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Reconsolidation: the advantage of being refocused

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Ample evidence suggests that upon their retrieval, items in long-term memory enter a transient special state, in which they might become prone to change. The process that generates this state is dubbed 'reconsolidation'. The dominant conceptual framework in this revitalized field of memory research focuses on whether reconsolidation resembles consolidation, which is the process that converts an unstable short-term memory trace into a more stable long-term trace. However, this emphasis on the comparison of reconsolidation to consolidation deserves reassessment. Instead, the phenomenon of reconsolidation, irrespective of its relevance to consolidation, provides a unique opportunity to tap into the molecular, cellular and circuit correlates of memory persistence and retrieval, of which we currently know only little.

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Introduction

Even newcomers to the field of memory consolidation quickly observe that the debate on reconsolidation (see glossary) is not at all that new. Yet, they also realize that novelty is not a prerequisite for genuine excitement. The debate on whether items in long-term memory are consolidated just once per item shortly after their encoding or regain upon their reactivation renewed sensitivity to amnesic agents is as emotional as it used to be 40 years ago, and perhaps now even more so. In recent years this revitalized dispute has triggered a surge of publications on reconsolidation. Within less than a decade, the average publication rate of the reconsolidation community has increased over 50 fold, and is now approaching the alarming rate of one paper per week. The only solace offered to the potentially alarmed reader is that the ratio of reviews to original research papers is rather high,

meaning that the level of novelty to be digested is acceptable.

Admittedly, the present discussion could tilt the balance even further in favor of the polemics versus the data. As a pre-emptive measure, this treatment of the literature is kept minimal (for a review of the field up until its renaissance in 2000, see Sara [1]; for the influential harbinger of that renaissance, see Nader *et al.* [2]; for coverage of the literature up to 2004, see Dudai [3] and Alberini [4]). Here, I promote the following viewpoints. First, reconsolidation studies, which seemed to wave proudly an anti-paradigmatic revolutionary flag, now risk becoming another scientific paradigm, which, unless shaken a bit at the outset, will inevitably end up stagnating till a new revolution erupts. Second, in attempting to understand reconsolidation, quite a number of contemporary studies employ similar approaches to those used 40 years ago, and, therefore, they are bound to yield similar answers, or lack of answers. Third, the conceptual focus of research in this field, which is to construe reconsolidation in the framework of consolidation, blurs a potentially more rewarding goal. This goal is to contribute to the understanding of memory persistence and retrieval, of which we know so little, but without which memory will never be understood.

Reconsolidation is generalized to many experimental systems and protocols

Reconsolidation is no longer considered by many as an eccentric phenomenon that can be detected in a few systems only during certain hours of the day. Data accumulated during the past few years have extended significantly the number of memory systems and protocols that display reconsolidation. These now include invertebrates and vertebrates, simple and complex learning, and aversive and reward conditioning (for a selection of recent examples of species and protocols, see [5–10,11••, 12–15,16••]).

Reconsolidation, however, might not be universal

Whereas consolidation has, to date, been detected in every type and instance of long-term memory formation [3], in the case of reconsolidation the situation seems to be different (e.g. [17]; for a review of earlier reports that failed to find reconsolidation, see Dudai [3]). In certain systems reconsolidation could not be detected, and in others, conditions have been observed in which the phenomenon disappears. This has led to the notion that there are boundary conditions for reconsolidation [18]. The search for such boundary conditions is guided by the

Glossary

Amnesic agents: Chemical or physical agents, such as inhibitors of protein synthesis, electroconvulsive shock, or distracting sensory stimuli, that cause amnesia if applied before consolidation is completed.

Dual-trace hypothesis: The hypothesis that memory items exist in two consecutive states, the first short-term and unstable, the second long-term and relatively stable.

Experimental extinction (alias extinction): The decline in the frequency or intensity of a learned response following the withdrawal of the stimulus that has reinforced the learning (i.e. the reinforcer).

Memory consolidation: A hypothetical process in which short-term memory is converted into long-term memory. The textbook account is that items in long-term memory undergo consolidation just once, shortly after their encoding.

Memory encoding: The acquisition by the neuronal system of information that culminates in memory.

Memory reactivation: The process in which items in long-term memory, which are assumed to persist over time mostly in a dormant, inactive state, become active, for example, in memory retrieval or in memory maintenance over time.

Post-reconsolidation amnesia: The blockade of memory performance that is observed when amnesic agents are applied during the hypothetical reconsolidation period.

Reconsolidation: A hypothetical process in which a consolidated memory item is rendered transiently malleable shortly after its reactivation. The 'reconsolidation hypothesis' leaves open the possibility that consolidation occurs more than just once per memory item.

hope that they will unveil underlying mechanisms and function.

Reconsolidation is not re-consolidation

Further evidence has been accumulated in recent years concerning the involvement in reconsolidation of identified membrane receptors, downstream signal transduction cascades and transcription factors, subsets of protein synthesis dependent mechanisms and identified neuronal circuits [10,13,15,16^{••},19–22,23^{••},24,25^{••},26]. Of special interest are those studies that further differentiate the molecular and circuit mechanisms of reconsolidation from those of consolidation, and that hence provide extra weight to the conclusion that reconsolidation is not a faithful replay of consolidation [19–21,23^{••},26].

Blockade of reconsolidation is not facilitated extinction

Multiple lines of evidence also now exist to refute the possibility that the amnesia following blockade of reconsolidation (post-reconsolidation amnesia) is only an enhanced experimental extinction (see glossary) of the original memory. This evidence is based on behavioral, anatomical and molecular studies. In the case of fear conditioning in the rat, post-reconsolidation amnesia was shown to lack the typical behavioral attributes of extinction, including context-dependent renewal, spontaneous recovery and unconditioned stimulus (US)-induced-reinstatement of the extinguished trace [5]. Furthermore, reconsolidation was found to occur even in retrieval in which the reinforcer was not withdrawn,

which is unexpected of extinction [5]. In the case of conditioned taste aversion in the rat, amygdalar circuits that subserve extinction are not necessary for reconsolidation [20]. In addition, in fear conditioning in the rat, different molecular mechanisms were found to be required for extinction and reconsolidation, respectively [25^{••},27]. Furthermore, in several systems, including those in invertebrates, lower vertebrates and mammals, extinction and reconsolidation were actually mutually exclusive, possibly because they are competing for shared plasticity resources [28,29]. It is noteworthy that a potential cellular correlate of competition for protein-synthesis dependent neuronal plasticity resources, in synapses that undergo long-term potentiation (LTP), was demonstrated recently in the hippocampus, see Fonseca *et al.* [30[•]].

Reconsolidation entails not only risks to the reactivated memory but also gains

In the majority of experiments on reconsolidation, amnesic agents are used to identify the phenomenon. However, recent reports have augmented the view, expressed earlier [1], that reconsolidation might also provide a window of opportunity for the strengthening of the memory trace [6,25^{••}]. Of particular interest in this context is the recent report that activation of amygdalar protein kinase A (PKA), a key component of the synaptic plasticity machinery, was sufficient to enhance fear memory provided that the memory was reactivated. Complementary to this was the finding that inhibition of PKA induced post-retrieval amnesia, again, only if the memory was reactivated [25^{••}].

A related question is, if reconsolidation is indeed disrupted by amnesic agents, how widespread will the effect be on the network of associations of the reactivated memory item? Are all the associations of that item at risk? A recent study, using higher-order conditioning to tap into remote associations in the rat, indicates that this concern is unfounded: only associations that were directly reactivated, not those indirectly reactivated (i.e. higher-order), underwent reconsolidation in the amygdala of the fear-conditioned rat [31^{••}].

Is reconsolidation an updating mechanism?

A more generalized interpretation of the aforementioned data is that reconsolidation is a manifestation of a memory updating mechanism, that is, adapting the reactivated memory to the new circumstances. This idea has been around in the field for some time now [1,3,32]. Recent data on this are, however, conflicting. In the case of long-term taste memory in the insular cortex of the rat, post-retrieval intracortical blockade of protein synthesis disrupted memory only if the experience was updated, suggesting that retrieved memory is modified as part of an updating mechanism [33[•]]. But another study led to a different conclusion. Tronel *et al.* [34^{••}] used higher order

conditioning of inhibitory avoidance in the rat to identify memory updating, and specific molecular and cellular signatures to dissociate consolidation from reconsolidation. They found that linking new information to the reactivated memory is mediated by consolidation and not reconsolidation [34••].

Boundary conditions of reconsolidation

To date, several conditions have been proposed to constrain reconsolidation. The first is trace dominance, that is, the ability of the association to control behavior after retrieval [28]. As noted above, in several systems, if the trace extinguishes, the extinction trace, which hence controls behavior, rather than the original trace which does not, becomes transiently sensitive to the amnesic agents [28,29,35]. The second is the age of memory; in some systems, older memories become less amenable to reconsolidation [27,36]. The third is mismatch between what the animal expects and what actually occurs; such mismatch was reported to promote reconsolidation [37•]. Engagement of a memory encoding mode in the reactivation session was also recently found to promote reconsolidation in spatial memory in the rat (RGM Morris *et al.* submitted). It is noteworthy that mismatch of the expected and the actual, that is, surprise, is expected to drive encoding [38].

Promising clinical applications

The potential for exploiting reconsolidation for therapeutic purposes is a major incentive in this field, and the attempts to harness this phenomenon for clinical use progress in parallel with the attempts to understand what the phenomenon really means. First and foremost, there are ongoing attempts to use reconsolidation to ameliorate post-traumatic stress disorder (PTSD). One method that has been explored involves administration of a beta adrenergic blocker as a potential post-reconsolidation amnesic agent to PTSD patients. This type of blocker, which is widely used to treat hypertension, blocks reconsolidation in the amygdala of fear-conditioned rats [21], and is used in acute trauma in the hope that it will diminish the probability of subsequent PTSD [39]. The preliminary data from reconsolidation studies in humans seem to warrant further careful exploration of this potential option [40]. Another potential clinical use of this phenomenon is suggested by a recent finding that disrupting reconsolidation of drug-of-abuse memories reduces cocaine-seeking behavior in the rat [11••]. Clearly, attempts to bring reconsolidation into the clinic will benefit from a better understanding of what disruption of reconsolidation means to brain and behavior, particularly in the long-run.

Interim summary: what reconsolidation is, and what it is not

Recent developments in the field can be combined with earlier findings to support the following heuristic conclusions:

1. Reconsolidation is a temporarily altered state of the memory trace following memory reactivation. This altered state is characterized by increased sensitivity to amnesic agents, such as inhibitors of macromolecular synthesis, possibly because of enhanced plasticity of the neuronal circuit that encodes the memory trace or parts of it.
2. Reconsolidation is widespread but possibly not universal. It is constrained by retrieval and post-retrieval conditions, our knowledge of which does not yet form a coherent narrative.
3. Reconsolidation is not a faithful replay of consolidation. It might share mechanisms and even functions with consolidation, but etymologically it is a misnomer. Sharing mechanisms *per se* is not uncommon in biological systems that have different roles. For example, a glandular response to a hormone shares cellular mechanisms with encoding; response to injury also shares cellular mechanisms with encoding [41] — still, nobody terms memory ‘reinjury’. Yet the term ‘reconsolidation’ became widespread and consolidated in the collective memory of the field to such a degree that it is now impractical to change.
4. Reconsolidation certainly does not mean that once retrieved, the trace disintegrates and has to be constructed anew. It is assumed that *in vivo*, reconsolidation could augment, weaken or otherwise alter the memory item and its associations, or have no long-term effect on the memory. We do not normally swallow amnesic agents while recollecting; post-activation amnesia is only a laboratory manipulation that enables detection of reconsolidation.

A shift in focus is needed

The field of reconsolidation is a victim of its own history. This is felt in both the conceptual and the methodological areas. It is consistently evaluated in the context of a conceptual framework of the dual-trace hypothesis (see glossary), which assumes the existence of memory phases (short and fleeting, long and stable), and in the context of consolidation, which converts the ephemeral trace into the seemingly secure world of engrams. This situation might prove to be a far from optimal jump-off for a scientific endeavor. Indeed, part of the current methodology in this field is a replay of experiments conducted 30–40 years ago, in trying to prove that post-reconsolidation amnesia is reversible and, therefore, that reconsolidation is not re-consolidation (the alternative, that the amnesia is at least sometimes permanent, is inherently impossible to confirm, because it relies on negative results). The field has been there already. Furthermore, the question of whether some types of post-consolidation amnesia are permanent or not is also occasionally pushed under the rug, and the idea that they reflect retrieval deficits rather than storage deficits is alive and kicking [42,43,44•]. It is therefore uncertain whether permanence of amnesia can

serve as a criterion for the similarity or lack of similarity of reconsolidation and consolidation. Having said all this, rejuvenators of 'reconsolidation' should, however, avoid preaching for a premature paradigm based primarily on demotion of the older consolidation paradigm.

Let's consider the following imaginary scenario. In a world that has just become enchanted with the science of memory, the sages identify as the most important research question that of memory retrieval, that is, the expression of experience-dependent internal representations, because they reach the conclusion that in the absence of retrieval, memory is an empty concept [45]. Study sessions and grant committees follow the zeitgeist, and soon enough a finding is announced and replicated all over: when memories are retrieved they are plastic, and while they are plastic funny things happen to them, including becoming susceptible to interference by amnesic agents. The standard experimental protocol is straightforward: train to criterion, wait a few days, then test performance. Lo and behold, an excessively busy postdoc forgets to train the rats, yet still finds that the first performance of the new task opens a time window during which amnesic agents can block some type or another of subsequent performance. The sages immediately conclude that the neuronal circuits that encode relevant knowledge become active in the training session, hence they are plastic and sensitive to amnesic agents. In this unheard of scientific community, in which the study of retrieval preceded the study of encoding, reconsolidation is not called reconsolidation, and is not questioned. Rather, both encoding and retrieval are considered to involve active states of internal representations, which are more plastic and malleable than the inactive states [46].

Given that even ardent and thoughtful defenders of the classical consolidation hypothesis agree that something interesting and different happens when the long-term trace is reactivated [35], the question is how we proceed from here. My opinion is that as a first step, we should avoid considering the phenomenon of reconsolidation as an adversary of the consolidation hypothesis or as an annoyance in the seemingly calm neighborhood of expertise on amnesia. Rather, we should treat it, very cautiously and respectfully, as an opportunity to explore the dynamics of the memory trace, particularly during and shortly before and after its expression. Reconsolidation is a reasonably reproducible experimental tool that could unveil what happens in memory circuits when their representations are reactivated and strive to control behavior. It might prove useful in dissecting processes and mechanisms that are correlated with retrieval, or are entailed by it. It might illuminate the similarities and differences between encoding and retrieval modes. And it might also cast light on the biological processes and mechanisms of memory persistence. Molecular, cellular and circuit connoisseurs should take restrained notice.

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