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Modulation of Learning and Memory: A Shared Framework for Interference and Generalization

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Abstract—The human brain is known by its ability to modify and update existing memories, mediated by underlying neuronal plasticity. This ability is facilitated by two main phenomena, interference and generalization. Interference occurs when a new memory harms, or is being harmed by, a different memory that was acquired in temporal proximity to it. Generalization on the other hand, refers to the case in which a learned memory is expanded beyond its specific properties. While each of these two phenomena may be well known separately, we review recent evidence primarily in perceptual and motor skill memory, spanning synaptic, neural systems-level, and behavioral research, suggesting that although the outcomes are different, the underlying neural and behavioral processes responsible for their inducements share numerous commonalities. The reviewed literature may imply a common mechanism underlying these two phenomena, and suggests a unified framework of memory and learning in the human brain. © 2018 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: skill learning, motor learning, perceptual learning, memory, plasticity, interference, generalization.

INTRODUCTION

Learning new information may involve serial acquisition of memories. Oftentimes, new memories are acquired on the basis of pre-existing knowledge, and thus an interaction between the new and existing memories is inevitable. This interaction can trigger one of two outcomes: either segregate the memories into two independent entities, or integrate them into a single merged memory. On the one hand, a merged memory can include information from both new and pre-existing memories, thus creating a single memory with broader properties. On the other hand, however, a merged memory can include partial information from one of the memories, disrupting the second memory trace. These two processes are also known as *Generalization* and *Interference*, correspondingly. As will be reviewed here, interference and generalization share common features reported across behavioral, synaptic, and systems-level neuroscience studies, suggesting a main shared mechanism underlying the neural plasticity of memories.

Behavioral level

From a behavioral point of view, generalization and interference are both induced by an interaction of two different memory traces, within a short temporal offset.

On the one hand, such interaction could cause a competition between the memory traces, resulting in interference, expressed as a decrease in performance (Postman and Underwood, 1973). On the other hand, the memory learned in the first task could be transferred to the new task, resulting in generalization, expressed as enhancement of performance efficacy, and in extension of the memory trace to novel boundaries beyond its originally encoded features (Guttman and Kalish, 1956; Censor, 2013).

Interference is caused when two memories are activated successively. This phenomenon was revealed in a seminal study in 1900 by Müller and Pilzecker (see Lechner et al., 1999), showing that verbal memory strength deteriorated when an interfering syllable list was presented following encoding. Since then, in parallel to Pavlovian concepts of short-term behavioral inhibition (of reflexes independent of memory, Pavlov (1927) PI (2010), a large number of studies have demonstrated the existence of active memory interference, across different memory types (for example see de Beukelaar et al., 2014; Yotsumoto et al., 2009; Seitz et al., 2005; Been et al., 2011; Dunsmoor et al., 2018). Evidently, as the time-window between the presentations of both memories lengthens, interference is less prone to occur (Brashers-Krug et al., 1996; Korman et al., 2007). Moreover, the directionality of interference has been documented across two temporal chains of events: the first memory can be overridden by a later one, an effect termed ''retroactive interference'' (Dewar et al., 2007), or the acquisition of

the first memory would not allow a new one to be learned, known as "proactive interference" (Wixted and Rohrer, 1993).

Generalization refers to the ability to link two memories, and apply information from one memory to another. In a landmark paper (Shepard, 1987), generalization was suggested to be dependent on the similarity between two stimuli, decreasing its occurrence exponentially with the distance in psychological space. This concept was adapted to a Bayesian model, extended to address multiple memory traces (Tenenbaum and Griffiths, 2001). Experimentally, generalization is a widely studied phenomenon, reported in motor (Ossmy and Mukamel, 2016), perceptual (Xiao et al., 2008) and semantic (Friedrich et al., 2015) memories in humans, as well as fear generalization in animal models (Ghosh and Chattarji, 2015; see below). Of note, generalization is often termed "transfer", indicating the transfer of learned skill or memory, from one realm to another. For example, procedural memory generalization can refer to the transfer of a memory either to the untrained eye, retinal location (Karni and Sagi, 1993; Xiao et al., 2008), hand (Grafton et al., 2002; Criscimagna-Hemminger et al., 2003; Birbaumer, 2007; Perez et al., 2007), stimulus (Ahissar and Hochstein, 1997; Aberg et al., 2009; Harris et al., 2012), motor-goal (de Xivry et al., 2011), or to other contexts (Krakauer et al., 2006). Interestingly, while interference is a bi-directional phenomenon, generalization usually occurs in a single direction, where the second memory benefits from the acquisition of the first memory.
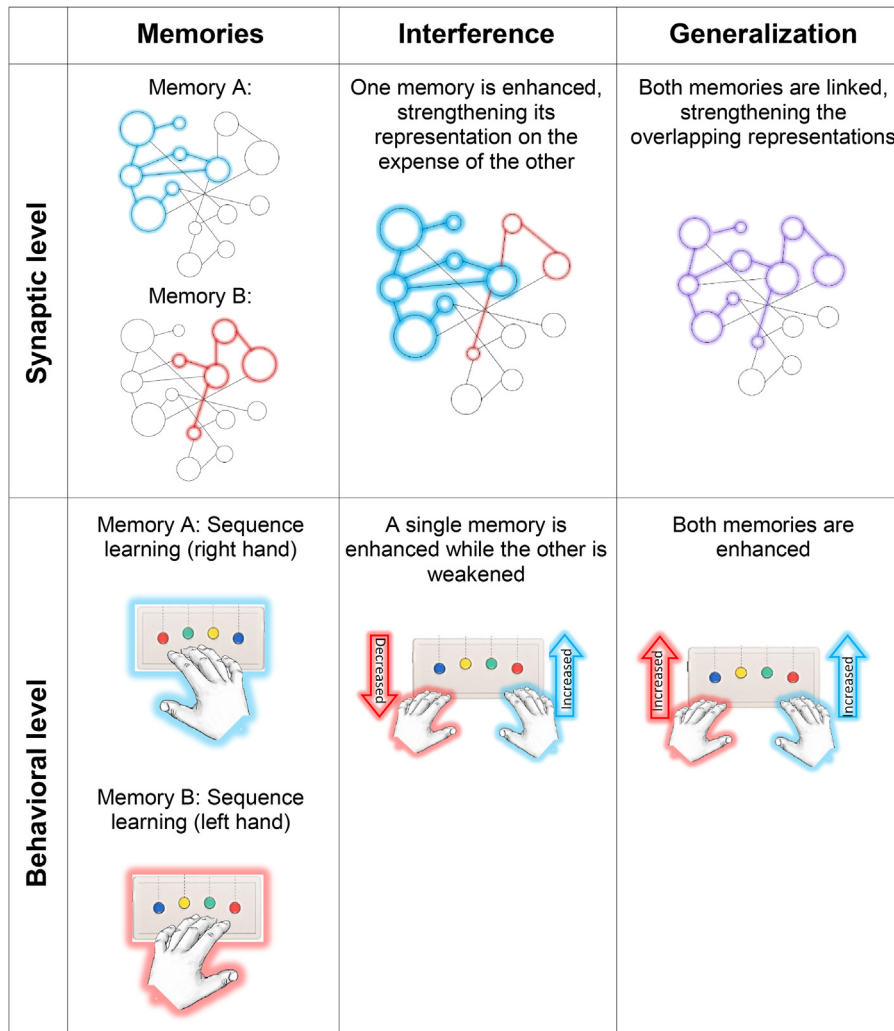
Systems and synaptic level

Generalization and interference share commonalities at the neural level as well, possibly pointing to a shared neural mechanism underlying both phenomena. Facilitated by methodological developments, interference and generalization can be causally investigated at the systems level, through cortical non-invasive brain stimulation techniques (Dayan et al., 2013). For example, in the motor system, interference was induced with inhibitory 1-Hz transcranial magnetic stimulation (TMS) applied over primary motor cortex (M1) during practice of fast finger movements, resulting in disrupted behavioral improvements (Muellbacher et al., 2002). Similarly, application of 1-Hz TMS over the supplementary motor area (SMA) before the execution of hand movement in the serial-reaction-time task decreased the generalization of the motor skill from one hand to the other (Perez et al., 2007). In addition, neuroimaging studies revealed that generalization of a learned skill between hands is based on bilateral motor cortex activation (Gabitov et al., 2016; Fujiwara et al., 2017), as well as SMA activation (Lefebvre et al., 2012). Interestingly, studies combining neuroimaging and non-invasive brain stimulation showed that interference induced by repetitive TMS modulated the connectivity between cortical areas and the basal ganglia (Censor et al., 2014a,b). Consistently, interference between different motor sequences was found to be related to a decrease in cortico-striatal activity (Albouy et al., 2016).

Overall, the evidence above suggests that generalization and interference share common systems-level neural mechanisms. That is, activity and functional connectivity within core regions of the motor network facilitate generalization, and their downregulation induces interference.

In parallel, studies have extensively examined the synaptic-level mechanisms underlying generalization (Ciocchi et al., 2010; O'Donnell and Sejnowski, 2014; Ghosh and Chattarji, 2015; Lopresto et al., 2016; Yokoyama and Matsuo, 2016) and interference (Fonseca et al., 2004; Martínez et al., 2012; Sajikumar et al., 2014; Rashid et al., 2016). According to these studies, the underlying synaptic mechanisms differ between generalization and interference, although both occur when two distinct memories, represented as two neural ensembles (Josselyn et al., 2015) are co-activated. Thus, while interference occurs due to a competition over protein-synthesis resources between neural ensembles, generalization is likely caused by reduced segregation between the relevant ensembles. Interestingly, a recent collection of studies have suggested that the process of neurogenesis mediates the interaction between both phenomena. Particularly, enhanced neurogenesis was found to decrease generalization by increasing pattern separation (Aimone et al., 2011; Kheirbek et al., 2012). Furthermore, Epp and colleagues (2016) found that hippocampal neurogenesis regulates interference in mice. As mentioned above, interference can be either retroactive or proactive, differentiated by the performance outcome. In this study (Epp et al., 2016), following the acquisition of a spatial memory, hippocampal neurogenesis was enhanced (van Praag et al., 1999), leading to a reduction in the existing memory performance, demonstrating increased retroactive interference. Similarly, additional experiments in the same study showed that a decrease in hippocampal neurogenesis, was associated with stabilization of existing memories, and a decreased ability to encode new, conflicting information, demonstrating proactive interference. On the other hand, Montgomery et al. (2016) have shown that generalization is modulated by hippocampal functioning. In this study, hippocampal dysfunction in mice was shown to reduce the ability to generalize existing memories. Overall, these studies demonstrated that both generalization and interference were modulated by hippocampal activity.

A shared framework

Learning and memory studies have occasionally looked into interference and transfer within the same study (Postman and Stark, 1969; Shea and Morgan, 1979). Few studies have even referred to interference as "negative transfer" (Perkins and Salomon, 1992), emphasizing the relation between transfer, i.e. generalization, and interference. However, although studies combining both phenomena within the same framework could provide strong evidence of the commonalities and a possible dissociation, most current research is focused on extensive examination of interference or generalization in separate studies, resulting in detailed investigation of each phenomenon, at the cost of a wider perspective. Even though studied separately, due to the frequent occurrence of

Fig. 1. A comparison between Interference and Generalization across the behavioral and synaptic levels. At the synaptic level, memory ensembles are represented as two tree graphs. Following interference, one representation is strengthened on the expense of the other, whereas following generalization both ensembles are merged, strengthening both memories. At the behavioral level, the presented example is taken from the motor skill memory, depicting each hand as representing a memory trace A or B (for example see Herszage and Censor, 2017). Following interference, the skill of one hand is strengthened and the other is weakened, while following generalization intermanual transfer occurs, where improvements in one hand are transferred to the other, enhancing the performance of both hands.

generalization and interference in daily life, and the significance of understanding how these processes operate following neural insults, this review will discuss both phenomena, while pointing to similarities and dissimilarities across behavioral domains, as well as the underlying neural mechanisms (see Fig. 1). The goal here is to review converging abundant neuroscience studies pointing to a possible shared coherent framework, including both generalization and interference. As suggested in the conclusions, the evidence points to a shared framework which may provide a wider understanding of modulation of learning processes and encourage future research to reveal the shared neural mechanism underlying both phenomena. Of note, while other memory domains are mentioned, this review will mainly focus on

perceptual and motor skill memories. These types of memories provide comprehensive evidence for the study of long-term learning and memory, showing consistent improvements in memories both within- and between-sessions.

THE TEMPORAL DIMENSION OF GENERALIZATION AND INTERFERENCE

To further enrich the concept of a shared neural mechanism, we will review studies collectivity examining how generalization and interference interact with the known temporal dimension of memory processes. Such examination could expand the commonalities described above, but also suggest a possible dissociation between the two to be determined in future studies.

Temporal offset

As mentioned above, in order to evoke either interference or generalization, the brain has to be exposed to two different memories, with a temporal offset between them. This temporal offset plays a crucial role in inducing such plasticity processes, and currently functions as a basic assumption of many studies looking into both interference and generalization. When the temporal offset between the memories is longer than 6–8 h, the efficacy of plasticity interactions declines, reducing the likelihood of an interaction between the memories, and thus resulting in a decreased probability of both interference (Walker et al., 2003; Korman et al., 2007) and generalization (Zeithamova and Preston, 2017). Importantly, the idea of shortening the temporal offset between successive memories is supported by synaptic evidence. As mentioned above, interference and generalization are caused by an interaction between two neural ensembles, causing either competition over protein-synthesis resources, or reduced segregation, respectively. This interaction between ensembles can occur if both ensembles are co-activated, and thus the probability of this interaction to occur depends on the time window between the activation of both memory ensembles. It has also been reported that under some circumstances, if both memories are similar enough, interference may even occur if the temporal offset is as long as 24 h (Been et al., 2011).

Sleep and consolidation

Another common temporal aspect for both generalization and interference of memories is sleep. Sleep provides an opportunity for memories to stabilize through the process of consolidation (Diekelmann and Born, 2010). During consolidation, new memories, known to be initially labile, are reconstructed as more stable representations which then integrate into long-term memory networks. If following initial acquisition no other interfering memory was presented, the memory will undergo proper consolidation. In procedural memory, some tasks even show improvement between sessions or days without between-session practice, termed "offline gains" (Karni and Sagi, 1991; Karni et al., 1995). These improvements require the completion of memory consolidation, often during sleep (for a review see King et al., 2017).

Sleep has been suggested to strengthen a memory through two parallel actions: stabilization and enhancement (Walker, 2005; Stickgold and Walker, 2013). In support of this view, other models have suggested a differentiation between the enhancement and stabilization stages during sleep (Mednick et al., 2003; Albouy et al., 2015). For example, Mednick et al. (2003) have shown that in perceptual learning, a brief nap containing both slow-wave sleep (SWS) and rapid eye movement (REM) sleep is sufficient for complete consolidation. Furthermore, this study suggested that different stages in sleep have different functions in consolidation. Namely, the enhancement stage occurs during REM sleep, while stabilization occurs during SWS. Based on this set of models, it is conceivable that strengthening memories during consolidation occurs due to processes that simultaneously increase generalization but decrease interference. Specifically, during the stabilization stage, memories develop a higher resistance to future interference (Ellenbogen et al., 2009; Abel and Bäuml, 2014), possibly afforded by normalization of synaptic strength occurring during sleep (Tononi and Cirelli, 2006). Meanwhile, in the enhancement stage, newly acquired memories are reorganized and incorporated with previous knowledge by means of increasing generalization during sleep (Sterpenich et al., 2014; Friedrich et al., 2015). In episodic memories, the enhancement of generalization during sleep was suggested to occur due to the transfer of memories between different brain areas, mainly from hippocampal areas to the neocortex (McClelland et al., 1995; Frankland and Bontempi, 2005; Tse et al., 2011; McClelland, 2013). Although enhancement of generalization during sleep in other memory types is likely to be driven by reorganization of the memory trace across different brain areas as well, its dependency on hippocampus-neocortex trajectory is yet unknown. In sum, multiple lines of evidence accumulate to explain the contribution of sleep to both phenomena – simultaneously enhancing generalization while decreasing interference. In light of the evidence described above, further research testing both generalization and interference phenomena in the same combined study could establish the validation of such compound mechanism of memory interaction during sleep.

Reactivation and reconsolidation

Abundant evidence has shown that memories continue to be dynamic even after their stabilization and initial consolidation (Nader and Hardt, 2009; Dudai, 2012). Reactivation of memories opens time-restricted windows, during which the memory is susceptible to modification, and can result in its degradation, stabilization, strengthening, or updating (Nader et al., 2000; Walker et al., 2003; Lamprecht and LeDoux, 2004; Suzuki et al., 2004; Censor et al., 2010; Amar-Halpert et al., 2017; Yokose et al., 2017).

A seminal study in rodents has shown that infusion of protein synthesis inhibitors to the amygdala following reactivation of a fear memory, results in memory degradation observed on the following day (Nader et al., 2000). Since then, evidence has been accumulating for similar processes in humans (for example see Schiller et al., 2010; Walker et al., 2003), initially primarily implementing behavioral interference paradigms, paired with reactivation of a consolidated memory. For example, Walker and colleagues (2003) had participants encode and consolidate a motor memory of sequential finger movements. On a separate day, the memory was reactivated by performance of several trials of the memorized task. Following this reactivation, participants were required to perform a novel, "competing" sequence of finger movements. The results showed interference with the original memory trace, exhibiting reduced performance on the day following its reactivation. This impairment in memory strength was indicative of a disrupted motor memory reconsolidation process. Similar studies have been conducted in additional memory domains, including fear conditioning (Schiller et al., 2010), and episodic memory (Forcato et al., 2007).

Of note, recent evidence questioned the ability of the reactivation-reconsolidation framework to induce modifications of consolidated memories (Hardwicke et al., 2016). However, this criticism was focused on one study (Walker et al., 2003), in which the main behavioral effect was based on accuracy as the end-point measure, different from the commonly used end-point measure which combines speed and accuracy (Korman et al., 2007; Censor et al., 2014b; de Beukelaar et al., 2014). Combining speed and accuracy as the end-point measure is well established and highly replicable across labs and studies, showing that memory reactivation can indeed allow prevention of strengthening of previously consolidated memories, including both studies by Hardwicke et al. (2016) and Walker et al. (2003) as well as others (Censor et al., 2014a,b; de Beukelaar et al., 2014), showing modifications also at the brain system level. Such modifications of memory strength following its reactivation, may carry important implications even if not solely explained by a reconsolidation mechanism. Along with enhanced understanding of the behavioral processes underlying modification of human memories following their reactivation, studies have started looking into the underlying neural mechanisms (Sandrini et al., 2015). For example, in the motor domain, inhibitory 1-Hz transcranial magnetic stimulation (TMS) over M1

synchronized with motor sequence memory reactivation, resulted in impaired memory strength compared to control stimulation, pointing to the role of M1 in processing of reactivated motor memories to enable their efficient strengthening (Censor et al., 2010). A subsequent study, using fMRI measurements, showed that such non-invasive interference with M1 processing following motor memory reactivation, resulted also in decreased cortico-striatal co-activations, providing task-free (Censor et al., 2014b) and task-based signatures of the interfered memory (Censor et al., 2014a). Pharmacological interventions, applying propranolol (a β-adrenoceptor antagonist shown to reduce retention in animal models, Liang et al., 1986) synchronized with fear memory reactivation, showed interference with memory strength measured on the following day (Kindt et al., 2009). In addition, electroconvulsive therapy (ECT) following memory reactivation in depression patients, disrupted emotional episodic memories (Kroes et al., 2014).

Studies in episodic memory have pointed to reconsolidation as a possible update mechanism for incorporation of new information. In these studies, when a memory for a list of words was reactivated followed by exposure to a new list of words, it remained intact but words from the new list were also merged into the original memory (Hupbach et al., 2007, 2008; Forcato et al., 2010). It remains to be determined whether such an update mechanism can also be used to generalize reactivated memories to untrained tasks.

In sum, while interference frameworks have been used to demonstrate the mechanisms underlying the susceptibility of reactivated memories to future modification, the reactivation time-window can induce additional effects of memory strengthening and generalization. For example, a recent study has shown that inducing task variations following memory reactivation can result in memory strengthening (Wymbs et al., 2016), consistent with memory strengthening observations in animal models (Frenkel et al., 2005; Lee, 2008). Whether the outcome of memory reactivation-modification processes would result in interference or generalization may rely on different factors such as those related to the temporal dimension, for example the length of reactivation (Pedreira and Maldonado, 2003; de Beukelaar et al., 2014) and the age of the reactivated memory (Milekic and Alberini, 2002; Eisenberg et al., 2003). In light of recent observations in rodent fear memory generalization following memory reactivation (Vanvossen et al., 2017), future research should determine the link between interference and generalization across human memory domains.

EVIDENCE ACROSS MEMORY DOMAINS

The concept discussed here, of shared mechanisms underlying interference and generalization, is supported by an abundant number of studies, spanning across multiple fields - including procedural memories, motor (Korman et al., 2007; de Beukelaar et al., 2014; Ossmy and Mukamel, 2016; Herszage and Censor, 2017) and perceptual (Seitz et al., 2005; Yotsumoto et al., 2009;

Been et al., 2011; Shibata et al., 2017), as well as declarative (Chan et al., 2013; Friedrich et al., 2015; Shapiro and Levy-Gigi, 2016), emotional memories (Dunsmoor et al., 2018) and working memory (Jonides and Nee, 2006; Holmes et al., 2009). Although this review focuses on perceptual and motor skill memories, a large number of studies in other domains demonstrated similar properties, pointing to a shared framework of generalization and interference in those memory types as well.

Further evidence in perceptual and motor skill learning

In the motor system, studies have tried to reveal methods to improve learning strategies, by either preventing interference, or enhancing generalization. For example, prevention of motor interference was allowed if a new memory was presented within the reactivation-induced time window of an existing memory (Herszage and Censor, 2017). Correspondingly, several studies have reported strategies of generalization enhancement (Xu, 2013; Ossmy and Mukamel, 2016). For example, inter-manual transfer, a known form of generalization in the human motor system, was found to be improved by online visual feedback using 3D virtual reality devices, depicting participants' left immobile hand moving simultaneously with their right, practicing hand. Generalization to the left hand was further enhanced, when left-hand fingers were yoked to passively follow right-hand voluntary movements (Ossmy and Mukamel, 2016). In a different study, wrist training prevented both the interference and generalization that subsequent arm training could enable (Krakauer et al., 2006). This study suggested an overlap between boundary conditions of generalization and interference, revealing shared limitations for both phenomena.

Studies in perceptual learning have shown that extensive training with a visual texture discrimination task (Karni and Sagi, 1991), results in within-session performance deterioration (Censor et al., 2006; Ofen et al., 2007), persisting also when sessions are spaced several hours apart and avoided by mid-day naps (Mednick et al., 2002, Mednick et al., 2005). These effects, suggested to relate to sensory adaptation (reduced sensitivity due to repeated stimulation, Censor et al., 2006; Harris et al., 2012), were shown to interfere with between-session off-line learning gains (Censor et al., 2006, 2009; Censor and Sagi, 2008). Of note, a tight link has been demonstrated between these adaptation-interference effects, and generalization of learning to untrained visual field locations. Harris and colleagues (2012) trained participants in the texture discrimination task, with the target appearing at a fixed location. Adaptation was removed by changing the orientation offset between target and background (Greenlee and Magnussen, 1988). They showed that removing adaptation resulted in complete generalization of learning to a new target location, suggesting that this interference alters generalization by inducing local sensory adaptation in early visual representations (Harris et al., 2012). Recent studies have further shown that the degree of interference induced by extended training, is determined by the variations in temporal structures of the trained visual stimuli. Largest interference with

between-session learning was observed with the largest amount of temporal conditions, changing gradually during training (Censor et al., 2016; Shibata et al., 2017). In sum, the above studies suggest a link between interference and generalization processes, further pointing to potentially shared underlying mechanisms.

Interactions across modalities

Interference and generalization can occur not only within the same memory system, but rather between different memories as well (Brown and Robertson, 2007; Gagné and Cohen, 2016; Mosha and Robertson, 2016). One example demonstrates the strong link between generalization and interference: Mosha and Robertson (2016) investigated the relationship between two memory types, semantic memory tested through a word-list task, and procedural memory, tested through a motor skill task. Both tasks shared a common order of either words or a motor sequence, and were presented in an A-B-A order, where A was a word list task and B was the motor skill, or vice-versa. Results showed generalization between the motor skill and the word list task, evident as improved performance in task B, i.e transfer of learning either from the motor skill to the word list or vice-versa, depending on the order of the tasks. In addition, further experiments revealed interference, evident as a decrease in performance of the first task A. Interestingly, when the interaction between the memories was deliberately weakened, either by modifying the order in one of the tasks, or by lengthening the time window between the tasks, both generalization and interference were prevented (Mosha and Robertson, 2016), demonstrating the tight connection between generalization and interference, even across different memory domains.

EVIDENCE ACROSS THE LIFE SPAN IN NORMAL AND IMPAIRED CONDITIONS

The commonalities between generalization and interference change in a coordinated fashion across the life span, supporting the concept reviewed here, and emphasizing the need for future research. Furthermore, these phenomena share yet another commonality when regularization is impaired, a condition associated with different known disorders.

Evidence across the life span

Cognitive decline, or age-associated memory impairment (Crook et al., 1986; Kelly et al., 2006), together with the stabilization of neural plasticity occurring throughout development in children (Stiles, 2000), modulate the effects of interference and generalization on learning and memory across the human life span. Based on the trade-off between generalization and interference, improved cognitive ability may require reduced interference and enhanced ability to generalize learned memories. Thus, cognitive decline in the elderly population is predictably related to stronger interference, and lower ability to generalize memories.

In accordance with this view, a large battery of studies have looked into both phenomena across different ages. Interference was found to have a higher effect on older individuals, either when comparing 17-year old with younger 9- and 12-year-old participants (Dorfberger et al., 2007), or when comparing older adults with middle-aged adults (Shapiro and Levy-Gigi, 2016). Similarly, generalization was found to be modulated with age as well (Hayne et al., 2003; Basak et al., 2008; Jaeggi et al., 2011). Providing a thorough investigation of this modulation of generalization across the life span, Dahlin and colleagues (2008) tested the generalization between two tasks: the n-back task and the letter memory task. In accordance with the hypothesis mentioned above, while young adults exhibited proper transfer, older adults could not show any transfer. Interestingly, fMRI measurements from the same study found deficient striatal functioning, which was suggested as a systems-level explanation for such age-related lack of transfer.

These life-span modulations are consistent with animal models as well. For example, a prominent study (Cai et al., 2016) found that older mice, which are known to have reduced cellular excitability, showed no transfer between fear memories, while young adult mice showed predicted transfer. Moreover, increasing cellular excitability in these older mice during the co-activation of the memories, allowed them to create an association between both memories, which was otherwise not possible.

Impaired regularization

The brain elegantly maintains regularization of learning processes, but when this regularization is impaired, undesirable outcomes may occur. Specifically, over-generalization can result in increased rates of false-positive errors, while over-interference can culminate in amnesia, preventing the acquisition of new memories. Similarly, under-generalization can result in increased rates of misses, while under-interference, although usually studied as a desirable outcome, could prevent the normal prioritization of new memories, possibly leading to impaired retrieval or inflexible behavior. In semantic learning for instance, over-generalization might refer to erroneously relating between concepts, which was found to be evident in semantic-dementia patients (Lambon Ralph et al., 2010). This study further reported that semantic-dementia patients made simultaneously under- and over-generalization errors, indicating impaired regularization in both directions (Lambon Ralph et al., 2010). Over-generalization is widely studied in fear memories as well, and was suggested as a main mechanism underlying panic disorders (Lissek et al., 2009) and anxiety disorders (Dunsmoor et al., 2011; Cha et al., 2014; Lissek et al., 2014; Laufer et al., 2016). The relation between over-generalization and anxiety disorders is rooted in fear conditioning. In healthy subjects, during initial fear conditioning, a stimulus is linked with an aversive result, following which the same stimulus would evoke a similar anxiety response. However, when this conditioning is over-generalized, even scarcely related stimuli can

evoke such anxiety response, a behavior that can lead to different anxiety disorders.

As both transfer and interference are based on synaptic mechanisms demanding synaptic plasticity (see section *Systems and synaptic level*), impaired regularization of such phenomena possibly relates to abnormal brain plasticity. Such abnormalities were previously discussed as characteristics of different disorders, such as schizophrenia (for review see Stephan et al., 2006), autism spectrum disorders and Alzheimer's disease (Battaglia et al., 2007; Oberman et al., 2010; Pascual-Leone et al., 2011; Di Lorenzo et al., 2016). Indeed, patients with such disorders express more interference and impaired generalization correspondingly. For example, patients with mild Alzheimer's disease show higher proactive interference in semantic memory (Loewenstein et al., 2004), and a lower ability to generalize new memories (Bódi et al., 2009). Therefore, cognitive impairment in such disorders might stem from abnormal plasticity resulting in impaired generalization or amplified interference. This notion might advance related research as well as accurate modeling of these disorders.

CONCLUSIONS

To date, generalization and interference have mainly been investigated as two distinct phenomena of the memory system. However, the evidence discussed here suggests that these two are strongly related. This concept is based on commonalities at the behavioral, systems, and synaptic levels, all indicating that although generalization and interference result in different outcomes, their initiation and the underlying processes share multiple similarities.

The studies discussed here demonstrate that generalization and interference occur under similar conditions. Namely, both require a short temporal period between the presentations of two memories (Walker et al., 2003; Korman et al., 2007; Zeithamova and Preston, 2017), and both are enabled even when one of the memories is an existing reactivated memory (Walker et al., 2003; Censor et al., 2014b; de Beukelaar et al., 2014; Wymbs et al., 2016). Mechanistically, both generalization and interference stem from an interaction between two memories, which leads to an overlap between the synaptic engrams corresponding to both memories (Rashid et al., 2016; Yokose et al., 2017). This overlap can either result in interference, weakening one engram, or in generalization, creating a merged strengthened engram (see Fig. 1). Furthermore, in light of the suggested common framework, the studies reviewed here (Mednick et al., 2003; Walker, 2005; Albouy et al., 2015), converge to indicate that consolidation processes during sleep may transform the obtained systems-level modulations into persistent patterns through a parallel bimodal mechanism, enhancing generalization and reducing interference simultaneously (see section *Sleep and consolidation*). Maintaining the balance between generalization and interference is crucial for normal behavioral performance. Under-generalization can result in an increased rate of misses (Lambon Ralph et al., 2010),

while under-interference, although usually studied as a desirable outcome, could prevent the normal prioritization of new memories. This set of undesirable outcomes raises the importance of a profound understanding of generalization and interference in clinical populations. Future research focusing on preventing lower or higher rates of generalization and interference, could benefit cognitive performance in these populations.

Although multiple studies have indeed indicated a relation between generalization and interference, the detailed essence of this relation is yet unknown. Are generalization and interference based on the same neural processes? Or are they driven by distinct processes, which due to the importance in maintaining correct balance allowing efficient learning, were developed to operate in a complementary manner? Recent advances in analysis methods, combined with strong experimental tools, such as non-invasive brain stimulation in humans, and optogenetics in animal models, may provide additional mechanistic explanations, and reveal the extent of the neural overlap between generalization and interference. Future research, producing a simultaneous examination of both generalization and interference, possibly by testing both within a shared framework, could reveal the mechanisms connecting between generalization and interference. Furthermore, such studies could determine if both phenomena are linked mainly at the outcome level, or that both are linked at a more basic level, stemming from a common mechanism providing the ability to coordinate between the two and indicate a strong causal connection.

Computational modeling and neurobiology studies have suggested that the interaction of memory persistence and its decay are crucial for proper cognitive functioning of the human memory system (Richards and Frankland, 2017). Respectively, forgetting was suggested to be crucial because it allows flexible behavior, preventing overfitting to peculiar occurrences. This evidence is supportive of the notion presented here, since on the one hand interference can induce memory decrease (i.e. forgetting), but on the other hand this decrease is crucial to allow generalization, preventing over-fitting and enhancing the flexibility of the memory system. In addition, the shared framework described above shares further similarities with concepts from computational neuroscience. Namely, pattern separation refers to the ability to distinguish between similar inputs (Clelland et al., 2009), possibly relating to the phenomenon of memory interference, while pattern completion refers to the ability to update existing knowledge with new information (O'reilly and McClelland, 1994), possibly relating to memory generalization. In accordance with the commonalities between interference and generalization discussed above, studies evaluating spatial memories in rodents suggested that both pattern separation and pattern completion occur in the hippocampus, with separation processes occurring in the CA3, and completion in the dentate gyrus (for a review see Rolls, 2013; Kesner and Rolls, 2015).

Of note, most of the evidence reviewed here is based on motor and perceptual learning studies, alongside

studies from other memory domains. Although studied across different types of memories, they may point to the existence of a shared framework. However, as accepted in memory research, inferring from one memory domain to the other should be done cautiously, while noting possible points of uniquenesses per each memory type. For example, dopamine is known to play a crucial role in learning (Waelti et al., 2001), but since its receptors are not evenly distributed between motor and visual cortices (Lidow and Goldman-Rakic, 1994), its contribution to learning may differ between perceptual and motor learning. Future studies testing two memory domains within the same study, as done by Mosha and Robertson (2016), could determine to what extent generalization and interference share a common mechanism across memory domains.

Altogether, the data reviewed here converge into a pattern of shared neural substrates (see section *Systems and synaptic level*) and processes (such as neurogenesis and sleep) mediating generalization and interference, which possibly maintain a necessary balance between both phenomena, to allow proper learning. This may explain the behavioral results showing that both interference and generalization are activated in similar conditions of learning, sharing comparable behavioral timescales. In addition, this may account for increased interference and impaired generalization in aging and conditions involving abnormal regularization (see section *Evidence across the life span in normal and impaired conditions*).

In sum, the synergy between memory generalization and interference is apparent in multiple memory domains, and evident across the life span, playing a crucial role in the human brain. The extent of the overlap between these phenomena is yet to be revealed, but the concept of a shared, reciprocal relation between the two is well based across the scientific literature, and may lead to advances in learning and memory research, providing both neuro-rehabilitation methods, as well as improved learning strategies in healthy subjects.

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