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The fate of memory: Reconsolidation and the case of Prediction Error.

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Highlights

- A Prediction Error is a mismatch between expected and current events.
- Prediction error has different forms and neural signatures throughout the brain.
- Reconsolidation updates consolidated memories content and strength.
- Memory reconsolidation has boundary conditions.
- Prediction Error drives memory acquisition and memory reconsolidation.

Abstract.

The ability to make predictions based on stored information is a general coding strategy. A Prediction-Error (PE) is a mismatch between expected and current events. It was proposed as the process by which memories are acquired. But, our memories like ourselves are subject to change. Thus, an acquired memory can become active and update its content or strength by a labilization-reconsolidation process. Within the reconsolidation framework, PE drives the updating of consolidated memories. Moreover, memory features, such as strength and age, are crucial boundary conditions that limit the initiation of the reconsolidation process. In order to disentangle these boundary conditions, we review the role of surprise, classical models of conditioning, and their neural correlates. Several forms of PE were found to be capable of inducing memory labilization-reconsolidation. Notably, many of the PE findings mirror those of memory-reconsolidation, suggesting a strong link between these signals and memory process. Altogether, the aim of the present work is to integrate a psychological and neuroscientific analysis of PE into a general framework for memory-reconsolidation.

Keywords: conditioning models; dopamine; expectation; hippocampus; prediction error; memory labilization; memory reactivation; memory reconsolidation; memory strengthening; memory updating; reminder; surprise.

1. Introduction.

“Life must be understood backwards.

But then one forgets the other principle:

that it must be lived forwards”.

Kierkegaard, S. Journals IV A 164 (1843)

“*Unless you expect the unexpected you will never find truth,*

for it is hard to discover and hard to attain.”

Heraclitus, Fragments (VI B.C)

Our memories like ourselves are subject to change. Thus, an acquired memory can become active and update its content or strength by a reconsolidation process (Alberini, 2011; Finnie and Nader, 2012; Forcato et al., 2014; Lee, 2009). The brain is constantly encoding, consolidating and reconsolidating (see Figure 1 for definitions) the features in the environment (Dudai, 2012). Plasticity and learning are key factors that operate updating and guiding these representations and behaviors. This ability allows not only us but also animals, to better adapt to and prepare for present or future events, anticipating outcomes (Dickinson, 2012; Rescorla, 1988). To account for these phenomena, some authors propose the term “predictive brain” (Bubic et al., 2010; Dudai, 2009; Koster-Hale and Saxe, 2013) as the ability to make predictions

based on stored information as a general coding strategy (Bar, 2009, 2007; Ouden et al., 2012). Thus, in these terms, memory is flexible, malleable and in a permanent state of construction and re-construction (Bartlett, 1932; Schacter et al., 2012; Schacter and Addis, 2007).

Furthermore, there is evidence which indicates that there is an overlap between the processes of retrieving past events and imagining future ones (Schacter et al., 2008). In fact, several clinical case studies showed that patients with severe amnesia (i.e. hippocampal lesion) are impaired not only in retrieving stored experiences, but also in predicting personal future or possible events (Hassabis et al., 2007; Hassabis and Maguire, 2007).

Surprise and mismatches produce an error in prediction, between expected and current events, and affect different stages of learning and memory (Dudai, 2012; Exton-McGuinness et al., 2015; Pearce and Mackintosh, 2010; Rescorla and Wagner, 1972). For decades, the prediction error (PE) was proposed as the process by which memories are acquired (Le Pelley, 2004; Pearce and Mackintosh, 2010; Roesch et al., 2012) and recently, within the reconsolidation framework, some evidence indicates that PE drives the updating of consolidated memories (Exton-McGuinness et al., 2015; Pedreira et al., 2004; Sevenster et al., 2014, 2013, 2012).

We aim to timely integrate traditional learning theories relevant to prediction error and recent findings in the reconsolidation areas regarding memory destabilization and their boundary conditions. In this work, we will highlight the role of the Prediction Error

(PE) during memory acquisition and reconsolidation. The PE is proposed as a useful framework to understand the boundary conditions for reconsolidation to occur (Exton-McGuinness et al., 2015). Given that a mismatch between expected and current outcomes is a surprising event, the first section of this review is dedicated to the analysis of surprise in learning and the contribution of Kamin's proposal. The second section reviews the three major models of conditioning and their neural signatures. The final section reviews PE as a key boundary condition for memory reconsolidation. In these terms, error processing and prediction error are key to labilize memory. Altogether, the aim of the present work is to integrate different levels of analysis of prediction error into a general framework for memory reconsolidation.

2.1. Surprise and Learning.

In the anonymous classical Roman textbook of *ars memoriae "Rhetorica ad Herennium"* it is read: *"When we see in everyday life things that are petty, ordinary, and banal, we generally fail to remember them, because the mind is not being stirred by anything novel or marvelous. But if we see or hear something exceptionally base, dishonorable, unusual, great, unbelievable, or ridiculous, that we are likely to remember for a long time".* Unexpected events play a major role in acquisition by eliciting PEs (Le Pelley, 2004; Schultz and Dickinson, 2000). Surprising or novel events are better remembered than expected ones (Dudai, 2002; Habib et al., 2003; Tulving et al., 1996). Extreme examples are traumatic memories like those observed in Post Traumatic Stress Disorder (PTSD).

Since in the neuropsychobiology literature the terminology is, sometimes confusing, it is worth defining the concepts of novelty and surprise. Both concepts are related to attention and learning facilitation (Lisman and Grace, 2005; Mackintosh, 1975; Rescorla and Wagner, 1972). Moreover, sometimes novelty and surprise accompanies each other. However, here we understand in Berlyne and Barto´s (Barto et al., 2013; Berlyne, 1960) terms that, an event is **novel** if it is not stored in our memory. It means that we have no prior expectation about a given event because we haven't had any experience before. Hence, novelty supports the formation of a new memory trace. On the contrary, a **surprise** could be defined as a mismatch between a prediction and what actually happened. It implies some form of previous experience which generated the current prediction. Therefore, surprise implies the adjustment of predictions based on current outcomes.

When a cue is already primed in working memory or is a redundant predictor of the outcomes, attention to that cue is reduced and learning is impaired (Kruschke, 2003; Le Pelley, 2004; Mackintosh, 1975; Mackintosh and Turner, 1971). Tulving (Habib et al., 2003; Tulving et al., 1996) proposed that, some brain structures are involved in a novelty/encoding switch: the higher the novelty the more probable the memory to be stored or recognized. The system distinguishes between new / old information and determinates the necessity of encoding. Unexpected events are a necessary condition for acquisition to occur and rehearsal process might facilitate acquisition. Here rehearsal means an elaborative process that increase associative connections of a memory. In Lewis terms "*If the target event is surprising or unexpected, the rehearsal process is engaged to interpret the event, to fit it into an existing memory*

system, or to recognize and differentiate the new event from other events." (Lewis, 1979). However, an excessive amount of surprise (e.g. cue competition or post trial surprising events) may have a detrimental effect during acquisition of a similar task. Accordingly, a new unexpected stimulus, may "hijack" attentional resources affecting original memory acquisition (Wagner et al., 1973).

Surprise can have any valence (positive or negative), it is one of the most common human experiences, it has a recognizable face expression and it is a useful response adjustment to the environment for survival (Meyer et al., 1991). It could be understood as a sudden and unexpected encounter or as an unanticipated mismatch between the actual on-line representation and the off-line stored information (Barto et al., 2013; Dudai, 2002). Many authors (Barto et al., 2013; Meyer et al., 1991; Schützwohl, 1998) suggested that surprise could be an evolutionary mechanism which function is to analyze the event and motivate discrepancy removal: updating the discrepant representation or creating a new one. These authors described the surprising reaction as an adaptive response, consisting in the subjective feeling of surprise (subjective level indexed by verbal reports in humans), the interruption of ongoing activities (indexed by the latency of action), and increasing attention to the mismatch eliciting event (behavioral level indexed by the memory).

Different experiments had identified specific brain responses only appearing when mismatch events occur. In this sense, in event related potential studies with EEG, a positive wave/deflection at 300 ms (P300) or 400 ms (P400) were detected with the omission of predicted stimulus or when the stimuli are presented in an unfamiliar

context stimulus (Sutton et al., 1965; Halpern and Tapper, 1971). Some neuromodulatory mechanisms may be involved in detecting incongruence like cholinergic (Mishkin and Murray, 1994; Naor and Dudai, 1996), noradrenergic (Kitchigina et al., 1997), dopaminergic systems (Schultz, 2007) and the endo-opiod system (in humans: Chaves et al., 1988; animals: Izquierdo et al., 1984; Izquierdo and McGaugh, 1985) In conclusion, surprising events gain animal attention and facilitate memory acquisition.

2.2. Conditioning and Kamin´s Proposal.

Classical conditioning involves the process by which the representation of two events (stimulus) become associated and then, one of them (CS) is capable of predicting the occurrence of the other (US; Anrep and Pavlov, 1927; Rescorla, 1988). However, learning is not an automatic process; the CS must be a non-redundant predictor of the occurrence of the US for acquisition to occur. Beyond contiguity, many authors made seminal contributions, proposing that the CS must provide information about the US (e.g. valence, timing), Rescorla highlighted “contingency” and “predictability”, Kamin “surprise”, Gallistel the “informativeness” and Wagner the “validity” of the US. All this influential theories posited that PE is the most important factor during acquisition. When the outcome of an event is surprising, a PE is generated and this engages learning (Le Pelley, 2004; Pearce and Mackintosh, 2010; Roesch et al., 2012). Otherwise, when the expectations match the actual events (no PE), no surprise is induced and in consequence, no learning occurs. Therefore, learning, in

experimental terms, represents an error-driven process by which animals adjust their prediction regarding event occurrence (Hayden et al., 2011).

One of the first to consider this process was Kamin (1969) and the discovery of the blocking effect (Kamin, 1969). He first trained a group of rats with a noise as a CS A (phase 1) in association with a shock (US). After conditioning to CS A, he introduced a light as a second CS B (phase 2), presented simultaneously with A (AB compound) and continued receiving the US. In this condition, when presented separately at testing, animals responded strongly to CS A and little to CS B. Furthermore, the stimulus A blocked the acquisition of stimulus B in phase 2, and learning was impaired. Why did the animals fail to acquire associative strength to CS B? According to Kamin, surprising events must occur in order to learn about an already well predicted outcome. In another set of experiments he observed that a more intense US in phase 2 unblocked the CS B. Thus, rats were conditioned to CS B as well as the pre-trained CS A. Kamin proposed that surprise, that is, an increase in US magnitude, unblocked learning about B. He also suggested that it depends on "backward scanning" (rehearsal) in the short-term memory which allows a retrospective processing when the events are altered. Otherwise, when the received US is already predicted, learning ceases.

3. Prediction Error: Models and Neural Correlates.

The brain is an extraordinary organ, capable of making predictions and learning from errors (error correction, PE) (Bar, 2007; Dudai, 2009; Ouden et al., 2012; Rescorla

and Wagner, 1972). To do so, it is sensitive to changes in the environment, either the addition or omission of important events (mismatch), their timing or magnitude. A PE is the difference between the presented outcome and prediction made. It represents how surprising and certain was the outcome of the prediction made by the animal. The source of the PE could be based on **a)** online sensory processing which generates a short time scale prediction (i.e. seconds, minutes), or **b)** consolidated memories, prior expectations, cognitive schemas (Koster-Hale and Saxe, 2013; Ouden et al., 2012). The last ones could generate not only short but also large time scale predictions from minutes to month or years (Koster-Hale and Saxe, 2013). Typically, in an electrophysiological recording, the PE shows an increase in neural activity after unexpected events and a decrease in predicted ones (Schultz, 2007; Schultz and Dickinson, 2000; Smith et al., 2006). PE signals were found across several regions of the brain and in multiple functions like visual, auditory, somatosensory perception, attention, action, language, cognitive control and motivational value processing (Bubic et al., 2010; Garrison et al., 2013; Koster-Hale and Saxe, 2013; Niv and Schoenbaum, 2008; Ouden et al., 2012; Roesch et al., 2012). For example, a classic perceptual PE task is the oddball paradigm, in which the presentation of a deviant oddball stimulus in a sequence of repeated common stimuli generates an increase in neural activity in sensory areas. In electrophysiological studies, this is known as “Mismatch Negativity Effect” and it was found in different sensory modalities and even in inter-sensory processing (Garrido et al., 2009). A similar effect is found in the superior temporal sulcus (STS) in response to observed actions in social cognition: the activation of STS is reduced when the observed action is predicted and enhanced when it becomes less predicted (Koster-

Hale and Saxe, 2013). This and other brain areas have the same pattern of activation when predicting other beliefs and desires (consistent vs. inconsistent), preferences and behaviors (Brown and Brüne, 2012).

Furthermore, the PE reflects a general neural coding strategy which functionality is to **a)** make sense of sensory input, **b)** detect unexpected events for reorienting response and **c)** compute the magnitude and precision of the error generated (Bayer and Glimcher, 2005; Le Pelley et al., 2010; Ouden et al., 2012).

Within the learning and memory framework, there is now some agreement that PE is the mechanism by which acquisition is driven (Glimcher, 2011; Ouden et al., 2009; Pearce and Mackintosh, 2010; Rescorla and Wagner, 1972; Schultz and Dickinson, 2000; Steinberg et al., 2013). At the heart of the theory lies the Rescorla - Wagner (1972) proposal: *'(...) organisms only learn when events violated their expectations'*. PE was found to be involved in Pavlovian and instrumental conditioning using behavioral studies in the 70´ and recently using modern techniques (EEG, fMRI and optogenetics; Garrison et al., 2013; Schultz, 2007; Steinberg et al., 2013). As it was stated, PE regulates behavior and determines what and how much is learned (Figure 2). The error in prediction leads to the updating of behavioral response or associative strength between stimulus until the outcome can be fully anticipated (positive PE; Niv and Schoenbaum, 2008; Schultz and Dickinson, 2000). In this sense, the PE acts as a teaching signal. When this is achieved and the PE is near zero (no surprise), no further learning or behavioral changes occur (no PE; i.e. blocking effect).

The success of PE consisted in explaining several conditioning phenomena, such as blocking, overshadowing, patterning, etc. (Domjan, 2014; Ludvig et al., 2012; Miller et al., 1995). Starting with the findings of the role of dopaminergic neurons in the signaling of positive and negative PE, there is a current growth interest in the study of different PE signals and learning models throughout the brain. Neural correlates of PE were studied following conditioning models. These could be divided in two categories: US processing models (Rescorla-Wagner, Sutton-Barto) and CS processing models (Mackintosh, Pearce-Hall).

The former claim that signed PEs have a direct impact on the associative strength of a cue. A positive PE (unexpected US or underexpected US) increases the association (excitatory conditioning), whereas a negative PE (no-US or overexpected US) decreases association (inhibitory conditioning), and zero PE (expected US) makes no change in the associative strength. For the latter, unsigned PEs have an indirect effect, modulating the attention or associability of a given cue. Positive and negative PE in these models strengthen the association increasing the attention paid to those cues.

Actual evidence supports the co-existence and integration of both models across different brain regions (Boll et al., 2013; Klavir et al., 2013; Roesch et al., 2012; Schultz and Dickinson, 2000). In the next section we will review the classical US and CS processing models and their neural correlates.

3.1. US Processing models.

3.1.1. The Rescorla - Wagner model of conditioning (1972).

The Rescorla-Wagner (RW) model (Rescorla and Wagner, 1972) was probably the most influential theory on learning to date. In spite of some failures (Miller et al., 1995), their delta rule proposal is present in the majority of current models. It had an impact on different fields, such as causal human learning, category learning, cue outcome contingency, judgment of causality and neural networks (Gluck et al., 2013; Siegel and Allan, 1996). The RW model focuses on US processing and how well it is predicted by all the stimuli present in a trial (summed error term). The core assumption of the model is that learning is guided by PE.

RW Learning Rule:

(1) $\Delta V_x = \alpha_x \beta \, (\lambda - V)$

The equation describes the change in associative strength from trial to trial (ΔV) where V represents the current associative strength of all the stimuli present, α is the salience of the CS or learning rate parameter –remaining constant as β. β accounts for the US salience and intensity (see Table 1). So, increasing α or/and β makes the learning process faster. λ represents the maximum associative strength that the US can have; it is the upper limit of the learning curve. The CS cannot elicit a greater response than the one produced by the US. A change in the associative strength occurs when there is surprise or violated expectations regarding the US in each trial

following the error correction rule (λ - V). The effectiveness of a US is given by how surprising it is (how different from expectations; λ - V). The PE determines the amount of learning in a given trial. The bigger the error, the greater the learning. In the first trials the gain in associative strength is maximal and lesser in the last ones (λ ≈ V). The RW model is considered a signed one because positive or negative PEs determines the direction of conditioning (gain or loss of associative strength of the same trace).

The RW model is also capable of explaining the blocking effect. In this sense, prior conditioning to CS A fully predicts the US (λ = V), so when the second stimulus B is added, all the associative strength supported by the US is on the side of A and B provides no new information about the US. The prediction error of the compound (AB) is near zero, and no conditioning to B is then observed. An increase in the US magnitude can unblock conditioning to B, gaining associative strength. In this situation the reinforcement is underpredicted and the PE is larger (λ>V).

This model could successfully explain a great variety of phenomena (i.e.: acquisition, overexpectation, overshadowing, etc.) although it has some flaws. Extinction, for the RW model, is an unlearning process, represented by a loss in associative strength. Current models of extinction (Bouton, 2004, 2002; Quirk and Mueller, 2008) propose that it consists in a new inhibitory learning (CS - noUS) that competes with the original memory. Consequently, the RW model fails to explain recovery extinction protocols (renewal, reinstatement, spontaneous recovery).

3.1.2. The Temporal Difference Model (Sutton-Barto 1981).

Finally, another influential US model is the Temporal Difference (TD) proposed by Sutton and Barto (O'Doherty et al., 2003; Sutton and Barto, 1981), which incorporates a continuous prediction of all future outcomes considering actual and past events (within-trial), instead of discrete trial-by-trial prediction (for simplicity's sake equation not shown). Considering that animals also learn to predict reward timing (Gallistel and Balsam, 2014), it proposes a time-estimation mechanism. This model is similar to the RW (updated by (λ - V)) but assumes that each event is encoded within a series of short components allowing the generation of intermediate predictions even before the actual outcome occurs. Hence, in this model, future outcome timing and quantity are predicted and updated at any given moment.

3.1.3. US Model Neural Correlates.

Using electrophysiological methods, Niv and Schoembaum (Niv and Schoenbaum, 2008) proposed three criteria of neural firing in order to detect a PE in a US processing model: **a)** a phasic increase to unexpected reinforcement (positive PE, λ>V), **b)** a decrease when reinforcement is omitted (negative PE, λ<V), **c)** no change to predicted reinforcement (zero PE, λ=V). Neural firing correlates with changes in behavior. That is, an increase or decrease in the expected response occurs when the US is presented or not (Figure 3 and 4). This pattern is typically found in a vast population of neurons from different parts of the brain as shown in Figure 3 for midbrain dopaminergic (DA) neurons, one of the most studied neurons. Notably, the

dopaminergic system is crucial for detection of mismatches and/or novelty (Lisman and Grace, 2005; Schultz et al., 1997; Smith et al., 2006). For example, at the beginning of an appetitive conditioning training, an unexpected reinforcement / reward such as juice, produces a phasic response (positive PE). No change in the signal is observed in response to the predictor cue (CS, i.e. light). As the training continues, the neural firing is then transferred to a CS predictor. The system is sensitive to the omission of an expected reinforcement (negative PE) and its specific timing (Figure 3). In these cases, a negative PE is reflected by a decrement in their firing rates according to the RW and TD Models (Figure 3).

The opioid system was also found to be involved in PE signaling in rats and humans. (Eippert et al., 2008; McNally et al., 2004a, 2004b). Prediction error neural signals have been noted in different brain areas, such as the striatum, amygdala, orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulated (ACC) and other motor areas (Figure 5; Berns et al., 2001; Delgado et al., 2008; Fletcher et al., 2001; Furlong et al., 2010; Garrison et al., 2013; Hollerman and Schultz, 1998; Johansen et al., 2010; McNally et al., 2011; O'Doherty et al., 2003; Ploghaus et al., 2000; Schultz, 2007; Schultz and Dickinson, 2000; Watanabe, 1989). As Schultz and Dickerson suggested (Schultz and Dickinson, 2000), the anatomical organization of these populations of neurons allows a PE to be broadcast as a global message to large post-synaptic structures and be involved in long-lasting changes in neuronal plasticity (Figure 5).

Another line of evidence for the US models, comes from the study of the role of the amygdala in fear conditioning (McNally et al., 2011). It is known that the amygdala

either encodes or modulates the association between CS and US during fear learning (McGaugh, 2004; Phelps and LeDoux, 2005). The US acts as a teaching signal in the CS input from the lateral amygdala inducing synaptic plasticity. Neurons in the Lateral amygdala respond strongly to unpredicted (positive PE) rather than predicted US presentations (McNally et al., 2011). Interestingly, variations in US processing during acquisition were revealed using single unit electrophysiology and imaging studies. A decrease in US-evoked depolarization in the lateral amygdala, and periaqueductal gray neurons are observed when the US becomes well predicted. Moreover, a reversion takes place when the CS is omitted (negative PE; Johansen et al., 2010). Also, c-fos activity in the lateral amygdala and associated areas, such as prefrontal cortex and thalamus are found to be maximal when the US is non-well predicted (positive PE; Furlong et al., 2010).

In humans, PE signaling was found across many brain areas during Pavlovian or instrumental conditioning using either appetitive or aversive settings (Brovelli et al., 2008; Delgado et al., 2008; Gläscher et al., 2010; Jocham et al., 2011; Li et al., 2011a, 2011b; O'Sullivan et al., 2011; Seymour et al., 2007; Spoormaker et al., 2011; Valentin and O'Doherty, 2009).

Garrisona and co-workers (Garrison et al., 2013) recently made a meta-analysis of PE in fMRI findings. The literature showed similar results as in animal studies, such as the activation of the ventral tegmental area (VTA), thalamus, amygdala, hippocampus, insula, etc. in response to the difference between expected and actual reinforcement. It was also found in humans, that the striatum alongside the prefrontal

cortex and anterior cingulate cortex (ACC) activity, are key areas to PE processing. It is worth pointing out that, appetitive (i.e. attractive faces, money, food) and aversive (i.e. fear conditioning) paradigms generate distinct PE neural signatures (Delgado et al., 2008; Garrison et al., 2013).

Regarding declarative memory and non-reinforced learning, further research is needed. However, Rodriguez (Rodriguez, 2009) used a cue-outcome association protocol, where the subjects had to learn to predict the weather according to complex visual figure associations. In agreement with US models, he found higher hippocampal activation after a positive PE and a decrease after a negative PE. The reverse pattern of activation was found in the ACC (Rodriguez, 2009).

In conclusion, positive and negative PEs are coded in diverse regions throughout the brain. According to US processing models, a positive PE ($\lambda > V$) correlates with an increase in neural activity, whereas a negative PE ($\lambda < V$) has the opposite effect (Figure 3). As it was mentioned above, PE neural correlates were observed in Pavlovian and instrumental conditioning using either appetitive or aversive stimuli in several species (i.e. humans, rats, monkeys).

There is an overlap between the brain areas involved in learning and memory and those where neural activity is triggered by a PE (i.e. the amygdala and hippocampus during Pavlovian conditioning).

3.2. CS Processing models.

3.2.1. The Mackintosh model of conditioning (1975).

A different approach of associative learning is the CS modulation models. Attention and how the CS is processed during acquisition are essential to these theories. Attention could be described as a collection of interrelated processes that converge to produce task relevant behavior (Allport, 1989; Maddux et al., 2007). These processes could be bottom-up or top-down and are involved in event detection, orienting response, different aspects of memory, arousal, vigilance, etc. (Gazzaley and Nobre, 2012; Holland and Maddux, 2010; Le Pelley et al., 2010; Posner and Petersen, 1989).

Mackintosh proposed that attention has a limited capacity for stimuli processing. The amount of attention an animal devotes to events depends on how surprising the US was on the preceding trial and determines learning about those cues. Therefore, there is a competition among cues to "short term memory" buffer access (nowadays is referred as "working memory"; Baddeley, 2012; Mackintosh, 1975).

In contrast with the US models, the core assumption of Mackintosh's proposal is that α parameter (CS salience, associability) is not fixed and can change as a result of experience with reinforcement. A CS receives more attention (increases α) when it is a good predictor of a US than when it is a poor predictor of a US. When a stimulus is not correlated with changes in reinforcement, it is ignored and α decreases. Within

this theory, learning takes place when attention is gained by the best predictor of the outcome in relation with all the stimuli presented. The CS processing is not affected by the presence of other stimuli (separable error terms). Similar to the US models, the mismatch between actual and expected US (PE) determines the amount of change in associative strength.

Mackintosh learning rules:

(See Table 1 for additional description)

(1) $\Delta\alpha$ positive if $|\lambda - V_A| < |\lambda - V_x|$

$\Delta\alpha$ negative if $|\lambda - V_A| \geq |\lambda - V_x|$

(2) $\Delta V_A = \alpha_A (\lambda - V_A)$

In relation to blocking of the AB compound, the Mackintosh theory stated that CS A is a good predictor and the added CS B is a poor and redundant one. Then B is ignored because it predicts no change in reinforcement, hence there is no conditioned response to B.

Within this framework unblocking led Mackintosh and his group to a series of interesting results concerning the role of surprise in learning. Over studies beginning in 1976 (Dickinson et al., 1976), Mackintosh et al. were able to unblock B using a conditioned suppression and discriminated lever press bar in rats. They found enhanced conditioning to B not only when the US magnitude was increased during AB compound training, but also when a second surprising US was added (Baker and

Mackintosh, 1979; Dickinson et al., 1976; Dickinson and Mackintosh, 1978; Mackintosh et al., 1977). Moreover, unblocking was also observed when the second expected US was either delayed or omitted (Dickinson et al., 1976). A qualitative change in the US also attenuates blocking (Blaisdell et al., 1997), but not when its valence is switched (Dickinson and Mackintosh, 1979).

As Mackintosh and co-workers wrote "*For significant conditioning to occur to the new element, it is only necessary to prevent this decline in α. Provided that it signals some event not already predicted by the pretrained element, whether this be the addition, postponement, or omission of a second shock, the value of an associated with the new element may be maintained at a level sufficient to produce significant conditioning. The surprising event does not itself reinforce that conditioning; it serves to maintain attention to a stimulus that otherwise be ignored and thus enables the reinforcer actually paired with that stimulus to have its normal effect.*" (Dickinson et al., 1976).

The RW model stated that any omission in the reinforcement decreases the associative strength of the elements (AB compound, α is fixed) however, the Mackintosh model predicts an increase in α associability. In other terms, B could be learned and therefore unblocking occurs.

3.2.2. The Pearce – Hall model of conditioning (1980).

Another influential CS modulation theory of learning is that of Pearce and Hall (PH) (Pearce and Hall, 1980). The PH model states that learning depends on how the associability of the CS (α) changes according to its predictive power. In contrast to Mackintosh, for the PH model, error processing takes into account all values of presented stimuli (summed error). Conditioned stimulus associability (α parameter) increases or remains high when it fails to fully predict the US and decreases when it accurately predicts its consequences. In other words, PE is able to modulate attentional resources affecting subsequent learning.

PH Learning Rules are the followings:

(3) $\Delta V_A = S_A \alpha_A \lambda,$

$\alpha_A^n = \left| \lambda^{n-1} - V_A^{n-1} \right|$

Acquisition takes place by discrete trials with each CS – US pairings. Here, *S* represents CS salience, λ US intensity and both remain constant. The α parameter is determined by the CS associability and, it is modified by prior experience according to the discrepancy (PE) between maximum and current associative strength $\left|\lambda - V\right|$ (see Table 1).

The PH model is unsigned, since its equations include the absolute value (module) of the discrepancy. This allows an increased CS processing (α) even when the presented US magnitude is smaller than expected. Moreover, a single omission of a predicted US can cause attention enhancement resulting from frustration or relief, depending on the type of conditioning (appetitive vs. aversive, see reconsolidation section).

The PH model suggests that cues compete to gain access to a limited capacity of attention in order to be processed. The stimuli that can cause a PE gain more attention than those fully expected (Hall and Pearce, 1982; Pearce and Hall, 1980). In the former, there is controlled processing, while the latter is automatic. In order for conditioning to occur, this system must simultaneously process the CS-US representations. When an US is presented, a comparison is made between the actual US and that predicted by all the cues presented. Learning will further as long as a PE is detected. On the contrary, when the discrepancy falls near zero (no PE) no more learning occurs.

Within this framework blocking takes place when the CS A well predicts the US. When the second CS (B) is added, little attention is paid to it and hence no further learning occurs. The PH model predicts that in the first AB compound trial, α increases because B is novel, but since B signals no change in the outcome (PE), α has an abrupt decrease near zero in the following trials. Likewise, unblocking occurs because any significant change in the US (e.g. addition, omission, magnitude change), can increase attention and the α parameter.

Inhibitory learning, like extinction, is considered a new learning that inhibits the excitatory CS-US association. The course of inhibitory conditioning is similar to that of excitatory. The associative strength increases with the US omission and remains constant when there is no PE. The Lambda (λ) value of the inhibitory reinforcement is determined by the relief or the frustration produced by the US omission. Unlike for the

RW model (inhibitory learning represents a loss in associative strength), it can predict extinction recovery protocols (Bouton, 2002).

3.2.3. CS Processing Neural Correlates.

Unlike the US processing models, in the CS ones, the absolute value of a PE (unsigned) modulates the amount of attention paid to a cue in subsequent trials and the extent of learning $|\lambda - V|$. During conditioning, events become less surprising ($|\lambda - V| = 0$). Therefore, according to the PH model, underexpected $|\lambda > V|$ and/or overexpected outcomes $|\lambda < V|$ should have a similar neural activity (Figure 4). Specific populations of neurons will always enhance their signaling regardless of PE cause (US presence/absence or CS valence).

This kind of PE signaling was found in basolateral amygdala (BLA) neurons ACC, central nucleus and prefrontal regions, and the posterior parietal cortex, either in appetitive or aversive settings (Figure 5; Bryden et al., 2011; Holland and Maddux, 2010; Li et al., 2011b; Roesch et al., 2012, 2010a, 2010b, 2009, 2007; Takahashi et al., 2009; Valentin and O'Doherty, 2009).

The amygdala plays a major role in fear memory consolidation, reconsolidation and associative learning (Finnie and Nader, 2012; McGaugh, 2004; Phelps and LeDoux, 2005). From an evolutionary perspective, it is reasonable to think that the amygdala generates an unsigned PE considering its role in danger detection, emotion and memory (Phelps and LeDoux, 2005). This unsigned PE, as predicted by the PH

model, could influence, arousal-mediated, the error-driven learning. Holland and colleagues showed that lesions in the central nucleus of the amygdala impairs orienting response to surprise, reward timing information (Holland and Maddux, 2010; Maddux et al., 2007) and enhancement in CS processing (associability) after the omission of expected events in an appetitive task. Moreover, Calu et. al. (Calu et al., 2010) have shown the specific role of the central nucleus of the amygdala in reinforcement omission signaling (unsigned PE). They also found that midbrain dopamine neurons show an inverse pattern (signed PE; Roesch et al., 2010a). The amygdala is also involved in surprise (Belova et al., 2007; Davis et al., 2001), response to unexpected outcomes and unpredictability (Belova et al., 2007), aversive error signaling (Matsumoto and Hikosaka, 2009; Ungless et al., 2004), attentional shift (Holland and Maddux, 2010; Roesch et al., 2012) and reinforcement timing (Díaz-Mataix et al., 2014; Holland and Gallagher, 2004).

Interestingly, using rats in a choice task in which odors predicted different rewards, Roersh (Roesch et al., 2010a), found that BLA neurons increased firing when a surprising reinforcement was presented (positive PE). Moreover, when an expected reward was omitted (negative PE), BLA neurons had a higher response. This and other reports (Calu et al., 2010; Holland and Gallagher, 1993; Roesch et al., 2012) reveal that the amygdala is crucial for attentional enhancement generated by a negative PE.

The activity of amygdala differs from dopamine neurons not only because these neurons decrease their firing rate after a negative PE but also, it appears later and

their signaling is much broader in comparison with amygdala neurons. Even more, the response of the latter increase after many trials independently of the reward shift (up / down; Calu et al., 2010).

In humans, an increase in skin conductance response was described after the omission of a predicted US in fear learning (Dunsmoor and LaBar, 2012). Similarly, attentional enhancement towards emotional face expressions after unpredictable timed sound pulses correlates with BLA activity (Herry et al., 2007).

3.3. Integration between models.

CS and US processing models have been posited as rivals for a long time. There is accumulated evidence in favor of both views, thus making these theories not only compatible but also true to some extent (Domjan, 2014). Some authors (Le Pelley, 2004; Le Pelley et al., 2010; Pearce and Mackintosh, 2010) have recently begun to integrate these theories into hybrid models in order to include: **a)** summed and separable error terms, **b)** CS-US processing and **c)** the Mackintosh and PH types of attention processing (see below).

For example, Mackintosh proposed that attention increases to the best predictor while the PH model stated the opposite (Hall and Pearce, 1982; Mackintosh, 1975; Pearce and Hall, 1980). In order to tackle this contradiction, the PH model differentiates between two kinds of attentional processes. Attention during learning decreases when the CS consequences are well predicted, while it could be restored in the face

of a surprising event (PH model). The other attention is related to performance. In this condition, animals guide their behavior paying more attention to the best predictor of the outcomes (Mackintosh model). Hence, these two kinds of attention provide the basis for hybrid model development (Le Pelley, 2004; Pearce and Mackintosh, 2010).

Boll and colleagues (Boll et al., 2013) integrate both into a hybrid model using an aversive reversal paradigm in humans. They demonstrated that an unsigned PE signal (according to the PH model) was observed in the amygdala and the ventral midbrain, when unexpected shocks and unexpected omissions occurred. The intensity of the signal decreased when the US was fully predicted and increased again with a reversal training (negative PE). Using fMRI, Li et. al. (Li et al., 2011b), found a similar dissociation between CS and US processing in the ventral striatum and amygdala. In another study, Belova and co-workers (Belova et al., 2007) showed that the amygdala modulated expectations and generated multiple signals during learning. Using trace conditioning in monkeys, they found that a specific population of amygdala neurons increased, decreased or maintained their firing rates during the omission of an appetitive or aversive US. This pattern had a strong correlation with observed behavior, suggesting that different populations of amygdala neurons are sensitive to signed and unsigned errors during learning.

Hybrid models were also supported by a recent work, where Klavir et. al. (Klavir et al., 2013) found a crosstalk between two brain structures, the amygdala and the ACC. In this sense, they reported the co-existence and temporal coding of signed and unsigned errors using trace fear conditioning in monkeys. Critically, the authors

showed that, when the association was reversed, there was an increase in the functional connectivity between ACC and the BLA. This study described two populations of BLA neurons: the “unsigned error” and “signed error” neurons. Simultaneous recording revealed that the “unsigned error” neurons in the BLA fire before dorsal ACC and that, the “signed error” BLA neurons follow the activity of the dorsal ACC neurons. These results suggest that unsigned errors are first generated in the amygdala and then, sent to the dorsal ACC. There, a new stimulus-value encoding either positive or negative is given and then it returns to the amygdala.

CS and US processing models are dissociable but may have a complementary role in learning and memory (Figure 5; Boll et al., 2013; Calu et al., 2010; Domjan, 2014; Le Pelley, 2004; Roesch et al., 2012). The brain uses both signals and integrate them in order to learn or update stored information. The interconnection that signal CS and US processing consist in a wide brain network that includes hippocampus, VTA, BLA, central nucleus of amygdala, ACC, among others (Goosens, 2011; Hayden et al., 2011; Ploghaus et al., 2000; Roesch et al., 2012; Schultz, 2007). Notably, the same areas are involved during memory acquisition and memory processes. Considerable efforts are needed to integrate the neural correlates found in US and CS processing models taking into accounts the new proposals of hybrid models of learning (Le Pelley et al., 2010; Pearce and Mackintosh, 2010). This new framework will allow us a better understanding of learning, acquisition and memory processes.

3.4. The Hippocampus case.

The hippocampus represents a special case for PE studies because on the one hand, PE signals were found to be compatible in both US and CS processing models, and on the other, hippocampus was discovered to be a mismatch – novelty detector (Kumaran and Maguire, 2009a, 2007a; Lisman and Grace, 2005). For example, during the first trials of fear conditioning in animals (when the reinforcement is more surprising) the hippocampal activity is maximal (positive PE; Knight et al., 2004). The enhanced hippocampal activity is also required when the outcomes become less predicted or occur in an unsigned way (Maren et al., 1997; Rudy and Matus-Amat, 2005). The hippocampus is also necessary during the omission of expected outcomes (negative PE) like in the first trials of extinction training, partial reinforcement and context-shift detection (Goosens, 2011; Tsetsenis et al., 2007). Ploghaus (Ploghaus et al., 2000). The use of fMRI in an associative task between lights and different outcomes (painful heat, no stimulation and non-painful warmth), showed that the hippocampus had higher levels of activation when different mismatches occurred. That is: **1)** when the subjects received an unexpected US (positive PE), **2)** when the cue was changed and, **3)** when there was an US unexpected omission (negative PE).

Classical studies performed by O´Keefe and Nadel (O'keefe and Nadel, 1978) and recently by Fyhn (Fyhn et al., 2002), using electrophysiological recordings, showed that hippocampal neurons increase firing when the escape platform in a water maze was moved to a novel (unexpected) position after having trained the subjects to the previous escape position for several days. In addition, immediate-early gene

activation (c-fos and Zif268) correlated with hippocampal activity caused by novelty (Aggleton and Brown, 2005; Amin et al., 2006; Wan et al., 1999).

However, in other non-PE frameworks, the hippocampus is involved in a wide variety of memory functions, prospective memory, detection of novelty, unexpected events, predictions and associative mismatches (Goosens, 2011; Hassabis et al., 2007; Izquierdo et al., 1984; Maren, 2014; Nyberg, 2005; Ploghaus et al., 2000; Schacter et al., 2012; Squire, 1992). The predictive functions of the hippocampus might be related to the capacity to abstract rules ("extraction of regularities") and bind different memory elements (cue – time – context) in a coherent representation (Eichenbaum, 2004; Kumaran and Maguire, 2009a). Acetylcholine and dopamine are neurotransmitter candidates for this process to occur (Holland and Maddux, 2010; Lisman and Grace, 2005).

Interestingly, the hippocampus is involved in the unique task of switching between encoding and retrieval, in order to avoid overwriting, overlapping or catastrophic interference between new and old information (Figure 6; Gluck et al., 2013; Hasselmo and Schnell, 1994; Kumaran and Maguire, 2009b; Lisman and Grace, 2005; Tubridy and Davachi, 2011; Vinogradova, 2001).

The hippocampus and other medial temporal lobe areas act in an autoassociative manner (Gluck and Myers, 1998). To do so, the hippocampus produces "pattern completion" and "pattern separation", and determines when to update an already stored memory representation or to create a new one (Bakker et al., 2008; Rolls,

2013). When an item is cued, the hippocampus completes the input and recovers the full pattern (pattern completion; Eichenbaum, 2004; Wallenstein et al., 1998). Specifically, numerous models proposed that pattern separation and match-mismatch computation (comparison) were processed in the CA1 region with information incoming from the CA3 region (Duncan et al., 2012; Lisman and Grace, 2005; Nyberg, 2005; Vinogradova, 2001).

In computational models, novelty signals are the result of the operation of a comparator (Vinogradova, 2001), which discharges when discrepancy is detected between a current sensory input and the expected one based on past experience. Moreover, pattern completion allows memories to be reinstated from a partial input, which is a mechanism that putatively reactivates past episodes (Alvarez and Squire, 1994). Therefore, it has been proposed as a potential mechanism related to the comparator. Thus, similar to what happens with PEs, if the inputs match, no new information is detected and plasticity may not occur (Lisman and Grace, 2005). A comparison between the stored information and the actual input is performed by the left hippocampus and probably within the CA1 area (Figure 6; Chen et al., 2011; Duncan et al., 2012; Kumaran and Maguire, 2007b; Lisman and Grace, 2005). However, it has been postulated that if the inputs do not match (pattern separation), a mismatch signal is transmitted via a descending loop from the hippocampus and might trigger activation of dopaminergic VTA neurons (Lemon and Manahan-Vaughan, 2006; Lisman and Grace, 2005). The subsequent increase in dopamine release in the hippocampus engages acquisition or memory updating.

Kumaran and Maguire proposed that hippocampus acts as a mismatch detector and might encode temporal order representation (Kumaran and Maguire, 2006). In their experiments, subjects viewed sequences of trial-unique objects (i.e. A, B, C, D) while performing an incidental target detection task. Then, in a second trial, object quartets were presented: in the same order, two (A, B, D, C) or all of them (D, C, B, A) were switched. The results revealed that neural activity on the left hippocampus distinguished the partially rearranged object sequence. Further, when the spatial location of the objects was partially changed, significant left hippocampal activity was observed under conditions of associative match–mismatch (Kumaran and Maguire, 2007b). Altogether, these results suggest that hippocampal mismatch signals are triggered when there is an overlapping between the novel sensory input and stored representations. Moreover, Honey (Honey et al., 1998), reported that hippocampal lesions impair associative mismatch detection in an audiovisual sequence.

As in the PE, when an already learned cue is presented and reinstates the original learning situation (stored memory), animals anticipate and make the proper predictions. Only when predictions are violated does mismatch occur. Consequently, attentional and learning processes are initiated (Goosens, 2011; Lisman, 1999). These results highlighted the role of the hippocampus in updating the stored information and in the importance of predictions (Fyhn et al., 2002; Goosens, 2011; Kumaran and Maguire, 2009b).

In conclusion, several brain regions generate signed and unsigned PE signals compatible with both CS and US processing models. The hippocampus, amygdala

and VTA are fundamental in PE signals and mismatch detection. However, as Bouton pointed (Bouton, 1993) that these models lack the study of long-term retention interval and the fate of memory.

To the best of our knowledge, there are few studies regarding the role of PE on an already consolidated memory and how this process can update its content or strength (Alberini, 2005; Lee, 2009; Sara, 2000). In the next section we will address the parameters to generate a PE able to induce the labilization-reconsolidation process.

4. The Reconsolidation Process.

After acquisition, a short-term memory require a consolidation process, which turns this labile trace into a stable and long lasting one (McGaugh, 2000; Müller and Pilzecker, 1900). Memories are dynamic rather than static and, after being consolidated, they can be modified through further experience (see Figure 7). Thus, inactive memories can be reactivated through the presentation of cues (reminders) already existent at the time of acquisition. This results in memory reactivation (labilization), followed by a process of re-stabilization known as reconsolidation (Dudai, 2012; Nader et al., 2000; Sara, 2000). Within this framework, the reconsolidation process opens the possibility to introduce modifications into the original acquired information, updating its content or strength (Alberini, 2005; Exton-McGuinness et al., 2015a; Sara, 2000) and relevance (Lee, 2009).

Several studies have established that reconsolidation: **a)** is a universal phenomenon preserved across species and observed in almost all kinds of learning protocols (Dudai and Eisenberg, 2004; Lee, 2009; Schiller and Phelps, 2011); **b)** It requires RNA transcription, protein synthesis, NMDA receptor activity and the involvement of many neuromodulators (Alberini, 2013; Boccia et al., 2004; Finnie and Nader, 2012; Nader and Hardt, 2009), **c)** memory reconsolidation neurobiological mechanisms are very similar to those in consolidation although not identical (Alberini, 2013, 2005; Lee et al., 2004; Li et al., 2013); **d)** it has boundary conditions: memory retrieval is a necessary condition but it is not enough to reconsolidate it (Dudai 2006; Exton-McGuinness et al. 2015; Forcato et al. 2009).

4.1. Boundary Conditions of the Reconsolidation Process.

Many reports have established that presentation of a reminder (e.g. context, CS or US alone) affects memory acquisition, storage or retrieval (Bjork, 1975; Gisquet-Verrier and Riccio, 2012; Hardt et al., 2010; Spear, 1973). Reminder treatments induce recovery from: extinction (Bouton, 2002), overshadowing (Kasprow et al., 1982), blocking (Blaisdell et al., 1999), spontaneous forgetting (Deweer et al., 1980; Zhou and Riccio, 1994), etc. (Miller and Springer, 1974; Spear, 1981; Spear and Riccio, 1994; Urcelay, 2012). Moreover, a specific reminder presentation can trigger reconsolidation process.

The interaction between the reactivation session and the characteristics of the target memory determines whether memory retrieval could induce memory expression,

labilization-reconsolidation and/or new learning (Alberini, 2013; Osan et al., 2011a; Piñeyro et al., 2014). Several boundary conditions were proposed for reconsolidation to occur; such as: **a)** memory age (Baratti et al., 2008; Boccia et al., 2006; Dudai and Eisenberg, 2004; Forcato et al., 2014, 2013; Frankland et al., 2006; Inda et al., 2011; Milekic and Alberini, 2002; Suzuki et al., 2004), **b)** strength (Dudai and Eisenberg, 2004; Forcato et al., 2013; García-DeLaTorre et al., 2009; Lee, 2010; Morris et al., 2006; Reichelt and Lee, 2013a; Suzuki et al., 2004; Taylor et al., 2009; Wang et al., 2009; Winters et al., 2009) **c)** rate of reinforcement (Morris et al., 2006; Sevenster et al., 2014, 2013), **d)** reminder session features (Bustos et al., 2009; Eisenberg et al., 2003; Forcato et al., 2009; Lee et al., 2006a; Pedreira and Maldonado, 2003; Sevenster et al., 2012a; Suzuki et al., 2004), **e)** extinction (Inda et al., 2005; Lee et al., 2006b; Merlo et al., 2014; Osan et al., 2011b; Suzuki et al., 2004), **f)** new learning opportunity (Besnard, 2012; Besnard et al., 2012; Haubrich et al., 2015; Rodriguez-Ortiz et al., 2005; Rodriguez-Ortiz and Bermudez-Rattoni, 2007) and **g)** mismatch between expected and current events (PE) (Dudai, 2012; Exton-McGuinness et al., 2015; Forcato et al., 2009; Pedreira et al., 2004; Reichelt and Lee, 2013a; Sevenster et al., 2014, 2013, 2012). Nevertheless, considering that labilization in memory reconsolidation might be proportional to the generated PE, certain boundary conditions (such as memory age/strength) can be overcome by manipulating the reactivation phase in ways that would be expected to produce a stronger PE (see references above, for a review see Alberini et. al, 2013).

Reconsolidation is typically revealed by the absence (impairment) of the target memory at testing using pharmacological or behavioral tools (Lee, 2009). The most

frequently used reminder session is a negative PE (λ<V), that is, the omission of an expected reinforcement after the cue presentation or context (CS) associated with training. However, others have been able to trigger reconsolidation using a positive PE (λ>V, CS-US, or US alone, Table 2). Other authors used, instead, a change in contingency or generate a temporal mismatch (change in the expected US time). These results suggest that PE seems to be mandatory during the reactivation session in order to initiate memory reconsolidation. In line with what CS and US processing models suggest for acquisition, labilization in memory reconsolidation depends on the amount of PE generated. We will next review the PE findings with regard to memory reconsolidation.

4.2. Negative PE (λ< V) requirement in the reconsolidation process.

A non-reinforced trial (negative PE) during reactivation is the most typical way to induce reconsolidation (Table 2). According to conditioning models, as the US becomes well predicted, its omission should induce the greatest PE (λ<V, where λ=0 and V=predicted US with the current associative strength). Beginning with the seminal work of Nader et. al (Nader et al., 2000), the negative PE allowed to discover several molecular bases (see reviews, (Bonin and De Koninck, 2015; Dudai, 2006; Finnie and Nader, 2012; Jarome and Lubin, 2014; Tronson and Taylor, 2007) and its boundary conditions. For example, using crab *Neohelice granulata* in a contextual memory, Pedreira et al. (Pedreira et al., 2004) first trained the animals to associate the learning context (CS) with a visual danger stimulus (US). Twenty four h later animals were re-exposed either to the context alone or the context plus the visual danger stimulus.

Both groups were injected with a protein synthesis inhibitor immediately after memory reactivation and tested 24 h afterwards. Only animals re-exposed to the CS in absence of the US (λ<V) showed a memory impairment. When the outcome of the CS was fully predicted (no PE, λ=V), the reconsolidation process was not triggered. The results showed the importance of the reminder structure. A mismatch between expected (US presentation) and current events (no-US) seems to be a necessary condition to labilize memory.

Forcato et. al (Forcato et al., 2009, 2007) studied different types of reminder during the reactivation session on paired associated declarative memory in humans. During acquisition, subjects were trained with a list of non-sense syllables (context – syllable cue + target). The reactivation session on day 2 included three different reminders of the training session: the context-reminder (context alone), the cue-reminder (context + syllable cue without the possibility of completion of the target) and the cue-response reminder (contextual and syllable cues with the possibility of completion). A second list of non-sense syllables was used to interfere the target memory. Only the group that received the cue-reminder, prior to the second list learning, showed memory impairments to the first list. The other reminders failed to induce memory labilization, leaving target memory intact because they omit the learned cue (context reminder) or replay the learned situation on day 1 (cue response reminder). Memory labilization does not occur when the stimuli are predictable (context and response reminder). A mismatching component, which omits the possibility to respond to the cue, is needed to induce the reconsolidation process.

In another report, Sevenster and co-workers (Sevenster et al., 2012) used fear conditioning in humans and showed that propranolol only failed to impair memory reconsolidation when there was nothing to be learned during reactivation session (no PE). Previous reports of the same group (Kindt et al., 2009; Kindt and Soeter, 2011) used β-adrenergic blockade during negative PE reactivation (no-shock) to disrupt the reconsolidation process. Moreover, they found that when the shock electrodes, which delivered the US during training, were not attached (no PE) during reactivation, and the outcome was, therefore, fully predicted, fear memory was unaffected by propranolol, since it was not labilized.

More recently, two studies (Liu et al., 2014; Zeng et al., 2014) found similar results using a less-aversive US-alone presentation during the reactivation session. It is reasonable to hypothesize that a weaker US-alone presentation might induce the reconsolidation process by a negative PE because it is overexpected. In other words, the intensity of US stored representation is stronger than the received one during the reactivation session ($\lambda<V$). Previous reports stated that reconsolidation blockade is specific to the reactivated CS, leaving the non-reactivated ones intact (Dębiec et al., 2010; Doyère et al., 2007; Oyarzún et al., 2012; Schiller et al., 2010). Notably, Liu et. al.(Liu et al., 2014), revealed that a weaker US-alone presentation followed by extinction training is able to target all CS associated with that cue and provide long-lasting fear reduction. Furthermore, Weems and colleagues matched the above mentioned laboratory setting with real life events (Weems et al., 2014) showing that a lower exposure to a traumatic event (Hurricane Gustav) allows the memory to update the one which had more devastating consequences (Hurricane Katrine). People

exposed to these events showed reduced negative memories and posttraumatic stress symptoms.

On the other hand, another form of negative PE, namely overexpectation, was recently used during reactivation session to induce memory labilization (Table 2). Overexpectation represents a typical protocol that favors US-processing models. During acquisition, two separated stimuli are associated with the same reinforcement. Then both stimuli are presented in compound, but the amount of reinforcement is held equal. Thus, overexpectation consists in a reduced response to each separate stimulus after compound training (Lattal and Nakajima, 1998).

The RW model anticipates this outcome, because at the beginning of the compound training, the expected US (sum of both stimuli) doubles the maximum of each individual stimulus presented ($\lambda<V_1+V_2$). As a result, each compound trial reduces associative strength due to a negative PE (the US is overexpected) (Miller et al., 1995; Rescorla and Wagner, 1972). In this sense, within the reconsolidation framework, Reichelt and Lee (Reichelt and Lee, 2013b) made straightforward contributions showing that overexpectation can destabilize an appetitive memory. In order to do so, rats required 4 days, but not 1 of overexpectation training. Moreover, NMDA receptors seem to be involved in negative PE processing (memory impairment). As stated before, the dopaminergic system is critical for novelty and negative PE detection. Then, these authors prevented memory labilization by blocking the dopaminergic system in the VTA (Reichelt et al., 2013). In this circumstance, post-reactivation NMDAR antagonist effects were no longer observed.

Thus, this report provided a direct link between dopaminergic signals, PE and reconsolidation.

When dealing with memory reconsolidation, most studies used a negative PE omitting the US. However, it is worth pointing out that, in conditioning processing models and considering the abovementioned results, there are several ways to induce a negative PE and, in consequence, memory reconsolidation processes (Table 2).

4.3. Positive PE (λ>V) requirement in the reconsolidation Process.

It has been said that the most common reactivation session consists of a negative PE where the CS is presented and the US, omitted. However, there are few reports where a learning trial (positive PE) is used instead (Table 2). These studies mostly revealed that it is possible to trigger reconsolidation process with a positive signaled or unsignaled PE in weak memories prior to asymptotic learning (λ>V). This makes sense considering that the change in memory strength is proportional to the PE generated (λ-V). In consequence, an already fully predicted US during the reactivation of a strong memory is unable to induce a PE (zero PE, λ=V; Díaz-Mataix et al., 2013; Rodriguez-Ortiz et al., 2005; Sevenster et al., 2013a; Wang et al., 2009). On the contrary, a reinforced trial should generate a larger PE in a weak memory leading to memory labilization - restabilization. Duvarci and Nader (Duvarci and Nader, 2004) found that a reinforced trial is capable of destabilize a fear memory trained with a single conditioning trial. Similar results were found in other type of memories (Eisenberg and Dudai, 2004; Milekic et al., 2006; Sevenster et al., 2013b).

Evenmore, Lee (Lee, 2008) reported that a learning trial during reactivation not only labilizes a fear memory, but also strengthens it through reconsolidation (see below). Similarly, a US-alone presentation was found to trigger reconsolidation process suggesting bidirectional associations between cues (Díaz-Mataix et al., 2011; Gerolin and Matute, 1999; Liu et al., 2014; Zeng et al., 2014). Díaz-Mataix and colleagues (Díaz-Mataix et al., 2011) using pharmacological interventions and electrophysiological recording, showed that a US-alone presentation of the same intensity as that used in training, followed by a MAPK inhibitor, disrupts fear memory resulting in a depotentiated CS neural response. One would expect that, during the reactivation of a strong memory, a training-identical US-alone presentation should not induce the reconsolidation process ($\lambda=V$). However, it is unknown whether increasing the US intensity during the reactivation session might lead to memory updating ($\lambda>V$, positive PE).

Several conditioning procedures, such as sensory preconditioning, partial reinforcement, and/or latent inhibition, among others, reveal how stored information affects subsequent learning. Some authors suggested that we learn more and faster about the best previously informative cue (best predictor; Le Pelley, 2004; Mackintosh, 1975) or even the poorest outcome predictor (Pearce and Hall, 1980). However, it is important to note that the amount of CS-processing (attention) on a given trial or during the reactivation session depends, at least partially, on the associative history of that CS. In this line of evidence, Sevenster et. al (Sevenster et al., 2013b) proposed a declarative memory index of memory labilization (the US expectancy as rated by the subjects), and they tested whether a positive or negative

PE could induce the reconsolidation process of a fear memory. A previous study of another group (Dunsmoor et al., 2012, 2008) reported how cognitive expectations modulate the response magnitude to the US and the fMRI related activity. In Sevenster's study, three groups were trained in differential fear conditioning. Two groups were trained with a 100% rate of reinforcement (control-no PE and negative PE) and the remaining group with a 33% rate of reinforcement (positive PE). At the reactivation session, which took place 24 h after training, the no PE and the positive PE groups received a single reinforcement trial, while in the negative PE group the reinforcement was omitted. It was found that propranolol, administered immediately post-reactivation, reduces fear in a subsequent test only when a PE (positive or negative) is produced. Moreover, the authors suggest that memory labilization could be predicted taking into account changes in subject US-expectancy ratings. The negative PE group induced labilization during reactivation because the expectation of a well-learned memory was violated ($\lambda<V$). In the positive PE group, the reinforcement trial represents a new learning opportunity of a non-asymptotic memory (a non-fully predicted US presentation, $\lambda>V$). Moreover, the reinforcement trial in the control group failed to induce PE and consequently the reconsolidation process. This negative finding could be attributable to the already fully predicted outcome ($\lambda=V$).

Finally, it has been recently reported that neither one nor four reminders (without reinforcement) induce a PE able to destabilize a partially-reinforced fear memory during acquisition (50 % non-random). Only the group that received two reminders showed a change in the US expectancy and a persistent reduction in fear only in

those subjects receiving propranolol after reactivation. Four reminder presentations, even when producing a negative PE, induce a new learning situation (extinction).

Altogether, these results highlight the importance of the training history and different reactivation possibilities (Table 2). Memory systems are capable of detect subtle differences between training and reactivation. Accordingly, it might create a new memory or reformulate the old one granting memory with extraordinary malleability and function in everyday life.

4.4. Other forms of PE in the reconsolidation process.

Instrumental conditioning seems to be more resistant to reconsolidation manipulations and many authors failed to reveal its existence (Cammarota et al., 2004; Exton-McGuinness et al., 2015a, 2014; Lee and Everitt, 2008; Mierzejewski et al., 2009). Moreover, in an inhibitory avoidance task, it was described a transient memory impairment infusing muscimol, a GABA-A agonist (Amaral et al., 2007).

However, Tedesco et. al. (Tedesco et al., 2014) and Exton-Mcguiness et al (Exton-McGuinness et al., 2014), have recently disclosed the reconsolidation phenomena in instrumental settings. In this study, MK-801 administration only disrupted memory reconsolidation in an appetitive lever task when the reward contingency was changed from a Fixed-Ratio-1 to a Variable-Ratio-20 schedule (Exton-McGuinness et al., 2014). Notably, the NMDA antagonist was ineffective when using a non-reinforced

reactivation (negative PE) or a switch to a Fixed-Ratio-20 schedule (Reichelt et al., 2013). These results should be cautiously interpreted within the CS or US learning models. In the first ones, a change to a Variable-Ratio schedule contingency during reactivation should generate surprise and an increase in unpredictability (Holland and Maddux, 2010; Mackintosh, 1975; Pearce and Hall, 1980; Pearce and Mackintosh, 2010). Thus, the attention to that cues are increased by PE signals, forcing the memory to update. In a US learning model, such temporal differences which also take time into account, the switch to a Variable-Ratio schedule should trigger a PE signal by the means of a change in all the future rewards predicted (Sutton and Barto, 1981).

Similarly, a recent study using rats (Díaz-Mataix et al., 2013), showed that a temporal PE during reactivation triggers reconsolidation of a strong fear memory. Since CS-US time interval is encoded during acquisition (Díaz-Mataix et al., 2014; Gallistel and Balsam, 2014), a shift in this time interval generates a PE during memory reactivation (Sutton and Barto, 1981). Previously, in other reports it was found that changes in reward timing could generate a PE signal in DA neurons in VTA (Roesch et al., 2007) and also in the amygdala (Díaz-Mataix et al., 2014; Holland and Gallagher, 2004; Wheeler and Holland, 2011).

Finally, another type of reactivation session consist in presenting the training cue and the new information simultaneously in order to update the memory (Rodriguez-Ortiz et al., 2005; Rodriguez-Ortiz and Bermudez-Rattoni, 2007). Recently, Haubrich et. al (Haubrich et al., 2015) first trained rats in contextual fear conditioning for three days

and then he used counterconditioning training. They found that exposure to the training context in the presence of appetitive stimuli either by three reactivation sessions of 3 min each, separated by two days, or a single 9-min one, impaired fear memory (“suppressed”).

4.5. Memory strengthening by positive or negative PE in Reconsolidation.

Labilization-reconsolidation process allows both memory updating and strengthening. Many researchers studied memory enhancement after its labilization, using pharmacological agents, which affect the re-stabilization phase (Blake et al., 2013; Boccia et al., 2011, 2010; Carbo Tano et al., 2009; Coccoz et al., 2013, 2011; Frenkel et al., 2005; Rodríguez et al., 2013); while others, over the past decade, showed that it is possible to modify the strength, persistence and precision of a consolidated memory simply by triggering the reconsolidation process itself (Alvares et al., 2013; Corlett et al., 2009; de Oliveira Alvares et al., 2012; Forcato et al., 2013, 2011; Fukushima et al., 2014; Inda et al., 2011; Jacques and Schacter, 2013; Lee, 2008; Wiltgen and Silva, 2007).

It is reasonable to think that only a consolidated weak memory could be strengthened by a learning trial (positive PE) because the US is not fully predicted ($\lambda > V$). However, things might be different when considering that one or several non-reinforced trials (negative PE) during reactivation are able to strengthen a consolidated memory.

According to signed US processing models (see section 3.1), a negative PE should decrease the associative strength of the memory (λ<V). Instead, an unsigned CS processing model, like that of PH (see section 3.2.2), would predict a continuum between memory strengthening (when the number of non-reinforced trials is insufficient to produce new learning) and new inhibitory learning (extinction). Thus, a few non-reinforced trials should generate a PE signal, which increases the attention paid to that predictor cue (i.e. further processing by rehearsal) leading to memory strengthening $|\lambda<V|$, while several non-reinforced trials should lead to extinction. Interestingly, there remains a "limbo" in the two processes, where neither of them were appeared (Merlo et al., 2014; Sevenster et al., 2014a). For example, Inda and co-workers (Inda et al., 2011) trained rats in inhibitory avoidance tasks and 24 hs. later, animals were exposed to the training context $|\lambda<V|$ without reinforcement for several days. They found that repeated reactivations strengthened the recent fear memory and prevented forgetting. Fukushima et. al replicated the results (Fukushima et al., 2014) revealing a complex interaction between memory reconsolidation and memory strengthening involving different brain regions (hippocampus, amygdala, prefrontal cortex) and pathways (calcineurin - proteosome, cAMP).

In a contextual fear memory paradigm, Lee (Lee, 2008) found that a second learning trial strengthened a weak consolidated memory (positive PE, λ>V), but only when it had been previously reactivated. Interestingly, impairing memory reactivation with a pharmacological agent hindered the improvement effect of additional learning on the target memory.

However, the strengthening function of reconsolidation could be limited to the passage of time (boundary condition), reactivation of an old memory (i.e. 4 weeks) may lead to facilitation of extinction (Inda et al., 2011). A similar conclusion for the case of humans was reported by Forcato et. al using pairs of non-sense syllables (see above for details, (Forcato et al., 2014, 2013). They found that repeated presentations of a specific reminder 24 h after training, strengthened a declarative memory, improved precision and turned the target memory more resistant to interference. Even a single reactivation session improved memory persistence. However, this effect was not present if reactivation was performed 7 days after training, since the memory become old. Notwithstanding, De Oliveira Alvares et al. (Alvares et al., 2013) in contextual fear conditioning showed that context re-exposure (negative PE) strengthened memory and improved precision, persistence and discrimination between the contexts in a 2-day or 14-day old memory.

We have reviewed the induction of the labilization-reconsolidation process in different settings by means of a specific PE during the reactivation session. But other parameters interact with the PE requirement suggesting an interaction between the characteristic of the retrieved / reactivated memory and the reminder used. Altogether, these determines the boundary conditions of memory reconsolidation. In this sense, mixed results were found with age (Baratti et al., 2008; Brunet et al., 2008; Coccoz et al., 2013; Debiec et al., 2002; Eisenberg and Dudai, 2004; Forcato et al., 2014; Frankland et al., 2006; Inda et al., 2011; Milekic et al., 2006; Robinson and Franklin, 2010, 2010; Steinfurth et al., 2014; Wang et al., 2009; Wichert et al., 2011) and strength (Díaz-Mataix et al., 2013; Eisenberg and Dudai, 2004; Forcato et al.,

2013, 2013; García-DeLaTorre et al., 2009; Morris et al., 2006; Suzuki et al., 2004, 2004; Taylor et al., 2009; Wang et al., 2009; Wichert et al., 2012; Winters et al., 2009) of the reactivated memory and with the reminder duration (Bustos et al., 2009; Eisenberg et al., 2003; Lee et al., 2006b; Pedreira and Maldonado, 2003; Suzuki et al., 2004). However, negative findings may be due to the use of only one type or inappropriate reminder or insufficient reactivation sessions (Exton-McGuinness et al., 2015; Finnie and Nader, 2012). For example, strong and old memories were reported to be destabilized using the appropriate reminders (see references above): **a)** duration or number of reactivation sessions, **b)** specific target pharmacological tools or **c)** a special type of reminder considering training history. Thus, there is no universally effective reactivation session for all types of memories and protocols (Table 2). Moreover, some authors proposed the existence of a down-regulation of molecular mechanisms which destabilize memories and could be transient or reversible in nature (Finnie and Nader, 2012).

Here we highlighted that different forms of PE differentially affect memory acquisition and / or reconsolidation, pointing out the similarity between new memories and reactivated ones. Lastly, one might ask: how could I learn more from or change something that will happen exactly as I expected it will? The response is simple: when the outcome differs from what I initially predicted, although it might differ in several dimensions other than presence / absence and intensity, like in the cases reviewed of negative and positive PE. Furthermore, it has been shown that training history, time, contingency and the presence of new information can also induce the labilization-reconsolidation process, but these may not be the only factors.

The question resembles that of blocking-unblocking effects. In these protocols, an acquired memory blocks the acquisition of another since its outcome is already predicted. Prediction error or PE-like events are necessary conditions in order for a new element to become a predictor. Similar to PE findings in the reconsolidation field reviewed above, changing the timing of events (CS-US) and the reinforcement intensity unblocked learning to the new element (Blaisdell et al., 1999, 1997; Dickinson et al., 1976; Dickinson and Mackintosh, 1979; Holland, 1984; Kamin, 1969; Mackintosh et al., 1977; Mackintosh and Turner, 1971; McNally et al., 2004b).

4.6. The relationship between PE and the reconsolidation process.

Different types of PE signals co-exist in the brain and serve as a helpful tool to understand the reconsolidation process and its biological functions. Having that in mind: Why does the presentation of a reminder in a consolidated memory generate a PE? Here is one potential explanation. An effective cue reminder, which can trigger reconsolidation, is one that induces a mismatch process, either because it entails an unexpected change in the original training situation, presents new information or presents a learning trial which has not been well predicted by the current associative strength. Hence, an effective reminder capable of labilizing memory is one which elicits a PE signal. It could be a CS, a US, the context alone, contingency, timing or any other parameter that could have affected acquisition. This is similar to that proposed by Lewis and Spear (Lewis, 1979) related to similar sensitivity to all those

parameters mentioned above on memory consolidation and reconsolidation processes. As Le Pelley noted "*If the US is not well predicted by a CS then it is able to support more learning with respect to that CS than if it is already well predicted*" (Le Pelley, 2004).

In Figure 8 we show a link between PE and the labilization-reconsolidation process. Since there is no universally-effective reactivation session, different forms of PE (positive, negative or others forms) should be effective to induce memory reconsolidation depending on the characteristic of memory (i.e. strength, age, training history, type of memory) and the reminder used (selected cue, duration, timing).

Furthermore, some of the findings regarding unblocking effects (see above), could be translated to the reconsolidation research. For example, could the addition of a second reinforcement presentation during the reactivation session induce the reconsolidation process ($\lambda > V$)? In the same way, could the omission of an expected second reinforcement labilize memory ($\lambda < V$)? Changing timing between or within events? Finally, could the changing of the locus of the stimuli presentation induce the labilization-reconsolidation process? How relevant or informative must the change in the parameters be in order to cause significant surprise or trigger the reconsolidation process? All of these questions remain unanswered and open to debate.

5. Conclusions.

Overall, here we attempted to extend the idea of the close relationship between PE, learning and memory. Their dynamic nature interacts in order to acquire new and update stored information. Notably, many of the PE findings mirror those of memory reconsolidation, suggesting a strong link between these signals and memory process. Specially, it is worth mentioning the importance of the dopamine system because it seems to be involved in all the fields reviewed here (novelty detection, CS-US, hippocampus and reconsolidation; Roesch et al., 2012). Nevertheless, other neuromodulatory memory systems, such as the sometimes forgotten endo-opiod system (β-endorphin; Izquierdo et al., 1984) should not be discarded (novelty detection / processing).

If PE is proposed to be the driving force of learning and of the reconsolidation process, then it is reasonable to think that both could be sensitive to the same factors. Furthermore, we highlighted that, in order to analyze how the labilization-reconsolidation process is induced, one must take into account the characteristics of the reactivated memory and the reminder used. The same reactivation session, which elicits a PE, could have different effects in the same memory type (young vs old memories) and different reactivation sessions could have the same effect in different memories (reactivation by negative or positive PE).

It is already known that PE has different signatures throughout the brain. Future research should aim at including it within the memory reconsolidation framework. Moreover, it would be of importance to know how the brain computes errors and how these predictions are made. It is essential to point out that the US and the CS processing models reviewed here do not totally predict all the findings regarding

memory reconsolidation, especially since neither takes into account the time and age factors in memories. However, these models could serve as a useful framework to understand some of the reconsolidation results and its updating function. Moreover, as with reconsolidation, the PE models are still a growing field.

Further, understanding how the memory changes from inactive to active through a PE does not only have basic scientific interest, but it also could have an enormous impact on the clinical field. The reconsolidation process could be applied in the treatment of psychiatric disorders, updating the maladaptative content of memories or strengthening daily-life memories in neurological disorders.

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Figure 1. Glossary of different memory concepts used in text.

GLOSSARY:

Acquisition: A process by which an experience is encoded in a specific way and, eventually, converted into a memory trace.

Conditioning: The most common and universal form of associative learning. In Classical or Pavlovian conditioning the subjects learns a predictive relation among stimuli whereby a Conditioned Stimulus (CS) is reinforced by an Unconditioned Stimulus (US) during training. In the Instrumental or Operant form of conditioning, subjects learn the relation among stimuli, their actions and outcomes.

Consolidation: The neural process by which the unstable acquired / learned information is stabilized and transformed into a long lasting representation.

Contingency: The US presentation must have a dependency on the prior presentation of the CS. That is to say, the comparison between: the probability of receiving a US in the presence of a CS and the probability of receiving a US in the absence of the CS.

Labilization / Destabilization: A transient process by which a previously consolidated memory becomes again sensitive to disruptive agents.

Memory: The retention over time of experience-dependent internal representations or of the capacity to reactivate or reconstruct such representations. It supposes the ability to encode, store, retrieve and change learned information.

Prediction Error: A mismatch between expected and current events. It is a measure of how unexpected or surprising is the occurrence of the events.

Reactivation: The process by which a memory pass from an inactive to an active form resulting in memory labilization-reconsolidation.

Figure 2. Prediction error in learning. A) Increase in associative strength over time. Once asymptotic, further trials produce no learning. **B)** The US expectation increases in correlation with the associative strength. **C)** Prediction error decreases over time and no surprise occurs.

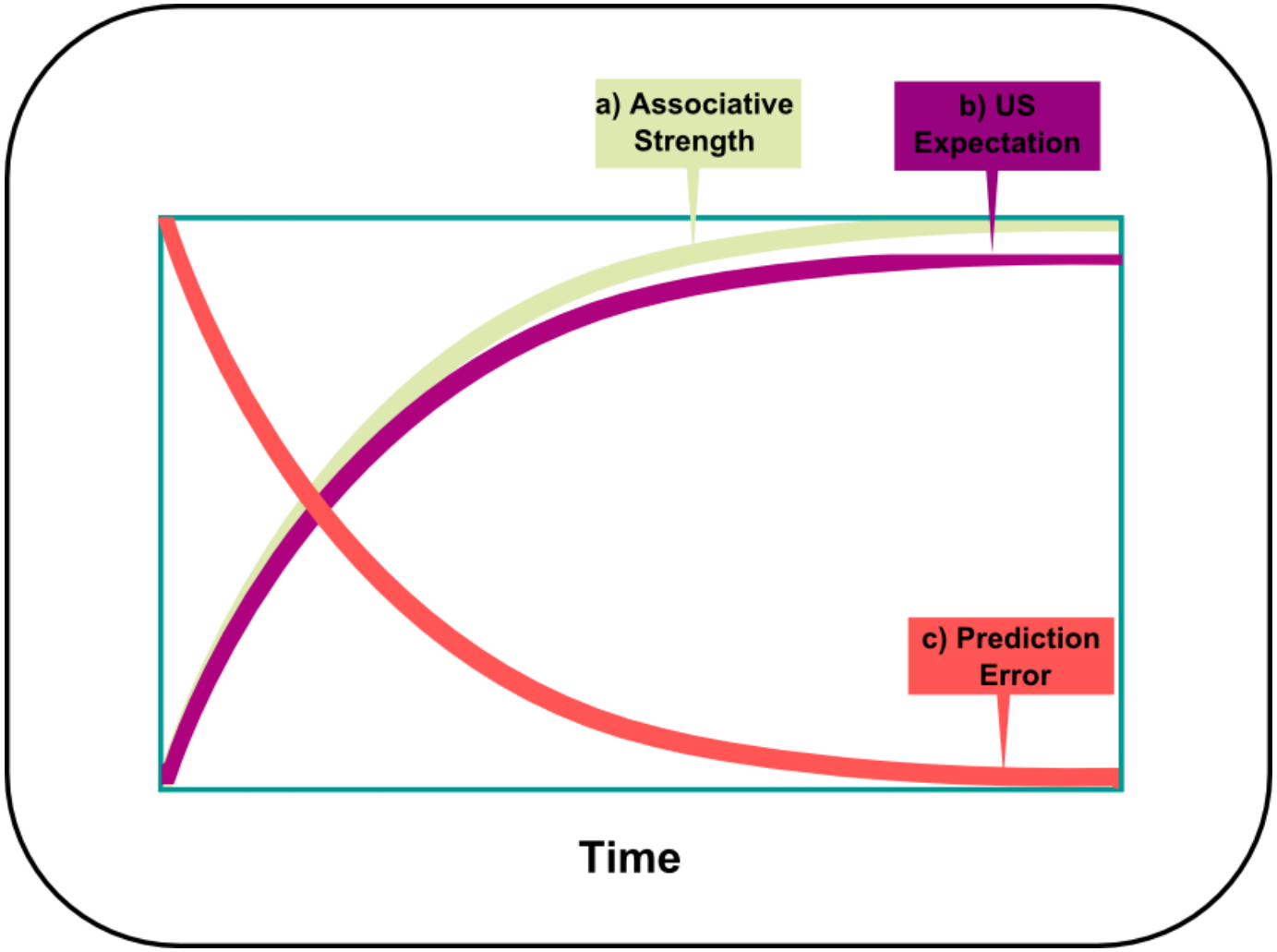

Figure 3. Dopamine neurons response to Prediction Errors. A) Firing of dopamine neurons increase after unpredicted reward (positive PE). **B)** After conditioning dopamine signal is transferred to the predictor CS. **C)** Omission of predicted reward (negative PE) induce a depression of dopamine firing. **D)** and **E)** Change in reward timing (earlier or later) induces a positive or negative PE signal. **F)** Dopamine response is proportional to reward probability and the error generated.

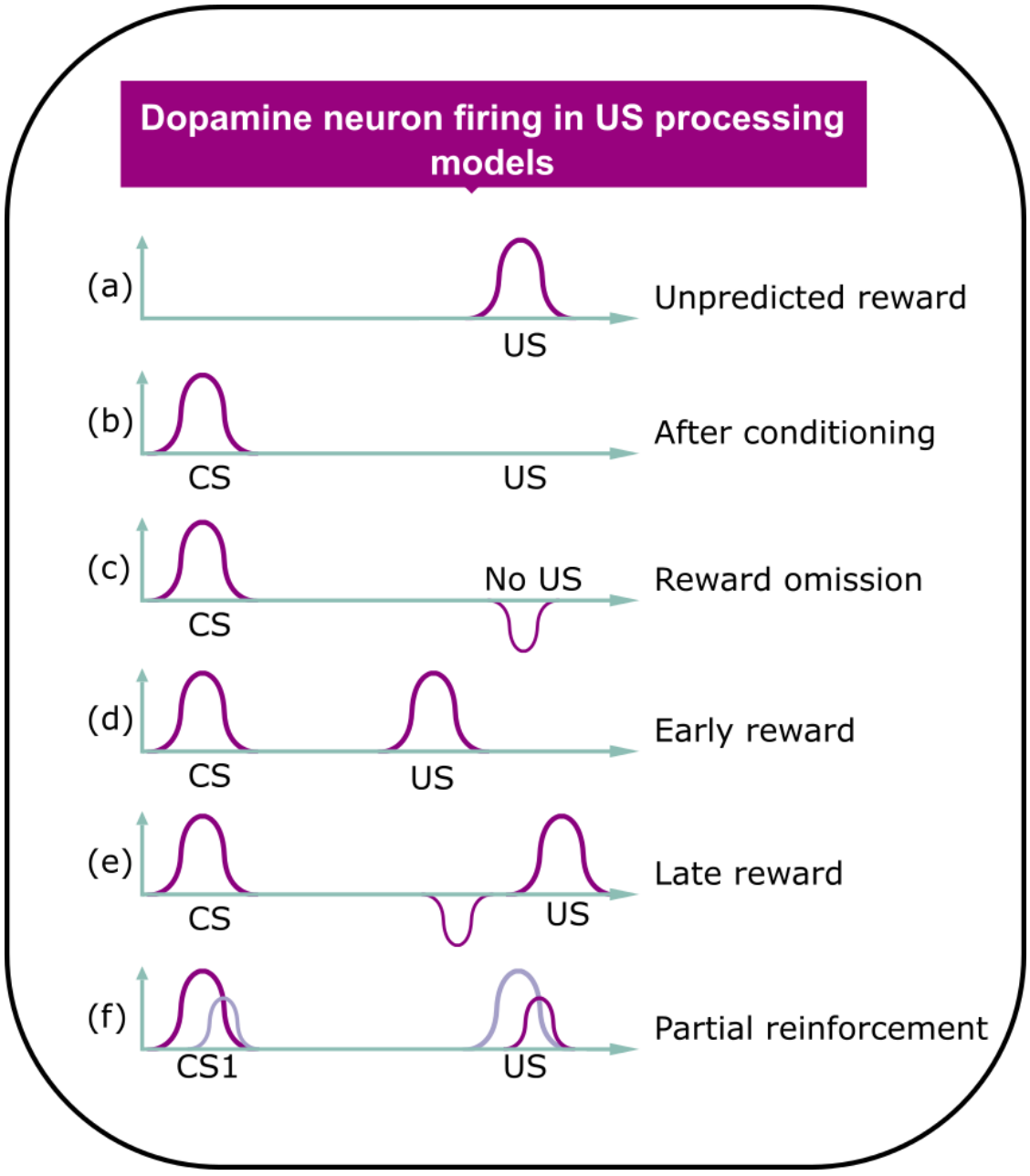

Figure 4. Expected neuronal firing after PE in US and CS processing models. A) US processing models are signed ones. After a positive PE, neuron-firing increases (i.e. dopamine neurons) in relation to baseline; and after a negative PE, the opposite response emerges, as predicted by the RW and Temporal Difference models. **B)** CS processing models are unsigned. Neural firing (i.e. BLA neurons) proportionally increases to the absolute value of the PE either after underpredicted or overpredicted reinforcement, according to the Mackintosh and PH models.

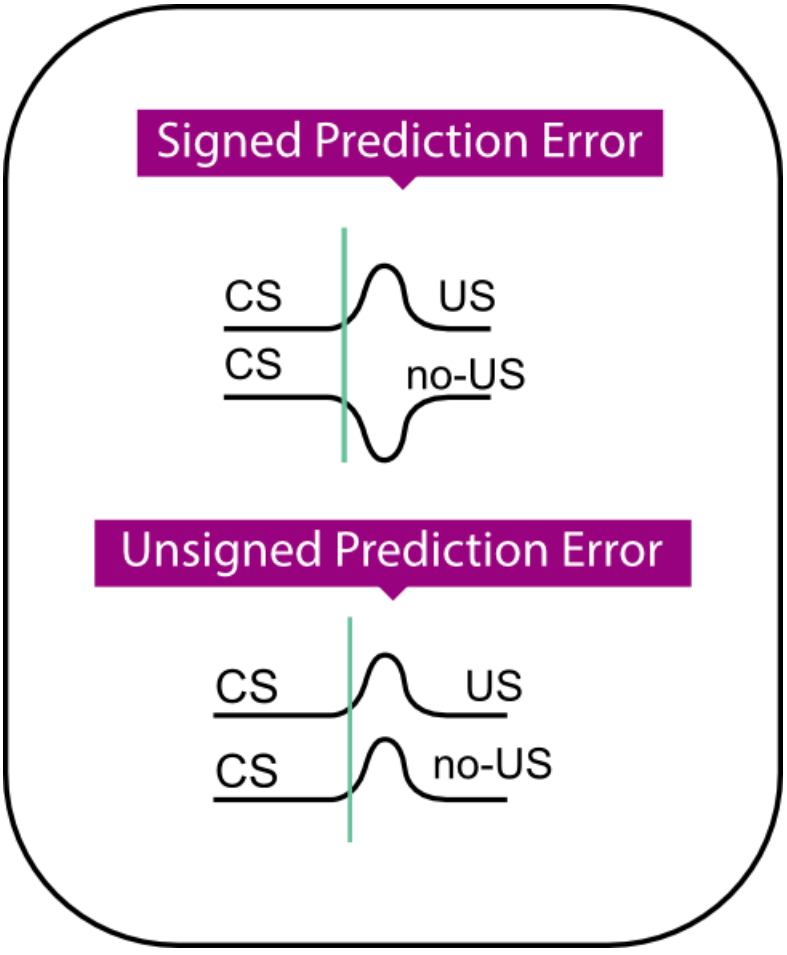

Figure 5. Brain illustration showing the most reported areas in which signed and unsigned Prediction Error were detected.

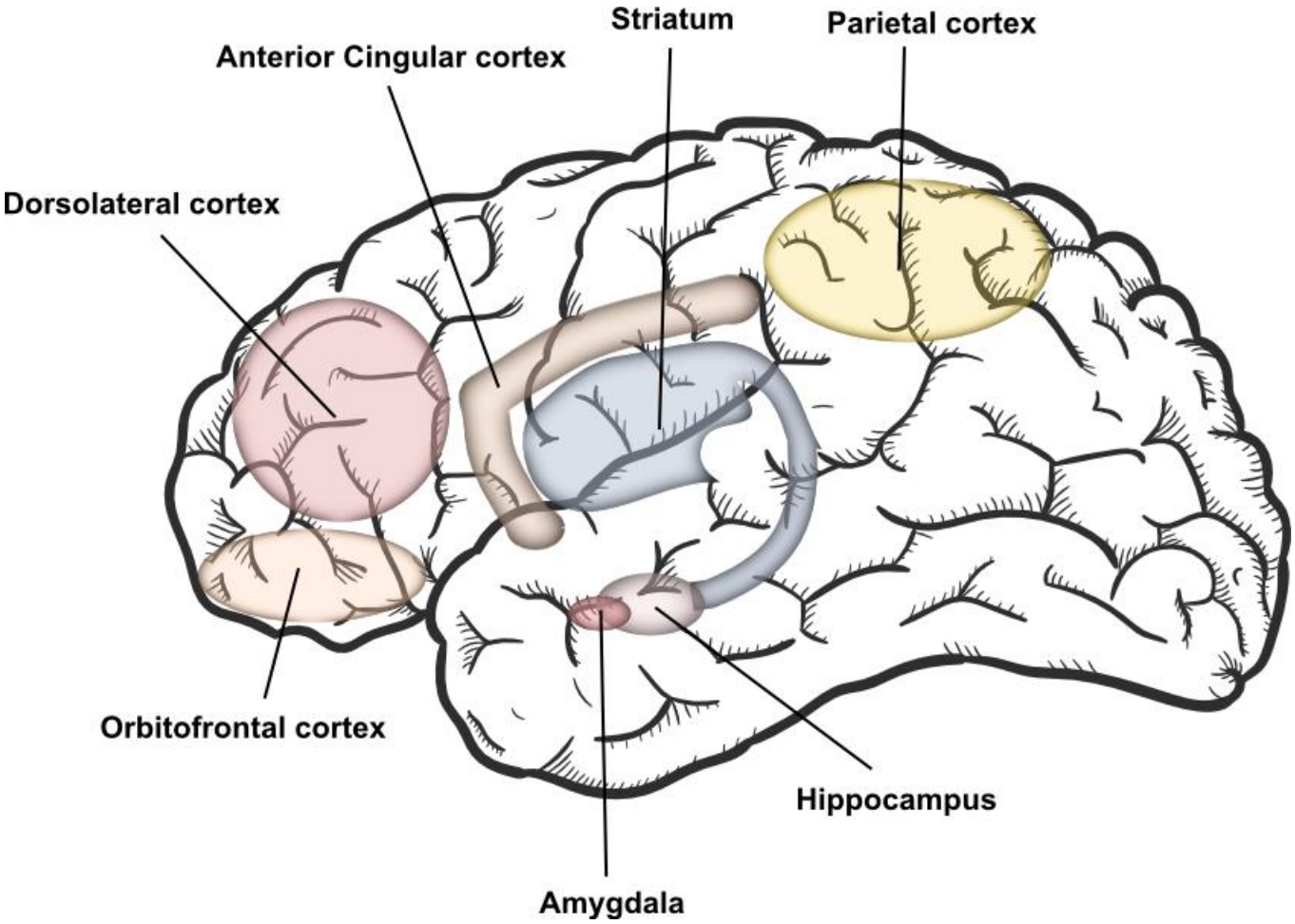

Figure 6. Diagram of the Hippocampus as a comparator. Information enters the entorhinal cortex layers and into the dentate gyrus and the CA3, where the stored memory is reconstructed / retrieved (pattern completion). The CA1 compares the predictions made by the reconstructed pattern of the dentate gyrus and the CA3 and the online sensory input of the entorhinal cortex layers. The hippocampus acts as a switch between encoding and retrieval depending on the comparison made (match – mismatch; *adapted from Lisman and Grace, 2005*).

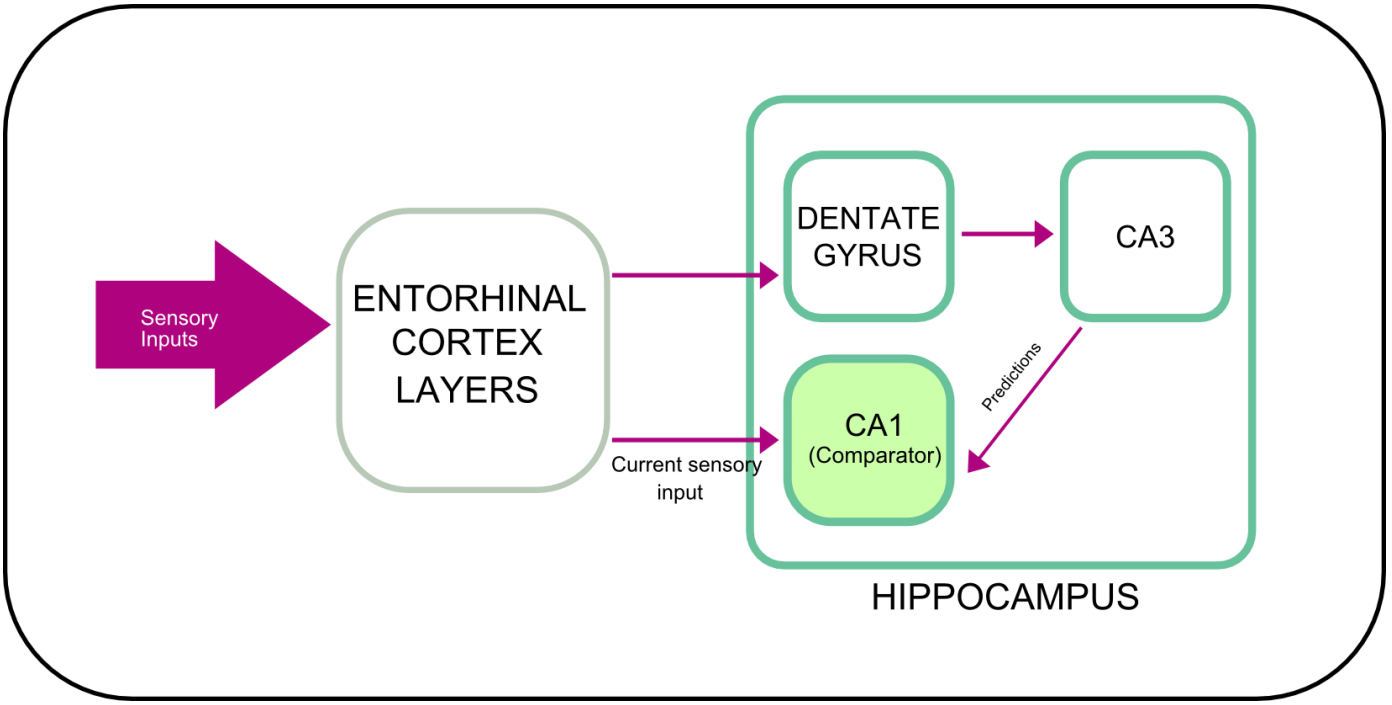

Figure 7. Schema of memory phases. Initially new information is acquired and sensitive to disruption (labil). This memory is then stabilized trough a consolidation process. Afterwards, a reminder presentation may render a consolidated memory unstable, trough a destabilization process that requires its re-stabilization in order to persist (reconsolidation).

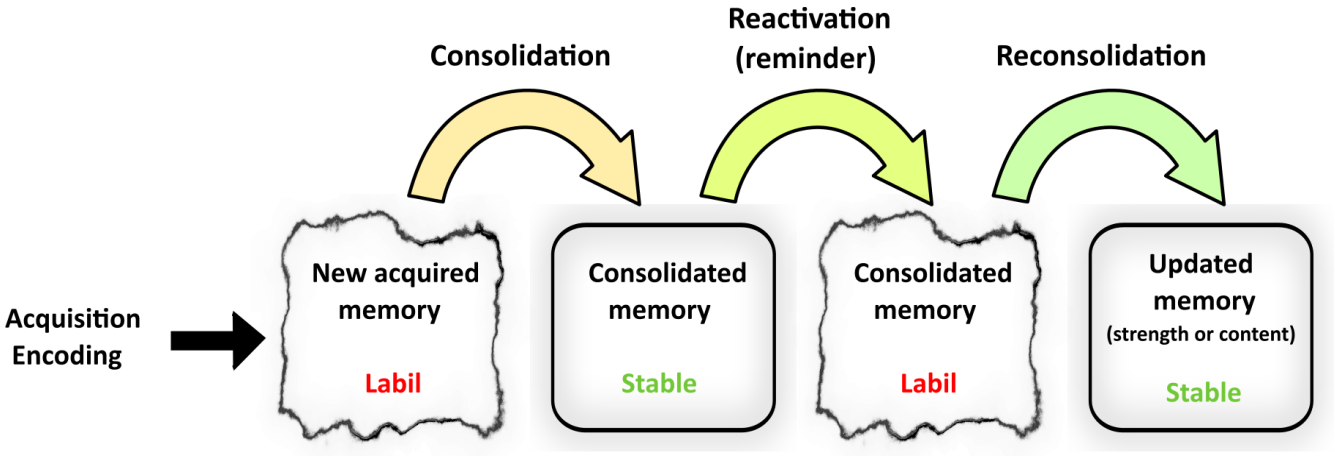

Figure 8. Different PE signals trigger memory reconsolidation. 1) When a cue is presented, the similarity between training and reactivation is needed in order to make a proper prediction of the learned situation. A similar-to-training context should enable a proper prediction and a dissimilar context should induce new learning. **2)** A Prediction is made, which anticipates future or possible state of affairs. **3)** An expected outcome confirms the prediction (match - retrieval); an unexpected outcome or surprising event induces a PE (mismatch - reactivation) which triggers the reconsolidation process, leading to memory updating (content or strength) and adjustment for future predictions. **4)** A repeated series of mismatching events constitutes a training thus leading to new learning.

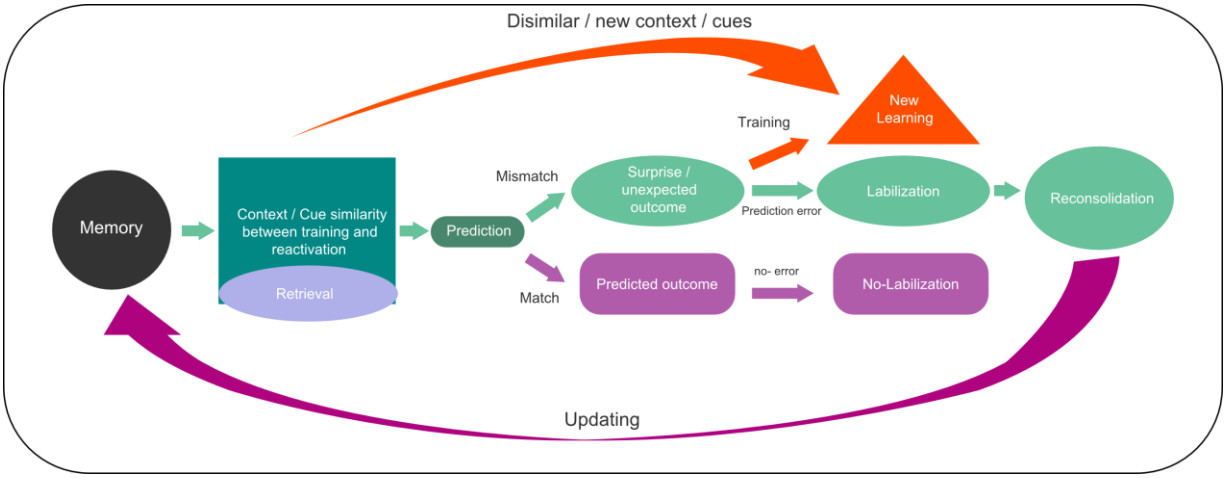

Table 1. Summary of the US and CS processing model parameters.

	US processing models (RW) $\Delta V_x = \alpha_x \beta (\lambda - V)$	**CS processing models (PH)** $\Delta V_A = S_A \alpha_A \lambda$, $\alpha_A^n = \lvert \lambda^{n-1} - V_A^{n-1} \rvert$
α	CS Salience	Associability
	Fixed	Subject to change
β	US salience	
	Fixed	--------
λ	Presented US	Presented US
	US characteristics	US characteristics
V	Expected US	Expected US
	Current associative strength	Current associative strength
S		CS Salience
	--------	Fixed
Prediction Error	Signed / bidirectional	Unsigned

Table 2 Different PE reported to trigger the labilization-reconsolidation process.

Reactivation Session	Observation	Reference
CS-only (cue or context)	*1.* Duration (short vs. long) *2.* Memory strength *3.* Memory age *4.* Training history	Alvares et al. 2013; Brunet et al. 2008; Bustos et al. 2009; Carbo Tano et al. 2009; Debiec et al. 2002; Eisenberg y Dudai 2004; Inda et al. 2011; Kindt and Soeter 2011; Lee et al. 2006b; Milekic et al. 2006; Nader et al. 2000; Pedreira et al. 2004; Pedreira y Maldonado 2003; Robinson y Franklin 2010; Schiller et al. 2010; Steinfurth et al. 2014; Suzuki et al. 2004; Wang et al. 2009; Winters et al. 2009
US-only	Equal or lower intensity than in training	Díaz-Mataix et al. 2011; Liu et al. 2014; Zeng et al. 2014
CS – US pairing	Equal intensity and context as in training	Duvarci and Nader 2004; Eisenberg et al. 2003; Lee 2008; Milekic et al. 2006; Sevenster et al. 2013
CS simultaneously presented with new information / new	Reactivation session in compound or followed with novel information	Boccia et al. 2005; García-DeLaTorre et al. 2009; Haubrich et al. 2015; Rodriguez-Ortiz et al.

learning.		2005; Winters et al. 2011
Compound cues previously and separately trained	Overexpectation procedure	Reichelt et al. 2013; Reichelt and Lee 2013b
Change in the US timing	The US is presented sooner than expected	Díaz-Mataix et al. 2013
Change in reward contingency	From fixed to variable interval ratio in an instrumental setting	Exton-McGuinness et al. 2014