Overview

Stress and cognition

Carmen Sandi*

Stress can affect cognition in many ways, with the outcome (i.e., facilitating or impairing) depending on a combination of factors related to both stress and the cognitive function under study. Among the factors identified as particularly relevant to define the cognitive effects of stress are the intensity or magnitude of stress, its origin (i.e., whether triggered by the task or externally), and its duration (i.e., whether acute or chronically delivered). At the cognitive end, the specific cognitive operation (e.g., implicit or explicit memory, long-term or working memory, goal-directed or habit learning) and information processing phases (e.g., learning, consolidation, and retrieval) are essential as well to define stress effects. The emerging view is that mild stress tends to facilitate cognitive function, particularly in implicit memory or simple declarative tasks or when the cognitive load is not excessive. Exposure to high or very high stress acutely (whether elicited by the cognitive task or experienced before being trained or tested in the task) or chronically impairs the formation of explicit memories and, more generally, of those that require complex, flexible reasoning (as typically observed for hippocampus- and prefrontal cortex-related functions) while improving performance of implicit memory and well-rehearsed tasks (as reported for amygdala-dependent conditioning tasks and for striatum-related processes). In addition to these general principles, there are important individual differences in the cognitive impact of stress, with gender and age being particularly influencing factors.

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INTRODUCTION

Cognitive function can be greatly influenced by stress. In fact, the modulatory capacity of stress on cognition is well known to everyone typically out of own experience, with situations that can range from the mild interference that exposure to brief stressors can induce on the ongoing processing of information to the impact of traumatic experiences on the establishment of enduring and devastating memories. Importantly, although the majority of studies so far have focused on stress effects on memory function—which will be the main focus of this overview—most cognitive operations (from attention to decision making) are, in fact, susceptible to be affected by stress.

The intrinsic nature of the close interactions between stress and cognition plausibly reflects its adaptive power throughout evolution. Their intimate crosstalk is supported by a high degree of overlap in the neurobiological systems that sustain these respective functions. Thus, the physiological systems classically activated in response to stress, notably represented by the sympathetic nervous system, the hypothalamus–pituitary–adrenocortical (HPA) axis and central neurotransmitter and neuropeptide systems,[1] have all effector mechanisms in brain circuits that play central roles in information processing. Getting access to their brain targets is straightforward for the adrenocortical hormones glucocorticoids (GRs)—the final products of the HPA axis—because of their lipophilic nature that enables them to readily cross the blood–brain–barrier. GR (e.g., corticosterone being the naturally occurring GR in rodents and cortisol in humans) can exert slow genomic actions through binding to classical GR and mineralocorticoid (MR) receptors, as well as displaying rapid nongenomic effects through actions on membrane-associated GR and MR.[2,3]

*Correspondence to: carmen.sandi@epfl.ch
Brain Mind Institute, School of Life Sciences, Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland

However, circulating levels of the adrenomedullary hormones epinephrine and norepinephrine from the activated sympathetic nervous system seem to require the activation of intermediate signaling pathways (i.e., the vagus nerve and the nucleus of the solitary tract) to indirectly stimulate central noradrenergic pathways and, thereby, brain function.[4] The interaction of glucocorticoids and adrenergic systems in specific brain regions—notably, but not only, the basolateral amygdala—has proved an essential mediating mechanism for a wide variety of the actions displayed by stress on cognition.[5,6]

Although the cognitive effects of stress are frequently assumed to be detrimental, there are many instances in which cognitive functions are not impaired by stress or are even improved. As we will detail below, the specific effect induced by stress depends on a number of factors related to both stress characteristics and to specific aspects of the cognitive function under consideration. In this overview, we first emphasize the importance of taking into account the combinatorial constellation of specific factors when trying to develop an integrative model explaining stress effects on cognition. Then, we discuss progress on the outstanding questions that have been identified in the field over the past two decades. Finally, we conclude by putting forward the general principles emerging from this exploding field on the interactions between stress and cognition.

STRESS AND COGNITION—THE BIG PICTURE: FACTORS AFFECTING STRESS EFFECTS ON COGNITION

In attempting to systematically address what are the effects of stress on cognitive function, it is mandatory to deal with the complexity inherent to both terms, stress and cognition.

Stress-Related Factors

Although stress is a vague concept and there is no absolute consensus in the literature as to its exact meaning, a classical view considers that stress implies any challenge to the homeostasis of an individual that requires an adaptive response from that individual.[7] Despite recent attempts to re-conceptualize the term 'to be restricted to conditions where an environmental demand exceeds the natural regulatory capacity of an organism, in particular situations that include unpredictability and uncontrollability',[8] the term stress is typically and widely used to refer to conditions ranging from mild challenges to extremely aversive conditions.

In addition to the just mentioned differences in stress intensity and on its degree of controllability and predictability, two other stress-related factors have received particular attention in the literature dealing with the cognitive effects of stress (Figure 1). One is related to stress frequency and/or duration, and generally focuses in two main dichotomized categories, acute versus chronic stress. The other one refers to the degree to which stress is linked to the task. This is generally reflected in two major categories: 'intrinsic' stress when it is triggered by the task or closely associated in time to the cognitive challenge versus 'extrinsic' stress when it is experienced outside the task or context and not contingent to the information processing under study.[9–12]

Cognition-Related Factors

On its turn, cognition is as well a broad concept that involves a variety of processes that deal with information and manipulate representations in the brain with the goal of producing a suitable response. They range from perception and attention to various types of memory, language and executive control processes.[13] The vast majority of research dealing with the cognitive effects of stress has covered quite comprehensively stress actions on different aspects of memory function, including its different phases (acquisition, consolidation, retrieval, etc.), operations (working memory vs long-term memory), types (implicit vs explicit), and strategies (habit vs goal-directed; Figure 1).

Given the scope of aspects defining both, stress and memory function, the combinatorial possibilities that can be tackled in specific experiments are multiple. Figure 2 shows this idea using the roulette metaphor, with the insert boxes in each of the panels exemplifying some of the combinations of factors that are frequently found in particular studies in the literature and that, typically, give rise to different outcomes. As will be discussed below, while the constellation of elements in the insert in Figure 2(a) generally facilitates the cognitive process under study, those in Figure 2(b) tend to lead to its inhibition. In this article, we can clearly not cover the whole spectrum of possibilities represented in these roulettes, mostly due to the existence of gaps in the literature for some of the combinations. Instead, we will focus on those factors for which there are substantial relevant data to provide a coherent picture, addressing the outstanding questions and topics that have concentrated most of the relevant research in the field.

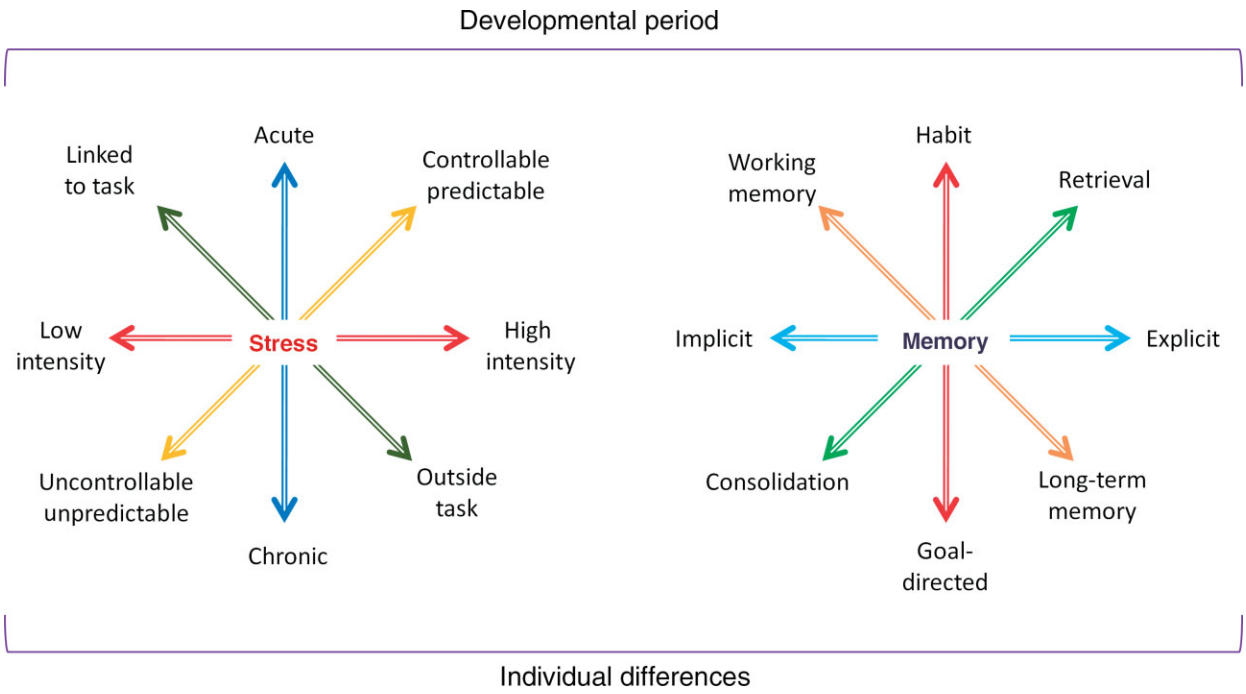

FIGURE 1 | Scheme depicting the relevant factors related to both stress and cognition that account for the cognitive outcome of stress. Developmental age and individual factors will also influence the outcome of the interaction between stress and cognitive factors.

The Importance of Individual Differences

Before addressing the general principles in the literature, we should first acknowledge the existence of important differences in the way individuals are affected in their cognitive capabilities when exposed to particular stress conditions. Although the topic has not been systematically addressed, evidence from the animal and human literature indicates the existence of considerable variability in the vulnerability of individuals to display cognitive changes when exposed to stress. Whereas some individuals are particularly 'vulnerable', others seem to be quite 'resistant' to the effects of stress. These differences could be due to predisposing factors, previous life experiences or, more likely, both. Among the individual factors, gender,[14–17] genetic endowment,[18] personality traits,[19–21] and age[22,23] can play an important role in the cognitive consequences of stress (Figure 1). Dealing with the contribution of these individual factors is well outside the scope of this review. Therefore, genetic and personality background will be disregarded, with effects reported here accounting for the average of the studied populations. Regarding gender, we should acknowledge that most of the literature available and discussed here has been obtained in adult males, and therefore any conclusion reached cannot automatically be translated to females or to other developmental ages. Another aspect that will not be addressed here but that certainly contributes to the complexity of stress and cognitive interactions is the enormous programing power that stress has, when experienced at different developmental periods, on later stress reactivity and cognitive capabilities.[24–26]

MEMORY STRENGTH AS A FUNCTION OF STRESS INTENSITY—LINEAR VERSUS INVERTED-U-SHAPE EFFECTS

The importance of the factor stress 'intensity' to determine the direction of stress effects in cognition, in general, and in memory function in particular has been recognized in the literature for a very long time. Although the predominant belief is probably that an inverted-U-shaped function can explain the relationship between stress intensity and memory (i.e., with low and high stress levels impairing memory, whereas intermediate levels facilitating it), this stress–memory relationship seems to not apply to classical conditioning processes. Rather, a systematic review of the literature[12] concluded the existence of a linear relationship between stressor intensity and the strength of the memory formed in conditioning studies, with an asymptotic waveform for high-to-very-high stress intensities. Typically, studies involving fear conditioning and manipulating shock

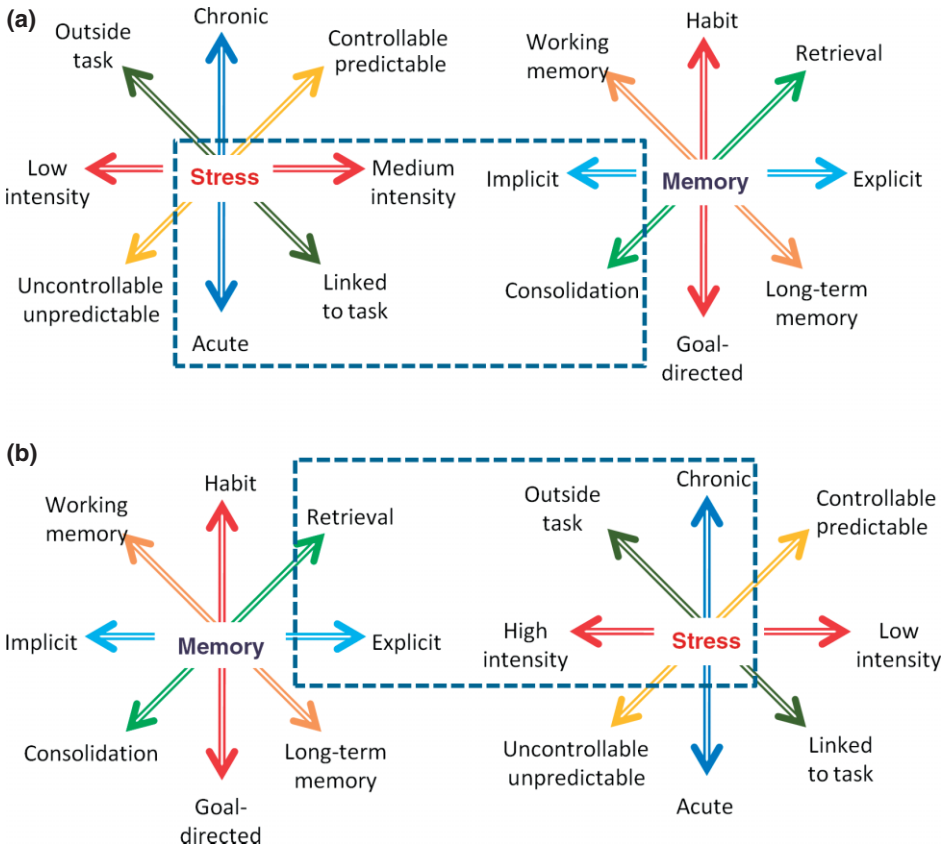

FIGURE 2 | Scheme showing the roulette metaphor for different combinatorial possibilities occurring in the intersection between specific stress conditions and cognitive processing and defined by the elements inserted in each box. (a) Elements in the insert include a constellation of factors exemplifying conditions in which an acute, medium intensity stressor is acutely triggered by an implicit memory task and elevated during the consolidation period—according to the literature, this constellation will typically lead to improved memory as compared to lower stress conditions. (b) The constellations of elements here include a chronic stress situation of high intensity experienced before individuals are exposed to the retrieval of an explicit memory task—according to the literature, the expected results in this case will be impaired retrieval as compared to a nonstress condition.

intensity at training observed a positive correlation with the level of freezing displayed by animals at the testing session.[27–31] This fits, in fact, with studies performed on discrimination learning in mice by the instigators of the inverted-U-shape function, Yerkes and Dodson,[32] who found that the impact of stress intensity on 'easy' tasks followed as well a linear relationship. Glucocorticoids were implicated in the linear relationship between stress and strength of conditioning.[27,33]

However, the so-called Yerkes–Dodson law implies that cognitive performance in 'difficult' tasks is best when an individual is under optimal stress, while it is impaired under conditions above or below optimal stress levels.[32,34] Although the strongly intuitive appealing of this proposal made it gaining high popularity, the validity of the law has been repeatedly criticized because of important methodological weaknesses.[35] In the domain of animal learning that has pioneered studies in this field, it is surprising to note that, until recently, not a single report had described an inverted-U-shape function for an explicit (effortful or 'difficult') task under the same experimental conditions. Claims for the existence of an inverted-U-shape relationship were made using independent observations from different experimental approaches examining either the ascending (i.e., facilitating) or descending (i.e., impairing) parts of the function, and typically mixing situations in which stress was 'triggered by the task' with others in which it was delivered 'outside the task'.[12,36,37] Thus, using the Morris water maze variations in the water temperature provided evidence for the ascending branch, with rats trained at 19°C displaying higher corticosterone levels and performing better than rats trained at 25°C[38,39] (see also Ref 40 for an example in mice). Recent evidence suggests that the facilitating effects of stress and glucocorticoids might implicate rapid spinogenesis via GRs.[41] Independently, the fact that training rats at lower water temperatures (12°C) led to

impaired learning[42] was interpreted as evidence for the complementary descending branch of the inverted-U-shape.[12] Recently, experimental evidence supporting the existence of an inverted-U-shaped relationship for performance under the same experimental conditions was presented in the hippocampus-dependent learning task radial arm water maze.[43] Rats trained at 19°C made fewer errors than animals trained at either higher (16°C) or lower (25°C) stress conditions. This function was already observed by the last trial of day 1 and maintained on the first trial of day 2, confirming the existence of an inverted-U-shape memory function according to stressor intensity during the early learning and memory phases in a hippocampus-dependent task. With overtraining, initial differences due to variations in stress level seem to disappear.

Studies using manipulations of the noradrenergic[44] and glucocorticoid[45–47] systems have successfully substantiated the inverted-U-shape relationship between hormonal levels and both learning and synaptic plasticity. Electrophysiological studies have implicated the basolateral amygdala in the biphasic effect of stress on hippocampal synaptic plasticity.[48]

THE RELEVANCE OF THE SOURCE OF STRESS WITH REGARDS TO THE LEARNING TASK ON MEMORY FORMATION

The relationship between stress intensity and learning and memory discussed above was centered in situations in which stress was elicited by the training task (in our terminology, 'intrinsic' stress). To our knowledge, there are no systematic studies addressing how variations in the intensity of externally delivered ('extrinsic') stress would affect different types of learning. Instead, there are many studies that evaluated the effect of a single acute stress session delivered either before or after (i.e., 'extrinsic') training individuals in different training tasks. When we look at the outcome taking into account the memory type, a consistent pattern emerges. On the sake of clarity, we will discuss this literature according to the classification of memory types that distinguishes between 'explicit' or 'declarative' memory about facts and events and 'implicit' or nondeclarative memory that is expressed through performance, such as skill learning and habit learning.[49] However, it is important to note that both memory systems should not be regarded as necessarily separated as they frequently interact, and emerging evidence indicates that they can as well profoundly overlap.[50]

Implicit Memory

Overall, *exposure to stress shortly before training* individuals in implicit memory tasks leads to improved performance. In classical conditioning tasks, stress experienced before training was consistently shown to facilitate conditioning in male individuals.[51] For example, in studies evaluating eyeblink conditioning in male rats, high-to-very-high stressful situations potentiated conditioning of both hippocampal-dependent and independent eyeblink conditioning tasks.[52] In men, exposure to psychosocial stress subsequently enhanced classical conditioning for negative but not positive stimuli in a 'Pokemon' task[53] as well as performance in a priming task.[54,55] Similarly, exposure to stress was shown to facilitate fear conditioning in rats[56,57] and humans.[58] Glucocorticoids were found to be implicated in these facilitating effects of stress, as shown for eyeblink conditioning in rats[59] and fear conditioning in rats[60] and humans.[58] Interestingly, stress-enhanced fear learning in rats was found to be resistant to the effects of immediate massed extinction, a phenomenon that might have implications to understand similar deficits observed in PTSD patients.[61] Evidence points out the amygdala as a key potential substrate for these effects, with evidence for rapid and long-lasting dendritic hypertrophy in the basolateral amygdala and heightened anxiety following a single stress session or elevated glucocorticoid levels.[62]

On its turn, *when stress was given after training*, it was either inefficient to affect the acquired implicit memory (as it was the case for eyeblink conditioning when followed by the same stressor that facilitated learning when given pretraining[59]) or, again, exerted facilitating effects (as shown for fear conditioning[63]).

Explicit Memory

The impact of *prior acute stress* in explicit memory is less clear. Frequently, neither performance at training, nor short-term memory when tested closely after training are obviously affected, but there is impaired long-term recall of the information acquired under the effect of stress. This sort of effects was found in animals submitted to strong stress and has been reported for the Morris water maze,[64–66] the radial arm water maze[67] and for the non-spatial object-recognition memory.[68] However, in a paradigm based on the recognition of a newly formed social hierarchy in rats, prior stress facilitated the establishment of a subordination memory[69] possibly through a facilitating glucocorticoid action in memory consolidation.[70]

In humans, psychosocial *stress given before training* had mixed effects, including a lack of

effects[55,71] on verbal tasks, as well as the impairment[72] and facilitation[53] of spatial memory. Exposure to a mild physical stressor in men (i.e., the cold pressor test for 1 min) facilitated performance in two hippocampus-dependent tasks, including a virtual Morris water task.[73] Several studies indicated that memory for emotional information tends to be facilitated by prior stress exposure, with memory for neutral information not being affected or even impaired by prior stress, as shown both for words[74,75] and for specific aspects of episodic memory.[76] The facilitating effect of stress on memory for emotional words was particularly observed for negative, rather than positive words[75] and when stress was given immediately, but not 30 min, before learning.[77] Enhanced cortisol responses predicted the magnitude of both stress-induced impairing[72,76,77] and facilitating effects[75,78]; but note that some studies found positive correlations between enhanced cortisol levels at encoding and the formation of false memories.[76] Accordingly, administration of cortisol before learning facilitated long-term memory for emotionally arousing pictures.[79] In a verbal learning task, exposure to psychosocial stress was found to facilitate recall of verbal information only in individuals that showed high cortisol responses to a psychosocial stress challenge.[80] In addition to direct effects of stress in the hippocampus,[81] amygdala activation by stress can on its turn affect hippocampal plasticity,[66,82] including the alteration of firing properties in hippocampal place cells and, thus, affect the processing of explicit information.[83]

Although the examples of studies examining the effects of *posttraining stress* in explicit memory are scarce, rodent studies tend to report impairing effects, with the potential for impairing effects depending on a number of factors: (i) the training intensity and learning acquisition; with only labile, not overtrained memories being susceptible to immediate disruption by stress; (ii) the timing between training and stress delivery; with time short lapses of around 5 min between training and stress delivery being effective to disrupt memory consolidation while longer lapses of around 5 hours being ineffective.[84] In agreement with this view, exposure to a highly stressful experience in rats (i.e., cat exposure for 30 min) immediately after spatial learning impaired memory formation.[37] Activation of GR in the basolateral amygdala has been implicated in the disruptive effects of stress on the consolidation of hippocampal-dependent learning.[85]

However, in humans, *stress given posttraining* facilitated memory consolidation, leading to enhanced performance in recall tests given 24–48 hours afterward.[71,86,87] As shown for pre-learning stress (see above), memory for emotional but not neutral information was found to be selectively facilitated by post-learning stress exposure[88] (but see Ref 89 for the opposite example). Importantly, cortisol and sympathetic activity were positively correlated with the memory enhancing effects of stress.[71,87]

Although the differences in the results respectively obtained in animal and humans are difficult to reconcile, two key factors appear as strikingly different between studies including humans and non-human animals: the severity of the stressors used and the stressful nature of the learning tasks. In our view, stressful situations employed in animal studies (e.g., restrain; shocks; exposure to predators) are considerably more severe (frequently involving life-threatening situations) than those applied in human studies (e.g., brief arm immersion in cold water; evaluative interviews). As a consequence, studies in the different species would generally fall in different stress intensity categories, with those in humans tending to involve milder extrinsic stress manipulations than animal studies. This is well-documented in the substantially higher fold-increases in glucocorticoid levels reported in the rodent stress literature than in human studies. Likewise, learning tasks given to animals are generally stressful (e.g., water maze learning) while those given to humans are less generally less threatening (e.g., words lists, pictures). Thus, most animal studies exploring the impact of extrinsic stress tend to involve the competition between the exogenously given and the task-elicited stress, while the degree of intrinsic stress in the memory tasks in humans would normally be much lower. Accordingly, the different stress levels resulting from the interaction between these two factors in animal and human studies might explain the very different memory outcomes typically reported for the effects of intrinsic stress on explicit memories in the different animal species.

Concluding About the Impact of the Source of Stress: Intrinsic Versus Extrinsic to the Task

Thus, experiencing stress at learning (i.e., training phase), either when stress is triggered by the task (i.e., intrinsic) or administered exogenously (i.e., extrinsic) consistently exerts a facilitating effect in implicit tasks. Increasing levels of intrinsic stress lead to a linear asymptotic enhancement of implicit memory, while extrinsic stress seems to shift this linear effect to the left (Figure 3). In explicit memory tasks, an inverted-U-shape is found with increasing stress intensity. Extrinsic stress, though not always having obvious effects on performance

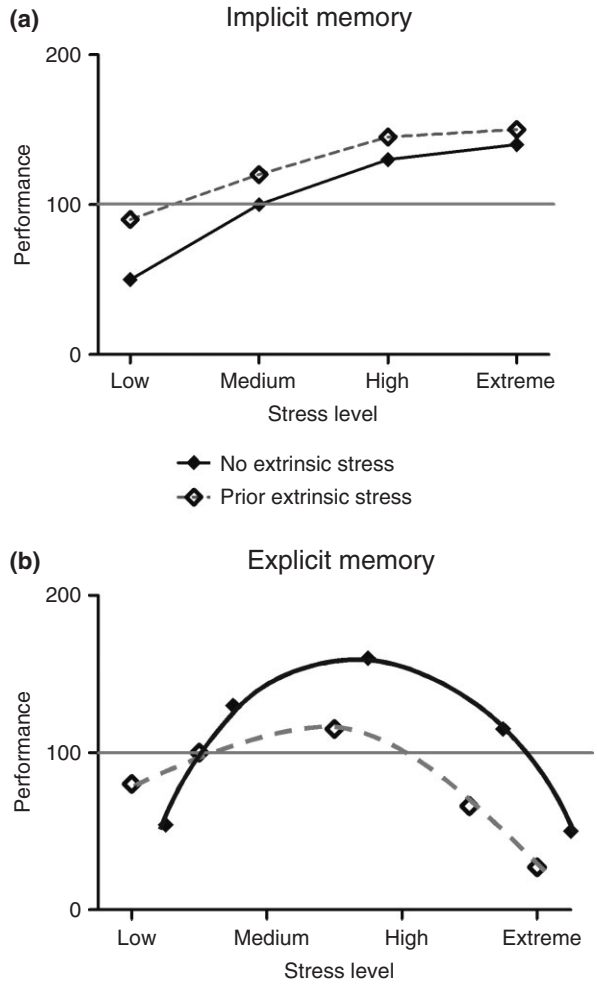

FIGURE 3 | Scheme showing the effects of intrinsic and extrinsic stress in different memory types. (a) Intrinsic stress that occurs within the training task tends to induce a linear facilitation of implicit memory. Further stress—extrinsic—given either before or after training in implicit tasks exerts a facilitating effect, shifting the memory function to the left. (b) The relationship between intrinsic stress and the formation of explicit memories tends to follow an inverted-U-shape, with low and high stress levels triggered by the task leading to worse performance than intermediate stress levels. When extrinsic stress is experienced before or after training, there is a shift of the memory curve to the left and downward, the most consistent effect being for high extrinsic stress impairing explicit memories. The same impairing effect is observed for explicit memory retrieval and for prefrontal cortex-dependent memory functions.

during training in explicit tasks, it seems to shift the memory curve to the left as well as downward (Figure 3); i.e., moderate stress experiences would facilitate performance for low stressful tasks, while highly stressful experiences would interfere with the transfer of the processed information into a long-term memory. Under moderate stress, emotional information tends to be more susceptible than neutral information to be facilitated by stress. Thus, extrinsic stress interacts in subtle and learning type-specific manners with explicit memory formation.

A general principle that emerges from the reviewed data is that what matters is the total amount of stress (extrinsic plus intrinsic) experienced at training and during the immediate posttraining period, with increasing levels facilitating inducing a linear facilitation in implicit memory tasks, while inducing inverted-U-shape effects in explicit memory tasks.

STRESS EFFECTS ON MEMORY RETRIEVAL

Whereas, as we have seen, stress effects at learning and during the consolidation period have been studied with regards to both implicit and explicit memory types, most of the work addressed to investigate the impact of stress on the retrieval of previously acquired information has focused, almost exclusively, in how extrinsic stress affects immediate recall of explicit information. Tangential information for stress effects in implicit information can be derived from studies involving systemic administration of stress hormones shortly before retrieval in a fear conditioning task, with the outcome of those experiments being, again, improved retention in animals that had been trained days and even months before being submitted to the recall test.[90]

Regarding explicit memories, consistent evidence indicates that stress and glucocorticoids, when given shortly before testing, impair the retrieval of hippocampus-dependent memory, both in rodents[67,91] and humans.[87,92,93] Infusion of a GR agonist into the dorsal hippocampus before testing impairs retrieval[94] and viral expression of a transdominant GR in the dentate gyrus prevents retrieval impairment by corticosterone.[95] Intriguingly, studies in mice indicate that short exposures (i.e., 2–5 min) to restraint stress might be more effective than longer exposures (i.e., 10 min),[96] while a certain lapse of around 30 min between stress administration and cognitive challenge was by large more effective than shorter time lapses both in rats[91] and humans.[92] But note that a longer time lapse of 4 h was ineffective to impair recall of information.[91] Another factor that might play a role is the duration between acquisition and retrieval, with an intermediate phase of memory (from around 2 h to 4 days) being particularly susceptible to disruption by stress.[96]

In agreement with a large body of data indicating the existence of intricate interactions between

glucocorticoids and norepinephrine in the cognitive effects of stress,[1,97] recent work has implicated β-adrenergic neurotransmission in the hippocampus, but not in the amygdala,[98] in the impairing effects of stress and glucocorticoids[99,100] and, more precisely, the activation of β2-adrenergic receptors.[96] Noticeably, corticosterone effects on memory retrieval seem to be membrane-mediated, non-genomic, as infusion of protein-conjugated corticosterone that selectively activates membrane receptors impairs, as well, memory retrieval[101] while corticosterone-induced impairing effects could not be blocked by administering a protein synthesis inhibitor.[102]

THE IMPACT OF STRESS DURATION ON MEMORY FORMATION—ACUTE VERSUS CHRONIC EFFECTS

As just reviewed above, acute extrinsic stress tends to facilitate implicit memory processes while producing mixing results in explicit memory tasks that depend on the task-elicited stress levels (as well as cognitive load). If we were only to consider highly stressful situations, the effects of acute stress in both classes of memory processes would be considered opposite: facilitating for implicit, while impairing for explicit memory. In this section, we will inquiry how chronic stress affects these same processes.

Explicit Memory

Originally, research aimed at understanding the effects of chronic stress on cognitive function focused, to a great degree, on memory tasks related to hippocampal function. This is a field that continues receiving nowadays close attention after more than two decades of very intensive research. This interest was originally motivated by early evidence indicating profound changes in hippocampal morphology following chronic stress.[81] From the pioneering findings of dendritic atrophy in hippocampal CA3 pyramidal neurons following chronic stress exposure in rats,[103] a full range of structural alterations in all hippocampal subregions has been subsequently described.[81,104–106]

A critical feature determining the effects of chronic stress on explicit memory is the length of the stress protocols. In rats, whereas 3 to 6 weeks of chronic stress generally leads to impairing effects (see below), similar stress procedures given for 10–13 consecutive days were reported to, instead, lead to improved spatial learning, both in the radial arm maze[107] and in the Morris water maze.[108] The majority of studies involving longer stress exposure that have provided important support for a functional-behavioral translation of the chronic stress-induced alterations in hippocampal structure have focused on spatial memory. In rodents, impaired effects of chronic stress exposure in spatial learning were observed throughout a wide variety of tasks, including the radial arm maze,[109] radial arm water maze,[110] Y maze,[111] and Morris water maze.[112–115] Some of these impairments were of small magnitude[112,115] as well as reversible and temporally limited, and blocked by treatments that prevent the development of stress-induced atrophy of dendrites in hippocampal neurons.[111,116]

A line of research has questioned the hippocampal structural alterations as the only explanation to account for the impairing effects of chronic stress in hippocampus-dependent memory tasks. Instead, elevated glucocorticoid levels induced by chronic stress were proposed to be critical in the memory retrieval deficits induced by hippocampal damage. Evidence for this proposal was provided by studies showing that reducing CA3 lesion-induced elevated plasma corticosterone levels with the glucocorticoid synthesis inhibitor metyrapone prevented observing a lesion-induced recall deficit in the water maze task.[117] In addition to corticosterone elevations, stress-induced reduction in hippocampal glucocorticoid receptor expression at the time of behavioral assessment was also implicated in memory deficits induced by chronic stress.[118] In our view, both hippocampal morphological changes and elevated glucocorticoids probably contribute to the described effects. Note that glucocorticoids have been, as well, implicated in chronic stress-induced alterations in hippocampal structure.[103]

Available evidence for the impact of chronic stress in explicit memory in healthy humans is scarce, essentially due to the ethical constraints inherent to expose humans to repeated stress in experimental studies.[119] Indirect evidence, though, seems to support a role. For example, reduced hippocampal volume has been reported in individuals with low self-esteem, a trait that strongly predicts increased reactivity to stress.[120] Furthermore, elevations in plasma cortisol levels occurring over years in older adults were found to negatively correlate with hippocampal volume and performance in explicit memory tasks.[121] Noticeably, there is emerging evidence indicating that chronic exposure to stress and/or glucocorticoids worsens cognition and neuropathology in humans with Alzheimer's disease[122] and in rodent models of the disease.[123]

Due to the mentioned constraints to perform experimental studies of chronic stress, much of

the available information is derived from studies focusing on stress-related neuropsychiatric disorders. This approach has provided substantial evidence to establish a link between accumulated exposure to stress and impaired hippocampal function in humans. Thus, in major depressive disorder, a clinical condition highly sensitive to stress and that curses with reduced hippocampal volume, the greatest degree of cognitive impairment is on memory parameters that are greatly dependent on hippocampal function (for a review, see Ref 124). In this connection, a relevant hypothesis has been recently put forward emphasizing a key role for cognitive factors in the link between stress, anxiety and psychopathology.[21,125]

Implicit Memory

As shown for acute stress, chronic stress facilitates as well fear conditioning.[116,126] These findings are classically interpreted in the light of parallel morphological observations indicating that stress induces synaptic remodeling, spinogenesis and increased dendritic branching in the basolateral and medial amygdala along with increases in anxiety (for a review, see Ref 127). Importantly, only those chronic stress protocols that result in dendritic atrophy in the basolateral amygdala lead to increases in anxiety-like behavior,[128,129] raising the issue of the specificity of the stress-induced enhancement of fear conditioning to the cognitive domain. An alternative explanation would imply that increased anxiety in these animals might result in enhanced emotional responsiveness to environmental stimuli that could overlap with enhanced fear learning, as suggested by enhanced freezing responses observed at training in chronically stressed animals.[60,126,130]

The Impact of Chronic Versus Acute Stress

Therefore, the effects of chronic stress on the different types of learning are overall consistent with the effects observed under high acute stress conditions, with implicit memory being facilitated while explicit memory impaired. This is a remarkable finding given that the underlying mechanisms respectively triggered by acute and chronic stress are distinct in many respects.[24,81,104,131,132] Whereas glutamatergic systems have been emphasized as major players in the wide variety of acute stress effects,[132,133] a much larger number of molecules have been identified as critical targets of chronic stress, including various neurotransmitters, signal transduction pathways, neurotrophic factors, and epigenetic modulators.[81,134–136] One of the molecules that has been causally involved in the behavioral effects of chronic stress is the neural cell adhesion molecule (NCAM), a glycoprotein that participates in cell-cell binding and activity-dependent synaptic rearrangements.[104,130,137,138]

WORKING MEMORY, REVERSAL LEARNING AND EXECUTIVE FUNCTION

Accumulated evidence supports a strong modulatory role for stress, both acute and chronic, on higher-order cognitive functions supported by the prefrontal cortex (PFC). In fact, the PFC is the brain region that presumably responds with a greatest sensitivity to stress, as indicated by both the rapid changes observed in prefrontal cognitive abilities and by the magnitude of the observed effects with progressive stress exposure.[131]

Following acute stress, the reported effects are, however, quite varied. Thus, in rodents, although deleterious effects on working memory are frequently reported, several studies have indicated lack of effect or even a facilitating one (for a review, see Ref 139). In humans, a similar picture is emerging, with examples for both impairing[53,140–142] and enhancing[142–146] effects of acute stress in working memory function, cognitive flexibility and decision-making.[147,148] Differences across studies on factors such as stress intensity and cognitive load probably account for these divergent effects. Biphasic effects resulting from variations in stress intensity are believed to be mediated by differential effects of progressive dopamine (through D1 receptor stimulation) and norepinephrine (probably involving β_1-receptor stimulation) levels. Thus, mild increases in these monoamines associated to moderate stress exposure enhance functional connectivity within PFC networks (for a review, see Ref 131). However, under high and uncontrollable stressful situations, excessive release of these neurotransmitters impairs PFC function and associated behaviors.[131,145,149,150] GRs in the PFC appear to regulate stress-evoked dopamine efflux and associated working memory impairment.[151] Another important variable that seems to account for the differential effects of acute stress is the timing between stress activation and memory challenge. When testing rats in a T-maze delayed alternation task was carried out 4 or 24 hours after exposure to stress, performance was improved in a GR-dependent manner.[152] Noticeably, delayed—but not immediate—effects of glucocorticoid administration in humans (and, thus, indicative of slow glucocorticoid actions) improved working memory performance and increased neuronal

activity during performance in the dorsolateral PFC depending on task load.[153]

On its turn, under chronic stress conditions, PFC-dependent cognitive functions are consistently impaired.[131,139,154] In addition to examples of alterations in attentional set-shifting both in rats[155] and humans,[156] a variety of PFC-dependent memory processes—e.g., working memory, reversal learning, fear extinction—have been found to show deficits following chronic stress. Working memory impairment following chronic stress has been observed in animals using different tasks, including spatial delayed alternation tasks[157,158] and a Morris water maze version in which subjects are requested to learn a new platform position each day across several trials.[159] Importantly, altered working memory performance is observed in association with increased perseveration, reflecting the commitment of consecutive errors during task performance.[158] Reversal learning impairment was also reported in rats using the Morris water maze by moving the hidden platform to the opposite location at which animals were repeatedly trained in the reference memory version of the task.[159] In humans performance in attention-executive function tasks was found to be impaired in dementia caregivers, a group of subjects typically submitted to cumulative stress.[160] Finally, extinction of fear conditioning—a memory process that involves as well the mPFC[161]—was also shown to be notably impaired by chronic stress.[17,162] Alterations in all these PFC-dependent memory types are typically observed in chronic stress-associated neuropsychiatric conditions, such as depression[163] and posttraumatic stress disorder (PTSD).[164]

Among the potential mechanisms mediating these behavioral effects of chronic stress, animal studies have highlighted marked morphological alterations in the medial PFC, but not orbitofrontal cortex,[155] with several signs of atrophy (e.g., reductions in spine density and dendritic branching in specific cortical layers to spine loss) particularly observed in layer II/III neurons (for a review, see Ref 154). Remarkably, these changes seem to be subregions specific, as dendritic atrophy was not observed in rats in the projection infralimbic PFC neurons that project to the amygdala.[165]

In summary, the message that emerges from this literature is that PFC-dependent cognitive functions are impaired by exposure to high and/or sustained stress levels; however, under milder acute stress situations, there is a window of opportunity for their improvement. This pattern resembles to a large extent the relationship between stress and explicit memory discussed above.

STRESS EFFECTS ON MEMORY SYSTEMS: HABIT VERSUS GOAL-DIRECTED BEHAVIOR

One of the latest advances in the field has been the recognition that stress can affect the contribution of different memory systems to cognitive performance.[166] The emerging view is that exposure to high stress levels tend to switch performance of tasks from the use of flexible cognitive operations to the use of more rigid strategies or habit memory. This pattern has been documented in animals and humans, as well as following acute and chronic stress exposure.

Under acute stress, one of the pioneer studies showed that exposure to a strong stressor prior learning can alter learning strategies in a modified version of the Morris water maze. Rats were trained to find a hidden but cued platform either under stress or control conditions. Subsequently, they were given a test in which the platform and cue were relocated. Rats that had been trained under stress tended to follow a stimulus-response strategy, searching for the platform around the new cue location, whereas controls followed a spatial strategy, with their search focused on the former platform location.[82] The amygdala[82] and glucocorticoids[166] have been implicated in the transition from spatial to stimulus-response memory systems. Subsequent work in humans using a psychosocial stressor further established that stress prior to learning facilitates simple stimulus-response learning strategies in humans-at the expense of a spatial, more cognitive learning strategy.[167] These observations were then extended to strategies guiding operant or instrumental learning. Human subjects were trained, either following stress or control conditions, to perform two instrumental actions that were associated with two distinct food outcomes. Then, one of the food outcomes was devalued by allowing subjects to ingest till saturation with that food. When exposed again to a session involving the two instrumental actions in extinction, stressed subjects—as opposed to controls- were not sensitive to the change in the value of the food outcomes.[168] Again, this data suggested that acute stress lead to habit performance at the expense of goal-directed behavior. Functional neuroimaging data has documented parallel changes in the engagement of memory systems in the human brain, with stress impairing the use of the hippocampus-dependent system and allowing the striatum to control behavior.[169]

Chronic stress influences as well the switch between cognitive systems in a very consistent manner. Evidence was first obtained in mice and men in

parallel, showing that chronic stress shifts as well cognitive performance from spatial to stimulus-response learning strategies.[170] A landmark study in rats provided behavioral and morphological evidence in support of the view that chronic stress biases decision-making strategies, affecting the ability of stressed animals to perform actions on the basis of their consequences. Using two different operant tasks, Dias-Ferreira et al.[171] showed that rats subjected to chronic stress become insensitive to changes in outcome value and resistant to changes in action-outcome contingency. Importantly, this study also showed that chronic stress causes opposing structural changes in the associative and sensorimotor corticostriatal circuits underlying these different behavioral strategies with atrophy of medial prefrontal cortex and the associative striatum and hypertrophy of the sensorimotor striatum. The authors suggested that the relative advantage of circuits coursing through sensorimotor striatum observed after chronic stress leads to a bias in behavioral strategies toward habit. Recently, the same type of effects have been confirmed in humans in a study evaluating behavioral and brain responses to instrumental tasks in medical students submitted to chronic stress during the exams period.[172] The study confirmed that chronic stress transiently biases decision-making strategies in humans toward habits and shifts brain activation from the associative to the sensorimotor circuits. Importantly, these functional changes were found to be paralleled by atrophy of the medial prefrontal cortex and the caudate.

CONCLUSIONS

The findings discussed in this overview allow us to conclude that stress intensity is a major defining factor of the effects of stress in cognition. Overall, mild stress tends to facilitate cognitive function, particularly in simple tasks or when the cognitive load is not excessive. The effects of high or sustained stress mostly depend on the cognitive process under study, with deficits typically observed for hippocampus- and prefrontal cortex-related functions, while improvement for simple implicit tasks and striatum-related processes.

More generally, the general view that emerges is that exposure to high-to-very-high stress acutely (whether elicited by the cognitive task or experienced before being trained or tested in the task) or chronically impairs performance on explicit memory tasks that require complex, flexible reasoning while improving performance on implicit memory tasks, in simple declarative memories and in well-rehearsed tasks. In addition to fitting with impairing stress effects in hippocampus-dependent memories and facilitating effects in amygdala-dependent conditioning processes, this view fits with the impairments observed in cognitive tasks that rely on PFC operations and with simultaneous sparing or enhancement of habits that rely on basal ganglia circuits.[131,173,174]

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