Research

Memory destabilization during reconsolidation: a consequence of homeostatic plasticity?

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Remembering is not a static process: When retrieved, a memory can be destabilized and become prone to modifications. This phenomenon has been demonstrated in a number of brain regions, but the neuronal mechanisms that rule memory destabilization and its boundary conditions remain elusive. Using two distinct computational models that combine Hebbian plasticity and synaptic downscaling, we show that homeostatic plasticity can function as a destabilization mechanism, accounting for behavioral results of protein synthesis inhibition upon reactivation with different re-exposure times. Furthermore, by performing systematic reviews, we identify a series of overlapping molecular mechanisms between memory destabilization and synaptic downscaling, although direct experimental links between both phenomena remain scarce. In light of these results, we propose a theoretical framework where memory destabilization can emerge as an epiphenomenon of homeostatic adaptations prompted by memory retrieval.

[Supplemental material is available for this article.]

After retrieval, processes such as reconsolidation or extinction can alter the content and/or strength of memories. Behavioral studies typically describe these two phenomena as separate entities that are triggered by distinct retrieval conditions. In fear conditioning, for example, a long session of nonreinforced re-exposure to the context leads to a decrease in the conditioned response through extinction, while shorter re-exposure durations lead to reconsolidation and reinstate susceptibility to amnesic agents (Pedreira and Maldonado 2003; Bustos et al. 2009). Other boundary conditions such as the strength and age of the memory and the degree of prediction error can also influence which process will occur (Eisenberg et al. 2003). However, it is still unclear how the transition between these opposite behavioral outcomes develops, and studies suggest it includes a period in which neither process occurs (Merlo et al. 2014; Cassini et al. 2017).

Pharmacological interventions such as protein synthesis inhibitors can block both reconsolidation and extinction, suggesting that similar plasticity systems might underlie the two phenomena. To address this hypothesis, Osan et al. (2011) investigated the transition between them using an attractor neural network model, in which the interaction between Hebbian plasticity and a mismatch-driven synaptic weakening process led to different behavioral outcomes, depending on the similarity between the original learning and the new experience. Although their results showed that both reconsolidation and extinction could be produced by similar plasticity systems, the mismatch-induced degradation term was not related to a biologically plausible form of plasticity, making this a largely theoretical proposal.

Nevertheless, pharmacological evidence does suggest the existence of a memory destabilization system, which includes mechanisms such as NMDA receptors (Ben Mamou et al. 2006; Milton

et al. 2013; Nakayama et al. 2016; Yu et al. 2016), the ubiquitin-proteasome system (Lee 2008; Lee et al. 2008; Da Silva et al. 2013; Fustiñana et al. 2014), CB1 receptors (Lee et al. 2019), L-type voltage-gated calcium channels (LVGCCs) (Suzuki et al. 2008) and calcineurin (Fukushima et al. 2014; Yu et al. 2016). This set of mechanisms, derived from behavioral studies in which destabilization is blocked by pharmacological agents, can be useful to speculate on possible synaptic correlates of memory destabilization.

Interestingly, there is evidence that some forms of negative synaptic plasticity share molecular mechanisms with memory labilization. The induction of long-term depression (LTD), for example, requires NMDA receptors in the hippocampus (Dudek and Bear 1992) and involves endocannabinoids as retrograde messengers in the striatum (Gerdeman et al. 2002), neocortex (Nevian and Sakmann 2006), and cerebellum (Qiu and Knöpfel 2009). Beyond Hebbian mechanisms, synaptic weakening can also be induced by homeostatic plasticity, which adjusts synapse number and/or strength in response to chronic changes in neural activity (Marder and Goaillard 2006; Turrigiano 2012). Several types of plasticity can drive homeostatic adjustments at the cellular or network level (Table 1). Among these, synaptic weakening can occur through synaptic scaling (Turrigiano 2008), heterosynaptic plasticity (Chistiakova et al. 2014), and sliding threshold modifications (Keck et al. 2017a).

Unlike Hebbian plasticity, which is typically fast, homeostatic plasticity can take place across a variety of timescales (Zenke and Gerstner 2017). Synaptic downscaling in response to increased neuronal firing, for example, can take several hours to occur

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Table 1. Homeostatic plasticity types and their features

Homeostatic plasticity type	Spatial scale	Onset time	Spike-time dependence	NMDAR dependence	Response mechanisms	References
Synaptic scaling	Global (cell-wide)	Hours to days	Downscaling only	Downscaling only	Multiplicative change in synaptic weights	Turrigiano 2008; Siddoway et al. 2014
Heterosynaptic plasticity	Local synapses	Minutes to hours	Yes	Yes	Average changes in the weights of specific synapses, depending on initial synaptic properties	Chistiakova et al. 2014, 2015
Sliding threshold (BMC model)	Global (cell-wide)	Days	Yes	Yes	LTP/LTD threshold change, depending on initial synaptic properties	Keck et al. 2017a; Bridi et al. 2018
Excitation/inhibition balance	Global (circuit-wide)	Hours to days	No	Yes	Circuit-wide remodeling of inhibitory synapse clusters and dendritic spines	Chen et al. 2012; Bhatia et al. 2019; Sohal and Rubenstein 2019
Intrinsic excitability modulation	Local or cell-wide	Seconds to hours	No	Yes	Modifications of membrane conductance and voltage-gated ion channel expression, either locally or cell-wide.	Marder and Goaillard 2006; Gasselinet al. 2015; Debanne et al. 2019

“Spatial scale” refers to which spatial extent a given plasticity operates. Local mechanisms act on individual or small groups of synapses within a neuron, while other processes are able to evoke cell-wide or circuit-wide responses for excitability adjustment. “Onset time” denotes the time range in which each type of plasticity is commonly observed. “Spike-time dependence” describes whether a form of plasticity follows spike-timing plasticity rules. “NMDAR dependence” describes whether it depends on NMDA receptors. “Neuronal response to activity change” briefly describes the circuit and cellular adaptations to chronic changes in the firing rate. (BCM) Bienenstock–Cooper–Munro, (NMDAR) N-methyl-D-aspartate receptor, (LTP) long-term potentiation, (LTD) long-term depression.

(Turrigiano et al. 1998), matching the relatively slow decay in conditioned responses (Nader et al. 2000) and in synaptic potentials (Fonseca et al. 2006) after protein synthesis inhibition upon memory reactivation. Moreover, the activity dependence of synaptic downscaling makes it an interesting candidate to explain why memory destabilization requires reactivation to occur. Finally, synaptic downscaling also requires mechanisms implicated in labilization, such as NMDA receptor activation (Lee and Chung 2014), AMPA receptor endocytosis (Shepherd et al. 2006), LVGCC activity (Goold and Nicoll 2010; Lee and Chung 2014), and protein degradation (Jakawich et al. 2010).

To investigate whether homeostatic plasticity could be a feasible mechanism for retrieval-induced memory destabilization, we performed a computational study using two different network models, previously developed to study each of the processes separately (Osan et al. 2011; Auth et al. 2020). This was followed by systematic reviews of the molecular mechanisms of both phenomena and of existing links between homeostatic plasticity and memory destabilization in the literature.

Results

In order to study whether memory destabilization could arise from homeostatic plasticity, we used adaptations of two previously published computational models (Table 2). The first (Osan et al. 2011) studied the transition between reconsolidation and extinction in an attractor network, with labilization driven by mismatch between the training and reactivation patterns. The second (Auth et al. 2020) used a combination of Hebbian plasticity and homeostatic synaptic scaling to allocate stimuli as internal representations in a memory network.

In both models, we focus on whether synaptic scaling can mediate the different effects of Hebbian plasticity blockade on stored memories under various re-exposure conditions. More specifically, we seek to model the general results observed in Suzuki et al. (2004), in which a transition from simple retrieval to reconsolidation to extinction is observed with increasing re-exposure duration, leading to different effects of protein synthesis inhibition in

each case. As in Osan et al. (2011), we assume that longer re-exposure sessions are associated with increasing mismatch between the training and re-exposure context representations, and model the patterns accordingly in both models.

Investigating homeostatic plasticity as a destabilization mechanism in an attractor model of reconsolidation and extinction

Our first model is an adaptation of the attractor network described in Osan et al. (2011). This fully connected Hopfield-like network is composed of 100 neurons exhibiting graded activity from 0 to 1, driven by their recurrent connections and by an input cue that simulates an animal's current representation of its environment (Fig. 1A). In the original model, changes in recurrent connection weights occurred through a combination of Hebbian plasticity and a mismatch-induced degradation term, which weakened synapses that caused mismatch between the input cue and the pattern retrieved by the network. The combination of these two forms of plasticity led to transitions between simple retrieval, reconsolidation and extinction according to the degree of mismatch between initial learning and re-exposure, used by the investigators to model the duration of contextual re-exposure in fear conditioning.

In our adaptation of the model, the mismatch degradation term is replaced by a synaptic scaling term, which adjusts a neuron's synaptic input weights according to its firing rate. This term, adapted from Tetzlaff et al. (2013), compares a neuron's firing rate with a desired target activity, weakening all excitatory connections received by the neuron if this target is exceeded. Thus, while Hebbian plasticity reinforces the connections between two active neurons, synaptic weakening due to scaling occurs when the postsynaptic neuron is highly active in the absence of presynaptic activity (Fig. 1B).

The Hebbian learning term is associated with a parameter S that represents the biochemical requirements for this form of plasticity. As described in Osan et al. (2011), we vary S to simulate the effects of protein synthesis inhibitors or plasticity-enhancing drugs in consolidation, reconsolidation, and extinction.

Table 2. Model features

Properties	Model 1 (adapted from Osan et al. 2011)	Model 2 (adapted from Auth et al. 2020)
Type of neuron	Modified graded-response Hopfield (0-to-1 activity)	Rate-coded leaky integrator
No. of memory neurons	100	900
Connection topology	All-to-all	Circular connections with four-neuron radius
Cue input	Excitatory/inhibitory	Excitatory only
Cue topology	Individual cues for each neuron	Random divergent connections between input and memory areas
Inhibition	Inhibitory connections arise according to plasticity rules	All-to-all connection from inhibitory unit to memory area
Plastic connections	Between memory neurons	Between memory neurons and from cue to memory neurons
Plasticity types	Hebbian plasticity and synaptic scaling	Hebbian plasticity and synaptic scaling
Learning measure	Pattern similarity in retrieval with context cue	Mean connection weight within memory cluster

The table shows the type and number of neurons, the topology of connections between memory neurons, the type of cue input, the nature of inhibition, the presence of plasticity in individual connections, plasticity types and metrics to evaluate learning in the two models, adapted from Osan et al. (2011) and Auth et al. (2020).

Similarly, the synaptic scaling term is associated with a parameter κ that represents the ratio between Hebbian plasticity and synaptic scaling. Variation in κ is used to simulate the effects of destabilization blockers or enhancers in reconsolidation.

We model conditioning and re-exposure to a context using a sequence of three different cue patterns (Fig. 1C). After learning a cue pattern unrelated to fear conditioning, the network receives a noisy training cue activating two groups of neurons, one repre-

senting the context (four neurons) and another representing the fearful experience (10 neurons), leading to reinforcement of their connections through Hebbian plasticity. The third cue pattern simulates a re-exposure session, with activation of context neurons alongside a variable mix of fear neurons and a separate group of 10 neurons representing a safe environment. Short re-exposure sessions are modeled by learning cues that are similar to the training pattern, assuming that presentation of the context will initially

Figure 1. Attractor network model adapted from Osan et al. (2011) (A) Network architecture. The model consists of an attractor network representing a memory storage area, with a cue input that corresponds to an animal's current representation of the context. Connections from the memory network to the current representation are assumed but not explicitly modeled. (B) Network plasticity mechanisms. Simultaneous activation of two neurons (red) leads them to reinforce their connections through Hebbian plasticity. The Hebbian plasticity term also leads to formation of inhibitory connections from active to inactive neurons (blue), presumably mediated by inhibitory neurons that are not explicitly modeled. Increased activity in a neuron leads to activation of the synaptic scaling term, which lowers the neuron's input weights globally, leading to weakening of synapses when Hebbian reinforcement is absent. (C) Modeling of fear conditioning and reactivation. After learning an unrelated pattern and the training memory, the network undergoes a re-exposure session with an input whose similarity to the training pattern varies according to reactivation duration, with longer durations leading to progressively dissimilar patterns. After this, retrieval is measured by activating the shared neurons between both patterns (i.e., the context) and observing the attractor to which the network evolves.

trigger a strong fear response. For longer re-exposure sessions, activation of these neurons is gradually replaced by that of safety neurons as a function of re-exposure time (t), until the extinction pattern (with full activation of the safety neurons and no activation of fear neurons) is reached at the maximum duration ($t=10$). The retrieval test is simulated by presenting a cue pattern activating the context neurons and observing the activation pattern to which the memory network evolves. As in the original model, retrieval of the training memory attractor is assumed to lead to greater freezing behavior than other attractors (see the Materials and Methods for more detail).

Results obtained with the model are shown in Figure 2, which presents the mean results of 100 simulations with random initial levels of activation for each neuron. Under normal conditions, the memory network is able to form and retrieve the association between context and fear neurons, leading to retrieval of this memory and high freezing in the retrieval test. Blockade of Hebbian plasticity during the training session prevents this process, leading to a decrease in test freezing (Fig. 2A), as observed with protein synthesis inhibitor (PSI) administration before or shortly after fear conditioning (Schafe et al. 1999; Schafe and LeDoux 2000).

The effect of blocking Hebbian plasticity during reactivation, meanwhile, is contingent on re-exposure duration (i.e., the degree

of mismatch between training and reactivation cues). Short ($t=1$) (Fig. 2B) or intermediate ($t=6$) (Fig. 2C) re-exposure times lead to retrieval and reinforcement of the shock memory in the control group. In this case, blockade of Hebbian plasticity during reactivation leads to decay of the original memory, as observed experimentally with PSI injection (Nader et al. 2000). For longer re-exposure durations, the control group network converges to the extinction pattern, leading to low freezing at retrieval. In this case, extinction is blocked by inhibition of Hebbian plasticity, causing freezing to be higher than in control conditions (Fig. 2D), as has been shown in studies performing protein synthesis inhibition in different brain regions (Suzuki et al. 2004; Runyan and Dash 2005; Mamiya et al. 2009).

In accordance with experimental studies (Nader et al. 2000), the effect of PSIs during re-exposure does not occur if the original learning context is replaced by an unrelated cue pattern (Fig. 2E). The effect of blocking Hebbian plasticity during low and intermediate re-exposure is also abolished by blocking synaptic scaling (Fig. 2B,C), resembling studies in which interference with mechanisms such as protein degradation (Lee et al. 2008) or NMDA receptor activation (Ben Mamou et al. 2006) reverses the memory decay caused by PSIs in reconsolidation conditions. Interestingly, blockade of synaptic scaling also potentiates the effect of PSIs in blocking extinction (Fig. 2D), a prediction that up to our knowledge has not been directly tested experimentally. Nevertheless, this finding is compatible with the fact that inhibition of both protein synthesis (Runyan and Dash 2005) and protein degradation (Lee et al. 2008) in the hippocampus have been shown to impair extinction.

Parameter analysis of the model's behavior when different values of S (Supplemental Fig. S1) or κ (Supplemental Fig. S2) are used during re-exposure shows that the effects of PSIs are "dose-dependent," with greater inhibition leading to larger effects, while those of synaptic scaling blockade have sharper thresholds. We also evaluate how the strength of the original learning influences reconsolidation and extinction (Supplemental Fig. S3; Eisenberg et al. 2003; Suzuki et al. 2004). Different S -values in training cause transitions between both processes to occur at different re-exposure times in the control group, although very low training strength leads to low freezing at the retrieval test irrespective of re-exposure time or protein synthesis inhibition.

A summary of results for varying re-exposure times can be found in Figure 2F, in which a sharp nonlinear transition between reconsolidation and extinction appears around $t=7$ with standard parameters. These results—as those of the original model—thus fail to account for the "limbo" period observed between reconsolidation and extinction in some studies (Flavell and Lee 2013; Merlo et al. 2014; Cassini et al. 2017; Franzen et al. 2019). Moreover, they differ from those of Osan et al. 2011 in that memories are sensitive to reconsolidation even with short re-exposure times (i.e., in the

Figure 2. Effects of Hebbian plasticity blockade in different protocols. Bars represent mean $\pm$ SEM of freezing values in the retrieval test, calculated on the basis of the retrieved attractor (see the Materials and Methods), for 100 simulations with control conditions (brown), Hebbian plasticity blockade by PSI injection (blue) or simultaneous Hebbian plasticity and synaptic scaling blockade (green). Treatments occur at different moments, as shown by the timelines above graphs, in which M1 represents an unrelated pattern, M2 corresponds to the training memory, and t indicates re-exposure duration. (A) Amnesic effect of Hebbian plasticity blockade (PSI) during initial learning of the shock memory. (B) Amnesic effect of Hebbian plasticity blockade in a short ($t=1$) re-exposure session. (C) Amnesic effect of Hebbian plasticity blockade in an intermediate ($t=6$) re-exposure session. (D) Extinction disruption by Hebbian plasticity blockade in a long ($t=10$) re-exposure. (E) No effect of plasticity blockade when an unrelated pattern (M3) is used as an input. Blockade of synaptic scaling (No Scal.) reverses the effect of PSI injection in reconsolidation conditions (shown in B,C) but potentiates extinction blockade in D. (F) Summary of test freezing for the control and PSI groups using varying re-exposure times. A nonlinear transition between reconsolidation and extinction is observed between $t=6$ and $t=7$, leading to opposite effects of PSIs in reconsolidation and extinction.

absence of mismatch). This occurs because the Hopfield-like framework performs very accurate pattern completion when the attractor is reached, leading to similar network activity for short and moderate re-exposure times (Supplemental Fig. S4). Thus, plasticity rules that are based solely on the activity of the memory network (as in the case of our model) will lead to similar results between these conditions and fail to match experimental results in which reconsolidation blockade is contingent upon mismatch (Pedreira et al. 2004; Morris et al. 2006). Nevertheless, mismatch dependence might occur in models with noisier retrieval, in which re-exposure patterns become progressively dissimilar from training as mismatch increases.

Generating reconsolidation and extinction-like behavior in a network model of homeostatic plasticity

To study whether the network behavior observed in our adaptation of the model by Osan et al. (2011) could be translated to existing computational models investigating homeostatic plasticity, we used a memory allocation model adapted from Auth et al. (2020). This model was originally used to show that a combination of Hebbian learning and synaptic scaling could account for pattern separation in a recurrently connected network, allocating distinct memories to different neuronal populations when partially overlapping cue patterns were presented.

The model is composed of an input area and a memory network, as well as an inhibitory unit connected to the latter (Fig. 3A). The input area is composed of 36 rate-coded neurons that transmit information to a 900-neuron memory network through random feed-forward connections, with each neuron in the latter receiving connections from four neurons in the former (Fig. 3B). The memory network is stimulated by setting the firing rate of neurons in the input area to 130 Hz for active neurons and 0 for inactive ones. It stores internal representations of the environment in its recurrent connections, with each neuron connecting to neighboring neurons within a radius of four units in a toroidal topology (Fig. 3C). The inhibitory unit has bidirectional connections with all neurons in the memory area and regulates global activity.

We consider all connections between excitatory neurons in the model to be plastic. A Hebbian plasticity term is activated when presynaptic and postsynaptic neurons fire simultaneously; in our adaptation, we varied its constant S to simulate the effect of protein synthesis inhibitors. As in our first model, the synaptic scaling term in the model is dependent on a comparison between postsynaptic firing rate and an activity target (Tetzlaff et al. 2011, 2013). To simulate the effects of blocking synaptic scaling, we var-

Figure 3. Homeostatic plasticity model adapted from Auth et al. (2020). (A) Context representation is encoded by the activation of the 36 neurons in the input area. These neurons stimulate the 900 neurons in the memory network, which have recurrent connections and bidirectional connections with an inhibitory unit. (B) Each excitatory neuron in the memory network receives connections from four different excitatory neurons in the input area. (C) Recurrent connections within the memory network are made with neighboring neurons in a radius of four, in a toroidal topology. (D) Protocol used to model contextual fear conditioning with different re-exposure durations. For the training session, a pattern representing the aversive stimulus is presented. Afterward, reactivation is modeled by an input that varies according to re-exposure duration. Short re-exposure durations correspond to patterns similar to that of the training session, while progressively longer durations lead to gradual replacement of neurons in the original input by new ones. After each session, the recurrent weight of neurons representing each pattern is obtained by finding clusters of at least 30 neurons with mean recurrent weights >40 (see the Materials and Methods). When no cluster is found, the mean weight is considered to be equal to the global mean recurrent weight of the memory network.

ied the constant κ , representing the ratio of Hebbian plasticity and synaptic scaling.

As in the first model, our stimulation protocol aims to model fear conditioning followed by different durations of re-exposure to the context. Training consists of presenting a cue stimulus similar to those used in the original model. This is followed by a re-exposure session, in which we again assume that increasing duration leads to a gradual increase in mismatch between the training and re-exposure patterns. With a short re-exposure time ($t=0$), the same neurons from the training session are activated in the input network, while progressively longer re-exposures lead to stepwise substitution of these neurons by new neurons until the pattern is completely different (i.e., a pure extinction pattern) (Fig. 3D). Even when input cues are totally distinct, some degree of activation overlap by the cue can still occur in the memory area due to

the random divergent connections between neurons in both networks.

After the training and re-exposure sessions, we analyzed the synaptic weight matrices in the memory network to look for neuronal clusters representing each memory. Figure 4 presents mean results for 20 simulations with random initial conditions and different connection architectures between the input area and the memory network. The fear memory cluster formed during the training session is observed both after training and after re-exposure of any duration in the control group (Fig. 4A). If there is some degree of mismatch between the training and reactivation sessions, this cluster is sometimes updated and allocated in a new region that partially overlaps with the original one. When longer

re-exposure times are used, a second memory cluster is formed, which is analogous to an extinction memory and coexists with the original one in the network.

When Hebbian plasticity is decreased to simulate the effect of protein synthesis inhibition, the fear memory cluster is maintained when short re-exposure times are used (Fig. 4B). With intermediate re-exposure durations, however, the decrease of Hebbian plasticity leads to marked weakening of synaptic weights in the original memory cluster, mediated by uncompensated synaptic scaling. With longer re-exposure times, the fear memory is preserved, but formation of the extinction cluster is blocked. Figure 4C shows the mean recurrent weight of the cluster representing the training session for simulations with different re-exposure

Figure 4. Effects of Hebbian plasticity blockade on synaptic weights within memory clusters. (A) Representation of recurrent synaptic weights in the memory area for the control group after training (left panel) and after reactivation with different re-exposure durations in a representative simulation (right panels). Heat map represents the mean of recurrent weights for each neuron in the memory network, displayed on a 30×30 grid. A single cluster, corresponding to the fear memory, is observed after training and after short re-exposures, while longer re-exposure durations lead to the formation of a second cluster representing extinction. (B) Same as A, but with protein synthesis inhibition during re-exposure. Decrease of Hebbian plasticity weakens synaptic weights in the fear memory cluster, particularly in intermediate re-exposure durations, and prevents the formation of the extinction cluster. (C) Mean weight value of the fear memory cluster in control (blue) and PSI (red) condition after training and re-exposure with varying duration. Lines represent means of 20 simulations with different connection topologies and starting conditions. Dashed green line shows the global connection weight of the network under control conditions, including neurons inside and outside the clusters. (D) Mean weight value of the extinction memory cluster after different durations of re-exposure under control and PSI conditions. (E) Ratio between the fear and extinction memories for re-exposures of different durations with and without PSIs. Hebbian plasticity blockade has little effect after short re-exposure duration, decreases the ratio for intermediate durations and increases it for long durations.

durations. Protein synthesis inhibitors lead to a reduction in synaptic strength for all durations, but this effect is more marked in intermediate re-exposure times (i.e., t -values between 6 and 8), and is reduced for longer re-exposure sessions in which extinction is observed. Meanwhile, the extinction memory cluster starts to appear between t -values of 8–10, reaching a plateau for $t \geq 14$, but is not formed when Hebbian plasticity is blocked (Fig. 4D).

When a normalized ratio is used to assess the balance between the fear and extinction memories (Fig. 4E), the net effect of PSIs on this measure (which can be thought of as representative of test freezing) is neutral at short re-exposure times, negative at intermediate times and positive at longer times, similarly to what is observed in Osan et al. (2011) and in experimental studies using varying durations of fear conditioning (Suzuki et al. 2004). These results are qualitatively similar to the ones obtained in the previous model, with two exceptions: (1) Mismatch is now required for reconsolidation blockade to occur, as in Osan et al. (2011) and several experimental studies (e.g., Pedreira et al. 2004; Morris et al. 2006), and (2) there is a point between reconsolidation and extinction conditions in which the effects of PSIs on both memories cancel each other out ($t=8$), which may be considered analogous to the so-called “limbo” period (Merlo et al. 2014; Cassini et al. 2017).

We checked the robustness of our analysis by using different minimum cluster sizes and weight thresholds for clusters. Variation in minimum cluster size (p) has negligible effects on the mean weight values observed (Supplemental Fig. S5), while mean weight threshold does affect the results when set too low or too high, but not for values between 30 and 50 neurons (Supplemental Fig. S6).

Investigating molecular mechanisms of memory destabilization in the literature

To investigate whether experimental data support the possibility that homeostatic plasticity underlies memory destabilization, we performed a systematic review to investigate the molecular mechanisms implied in behavioral studies of destabilization (see the Materials and Methods for search terms and other details). After screening 769 articles, we extracted a total of 88 experiments from 41 studies that investigated the effect of a pharmacological or genetic manipulation on reconsolidation blockade caused by another intervention (Supplemental Fig. S7). The molecular targets analyzed in these studies are presented according to brain structure on Table 3.

Most structure-specific studies were aimed at the amygdala or hippocampus, while others targeted the whole brain through systemic injections. For intra-amygdala infusions, NMDA receptors were the most commonly studied mechanism, with both nonspecific and GluN2B antagonists shown to block destabilization. In the hippocampus, the ubiquitin-proteasome system was the most studied mechanism, with its inhibition found to block not only destabilization, but also memory enhancement in some studies. LVGCCs and CB1 receptor antagonists were also shown to block destabilization in the hippocampus in multiple studies. CB1 and dopaminergic receptors, as well as the ubiquitin-proteasome system, were implicated in memory destabilization in the two structures, suggest that a similar labilization system could be at work in both brain regions.

Other brain regions studied were the perirhinal cortex, nucleus accumbens, medial prefrontal cortex and ventral tegmental area, but these were evaluated in isolated studies investigating particular mechanisms. Studies with systemic injections in rodents confirmed the role of NMDA receptors, LVGCCs and CB1 receptors, and added other candidates such as nitric oxide and muscarinic, β -adrenergic and H3 receptors, although these were evaluated in a smaller number of studies. Interestingly, studies in *Aplysia* also

found the ubiquitin-proteasome system and nitric oxide to be important for destabilization, suggesting that this memory labilization system is present in invertebrates as well.

Of note, experiments with negative results—that is, showing the lack of effect of a pharmacological manipulation on destabilization—were very uncommon, comprising only 9% of our sample (this does not include studies of boundary conditions that show a negative effect of an intervention in a particular condition—i.e., dose or timing—but a positive one in another, which are shown in Supplemental Table S1). Moreover, most of these were drawn from studies in which another intervention was found to be effective. This suggests that publication bias is likely in this field of study, meaning that the apparent consistency in the results included in the table should be interpreted with caution. Lack of publication of negative results also makes it harder to evaluate whether discrepancies in labilization mechanisms exist across structures or species.

Involvement of destabilization mechanisms in synaptic downscaling

To investigate the relationship between the molecular mechanisms underlying memory destabilization and homeostatic plasticity, we went on to review which of the components described in Table 3 have been studied in experimental models of homeostatic plasticity. For this, we focused on synaptic downscaling, which is arguably the best studied model of homeostatic plasticity, and corresponds more closely to the implementation used in our models. By combining data from a synaptic scaling systematic review data set (Moulin et al. 2020) and manual searches in PubMed (see the Materials and Methods), we identified 13 articles that conducted experiments studying nine molecular mechanisms of memory destabilization (Table 4). Importantly, this search strategy focused on identifying whether established mechanisms of destabilization are also important for downscaling; thus, it would not be expected to identify mechanisms of downscaling that are not involved in destabilization.

In these studies, we found consistent evidence that AMPA receptor endocytosis, LVGCCs and the ubiquitin-proteasome system, are necessary for synaptic downscaling. Experiments targeting NMDA receptors and Na^+ channels demonstrated that they are required for downscaling induced by synaptic receptor activation (i.e., by bicuculline or UV-controlled presynaptic terminal excitation); however, their inhibition did not impact optogenetically induced downscaling, in which excitation is independent of synapses. Concerning intracellular signaling, only one article suggested that the phosphatase PP1 is required for homeostatic plasticity. Calcineurin and CaMKII were found to be regulated during the homeostatic response to chronic excitation, but were not necessary for it to occur. Last, there is conflicting evidence on the role of protein synthesis, with different models yielding distinct results. While an effect of PSIs was observed on the AMPAR component of optogenetically induced downscaling, this was not the case for the NMDAR component in the same model, or for light-gated GluR6 stimulation-mediated downscaling.

Discussion

Homeostatic plasticity can account for memory destabilization in computational models of reconsolidation and extinction

By using two different computational models, we investigated the hypothesis that synaptic scaling acting as a destabilization mechanism might account for the different effects of protein synthesis inhibition on reconsolidation and extinction. Our results are in

Table 3. Molecular mechanisms for memory destabilization

Target	Number of experiments	Species	Task	Main outcome (experiments)
Amygdala				
NMDA				
GluN2B antagonism (ifenprodil)	5	Rat; mouse	AFC; CFC; CPP	Blocks destabilization (Ben Mamou et al. 2006; Merlo et al. 2015; Nakayama et al. 2016; Yu et al. 2016)
Antagonism (e.g., MK-801)	2	Rat; mouse	AFC; CPP	Blocks destabilization (Ben Mamou et al. 2006; Li et al. 2016)
GluN2A overexpression	1	Mouse	AFC	Blocks destabilization (Holehonnur et al. 2016)
Partial agonism (D-cycloserine)	1	Rat	CFC	Enhances destabilization (Espejo et al. 2016)
NR2A antagonism (NVP-AAM077)	1	Mouse	CPP	No effect (Yu et al. 2016)
Ubiquitin-proteasome system				
Proteasome inhibition (β -lactacystin)	3	Rat; mouse	AFC; CFC; IA	Blocks destabilization (Jarome et al. 2011); blocks destabilization and enhancement (Fukushima et al. 2014)
CB1 receptors				
Antagonism (SR141716)	1	Rat	CFC	Blocks destabilization (Lee et al. 2019)
Dopaminergic receptors				
D1 antagonism (SCH23390)	1	Rat	AC	Blocks destabilization (Merlo et al. 2015)
D2 antagonism (sulpiride)	1	Rat	AC	Blocks destabilization (Merlo et al. 2015)
Nonselective dopamine antagonism (α -flupenthixol)	1	Rat	AC	No effect (Merlo et al. 2015)
AMPA receptors				
GluA2 endocytosis blockade (e.g., Tat-GluA2 _{3Y})	2	Rat	AFC	Blocks destabilization (Hong et al. 2013; Shehata et al. 2018)
Antagonism (e.g., LY293558)	3	Rat	AFC; CTA	Impairs retrieval (Ben Mamou et al. 2006; Rodriguez-Ortiz et al. 2012) and no effect (Milton et al. 2013)
Calcineurin				
Inhibition (e.g., FK-506)	3	Mouse	CPP; IA	Blocks destabilization (Fukushima et al. 2014); blocks destabilization and enhancement (Yu et al. 2016)
Autophagy				
Inhibition (spautin-1)	1	Rat	AFC	Partially blocks destabilization (Shehata et al. 2018)
Induction (tat-beclin1)	1	Rat	AFC	Enhance destabilization (Shehata et al. 2018)
PP1				
Inhibitor (e.g., okadaic acid)	2	Mouse	CPP	Blocks destabilization (Yu et al. 2016)
CaMKII				
Inhibitor (Myr-AIP)	1	Rat	CFC	Blocks destabilization (Jarome et al. 2016)
Hippocampus				
Ubiquitin-proteasome system				
Proteasome inhibition (e.g., β -lactacystin)	6	Rat; mouse	CFC; MWM; OR	Blocks destabilization (Lee et al. 2008; Choi et al. 2010; Da Silva et al. 2013; Sol Fustiñana et al. 2014; Furini et al. 2015); blocks destabilization and enhancement (Lee 2008)
CB1 receptors				
Antagonism (SR141716)	3	Rat; mouse	CFC; MWM	Blocks destabilization (Suzuki et al. 2008; Kim et al. 2011; Lee et al. 2019)
Dopaminergic receptors				
D1 antagonism (SCH23390)	1	Rat	OR	Blocks destabilization (Rossato et al. 2015b)
GABA receptors				
GABAa agonism (muscimol)	2	Rat	MWM	Impairs retrieval (Rossato et al. 2015a)
mGluRs				
mGluR1 agonism (3HPG)	1	Rat	CFC	No effect (Lee and Flavell 2014)
LVGCCs				
Antagonism (verapamil)	2	Mouse	CFC; MWM	Blocks destabilization (Suzuki et al. 2008; Kim et al. 2011)
Na⁺ channels				
Blockade (tetrodotoxin)	1	Rat	CFC	Blocks destabilization (Lee and Flavell 2014)
Perirhinal cortex				
Cholinergic receptors				
M1 antagonism (pirenzepine)	1	Rat	OR	Blocks destabilization (Stiver et al. 2017)
M1 agonism (CDD-0102A)	1	Rat	OR	Enhances destabilization (Stiver et al. 2017)
Muscarinic antagonism (scopolamine)	1	Rat	OR	Blocks destabilization (Stiver et al. 2017)
Nonselective agonism (carbachol)	2	Rat	OR	Enhances destabilization (Stiver et al. 2017)
Ubiquitin-proteasome system				
Proteasome inhibition (β -lactone)	1	Rat	OR	Blocks destabilization (Stiver et al. 2017)
IP3Rs				
Inhibition (e.g., xestospongic C)	2	Rat	OR	Blocks destabilization (Stiver et al. 2017)
GABA receptors				
GABAa agonism (muscimol)	1	Rat	OR	Impair retrieval (Balderas et al. 2013)

Continued

Table 3. *Continued*

Target	Number of experiments	Species	Task	Main outcome (experiments)
Nucleus accumbens core				
Ubiquitin-proteasome system Proteasome inhibition (e.g., MG132)	2	Rat	CPP	Blocks destabilization (Ren et al. 2013)
Nucleus accumbens shell				
Ubiquitin-proteasome system Proteasome inhibition (β -lactacystin)	1	Rat	CPP	No effect (Ren et al. 2013)
Medial prefrontal cortex				
GABA receptors GABA _A agonism (muscimol)	2	Rat	MWM	Blocks destabilization (Rossato et al. 2015a)
Ventral tegmental area				
Dopaminergic receptors D2 antagonism (sulpiride)	1	Rat	AFC	Blocks destabilization (Reichelt et al. 2013)
Systemic injection				
NMDA Partial agonism (D-cycloserine)	6	Rat	CFC	Enhances destabilization (Bustos et al. 2010; Ortiz et al. 2014; Espejo et al. 2016) and no effect (Ortiz et al. 2014)
Ubiquitin-proteasome system Proteasome inhibition (β -lactacystin)	1	<i>Aplysia</i>	BS	Blocks destabilization (Lee et al. 2012)
Cholinergic receptors M1 antagonism (dicyclomine)	1	Rat	OR	Blocks destabilization (Stiver et al. 2017)
M2 antagonism (AF-DX 116)	1	Rat	OR	Blocks destabilization (Stiver et al. 2017)
Muscarinic antagonism (scopolamine)	1	Rat	OR	Blocks destabilization (Stiver et al. 2017)
Muscarinic agonism (oxotremorine)	1	Rat	OR	Enhances destabilization (Stiver et al. 2017)
CB1 receptors Antagonism (SR141716)	1	Mouse	CFC	Blocks destabilization (Suzuki et al. 2008)
Nitric oxide Inhibition (e.g., 7-nitroindazole)	5	Snail; rat	AFC; CFC	Blocks destabilization (Balaban et al. 2014; Bal et al. 2017)
Scavenger (carboxy-PTIO)	1	Snail	CFC	Blocks destabilization (Balaban et al. 2014)
Dopaminergic receptors D1 agonism (SKF38393)	1	Rat	AFC	No effect (Flavell and Lee 2019)
D1 blockade (modafinil)	1	Rat	AFC	No effect (Flavell and Lee 2019)
Calcineurin Inhibition (e.g., FK-506)	2	Mouse	IA	Blocks destabilization and enhancement (Fukushima et al. 2014)
LVGCCs Antagonism (e.g., nimodipine)	3	Rat; mouse	CFC	Blocks destabilization (Suzuki et al. 2008; De Oliveira Alvares et al. 2013; Haubrich et al. 2015)
H3 receptors Antagonism (thiopramide)	1	Mouse	CFC	Blocks destabilization (Charlier and Tirelli 2011)
β-Adrenergic receptors Antagonism (propranolol)	1	Mouse	CFC	Blocks destabilization (Lim et al. 2018)

(AC) Appetitive conditioning, (AFC) auditory fear conditioning, (AMPA) α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, (BS) behavioral sensitization, (CaMKII) calcium/calmodulin-dependent protein kinase type II, (CB1) endocannabinoid receptor type 1, (CFC) contextual fear conditioning, (CPP) conditioned place preference, (CTA) conditioned taste aversion, (GABA) γ -aminobutyric acid, (H3) histamine H3 receptors, (IA) inhibitory avoidance, (IP3Rs) inositol trisphosphate receptors, (LVGCCs) L-type voltage-gated calcium channels, (MWM) Morris water maze, (NMDA) N-methyl D-aspartate receptor, (OR) object recognition, (PP1) protein phosphatase 1.

agreement with behavioral experiments where a short nonreinforced contextual re-exposure causes reconsolidation, whereas a longer re-exposure duration leads to extinction. More specifically, when Hebbian plasticity is blocked to simulate protein synthesis inhibition during memory reactivation, a decrease in memory retrieval is observed with short re-exposure durations, while at longer durations memory decrease occurs in control conditions, but not when protein synthesis is blocked (Suzuki et al. 2004). In the case of the second model, our results also match the experimental observation that some degree of mismatch between training and re-exposure (Pedreira et al. 2004; Sevenster et al. 2014) or a minimum duration of re-exposure (Suzuki et al. 2004; Bustos et al. 2009; Alfei et al. 2015) is necessary for reconsolidation to occur.

Both models are based on abstract networks whose limitations should be noted, such as the absence of realistic topology, the use of nonspiking neurons, and an abstract concept of time. The results in both cases also critically depend on the assumption that mismatch between representations increases with greater durations of contextual re-exposure, as postulated by Osan et al. (2011). Moreover, not every experimental result was equally mimicked by both frameworks; in particular, our second model was more successful in suggesting a requirement of mismatch for reconsolidation to occur (Pedreira et al. 2004; Morris et al. 2006) and the existence of a “limbo” transition state between reconsolidation and extinction (Flavell and Lee 2013; Merlo et al. 2014; Cassini et al. 2017; Franzen et al. 2019). Nevertheless, bearing in

Table 4. Role of labilization mechanisms in synaptic downscaling

Mechanism	Interference method	Excitation mechanism	Biological model	Effect on downscaling
NMDA receptors	1. APV 2. APV/ifenprodil 3. APV 4. APV	1. Optogenetics (ChR2) 2. Light-gated GluR6 stimulation 3. Bicuculline 4. Bicuculline	1. Mouse organotypic hipp. cultures. 2. Rat primary hipp. cultures. 3. Rodent primary cortical cultures and hipp. slices 4. Rat primary hipp. cultures	1. No effect (Goold and Nicoll 2010) 2. Inhibition of AMPAR single-synapse downscaling (Hou et al. 2011) 3. Inhibition of AMPAR downscaling (Qiu et al. 2012) 4. Inhibition of downscaling (Lee and Chung 2014)
Ubiquitin-proteasome system				
Proteasome function	Lactacystin	Bicuculline	Rat primary hipp. cultures	Inhibition of downscaling (Jakawich et al. 2010)
Nedd4 (E3 ubiquitin ligase)	1. N.A. 2. Nedd4-1 shRNA hairpin expression 3. Lentiviral-induced expression of Nedd4-2	1. Light-gated GluR6 stimulation 2. Bicuculline 3. PicROTOXIN	1. Rat primary hipp. cultures. 2. Rat primary hipp. and cortical cultures 3. Primary hipp. and cortical cultures of Fmr1 KO mice	1. Chronic synaptic stimulation increases Nedd4-1 expression (Hou et al. 2011) 2. Inhibition of downscaling (Scudder et al. 2014) 3. Rescue of downscaling in Fmr1 KO neurons (Lee et al. 2018)
AMPA receptors				
GluA2 expression	Genetic deletion	Optogenetics (ChR2)	Mouse organotypic hipp. cultures	Inhibition of AMPAR downscaling (Goold and Nicoll 2010)
MeCP2 (regulates GluA2 expression)	1. Genetic deletion or shRNA expression 2. Genetic deletion	1. Bicuculline 2. Bicuculline	1. Rat/mouse cortical primary cultures and hipp. slices 2. Mice hipp. primary cultures	1. Inhibition of downscaling (Qiu et al. 2012) 2. Inhibition of AMPAR downscaling (Xu and Pozzo-Miller 2017)
Arc/Arg3.1 (Induces AMPAR endocytosis)	Genetic deletion	Bicuculline	Rat/mouse hippocampal and cortical neurons	Inhibition of AMPAR downscaling (Shepherd et al. 2006)
Calcineurin	1. FK-506 2. N.A.	1. Light-gated glut. receptor (GluR6) 2. Bicuculline	1. Rat primary hipp. cultures 2. Mouse cortical primary cultures	1. No effect on AMPAR downscaling (Hou et al. 2011) 2. Chronic stimulation reduces calcineurin levels (Diering et al. 2014)
LVGCCs	1. Nifedipine 2. Nimodipine 3. Nifedipine 4. Nifedipine	1. Optogenetics (ChR2) 2. Bicuculline 3. Bicuculline 4. Optogenetics (ChR2)	1. Mouse organotypic hipp. cultures 2. Rat primary cortical cultures 3. Rat primary hipp. cultures 4. Rat hipp. slice culture	1. Inhibition of AMPAR and NMDAR downscaling (Goold and Nicoll 2010) 2. Inhibition of AMPAR downscaling (Siddoway et al. 2013) 3. Inhibition of downscaling (Lee and Chung 2014) 4. Inhibition of dendritic spine downscaling (Mendez et al. 2018)
PP1	Viral vector transfection	Bicuculline	Rat primary cortical cultures	Inhibition of AMPAR downscaling (Siddoway et al. 2013)
CaMKII	1. myr-CaMKIIN or myr-AIP 2. KN62	1. Optogenetics (ChR2) 2. Light-gated GluR6 stimulation	1. Mouse organotypic hipp. cultures 2. Rat primary hipp. cultures	1. CaMKII expression inhibits AMPAR but not NMDAR downscaling. Inhibition of CaMKII has no effect on AMPAR or NMDAR downscaling (Goold and Nicoll 2010) 2. No effect on downscaling (Hou et al. 2011)
Na⁺ channels	1. Tetrodotoxin 2. Tetrodotoxin 3. Tetrodotoxin 4. Tetrodotoxin	1. Bicuculline 2. Optogenetics (ChR2) 3. Light-gated GluR6 stimulation 4. Optogenetics (ChR2)	1. Rat auditory cortex slices 2. Mouse organotypic hipp. cultures 3. Rat primary hipp. cultures 4. Rat hipp. slice culture	1. Inhibition of bicuculline-induced downscaling (Zhang et al. 2009) 2. No effect on optogenetically induced AMPAR or NMDAR downscaling (Goold and Nicoll 2010) 3. Inhibition of AMPAR downscaling (Hou et al. 2011) 4. No effect on dendritic spine downscaling (Mendez et al. 2018)
Protein synthesis	1. Cycloheximide/DRB/anisomycin 2. Anisomycin	1. Optogenetics (ChR2) 2. Light-gated GluR6 stimulation	1. Mouse organotypic hippocampal slice cultures 2. Rat primary hipp. cultures	1. Inhibition of AMPAR, but not NMDAR, optogenetically induced downscaling (Goold and Nicoll 2010) 2. No effect on AMPAR downscaling (Hou et al. 2011)

Columns summarize the main findings, models, and intervention methods of articles investigating the role of memory destabilization components in synaptic downscaling. (AMPA) α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, (APV) D(-)-2-amino-5-phosphonopentanoic acid, (CaMKII) calcium/calmodulin-dependent protein kinase type II, (ChR2) channelrhodopsin-2, (UV) ultraviolet, (DRB) 5,6-dichloro-1- β -D-ribofuranose-2,3,5-trisubstituted benzimidazole, (hipp.) hippocampal, (KO) knockout, (LVGCC) L-type voltage-gated calcium channels, (MeCP2) methyl-CpG binding protein 2, (NMDA) N-methyl D-aspartate receptor, (PP1) protein phosphatase 1, (TTX) tetrodotoxin.

mind the constraints inherent to the models, our results suggest that destabilization after contextual re-exposure could feasibly emerge as a byproduct of synaptic scaling-like homeostatic plasticity.

The hypothesis that homeostatic plasticity plays a role in memory phenomena such as memory consolidation and recall has been addressed in other computational models (Tetzlaff et al. 2011, 2013; Zenke et al. 2015). Tetzlaff et al. (2013) proposed a dynamic neural circuit where a combination of Hebbian plasticity and synaptic scaling determines memory maintenance during synaptic reactivation. In this setup, memories with weights that surpass a certain threshold are consolidated by spontaneous reactivation, while others decay over time. Scaling in this model also accounted for the destabilization effects of new learning after recall of a motor memory (Walker et al. 2003; but see Hardwicke et al. 2016 for contradictory results): If retrieval was followed by learning of a partially overlapping pattern, the weights underlying the first memory were disrupted. This effect is analogous to what is found in our second model, but was observed in the absence of Hebbian plasticity blockade in that case.

Molecular mechanisms involved in synaptic downscaling and labilization

Although homeostatic plasticity provides an elegant explanation for the dependence of destabilization on memory recall, this is still a speculative hypothesis. Both computational models, after all, are abstract connectionist networks that should be considered heuristic guides to generate conceptual ideas, rather than proof-of-principle of a theory. We thus attempted to investigate whether there is experimental evidence to support this connection by systematically reviewing the experimental literature. We found that several molecular mechanisms are involved in both memory destabilization and synaptic scaling, suggesting shared requirements for the induction of both phenomena. Studies of destabilization generally test whether pharmacological agents can prevent the reconsolidation-blocking effects of drugs such as PSIs in behavioral tasks; thus, detecting relevant studies is relatively straightforward. The literature on homeostatic plasticity, on the other hand, is more varied, using different models to study synaptic responses to changes in firing rate and/or network activity. Thus, it is not always clear whether phenomena are comparable across diverse models and preparations, even within the specific field of synaptic downscaling.

Investigations of labilization mechanisms typically use PSIs such as anisomycin to block reconsolidation, indicating that they do not prevent memory destabilization. Thus, a requirement for a putative synaptic mechanism of destabilization is that it should not critically depend on protein synthesis—or at least should be less reliant on it than Hebbian plasticity. For synaptic downscaling, different effects of PSIs have been observed. Goold and Nicoll (2010) demonstrated that cycloheximide and anisomycin blocked the AMPAR, but not the NMDAR component of synaptic downscaling after chronic optogenetic stimulation. On the other hand, Hou et al. (2011) showed that anisomycin did not interfere with GluA1 reduction induced by light-gated GluR6 stimulation in hippocampal cultures. Additionally, a recent study performed a comprehensive mapping of synaptic proteins regulated by synaptic scaling, showing that most synaptic proteins exhibited a decrease in synthesis during bicuculline-induced downscaling (Dörbaum et al. 2020). Thus, the requirement of protein synthesis for downscaling seems to differ across models; nevertheless, at least in some instances, this type of plasticity seems to occur in spite of protein synthesis inhibition.

The majority of mechanisms implicated in destabilization have been identified in studies of fear conditioning, and concern

signaling via cell surface receptors. These include GluN2B-containing NMDARs (Ben Mamou et al. 2006; Merlo et al. 2015; Nakayama et al. 2016; Yu et al. 2016) and LVGCCs (Suzuki et al. 2008; Kim et al. 2011; De Oliveira Alvares et al. 2013; Haubrich et al. 2015), as well as the internalization of GluA2-containing AMPARs (Hong et al. 2013; Shehata et al. 2018). There is evidence that each of these cell surface mechanisms is important for synaptic downscaling. NMDARs are necessary for synaptic downscaling induced by bicuculline in hippocampal slice cultures (Qiu et al. 2012) and dissociated hippocampal neurons (Lee and Chung 2014), although Goold and Nicoll (2010) showed that APV treatment did not inhibit optogenetically induced downscaling in hippocampal cultures, suggesting that the role of NMDARs is associated with glutamatergic-driven network activation. AMPARs are a primary mechanism for expression of homeostatic plasticity through alterations in their number, composition, and biophysical properties (Diering and Hugarir 2018). Supporting evidence includes the observations that synaptic scaling relies on a switch between GluA2-containing and GluA2-lacking AMPARs (Chowdhury and Hell 2018), and that optogenetically induced AMPAR downscaling does not occur in GluA2-deficient mice (Goold and Nicoll 2010). Finally, LVGCCs have been shown to be necessary for AMPAR and NMDAR downscaling, both after optogenetic stimulation (Goold and Nicoll 2010) and after prolonged stimulation with AMPA (Lin et al. 2000) or bicuculline (Lee and Chung 2014).

Intracellularly, the primary mechanism of destabilization is protein degradation by the UPS, as evidenced by the effect of the proteasome inhibitor lactacystin on destabilization when injected into the hippocampus (Lee 2008; Lee et al. 2008; Choi et al. 2010; Da Silva et al. 2013; Lee and Chung 2014), amygdala (Jarome et al. 2011; Fukushima et al. 2014), perirhinal cortex (Stiver et al. 2017), or nucleus accumbens (Ren et al. 2013). Lactacystin also blocks slow homeostatic changes caused by chronic treatment with bicuculline in cultured hippocampal neurons (Jakawich et al. 2010). However, most of the evidence on UPS involvement in synaptic downscaling comes from work with Nedd4 (E3 ubiquitin ligase enzyme), which targets proteins for ubiquitination. Hou et al. (2011) demonstrated that Nedd4 expression increases after chronic neuronal stimulation to mediate AMPAR ubiquitination. Other studies showed the involvement of Nedd4 in synaptic downscaling by knocking down its endogenous protein levels (Scudder et al. 2014) and by expressing Nedd4-2, an ubiquitin ligase from the same family, to restore synaptic downscaling (Lee et al. 2018).

A synaptic model for memory destabilization proposed by Finnie and Nader (2012) proposes that reactivation allows calcium influx at the synapse through LVGCCs, with second messengers such as protein phosphatases altering neuronal excitability by modulating NMDARs and AMPARs at the synapse through processes such as GluA2 endocytosis. One would expect that, if this hypothesis holds true, the calcium influx promoted by LVGCCs during memory reactivation might trigger synaptic downscaling pathways that use molecules such as Arc/Arg3 (Chowdhury et al. 2006) and MeCP2 (Qiu et al. 2012), known to regulate AMPA receptor trafficking in models of homeostatic plasticity.

Theoretical and experimental evidence for a role of homeostatic plasticity in destabilization

Theories postulating a role for homeostatic plasticity in memory need to take into account that homeostatic processes such as synaptic scaling operate in a timescale of hours or days (Zenke and Gerstner 2017). Thus, the latency for a memory to decay after reconsolidation blockade – around 4 h after protein synthesis blockade (Nader et al. 2000)—could be related to the time required by homeostatic plasticity to occur (Ibata et al. 2008). In fact, the existence of reconsolidation-extinction transitions seems to imply

that most synaptic decay occurs after reactivation—as if destabilization occurred within reactivation session, PSIs and other amnesic agents would be expected to cause amnesia in extinction conditions. The fact that postreactivation intrahippocampal infusions are able to impair destabilization (Suzuki et al. 2008) also indicates that mechanisms of memory destabilization are active in this structure for some time after the memory reactivation session.

On the other hand, memory destabilization is triggered by the reactivation session itself, which typically lasts only a few minutes. This is in contrast to the protocols used to induce synaptic scaling, which usually require hours of continued overstimulation *in vitro*. That said, Mendez et al. (2018) showed changes reminiscent of homeostatic plasticity after 10 min of *in vivo* stimulation, while Moulin et al. (2019) observed similar effects with low-frequency stimulation over a 24-h period. Thus, it is possible that *in vivo* scaling-like homeostatic plasticity could result from periodic reactivations of memory engrams occurring during the post-re-exposure period (Wittenberg et al. 2002). Nevertheless, one cannot rule out the possibility that induction of memory destabilization might be initiated by activation of faster forms of homeostatic plasticity, such as those mediated by CB1 receptors (Song et al. 2015), either during or shortly after re-exposure.

The idea that homeostatic plasticity can play a role in memory processes is not new; however, it has not been explored in detail, as shown by a systematic review of the literature linking both processes (for full results, see the Materials and Methods; [Supplemental Table S2](#)). While there are computational models suggesting that homeostatic plasticity is related to memory phenomena (Tetzlaff et al. 2013; de Camargo et al. 2018; Susman et al. 2019), experimental evidence for this relationship is still scarce. Perhaps the most direct attempt at connecting both processes comes from Mendez et al. (2018), who used optogenetically induced spike trains in hippocampal granule cells of mice to trigger *in vivo* homeostatic changes. This protocol decreased excitatory synaptic density while increasing inhibitory synapses through an LVGCC-dependent mechanism. When these spike trains were induced during an extinction session, lower freezing activity was observed in a subsequent test. These results are in line with the view that, at least in some cases, extinction might have a destabilization component occurring along with the learning of a new association, as suggested by previous work (Barad 2006; Almeida-Corrêa and Amaral 2014; Popik et al. 2020) and by our own model results (see Fig. 2D).

Another set of views postulating a role for basic plasticity mechanisms in memory destabilization comes from the observation that reconsolidation-like effects are not restricted to learning paradigms in vertebrates, but are also observed in more reductionist preparations. Studies of the gill-and-siphon withdrawal reflex in *Aplysia* showed that nonassociative long-term facilitation was reversed when heterosynaptic reactivation occurred in the presence of rapamycin, an inhibitor of ribosomal protein synthesis (Hu and Schacher 2014). For associative long-term facilitation, on the other hand, destabilization required homosynaptic reactivation (Hu and Schacher 2015). Reconsolidation-like phenomena were also observed in spinal cord pain processing circuits of mice injected with capsaicin to induce mechanical hyperalgesia, with anisomycin reducing hyperalgesia only when paired with another capsaicin injection (Bonin and De Koninck 2014). This prompted the investigators to postulate that such effects could be due to homeostatic plasticity mechanisms, and that reconsolidation might not be best conceptualized as a behavioral phenomenon (Bonin and De Koninck 2015).

Conceptual gaps and future directions

Although the destabilization-reconsolidation process has typically been hypothesized to serve a high-level cognitive function in

memory updating (Lee 2009; Exton-McGuinness et al. 2015; Fernández et al. 2016), it is important to recognize that its existence does not imply a functional role (Dudai 2004). Nevertheless, the accumulation of evidence that the destabilization of memories occurs preferentially under conditions of memory updating (Lee 2009; Rodríguez-Ortiz and Bermúdez-Rattoni 2017) strongly supports a cognitively functional process. This is in contrast to the more basic compensatory nature of homeostatic plasticity (Siddoway et al. 2014), which is usually seen as a low-level property of neuronal physiology. That said, categorization of mechanisms as high-level/cognitive versus low-level/physiological may represent an artificial dichotomy, as evolution can lead to repurposing of traits or mechanisms for different purposes than those for which they have evolved (Lloyd and Gould 2017).

The fact that many cellular mechanisms that are functionally implicated in destabilization have also been shown to be important for synaptic downscaling (at least under certain circumstances) opens up the possibility that destabilization might be an emergent property of homeostatic plasticity that arises from patterns of neuronal activity induced by memory reactivation. Moreover, if homeostasis is detrimental to the previously adjusted synaptic weights that encode a memory in a neuronal network, this would justify the requirement of a reconsolidation process to ensure preservation of the memory trace. This adds to the argument that destabilization-reconsolidation is a universal property of memories (Lee 2009) as in this case it would emerge from a fundamental property of neuronal function.

The results of our second model are consistent with downscaling being preferentially engaged under conditions of conflicting information or mismatch during retrieval that would be expected under memory-updating conditions. In this simple attractor network, this happens as a natural consequence of noisier retrieval when patterns diverge between training and re-exposure. Such a view must be balanced, however, against the evidence for the involvement of prediction error signals in destabilization (Reichelt et al. 2013; Das et al. 2015; Exton-McGuinness et al. 2015; Sinclair and Barense 2019). Detection of mismatch/prediction error within memory-encoding areas could thus be implemented both by novelty signals sent by other brain structures (such as the ventral tegmental area) and by internal network dynamics (as occurs in our model). Support for this view comes from the asymmetry in the requirements of destabilization mechanisms: While dopamine D1 receptors are required for fear memory destabilization, for instance (Merlo et al. 2015; Flavell and Lee 2019), their activation alone is not capable of inducing it (Flavell and Lee 2019). Thus, it is possible that multiple processes are necessary for successful memory destabilization, including an interaction between dopaminergic signaling and local network plasticity.

Many other questions still need to be addressed before a role for homeostatic plasticity in memory destabilization can be asserted. Classic destabilization studies with reversal of reconsolidation blockade could be used to study whether canonical molecular components of homeostatic plasticity, such as the immediate-early genes *Homer1a* (Hu et al. 2010) and *Arc/Arg3.1* (Gao et al. 2010) are involved in destabilization. Another molecule involved in synaptic scaling that has not been implicated in destabilization is brain-derived neurotrophic factor (BDNF) (Reimers et al. 2014). Interestingly, even though BDNF has been extensively implicated in memory consolidation (Bekinschtein et al. 2014), it has been suggested not to be as important in reconsolidation (Lee et al. 2004; Lee 2008). This could be due to the fact that, if inhibiting BDNF function affects not only Hebbian plasticity but destabilization mechanisms as well, it could lead the net effect of this intervention on a reactivated memory to be neutral.

Nevertheless, evidence obtained by investigating the role of synaptic scaling mechanisms in memory destabilization

paradigms will still be correlative. For a causal link, experiments that can induce or inhibit homeostatic plasticity in neurons related to a fear memory engram through artificial stimulation can provide more direct evidence. Particularly, if methods for optogenetically induced homeostatic plasticity in vivo such as that used by Mendez et al. (2018) indeed trigger destabilization, pairing this stimulus with reconsolidation blockers such as anisomycin should lead to a reduced fear response in animals.

Even with these more sophisticated studies, however, one still runs into the question of specificity—after all, it is unlikely that the effects of neuronal overstimulation are limited to a particular plasticity process (Keck et al. 2017b). Nevertheless, the notion of a “particular plasticity process” might be in itself a paradigm in need of revision, as the division between well-delineated, individual classes of plasticity is more of an epistemic convention than a fact of nature. With a plethora of processes in distinct models and preparations falling within the umbrella of homeostatic plasticity, the most useful way to classify them in order to advance research is not obvious, as both overgeneralization and overspecificity can hamper progress (Fox and Stryker 2017). Combining advances in this field with those in memory research and its own distinct paradigms presents a further challenge that can only be overcome by better communication between experimentalists and theorists on both sides.

Materials and Methods

Computational models

Model 1—adaptation of Osan et al. (2011)

The network consisted of a circuit with 100 units connected in an all-to-all manner. Each neuron i in the attractor network had a neuronal activity u_i that varied continuously from 0 to 1 and changed according to

$$\tau \frac{du_i}{dt} = -u_i + \frac{1}{2} \left[1 + \tanh \left(\sum_{j=1}^N w_{ij} u_j + I_i \right) \right],$$

where τ is the neural time constant, which is a combination of properties that denote decay or persistent activity outside the task, and w_{ij} represents the synaptic weight associated with a particular connection. I_i represents the input provided to the memory network by sensory stimulus from the environment and internal information. The feedback from the memory network to the cue input was not explicitly modeled; nevertheless, it is assumed to be necessary to account for changes in the animal's internal representation according to learned experience.

For this model, we used a synaptic weight matrix W , where each synapse has a weight w_{ij} that varies continuously from -1 to 1 . Weight changes (ΔW) in the model can be described as

$$\Delta W = -W + HLP + SC,$$

where HLP is the Hebbian learning plasticity term and SC is the synaptic scaling term. Both terms are matrices that are dependent on the steady-state neuronal activation reached after cue presentation. Weight values that fall outside the weight range after updating are truncated at 1 or -1 .

The Hebbian learning plasticity term can be described as

$$HLP = S(\bar{u}^T \times \bar{u}) - S[(1 - \bar{u})^T \times \bar{u}],$$

with the notation $B \times A$ denoting connections from A to B . S is a factor that represents the biochemical requirements of Hebbian plasticity and $\bar{u}$ is a vector $[\bar{u} = (u_1, u_2, u_3, \dots, u_N)]$ that represents the stable state of network activity. Thus, when two neurons fire to-

gether, their connections are reinforced. If a presynaptic neuron fires while the postsynaptic one is inactive, an inhibitory connection is created. Although a realistic implementation of the rule would require modeling the participation of inhibitory interneurons in the process, this simplification allows attractor functioning to occur while eliminating the artificial negative activations and “mirror attractors” found in the original Hopfield graded activity formulation (Hopfield 1984). Blockade of Hebbian plasticity to model the use of PSIs was achieved by setting S to 0 .

The synaptic scaling term can be described as

$$SC = \kappa^{-1}(u_t - u_i) \times (w_{ij})^2,$$

where κ is the ratio between Hebbian plasticity and scaling and u_t is the desired homeostatic activity for the network. Therefore, synaptic scaling adjusts connection weights on the basis of a comparison between a neuron's output activity u_i against a desired target activity u_t . When active, this term influences all excitatory connections w_{ij} from presynaptic neurons i to postsynaptic neuron j .

Learning was induced by providing a noisy input equals to $I_i^{learn} \times \vartheta$ for neuronal activation and $-I_i^{learn} \times \vartheta$ for neuronal inhibition. The input was modulated by a noise term ϑ from a uniform distribution $[0.9, 1.1]$. In the training session, the neurons representing context and aversive neurons were activated while other neurons were inhibited. In the nonreinforced re-exposure session, the cue input is given by

$$I = (I_3 - I_2) \times f(t) + I_2,$$

where vectors I_2 and I_3 represent the cue inputs for the training and extinction pattern, respectively, and t represents re-exposure duration, varying from $t_{min} = 0$ to $t_{max} = 10$. For the encoding of re-exposure time in the input cues, we used a sigmoid function defined as

$$f(t) = \frac{1}{1 + \exp\left(\frac{t_{max} - t}{2}\right)}.$$

Retrieval tests consisted of activating the neurons that represent the context while maintaining the input to other units at 0 . After the input was given, the pattern to which the network evolved determined the degree of freezing in the test session, with retrieval of the training pattern resulting in 90% freezing and other patterns resulting in 10% freezing. For pattern determination, we compared the current activity of each neuron with that of the same neuron in the training pattern. For this binary comparison, we set an activity threshold at $ui = 0.75$; thus, neurons with $u_i \geq 0.75$ were considered active, while the ones with values below this threshold were inactive. A neuron i was deemed similar when it was active or inactive both at the end of the retrieval session and in the training pattern. The fear memory was considered to be successfully retrieved when it had >95% similarity with the training pattern in this classification. We performed 100 simulations with different initial conditions in the retrieval session and obtained the mean $\pm$ SEM freezing behavior for each re-exposure time. All model simulations were developed using Matlab R2018a.

To check the robustness of our results to different parameters, we varied the value of S during training or re-exposure and the value of κ during re-exposure. S during re-exposure was varied from 0 to 1 with steps of 0.025 in Supplemental Figure S1. κ during re-exposure was varied from 0 to 4 with steps of 0.2 in Supplemental Figure S2. S during training was varied from 0 to 2 with steps of 0.1 in Supplemental Figure S3.

If not stated otherwise, we used the parameters described in Table 5. Code for the simulations is available at https://github.com/Felipe-espinelli/scaling_destabilization_models.

Model 2—adaptation of Auth et al. (2020)

The model was composed of an input area and a memory network with 36 and 900 neurons, respectively. The memory network was a

Table 5. Model parameters used by the attractor network adapted from Osan et al. (2011)

Variable	Description	Value
S	Biochemical requirements for Hebbian synaptic plasticity	0.8
u_i	Desired target activity of synaptic scaling	0
κ	Ratio between Hebbian plasticity and scaling	1.2
N	Number of neurons	100
τ	Neural time constant	1
I_i^{learn}	Learning input strength	8
I_i^{ret}	Retrieval input strength	8

grid of 30×30 neurons organized in a toroidal topology; each of them connected with four random neurons in the input area and with their nearest neighbors in the memory area within a radius of four neurons. An inhibitory unit represented a population of inhibitory neurons connected bidirectionally in an all-to-all manner with neurons in the memory area.

For each excitatory neuron j in the memory area ($j \in \{1, \dots, N^M\}$), the membrane potential u_j was determined by the following differential equation:

$$\frac{du_j}{dt} = -\frac{u_j}{\tau} + R \left(\sum_i^N w_{j,i}^{rec} F_i - w_{j,inh} F_{inh} + \sum_k^N w_{j,k}^{ff} I_k \right).$$

Afterward, the firing rate F_j of each neuron j was dependent on the membrane potential u_j as follows:

$$F_j(u_j) = \frac{\alpha}{1 + \exp[\beta(\varepsilon - u_j)]}.$$

Initial membrane potential and firing rate were drawn from a normal random distribution with a mean of 0 and a variance of 1.

The inhibitory unit updated the membrane potential u_{inh} and converted it into a firing rate F_{inh} as described below:

$$\frac{du_{inh}}{dt} = -\frac{u_{inh}}{\tau_{inh}} + R_{inh} \times \sum_i^N w_{inh,i} F_i$$

and

$$F_{inh}(u_{inh}) = \frac{\alpha}{1 + \exp[\beta(\varepsilon - u_{inh})]}.$$

Excitatory feed-forward and recurrent connections were plastic, while others remained constant. These weight changes were dependent on a combination of Hebbian synaptic plasticity and synaptic scaling. The feed-forward synaptic weight $w_{j,k}^{ff}$, formed by connecting an excitatory input neuron k ($k \in \{1, \dots, N^I\}$) to a memory neuron j ($j \in \{1, \dots, N^M\}$), was initially drawn from a uniform distribution $[0, 0.7 \times \hat{w}^{ff}]$ with weight changes described as

$$\frac{dw_{j,k}^{ff}}{dt} = \mu [F_j I_k + (\kappa^{ff})^{-1} \times (F^T - F_j) \times (w_{j,k}^{ff})^2] \times c_{j,k}^{ff},$$

where $c_{j,k}^{ff}$ is a feed-forward connectivity matrix, with each unit equal to 1 if the connection exists or 0 if it does not.

Recurrent synaptic weights $w_{j,i}^{rec}$, formed by connecting an excitatory memory neuron i ($i \in \{1, \dots, N^M\}$) to a memory neuron j ($j \in \{1, \dots, N^M\}$), were initially set as $0.25 \times \hat{w}^{rec}$ with weight changes described as

$$\frac{dw_{j,i}^{rec}}{dt} = \mu [F_j F_i + (\kappa^{rec})^{-1} \times (F^T - F_j) \times (w_{j,i}^{rec})^2] \times c_{j,i}^{rec}.$$

where $c_{j,i}^{rec}$ is a feed-forward connectivity matrix, with each unit equal to 1 if the connection exists or 0 if it does not.

A training session was simulated by activating 18 input area neurons with an input rate of 130 Hz, while the remaining ones received 0 Hz. This activation was performed in 10 periods of 5 sec each, with a 1-sec rest period between them. For nonreinforced re-exposure, we also used 10 periods with 5 sec of activation and 1 sec of rest. For the shortest possible reactivation ($t=0$), the input pattern in the re-exposure session was identical to the training cue. Progressively longer re-exposure durations were simulated by substituting input neurons from the training cue by those representing the extinction pattern, two at a time. Thus, the longest possible re-exposure ($t=18$) corresponds to the full extinction pattern, while for intermediate values t corresponds to the number of divergent neurons between the training and re-exposure patterns. As in the training session, activated neurons were stimulated at 130 Hz while the others were set at 0 Hz.

All model simulations were developed using Python 3.7, with the code available at https://github.com/Felippe-espinelli/scaling_destabilization_models. Equations were solved using the Euler method with a time step of 0.005 sec. For each time step, the network was updated in the following order, (1) membrane potential of each neuron in memory area, (2) membrane potential of inhibitory unit, (3) firing rate of memory area, (4) firing rate of inhibitory unit, (5) recurrent weight, and (6) feed-forward weight. All model parameters are described in Table 6.

Cluster analysis

Each consolidated memory was represented by the network as a cluster of neurons recurrently connected by strengthened memory weights. Memory clusters after the training session were defined as neurons with a mean postsynaptic weight for all their recurrent connections above a threshold ϕ , set to 40 for the main simulations. As random connections can occasionally rise above this threshold, we only defined a cluster if a minimum amount ρ of 30 neurons was above the threshold. When a cluster was identified, the mean connection weight between neurons belonging to the cluster was used as a measure of memory strength. If no clusters were identified, memory strength was defined as the global mean weight of the network.

To identify modifications in consolidated clusters and formation of new ones after re-exposure, we initially identified the training session cluster. Neurons that had a recurrent connection with

Table 6. Model parameters used in the adaptation of Auth et al. (2020)

Variable	Description	Value
τ	Membrane time constant (memory area)	0.01
R	Membrane resistance (memory area)	1/11
N^M	Number of neurons in memory area	900
N^I	Number of neurons in input area	36
I_k	Input rate	{0,130}
α	Maximum firing rate	100
β	Sigmoid steepness	0.05
ε	Sigmoid inflexion point	130
μ	Plasticity time constant	1/15
F^T	Target firing rate	0.1
κ^{rec}	Scaling time constant (recurrent)	60
κ^{ff}	Scaling time constant (feed-forward)	720
τ_{inh}	Membrane time constant (inhibitory unit)	0.02
R_{inh}	Membrane resistance (inhibitory unit)	1
$w_{inh,i}$	Synaptic weight: memory area to inhibitory unit	0.6
$w_{j,inh}$	Synaptic weight: inhibitory unit to memory area	6000
$\hat{w}^{rec}$	Initial recurrent synaptic weights	$\sqrt{\frac{\kappa^{rec} \alpha^2}{\alpha - F^T}}$
$\hat{w}^{ff}$	Initial feed-forward synaptic weights	$\sqrt{\frac{\kappa^{ff} \alpha \times 130}{\alpha - F^T}}$

any neuron from the original training cluster were considered to be part of the training cluster if the mean weight of all their postsynaptic connections was above the threshold ϕ . This allowed slight modifications in cluster position to be viewed as an update of the original memory rather than a new cluster. Neurons with recurrent weights above the threshold that did not connect to the training cluster were considered as being part of a new (extinction) cluster. Note that all active neurons that did not belong to the training cluster were placed in the extinction cluster, even if they had no mutual connections between them.

Systematic review of labilization mechanisms in different structures

Search strategy

The protocol for this systematic review was preregistered in the Open Science Framework at <http://doi.org/10.17605/OSF.IO/ZHPR4>. Briefly, we performed a search in PubMed and Web of Science using the search terms (destabili* OR labil*) AND (reconsolidat* OR reactivat*), including studies published until November 4, 2019. These terms were developed and refined based on a systematic review performed by our group as part of a previous study (Lee et al. 2019).

Study selection

Two independent investigators (F.E. Amorim and R.L. Chapot) screened titles and abstracts for (1) original studies; (2) written in English, that (3) included experiments evaluating the modulation of reconsolidation blockade by an intervention targeting a specific molecular mechanism. We used the Rayyan platform (Ouzzani et al. 2016) to select studies and exclude duplicates. An article proceeded to the full-text screening stage if it was included by at least one reviewer. Agreement between investigators in this stage was 98.3%.

Inclusion criteria in full-text screening (which included supplemental material when available) were the following: (1) studies describing the behavioral effects of an intervention directed at a specific molecular mechanism, (2) performed up to 6 h before or after a reactivation session that (3) modulated the effect of reconsolidation blockade by another drug (e.g., anisomycin and MK-801). As in the previous step, two reviewers (F.E. Amorim and R.L. Chapot) evaluated all studies. Disagreements were discussed and solved with the help of a third investigator (O.B. Amaral).

Information from each article was extracted by a single reviewer and reviewed by the other. Extracted variables included the reconsolidation inhibitor used, its injection time and site, the destabilization treatment with its own infusion time and site, the molecular target of the treatment and the behavioral outcome as described by the investigators. All extracted information was inserted in a .xls spreadsheet (Supplemental Raw Data 1).

Review of the role of memory destabilization mechanisms in synaptic downscaling

To search for articles relating mechanisms of memory destabilization to synaptic downscaling, we initially analyzed the data set from a recent scoping review of the field that included 168 studies (Moulin et al. 2020). One of the investigators (T.C. Moulin) screened the full text of 51 articles in which chronic excitation experiments were performed to induce downscaling, along with pharmacological or genetic interventions to investigate the underlying molecular machinery. All articles reporting results relating synaptic downscaling to one of the memory destabilization components described in Table 3 were selected for further analysis, irrespective of their results.

As the analyzed systematic review data set comprised studies published until 2017, we manually performed individual searches combining the term “synaptic scaling” with keywords associated with the molecular mechanisms shown in Table 3 to obtain updated results. The searches were performed on June 29, 2020, using the following search terms: “synaptic scaling AND NMDA” for NMDA

receptors, “synaptic scaling AND (UPS OR ubiquitin*)” for the ubiquitin-proteasome system, “synaptic scaling AND AMPA” for AMPA receptors, “synaptic scaling AND calcineurin” for calcineurin, “synaptic scaling AND L-type calcium channel” for LVGCCs, “synaptic scaling AND (PP1 OR protein phosphatase-1)” for PP1, “synaptic scaling AND CaMKII” for CaMKII, “synaptic scaling AND (sodium channels OR Na channels)” for Na⁺ channels, “synaptic scaling AND (“protein synthesis” OR cycloheximide OR anisomycin)” for protein synthesis, “synaptic scaling AND (cholinergic receptor OR acetylcholine receptor)” for cholinergic receptors, “synaptic scaling AND CB1” for CB1 receptors, “synaptic scaling AND nitric oxide” for nitric oxide, “synaptic scaling AND dopamine receptor” for dopaminergic receptors, “synaptic scaling AND autophagy” for autophagy, “synaptic scaling AND histamine receptor” for H3 receptors, “synaptic scaling AND IP3” for IP3Rs, and “synaptic scaling AND beta adrenergic receptor” for β -adrenergic receptors. The term “NOT review” was added to all searches in order to narrow the results to original studies.

Articles investigating synaptic downscaling were identified through abstract and full-text screening by a single investigator (T.C. Moulin). Inclusion criteria were (1) articles written in English, (2) presenting original results, and (3) describing animal experiments using chronic stimulation of neurons to study synaptic downscaling. If the title and abstract were not clear about the three criteria described above, articles were still considered for full-text screening. Articles were included after full-text screening if they described experiments manipulating and/or measuring the activity or expression of the molecule of interest as part of a protocol previously or concurrently shown to induce synaptic downscaling. The main findings and brief descriptions of the methods and biological models from the 13 articles describing the involvement of a memory destabilization mechanism in synaptic downscaling were included in Table 4.

Systematic review of connections between homeostatic plasticity and memory phenomena

Search strategy

A systematic review was performed in PubMed and Web of Science using the search terms ([“destabilization” OR “destabilisation” OR “labilization” OR “labilisation” OR “labile” OR “reconsolidation” OR “reactivation” OR “extinction*” OR “recall” OR “retrieval” OR “update” OR “updating” OR forget*] AND [“memory” OR “learning” OR “conditioning” OR “plasticity”] AND [“homeostatic” OR “synaptic scaling” OR “heterosynaptic” OR “metaplasticity”]). We refined search terms in order to include studies that we considered important to the subject prior to the review (Tetzlaff et al. 2011, 2013; Bonin and De Koninck 2014; Zenke et al. 2015; Mendez et al. 2018). The search included articles published until November 4, 2019, and there were no exclusion criteria for article type.

Study selection

Title and abstract screening excluded (1) articles not in English and (2) articles without mentions to memory phenomena such as reconsolidation, extinction or labilization or homeostatic plasticity. To be included, at least one reviewer had to include the reference for it to proceed to the next screening stage. Agreement between reviewers in this stage was 84.3%.

The second screening stage considered the full text of the article, including supplemental material if available. Two investigators (F.E. Amorin and R.L. Chapot) included studies for later data extraction if they demonstrated or discussed a direct relationship between memory processes (e.g., reconsolidation, extinction, and labilization) and homeostatic plasticity. A reason for the exclusion of an article had to be included in this step. Disagreements between reviewers in this step were solved with the help of a third one (O.B. Amaral). Included studies were used for the discussion section and are listed in Supplemental Table S2, with the search flowchart presented in Supplemental Figure S8.

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