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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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Contents

> 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;

Sara, 2000). This susceptibility to change implies a labile (active) memory, which requires re-stabilization in order to persist (reconsolidation). The beginning of this process is neither automatic nor mechanic. If every time we remind previous experiences, memory reconsolidation is triggered, it would be risky since memory is at stake during this process. Boundaries conditions of memory reconsolidation would entail a protective factor. Memory reconsolidation requires the presentation of a specific reminder of the stored experience, capable of induce a PE. When our predictions or understanding of the world do not fit with the current experience, the detection of this incongruence triggers the destabilization-reconso lidation process, which allows us to adjust our internal models. Therefore, memory guarantees us to better adapt to a changing world by predictions based on our past experiences (models) and the extraction of regularities. Thereby, PE is a unifier concept within memory field, as it is the driving force of memory acquisition and updating revealing memory functionality as a whole.

3. Prediction error and molecular mechanisms of memory reconsolidation

In the last 20 years the neurobiological mechanisms of memory reconsolidation were studied using different animal models and learning protocols (Flavell, Lambert, Winters, & Bredy, 2013). To reveal the involvement of a given molecule during the reconsolidation process, it is typically used a reminder session which induces a positive or negative PE (i.e. CS-US pairing or a CS only presentation, respectively). In these studies, several pharmacological tools are used immediately after the reactivation session in order to target the re-stabilization phase. However, in order to disentangle the mechanisms of memory destabilization, which leads ultimately to reconsolidaton, it is required to demonstrate that an experimental intervention prevents the disruptive effect on memory of another amnesic drug. Contrary to the role of PE on memory acquisition (Schultz, 2015), its molecular and physiological underpinning during memory reconsolidation are still unclear. To the best of our knowledge there are no studies demonstrating a direct link between PE and molecular mechanisms of memory destabiliza tion-reconsolidation. Accordingly, PE might be inferred after an effective reactivation session able to trigger memory destabiliza tion-reconsolidation. Most of the findings on the mechanisms of memory destabilization were based on the induction of a negative PE (omission of the expected outcome) during memory reactivation.

In the following section, we will focus on those papers related to PE-induced destabilization from cellular to neurotransmitter level of analysis.

A well-known cellular mechanism controlling protein turnover is the ubiquitin and proteasome system, in which polyubiquitinated proteins are degraded by the proteasome complex. This system is required in order to occur remodeling of synapses during memory reconsolidation (Jarome, Ferrara, Kwapis, & Helmstetter, 2016). The increase in protein degradation may contribute to both the destabilization of consolidated memory and the restabilization of the updated memory (Ehlers, 2003; Lopez Salon, Pasquini, Besio Moreno, Pasquini, & Soto, 2003; Pettigrew, Smolen, Baxter, & Byrne, 2005). Lee et al. (2008) demonstrated that protein degradation after memory reactivation is important for the destabilization of preexisting memory, rather than for the restabilization process. They coinfuse a protein synthesis inhibitor (anisomycin) and a proteasome inhibitor (clasto-lactacystin-b-lactone) into mouse's hippocampus immediately after retrieval, preventing the memory impairment caused by the single infusion of anisomycin 24 h post retrieval. This result indicates that the inhibition of the proteasome impedes the destruction process of the previously consolidated memory, maintaining the behavioral response even when the reconsolidation is inhibited without new protein synthesis.

We already discussed the role for ubiquitin–proteasome mediated protein degradation in the memory reconsolidation process. Still, little is known on how protein degradation is regulated downstream during the reconsolidation process. The calcium–calmodulin dependent protein kinase II (CaMKII) is directly activated by increased intracellular calcium levels. It has been shown that simultaneously blockade of CaMKII and protein synthesis actually rescued the memory impairments that normally resulted from protein synthesis blockade (Jarome et al., 2016). However, the study of the role of CaMKII in memory reconsolidation processes have found mixed results, with some indicating normal memory retention following post-retrieval inhibition of CaMKII signaling (Arguello et al., 2014; Da Silva, Cardoso, Bonini, Benetti, & Izquierdo, 2013; Sakurai, Yu, & Tan, 2007). It is already known that CaMKII regulates proteasome activity and phosphorylation in *in vitro* and *in vivo* experiments (Bingol et al., 2010; Djakovic, Schwarz, Barylko, DeMartino, & Patrick, 2009; Djakovic et al., 2012; Jarome, Kwapis, Ruenzel, & Helmstetter, 2013), though this relationship has never been examined during memory reconsolidation. Furthermore L-type voltage-gated calcium channels (LVGCCs) and cannabinoid receptor 1 (CB1) were also involved in the destabilization of a fear pavlovian conditioning (Suzuki, Mukawa, Tsukagoshi, Frankland, & Kida, 2008). Suzuki et al. (2008) demonstrated that pharmacological blockade of these processes protect retrieved memories from the effects of an amnesic agent.

Glutamatergic neurotransmission is critical for almost every memory phase. Infusions of ifenprodil, an NMDA antagonist that inhibit the NR2B subunit receptor, in the amygdala was able to prevent anisomycin-induced amnesia when injected before but not after retrieval (Ben Mamou, Gamache, & Nader, 2006; Milton et al., 2013). Conflicting results were reported regarding AMPA receptors (Ben Mamou et al., 2006; Hong et al., 2013; Rao-Ruiz et al., 2011; Yu, Huang, Chang, & Gean, 2016). Yu and co-workers suggested a critical role of AMPARs endocytosis in mouse's BLA in order destabilization of consolidated memory to occur (Yu et al., 2016). Moreover, phosphorylation of GluR1 at Serine-845 (p-GluR1-Ser845) increases both channel open probability and surface expression of this receptor (Banke et al., 2000; Man, Sekine-Aizawa, & Huganir, 2007). In their paper, they hypothesized that after memory retrieval there is an increase in glutamate release and NMDARs' activation leading to Ca^{2+} influx. The intracellular increase in Ca^{2+} stimulates calcineurin activity, resulting in dephosphorylation of p-GluR1-Ser845 to elicit AMPARs endocytosis and destabilization of memory.

Dopaminergic neurons in the midbrain (ventral tegmental area (VTA) and substantia nigra) have been identified as key components on both attention and expectation of an outcome, being implicated in the destabilization and updating of memories under normal behavioral conditions (Reichelt et al., 2013; Schultz, 2015). Experiments carried on in both primates and rodents demonstrated that these neurons are able to report the occurrence of appetitive events and also respond to errors between what animals consider a reward has to be (interpreted by what they were taught during training trials) and what they actually received (Mirenowicz & Schultz, 1996; Roesch, Esber, Li, Daw, & Schoenbaum, 2012). That is, dopaminergic neurons will react only if the time of the reward is uncertain or the magnitude of the reward is different of what was expected (Roesch, Calu, & Schoenbaum, 2007). In this sense, neurons will increase the firing of action potentials if the reward is better than predicted (positive PE), will not change the rate of firing if the reward occurs as predicted (no PE), and will decrease the amount of action potentials fired if the reward is worse than predicted (negative PE). Unlike dopamine firing neurons in the VTA, Basolateral amygdala (BLA)

neurons will increase their firing rates regardless of the type (positive or negative) of PE (Roesch et al., 2012; Wolfram Schultz, 2015).

Reinforcement learning models suggest a number of different ways in which dopamine neurons could represent value in these learning situations: (a) dopamine neurons could report the value of the option that the animal is going to select (Q value achieved by State-Action-Reward-State-Action - SARSA - learning), (b) dopamine neurons could represent the average value of all available options (V-learning) or (c) dopamine neurons could report the value of the best possible option independent of which is ultimately selected (Q-learning). It is still unclear which of these predictions may be taken place, as, depending on the animal model, neural data supports more than one option (Morris, Nevet, Arkadir, Vaadia, & Bergman 2006; Niv, 2009; Roesch et al., 2007).

Results of experiments carried on in rodent models suggest Q-learning as the most consistent learning situation where dopamine neurons could represent value (Niv & Schoenbaum, 2008; Roesch et al., 2007; Schultz, 2015). By allowing error signals to reflect the best available option, this model dissociates error signaling from subsequent actions. As a result, learning for antecedent events is not penalized when animals choose to explore less valuable alternatives. Such exploratory behavior would allow animals to recognize when existing knowledge needs to be updated to reflect changing conditions. However, when studying primates' behavior, the authors reported that dopamine neurons always reflected the value of the cue that was ultimately selected (Morris et al., 2006). These results were interpreted as showing that the activity of dopamine neurons complied with the predictions of SARSA learning.

In the last paragraphs, we highlighted the role of dopaminergic transmission in PE process. Noradrenaline (NA) and Acetylcholine (Ach) are essential for detection of unexpected or expected environmental changes in the stimulus-response-outcome contingencies (Bland & Schaefer, 2012). Throughout the years, experimental evidence supported the hypothesis that Ach plays an essential role in learning and memory processes (C. M. Baratti, Boccia, & Blake, 2009; Power, Vazdarjanova, & McGaugh, 2003; Prado-Alcald, Fernandez-Ruiz, & Quirarte, 1993). In these sense, our lab had developed a series of studies over the last 12 years reporting that central cholinergic system seems to be involved in modulation of acquisition, consolidation, reconsolidation, extinction, and retrieval of information in an inhibitory avoidance paradigm (Baratti et al., 2009; Blake, Boccia, Krawczyk, & Baratti, 2013; Blake, Boccia, Krawczyk, Delorenzi, & Baratti, 2012; Blake, Krawczyk, Baratti, & Boccia, 2014; Boccia, Blake, Acosta, & Baratti, 2006; Boccia, Blake, Baratti, & McGaugh, 2009; Boccia, Blake, Krawczyk, & Baratti, 2010). Furthermore, Winter and colleagues (Stiver et al., 2015) found a connection between the novelty-induced object memory initial destabilization and the cholinergic transmission via muscarinic receptors.

4. Clinical implications of memory reconsolidation

Cognitive neuroscience and its contributions to psychiatry (Bouton, Mineka, & Barlow, 2001; Eysenck, 1976; Mineka & Zinbarg, 2006; Rachman, 1991) attributed a close link between memory (formation, maintenance, and utilization) and mental disorders (Halligan & David, 2001; Nader, Hardt, & Lanius, 2013). In this framework, memory reconsolidation was posited, in some cases, as the mechanism for some psychopathologies maintenance and in others to offer a novel therapeutic tool (Philip R. Corlett, Krystal, Taylor, & Fletcher, 2009; Debiec, 2012; Ecker, 2015; Pitman, 2011; Sevenster et al., 2013; Taylor, Olausson, Quinn, & Torregrossa, 2009). Moreover, the reconsolidation process might be responsible for psychotherapeutic treatment outcome (Fernández et al., 2016; Lane, Ryan, Nadel, & Greenberg, 2014; Nader et al., 2013). Since memory reconsolidation acts on the re-storage process, it constitutes a promising tool for "editing memories" and, theoretically, it would impair any psychopathology recovery or generalization. However, outside the laboratory settings such as in clinical ones, it is unclear how the reconsolidation process might work. If the reconsolidation process was triggered either every time a memory is retrieved or a PE is detected, then it would be relatively simple to change or adapt dysfunctional behavior or memories such as those observed in numerous mental illnesses.

Several translational approaches of memory reconsolidation have shown promising results using either positive or negative PE as reactivation session. In these studies, propranolol (beta-adrenergic antagonist) was able to impairs memory reconsolidation either for emotional or appetitive memories (substance abusers; (Brunet et al., 2008, 2014; Lonergan et al., 2016; Przybyslawski & Sara, 1997; Saladin et al., 2013; Soeter & Kindt, 2015; Xue et al., 2012). Regarding anxiety disorders, mixed results were found in PTSD patients or subjects exposed to a highly aversive experience (Brunet et al., 2008, 2014).

Neuropsychiatric disorders are responsible for more than a quarter of health loss due to disability, more than 20-fold greater than cancer and around eight times greater to diseases attributed to cardiovascular pathologies (Murray, Health, Organization, & Bank, 1996). A systematic review and meta-analysis performed between 1980 and 2013 suggest that 20% of the population experienced a common mental disorder within a 12-month period based on surveys undertaken in 59 countries performed in 155 general populations (Steel et al., 2014). According to the NIH register, in 2014 it was estimated that 43.6 million adults (aged 18 or older) suffer from mental disorders, representing an 18.1% of all adults in the US (https://www.nimh.nih.gov/health/statistics/prevalence/any-mental-illness-ami-among-us-adults.shtml). The most prevalent psychiatric disorders are depression and anxiety meanwhile the less prevalent are bipolar and eating disorders and schizophrenia, among others (Baxter, Patton, Scott, Degenhardt, & Whiteford, 2013). In this sense, 18.1% of US adult population has suffered from anxiety in the last 12 months and 22.8% of these cases were severe; 6.7% had at least one major depressive episode in 2014 and 1.1% suffered from schizophrenia. These highlight the importance of psychiatric disorders on public health and moreover, the cost either direct or indirect, associated with mental illness. Several pharmacological treatments are nowadays targeted against these disorders; benzodiazepines (anxiolytic) and aripiprazole (antipsychotic medication) are among the most prescribed or highest selling drugs (http://www.medscape.com/viewarticle/825053#vp_3). Notwithstanding, for a better outcome and in order to reduce relapse, cognitive behavioral therapy combined with pharmacotherapy represent the best choice for treatment of these disorders (American Psychiatric Association Practice Guidelines: http://psychiatryonline.org/guidelines). Cognitive behavioral therapy (CBT) is a psychosocial intervention (Beck & Dozois, 2011; Knapp & Beck, 2008) being the most widely used evidence-based practice for treating mental disorders. The main purpose of CBT is to develop individual coping strategies in order to target current problems and aims to change dysfunctional cognitive patterns (thoughts, beliefs, attitudes, etc.) and behaviors (Beck, 1979; Beck & Dozois, 2011). It is used not only to treat depression but also a number of mental health conditions (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; McKay et al., 2015; Zhu et al., 2014).

It is a clinical relevant issue how memory processes (enhanced consolidation, impaired extinction and/or impaired updating or reconsolidation) are affected in psychiatric disorders. In the next section we will highlight the functional role of memory reconsolidation in psychiatric disorders maintenance.

4.1. Computational models of psychiatric disorders

Computational psychiatry combines different levels and types of computation with multiple types of data (reinforcement learning, bayesian modeling, etc.) in order to improve understanding, prediction and treatment of mental illnesses (Friston, Stephan, Montague, & Dolan, 2014; Huys, Maia, & Frank, 2016; Moutoussis, Story, & Dolan, 2015). Bayesian approaches try modeling brain functions in situations of uncertainty similar to the optimal described by Bayesian statistics. In this sense different models of anxiety, schizophrenia, addiction, depression, etc., have been proposed based on Bayesian and Reinforcement learning (Chekroud, 2015; Edwards, Adams, Brown, Pareés, & Friston, 2012; Schwartenbeck et al., 2015; Paulus & Stein, 2006; Corlett et al., 2009). One of the main benefits of Bayesian models relies in how we act in response to incongruence and try to compensate them. In other words, when a mismatch between observed and predicted events is detected (PE), the system tries to minimize PE through error correction (learning/updating). That is, one of the main functions of our brain, if not the main, is to predict outcomes of the world. "The perfect scenario" would then be: a world where our prediction fits the outcome (no error in prediction), turning it into a not surprising and predictable one.

Accordingly, beliefs are probability distributions about causes and states of the world which are constantly updated with new information. Abnormal beliefs occur when they are not updated and the system becomes inflexible (Corlett et al., 2009; Edwards et al., 2012; Fletcher & Frith, 2009). Prediction error might be reduced using two different strategies: (a) adjusting the model according to new information (accommodation, memory acquisition or reconsolidation), (b) adjusting the input to fit the model (assimilation; Edwards et al., 2012; Kanai, Komura, Shipp, & Friston, 2015; Piaget, Cook, & Norton, 1952; Proulx, Inzlicht, & Harmon-Jones, 2012; Seth, 2013).

In normal settings, there is an equilibrium among PE minimization strategies (accommodation vs. assimilation). Moreover, computational psychiatry posits that a dysregulation in the delicate balance between these processes might be occurring in mental illnesses (e.g. anxiety disorders and schizophrenia), contributing to its maintenance.

4.2. Anxiety disorders

Normal anxiety is considered an adaptive response to different stressors and/or the anticipated presence of danger. Whereas normal anxiety is short lived and does not usually interfere with our life dramatically, anxiety disorders tends to be a chronic illness that has a significant impact on our daily activities (Grupe & Nitschke, 2013). Anxiety disorders have different symptoms dimensions such as: (a) physiological symptoms (muscle tension, palpitations, dizziness, nausea, etc.), (b) cognitive symptoms (fear of losing control or "death", hypervigilance, excessive worry, etc.), (c) behavioral symptoms (avoidance, freezing, safety-seeking, etc.) and (d) emotional symptoms (nervousness, fearfulness, impatience, frustration, etc.). However, symptoms may differ depending on the type of anxiety disorders.

Most of the time, predictions about future negative/catastrophic events (death, illness, attacks, etc) performed by those suffering from anxiety are not fulfilled (negative PE). Then, it would be reasonably to think that when a person suffers from an untreated anxiety disorder, the repeated violation of expectations (PE) would first destabilize and re-stabilize memory (update prior predictions) with new safety information (Clark, 1999; Salkovskis, 1991). For instance, a patient suffering from dog-phobia after thousands of unharmed encounters or exposures would change his beliefs and predictions in accordance of his errors in expectations (self-correction). However, rarely of these occur and dysfunctional memories are maintained or strengthened. Nevertheless, several other key processes are postulated to be involved in the maintenance of pathological anxiety response to threat uncertainty (for a review see Clark, 1999). At this point, the reader might be asking himself: how then anxiety disorders persist after all the mismatches among prior belief and actual outcomes? Is it memory reconsolidation-updating function affected? We proposed that maladaptive accommodation or memory updating mechanisms are responsible for anxiety disorders maintenance. After an anxiety situation, which destabilizes memories (predictions are not fulfilled), strong-prior beliefs or strong and precise memories cancel the up-flow information generated by the error, obliterating the memory content updating. In other words, there is a strong top-down modulation able to affect experience. Therefore, anxiety disorders might be maintained, at least in part, by an impaired PE processing toward an accommodation against assimilation (see definition above); then basic and clinical research on memory reconsolidation has a potential clinical translational for psychiatric diseases.

4.3. Schizophrenia

Schizophrenia is characterized by serious problems with cognition, behavior and/or emotions (DSM-V; Association & others., 2013). It involves positive (i.e. hallucinations, delusions) and negative symptoms (i.e. disorganized speech, blunted affect). From a computational point of view, it was proposed that and imbalance in dopaminergic signaling (tonic vs phasic) would be responsible for hallucinations and delusions (Corlett, Honey, & Fletcher, 2007). Direct and indirect pathways are modulated via excitatory D1 receptors and inhibitory D2 receptors respectively, and both have been proposed to mediate either reward or aversive PE's. Moreover, the precision or salience of PE's signaling by dopamine seems to be crucial in the striatum (Friston et al., 2014; Lammel, Ion, Roeper, & Malenka, 2011; Schultz, Dayan, & Montague, 1997).

In contrast to anxiety where accommodation prevails against assimilation (see above), in schizophrenia, depending on the positive symptoms observed, the imbalance toward accommodation or assimilation might explain delusions or hallucinations respectively. Accordingly, there might be a loss of high level precision in the brain schemas which might lead in generalized cognitive problem and overattention to sensory stimuli (Corlett et al., 2007; Gradin et al., 2011). This imbalance between high and low prediction's precision level, might contribute to unusual belief strength, which might explain positive symptoms. That is, when hallucinating low level PE (strong bottom-up modulation) is significant higher comparing to high-level PE (weak top-down modulation), prior belief incorporating unusual and unlikely information into associated memories. The opposite is proposed for delusions, favoring top-down modulation (strong memory based prediction) in detriment of bottom-up (actual sensory input).

5. Conclusions

Throughout this review, we aimed to summarize the relevance of PE as a key factor for determining the fate of memories, its neurobiological mechanisms and its role in psychopathology. Moreover, research on memory reconsolidation and computational psychiatry will open new avenues not only to better comprehend the neurobiology of these psychopathologies but also to open new treatment time-windows opportunities to ameliorate sign and symptoms in order to have a better patient prognosis.

Traditionally, the translational perspective of memory reconsolidation was aimed to improve current treatments of mental disorders. Here, we extend beyond this traditional point of view, focusing on the maintenance of mental disorders stressing the role of a dysfunctional PE minimization strategy during memory reconsolidation.

All in all, PE is proposed as a driven-force for memory reconsolidation and acquisition revealing the similarity between new memories and reactivated ones. As it was put forward by McKenzie and Eichenbaum: are newly acquired memories saved on a blank slate (*"tabula rasa"*) or are they incorporated into preexisting schemas (McKenzie & Eichenbaum, 2011)? One of the main questions in memory research, which has not been addressed yet, is whether similar experiences are store separately (consolidation anew) or incorporated as whole by adding or deleting information (reconsolidation). Studies on memory consolidation and reconsolidation aims to answer this question and in this regard, the integration of PE on the memory field might help to elucidate the above puzzle.

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