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Review

Does reconsolidation occur in natural settings? Memory reconsolidation and anxiety disorders

Rodrigo S. Fernández[a], María E. Pedreira[a,1], Mariano M. Boccia[b,*,1]

[a] Laboratorio de Neurobiología de la Memoria, Departamento de Fisiología y Biología Molecular y Celular, IFIBYNE-CONICET, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, 2do piso, Buenos Aires, Argentina

[b] Laboratorio de Neurofarmacología de los Procesos de Memoria, Cátedra de Farmacología, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, 5to piso, Buenos Aires, Argentina

HIGHLIGHTS

- A prediction error is a mismatch between expected and current events.
- Reconsolidation updates consolidated memories content and strength.
- Prediction error drives memory acquisition and memory reconsolidation.
- Anxiety disorders are maintained through impaired memory updating.
- Anxiety disorders could be characterized by a dysfunctional prediction error minimization strategy.

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ABSTRACT

In normal settings, our brain is able to update its stored representations in content, strength, and/or expectations by the memory reconsolidation process. Thus, a reactivated memory enters in a transient labile state (destabilization) followed by a re-stabilization phase in order to persist (memory reconsolidation). Cognitive neuroscience and its insight into psychiatric problems attributed a close relationship between memory (formation, maintenance, and utilization) and several mental disorders. In this framework, the reconsolidation process could be not only the mechanism for maintenance of some psychopathologies, but also open a novel therapeutic window. Here we aim to integrate recent experimental and theoretical research on memory reconsolidation and anxiety disorders maintenance. We propose a bayesian-like model about anxiety disorders persistence and postulate a new theoretical framework for how anxiety disorders are maintained through impaired memory updating due to a dysfunctional prediction error minimization strategy and anticipatory responses to threat.

> "*Men are disturbed not by the things that happen, but by their opinion of the things that happen.*"
>
> Epictetus, The Enchiridion (135 A.C)

In normal settings, our brain is able to update its stored representations in content, strength, and/or expectations by the memory reconsolidation process (Dudai, 2012a; Forcato, Fernandez, & Pedreira, 2014; Lee, 2009). Thus, a reactivated memory enters in a transient labile state followed by a re-stabilization phase in order to persist (Nader, Schafe, & Le Doux, 2000; Sara, 2000). Memory reconsolidation is proposed as the mechanism by which memories are changed. From its reappearance, the potential therapeutic use was critically considered as a recurrent topic (Alberini, 2005; Corlett, Krystal, Taylor, & Fletcher, 2009; Kindt, Soeter, & Vervliet, 2009; Karim Nader, Hardt, & Lanius, 2013; Schiller et al., 2010).

Research in memory reconsolidation opened possible translational ideas. Cognitive neuroscience and its insight into psychiatry problems (Bouton, Mineka, & Barlow, 2001; Eysenck, 1976; Gordon, 1981; Mineka & Zinbarg, 2006; Rachman, 1991) attributed a close relationship between memory (formation, maintenance, and utilization) and mental disorders (Halligan & David, 2001). In this framework, the reconsolidation process could not only be the mechanism for maintenance of some psychopathologies, but also open a novel therapeutic window (Corlett, Frith, & Fletcher, 2009; Debiec, 2012; Ecker, 2015; Lane, Ryan, Nadel, & Greenberg, 2014; Pitman, 2011; Sevenster, Beckers, & Kindt, 2013; Taylor, Olausson, Quinn, & Torregrossa, 2009). Pharmacological

* Corresponding author.
E-mail addresses: rodrigofernandez@fbmc.fcen.uba.ar (R.S. Fernández), mpedreira@fbmc.fcen.uba.ar (M.E. Pedreira), mboccia@ffyb.uba.ar (M.M. Boccia).
[1] These authors contributed equally to this work.

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or behavioral Interventions on memory reconsolidation processes could be of therapeutic potential for mental disorders (Brunet et al., 2008; Das, Lawn, & Kamboj, 2015; Debiec, LeDoux, & Nader, 2002; Lee, Di Ciano, Thomas, & Everitt, 2005; Schiller et al., 2010; Soeter & Kindt, 2015).

Memory reconsolidation is a universal phenomenon observed across species but its occurrence has boundary conditions (Dudai, 2012b; Finnie & Nader, 2012; Lee, 2009; Nader & Hardt, 2009). Specifically, in laboratory settings, memory reconsolidation is triggered when the outcomes differ from predicted (prediction error, PE; Dudai, 2012b; Exton-McGuinness, Lee, & Reichelt, 2015; Fernández, Boccia, & Pedreira,2016; Pedreira, Pérez-Cuesta, & Maldonado, 2004; Reichelt & Lee, 2013; Rescorla & Wagner, 1972; Sevenster et al., 2013; Sevenster, Beckers, & Kindt, 2014). Since there is no universally-effective reactivation session, different forms of PE (positive, negative or others forms) are able to induce memory labilization depending on: 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; Boccia, Blake, Acosta, & Baratti, 2005; Bustos, Maldonado, & Molina, 2008; Eisenberg & Dudai, 2004; Forcato, Fernandez, & Pedreira, 2013; Inda, Muravieva, & Alberini, 2011; Lee, 2010; Morris et al., 2006; Pedreira et al., 2004; Sevenster et al., 2013; Suzuki et al., 2004; Wang, de Oliveira Alvares, & Nader, 2009). Therefore, a mismatch between expected and current events (PE), induces memory reconsolidation, 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.

Recently it was proposed that reconsolidation mechanism might be responsible of psychotherapeutic treatment outcome (Lane et al., 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 works. If the reconsolidation process were 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 several mental illnesses.

Imaging the following scenario: a person attending a rock concert when suddenly, he begins to perceive his hands sweating and his heart beating hard. He feels uncertain about whether these sensations are normal or threatening (disrupted expected value calculation). Automatic thoughts came out about the probability and severity of having a heart attack, so he decides to focus on his heart rate using his fingers. The attention paid to his tachycardia and dizzy feelings (increased threat-biased cognitive errors), confirms that he is in danger and an imminent catastrophe could occur (cognitive error processing). A friend sees him pale and tells him to relax, giving him plausible reasons of his state such as the physical effort performed during the concert (jump, sing, excitement, etc). Instead of focusing in his friend's rational explanation and many other safety signals, he notices that the emergency exits are too far and that there are too many people ahead (deficient safety elaboration). Further, he believes that medical assistants could take too long in the case of a heart attack and he also realizes that it has been hours since his last drink of water. Finally, he decides to push people in order to get the emergency exits (behavioral and cognitive avoidance). Outside the venue, he feels nervous and drinks water, thinking that he should best go to a hospital because next time could be worse (heightened reactivity to threat uncertainty). Next months and years, he still experiences the same negative emotions and thoughts (enduring threat-related beliefs).

The human behavior described above is much more frequent than we think. However it is worth pointing out that the outcome for each person suffering from this kind of feelings would be different. Same person might never experience a panic attack again because their negative thinking seems to be self-correcting (Clark, 1999; Salkovskis, 1991). Meanwhile others may develop and maintain a panic disorder over years. In this last case, within the reconsolidation framework, one might ask: why after hundreds or thousands of panic attacks, where predicted outcomes (heart attacks, negative evaluation by others, fainting, etc.) differed from expected, subjects did not update their memory predictions/expectations? Why after a PE, that would destabilize memory followed by safety outcomes, reconsolidation process did not act? How misinterpretations are still not disconfirmed?

It is a clinical relevant issue how anxiety disorders are maintained. Longer intervals between onset of psychopathology and its treatment is a reliable predictor of less likely remission (Blom et al., 2007; Eisen et al., 2013). Without treatment (psychotherapy and/or pharmacotherapy), anxiety disorders tend to be chronic (Barlow, Rapee, & Brown, 1992; Kessler et al., 2005; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Accordingly, it seems very similar and related to the boundary conditions of memory reconsolidation such as memory strength and age. In this sense, memory updating with safety information (unfulfilled negative predictions) seems to be impaired.

Here we aim to integrate recent experimental and theoretical research on memory reconsolidation and anxiety disorders maintenance. We propose a bayesian-like model about anxiety disorders persistence. We postulate a new theoretical framework on how anxiety disorders are maintained through impaired memory updating by dysfunctional PE signal and core responses typically associated with anxiety disorders (anticipatory responses to threat).

1. Memory reconsolidation and prediction error

In an ever-changing environment, it is crucial to extract regularities, based on past events in order to predict the future. This allow animals to anticipate possible or future outcomes, increasing the odds to obtain desired ones (i.e rewards) and avoid the aversive ones (i.e punishment; (O'reilly, 2013).

The brain is a predictive organ and one of its main functions is to generate models of the world and predict the future (Bubic, Von Cramon, & Schubotz, 2010; Buzsáki, Peyrache, & Kubie, 2014; Den Ouden, Kok, & De Lange, 2012; Dudai, 2009; Friston, 2010; Niv, 2009),that is, future sensory inputs, consequences of actions, reward probabilities, aversive events or different outcomes (Bubic et al., 2010; Den Ouden et al., 2012; Eldar, Rutledge, Dolan, & Niv, 2015; Garrison, Erdeniz, & Done, 2013; Koster-Hale & Saxe, 2013; Niv & Schoenbaum, 2008; Roesch, Esber, Li, Daw, & Schoenbaum, 2012). Nowadays there is new focus within the neuroscience field in order to understand how the brain performs these kinds of functions. Although, statistical regularities of the world can be extracted (making models), their rules are subject to gradual or abrupt changes (Bland & Schaefer, 2012; Mathys, Daunizeau, Friston, & Stephan, 2011; Pearson, Heilbronner, Barack, Hayden, & Platt, 2011). Thus, an animal whose behavior is rigid and could not accommodate to new environment contingencies, is maladaptive. Some authors proposed that the most fundamental brain mechanism is the PE minimization by which the error generated by the difference between current and expected events, update the subjects model of the world and their predictions in the light of new evidence/information (Clark, 2013; Friston, 2010).

This mechanism leads to a reduction in surprise and uncertainty by means of memory acquisition or memory updating, until the outcome can be fully anticipated (zero or near zero PE). Surprise here means that outcomes may be under/overpredicted (positive or negative PE) or better/worse than predicted. Prediction error then, acts as a teaching signal (“driving-force”). When PE is near zero (no surprise), no further learning or behavioral changes occur (no PE; i.e. blocking effect).

As previously stated, reconsolidation process is crucial for the modification of existing memories and the mechanism by which the strength and/or content of consolidated memories are updated (de

Oliveira Alvares et al., 2012; de Oliveira Alvares et al., 2013; Forcato et al., 2013, 2014; Forcato, Rodríguez, & Pedreira, 2011; Inda et al., 2011). Thus, after PE detection during retrieval, consolidated memories become reactivated (labile), followed by a process of re-stabilization (reconsolidation; Dudai, 2012a; Lee, 2009; Nader et al., 2000). A mismatch (PE) during reactivation is necessary but not sufficient for reconsolidation to occur (Forcato, Argibay, Pedreira, & Maldonado, 2009; Pedreira et al., 2004; Sevenster et al., 2013, 2014).

Memory features such as strength and age are crucial boundary conditions that limit the reconsolidation process (Baratti et al., 2008; Eisenberg & Dudai, 2004; Forcato et al., 2013; Inda et al., 2011; Milekic & Alberini, 2002; Suzuki et al., 2004; Wang et al., 2009). However, several reports have shown overcoming these limitations when proper reactivation parameters were used (Bustos et al., 2008; Coccoz, Sandoval, Stehberg, & Delorenzi, 2013; De Oliveira Alvares et al., 2013; Díaz-Mataix, Martinez, Schafe, LeDoux, & Doyère, 2013; Steinfurth et al., 2014; Wichert, Wolf, & Schwabe, 2011, 2012; Winters, Tucci, & DaCosta-Furtado, 2009). Different studies have shown that during memory reactivation PE is able to induce reconsolidation process. Among them, several PE were used e.g.: omission or intensity reduction of the predicted outcome (negative PE, Carbo Tano, Molina, Maldonado, & Pedreira, 2009; de Oliveira Alvares et al., 2012; Inda et al., 2011; Kindt et al., 2009; Liu et al., 2014; Pedreira et al., 2004; Sevenster et al., 2013; Wang et al., 2009; Zeng et al., 2014), addition of learning trail in a weak memory (positive PE (Duvarci & Nader, 2004; Lee, 2008; Milekic, Brown, Castellini, & Alberini, 2006; Sevenster et al., 2013), change the outcome timing (temporal PE; Alfei et al., 2015; Díaz-Mataix et al., 2013) or modification of the summed expected outcome value (Reichelt, Exton-McGuinness, & Lee, 2013; Reichelt & Lee, 2013).

2. Translational approaches of memory reconsolidation

Translational approaches of memory reconsolidation have shown promising results. Propranolol (β-adrenergic antagonist) was used to interfere memory reconsolidation in animal models and humans (Kindt et al., 2009; Przybyslawski & Sara, 1997). Saladin et al. (2013) were able to impair drug-memory reconsolidation in cocaine abusers. Participants were exposed to two drugs cues (videos or pictures) 15 min apart each and immediately after the end of the second one; they received either propranolol or placebo. Propranolol significantly lowered drug craving score 24 h after memory reactivation, but not a week later. Similar results were found by Lonergan et al. (2016) using script driven memory reactivation in substance abusers but not in smokers (Das et al., 2015). In another study, Xue et al. (2012) used extinction procedures to disrupt reconsolidation (Agren et al., 2012; Schiller et al., 2010). Heroin addicts on withdrawal were exposed to a reactivation-exposure procedure. Memory reactivation was elicited by using a video containing drug-related cues. A control group watching neutral images was included. Then, the extinction session consisted of a 60-min exposure to heroin cues. A lower heroin-craving score was found in the group that 24 h before had watched the video with drug-related images (reactivation session) and had received the extinction session. The effect remained after 30 and 180 days. Based on these promising results, the authors concluded that it seems feasible to design new therapies to disrupt drug-abuse memories.

Another strategy used by Das et al. Das et al. (2015) in excessive alcohol drinking individuals was to disrupt memory reconsolidation using a negative PE. Subjects were presented with alcohol related cues but were not allowed to drink (memory reactivation using a negative PE), followed by counterconditioning. This procedure consisted in the association between previously rewarding cues with a new aversive consequence (extremely bitter solution). This intervention reduced attentional bias and cues-alcohol valuation. These effects remained at least, one week. Longer reactivation-intervention/testing interval must be performed in order to give further support and validity to these kinds of translational treatment.

In relation to anxiety disorders, mixed results were found in PTSD patients or subjects exposed to a highly aversive experience. In these experiments memory reactivation consisted in a script-driven imagery task of the negative experiences followed by the β blocker administration (propranolol). Brunet et al. (2008, 2014)) found reduced physiological response to the script one week later. On the contrary, Tollennar et al. (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009) using a similar protocol found no difference three weeks after memory reactivation. Recently, in patients suffering phobia to spiders, Soeter & Kindt (2015) found that propranolol administration after reactivation session which induced PE, was able to reduce fear. Interestingly, reconsolidation impairment persisted at least one year. Finally, the same group (Soeter & Kindt, 2013) reported that high trait anxiety predicted propranolol's failure of reconsolidation impairment in normal populations.

3. Memory reconsolidation and learning models

3.1. Associative learning models

Several learning models have been used to explain psychiatric and neurological disorders (Adams, Stephan, Brown, Frith, & Friston, 2013; Bouton et al., 2001; Chekroud, 2015; Corlett, Honey, & Fletcher, 2007; Mineka & Zinbarg, 2006; Montague, Dolan, Friston, & Dayan, 2012; Paulus & Stein, 2006). PE is considered the main parameter of learning in those models. At the same time, it was recently proposed that they might be able to explain reconsolidation process (Exton-McGuinness et al., 2015; Fernández et al., 2016; Lee, 2009). In the associative learning models, the error in prediction leads to the updating of value or associative strength between stimuli until the outcome can be fully anticipated (PE; Niv & Schoenbaum, 2008; Schultz & Dickinson, 2000). Thus, the PE generated 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). These models could be divided in two major categories: Unconditioned Stimulus (outcome-US) processing models (Le Pelley, Mitchell, & Le Pelley, 2010; Rescorla & Wagner, 1972; Sutton & Barto, 1981) and Conditioned Stimulus (cue-CS) processing models (Mackintosh, 1975; Pearce & Hall, 1980). All those models have in common is a given set of parameters to computationally describe the learning rate (associability), the CS and US salience that could be fixed or not (see Fernández et al., 2016).

In the associative learning models PE could serve different purposes. We already know that the size (value) of a PE is given by the difference between the expected and received outcome. However, at a mathematical, motivational and physiological level PE could be classified as signed or unsigned. Signed PE are those which acquire either positive or negative values depending on the motivational valence of the outcome (better or worse than expected) and is also reflected in the increase or decrease in the firing rate of specific neuron populations (i.e midbrain dopamine neurons). In contrast, unsigned PE have no information about the direction or valence of the PE and only signals the size of the error detected (non-negative values) in other brain areas (i.e basolateral amygdala). The US-processing models claim that signed PEs has a direct impact on the associative strength (value) of a cue. A positive PE (unexpected or underexpected outcome) increases the cue-outcome association (excitatory conditioning), whereas a negative PE (no-outcome or overexpected outcome) decreases association (inhibitory conditioning), and zero PE (expected outcome) makes no change in the associative strength. For the other models, unsigned PE has an indirect effect, modulating the attention or associability of a given cue. The absolute value of PE strengthens the association, increasing the attention paid to those cues. As with the US-processing models, when prediction matches its outcome (no-PE) no further learning or change in associative strength occurs.

Actual evidence supports the co-existence and integration of both

models across different brain regions (Boll, Gamer, Gluth, Finsterbusch, & Büchel, 2013; Klavir, Genud-Gabai, & Paz, 2013; Roesch et al., 2012; Schultz & Dickinson, 2000). The interconnection that signal CS and US processing consists in a wide brain network that includes different brain regions, among them, hippocampus, ventral tegmental area, basolateral amygdala, central nucleus of amygdala, anterior cingulate cortex (Goosens, 2011; Hayden, Heilbronner, Pearson, & Platt, 2011; Ploghaus et al., 2000; Roesch et al., 2012; Schultz, 2007).

3.2. Bayesian learning models

In the last years there was a growth in a new framework of bayesian learning models, which are posited to be computationally flexible and simultaneously retain the explanatory power of the CS and US processing models (Courville, Daw, & Touretzky, 2006; Dunsmoor, Niv, Daw, & Phelps, 2015; Friston, 2010; Gershman, Norman, & Niv, 2015). In the Bayesian models, learning represents a process of updating an individual's belief about the world, by integrating new and old information (Courville et al., 2006; Dunsmoor et al., 2015). The basic idea of bayesian learning is that animals infer the latent (unobservable) causal structure of the environment by clustering its experience (i.e. cue-outcome association; Courville et al., 2006; Gershman et al., 2015). A structure represents hierarchically the events of the world as a set of states (cues), actions and reinforcers with the associated transitions between them (Gershman & Niv, 2010). When similar events (observations) are detected they are clustered together and assigned to the same causes. For example, during a fear Pavlovian conditioning a CS (i.e a tone) is repeatedly paired with a US (i.e a shock). According to the associative learning models, learning is guided only by error reduction (PE) and it stops when the CS accurately predicts the US. On the contrary, in Bayesian models, Pavlovian conditioning constitutes a clustering process by which similar events and trials (the shock has the highest probability after the tone presentation) are grouped together by inferring the same latent cause. Then, animals do not learn a linear association between cues and outcomes (i.e. the tone does not cause the shock or vice versa), rather they infer the latent causal structure of the observed information (both the tone and the shock are generated by a common latent cause). Accordingly, an animal learns the causal structure between the statistical association of a latent (unobservable) cause and stimuli (cue-reinforcers).

These models formalized the idea that multiple associations could be formed between events depending on their statistical structure. Different phenomena such as acquisition, extinction or reconsolidation (Dunsmoor et al., 2015; Gershman et al., 2015; Gershman & Niv, 2010) could be understood in terms of how PE affects learning about causes. In the case of extinction training, when the CS is consistently presented without reinforcement, these models correctly predict the formation of a new “inhibitory” memory trace which competes with the original. During extinction, the animal clusters together the CS presentation in the absence of the US and infers a new active latent cause which signals unreinforcement. In these models, memory stores the parameters of past experiences in the form of latent causes. Since not every cause is present at the same time, animals infer about which one is active in order to determine memory updating (same cause plus new information), new memory formation (new cause) or simple memory retrieval (same cause; (Courville et al., 2006; Courville, Gordon, Touretzky, & Daw, 2003; Gershman & Niv, 2010, 2012). Therefore, Pavlovian conditioning is a clustering process. Similar cue-outcome associations are grouped and attributed to the same causes. When the statistical pattern radically changes (as in extinction training), the animal infers a different cause, separates it, and generates a new memory (Dunsmoor et al., 2015).

Reconsolidation according to these ideas could work as follows: When a cue is presented, the similarity between training and reactivation cues is needed in order to make a proper prediction of the situation. A similar-to-training context (same cause) should enable a proper prediction and a dissimilar context should induce new learning (different cause). When a prediction is made, it anticipates future or possible state of affairs. If the outcome of the prediction confirms expectation (match the expected cause and model of the world) only retrieval occurs. Instead, when an unexpected outcome or surprising event induces a PE (mismatch, same cause with new information), it triggers the reconsolidation process, leading to memory updating (content or strength) and adjustment for future predictions (change the model of the world). Finally, extinction could be understood as repeated series of mismatching events, which constitute a training leading to new learning (i.e. new or different cause).

Taking into account what has been said and in relation to anxiety disorders, why people suffering anxiety do not modify its cognition, assuming that the world is not as dangerous as they believed? Moreover, most of the times their predictions are not fulfilled. It would be reasonable to think that, when a person suffers from an untreated anxiety disorder the repeated violation of expectations would first destabilize and re-stabilize memory (update prior predictions or models of the world) with new safety information (Clark, 1999; Salkovskis, 1991). For example, a patient phobic to dogs, after thousands of unharmed encounters or exposures would change his beliefs and predictions in accordance of his errors in expectations. However, none of this occurs and dysfunctional memories are maintained or strengthened. Does reconsolidation process occur “spontaneously” in pathological anxiety? What is inside the core of anxiety that prevents proper memory updating? What processes are involved in the failure of learning from experience? We next review some ideas and propose new insights about anxiety disorders maintenance and their models of the world.

4. Anxiety disorders and anticipatory response to threat uncertainty

Anxiety disorders are the most prevalent mental illnesses, affecting the quality of life and normal functioning of people at all ages around the world (Kessler et al., 2005; Olatunji, Cisler, & Tolin, 2007). It includes several disorders, among them: specific phobia, social phobia, generalized anxiety disorder, post-traumatic stress disorder (PTSD) (according to DSM IV-TR). Common features of anxiety are: a) physiological symptoms (muscle tension, increased heart rate, palpitations, dizziness, nausea, sympathetic nervous system activation, etc.), b) cognitive symptoms (fear of losing control or “death”, confusion, hypervigilance, excessive worry, etc.), c) behavioral symptoms (avoidance, freezing, safety-seeking, etc.) and d) emotional symptoms (nervousness, fearfulness, impatience, frustration, etc.). In relation to normal population, people suffering from anxiety tend to have lower incomes, poorer physical-mental health, high comorbidity and impaired social and role functioning (Comer et al., 2011; Olatunji et al., 2007).

Fear and anxiety are highly related but could be differentiated by considering the level of uncertainty regarding the probability, timing or nature of future danger (Grupe & Nitschke, 2013; Hartley & Phelps, 2012; Rosen & Schulkin, 1998). Fear refers to an evolutionary innate emotional response to actual or perceived immediate threat/danger (LeDoux, 1998). On the contrary, anxiety manifests as a persistent and generalized defensive system, activated when predicted aversive events are perceived as a threat (Clark & Beck, 2011; Grupe & Nitschke, 2013; Paulus & Stein, 2006). The consequences of the anticipated events are perceived as highly negative, uncontrollable and uncertain (Beck & Dozois, 2011; Clark & Beck, 2011; McEvoy & Mahoney, 2012). Patients suffering from anxiety disorder experience negative affectivity along with a sense of vulnerability. A key feature of anxiety disorders then, is its future-orientation in the form of constants “what if” questions (e.g. “What if this time I go crazy?”, “What if I can't get to the hospital?”, etc. (Clark & Beck, 2011; Paulus & Stein, 2006).

A number of anxiety models assigned a key role to uncertainty as a unifying factor across anxiety disorders (Fig. 1; Carleton,

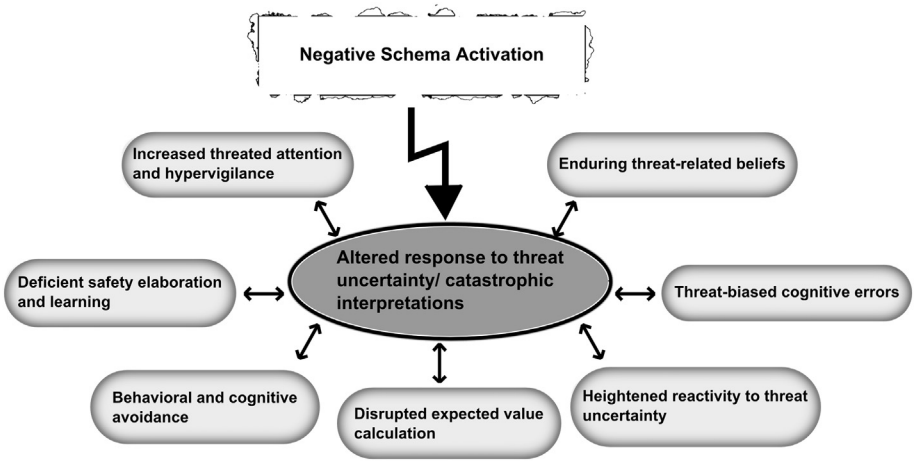


Fig. 1. Anxiety response to threat uncertainty (ARTU) in relation to negative schema activation. Negative schema activation by a situation and the ARTU processes modify information processing leading to anxiety symptoms. The items described in the figure, ARTU, are highly interconnected (see main text) and represent a failed attempt to reduce uncertainty of disconfirmatory information and regulate negative emotions.

Sharpe, & Asmundson, 2007; Gentes & Ruscio, 2011; Hirsh, Mar, & Peterson, 2012; McEvoy & Mahoney, 2012). In everyday life, a certain degree of uncertainty is a common feature of decisions (Bland & Schaefer, 2012). However, uncertainty sometimes could be experience as a threat. Highly anxious individuals consider the possibility of a negative event occurring as unacceptable, unfair and threatening irrespective of the probability of its occurrence (Carleton et al., 2007).

Now, we will follow on some common ideas derived from conceptualizations of Cognitive Behavioral Therapy (CBT; Barlow, 2004; Beck & Dozois, 2011; D. A. Clark & Beck, 2011) and the Uncertainty and Anticipation Model of Anxiety (Grupe & Nitschke, 2013) (discuss in section ARTU: Key processes in anxiety maintenance). Anxiety in a more broad sense is a result of uncertainty about future threats, which impairs the ability to cope with the predicted negative event.

Causes of anxiety disorders are unknown but they may develop from the interaction between genetic and learned vulnerabilities (diathesis-stress model; Beck & Dozois, 2011; Clark & Beck, 2010). These are acquired through learning over the course of years by building negative memory schemas (see section: Memory schemas and organization) which contain an individual's model of the world. Once activated by specific events, they are capable of modifying cognitive, emotional and behavioral processes (Beck & Dozois, 2011; Clark & Beck, 2011; Ghosh & Gilboa, 2014). Negative schemas play a key role in the etiology and maintenance of anxiety disorders because they are responsible for the predictions made and the misinterpretation of the outcomes.

Cognitive-Behavioral Therapy (Clark & Beck, 2011) conceptualization posits that anxiety response involves a-two-stage process where first, a given situation is erroneously perceived as highly threatening, probable and severe (automatic response). In other words, the probability and cost of predicted events are overestimated (Rachman, 1994). The second stage of the process involves an impaired processing of the safety aspects of danger and a sense of general vulnerability (elaborated response). This second reappraisal tends to underestimate the subjects' ability to cope with the anticipated aversive outcomes (Clark & Beck, 2011; Rachman, 1994). Thus, it is proposed that the intensity of anxiety response is given on the balance between the subjects predicted probability and severity of the threat and the evaluation of safety and coping abilities (Clark & Beck, 2011). From this perspective, anxiety refers to excessive anticipatory emotional, cognitive and behavioral response oriented to uncertainty about future threats (Grupe & Nitschke, 2013). The intolerance of uncertainty and activation of core schema beliefs leads to a maladaptive generalized response (anticipation) which involves an attempt to control or reduce uncertainty and the PE generated. This excessive anticipation produces anxiety and distress associated with an amygdala and insular cortex hyper-reactivity (Hartley & Phelps, 2012; Tovote, Fadok, & Lüthi, 2015).

We next: 1) summarize the cognitive and behavioral processes related to the etiology and maintenance of pathological anxiety response to threat uncertainty (ARTU; Fig. 1) and 2) propose hierarchical bayesian learning structures that intend to explain the basis for the maintenance of anxiety disorders from a memory perspective.

5. ARTU: key processes in anxiety maintenance

5.1. Disrupted expected value calculation

Individuals with anxiety disorders show an exaggerated threat appraisal about the probability and cost (severity) of negative rare or non-common events resulting in “pessimistic expectations” (Beck & Dozois, 2011; Clark & Beck, 2011; Grupe & Nitschke, 2013; Nelson, Lickel, Sy, Dixon, & Deacon, 2010). For example, people with panic disorders ranked arousal scenarios and negative physical outcomes more probable and severe (McNally & Steketee, 1985; Uren, Szabó, & Lovibond, 2004), claustrophobics overestimate the likelihood they will encounter closed spaces (Ost & Csatlos, 2000). Notably, anxious individuals tend to overpredict anxiety and aversive consequences to what actually happens when confronted to the anticipated event (e.g., Rachman, Levitt, & Lopatka, 1987; Rachman, Lopatka, & Levitt, 1988). Several studies have found similar results in high trait anxiety, chronic worrier's social anxiety, generalized anxiety disorder (GAD) and PTSD (Borkovec, Hazlett-Stevens, & Diaz, 1999; Butler & Mathews, 1983; Grupe & Nitschke, 2013).

5.2. Increased threatened attention and hypervigilance

In anxiety related disorders, attentional, interpretative, and memory bias have been described (Cisler & Koster, 2010; MacLeod & Mathews, 2012; Zlomuzica et al., 2014). Highly anxious individuals have attentional bias enhancement for negative cues and events (Cisler & Koster, 2010; MacLeod & Mathews, 2012). Since attention has a limited capacity, facilitated or enhanced threat detection impairs the identification of safety signals. There is extensive evidence that, relative to non-anxious individuals, highly anxious population have: 1) faster response latencies and detection of negative material (i.e. dot probe task, exogenous cuing, attentional blink, emotional stroop, etc.) and 2) a difficult to disengage attention from threat-related stimuli, in relation to neutral or positive stimuli (Cisler & Koster, 2010; Hartley & Phelps, 2012; MacLeod & Mathews, 2012; Mathews & MacLeod, 2005; Mogg & Bradley, 1998). In addition, anxious individuals show a tendency to interpret ambiguous scenarios in a negative way (cognitive interpretative bias; MacLeod & Mathews, 2012). For example, using homographs (DIE/DYE) or complete-fragment words, it was found that highly anxious individuals select a negative view to resolve ambiguity

(Hazlett-Stevens & Borkovec, 2004; MacLeod & Mathews, 2012; Mathews, Richards, & Eysenck, 1989). Finally, different reports established that people with anxiety disorders have an excessive retrieval of aversive memories and episodic/autobiographical memory impairment (Morgan, 2010; Zlomuzica et al., 2014).

5.3. Deficient/impaired safety elaboration and learning

Cognitive attentional bias towards threat disrupts safety signal identification and relief under uncertainty situations (Clark & Beck, 2011; Grupe & Nitschke, 2013; Lohr, Olatunji, & Sawchuk, 2007; Woody & Rachman, 1994). Importantly, it also increases the tendency to safety-seeking behaviors (avoidance) and impairs learning about the non-occurrence of events (Clark, 1999; Clark & Beck, 2011; Salkovskis, 1991). In our opinion learning impairment in these cases could also be extended to memory updating. For example, when socially anxious subjects were exposed to give a short speech they showed a retrieval deficit for positive adjectives (Mansell & Clark, 1999). On the other hand, GAD patients show an inability to reduce worry and regulate negative affect (Buhr & Dugas, 2012). Moreover, when confronted with ambiguous social information, highly anxious individuals had impaired learning of non-threatening interpretations (Amir, Beard, & Przeworski, 2005).

In fear conditioning experiments, anxious individuals showed a stronger fear response to predictive cues compared to controls (Lissek et al., 2005; Mineka & Zinbarg, 2006) and learning impairment to changes of environmental contingencies (Browning, Behrens, Jocham, O'Reilly, & Bishop, 2015). In addition, they have impaired or slower extinction learning and failure to discriminate between the aversive and neutral cues (Bouton et al., 2001; Grupe & Nitschke, 2013; Lissek et al., 2005; Mineka & Zinbarg, 2006). Emotional regulation using cognitive strategies were found to be also impaired (Hartley & Phelps, 2012).

5.4. Behavioral and cognitive avoidance

Behavioral and cognitive avoidance under threat uncertainty circumstances are expressed in many ways such as escape behavior, distraction, thought suppression, freezing, etc. (Borkovec & Lyonfields, 1993; Bouton et al., 2001; Clark, 1999; Clark & Beck, 2011; Rachman, 1991; Solomon & Wynne, 1954). For example, avoiding eye contact, means of transportation, or specific mental images, are typically related to social phobia, agoraphobia, and PTSD, respectively. These strategies produce partial relief and prevent subjects from being exposed to evidence or information that could contradict or disconfirm: a) current negative predictions and b) previous negative schemas. Moreover, these responses, paradoxically, may actually increase accessibility to negative schemas (Beck & Dozois, 2011; Wells & Matthews, 2014). Neurobiological basis of anxiety disorders were studied for decades in laboratory settings using Pavlovian fear conditioning (Bouton et al., 2001; Mineka & Zinbarg, 2006; Tovote et al., 2015) in multiple species. Two-factor theory proposed that anxiety disorders are acquired through Pavlovian conditioning and maintained by cognitive and behavioral avoidance of the fearful stimuli (Rachman, 1991, 1994).

Cognitive and behavioral avoidance are the most important factors determining failure of learning from experience. In other words, when catastrophically predicted events fail to occur, subjects interpret that they prevented them (Clark, 1999; Clark & Beck, 2011; Salkovskis, 1991) instead of learn or relearn that their prediction outcomes were unlikely. Several reports have shown that increased use of avoidance behaviors and thoughts is related to the maintenance/persistence and exacerbation of anxiety (Dunmore, Clark, & Ehlers, 1999, 2001; Salkovskis, 1991; Sloan & Telch, 2002). Avoidance reflects an ineffective defensive strategy for diminishing anxiety response (Barlow, 2004; Clark & Beck, 2011). For example, an agoraphobic individual might think that drinking water or taking a benzodiazepine protected him from having a stroke.

5.5. Heightened reactivity to threat uncertainty

When relationships in the environment are hard or impossible to predict, there is an increase in the reactivity to those cues (Browning et al., 2015; Carleton et al., 2007; Dunsmoor, Bandettini, & Knight, 2008; Grillon, Baas, Lissek, Smith, & Milstein, 2004; Mineka & Kihlstrom, 1978). Simultaneously, a significant high stress response occurs which leads to an increment in hypothalamic-pituitary-adrenal and sympathetic axes activity (Wolf, 2009). In the light of threat uncertainty, anxious individuals show a higher sympathetic physiological response when the nature, probability, and timing of events are difficult to anticipate (Buhr & Dugas, 2012; Herry et al., 2007; Lissek et al., 2005; Soeter & Kindt, 2013; Williams et al., 2014). For example, cues that signal 20% or 60% probability of reinforcement produces increased physiological responses than those which predict a 100% rate of reinforcement (Hefner & Curtin, 2012). Children with anxiety disorder experience more negative affect and amygdala response to ambiguous cues (Williams et al., 2014). Finally, since unpredictable events are also uncontrollable, the independence between self-action and outcomes increases an individual's sense of vulnerability (Barlow, 2004; Clark & Beck, 2011).

5.6. Threat-biased cognitive errors

Several reports have shown that different cognitive-processing errors/distortions, i.e., dichotomous thinking, overgeneralization, selective abstraction, etc. (Beck, 1979; Clark & Beck, 2011; Knapp & Beck, 2008) facilitate anxiety elaboration and maintenance. GAD patients were found to generate more imperative (“have to/should”) and catastrophic words (i.e. “death”, “pain”) than control individuals (Beck & Dozois, 2011; Suarez & Bell-Dolan, 2001). High anxiety individuals also show an “emotional reasoning” bias, in which the state of anxiety experienced is interpreted as evidence of imminent threat (“If I feel anxious, there must be danger”; Arntz, Rauner, & van den Hout, 1995; Barlow, 2004; Beck, 1979). Arntz et al. (1995) showed that patients were biased in their rating of hypothetical anxiety scripts by the presence of anxiogenic information.

5.7. Enduring threat-related beliefs

Aberrant information processing is fundamental in the etiology and maintenance of mental disorders (Barlow, 2004; Beck, 1979; Mansell & Clark, 1999). Once a negative schema is active it tends to dominate cognitive processing by top-down expectations and predictions about the occurrence and meaning of the events (Ghosh & Gilboa, 2014; Lewis & Durrant, 2011; Piaget, Cook, & Norton, 1952). This leads to a preferential processing bias about catastrophic beliefs of the self, the world, and the future. In anxiety disorders, schema content is associated to vulnerability and personal beliefs, threat, danger, and helplessness (Clark, 1999; Clark & Beck, 2010, 2011; Young, 1994).

6. Memory schemas and organization

Memories and beliefs are stored in highly interconnected networks building organized schemas involved in the interpretation of experience and information processing (models of the world). These schemas are formed by system consolidation, the gradual process of information reorganization and migration from hippocampus to neocortex (Dudai, Karni, & Born, 2015; Squire, Genzel, Wixted, & Morris, 2015). It is a slow process when no prior related-memories are stored (Tse et al., 2007; van Kesteren, Ruiter, Fernández, & Henson, 2012). However, when new information is presented that is congruent with prior expectations, system consolidation is faster (Kumaran, 2013; Tse et al., 2007, 2011; van Kesteren et al., 2012). As early theories proposed, schemas are slowly formed by learning and are responsible of the **assimilation** and **accommodation** of new information (memory

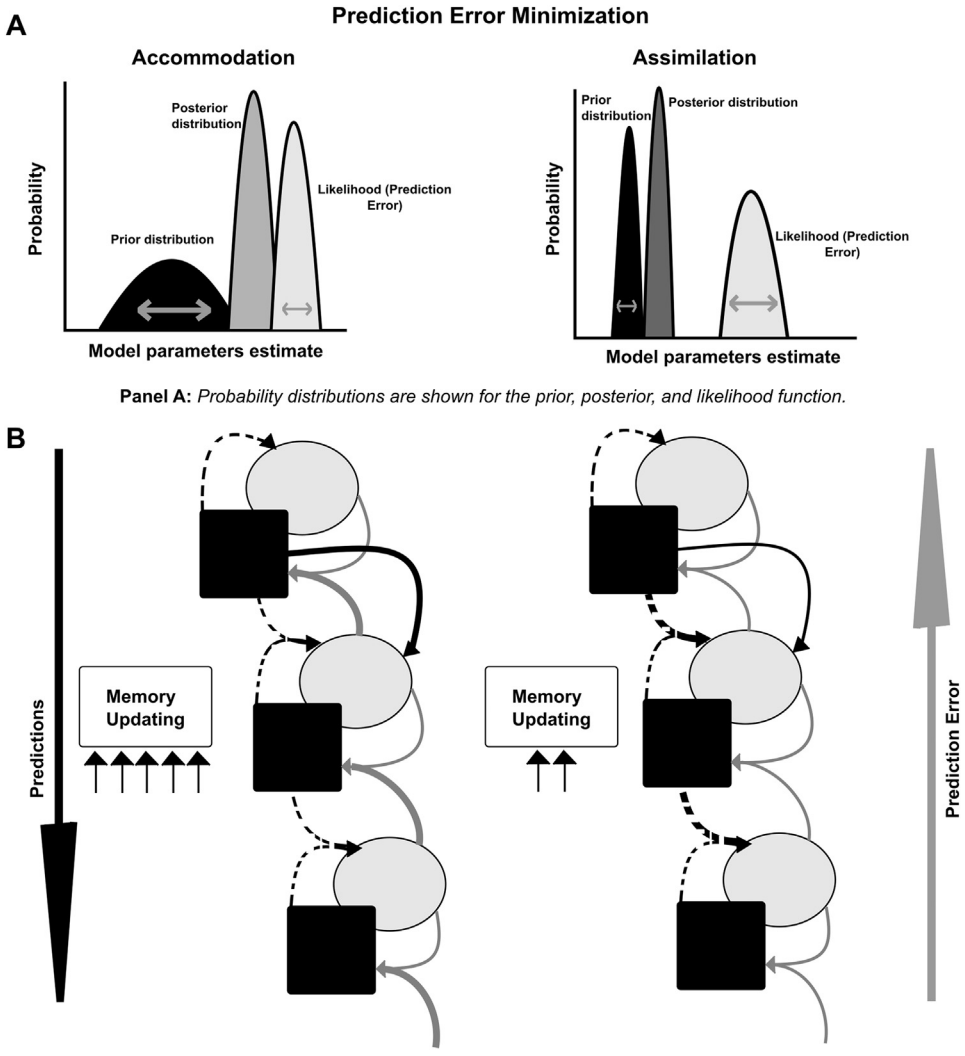


Fig. 2. Memory schemas as beliefs are not fixed and they rather change: Panel A: In Bayesian inference schema beliefs are a hierarchical structure of probability distributions that attempt to explain the (latent) causes of current input in the lower levels by reducing surprise and improving the precision of the predictions. Thereby, learning/updating turns the world in a (unsurprising) predictable system. Bayesian learning represents a process whereby prior beliefs are updated in posterior beliefs in the light of new evidence/information. Bayes rule update the posterior probability of a hypothesis considering prior beliefs (priors) about its probability and the likelihood of current evidence (see A – Upper panel). There are three key elements (estimates) in Bayesian learning/updating, each one with a given mean and precision (uncertainty): prior beliefs (Panel A – Black), likelihood (PE generated by current information) (Panel A – Light Gray) and the posterior belief (Panel A – Gray). Panel B: Schema processing is divided into: I) prediction (black dotted arrows and black boxes); II) prediction error (gray arrows and gray circles) processing units weighted by, and III) precision/uncertainty (continuous black arrows). When a mismatch is detected between observed and predicted events, the system tries to minimize PE using two different and complementary strategies: 1) **Accommodation** or strong memory updating (left): when an imprecise (uncertain) prior distribution is contrasted with a precise evidence/input, the posterior belief will be much closer to the information that caused the PE. Thus, the error is propagated upwards changing its prediction or content (model) (Panel B left – Light gray and black width arrows). 2) **Assimilation** or input change with little memory modification (right): when imprecise evidence/input confronts a precise prior belief, the posterior belief will be similar to the prior distribution (Panel B right, see arrows width). In normal settings, a balance between two strategies should exist, leading to an optimal integration between top-down priors and bottom-up PE. Panel C: Examples of accommodation and assimilation as PE minimization strategies in normal schema. The example is based on the one described above about a person during a rock concert. In normal settings there is a dynamic equilibrium between accommodation and assimilation which allows a person to have behavioral and cognitive flexibility.

updating; Bartlett & Burt, 2011; Ghosh & Gilboa, 2014; Piaget et al., 1952; van Kesteren et al., 2012). **Assimilation** here refers to changing the information or input to fit in with previous memories and **Accommodation** instead, defines the process by which the schema itself is changed or revised to fit in with the actual event or input (Clark, 2013; Piaget et al., 1952; Proulx, Inzlicht, & Harmon-Jones, 2012). Thus, schema facilitates encoding and memory organization. Multiple types of schemas have been proposed, such as motor, event, scene, semantic and cognitive schemas (Ghosh & Gilboa, 2014; Lewis & Durrant, 2011). For example, it was found that predictions based on prior knowledge potentiate multisensory representation of objects, associative rules formation, probabilistic statistical regularities and spatial memory (Ghosh & Gilboa, 2014; Kumaran, 2013; van Kesteren et al., 2012). In the literature of learning models, Mackintosh (1975) proposed that animals learn more about previously informative cues (better predictors of the outcome based on past experience). Furthermore, Bartlett & Burt (2011) showed how an unfamiliar story could be reconstructed in memories based on our own prior knowledge.

A hypothesis from studies using psychopathology cognitive models states that activation of specific hierarchical schema leads to aberrant information processing (Barlow, 2004; Halligan & David, 2001; Montague et al., 2012; Young, 1994). Once active, they tend to dominate by top-down modulation. In other words, in uncertainty situations, the subjects' appraisal of experience and behavior in the form of negative automatic thoughts lead to dysfunctional anticipatory processes. In anxiety disorders, negative schema activation predisposes individuals to catastrophic misinterpretations of the situations (Clark & Beck, 2010, 2011).

7. Bayesian learning and hierarchical structures

As described by memory schemas, much of human cognition and behavior is hierarchically structured (Botvinick, 2008; Botvinick, Niv, & Barto, 2009; Buzsáki et al., 2014). During development, simple operations are gradually integrated into larger wholes (Botvinick, 2008; Piaget et al., 1952). During an anxiety episode, automatic thoughts are dependent on higher beliefs (e.g. intermediate beliefs and schema) involved in top-down generation of predictions (Beck & Dozois, 2011).

In computational psychiatry, there are several Bayesian hierarchy models (Adams et al., 2013; Montague et al., 2012; Moutoussis, Story, & Dolan, 2015) formalizing the relationship between symptoms, environment, and neurobiology. In this regard, a model of anxiety was proposed based on the discrepancies in interoceptive perception (Paulus & Stein, 2006). Another example of computational psychiatry highlighted the role of PE in delusions and hallucinations in schizophrenia (Corlett et al., 2007; Fletcher & Frith, 2009), and finally, it was postulated a mechanism of inference failure and belief formation in somatoform disorder, addiction, and depression (Chekroud, 2015; Edwards, Adams, Brown, Pareés, & Friston, 2012; Schwartenbeck et al., 2015). A common element between these models is to consider how prior knowledge (schemas) affects our experience and how this experience updates our beliefs (Fletcher & Frith, 2009). According to Bayesian models, beliefs are probability distributions about causes and states of the world (see section 2.2). This probability is 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).

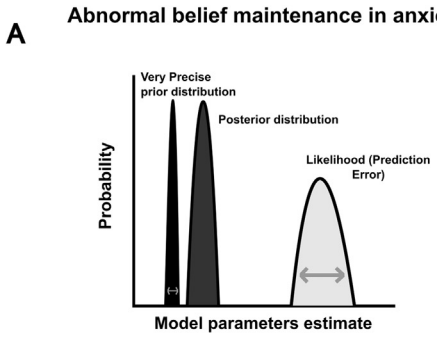
Bayesian statistics gave rise to the latent cause learning, predictive coding, and free-energy principle frameworks (Clark, 2013; Courville et al., 2006; Friston, 2010) which postulate that beliefs (probability distributions) are produced by top-down predictive signals that emerge from hierarchical models of causes of the world. These distributions are functions of the same latent or unobservable active cause of current input. The down-flow of predictions is adjusted by bottom-up PE's given by the current input at different levels of the hierarchy using the Bayes rule (Clark, 2013; Edwards et al., 2012; Friston, 2010). Similar to the schema literature, within this framework, PE can be reduced either by adjusting the model in accordance to the new information (accommodation, memory acquisition or memory reconsolidation, Fig. 2B) or adjusting the sensory input to fit the model (assimilation, Fig. 2B; Edwards et al., 2012; Kanai, Komura, Shipp, & Friston, 2015; Proulx et al., 2012; Seth, 2013). The usefulness of Bayesian models reside in the intention to describe how we react to incongruences or conflicting information and try to compensate them. In other words, when a mismatch between observed and predicted events is detected, the system tries to minimize PE using two different strategies: 1) accommodation or strong memory updating: when an imprecise (uncertain) prior distribution is contrasted with a precise evidence/input, the posterior belief will be much closer to the information that caused the PE. Thus, the error is propagated up-wards changing its prediction or content (model of the world); 2) Assimilation or action with little memory modification: when imprecise evidence/input confronts a precise prior belief, the posterior belief will be more similar to the prior distribution. In normal settings, a balance between two strategies should exist, leading to an optimal integration between top-down priors and bottom-up PE.

In a hierarchical structure, predictions at each level represent not only a prior belief about possible outcomes but also the most likely cause of events in the level below. A PE is generated when there is a discrepancy between top-down and current belief at the level detected (Kanai et al., 2015; Mathys et al., 2011; Rescorla & Wagner, 1972). Then, the produced error projects up-wards to higher levels. This results in a posterior better prediction and PE minimization on that level (Fig. 2 B). As in associative learning models (see Section 2.2), the cycle continue until the PE falls near “zero” (no PE) and no more learning/updating occurs. However, there is a difference between PE and the precision or uncertainty about the error. Beliefs and sensory input also are probability distributions with a mean value (prediction) and a degree of uncertainty (precision (Edwards et al., 2012; Gershman et al., 2015; Kanai et al., 2015). This precision or uncertainty modulates the impact of the PE in the lower levels of the hierarchy. Therefore, PE is weighted by precision, which acts as gain. The product determines the effect on learning/updating and prior beliefs. The rate of learning depends on the degree of outcomes surprise.

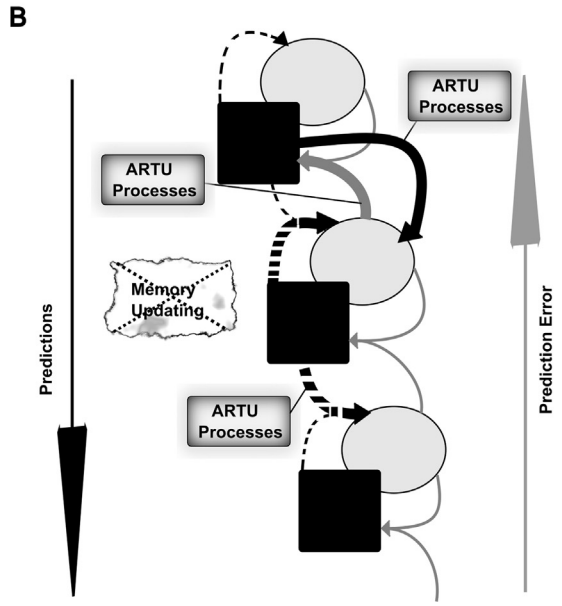
Notably, when a PE arises from a mismatch between a precise current input and a relative imprecise prior belief, the mean of the posterior belief (the product of the PE), will be closer to the mean of the current input (**accommodation**; Corlett et al., 2009; Edwards et al., 2012; Pearson et al., 2011). On the contrary, with a relative imprecise current information and a certain prior belief, the mean of the posterior belief (product of the PE) will be closer to the priors (**assimilation**). In normal situations, our cognitive system should use both strategies depending on the weight given to either actual evidence or prior beliefs (Fig. 2). This allows cognitive flexibility and behavioral adaptation. A given schema should accommodate (update) its content and relations to resolve inconsistency or assimilate conflicting information with little change (Proulx et al., 2012). In summary, as Edwards et al. (2012) stated, “*The potency of top-down prior beliefs in relation to bottom-up sensory evidence is controlled by the relative precision of the prediction errors as each level of the cortical hierarchy*”.

8. A Bayesian-like model for Anxiety disorders: is memory reconsolidation updating function impaired?

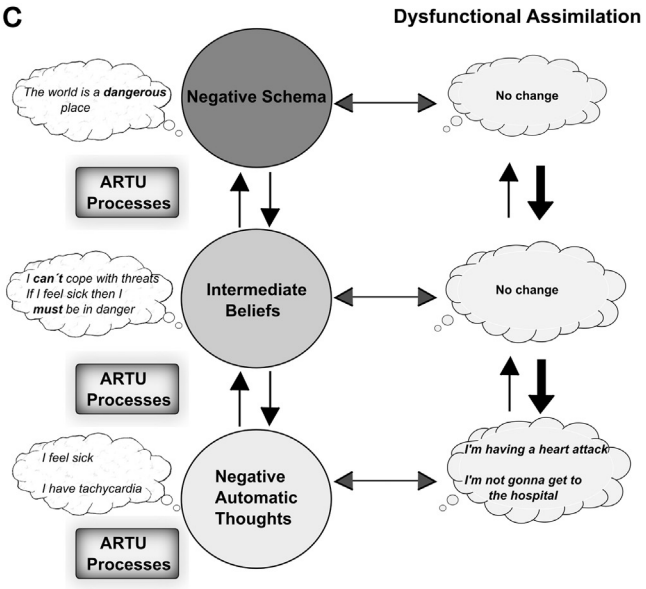
In accordance with CBT and Uncertainty and Anticipation Model of Anxiety models (see above, Beck & Dozois, 2011; Grupe & Nitschke, 2013) anxiety disorders could be developed by predisposing genetic risk factors and vulnerabilities gradually acquired through learning along the ARTU processes (i.e., negative or aversive early experiences and stress, vicarious learning, anxiety sensitivity, trait anxiety, etc.; (Bouton et al., 2001; Carleton et al., 2007; Clark & Beck, 2011; Grupe & Nitschke, 2013; Hartley & Phelps, 2012; Martin, Ressler,



Panel A: *Probability distributions are shown for the prior, posterior, and likelihood function*



Panel B: *Abnormal schema processing. Black Boxes and Dotted black arrows: prediction processing units; Gray Circles and arrows: prediction error processing units; Black continuous arrows: posterior precision processing; Width of arrows means relative importance weights of unit processing.*



Panel C: *Examples of a dysfunctional PE minimization strategy in anxiety disorders. Left clouds represents the initial (prior) beliefs and the right clouds the posterior beliefs. Strong top-down modulation of cognitive schema. Arrows width represents unbalanced processing (top-down vs. bottom-up).*

Fig. 3. Rigidity of updating mechanism in anxiety disorders. Panel A: Probability distributions, very precise prior, ARTU and PE favor assimilation. Panel B: PE signals that there has been a change, leading to an increase in uncertainty. In anxiety disorders, ARTU processes and assimilation mechanisms are engaged in order to reduce PE. New information, ambiguity, and uncertainty at each level is resolved according to strong-precise priors, changing interpretation of experience, and their original meaning. An abnormal prior (an enduring threat schema or altered expected value calculation) gains precision through increased attention and hypervigilance to threat cues. Along with cognitive errors, they inhibit safety signal identification and elaboration. This increase in precision ignores intermediate bottom-up PE and matches the prior belief. Finally, cognitive-behavioral avoidance and threat reactivity to uncertainty favor assimilation against accommodation (updating). This results in a congruent interpretation (cause) of the aversive event with the strong prior belief. Panel C: An example based on the one described above about a person during a rock concert which suffers a panic attack. From a phenomenological perspective, activation of negative schema controls the information processing by top-down modulation. A hierarchy of related memories/beliefs (negative schema) causes the subjective aversive experience (specific cognitions and images: automatic thoughts). Even when the anxiogenic event is concluded and the catastrophic predictions not fulfilled, ARTU processes and assimilation lead to symptoms maintenance and memory updating failure.

Binder, & Nemeroff, 2009; Mineka & Zinbarg, 2006; Murray, Creswell, & Cooper, 2009; Tovote et al., 2015). The interaction between these factors gives rise to negative schemas produced by experience that shapes the precision of prior belief and increases the strength of memories. One must assume that, during development, an aberrant balance between the "accommodations" and "assimilation" strategies of PE minimization might bias the construction of these schemas. During the onset of illness, the belief structure gradually loses flexibility and becomes insensitive to disconfirmatory information. At this point the reader might ask, how anxiety disorders are maintained in spite of several experiences and information that contradict and disconfirm memory schemas and their predictions? Why reconsolidation-update function does not affect memory content and related processing?

In order to answer this question, we propose that, altered memory updating (accommodation) mechanism is responsible for anxiety disorders maintenance (Fig. 3). The failure of learning from experience leads to persistence of symptoms, memory representations, and maladaptive predictions (Clark, 1999; Salkovskis, 1991). Then, new information, ambiguity, and uncertainty at each level are resolved according to strong-precise priors, changing interpretation of experience, and their original meaning. To clarify our proposal, in highly anxious individuals when strong and precise memories (dysfunctional schema – heavy weight prior beliefs) encounter a PE, the destabilization phase of reconsolidation begins. During the restabilization phase, the up-flow of the error generated, that would otherwise force memory content updating (schema re-organization), is affected or canceled. Moreover, PE minimization is accomplished by assimilation in accordance to prior belief facilitated by the ARTU processes (see Section 3.1). Hence, strong top-down modulation affects experience. Thus, there is a preeminence of dysfunctional strategies towards incongruences and a failed attempt to minimize the uncertainty of conflicting information (increase precision) of current situation (Fig. 3).

Anticipatory response to threat uncertainty (ARTU) processes plays a critical role in, a) impairing the up-flow of errors and decreasing the precision of new evidence and b) increasing the precision of the prior belief and prediction. One could hypothesize that enduring beliefs and altered value calculations could act as strong priors that bias conflicting information processing and its fate. That is, the activation of strong negative schema (i.e "the world is a dangerous place", Fig. 3) and its associated valuation, increases the negative expected value (probability and intensity) of predicted events based on current sensory input (i.e. tachycardia, palpitations). Multiple negative scenarios or outcomes are over-represented increasing the precision of priors (i.e "I'm might die"). Cognitive errors and attentional bias may increase the precision of priors, facilitating threat processing and inhibiting safety elaboration. Cognitive errors might help jumping to conclusions and resolve the uncertainty in an aversive manner, while attentional bias towards

threat impairs the error processing leading to a "safety signals blindness" (i.e hypervigilance to physiological activation, distortions in cognitive processing and ignoring the possible safety cues). Lastly, in the same line of thinking, heightened reactivity to uncertainty and cognitive-behavioral avoidance are also critically involved in updating (accommodation) cancellation and the persistence of dysfunctional belief/behavior. The subject is urged to stop the emotional response and avoid the perceived source of external threat (i.e abandons the stadium, visits the emergency services). Prior beliefs are not properly updated when the event-triggering anxiety is no longer present. Highly anxious individuals maintain their strong prior belief and reinterpret the previous conflicting information as schema congruent (assimilation): the individual may think that he "really was in danger" and "he almost died or faint".

In this regard, highly anxious individuals assign old causes to new events. Moreover, patients might attribute to ARTU processes (i.e avoidance) the capacity to prevent the predicted negative outcome. In summary, ARTU processes could affect different levels of the hierarchy and the PE processing and act as a "lock" for memory updating in anxiety disorders by preventing an adaptative error processing.

When prediction is not confirmed, memory could still be strengthened by reconsolidation processes (Alberini, 2005; Forcato et al., 2014) leading to an increase or generalization of symptoms (de Oliveira Alvares et al., 2012; Eysenck, 1976; Inda et al., 2011). Similarly, Eysenck (1976) proposed that the anxiety response per se, without the expected outcome, is aversive and acts as reinforcement.

Updating failure could also be influenced by the simple passage of time. In the psychiatric field, it is observed that duration of untreated psychopathology and the severity Fof symptoms are determinants of treatment outcome. Longer periods between the appearance of the symptoms (age of the pathology) and their severity (strength of the pathology) are significant predictors of relapse (Barlow, 2004; Blom et al., 2007; Eisen et al., 2013; Farooq, Large, Nielssen, & Waheed, 2009; Lambert, Karow, Leucht, Schimmelmann, & Naber, 2010; Van Os, Jones, Sham, Bebbington, & Murray, 1998).

Although there is no linear function of anxiety episodes (time) and anxiety severity, in certain occasions, the content-updating function of memory reconsolidation should occur in the lower level of the hierarchy (Fig. 3). This mechanism will eventually lead to the incorporation of relative safety information and balance the severity of symptoms. Further, this local change is very resistant to generalization to similar events or domains (Bouton, 1993, 2014). Since memories form hierarchical schemas (Ghosh & Gilboa, 2014; Piaget et al., 1952; van Kesteren et al., 2012), local content-updating by reconsolidation in the lower levels should occur without affecting the whole structure. In this sense, laboratory studies have shown that, for example, when different cues (i.e images) are associated with the same outcome (shock), only the reactivated stimulus could be labilized and interfered without affecting non-reactivated cues (Schiller et al., 2010). Interestingly, when different hierarchy cues are acquired to predict an aversive outcome (second-order conditioning), only the reactivation of the closer cue to the outcome is sensitive to pharmacological interventions affecting the "whole" memory (Dębiec, Doyère, Nader, & LeDoux, 2006). In addition, another report found that, when multiple cues are paired with an aversive consequence, reactivation using the predicted outcome (shock) is capable of compromising the entire memory (Liu et al., 2014).

In clinical settings a valuable CBT technique is the systematic desensitization (Wolpe, 1961), that is, the gradual exposure to anxiogenic hierarchy situations. Its success resides in the gradual use of anxiogenic stimulus, from the lower to the higher (Barlow, 2004; Clark & Beck, 2011). Another CBT example comes from cognitive restructuring (Knapp & Beck, 2008). This technique uses "automatic thought records" (Beck, 1979) in patient's anxiety episodes. They describe a negative situation (anxiogenic situation) and contrast explicitly the predicted outcome (intensity, duration, emotion, cognitions) with what actually happened (alternative explanation). During treatment there is a gradual change in specific low-level cognitions (spontaneous automatic thoughts) and predictions but, as it was previously stated, there is a difficulty to automatically generalize to higher beliefs (schemas; Beck & Dozois, 2011; Young, 1994).

9. Future challenges

Research on memory reconsolidation shed light on the mechanisms and conditions critical for memory updating. This path led to the idea that memory reconsolidation could have translational value in the psychiatric field. We aim to highlight the other side of the coin: how a dysfunction in memory reconsolidation could serve to maintain anxiety disorders. Following, we offer alternative hypotheses and suggestions for future research and potential clinical interventions.

First, most of memory reconsolidation studies were performed on animals and healthy young populations but only a few were carried out using clinical populations (Brunet et al., 2008, 2014; Das et al., 2015; Lonergan et al., 2016; Saladin et al., 2013; Soeter & Kindt, 2015; Xue et al., 2012). In laboratory settings (i.e Pavlovian conditioning, value based decisions, etc.) one could predict that people suffering from anxiety disorders would have more difficulty or be insensitive to memory interference or updating (i.e extinction training or imagery rescripting, after memory reactivation). In the same sense, it would be helpful to employ additional memory paradigms in memory reconsolidation research. For example, highly anxious individuals could more easily strength habit-memory by repeated reactivations, although this habit-memory could be resistant to modification or reversal (i.e outcome devaluation).

Second, there is a need to investigate the actual limitations of reconsolidation-based interventions in clinical settings. One might expect that traditional approaches (i.e a negative PE followed by new learning or propranolol, without targeting any ARTU process) may be effective in simpler anxiety disorders (specific phobias; Soeter & Kindt, 2015) in contrast to more complex ones. The effectiveness of these basic interventions could be proportional to the severity and complexity of the disorder (chronicity, comorbidity, intensity, etc.).

Third, different reports indicate that PE is "the key" for memory updating (Exton-McGuinness et al., 2015; Fernández et al., 2016). The main question yet to be solved is: how to alter ARTU processes in a way that could allow PE to adaptively update memory strength/content. In laboratory and clinical settings, knowledge about how ARTU are acquired and how they interact with memory systems is lacking. It would be useful to implement protocols with multiple measures (memory, attention, valuation, etc.) across different levels (i.e from genes to behavior) similar to the Research Domain Criteria initiative proposal (RDoc; www.nimh.nih.gov/research-priorities/rdoc/index.shtml). Some evidence indicates, for example, that after Pavlovian conditioning an attentional bias towards threat is acquired (Pischek-Simpson, Boschen, Neumann, & Waters, 2009; Shechner, Pelc, Pine, Fox, & Bar-Haim, 2012) and, in the opposite way, disrupting memory reconsolidation could affect this type of bias (Das et al., 2015). In clinical contexts, several reports found that: a) patient's improvement and recovery could correlate with a reduction in attentional bias towards threat or expected value calculation; b) ARTU processes might be modulated or changed by training. For example, exposure and response prevention (safety elaboration and avoidance prevention training), attentional training (learning to avoid threat/learning to attend threat) or interpretative training (learning to resolve the ambiguity in a positive way) could reduce anxiety symptoms (MacLeod & Mathews, 2012). However, mixed evidence is found regarding these last two interventions in isolation (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, M. H., 2007). Based on the above, it is clear that memory might be able to affect ARTU processes and vice versa. However, how should one proceed in a clinical context? Should one first aim to destabilize memory, strength the new incongruent information and then prioritize the ARTU processes or, proceed in the

opposite direction? It is unknown whether there is an ARTU's process more relevant than the others involved in anxiety disorders maintenance or if it is a specific composition or timing between them. We propose, based on memory reconsolidation updating function, that targeting ARTU processes by specific trainings might be a possible and complementary strategy. These specific trainings might, synergistically, contribute to diminish or change the content of dysfunctional schemas (hierarchically, by steps), while strengthening new responses and more adaptive information. For example: a) Reconsolidation mediated content updating: one would expect that targeting ARTU processes (i.e attentional training) conjointly with the new incongruent information (i.e extinction/exposure, reappraisal) during the reconsolidation window (i.e after a specific PE), should favor accommodation over assimilation process facilitating cognitive flexibility. The attentional bias training and the exposure, for example, should be performed together after a PE. It is worth pointing out that these techniques used apart or in different days should not have the same effect (only assimilation). b) Reconsolidation mediated strength updating: both ARTU processes targeted by training (i.e working memory, interpretative bias, attentional training bias) and the new conflicting information (i.e counterconditioning, new learning or extinction/exposure) constitute memories that, once acquired, they could compete with strong priors (i.e negative schemas). One could predict the persistence of more functional memories and flexible cognitive process, if both ARTU processes training and new conflicting information are reminded in a way capable to reactivate and strengthen them by memory reconsolidation. Moreover, the specific use of flashcards or cell phones reminders could be useful. Only those effective reminders able to generate a specific PE should strength memory.

Finally, neural signals involved in PE processing and memory reconsolidation in people suffering from anxiety disorders, will reflect a different pattern of brain activity, specifically in those areas involved in valuation, emotional learning, executive control, avoidance and decision making such as amygdala, striatum, anterior cingulate cortex, ventromedial and orbitofrontal cortex, etc.

10. Conclusions

Current CBT are the most effective treatments for anxiety disorders (Beck & Dozois, 2011; Otte, 2011). The strength of CBT interventions relies on how the therapist explicitly guides patients through their predictions, beliefs, and world models, in order to achieve schemas flexibility (Barlow, 2004; Beck & Dozois, 2011; Young, 1994). We began this review arguing the similarity between boundary conditions of memory reconsolidation and the maintenance of anxiety disorders. Research on memory reconsolidation is crucial to understanding not only anxiety disorders maintenance, but also to developing translational approaches to improve current interventions. Since anxiety disorders seem to be maintained, at least in part, by an impaired PE processing (assimilation rigidity), future techniques should improve not only the identification of patient prediction discrepancies but also regulation of the ARTU processes which seems to act as a lock for memory updating in anxiety disorders.

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Conflict of interest

None.

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