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Review

# Toward a better understanding on the role of prediction error on memory processes: From bench to clinic

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ABSTRACT

Experimental psychology defines Prediction Error (PE) as a mismatch between expected and current events. It represents a unifier concept within the memory field, as it is the driving force of memory acquisition and updating. Prediction error induces updating of consolidated memories in strength or content by memory reconsolidation. This process has two different neurobiological phases, which involves the destabilization (labilization) of a consolidated memory followed by its restabilization. The aim of this work is to emphasize the functional role of PE on the neurobiology of learning and memory, integrating and discussing different research areas: behavioral, neurobiological, computational and clinical psychiatry.



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> No one can see in a single instant the plenitude of his past. (. . .). The memory of man is not a sum; it is a disorder of undefined possibilities.
>
> Saint Augustine spoke, if I remember correctly, of the palaces and caverns of memory.
>
> The second metaphor is more just. Into these caverns I walked.
> [J.L. Borges, Shakespeare Memory (1983)]

## 1. Introduction

Like the famous statement, "it is not raining" or an absent friend in an appointment, the omission of expected events, can cause

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strong influence on animals and came to control behavior. Although, many things are not happening or a few other surprising events might be happening. It is essential for a mismatch to occur, that the occurrence or non-occurrence of an event to be already predicted or anticipated. Excitatory or inhibitory associations may be formed between two events even when one or both of them are absent (Holland & Sherwood, 2008). More importantly, the brain response generated by the surprising omission of an object contains information about the identity of the absent stimulus (Peelen & Kastner, 2011). Learning and memory theories have not traditionally paid much attention to how organisms learn about absent cues or whether animals are sensitive to the omission of events (Wasserman & Castro, 2005).

One of the most intriguing functions of our central nervous system resides in its ability to adjust to changing environments (Buzsáki, Peyrache, & Kubie, 2014; O'reilly, 2013). This ability implies storing past experiences and its associated values (rewards and punishments) allowing animals to make predictions about the occurrence, timing and magnitude of future events (Bubic, Von Cramon, & Schubotz, 2010; Niv, 2009; Sutton & Barto, 1981). We call this function memory and memory consolidation to the process by which an unstable acquired memory is transformed into a long-lasting one (McGaugh, 2000; Squire, Genzel, Wixted, & Morris, 2015).

In this context, the aim of this work is to integrate and discuss different research areas (behavioral, neurobiological, computational and clinical psychiatry) on the *neurobiology of learning and memory* emphasizing the functional role on prediction error.

## 2. Memory and prediction error

When memory systems engage in encoding mode, the stored representation generated is a constructive process subject to distortions rather than internal copy of the experience (Schacter, Norman, & Koutstaal, 2000). Therefore, retrieval from memory and prediction of future or possible scenarios are also reconstructive processes in nature. By general rule, animals acquire and optimize their predictions when initial expectations differ from its outcomes (Prediction error; Niv, 2009; Rescorla & Wagner, 1972). At the heart of the theory lies the original proposal put forward by Rescorla and Wagner (1972): '*(. . .) organisms only learn when events violated their expectations*'. Prediction error (PE) induces updating of consolidated memories in strength or content by memory reconsolidation (Exton-McGuinness, Lee, & Reichelt, 2015; Fernández, Boccia, & Pedreira, 2016). This process have two different neurobiological phases, which involves the destabilization (labilization) of a consolidated memory followed by its restabilization (Dudai, 2012; Lee, 2009). The surprising presentation of stimuli gains the animal attention which engages in a rehearsal process necessary for learning to occur or continue (Mackintosh, 1975; Wagner, Rudy, & Whitlow, 1973). If this process is interrupted memory could be impaired. In a more cognitive way, a reminder is a retrieval cue that reactivates the memory and stimulates further processing, turning memory from inactive to active state.

In other terms, learning refers to a reduction of surprise (error) and memory reconsolidation to the process by which an already stored representation is updated by unexpected outcomes. Here surprise (error) means that outcomes may be under/overpredicted (positive or negative PE) or better/worse than predicted. Consequently, PE determines what and how much is learned/updated. When PE is near zero (no surprise), no further learning/updating occurs (no PE). Different forms of PE such as: positive, negative and/or others, (Duvarci & Nader, 2004; Díaz-Mataix, Martinez, Schafe, LeDoux, & Doyère, 2013; Fernández et al., 2016; Pedreira, Pérez-Cuesta, & Maldonado, 2004; Reichelt, Exton-McGuinness, & Lee, 2013) were reported to induce memory destabilization constrained by: (a) memory features (i.e. strength, age, training history, type of memory) and (b) the type of reminder used (selected cue, duration, timing; Alfei, Monti, Molina, Bueno, & Urcelay, 2015; Baratti, Boccia, Blake, & Acosta, 2008; Bustos, Maldonado, & Molina, 2008; de Oliveira Alvares et al., 2012; Eisenberg & Dudai, 2004; Fernández, Bavassi, Forcato, & Pedreira, 2016; Inda, Muravieva, & Alberini, 2011; Sevenster, Beckers, & Kindt, 2013; Suzuki et al., 2004; Wang, de Oliveira Alvares, & Nader, 2009). Therefore, PE induces memory destabilization-recon solidation, either because it entails an unexpected change in the original training situation (i.e. addition, omission, timing), presents new information or presents a learning trial, which has not been accurately predicted.

Conceptualizations of reconsolidation formerly name "cue dependent amnesia" were put forward several decades ago (Gordon, 1981; Miller & Springer, 1974; Misanin, Miller, & Lewis, 1968; Misanin et al., 1968; Spear, 1973). Spear (1973) postulated the absolute similarity between new and reactivated memories and that both could be affected by similar factors. Hence, a reminder presentation reactivates memory turning it into an unstable form susceptible either to enhancement (Carbo Tano, Molina, Maldonado, & Pedreira, 2009; Eysenck, 1976; Fernández et al., 2016; Forcato, Fernandez, & Pedreira, 2014; Frenkel, Maldonado, & Delorenzi, 2005; Gordon, 1981) or disruption (Dudai, 2012; Spear, Miller, & Jagielo, 1990; Nader, Schafe, & Le Doux, 2000). Spear, Lewis and others (Lewis, 1976, 1979; Spear, 1973) proposed a retrieval theory similar to the reconsolidation theory held in the field today. Thus, memory reactivation could strength or update memory with new information. A memory is said to be active during original learning (consolidation) or after memory reactivation (reconsolidation). The more active the memory is, the more open to modification. Inactive memories are not subject to change.

In these sense, Lewis, 1979) stated that the functions of an active memory were: (a) register new inputs or stimulus salience; (b) associate two or more inputs; (c) integrate a new input with an already consolidated memory; (d) associate two well consolidated memories. When a memory is reactivated, it is re-encoded and further elaborated. This re-elaboration increases associative connections (facilitates later retrieval) and if it is interfered by a new learning situation or amnesic agents, amnesia or decrements in performance are observed (Exton-McGuinness et al., 2015; Wagner et al., 1973). Lewis wrote: "*In a real sense, rehearsal is a dynamic memory process, and it involves derived information, new integration of learning, perhaps a whole series of new associative learnings, each with its own brief fixation time*" (Lewis, 1976). Notwhistanding it could be inferred from Lewis (Lewis, 1976, 1979) papers that not every time a memory is retrieved, and consequently in active state, it can be modified. The rehearsal or recoding process that is responsible for the re-elaboration of the trace following memory reactivation, only occurs when a surprising event is detected or additional information is presented in a non-well predicted outcome (Mackintosh, 1975; Pearce & Bouton, 2001). When there is a perfect match between online input and stored information, no changes in memory take place. In regard, Lewis wrote: "*Perhaps the only new learning that occurs upon the appearance of familiar stimuli is that an old item has occurred again. Unexpected and surprising representations are held for a longer period of time. During this time coding occurs, one of whose purposes is to make the representation retrievable by fitting (association, further learning, coding) it into an existing memory assembly*" (Lewis, 1979).

Memory reconsolidation is the process by which consolidated memories could be updated in strength or content during time dependent period (Fernández et al., 2016; Nader et al., 2000;