the same is likely to be true of conflict between the CR and the instrumental action; such conflict could directly alter response vigor and so the size of any general transfer effect but has difficulty explaining variations in specific transfer because any general effect on performance should have similar effects across both actions.

The duration and timing of the CS can also affect transfer; Crombag et al. (2008a) found in mice that a CS+ lasting 10 s (with reward delivered during the last 5 s of the stimulus) produced strong conditioned reinforcement but no transfer, whereas a CS+ lasting 2 min (with rewards delivered randomly during the interval) produced robust transfer but no conditioned reinforcement. Delamater and Holland (2008) also examined the effects of varying the CS-US interval: results confirmed that sensory-specific stimulus-outcome associations (i.e., those underlying specific transfer) were established over a wide range of long but not short intervals. These results are also consistent with older studies, e.g. Meltzer and Brahlek (1970) where a long CS (120 s) led to positive transfer whereas a short CS led to suppression of responding, althought in that case the CS's were trained during instrumental conditioning and so it was not a canonical transfer design as defined here. [2] Delamater and Holland (2008) also found that conditioned responses (magazine approach) had an inverse relationship to the CS–US interval, with longer intervals leading to a lower magazine approach performance. As such, measures of conditioned responding such as magazine approach do not necessarily correlate with measures of specific transfer. This has also been confirmed by the finding that it is possible to have a CS which reduces magazine approach but still increases instrumental actions, as we will see below (Shiflett, 2012). Delamater and Oakeshott (2007) furnishes additional support for a dissociation between magazine approach and transfer. In a specific transfer paradigm they gave rats different amounts of Pavlovian training, ranging from 4 to 112 presentations of a 60 s CS. During the test sessions, the amount of magazine approach varied greatly between the different groups, with more training leading to more magazine approach. Also, a tendency to concentrate approaching during the last part of the CS (when the US was previously delivered) only developed for the group with most Pavlovian training. In contrast, the amount of transfer displayed was less influenced by length of training and the increase in lever pressing was more pronounced towards the end of the CS for all but the shortest training group. So both the amount and timing of magazine approach and transfer appear to develop during training at different rates.

Backward conditioning, in which the US precedes the CS, can also support transfer (Delamater et al., 2003; Shiflett, 2012; Cohen-Hatton et al., 2013); however depending on the US-CS

[2] But see also Van Dyne (1971) or Lovibond (1981) for short CS leading to suppression.

interval, backward conditioning can produce either Pavlovian excitors or Pavlovian inhibitors, i.e. CSs that, respectively, enhance or suppress Pavlovian responses such as conditioned approach. As a consequence, the influence of backward conditioning on transfer is complex and its application in a transfer paradigm can result in either positive (Shiflett, 2012; Cohen-Hatton et al., 2013) or 'negative' transfer effects (Delamater et al., 2003). The latter effects, observed in outcome specific transfer, often reflect the opposite of the standard excitatory specific transfer; i.e., rather than elevating the action that delivered the same outcome as that predicted by the stimulus, a backwardly paired CS can bias choice towards other actions that animals have learned do not deliver the backwardly paired US. This was explicitly investigated by Laurent and Balleine (2015) who compared the effect of a zero delay and of a 10-s delay between US and CS finding standard specific transfer with the former and the 'negative' or reversed transfer effect with the latter. Such effects suggest, therefore, that it is the information conveyed by the backwardly paired CS that is important for the direction of choice; i.e., that the CS can provide both information about the likelihood of a forthcoming outcome for use in action selection, but can also provoke direct changes in conditioned reflexes and that these need not be the same; indeed it is important to note in this context that the effect of backward conditioning on transfer can be dissociated from its effects on conditioned approach. Shiflett (2012) managed to train a backward CS that exhibited positive transfer but suppressed conditioned approach responses (i.e., CS presentation increased lever pressing but reduced magazine approach compared to baseline). Interestingly, in Laurent et al. (2015) and in Laurent and Balleine (2015) a backward conditioning procedure was used to obtain outcome-specific Pavlovian inhibitors for two different rewards. When testing specific transfer, these backward-CSs did not reduce pressing on the lever sharing the same reward as the CS, instead, they increased pressing on the lever paired with the other reward. This was used in Laurent and Balleine (2015) to demonstrate that rats can engage in a form of "counterfactual reasoning", meaning that they can use the information about an absent reward (furnished by the backwardly paired CS) to promote the selection of actions associated with other outcomes (in this case increasing responding on the other lever). One important aspect of these studies was the finding that specific inhibitory predictions mirrored the effects of excitatory predictions and altered action selection quite specifically away from the action delivering the outcome that the inhibitory stimulus predicted would be withheld. To confirm that this effect of backwardly pairing of CS and US was due to inhibition, Laurent and Balleine (2015) went on to assess the effects of conditioned inhibitors established using other methods; i.e., a feature-negative procedure and an overexpectation procedure. Both of these procedures produced identical effects to those induced by backward conditioning; i.e., whereas the conditioned excitors elevated performance of the action with which they shared an outcome, the conditioned inhibitors produced a shift away from the specific action delivering the outcome the inhibitor predicted would be withheld. In summary, excitatory and inhibitory conditioning exert symmetrically opposing effects on specific transfer; biasing choice towards or away from an action based on the information provided by the cues regarding the relative likelihood of earning some specific outcome or other. In humans, Alarcón and Bonardi (2016) used a specific transfer paradigm in which they also trained a Pavlovian inhibitor using a feature-negative design (i.e. A → O1, AX → ∅, with X being the stimulus trained as an inhibitor). When the inhibitor was paired with another CS associated with the inhibited outcome during the transfer test, it abolished specific transfer and the participants instead showed a tendency to respond on the other available response, paralleling Laurent and Balleine's (2015) results.

Lastly, we note that van den Bos et al. (2004) tried to vary the amount of reward associated with the CS (1 or 3 pellets) but found no effect of reward magnitude on transfer.

3.2. Instrumental factors

The amount of training and type of reinforcement schedule can alter the amount of transfer at test. Testing different variable-interval (VI) schedules Meltzer and Hamm (1974) found that VI's with longer intervals, which lead to lower response rates, produced stronger transfer effects. This might be due to transfer being easier to detect on a lower baseline and indeed many transfer experiments include a period of instrumental extinction prior to the test on the view that it makes positive transfer easer to detect (Dickinson et al., 2000). Lovibond (1981) used discrimination training on a single lever in which animals had to discriminate between two alternating periods of reinforcement (on a VR15 schedule S+, chamber fans on) and non-reinforcement (S−, chamber fans off). During the transfer test, the presence of the CS suppressed responding in the S+ period whereas during the S− period the CS produced positive transfer which lasted beyond the duration of the CS itself (10 s). This is consistent with the above reported findings because the S− period was indeed a period with lower baseline. Lovibond (1981) also verified that the enhancement of lever pressing occurred when the baseline was lowered by other means. In a second experiment, he tested the CS after rats had achieved a low baseline due to satiety: in this case, the CS tended to suppress responding rather than enhance it. This result tells us that it was probably not a lower baseline per se that produced the stronger transfer effects but rather the interaction between the expectancy of food generated by the CS and the expectancy of food controlled by the instrumental schedule (Lovibond, 1981). In other words, the CS is more effective on an extinguished baseline because it brings an expectation of food when the current expectation is low. The reduction in transfer observed when testing under satiety can also be seen as consistent with subsequent results by Corbit et al. (2007) and Aitken et al. (2016) which showed that satiety can abolish general transfer (see next section).

Beyond this, Holland (2004) showed that longer training on a VI schedule leads to an increase in the transfer effect when assessed in a single-lever paradigm. Subsequently, Wiltgen et al. (2012) showed that mice trained under a VI schedule exhibited more transfer than those trained under a random-ratio (RR) schedule using an outcome specific transfer design. However, although the group trained on the RR schedules was sensitive to devaluation – whereas a group trained on the VI schedules was not – both groups showed similar rates of performance during training. This is unusual; it is commonly found that ratio schedules promote far higher rates of responding than interval schedules (see Dawson and Dickinson, 1990) suggesting that, for some unspecified reason, the mice in the RR group may have failed to detect the full impact of the ratio contingency. Furthermore, what transfer Wiltgen et al. (2012) reported was clearly not specific transfer; both the same and different actions were elevated relative to baseline but did not differ from each other. The authors concluded that responding that is insensitive to devaluation, and so habitual, might be more sensitive to transfer effects than goal-directed actions and, while this could be the case, it is important to qualify this statement; the evidence suggests that habitual actions are more sensitive to general transfer than goal-directed actions. If this is true, this effect would also explain Holland's (2004) results, in which transfer correlated with the amount of VI training, with the effect growing larger as instrumental performance shifted from goal-directed to habitual control. Furthermore, in a number of studies, Balleine and colleagues have trained rats using ratio schedules and found very clear evidence of specific transfer (Corbit and Balleine, 2005, 2011; Laurent et al.,

2012, 2014; Laurent and Balleine, 2015). As such, Wiltgen et al.'s (2012) results may be anomalous, resulting from an effect specific to instrumental training rather than to the transfer test per se, or may reflect an effect on general as opposed to specific transfer. On balance it seems more likely that the latter is the correct conclusion.

3.3. Other factors and results

In a meta-analysis of 30 transfer studies, Holmes et al. (2010) found a correlation between the degree of transfer and the amount of phase 1 and phase 2 training, regardless of whether the Pavlovian or Instrumental training was conducted first. Increasing phase 1 training seems to increase transfer, whereas increasing phase 2 training seems to decrease it. It is not clear why this training effect emerged but, presumably, it has something to do with the stabilisation of Pavlovian and instrumental learning and, therefore, the relatively consistent impact of the outcome prediction on instrumental performance. Perhaps with less training the associative strength of the CS is still below asymptote and its associative status relatively ambiguous compared to better trained CS's. Specific transfer has been shown to be immune to devaluation: that is, pairing a food outcome with illness (LiCl-induced) prior to the test does not reduce the size of the effect in a subsequent test (Holland, 2004; see also Rescorla, 1994b using discriminative stimuli). However, Corbit et al. (2007) found that devaluation by satiation was able to eliminate general transfer while sparing specific transfer. This is in accord with earlier results that found no effect of devaluation on specific transfer (Holland, 2004) but apparently in contrast with Holland's (2004) results in which devaluation did not appear to affect transfer in a single-lever paradigm. Nevertheless, as suggested above, it is difficult to distinguish specific and general transfer using this kind of design and so this failure to find an effect could be due to any specific transfer component engaged by Holland's task. It is also possible that this discrepancy is due to the devaluation method used (satiation vs illness) or perhaps other variables. More recently Dailey et al. (2016) failed to detect transfer in a single-lever paradigm with the test conducted under satiety. Conversely, transfer was observed under satiety after administation of an antagonist of ghrelin, a peptide related to appetite signalling. Aitken et al. (2016) using a single-lever design with different foods for the Pavlovian and instrumental training, also confirmed that satiety can abolish general transfer.

Corbit and Balleine (2003a) showed that transfer can differentially affect components of an instrumental chain. In particular, they employed a paradigm where pressing a lever led to the appearance of a second lever and pressing this latter lever delivered the food reward. Devaluation and transfer differentially affected responding on these two levers. Transfer only enhanced responding to the proximal lever (i.e., the lever closest to reward delivery) whereas devaluation depressed responding on the more distal lever.

In a recent experiment, Gilroy et al. (2014) demonstrated that specific transfer can be affected by test context. They trained rats to press two levers for two different foods using two different contexts. In one group of rats (Group Differential), each lever-food pairing was trained in a specific context, whereas in the other group (Group Non-Differential) both lever-food pairings were trained in both contexts (alternating contexts in different training sessions). Pavlovian training was conducted in a third context for both groups. When tested for transfer in each of the three contexts, group Non-differential always showed specific transfer. In contrast, Group Differential failed to show specific transfer in the Pavlovian training context but, when tested in the instrumental contexts, showed specific transfer when the CS and the context where not associated with the same food reward. Thus, Group Differential exhibited less specific transfer overall than Group Non-differential. It can be speculated that the differential training reduced the effect of CS presentation by making the contexts more informative and thus rendering the cues redundant. We will discuss this result further in Section 7.

Some studies have explored the relationship between transfer and stress both acute and chronic, and between transfer and stress-related molecules such as corticotropine releasing factor (CRF) or glucocorticoids. Zorawski and Killcross (2003) tested the effects of dexamethasone, a glucocorticoid receptor agonist, in a specific transfer paradigm. They found that administering dexamethasone at the end of Pavlovian sessions impaired the ability of the CS trained during those sessions to evoke specific transfer. A similar result was also found by Pielock et al., 2013b. In 2006, Peciña et al. examined the effects of CRF microinjections in medial shell and found that the highest dose of 500 ng CRF (but not the 250ng dose) enhanced transfer in a single-lever paradigm. Later, Morgado et al. (2012) has found that chronic stress [3] can reduce specific transfer. A stress-free period reversed the effect. In a human transfer study (Pool et al., 2014) acute stress was also found to enhance transfer although Pielock et al. (2013a) failed to find an effect of acute stress on transfer in rodents, with both these studies using "single lever" paradigms. Soares-Cunha et al. (2014) also found that in utero exposure to elevated levels of glucocorticoids impaired both specific and general transfer in rats. Reduced levels of dopamine were observed in prefontral and orbitofrontal cortices and normalization of these levels (using either L-DOPA or a D2/3 agonist, but not a D1 agonist) restored transfer. In humans, Quail et al. (2016) examined the relationship between scores on the Depression Anxiety and Stress Scale (DASS) and transfer, using a full transfer paradigm which also included a fourth cue associated with no reward. Participants with higher scores on the Anxiety and Stress subscale showed higher cue-driven response vigour, meaning that they showed increased instrumental responding even in the presence of the fourth cue associated with no reward. High anxiety participants also seemed to show a somewhat blunted specific transfer, with the cues paired with the two instrumental rewards enhancing both the same and different instrumental actions to a similar degree, albeit this trend compared to low anxiety participants was not stastistically significant.

4. Neural substrates

4.1. Amygdala and nucleus accumbens

Starting from the beginning of this century, lesion studies on rats have begun to uncover the neural basis of the various transfer effects, reporting that both nucleus accumbens (Hall et al., 2001; Corbit et al., 2001; de Borchgrave et al., 2002) and amygdala (Blundell et al., 2001; Hall et al., 2001; Holland and Gallagher, 2003) are necessary for it to take place. During the first studies: an initial disagreement arose about which parts of amygdala (BLA or CeA) and which parts of nucleus accumbens were involved (Nacc Core or Shell). It was reported that CeA and Core, but not BLA or Shell were involved in transfer (Hall et al., 2001; Holland and Gallagher, 2003) and also the opposite pattern of results (Blundell et al., 2001; Corbit et al., 2001). These data were later reconciled when Corbit and Balleine (2005) introduced the full transfer paradigm which was able to distinguish specific transfer from general transfer. Specific transfer is abolished by BLA and Shell lesions whereas general transfer is abolished by CeA and Core lesions (Corbit and Balleine, 2005, 2011). Muscimol-induced inactivation of core and shell have

[3] Using a chronic unpredictable stress paradigm, composed of daily exposures of 1 h to one the following stressors: cold water, vibration, restraint, overcrowding, and a hot air stream.

similar effects as lesions of these structures (Corbit and Balleine, 2011). As a further confirmation, Shiflett and Balleine (2010) used a disconnection procedure between BLA and either medial shell or core and found that only the disconnection involving shell abolished specific transfer. Lingawi and Balleine (2012) found that both anterior and posterior CeA lesions abolished transfer in a single-lever paradigm (therefore presumably general transfer). Human fMRI studies have also confirmed the involvement of amygdala and ventral striatum in transfer (Talmi et al., 2008; Bray et al., 2008; Prévost et al., 2012; Mendelsohn et al., 2014).

Studies investigating the role of glutamate receptors are also in line with the dissociation of neural substrates involved in single and two-lever studies and furnish some details on the mechanisms working inside amygdala that mediate transfer. Mead and Stephens (2003a,b) used a single-lever paradigm to investigate the effects of AMPA receptor subunits GluR1 and GluR2 deletion in mice. Neither deletion impaired Pavlovian or instrumental training, however GluR1 deletion impaired conditioned reinforcement (usage of CS+ as reinforcers) leaving transfer intact, whereas GluR2 deletion impaired transfer while leaving conditioned reinforcement intact. The authors suggested that this dissociation might be explained by GluR1 and GluR2 deletion impacting learning in BLA and CeA respectively, as the behavioral consequences of these deletions mimicked the effects of lesions on these structures (Mead and Stephens, 2003b). This hypothesis was supported by a later finding by Johnson et al. (2007) who found that GluR1 deletion impaired specific transfer. In particular they found that mice without GluR1 expressed non selective transfer when trained in a specific transfer paradigm: i.e. they increased pressing on both levers to similar degree when presented with a CS paired with the outcome delivered by one of the levers, whereas wild-type mice showed specific transfer. All these results are thus consistent with the view that single-lever studies evoke general transfer (mediated by CeA) whereas the specific transfer in two-lever studies is mediated by BLA, without the necessary presence of CeA. However, subsequently Crombag et al. (2008b) found that mutations on GluR1 phosphorylation sites can abolish single-lever transfer in mice. This is at odds with previous results and it may be due to GluR1 deletion triggering different compensatory effects to those induced by alterating phosphorylation sites in Crombag et al. (2008b).

Malvaez et al. (2015) further characterized specific transfer processes in the BLA. They monitored glutamate concentrations during the transfer test and found that glutamate transients were time-locked to and correlated with only the instrumental pressing directed to the lever sharing the same outcome as the CS (i.e., in a specific transfer test). In addition, local blockade of AMPA receptors, but not NMDA receptors, abolished specific transfer. Related results were also obtained by George et al. (2009) who showed that the selective mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) reduced transfer in a single-lever study and by Murschall and Hauber (2005) who did not detect any impact on single-lever transfer using systemic AMPA/KA and NMDA blockade.

Leung and Balleine (2013) characterized the circuit downstream from the Nacc shell by investigating one of its main projections, the medial ventral pallidum (VP-m). Rats exposed to a specific transfer test showed higher expression of the cellular activity marker c-fos in both shell and VP-m compared to controls. Also, both VP-m inactivation and shell-VP-m disconnection procedures abolished specific transfer. In a previous study, lesions of mediodorsal thalamus (MD), which is further downstream as it receivess VP outputs, were found to impair specific transfer (Ostlund and Balleine, 2008). As a consequence, Leung and Balleine (2015) examined the functional contributions of both MD and VTA, which is another target of VP-m. Results showed that VP-m neurons projecting to MD were more active (c-fos) during the transfer test than those projecting to VTA, but it was the activation of these latter neurons that correlated with the absolute size of the transfer effect. Interestingly, by using a disconnection procedure Leung and Balleine (2015) then demonstrated that disrupting the VP-m to VTA pathway reduced the overall rate of responding (similar to a finding by Corbit et al. (2007) following VTA inactivation) whereas disconnecting the VP-m to MD pathway removed the bias of the specific predictive cues on choice (i.e., the specific transfer effect). In this latter VP-m to MD pathway disconnection, the CS elevated the performance of both actions; i.e. both the lever delivering the same outcome as the stimulus and the different action, suggesting that the VTA mediates the motivational component of specific transfer (overall rate of lever press performance) whereas the MD mediates the cognitive component (the effect of predictive learning on choice).

4.2. Molecular processes in nucleus accumbens

A series of studies has attempted to uncover the molecular underpinnings of transfer. Remus and Thiels (2012) investigated ERK kinase activation during transfer in core and shell. They found that CS presentations caused a significant increase in ERK activation in both subregions, with the effect being slightly more robust in the core than the shell. An in-depth review of molecular mechanisms involving ERK in transfer and instrumental conditioning can be found in Shiflett and Balleine (2011). Lex and Hauber (2008) examined instead the effects of D1 and D2 receptor antagonism using SCH-23390 and raclopride injections, respectively, into both core and shell. Both core and shell D1 antagonism abolished transfer in a single-lever paradigm, with D2 antagonism also reducing transfer but to a lesser extent. Similarly Peciña and Berridge (2013) tested the ability of dopamine stimulation (amphetamine microinjection) versus μ-opioid stimulation (DAMGO microinjection) in either core or shell to amplify transfer. Both amphetamine and DAMGO augmented the transfer effect in a single-lever design and did so when infused in both core and medial shell, excluding only a small far-rostral strip of shell. Consistently with this result, in Weber et al. (2016) administering a μ-opioid antagonist (naltrexone) reduced transfer in humans. In contrast to the effects of Lex and Hauber (2008), Laurent et al. (2014) found that SCH-23390, but not raclopride, injections specifically in the Nacc shell abolished transfer in a specific transfer paradigm. Furthermore, in a complex series of experiments, Laurent et al. (2014) showed that delta-opiod receptors (DORs) on cholinergic interneurons (CINs) mediate specific transfer in Nacc shell by altering CIN firing and their effect on D1-expressing medium-spiny neurons (MSNs). First, they confirmed the involvement of shell D1-expressing MSNs by measuring ERK phosphorylation (pERK) after the transfer test and by infusion of SCH-23390 and raclopride. Results showed enhanced pERK in D1 but not in D2-expressing MSNs confirming the effect of SCH-23390 relative to raclopride. They then provided data to support the interaction between processes involving DORs and D1Rs using asymmetrical infusions in the shell. The results showed that rats with infusions of SCH-23390 in one hemisphere and naltrindole (a DOR antagonist) in the other, exhibited no specific transfer. [4] In addition, electrophysiological recordings of CINs in Nacc shell slices taken after the transfer test confirmed alterations in their firing patterns when exposed to deltorphin (DOR endogenous ligand) compared to CINs in slices taken from rats exposed to non-contingent CS training. It was hypothesized that the effect of DOR on CIN firing altered acetylcholine release and that changes in acetylcholing release affected the activity of D1 neurons. With regard to this latter effect, it was further hypothesized that acetylcholine alters D1 MSN activity through the activity of Gi-coupled

[4] In Laurent et al. (2015) naltrindole infusions into shell were also shown to abolish the reversed specific transfer induced by backward conditioning

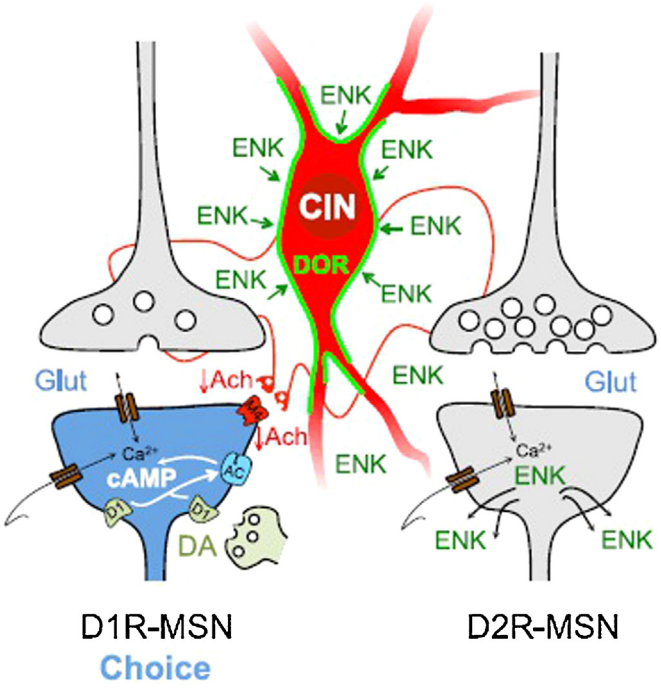

Fig. 3. Model of the complex interactions of opioid, cholinergic and dopamine systems in the Nacc shell during specific transfer, from Laurent et al. (2014). DOR receptors on CIN cell bodies are activated by ENK. ENK alters the firing pattern of CINs, leading to a lower Ach release. Lower Ach release leads to less activation of M4 receptors on D1R-expressing neurons. In turn, the lower activity of M4 permits cAMP pathway signalling, increased D1 neuron activity and so increased specific transfer expression. See text for details of the experiments leading to this model. Reprinted with permission.

M4 receptors recently found to be uniquely expressed on post-synaptic D1 MSNs. Increased activity at the M4 receptor has been found to inhibit D1 activity and reduced M4 binding to increase D1 activity. If DOR activity inhibits acetylcholine release and naltrindole blocks that reduction then a ready explanation for Laurent et al's results could be provided. To test this, Laurent et al. (2014) sought to block specific transfer using peripherally administered naltrindole and then to release that blockade by infusing the M4 antagonist MT3 into the Nacc shell. Although MT3 had no effect on its own, its infusion rescued specific transfer after it was abolished by natrindole, To summarize, Laurent et al. (2014) suggest that, in the Nacc shell, specific transfer is mediated by a complex interaction involving opioid, cholinergic and dopaminergic systems (see Fig. 3). The basis for this interaction is formed during Pavlovian training, with the increased expression of DORs on CINs at the cell membrane (Bertran-Gonzalez et al., 2013). DORs are then activated during the transfer test by enkephaline (ENK), the latter possibly released by D2 MSNs, altering CIN activity and causing lower acetycholine release overall and thus a lower level of M4 binding, resulting in increased D1 neuron activity and increased specific transfer as a consequence.

A confirmation of the involvement of acetylcholine in specific transfer can also be found in Ostlund et al. (2014a), were the effects of scopolamine (muscarinic receptor antagonist) and mecamylamine (nicotinic receptor antagonist) were tested. In this case, both muscarinic and nicotinic acetylcholine systemic antagonism impaired specific transfer. Collins et al. (2016) also examined the role of acetylcholine and its interaction with dopamine, however they focused on Nacc core, using a single-lever paradigm. Using local infusions of scopolamine and mecamylamine combined with fast-scan cyclic voltammetry they showed that acetylcholine antagonism can modulate both transfer and cue-evoked dopamine release in Nacc core. In particular, they showed that muscarinic receptor antagonism suppresses both transfer and cue-evoked dopamine release, while nicotinic receptor antagonism augments transfer and cue-evoked dopamine release. The discrepancy between these latter results and Ostlund et al.'s (2014a) results in which both scopolamine and mecamylamine impaired transfer may be either due to the type of infusions (systemic vs. local) or due to the paradigm used (specific transfer vs. single-lever).

4.3. Dorsal striatum

Corbit and Janak (2007b) found that inactivation of either dorsomedial (DMS) or dorsolateral (DLS) striatum in a specific transfer paradigm had different effects on transfer expression: DLS inactivation abolished specific transfer whereas DMS rendered transfer non-specific, with the CS increasing performance on both the same and different outcome lever. In a later study (Corbit and Janak, 2010), DLS, anterior DMS (aDMS) or posterior DMS (pDMS) were inactivated during Pavlovian and instrumental training: inactivation of DLS and pDMS appeared to impair the acquisition of stimulus-outcome (S-O) associations whereas aDMS and pDMS inactivation impaired response-outcome (R-O) associations, as revealed by Pavlovian and instrumental devaluation tests respectively. In all of the inactivation groups – aDMS, pDMS, and DLS – specific transfer was impaired in a subsequent transfer test. This was expected because specific transfer requires the integration of both S-O (Pavlovian) and R-O (instrumental) associations and any loss of these should, quite naturally, be predicted to impair this integrative process.

In contrast, Pielock et al. (2011) examined the effects of 6-OHDA induced DA depletion in aDMS and pDMS on transfer using a single lever transfer paradigm. Neither depletion had any effect in the single-lever transfer paradigm. Furthermore, in a second experiment that used the specific transfer paradigm, aDMS 6-OHDA again had no effect whereas in the pDMS it had only a minor, if any, effect, suggesting that the dopamine innervation of dorsal striatum is not necessary for transfer.

4.4. Midbrain structures

In a single-lever paradigm, Murschall and Hauber (2006) found that ventral tegmental area (VTA) inactivation by baclofen/muscimol can abolish transfer (supposedly general transfer). However, Corbit et al. (2007) using the same dose effective in Murschall and Hauber (2006) found in the full transfer paradigm that VTA inactivation only attenuated specific and general transfer; essentially reducing but not abolishing these effects.

El-Amamy and Holland (2007) used instead a disconnection procedure to separate CeA from either substantia nigra pars compacta (SNpc) or VTA. In a single lever paradigm, both CeA-SNpc and CeA-VTA unilateral lesion reduced transfer; a CeA-SNpc controlateral lesion (disconnection) also reduced transfer, with no additional effect to the unilateral lesion. Puzzlingly, CeA-VTA disconnection was found to restore transfer to control levels. The result was explained by reference to possible cross-hemispheric inhibitory connections between the two VTAs and CeA output to the SNpc (see also Lee et al., 2011).

4.4.1. Dopamine

Other results have, however, pointed to the involvement of dopaminergic areas such as VTA and SNpc in transfer. Dickinson et al. (2000) showed that dopamine antagonists (such α-flupenthixol) reduced transfer using a single-lever paradigm, a result also replicated in Wassum et al. (2011). Later, Lex and Hauber (2008) used D1 and D2 receptor antagonism in core and shell and

confirmed the ability of dopamine antagonism to reduce transfer in a single-lever paradigm. Conversely, transfer is potentiated by indirect dopamine agonists such as ampethamine (i.e. Wyvell and Berridge (2000), see also Section 5). Using fast-scan cyclic voltammetry Wassum et al. (2013) monitored dopamine release in real time in nucleus accumbens core and showed that during a single-lever transfer test phasic dopamine release evoked by the CS correlated with the increase in lever pressing. This result was also replicated in Aitken et al. (2016). Ostlund and Maidment (2012) instead examined the effects of flupentixol in a specific transfer paradigm, presenting both levers during the test session. They found that although flupentixol reduced the response invigoration generated by the CS, it did not influence the ability of the CS to bias action selection towards the lever sharing the same outcome as the CS. In humans, Weber et al. (2016) administered amisulpride (a selective D2/D3 antagonist) and found reduced transfer in a single-lever paradigm. All these results (and also Soares-Cunha et al. (2014), Laurent et al. (2014) described elsewhere in this review) indicate that the increase in lever pressing during the transfer effect is mediated by dopamine (and likely by VTA); interestingly, the bias towards one lever in a choice situation might be dopamine-independent instead (Ostlund and Maidment, 2012).

4.5. Prefrontal cortex

Basal ganglia structures such as the Nacc form a closed loop with prefrontal cortex and so, given the previous results, the involvement of PFC structures in transfer would be expected. Indeed, Ostlund and Balleine (2007) found that post-training lesions of OFC abolished specific transfer[5], while pre-training lesions had no effect. Subsequently Balleine et al. (2011) reported that this post-training effect was likely a product of sparing aspects of ventral OFC. Complete ventral and lateral OFC lesions produced pre-training deficits in specific transfer (Balleine et al., 2011). Similarly, Scarlet et al. (2012) found a reduction in specific transfer using pre-training OFC lesions, albeit using a very different paradigm. In Bradfield et al. (2015) lesions targeting the medial OFC did not eliminate transfer but instead made it non-specific: i.e. the CS no longer enhanced lever pressing in the *same* condition, but also in the *diff* condition. Despite both ACC and PL having connection with Nacc, Cardinal et al. (2003) found no effects of ACC lesions on transfer using a single-lever paradigm, whereas Corbit and Balleine (2003b) found no effects of PL lesions in a specific transfer paradigm. More recently, Keistler et al. (2015) found that bilateral IL lesions abolish specific transfer. They also employed an IL-Shell disconnection procedure and confirmed that IL mediates this effect via functional connectivty with Nacc shell, also part of the specific transfer circuitry.

4.6. Neural correlates

Finally, we briefly mention two studies that have investigated the neural correlates of transfer using electrophysiological recordings: Homayoun and Moghaddam (2009) and Saddoris et al. (2011). Both studies used a single-lever transfer paradigm. Homayoun and Moghaddam (2009) recorded from medial (mPFC), orbital prefrontal cortex (OFC) and dorsal striatum (DS) of freely moving rats during transfer test sessions. They found that the CS+ amplified neuronal responses to both instrumental nosepokes and Pavlovian approaches in all of these structures. However, the amplification of the instrumental responses correlated with the strength of transfer only in the mPFC and OFC but not DS. Morever, DS neurons represented transfer and approach behavior through mostly-segregated populations, whereas in mPFC and OFC they were represented in overlapping populations of neurons.

In Saddoris et al. (2011) electrophysiological recordings of the single lever transfer test session were conducted in the Nacc core and shell. Multiple groups were used with one exposed to separate cocaine self-administration training. In all groups, neurons in both core and shell encoded information about cues, rewards and responses. In control animals, core neurons were more likely to encode this information, which correlated with behavioral performance in the transfer test. However, neurons that expressed transfer-specific encoding (their lever-press related activity was increased during CS periods) correlated with transfer performance in the shell, but not in the core. The group with a history of cocaine self-administration showed increased transfer and increased neural encoding of task events in the shell. Generally, these studies are consistent with what has been found in lesion and inactivation studies; however, the possibility of mixed transfer effects emerging in single action studies likely accounts for the breadth of the observed effects.

5. Interaction with drugs of abuse

The importance of conditioned stimuli in promoting drug-taking and relapse is widely recognised in addiction research (Belin et al., 2009). Conditioned stimuli associated with drugs of abuse can promote drug use through various mechanisms, such as conditioned approach, conditioned reinforcement as well as Pavlovian-instrumental transfer (Belin et al., 2009). Despite this, relatively few studies have been conducted using the transfer paradigm with drugs of abuse. As an example, searching Pubmed with terms referring to transfer (e.g. PIT, transfer) and addiction (e.g. addiction, cocaine, ethanol, opiate) we found only 27 articles with experiments investigating the relationship between transfer and drugs of abuse. This is a small number compared to other paradigms used in addiction research, e.g. conditioned place preference, for which it is possible to find hundreds of results. As expressed by LeBlanc et al. (2012), this might be due to "experienced or perceived difficulties in generating the PIT [transfer] effect using conventional drug self-administration procedures".

Studies investigating transfer with drugs of abuse have involved different substances, including amphetamine (Wyvell and Berridge, 2000, 2001; Peciña et al., 2006; Peciña and Berridge, 2013; Hall and Gulley, 2011; Shiflett, 2012; Shiflett et al., 2013), cocaine (Kruzich et al., 2001; Saddoris et al., 2011; LeBlanc et al., 2012, 2013, 2014; Ostlund et al., 2014b), and ethanol (Krank, 2003; Ripley et al., 2004; Glasner et al., 2005; Corbit and Janak, 2007a; Krank et al., 2008; Milton et al., 2012; Depoy et al., 2014; Corbit et al., 2016) in rodents and tobacco (Hogarth et al., 2007, 2013b, 2014, 2015; Hogarth and Chase, 2011, 2012; Hogarth, 2012) and beer (Martinovic et al., 2014; Garbusow et al., 2014, 2016) in humans.

These studies show that transfer can be observed with drugs of abuse just as it is observed with natural rewards: a CS associated with drugs of abuse can enhance instrumental responding directed to the drug itself, just as a CS associated with food enhances food responding (e.g. Krank, 2003; LeBlanc et al., 2012; Hogarth et al., 2007). However, there are also some peculiarities of transfer when the subjects are exposed to drugs of abuse. Infact, some studies have found a stronger transfer effect in subjects that have been exposed to drugs of abuse compared to controls (Wyvell and Berridge, 2000,

[5] We note that in Ostlund and Balleine (2007) and in Ostlund and Balleine (2008) lesions of OFC and mediodorsal thalamus were reported to abolish specific transfer although rats actually kept pressing more in the *same* and *diff* conditions compared to the baseline. Although the effect was not statistically significant in those experiments, it is possible that these lesions do not abolish specific transfer but render it "non-specific". Indeed, in Leung and Balleine (2015), disconnection of VP-m from the MD produced a similar "non-specific" transfer effect such that the CS significantly elevated responding on both the *same* and *diff* lever.

2001; Peciña et al., 2006; Peciña and Berridge, 2013; Saddoris et al., 2011; LeBlanc et al., 2013). This enhancement of transfer can be found even when the subject has been previously sensitized and then given the transfer test when drug-free (Wyvell and Berridge, 2001; Saddoris et al., 2011). In other cases, drugs of abuse led to the CS enhancing instrumental responding for all rewards in conditions that usually lead to specific transfer instead (Glasner et al., 2005; Corbit and Janak, 2007a; Shiflett, 2012); i.e., the CS enhanced lever pressing similarly in both the *same* and *different* conditions in a specific transfer paradigm. Apparently, exposure to drugs of abuse (such as alcohol in Glasner et al., 2005; Corbit and Janak, 2007a or amphetamine in Shiflett, 2012) promoted the expression of general instead of specific transfer. A recent experiment (Corbit et al., 2016) confirmed that this is the case by showing that the transfer effect evoked by an alcohol paired CS on both an alcohol paired and a sucrose paired lever is mediated mainly by nucleus accumbens core, a structure involved in general (but not specific) transfer. In Corbit et al. (2016) rats were trained in a specific transfer paradigm using both alcohol and sucrose as rewards. An alcohol-paired CS increased responding to both alcohol and sucrose paired levers, while sucrose-paired CS increased responding more selectively to the same reward lever. Temporary inactivation of either nucleus accumbens core or shell using baclofen/muscimol injections altered these transfer effects: core inactivation reduced transfer induced on both levers by the alcohol CS while leaving transfer induced by a sucrose CS mostly intact directing performance towards the sucrose lever. In contrast, shell inactivation reduced the specificity of transfer while leaving both CS's capable of enhancing lever pressing on both levers.

As we said above, some of these studies have revealed increased transfer after exposure to drugs of abuse compared to drug-naive controls, wheares other have shown that drugs of abuse can lead to the expression of general transfer under conditions in which specific transfer is usually expressed. For brevity, in the following, we will refer to these findings as *potentiation* and *generalization* effects.

Interestingly, studies of transfer with drugs of abuse have so far shown either a potentiation of transfer by drugs of abuse or *generalization* effects but not both at the same time, with psychostimulant studies usually finding the former (Wyvell and Berridge, 2000, 2001; Peciña et al., 2006; Peciña and Berridge, 2013) and ethanol studies the latter (Glasner et al., 2005; Corbit and Janak, 2007a; Corbit et al., 2016). However, it seems likely that this difference is due to the paradigms used and not the substance. Indeed, Shiflett (2012) reported a *generalization* effect when testing amphetamine-sensitization effects on transfer. Studies finding *potentiation* have generally done so in a situation using drug-naive controls but only one rewarding outcome (thus they could not detect *generalization*); whereas studies finding *generalization* have used two rewards but no drug-naive controls (which prevented them from assessing any *potentiation*). It would be interesting to confirm this in a study that aimed to assess both *potentiation* and *generalization* effects at the same time. Nevertheless, it should be noted that not all studies have found these effects.

In some cases this can be attributed to the procedure: Krank (2003), Krank et al. (2008) and Kruzich et al. (2001) used only one reward for all subjects, thus making it impossible to detect either *generalization* or *potentiation*. However, Depoy et al. (2014) compared two groups of rats, one exposed to a prolonged chronic intermittent ethanol exposure (CIE, 16 daily bouts, using alcohol vapors) and a control group. The CIE group showed less transfer in a single-lever paradigm using food rewards. The authors suggested that this might related to the length of CIE, with shorter CIE promoting dorsal striatal-mediated behaviors whilst longer exposures might impair them (DePoy et al., 2013; Depoy et al., 2014). Ripley et al. (2004) also found less transfer in groups exposed to ethanol-withdrawal compared to controls, using a single-lever paradigm with sucrose as reward. However, rats exposed to ethanol had higher baseline levels of responding and the impairment in transfer was significant only when looking at the ratio between responding during the CS and the baseline. As we noted in Section 3, transfer is harder to detect when baseline responding is higher.

Drugs of abuse can alter dopamine transmission and dopamine is involved in the expression of transfer as we have seen in Section 4. Hence, a possible neural mechanism of *potentiation* might involve dopamine: Ostlund et al. (2014b) monitored phasic DA release in Nacc core using fast-scan cyclic voltammetry and reported that prior cocaine exposure enhanced both transfer and mesolimbic DA signalling, with both measures being correlated. In contrast, *generalization* might be related to the ability of drugs to promote habitual actions (LeBlanc et al., 2013). Given that specific transfer requires action-outcome encoding, it might be argued that a switch from goal-directed to habitual actions should also promote a switch from specific to general transfer, providing a possible explanation of the *generalization* effect. However, results from Hogarth et al. (2013b) suggested that a drug-induced switch to habitual actions did not cause a loss of specific transfer, at least in human subjects.

This latter study was part of a series by Hogarth and colleagues assessing habitual smokers in which transfer was used to understand the role of cues in drug-seeking (Hogarth et al., 2007, 2013b, 2014, 2015; Hogarth and Chase, 2011, 2012; Hogarth, 2012). In this series of studies, it was shown that a CS associated with tobacco biased choice towards tobacco-related actions in an instrumental choice test and that this effect was not diminished when tobacco was devalued by showing health warnings or through satiation (i.e. after a smoking session). In these studies, neither *generalization* nor *potentiation* effects were detected. It is possible that the presence of these effects might have been masked; for example the *potentiation* effect might be masked by the fact that the participants were all smokers, so there was no drug-naive control. However, there was a distinction between daily and non-daily smokers and no correlation was found between this factor and transfer. As for the *generalization* effect, we point out that the transfer test was always conducted as a choice test; thus the ability of the drug CS to prompt both choices may not be detected because an enhancement in both choices would balance each other out when analyzing proportion of choices.

As already mentioned, transfer and other Pavlovian conditioning effects are considered to play an important role in drug addiction (Belin et al., 2009). Milton and collegues have, therefore, studied how pharmacological intervention in memory reconsolidation processes could disrupt maladaptive Pavlovian associations. In particular, Milton et al. (2012) found that both transfer and Pavlovian approach effects can be disrupted using the NDMAr antagonist MK-801 in conjunction with Pavlovian memory reactivation in ethanol self-administering rats; in contrast, the β-adrenergic antagonist propranolol had no effect (although it was previously shown to affect conditioned reinforcement by Milton and Everitt, 2010).

Recently, studies have investigated the transfer effect in alcohol dependent subjects. In a first pilot study, Garbusow et al. (2014) tested transfer in both detoxified alcohol-dependent patients and controls. In their paradigm, instrumental actions led to either monetary rewards or losses and, similarly, Pavlovian CSs were associated with either monetary reward, with losses, or with pictures of drinks (alcohol or water). The patient group showed a stronger transfer effect on the negative transfer part of the experiment; i.e., they showed stronger suppression of instrumental responses by the CS associated with monetary losses. In a subsequent study this stronger transfer effect in the detoxified alcohol-dependent group was confirmed compared to controls (Garbusow et al., 2016). Indeed, in this study a stronger overall transfer effect was detected, not just an effect specific to the negative CS. In addition, participants

underwent fMRI scanning which found that BOLD activation in the left Nacc was related to the transfer effect. This activation was also predictive of relapse and alcohol intake during a 3 month followup, thereby establishing the clinical significance of transfer and its neural correlates for alcohol-dependence treatment. Martinovic et al. (2014), instead, tested transfer using beer and chocolate cues on a group of social drinkers but in this study no correlation was found between transfer effects and individual differences of drinking behavior. However, in this latter study, as in Hogarth studies of smokers, the participants were drug users (but not necessarily dependent) and no control group naive to the substance was used, which might account for their failure to find a *potentiation* effect.

Readers interested in the relationship between transfer, drugs of abuse and addiction might also refer to the recent review by Lamb et al. (2016) which analyzed some of the studies reported here in terms of their support for theories of addiction.

6. Human transfer

In the last decade, transfer has also been investigated in humans, with results similar to those previously shown in rodents. The presence of both specific and general transfer in humans has been confirmed (Nadler et al., 2011; Prévost et al., 2012; Watson et al., 2014). Studies using fMRI have also confirmed roughly the same main neural structures underlying transfer with the involvement of the amygdala (Talmi et al., 2008; Prévost et al., 2012; Mendelsohn et al., 2014) and NAcc (Talmi et al., 2008; Mendelsohn et al., 2014) or the nearby ventrolateral putamen (Bray et al., 2008; Prévost et al., 2012). More detailed confirmation such as the involvement of shell versus core in the two types of transfer might follow as fMRI resolution increases.

The tools and experimental approaches vary greatly among human transfer studies, with some employing a "game-like" paradigm with abstract rewards (Paredes-Olay et al., 2002; Allman et al., 2010) whilst others have employed paradigms similar to rodent studies using food rewards (Bray et al., 2008; Watson et al., 2014). In particular, Lovibond and Colagiuri (2013) developed a human paradigm very close to the rodent version (even using a food dispenser). Morris et al. (2015), on the other hand, have used perhaps the most ecologically valid paradigm involving the interaction with a simulated vending machine. Participants learned to associate different colors on the vending machine with different snack food outputs (the Pavlovian phase), whereas the instrumental phase involved choosing between two actions that tilted the machine and liberated different snack foods. As another interesting variant, one fMRI study confirmed the involvement of the amygdala and Nacc in transfer using motor imagery rather than the motor action: the instrumental action thus consisted in the participants imagining themselves throwing a ball or a rock with their right hand without actually moving it (Mendelsohn et al., 2014).

Some studies have investigated the role of devaluation in transfer, finding conflicting results: Allman et al. (2010) reported that devaluation was able to eliminate specific transfer whereas Watson et al. (2014) reported devaluation having an effect only on general transfer with no effect on choice bias (specific transfer). These differing results might be explained by the different paradigms used. In Allman et al. (2010) the participant played a "stock market game" in which devaluation was induced by ensuring one of the outcomes no longer had any monetary value; whereas in Watson et al. (2014) devaluation was generated by food satiation. The devaluation in Allman et al. (2010) was, therefore, of a more cognitive nature and it might have worked as an additional rule of the game instead of a "motivational" change, such as satiation, thus leading to the different result. Furthermore, Eder and Dignath (2015) also obtained specific transfer after devaluation and suggested that the previously contrasting results might also be due to using a primary reinforcer (food) vs. a secondary one (money). However, Eder and Dignath (2015) found that specific transfer on primary rewards can be eliminated by devaluation if the participants had to consume the reward that was made aversive. In particular, they ran two experiments using a liquid reinforcer that was devalued by pairing its consumption with bad tasting Tween20. In one case, participants had to drink the earned liquid rewards immediately after the transfer test, whereas in the other case they could just take the bottles home. Only in the first case, when they were asked to consume the devalued reward, did devaluation eliminate the specific transfer effect during the test. [6] It is interesting to note that Eder and Dignath's (2015) results were obtained using aversive devaluation, which might lead to different results compared to devaluation through satiation (see also Corbit et al. (2007) vs. Holland (2004) results in animal studies, Section 3). Subsequently Eder and Dignath obtained again a reduction of specific transfer through devaluation using a "stock-market game" similar to the one used by Allman et al. (2010). In this case, they also tested the effects of an "upvaluation" of the outcomes (an increase of their monetary value in the game) but observed no effect of the upvaluation on transfer (Eder and Dignath, 2016). Instead, Colagiuri and Lovibond (2015) tested transfer after variable amounts of instrumental training to manipulate satiation and provided data in support of transfer as a mechanism of food over-consumption. The overall results showed that participants with a low-baseline response rate, which had supposedly reached a higher level of satiation during the instrumental training, still showed a significant transfer effect. This further confirms that transfer is present after devaluation, at least when conducted using satiation. In contrast, high-baseline responders, which where supposedly less sated and more actively seeking the chocolate outcome, showed no significant transfer effect when tested with the CS+ but did show an inhibitory transfer effect when tested using the unpaired CS−. This latter finding is in line with the fact that positive transfer effects are harder to find when baseline responding is higher (see Section 3).

Beyond Colagiuri and Lovibond (2015), transfer as a mechanism of food over-consumption was also hypothesized in Watson et al. (2016). In this latter work, transfer using food rewards was tested and found in adolescents, as a part of an investigation about possible factors of an obesogenic environment.

Rosas et al. (2010) studied the relationship between specific transfer and extinction and found that extinction does not alter the ability of cues to promote specific transfer. This is consistent with the results of Delamater (1996) in rodents. In a recent study, Hogarth et al. (2014) further confirmed that extinction by non-reinforcement does not alter specific transfer. However, these authors also found that discriminative extinction training (pairing the CS with the extinction of an instrumental response) can abolish specific transfer, a result also found earlier by Gámez and Rosas (2005). In a third experiment, Hogarth et al. (2014) also managed to abolish specific transfer using explicit verbal instructions stating that the CS did not signal a more effective response-outcome contingency. These results suggest the hypothesis that the specific transfer effect might be of a hierarchical nature, with the CS signalling the efficacy of an action-outcome (A-O) contingency (Hogarth et al., 2014; Hogarth and Troisi, 2015). Thus, extinction procedures such as discriminative extinction or the verbal instructions targeting directly the S-(A-O) hierarchy are effective in blocking transfer whereas those targeting the simple S-O association are not. Of course such procedures may also be effective

[6] On a similar note, Colwill and Rescorla (1990) showed that whereas devaluation usually leaves some residual instrumental responding, this responding could be eliminated if the reward was delivered intraorally instead of into a magazine.

because they produce a form of instructed extinction of the instrumental contingency. Lastly, as already mentioned in Section 3, using a single-lever paradigm Lovibond et al. (2015) found a reduction in transfer after Pavlovian extinction of the CS. As the authors point out, one of the critical differences between their results and those previously reported was the fact that they focused on absolute response rate (using a single-lever paradigm), whereas other studies employed a choice test (specific transfer). Given that single-lever paradigms usually measure general transfer, we thus speculate that specific and general transfer might be differentially affected by CS extinction.

As already reported (see Section 5), human studies have also investigated transfer in the context of drugs of abuse, such as tobacco and alcohol (Hogarth et al., 2007, 2013b; Hogarth and Chase, 2011; Hogarth, 2012; Martinovic et al., 2014; Garbusow et al., 2014, 2016). In a series of studies (Hogarth et al., 2007, 2013b, 2015; Hogarth and Chase, 2011; Hogarth, 2012), Hogarth and colleagues showed with a transfer paradigm that cues related to cigarettes can affect smoking and that they do so independently of value (confirming that specific transfer is immune to devaluation as in Watson et al., 2014). Transfer was also investigated in alcohol users and abusers (Martinovic et al., 2014; Garbusow et al., 2014, 2016). Garbusow and colleagues investigated transfer in groups of detoxified alcohol-dependent patients and in controls, finding stronger effects in the patients group (Garbusow et al., 2014, 2016). The strength of transfer effect was also related to a stronger left Nacc activation and it was predictive of relapse and alcohol intake in a 3 months follow-up (Garbusow et al., 2016). Martinovic et al. (2014) tested transfer in social drinkers instead and they did not find a correlation between the behavioral transfer effect and individual differences in drinking behavior.

Freeman et al. (2014) developed a variant of transfer in which instrumental training was embedded in a Go-NoGo task; i.e., a normal single-lever paradigm was subdivided into trials in which an additional cue signaled a Go condition (the participant can press the lever) or NoGo (the lever must not be pressed). Within this paradigm, Freeman et al. (2014) and Freeman et al. (2015) investigated the mechanism of response suppression during CS+ "provocation", finding that NoGoCS+ trials suppressed CS+ response not only within the trial but also on the following trials.

Garofalo and di Pellegrino (2015) instead investigated individual differences in a single-lever transfer paradigm. In particular, they subdivided the participants into two groups according to their eye-gaze behavior during the Pavlovian phase. During CS presentations, those who spent most time fixating on the CS were considered sign-trackers, whereas those who spent most time fixating on the location where the reward would be delivered were classified as goal-trackers. The results of the transfer test showed that only sign-trackers increased their lever pressing when the CS was presented. Another study focusing on transfer and individual differences was conducted by Sebold et al. (2016) in which they tested 243 participants in both a transfer paradigm and in a two-step task aimed at distinguishing model-based vs. model-free reasoning (Daw et al., 2011). Model-based and model-free reasoning are computational concepts relating respectively to goal-directed and habitual behavior. Sebold et al. (2016) found a correlation between the transfer task and the two-step task, indicating that people exhibiting stronger transfer effects showed less model-based ("goal-directed") reasoning in the two-step task.

Human transfer has recently been used to characterize neuropsychiatric disorders. In particular, it has been used as a part of a wider array of tests to assess dysfunctions in goal-directed action in schizophrenia (Morris et al., 2015). Huys et al. (2016) tested patients with a major depressive disorder using a transfer paradigm that included both appetitive and aversive CS's, as well as instrumental responses that consisted in either approach or withdrawal from a stimulus. As in previous studies (Huys et al., 2011), healthy controls exhibited a transfer effect in which appetitive CS increased instrumental approach responses and decreased withdrawal response, whereas the aversive CS did the opposite. This "action specificity" was markedly reduced in depressed subjects and individuals with higher "action specificity" showed better recovery over the follow-up period (4–6 months). In Geurts et al. (2013b) transfer has also been investigated as a possible link to neuropsychiatric disorders associated with aggression.

While the focus of this review is on appetitive transfer, we note here that human transfer studies have also employed aversive transfer paradigms, i.e. the ones above mentioned Huys et al. (2011, 2016), Geurts et al. (2013b) or also Rigoli et al. (2012), Geurts et al. (2013a), Lewis et al. (2013). Lastly, as already reported in Section 3, using a human transfer paradigms Pool et al. (2014) found that acute stress enhanced transfer and Quail et al. (2016) found a correlation between DASS scores (Depression Anxiety and Stress Scale) and an enhanced cue-driven response vigour.

7. Theoretical aspects of transfer

Over many years, various theories of the general and, more recently, the specific transfer effect have been proposed. It has, for example, been argued that a Pavlovian CS affects instrumental actions by changing the animals' motivational state (Estes, 1943; Rescorla and Solomon, 1967); e.g., a CS associated with food could elicit a motivational state associated with hunger and thus promote instrumental actions towards food. However, this view does not explain specific transfer effects. The presence of both general and specific transfer can, however, be reconciled by adopting the Konorskian view (Konorski, 1967) that Pavlovian training can lead to two types of associations, one between the CS and the motivational/affective qualities of the US and one between the CS and specific sensory features of the US. This dual view fits the general/specific dichotomy, with specific transfer reflecting Pavlovian associations of the CS with more specific features of the US and general transfer the CS-motivational/affective state associations.

The associative-cybernetic model, reviewed more extensively elsewhere (Cartoni et al., 2013), is probably the most comprehensive model of transfer to date as it suggests mechanisms for both specific and general transfer and also a neural implementation (Balleine and Ostlund, 2007, see Fig. 4). In brief, it posits a S-O, O-R chain through associative and S-R memories to explain specific transfer and also a general enhancing of all instrumental actions through the association of stimuli with rewards. However, the model has some shortcomings and, in its current form, does not explain all transfer data. In particular, it does not explain why, in the full transfer paradigm, no general transfer is observed in either the *same* or *different* conditions. In its most recently described form (i.e., Balleine and Ostlund, 2007) the model appears to predict that in both these conditions the CS will elicit at least some general transfer: in the "same" condition this effect would be on top of the specific transfer effect, whereas in the *different* condition it should emerge alone as increased responding over baseline. Instead, lesioning the specific transfer circuit in the *same* condition does not reveal a residual general transfer component, whereas the *different* condition usually shows neither general nor specific transfer nor is responding in this condition influenced by any known neural manipulation. There is, currently, no mechanism in the model that can explain the lack of general transfer in these cases. It may, however, be possible to reformulate it in the light of recent data revealing the effects of inhibitory conditioning on transfer (e.g., Laurent and Balleine, 2015) to include specific 'no outcome' representations in the associative memory, which could result in

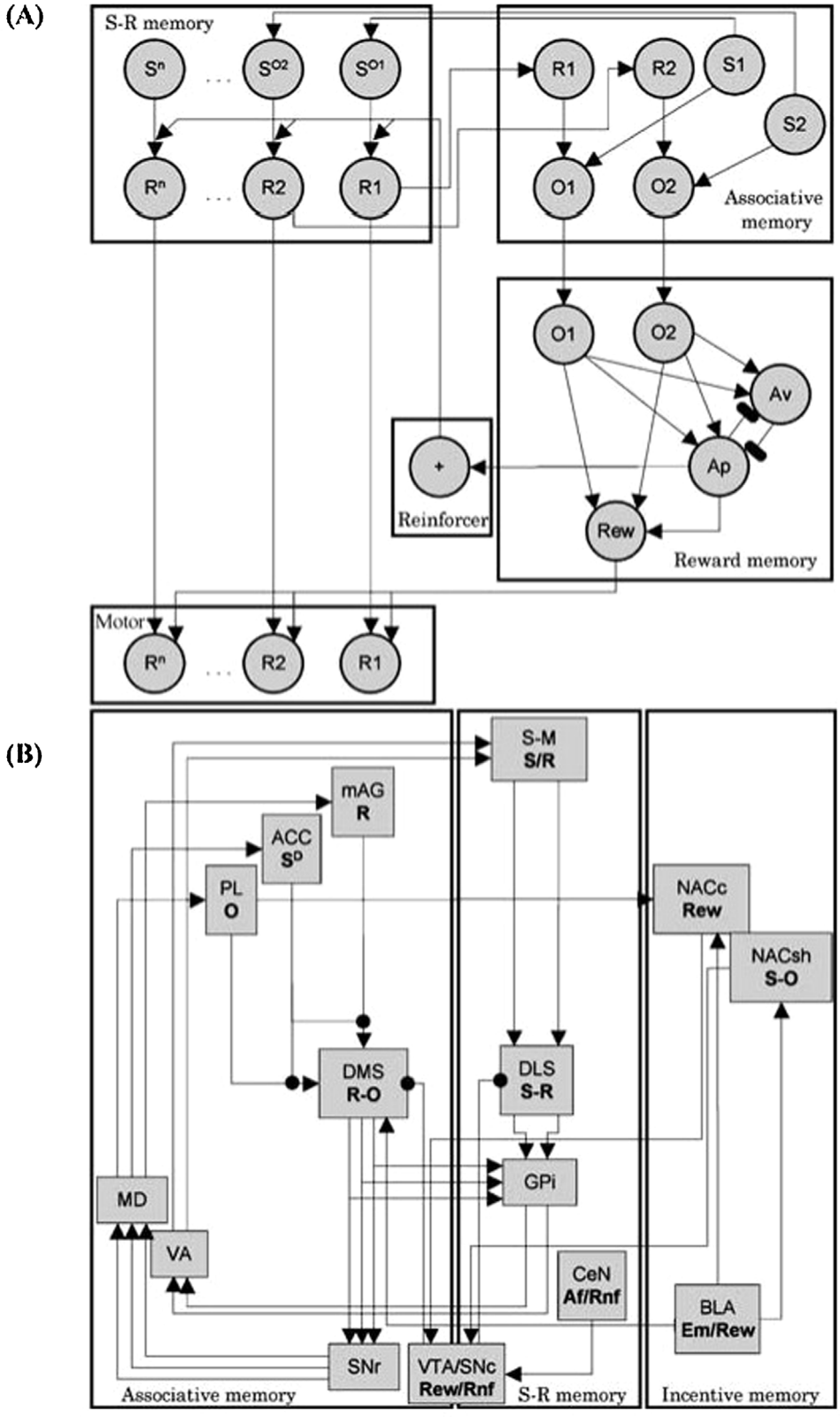

Fig. 4. Associative-cybernetic model by Balleine and Dickinson as reported by Balleine and Ostlund (2007). (a) Pavlovian CS associations (S-O) are stored in the associative memory and they can produce transfer using two pathways. On one side, each CS can prime the representation of its associated reward as an antecedent of a specific response: i.e. S1 primes S^{O1} in the S-R memory which then activates R1 (specific transfer). On the other hand, they also generate an expectancy of reward through connections to the Reward memory which can then enhance all responses (general transfer, using the connection from Rew to all the Motor responses). (b) Suggested neural substrates underlying each part of the model. Reprinted with permission.

more specific outcome predictions and so less general transfer. However, this re-formulation has yet to be tested quantitatively.

As an alternative theory, van den Bos et al. (2004) have proposed a behavioral chaining account of transfer. According to this proposal, CSs elicit magazine visits (due to Pavlovian training) and these in turn elicit lever presses due to a lever-magazine-lever behavioral chain that they argue is established during instrumental training. Under this hypothesis we would, therefore, expect a positive correlation between magazine entries and lever pressing because these responses would usually occur together one after another. However, this explanation does not seem to fit with those experiments that have presented both lever press and magazine approach timing data (e.g. see Fig. 6 of Holland and Gallagher, 2003). Magazine approach does not seem to correlate with lever pressing; indeed it has usually been found to interfere through competition and so, in many cases, to be the inverse of lever pressing.

Another alternative explanation of transfer has been proposed by Cohen-Hatton et al. (2013). These authors argued that transfer is due to CS-R associations formed during the instrumental and Pavlovian training sessions. They suggested that when Pavlovian training follows instrumental training, the experience of O also evokes the previously learned response R, due to the previously learned R-O association. As O and its evoked memory of R follow the CS, a CS-R association can also be formed alongside the CS-O association. Conversely if instrumental training follows Pavlovian training, it is the CS that is evoked in memory by the experience of O, due to the previously acquired CS-O association, allowing, again, an association to be formed between the CS and R. Thus, despite the two types of training being conducted in separate sessions, the evoked memories establish, on this account, associations between the Pavlovian stimuli and the instrumental responses. These associations would then lead to (specific) transfer on test, not through the integration of Pavlovian and instrumental conditioning on test but due to their integration during training. However, data from Gilroy et al. (2014) goes against this hypothesis. In their experiment one group of rats received instrumental training on two levers in a different context for each lever, whereas another group was trained with both levers in both contexts. Pavlovian training was always conducted in a third context. When given the transfer test in the Pavlovian context, the group of rats that received their training on the two levers in different contexts displayed almost no specific transfer compared to rats that received their instrumental training in both contexts. There is no obvious reason why making lever-training context specific would change the ability of evoked memories to form the S-R associations advocated by Cohen-Hatton et al. (2013) to explain transfer. Nor, on this account, is it clear why presenting the US and CS in a backward relationship separated by a 10-s interval should reverse the specific transfer effect, but not when presented without an interval, as Laurent and Balleine (2015) reported. Cohen-Hatton et al. (2013) argue that such an effect might rely on an inhibitory connection between S and R developing over the delay. But such an effect, whilst reducing the performance of that specific response, does not imply that the performance of other actions should increase above baseline as Laurent and Balleine (2015) demonstrate; the reversal of the standard transfer effect that allows an inhibitory CS to drive performance of alternative actions above baseline performance is simply not predicted by their account.

On the other hand, the context-specificity of transfer found by Gilroy et al. (2014) might be in agreement with proposals suggesting that CSs enhance instrumental responding by virtue of their predictive value (Hogarth et al., 2013a, 2014; Hogarth and Troisi, 2015; Cartoni et al., 2013). In particular, Hogarth has proposed that specific transfer works by enhancing the R-O relationship in a hierarchical manner: CS-(R-O). This account suggests that even though CSs are trained in separate sessions and have no veridical hierarchical relation to the instrumental schedule, they still act like discriminative stimuli that signal when a specific R-O relationship is in effect. In other words, the subject builds a hierarchical representation even if it is not warranted by the procedure. Indeed, this account is also in agreement with Lovibond (1981) results we cited earlier, where the transfer effect was particularly evident when the instrumental schedule was signalled as being in extinction (S−) compared to when it was signalled to be active (S+). This kind of account is also in line with the Gilroy et al. (2014) results if we think that, in the differential group (i.e., the group in which the two levers were trained in different contexts), the specificity of training supports the ability of the rats to distinguish when a lever is active compared to the non-differential group (i.e., in which both levers were trained in both contexts). Thus, it should be expected that a CS, as a discriminative stimulus, will provide greater benefit to the non-differential group. Indeed, the CS produced a robust specific transfer effect in the non-differential group; in contrast, in the differential group, specific transfer was observed only when testing was conducted in the instrumental context in which the lever was not trained and so where the action and the CS predictions with regards to the outcome were no longer identical.

Besides developing an understanding of the mechanisms of transfer, we think it will be important to explore and develop theories as to *why* transfer developed in the first place: i.e., its adaptive function. In Cartoni et al. (2013) we noted that specific transfer,

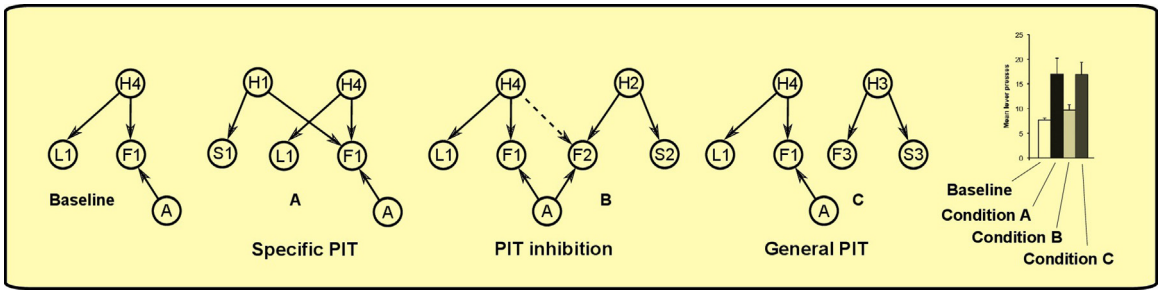

Fig. 5. Bayesian transfer model by Cartoni et al. (2013). In this model, both Pavlovian and instrumental conditioning are represented in terms of latent causes learning. The model is formed by a belief network, where latent causes are represented by nodes labeled with H (H1, H2, H3, H4), while CS are labeled S1, S2, S3 (sounds) and US with F1, F2 (foods); the A node represents the action of pressing a lever. During training the subject associates different latent causes to the different CS-US and lever-outcome pairings experienced. During the transfer test, the different latent causes interact producing the various transfer effects: (a) in the presence of a CS paired with the same food F1 as the lever, both latent causes, the one learned in the Pavlovian phase and the one learned in the instrumental phase, will increase the probability that food F1 will be delivered, thus increasing the expected *efficacy* of the action (the specific transfer effect); (b) due to the alternating training between the lever for food F1 and the lever for food F2, the subject has learned that the latent cause H4, associated with lever L1, actually diminishes the probability of food F2 being delivered (dashed line), thus inhibiting the effects of a CS paired with F2 (inhibition of general transfer); (c) when a CS paired with another food F3 is displayed, along with the presence of lever L1, two foods are predicted, raising the *value* of acting in the present (the general transfer effect). Histogram from Corbit and Balleine (2011). Reprinted with permission from Cartoni et al. (2013).

general transfer and the inhibition of general transfer can be related to three aspects of action, respectively: *efficacy*, *utility* and *context*. In all three cases the information provided by cues is used to better evaluate which action to select. Specific transfer is related to the efficacy of the actions, namely the opportunities that they have to reach their goal. This is compatible with the interpretation of CSs as discriminative stimuli providing information as to when an action is effective or not (Hogarth et al., 2014). In particular, the model proposed that CS's increase the estimated probability of receiving the outcome associated with an action (Fig. 5). This led us to the hypothesis that instrumental actions having a 100% chance of receiving a reward (i.e. continuously reinforced) should not be enhanced through specific transfer since the probability of reward is already at maximum. In Cartoni et al. (2015) we tested this hypothesis, showing that indeed specific transfer was reduced when instrumental actions were trained with continuous reinforcement (compared to an RR3 schedule), albeit it was not reduced to zero as predicted. In the model, general transfer is instead related to the utility of performing actions: i.e., the amount of rewards available by performing actions. In this case the CSs are supposed to signal the presence of additional resources in the environment thus promoting general activity to try to achieve them. Inhibition of transfer is related to the ability to take context into account and inhibit general transfer when those additional resources cannot be achieved. This might be merged with how specific transfer seems to work, as noted above in relation to Gilroy et al. (2014) where specific transfer signals are also dependant on the context. How these functions are mediated, both at the algorithmic levels (which variables are involved) and at the neural level remains an open question.

8. Conclusions and future directions

In this paper, we have reviewed a wealth of data on Pavlovian-instrumental transfer: we have seen how we can distinguish two types of transfer (specific and general), their relative neural substrates, and many of the factors interacting with them.

From the behavioral point of view, the paradigm has been improved to distinguish specific and general transfer and it is now applicable to human participants as well. Its reliability has grown sufficiently that it is proving useful to characterize pathologies as well, as we have seen for schizophrenia, addiction, and major depressive disorders (e.g., Morris et al., 2015; Garbusow et al., 2016; Huys et al., 2016).

Some questions remain open: as an example, the influence of devaluation procedures on transfer have had mixed results, possibly due to the different devaluation procedures used. In rodents, satiation abolished general transfer (Corbit et al., 2007; Aitken et al., 2016), but pairing with illness had no effect (Holland, 2004). In humans, specific transfer too had mixed results with "cognitive" devaluation able to cancel or reduce transfer (Allman et al., 2010; Eder and Dignath, 2016) whereas satiation did not affect it (Watson et al., 2014). Also, aversive devaluation was effective only if coupled with immediate consumption (Eder and Dignath, 2015).

As for the neural substrates, a number of areas, ranging from amygdala to the striatum and prefrontal cortex have been implicated in transfer. What is lacking at the moment is a system-wide view of how these areas interact together to produce the two types of transfer. So far a more detailed picture has been achieved locally for the Nacc shell and its projection to ventral pallidum (Laurent et al., 2014; Leung and Balleine, 2013, 2015). Assessing the interaction with DMS and DLS might be particularly interesting because they are recognized as fundamental areas for the two kinds of instrumental action: goal-directed and habitual actions respectively (Balleine and O'Doherty, 2010). A point of integration between Pavlovian and instrumental learning might also be the corticothalamic circuit, as suggested in Balleine et al. (2015). Establishing the site(s) of integration would provide the basis for exerting control over the way Pavlovian predictive learning affects choice, providing considerable insight.

On the theoretical side, a question remains as to the main functional variables on which transfer acts. For example, is specific transfer related to the evaluation of the efficacy of an action, as proposed by Hogarth et al. (2013a), Cartoni et al. (2013)? We have seen that one of the latest theories favours a hierarchical account of transfer (Hogarth et al., 2014; Hogarth and Troisi, 2015), where a CS signals the availability of a R-O relationship in the environment. This is also compatible with recent accounts of biconditional discrimination (Bradfield and Balleine, 2013) which point to the formation of such hierarchical associations S-(R-O). This would make the CS in transfer, or at least in specific transfer, a special form of discriminative stimulus, even if not explicitly trained as such, not being present during the instrumental training sessions.

On the general transfer side, an important open issue is why in some cases no "general motivating effects" are observed despite the presence of the CS: i.e. in the *same* or *different* conditions. There appears to be some form of inhibition present that has not yet been well specified (Corbit and Balleine, 2005, 2011). Laurent and Balleine (2015) shows that rats do not only learn which action lead to which outcome (positive R-O associations) but also which action does not earn which outcome (inhibitory R-O associations). This points to the possibility that, with more than one action, inhibitory R-O associations develop and it is these that allow animals to segregate the effects of the CS's on same and different actions. At the functional level, we have proposed that general transfer is manifest only when the CS signals additional achievable resources: so in the *same* condition general transfer is not present because the outcome is already predicted by the instrumental action, whereas in the *different* condition it might be the alternating training with the different lever that inhibits general transfer; the signalled outcome is not achievable in that situation (Cartoni et al., 2013). However, the mechanism of this inhibition remains to be discovered. We have reviewed some manipulations that lead to a "generalization" of the transfer effect (e.g. Glasner et al., 2005; Corbit and Janak, 2007a,b; Shiflett, 2012): if we interpret and investigate these as a "disinhibition" of general transfer perhaps they will provide some indication as to how the inhibition of general transfer is normally achieved. Indeed Corbit et al. (2016) have shown that the "generalized" transfer exhibited by an alcohol CS can be reduced by inactivating nucleus accumbens core rather than the shell, so this is consistent with the idea of the "generalization" being mediated by the same circuitry as general transfer.

On a higher level, we actually need more experiments on general transfer to establish whether it is purely a motivational phenomenon or whether it is mediated by a general representation of the appetitive outcome. In this context we could return to the issues surrounding motivational control of transfer particularly the irrelevant incentive effect (Dickinson and Dawson, 1987; Balleine, 1994) and establish whether those motivational effects are performance related or learning related. Perhaps the animal learns to class the outcome as a motivational type (e.g. food or fluid) or perhaps the energetic effects of stimuli associated with foods and fluids are simply gated by motivational state. There just have not been enough experiments on general transfer. We do not know much about the neural system mediating this form of transfer. Although CeN and NACcore are involved, are they connected in some way? No disconnection study between these structures has been conducted yet.

Another direction for future research would be to study transfer with more actions or chains of instrumental actions. Most studies on specific transfer have largely used two actions or choice between two transfer actions. It would be interesting to see how

things function in three or four action situations, which would also be a more ecological setting since we are often confronted with more than just two options. Using a two-step instrumental chain, Corbit and Balleine (2003a) found that the proximal element of the chain (but not the distal) were influenced by the CS in an outcome specific manner. Can general transfer affect instrumental chains? It would also be interesting to examine chains of different lengths or homogeneous vs. heterogeneous chains.

Whatever future studies are conducted, the experiments and phenomena reviewed here show that the increasing sophistication and reliability of the Pavlovian-instrumental transfer paradigm, its application to human participants, in both normal and pathological conditions, and its close connection with fundamental learning processes, such as instrumental and Pavlovian conditioning, will continue to make it a promising area of research in the years to come.

References

Aitken, T.J., Greenfield, V.Y., Wassum, K.M., 2016. Nucleus accumbens core dopamine signaling tracks the need-based motivational value of food-paired cues. J. Neurochem. 136 (5), 1026–1036.

Alarcón, D., Bonardi, C., 2016. The effect of conditioned inhibition on the specific pavlovian-instrumental transfer effect. J. Exp. Psychol. Anim. Learn. Cognit. 42 (1), 82–94.

Allman, M.J., DeLeon, I.G., Cataldo, M.F., Holland, P.C., Johnson, A.W., 2010. Learning processes affecting human decision making: an assessment of reinforcer-selective pavlovian-to-instrumental transfer following reinforcer devaluation. J. Exp. Psychol. Anim. Behav. Process. 36 (3), 402–408.

Balleine, B., 1994. Asymmetrical interactions between thirst and hunger in pavlovian-instrumental transfer. Q. J. Exp. Psychol. B, Comp. Physiol. Psychol. 47 (2), 211–231.

Balleine, B.W., Dickinson, A., 1998. Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. Neuropharmacology 37 (4–5), 407–419.

Balleine, B.W., Leung, B.K., Ostlund, S.B., 2011. The orbitofrontal cortex, predicted value, and choice. Ann. N. Y. Acad. Sci. 1239, 43–50.

Balleine, B.W., Morris, R.W., Leung, B.K., 2015. Thalamocortical integration of instrumental learning and performance and their disintegration in addiction. Brain Res. 1628 (Pt A), 104–116.

Balleine, B.W., O'Doherty, J.P., 2010. Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 35 (1), 48–69.

Balleine, B.W., Ostlund, S.B., 2007. Still at the choice-point: action selection and initiation in instrumental conditioning. Ann. N. Y. Acad. Sci. 1104, 147–171.

Baxter, D.J., Zamble, E., 1982. Reinforcer and response specificity in appetitive transfer of control. Anim. Learn. Behav. 10 (2), 201–210.

Belin, D., Jonkman, S., Dickinson, A., Robbins, T.W., Everitt, B.J., 2009. Parallel and interactive learning processes within the basal ganglia: relevance for the understanding of addiction. Behav. Brain Res. 199 (1), 89–102.

Bertran-Gonzalez, J., Laurent, V., Chieng, B.C., Christie, M.J., Balleine, B.W., 2013. Learning-related translocation of δ-opioid receptors on ventral striatal cholinergic interneurons mediates choice between goal-directed actions. J. Neurosci. 33, 16060–16071.

Bindra, D., 1974. A motivational view of learning perfomance, and behavior modification. Psychol. Rev. 81 (3), 199–213.

Blundell, P., Hall, G., Killcross, S., 2001. Lesions of the basolateral amygdala disrupt selective aspects of reinforcer representation in rats. J. Neurosci. 21 (22), 9018–9026.

Bradfield, L.A., Balleine, B.W., 2013. Hierarchical and binary associations compete for behavioral control during instrumental biconditional discrimination. J. Exp. Psychol. Anim. Behav. Process. 39 (1), 2–13.

Bradfield, L.A., Dezfouli, A., van Holstein, M., Chieng, B., Balleine, B.W., 2015. Medial orbitofrontal cortex mediates outcome retrieval in partially observable task situations. Neuron 88 (6), 1268–1280.

Bray, S., Rangel, A., Shimojo, S., Balleine, B., O'Doherty, J.P., 2008. The neural mechanisms underlying the influence of pavlovian cues on human decision making. J. Neurosci.: Off. J. Soc. Neurosci. 28 (22), 5861–5866.

Campese, V., McCue, M., Lázaro-Mu noz, G., Ledoux, J.E., Cain, C.K., 2013. Development of an aversive pavlovian-to-instrumental transfer task in rat. Front. Behav. Neurosci. 7 (November), 176.

Cardinal, R.N., Parkinson, J.a., Marbini, H.D., Toner, A.J., Bussey, T.J., Robbins, T.W., Everitt, B.J., 2003. Role of the anterior cingulate cortex in the control over behavior by pavlovian conditioned stimuli in rats. Behav. Neurosci. 117 (3), 566–587.

Cartoni, E., Moretta, T., Puglisi-Allegra, S., Cabib, S., Baldassarre, G., 2015. The relationship between specific pavlovian instrumental transfer and instrumental reward probability. Front. Psychol. 6 (November), 1–7.

Cartoni, E., Puglisi-Allegra, S., Baldassarre, G., 2013. The three principles of action: a pavlovian-instrumental transfer hypothesis. Front. Behav. Neurosci. 7 (November), 153.

Cohen-Hatton, S.R., Haddon, J.E., George, D.N., Honey, R.C., 2013. Pavlovian-to-instrumental transfer: paradoxical effects of the pavlovian relationship explained. J. Exp. Psychol. Anim. Behav. Process. 39 (1), 14–23.

Colagiuri, B., Lovibond, P.F., 2015. How food cues can enhance and inhibit motivation to obtain and consume food. Appetite 84, 79–87.

Collins, A.L., Aitken, T.J., Greenfield, V.Y., Ostlund, S.B., Wassum, K.M., 2016. Nucleus accumbens acetylcholine receptors modulate dopamine and motivation. Neuropsychopharmacology 41 (12), 2830–2838.

Colwill, R.M., Motzkin, D.K., 1994. Encoding of the unconditioned stimulus in pavlovian conditioning. Anim. Learn. Behav. 22 (4), 384–394.

Colwill, R.M., Rescorla, R.A., 1988. Associations between the discriminative stimulus and the reinforcer in instrumental learning. J. Exp. Psychol.: Anim. Behav. Process. 14 (2), 155–164.

Colwill, R.M., Rescorla, R.A., 1990. Effect of reinforcer devaluation on discriminative control of instrumental behavior. J. Exp. Psychol. Anim. Behav. Process. 16 (1), 40–47.

Corbit, L.H., Balleine, B.W., 2003a. Instrumental and pavlovian incentive processes have dissociable effects on components of a heterogeneous instrumental chain. J. Exp. Psychol. Anim. Behav. Process. 29 (2), 99–106.

Corbit, L.H., Balleine, B.W., 2003b. The role of prelimbic cortex in instrumental conditioning. Behav. Brain Res. 146 (1–2), 145–157.

Corbit, L.H., Balleine, B.W., 2005. Double dissociation of basolateral and central amygdala lesions on the general and outcome-specific forms of pavlovian-instrumental transfer. J. Neurosci. 25 (4), 962–970.

Corbit, L.H., Balleine, B.W., 2011. The general and outcome-specific forms of pavlovian-instrumental transfer are differentially mediated by the nucleus accumbens core and shell. J. Neurosci. 31 (33), 11786–11794.

Corbit, L.H., Fischbach, S.C., Janak, P.H., 2016. Nucleus accumbens core and shell are differentially involved in general and outcome-specific forms of pavlovian-instrumental transfer with alcohol and sucrose rewards. Eur. J. Neurosci. 43 (9), 1229–1236.

Corbit, L.H., Janak, P.H., 2007a. Ethanol-associated cues produce general pavlovian-instrumental transfer. Alcohol. Clin. Exp. Res. 31 (5), 766–774.

Corbit, L.H., Janak, P.H., 2007b. Inactivation of the lateral but not medial dorsal striatum eliminates the excitatory impact of pavlovian stimuli on instrumental responding. J. Neurosci. 27 (51), 13977–13981.

Corbit, L.H., Janak, P.H., 2010. Posterior dorsomedial striatum is critical for both selective instrumental and pavlovian reward learning. Eur. J. Neurosci. 31 (7), 1312–1321.

Corbit, L.H., Janak, P.H., Balleine, B.W., 2007. General and outcome-specific forms of pavlovian-instrumental transfer: the effect of shifts in motivational state and inactivation of the ventral tegmental area. Eur. J. Neurosci. 26 (11), 3141–3149.

Corbit, L.H., Muir, J.L., Balleine, B.W., 2001. The role of the nucleus accumbens in instrumental conditioning: Evidence of a functional dissociation between accumbens core and shell. J. Neurosci.: Off. J. Soc. Neurosci. 21 (9), 3251–3260.

Crombag, H.S., Galarce, E.M., Holland, P.C., 2008a. Pavlovian influences on goal-directed behavior in mice: the role of cue-reinforcer relations. Learn. Memory (Cold Spring Harbor, N. Y.) 15 (5), 299–303.

Crombag, H.S., Sutton, J.M., Takamiya, K., Holland, P.C., Gallagher, M., Huganir, R.L., 2008b. A role for alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid glur1 phosphorylation in the modulatory effects of appetitive reward cues on goal-directed behavior. Eur. J. Neurosci. 27 (12), 3284–3291.

Dailey, M.J., Moran, T.H., Holland, P.C., Johnson, A.W., 2016. The antagonism of ghrelin alters the appetitive response to learned cues associated with food. Behav. Brain Res. 303, 191–200.

Daw, N.D., Gershman, S.J., Seymour, B., Dayan, P., Dolan, R.J., 2011. Model-based influences on humans' choices and striatal prediction errors. Neuron 69 (6), 1204–1215.

Dawson, G.R., Dickinson, A., 1990. Performance on ratio and interval schedules with matched reinforcement rates. Q. J. Exp. Psychol. B 42 (3), 225–239.

de Borchgrave, R., Rawlins, J.N.P., Dickinson, A., Balleine, B.W., 2002. Effects of cytotoxic nucleus accumbens lesions on instrumental conditioning in rats. Exp. Brain Res. Experimentelle Hirnforschung. Expérimentation cérébrale 144 (1), 50–68.

Delamater, A.R., 1995. Outcome-selective effects of intertrial reinforcement in a pavlovian appetitive conditioning paradigm with rats. Anim. Learn. Behav. 23 (1), 31–39.

Delamater, A.R., 1996. Effects of several extinction treatments upon the integrity of pavlovian stimulus-outcome associations. Anim. Learn. Behav. 24 (4), 437–449.

Delamater, A.R., Holland, P.C., 2008. The influence of CS-US interval on several different indices of learning in appetitive conditioning. J. Exp. Psychol. Anim. Behav. Process. 34 (2), 202–222.

Delamater, A.R., LoLordo, V.M., Sosa, W., 2003. Outcome-specific conditioned inhibition in pavlovian backward conditioning. Learn. Behav. 31 (4), 393–402.

Delamater, A.R., Oakeshott, S., 2007. Learning about multiple attributes of reward in pavlovian conditioning. Ann. N. Y. Acad. Sci. 1104, 1–20.

DePoy, L., Daut, R., Brigman, J.L., MacPherson, K., Crowley, N., Gunduz-Cinar, O., Pickens, C.L., Cinar, R., Saksida, L.M., Kunos, G., Lovinger, D.M., Bussey, T.J., Camp, M.C., Holmes, A., 2013. Chronic alcohol produces neuroadaptations to prime dorsal striatal learning. Proc. Natl. Acad. Sci. U. S. A. 110 (36), 14783–14788.

Depoy, L., Daut, R., Wright, T., Camp, M., Crowley, N., Noronha, B., Lovinger, D., Holmes, A., 2014. Chronic Alcohol Alters Rewarded Behaviors and Striatal Plasticity.
Dickinson, A., Dawson, G.R., 1987. Pavlovian processes in the motivational control of instrumental performance. Q. J. Exp. Psychol. B, Comp. Physiol. Psychol. 39 (3), 201–213.
Dickinson, A., Smith, J., Mirenowicz, J., 2000. Dissociation of pavlovian and instrumental incentive learning under dopamine antagonists. Behav. Neurosci. 114 (3), 468–483.
Eder, A.B., Dignath, D., 2015. Cue-elicited food seeking is eliminated with aversive outcomes following outcome devaluation. Q. J. Exp. Psychol. (2006) (July), 1–15.
Eder, A.B., Dignath, D., 2016. Asymmetrical effects of posttraining outcome revaluation onoutcome-selective pavlovian-to-instrumental transfer ofcontrol in human adults. Learn. Motiv. (54), 12–21.
El-Amamy, H., Holland, P.C., 2007. Dissociable effects of disconnecting amygdala central nucleus from the ventral tegmental area or substantia nigra on learned orienting and incentive motivation. Eur. J. Neurosci. 25 (5), 1557–1567.
Estes, W.K., 1943. Discriminative conditioning I. A discriminative property of conditioned anticipation. Exp. Psychol. 32, 150–155.
Estes, W.K., Skinner, B.F., 1941. Some quantitative properties of anxiety. J. Exp. Psychol. 29 (5), 390–400.
Freeman, S.M., Alvernaz, D., Tonnesen, A., Linderman, D., Aron, A.R., 2015. Suppressing a motivationally-triggered action tendency engages a response control mechanism that prevents future provocation. Neuropsychologia 68, 218–231.
Freeman, S.M., Razhas, I., Aron, A.R., 2014. Top-down response suppression mitigates action tendencies triggered by a motivating stimulus. Curr. Biol. 24 (2), 212–216.
Gámez, A.M., Rosas, J.M., 2005. Transfer of stimulus control across instrumental responses is attenuated by extinction in human instrumental conditioning. Int. J. Psychol. Psychol. Ther. 5 (3), 207–222.
Garbusow, M., Schad, D.J., Sebold, M., Friedel, E., Bernhardt, N., Koch, S.P., Steinacher, B., Kathmann, N., Geurts, D.E.M., Sommer, C., Müller, D.K., Nebe, S., Paul, S., Wittchen, H.-U., Zimmermann, U.S., Walter, H., Smolka, M.N., Sterzer, P., Rapp, M.A., Huys, Q.J.M., Schlagenhauf, F., Heinz, A., 2016. Pavlovian-to-instrumental transfer effects in the nucleus accumbens relate to relapse in alcohol dependence. Addict. Biol. 21 (3), 719–731.
Garbusow, M., Schad, D.J., Sommer, C., Jünger, E., Sebold, M., Friedel, E., Wendt, J., Kathmann, N., Schlagenhauf, F., Zimmermann, U.S., Heinz, A., Huys, Q.J., Rapp, M.a., 2014. Pavlovian-to-instrumental transfer in alcohol dependence: a pilot study. Neuropsychobiology 70, 111–121.
Garofalo, S., di Pellegrino, G., 2015. Individual differences in the influence of task-irrelevant pavlovian cues on human behavior. Front. Behav. Neurosci. 9 (June), 1–11.
George, S.a., Hutson, P.H., Stephens, D.N., 2009. Differential effects of MPEP and diazepam in tests of conditioned emotional response and pavlovian-to-instrumental transfer suggests 'anxiolytic' effects are mediated by different mechanisms. Psychopharmacology 204 (3), 499–509.
Geurts, D.E.M., Huys, Q.J.M., den Ouden, H.E.M., Cools, R., 2013a. Aversive pavlovian control of instrumental behavior in humans. J. Cognit. Neurosci. 25 (9), 1428–1441.
Geurts, D.E.M., Huys, Q.J.M., den Ouden, H.E.M., Cools, R., 2013b. Serotonin and aversive pavlovian control of instrumental behavior in humans. J. Neurosci.: Off. J. Soc. Neurosci. 33 (48), 18932–18939.
Gilroy, K.E., Everett, E.M., Delamater, A.R., 2014. Response-outcome versus outcome-response associations in pavlovian-to-instrumental transfer: effects of instrumental training context. Int. J. Comp. Psychol. 27 (4), 585–597.
Glasner, S.V., Overmier, J.B., Balleine, B.W., 2005. The role of pavlovian cues in alcohol seeking in dependent and nondependent rats. J. Stud. Alcohol 66 (1), 53–61.
Hall, D.A., Gulley, J.M., 2011. Disruptive effect of amphetamines on pavlovian to instrumental transfer. Behav. Brain Res. 216 (1), 440–445.
Hall, J., Parkinson, J.a., Connor, T.M., Dickinson, A., Everitt, B.J., 2001. Involvement of the central nucleus of the amygdala and nucleus accumbens core in mediating pavlovian influences on instrumental behaviour. Eur. J. Neurosci. 13 (10), 1984–1992.
Hogarth, L., 2012. Goal-directed and transfer-cue-elicited drug-seeking are dissociated by pharmacotherapy: evidence for independent additive controllers. J. Exp. Psychol. Anim. Behav. Process. 38 (3), 266–278.
Hogarth, L., Balleine, B.W., Corbit, L.H., Killcross, S., 2013a. Associative learning mechanisms underpinning the transition from recreational drug use to addiction. Ann. N. Y. Acad. Sci. 1282, 12–24.
Hogarth, L., Chase, H.W., 2011. Parallel goal-directed and habitual control of human drug-seeking: implications for dependence vulnerability. J. Exp. Psychol. Anim. Behav. Process. 37 (3), 261–276.
Hogarth, L., Chase, H.W., 2012. Evaluating psychological markers for human nicotine dependence: tobacco choice, extinction, and pavlovian-to-instrumental transfer. Exp. Clin. Psychopharmacol. 20 (3), 213–224.
Hogarth, L., Dickinson, A., Wright, A., Kouvaraki, M., Duka, T., 2007. The role of drug expectancy in the control of human drug seeking. J. Exp. Psychol. Anim. Behav. Process. 33 (4), 484–496.
Hogarth, L., Field, M., Rose, A.K., 2013b. Phasic transition from goal-directed to habitual control over drug-seeking produced by conflicting reinforcer expectancy. Addict. Biol. 18 (1), 88–97.
Hogarth, L., Maynard, O.M., Munafò, M.R., 2015. Plain cigarette packs do not exert pavlovian to instrumental transfer of control over tobacco-seeking. Addiction 110, 174–182.
Hogarth, L., Retzler, C., Munafò, M.R., Tran, D.M.D., Troisi, J.R., Rose, A.K., Jones, A., Field, M., 2014. Extinction of cue-evoked drug-seeking relies on degrading hierarchical instrumental expectancies. Behav. Res. Ther. 59, 61–70.
Hogarth, L., Troisi, J.R., 2015. A hierarchical instrumental decision theory of nicotine dependence. Curr. Top. Behav. Neurosci. 23, 165–191.
Holland, P.C., 2004. Relations between pavlovian-instrumental transfer and reinforcer devaluation. J. Exp. Psychol., Anim. Behav. Process. 30 (2), 104–117.
Holland, P.C., Gallagher, M., 2003. Double dissociation of the effects of lesions of basolateral and central amygdala on conditioned stimulus-potentiated feeding and pavlovian-instrumental transfer. Eur. J. Neurosci. 17 (8), 1680–1694.
Holmes, N.M., Marchand, A.R., Coutureau, E., 2010. Pavlovian to instrumental transfer: a neurobehavioural perspective. Neurosci. Biobehav. Rev. 34 (8), 1277–1295.
Homayoun, H., Moghaddam, B., 2009. Differential representation of pavlovian-instrumental transfer by prefrontal cortex subregions and striatum. Eur. J. Neurosci. 29 (7), 1461–1476.
Huys, Q.J.M., Cools, R., Gölzer, M., Friedel, E., Heinz, A., Dolan, R.J., Dayan, P., 2011. Disentangling the roles of approach, activation and valence in instrumental and pavlovian responding. PLoS Comput. Biol. 7 (4), e1002028.
Huys, Q.J.M., Gölzer, M., Friedel, E., Heinz, A., Cools, R., Dayan, P., Dolan, R.J., 2016. The specificity of pavlovian regulation is associated with recovery from depression. Psychol. Med. 46 (5), 1027–1035.
Johnson, A.W., Bannerman, D., Rawlins, N., Sprengel, R., Good, M.A., 2007. Targeted deletion of the glur-1 ampa receptor in mice dissociates general and outcome-specific influences of appetitive rewards on learning. Behav. Neurosci. 121 (6), 1192–1202.
Keistler, C., Barker, J.M., Taylor, J.R., 2015. Infralimbic Prefrontal Cortex Interacts With Nucleus Accumbens Shell to Unmask Expression of Outcome-Selective Pavlovian-to-instrumental Transfer., pp. 509–514.
Konorski, J., 1967. Integrative Activity of the Brain. University of Chicago Press, Chicago, IL.
Krank, M.D., 2003. Pavlovian conditioning with ethanol: sign-tracking (autoshaping), conditioned incentive, and ethanol self-administration. Alcohol. Clin. Exp. Res. 27 (10), 1592–1598.
Krank, M.D., O'Neill, S., Squarey, K., Jacob, J., 2008. Goal- and signal-directed incentive: conditioned approach, seeking, and consumption established with unsweetened alcohol in rats. Psychopharmacology 196 (3), 397–405.
Kruzich, P.J., Congelton, K.M., See, R.E., 2001. Conditioned reinstatement of drug-seeking behavior with a discrete compound stimulus classically conditioned with intravenous cocaine. Behav. Neurosci. 115 (5), 1086–1092.
Lamb, R.J., Schindler, C.W., Pinkston, J.W., 2016. Conditioned stimuli's role in relapse: preclinical research on pavlovian-instrumental-transfer. Psychopharmacology 233 (10), 1933–1944.
Lansade, L., Coutureau, E., Marchand, A., Baranger, G., Valenchon, M., Calandreau, L., 2013. Dimensions of temperament modulate cue-controlled behavior: a study on pavlovian to instrumental transfer in horses (equus caballus). PLOS ONE 8 (6), e64853.
Laurent, V., Balleine, B.W., 2015. Factual and counterfactual action-outcome mappings control choice between goal-directed actions in rats. Curr. Biol. 25 (8), 1074–1079.
Laurent, V., Bertran-Gonzalez, J., Chieng, B.C., Balleine, B.W., 2014. δ-opioid and dopaminergic processes in accumbens shell modulate the cholinergic control of predictive learning and choice. J. Neurosci.: Off. J. Soc. Neurosci. 34 (4), 1358–1369.
Laurent, V., Leung, B., Maidment, N., Balleine, B.W., 2012. μ- and δ-opioid-related processes in the accumbens core and shell differentially mediate the influence of reward-guided and stimulus-guided decisions on choice. J. Neurosci.: Off. J. Soc. Neurosci. 32 (5), 1875–1883.
Laurent, V., Wong, F.L., Balleine, B.W., 2015. δ-opioid receptors in the accumbens shell mediate the influence of both excitatory and inhibitory predictions on choice. Br. J. Pharmacol. 172 (2), 562–570.
LeBlanc, K.H., Maidment, N.T., Ostlund, S.B., 2013. Repeated cocaine exposure facilitates the expression of incentive motivation and induces habitual control in rats. PLOS ONE 8 (4), e61355.
LeBlanc, K.H., Maidment, N.T., Ostlund, S.B., 2014. Impact of repeated intravenous cocaine administration on incentive motivation depends on mode of drug delivery. Addict. Biol. 19 (6), 965–971.
LeBlanc, K.H., Ostlund, S.B., Maidment, N.T., 2012. Pavlovian-to-instrumental transfer in cocaine seeking rats. Behav. Neurosci. 126 (5), 681–689.
Lederle, L., Weber, S., Wright, T., Feyder, M., Brigman, J.L., Crombag, H.S., Saksida, L.M., Bussey, T.J., Holmes, A., 2011. Reward-related behavioral paradigms for addiction research in the mouse: performance of common inbred strains. PLoS ONE 6 (1), e15536.
Lee, H.J., Wheeler, D.S., Holland, P.C., 2011. Interactions between amygdala central nucleus and the ventral tegmental area in the acquisition of conditioned cue-directed behavior in rats. Eur. J. Neurosci. 33 (10), 1876–1884.
Leung, B.K., Balleine, B.W., 2013. The ventral striato-pallidal pathway mediates the effect of predictive learning on choice between goal-directed actions. J. Neurosci.: Off. J. Soc. Neurosci. 33 (34), 13848–13860.
Leung, B.K., Balleine, B.W., 2015. Ventral pallidal projections to mediodorsal thalamus and ventral tegmental area play distinct roles in outcome-specific pavlovian-instrumental transfer. J. Neurosci. 35 (12), 4953–4964.

Lewis, A.H., Niznikiewicz, M., Delamater, a.A.R., Delgado, M.R., 2013. Avoidance-based human pavlovian-to-instrumental transfer. Eur. J. Neurosci. 38 (12), 3740–3748.
Lex, A., Hauber, W., 2008. Dopamine d1 and d2 receptors in the nucleus accumbens core and shell mediate pavlovian-instrumental transfer. Learn. Mem. 15 (7), 483–491.
Lingawi, N.W., Balleine, B.W., 2012. Amygdala central nucleus interacts with dorsolateral striatum to regulate the acquisition of habits. J. Neurosci.: Off. J. Soc. Neurosci. 32 (3), 1073–1081.
Lovibond, P.F., 1981. Appetitive pavlovian-instrumental interactions: effects of inter-stimulus interval and baseline reinforcement conditions. Q. J. Exp. Psychol. B, Comp. Physiol. Psychol. 33 (Pt 4), 257–269.
Lovibond, P.F., 1983. Facilitation of instrumental behavior by a pavlovian appetitive conditioned stimulus. J. Exp. Psychol. Anim. Behav. Process. 9 (3), 225–247.
Lovibond, P.F., Colagiuri, B., 2013. Facilitation of voluntary goal-directed action by reward cues. Psychol. Sci. 24 (10), 2030–2037.
Lovibond, P.F., Satkunarajah, M., Colagiuri, B., 2015. Extinction can reduce the impact of reward cues on reward-seeking behavior. Behav. Ther. 46 (4), 432–438.
Malvaez, M., Greenfield, V.Y., Wang, A.S., Yorita, A.M., Feng, L., Linker, K.E., Monbouquette, H.G., Wassum, K.M., 2015. Basolateral amygdala rapid glutamate release encodes an outcome-specific representation vital for reward-predictive cues to selectively invigorate reward-seeking actions. Sci. Rep. 5 (July), 12511.
Martinovic, J., Jones, A., Christiansen, P., Rose, A.K., Hogarth, L., Field, M., 2014. Electrophysiological responses to alcohol cues are not associated with pavlovian-to-instrumental transfer in social drinkers. PLOS ONE 9 (4), e94605.
Mead, A.N., Stephens, D.N., 2003a. Involvement of ampa receptor glur2 subunits in stimulus-reward learning: evidence from glutamate receptor gria2 knock-out mice. J. Neurosci.: Off. J. Soc. Neurosci. 23 (29), 9500–9507.
Mead, A.N., Stephens, D.N., 2003b. Selective disruption of stimulus-reward learning in glutamate receptor gria1 knock-out mice. J. Neurosci.: Off. J. Soc. Neurosci. 23 (3), 1041–1048.
Meltzer, D., Brahlek, J.A., 1970. Conditioned suppression and conditioned enhancement with the same positive UCS: an effect of CS duration. J. Exp. Anal. Behav. 13 (1), 67–73.
Meltzer, D., Hamm, R.J., 1974. Conditioned enhancement as a function of schedule of reinforcement. Bull. Psychonom. Soc. 3 (2), 99–101.
Mendelsohn, A., Pine, A., Schiller, D., 2014. Between thoughts and actions: Motivationally salient cues invigorate mental action in the human brain. Neuron 81 (1), 207–217.
Milton, A.L., Everitt, B.J., 2010. The psychological and neurochemical mechanisms of drug memory reconsolidation: implications for the treatment of addiction. Eur. J. Neurosci. 31 (12), 2308–2319.
Milton, A.L., Schramm, M.J.W., Wawrzynski, J.R., Gore, F., Oikonomou-Mpegeti, F., Wang, N.Q., Samuel, D., Economidou, D., Everitt, B.J., 2012. Antagonism at NMDA receptors, but not beta-adrenergic receptors, disrupts the reconsolidation of pavlovian conditioned approach and instrumental transfer for ethanol-associated conditioned stimuli. Psychopharmacology 219 (3), 751–761.
Morgado, P., Silva, M., Sousa, N., Cerqueira, J.J., 2012. Stress transiently affects pavlovian-to-instrumental transfer. Front. Neurosci. 6 (June), 93.
Morris, R.W., Quail, S., Griffiths, K.R., Green, M.J., Balleine, B.W., 2015. Corticostriatal control of goal-directed action is impaired in schizophrenia. Biol. Psychiatry 77 (2), 187–195.
Morse, W.H., Skinner, B.F., 1958. Some factors involved in the stimulus control of operant behavior. J. Exp. Anal. Behav. 1 (2), 103–107.
Murschall, A., Hauber, W., 2005. Effects of a systemic AMPA/KA and NMDA receptor blockade on pavlovian-instrumental transfer. Psychopharmacology 182 (2), 290–296.
Murschall, A., Hauber, W., 2006. Inactivation of the ventral tegmental area abolished the general excitatory influence of pavlovian cues on instrumental performance. Learn. Mem. (Cold Spring Harb., N. Y.) 13 (2), 123–126.
Nadler, N., Delgado, M.R., Delamater, A.R., 2011. Pavlovian to instrumental transfer of control in a human learning task. Emotion (Washington, DC) 11 (5), 1112–1123.
Ostlund, S.B., Balleine, B.W., 2007. Orbitofrontal cortex mediates outcome encoding in pavlovian but not instrumental conditioning. J Neurosci.: Off. J. Soc. Neurosci. 27 (18), 4819–4825.
Ostlund, S.B., Balleine, B.W., 2008. Differential involvement of the basolateral amygdala and mediodorsal thalamus in instrumental action selection. J. Neurosci.: Off. J. Soc. Neurosci. 28 (17), 4398–4405.
Ostlund, S.B., Kosheleff, A.R., Maidment, N.T., 2014a. Differential effects of systemic cholinergic receptor blockade on pavlovian incentive motivation and goal-directed action selection. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 39 (6), 1490–1497.
Ostlund, S.B., Leblanc, K.H., Kosheleff, A.R., Wassum, K.M., Maidment, N.T., 2014b. Phasic mesolimbic dopamine signaling encodes the facilitation of incentive motivation produced by repeated cocaine exposure. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 39 (10), 2441–2449.
Ostlund, S.B., Maidment, N.T., 2012. Dopamine receptor blockade attenuates the general incentive motivational effects of noncontingently delivered rewards and reward-paired cues without affecting their ability to bias action selection. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 37 (2), 508–519.
Paredes-Olay, C., Abad, M.J.F., Gámez, M., Rosas, J.M., 2002. Transfer of control between causal predictive judgments and instrumental responding. Anim. Learn. Behav. 30 (3), 239–248.
Peciña, S., Berridge, K.C., 2013. Dopamine or opioid stimulation of nucleus accumbens similarly amplify cue-triggered 'wanting' for reward: entire core and medial shell mapped as substrates for pit enhancement. Eur. J. Neurosci. 37 (9), 1529–1540.
Peciña, S., Schulkin, J., Berridge, K.C., 2006. Nucleus accumbens corticotropin-releasing factor increases cue-triggered motivation for sucrose reward: paradoxical positive incentive effects in stress. BMC Biol. 4, 8.
Pielock, S.M., Lex, B., Hauber, W., 2011. The role of dopamine in the dorsomedial striatum in general and outcome-selective pavlovian-instrumental transfer. Eur. J. Neurosci. 33 (4), 717–725.
Pielock, S.M., Braun, S., Hauber, W., 2013a. The effects of acute stress on Pavlovian-instrumental transfer in rats. Cogn. Affect. Behav. Neurosci. 13 (1), 174–185.
Pielock, S.M., Sommer, S., Hauber, W., 2013b. Post-training glucocorticoid receptor activation during pavlovian conditioning reduces pavlovian-instrumental transfer in rats. Pharmacol. Biochem. Behav. 104, 125–131.
Pool, E., Brosch, T., Delplanque, S., Sander, D., Pool, E., Brosch, T., Delplanque, S., Sander, D., 2014. Stress increases cue-triggered "wanting" for sweet reward in humans. J. Exp. Psychol.: Anim. Learn. Cognit. 41 (2), 128–136.
Prévost, C., Liljeholm, M., Tyszka, J.M., O'Doherty, J.P., 2012. Neural correlates of specific and general pavlovian-to-instrumental transfer within human amygdalar subregions: a high-resolution fmri study. J. Neurosci. 32 (24), 8383–8390.
Quail, S.L., Morris, R.W., Balleine, B.W., 2016. Stress associated changes in pavlovian-instrumental transfer in humans. Q. J. Exp. Psychol. 0218 (February), 1–29.
Remus, M.L., Thiels, E., 2012. Stimulus-specific and differential distribution of activated extracellular signal-regulated kinase in the nucleus accumbens core and shell during pavlovian-instrumental transfer. Brain Struct. Funct. 218 (4), 913–927.
Rescorla, R.A., 1991. Associations of multiple outcomes with an instrumental response. J. Exp. Psychol.: Anim. Behav. Process. 17 (4), 465–474.
Rescorla, R.A., 1994a. Control of instrumental performance by pavlovian and instrumental stimuli. J. Exp. Psychol. Anim. Behav. Process. 20 (1), 44–50.
Rescorla, R.A., 1994b. Transfer of instrumental control mediated by a devalued outcome. Anim. Learn. Behav. 22 (1), 27–33.
Rescorla, R.A., LoLordo, V.M., 1965. Inhibition of avoidance behavior. J. Comp. Physiol. Psychol. 59 (3), 406–412.
Rescorla, R.A., Solomon, R.L., 1967. Two-process learning theory: relationships between pavlovian conditioning and instrumental learning. Psychol. Rev. 74 (3), 151–182.
Rigoli, F., Pavone, E.F., Pezzulo, G., 2012. Aversive pavlovian responses affect human instrumental motor performance. Front. Neurosci. 6 (October), 134.
Ripley, T.L., Borlikova, G., Lyons, S., Stephens, D.N., 2004. Selective deficits in appetitive conditioning as a consequence of ethanol withdrawal. Eur. J. Neurosci. 19 (2), 415–425.
Rosas, J.M., Paredes-Olay, M.C., García-Gutiérrez, A., Espinosa, J.J., Abad, M.J., 2010. Outcome-specific transfer between predictive and instrumental learning is unaffected by extinction but reversed by counterconditioning in human participants. Learn. Motiv. 41 (1), 48–66.
Saddoris, M.P., Stamatakis, A., Carelli, R.M., 2011. Neural correlates of pavlovian-to-instrumental transfer in the nucleus accumbens shell are selectively potentiated following cocaine self-administration. Eur. J. Neurosci. 33 (12), 2274–2287.
Scarlet, J., Delamater, A.R., Campese, V., Fein, M., Wheeler, D.S., 2012. Differential involvement of the basolateral amygdala and orbitofrontal cortex in the formation of sensory-specific associations in conditioned flavor preference and magazine approach paradigms. Eur. J. Neurosci. 35 (11), 1799–1809.
Sebold, M., Schad, D.J., Nebe, S., Garbusow, M., Jünger, E., Kroemer, N.B., Kathmann, N., Zimmermann, U.S., Smolka, M.N., Rapp, M.A., Heinz, A., Huys, Q.J.M., 2016. Don't think, just feel the music: individuals with strong pavlovian-to-instrumental transfer effects rely less on model-based reinforcement learning. J. Cognit. Neurosci. 28 (7), 985–995.
Shiflett, M.W., 2012. The effects of amphetamine exposure on outcome-selective pavlovian-instrumental transfer in rats. Psychopharmacology 223 (3), 361–370.
Shiflett, M.W., Balleine, B.W., 2010. At the limbic-motor interface: disconnection of basolateral amygdala from nucleus accumbens core and shell reveals dissociable components of incentive motivation. Eur. J. Neurosci. 32 (10), 1735–1743.
Shiflett, M.W., Balleine, B.W., 2011. Molecular substrates of action control in cortico-striatal circuits. Prog. Neurobiol. 95 (1), 1–13.
Shiflett, M.W., Riccie, M., Dimatteo, R., 2013. The effects of amphetamine sensitization on conditioned inhibition during a pavlovian-instrumental transfer task in rats. Psychopharmacology 230 (1), 137–147.
Soares-Cunha, C., Coimbra, B., Borges, S., Carvalho, M.M., Rodrigues, A.J., Sousa, N., 2014. The motivational drive to natural rewards is modulated by prenatal glucocorticoid exposure. Transl. Psychiatry 4 (6), e397.
Stebbins, W.C., Smith, O.A., 1964. Cardiovascular concomitants of the conditioned emotional response inthe monkey. Science 144 (3620), 881–883.
Talmi, D., Seymour, B., Dayan, P., Dolan, R.J., 2008. Human pavlovian-instrumental transfer. J. Neurosci.: Off. J. Soc. Neurosci. 28 (2), 360–368.

Tomie, A., 1996. Locating reward cue at response manipulandum (cam) induces symptoms of drug abuse. Neurosci. Biobehav. Rev. 20 (3), 505–535.
Trapold, M., Overmier, J., 1972. The second learning process in instrumental learning. In: Black, A.H., Prokasy, W.F. (Eds.), Classical Conditioning. II. Current Research and Theory. Appleton-Century-Crofts, New York, NY.
van den Bos, R., van der Harst, J., Vijftigschild, N., Spruijt, B., van Luijtelaar, G., Maes, R., 2004. On the relationship between anticipatory behaviour in a pavlovian paradigm and pavlovian-to-instrumental transfer in rats (rattus norvegicus). Behav. Brain Res. 153 (2), 397–408.
Van Dyne, G.C., 1971. Conditioned suppression with a positive US in the rat. J. Comp. Physiol. Psychol. 77 (1), 131–135.
Walker, B.Y.K.C., 1942. The effect of a discriminative stimulus transferred to a previously unassociated response. J. Exp. Psychol. 31 (4), 312–321.
Wassum, K.M., Ostlund, S.B., Balleine, B.W., Maidment, N.T., 2011. Differential dependence of pavlovian incentive motivation and instrumental incentive learning processes on dopamine signaling. Learn. Mem. (Cold Spring Harb., N. Y.) 18 (7), 475–483.
Wassum, K.M., Ostlund, S.B., Loewinger, G.C., Maidment, N.T., 2013. Phasic mesolimbic dopamine release tracks reward seeking during expression of pavlovian-to-instrumental transfer. Biol. Psychiatry 73 (8), 747–755.
Watson, P., Wiers, R.W., Hommel, B., de Wit, S., 2014. Working for food you don't desire – cues interfere with goal-directed food-seeking. Appetite 79, 139–148.
Watson, P., Wiers, R.W., Hommel, B., Ridderinkhof, K.R., de Wit, S., 2016. An associative account of how the obesogenic environment biases adolescents' food choices. Appetite 96, 560–571.
Weber, S.C., Beck-Schimmer, B., Kajdi, M.-E., Müller, D., Tobler, P.N., Quednow, B.B., 2016. Dopamine d2/3- and μ-opioid receptor antagonists reduce cue-induced responding and reward impulsivity in humans. Transl. Psychiatry 6 (7), e850.
Wiltgen, B.J., Sinclair, C., Lane, C., Barrows, F., Molina, M., Chabanon-Hicks, C., 2012. The effect of ratio and interval training on pavlovian-instrumental transfer in mice. PLoS ONE 7 (10), e48227.
Wyvell, C.L., Berridge, K.C., 2000. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward "wanting" without enhanced "liking" or response reinforcement. J. Neurosci. 20 (21), 8122–8130.
Wyvell, C.L., Berridge, K.C., 2001. Incentive sensitization by previous amphetamine exposure: increased cue-triggered "wanting" for sucrose reward. J. Neurosci.: Off. J. Soc. Neurosci. 21 (19), 7831–7840.
Zorawski, M., Killcross, S., 2003. Glucocorticoid receptor agonist enhances pavlovian appetitive conditioning but disrupts outcome-specific associations. Behav. Neurosci. 117 (6), 1453–1457.