Emotional Hormones and Memory Modulation

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Introduction

Emotionally arousing experiences are generally well remembered. We know that from our own experiences as well as from extensive research findings. Memories of automobile accidents, fires, muggings, rapes, wartime battles, terrorists’ bombings, and other intensely emotional experiences are often reported as being ‘deeply etched in the brain.’ We also remember significant details of special occasions such as birthdays, bar mitzvahs, weddings, graduation ceremonies, and funerals as well as horrific events such as those of 11 September 2001. Milder emotional experiences such as those induced by praises, insults, or embarrassments also tend to be well remembered.

There are some obvious and partly correct explanations of why it is that emotional experiences (of either positive or negative valence) create strong memories. We may pay more attention to details during the experiences and we may repeatedly recall the experiences and, thus inadvertently, or purposefully, rehearse them. However, in addition, as discussed below, there is extensive evidence that neurobiological processes initiated by emotionally arousing experiences act automatically to strengthen memories of the experiences. And, it certainly seems highly adaptive to have such automatic processes that enable the significance of events to regulate their remembrance.

However, stress and emotional arousal not only induce strong memories of new information but can also impair our remembering. We all have, probably, experienced situations such as stressful examinations or job interviews during which we were simply not able to recall information. The evidence from many animal and human studies now indicates that the mechanisms that enhance the consolidation of new, emotionally arousing experiences are also responsible for the impairment of memory retrieval and working memory.

Stress Hormone Effects on Memory Consolidation

Emotionally arousing experiences induce the release of stress hormones from the adrenal glands. The adrenergic hormone epinephrine (adrenaline) is released into the circulatory system from the adrenal medulla, and the glucocorticoid cortisol (corticosterone in rodents) is secreted from the adrenal cortex. The extensive evidence that stimulant drugs (e.g., amphetamine) administered to rats or mice shortly after they are trained on a task enhance the consolidation of memory of the training suggested that stress hormones released by the training experience may act as endogenous modulators of memory consolidation. Considerable evidence supports this hypothesis. Epinephrine or glucocorticoid receptor (GR) agonists administered within minutes after training produce dose-dependent enhancement of the long-term retention of many different kinds of training experiences typically used in animal memory studies, including inhibitory avoidance, contextual and cued fear conditioning, spatial discrimination, conditioned taste aversion, and object recognition. Further, adrenoceptor antagonists or drugs that disrupt glucocorticoid functioning impair memory when administered post-training. As stress hormones administered an hour or longer after training do not affect subsequent memory, the effects obtained with administration shortly after training provide strong evidence that the hormones influence the consolidation of long-term memory that is initiated by the training experiences. There is also extensive evidence that epinephrine and glucocorticoids, as well as stressful conditions that stimulate their release, enhance memory consolidation in human subjects when administered shortly before or after learning.

Although epinephrine and glucocorticoid stress hormones have similar effects in enhancing memory consolidation, their effects are initiated through different mechanisms. Epinephrine does not directly affect brain activity as it does not pass the blood–brain barrier. The effects are mediated by the stimulation of β-adrenoceptors located on the ascending vagus nerve that projects to noradrenergic cells in the nucleus of the solitary tract (NTS) located in the brain stem. These noradrenergic cells directly innervate brain regions involved in memory consolidation, including the amygdala. The NTS may also influence noradrenergic activation via its projection to the locus coeruleus (LC), which has noradrenergic cells with more widespread projections to forebrain regions, including the hippocampus, cortex, and amygdala. The key role of the NTS in mediating epinephrine effects on memory is indicated by the finding that brief inactivation of cells in the NTS with lidocaine (to block sodium channels) prevents epinephrine-induced release of norepinephrine (NE) in other brain regions and blocks epinephrine influences on memory consolidation. Further, stimulating the NTS immediately after training...
by infusing β-adrenoceptor agonists directly into the NTS enhances memory. Thus, activation of receptors in the NTS plays a critical role in mediating the transmission of adrenergic signals from the periphery to brain systems that process memory for emotionally significant experiences.

Glucocorticoids are lipophilic and readily enter the brain when released or administered peripherally. Thus, they can directly activate adrenal steroid receptors located on brain neurons, where their effects on memory involve specific activation of low-affinity GRs. In contrast to the high-affinity mineralocorticoid receptors, GRs are activated only during emotional arousal. Glucocorticoid binding to GRs can affect gene transcription by direct binding of receptor homodimers to DNA. Glucocorticoids may also act postsynaptically on membrane-bound GRs to influence the β-adrenoceptor-cAMP pathway and work synergistically with noradrenergic influences to regulate activity of downstream molecular mechanisms, including that of the transcription factor cAMP response-element binding (CREB) protein. These effects may ultimately result in structural changes, for example, via modifications of cell adhesion molecules, and strengthen cell–cell interactions.

The findings of many experiments indicate that administration of glucocorticoids to animals shortly after training on learning tasks produces dose-dependent enhancement of memory consolidation highly comparable to that found with epinephrine. Importantly, memory is also enhanced by posttraining infusions of GR agonists administered directly into specific brain regions, including the NTS, cortex, hippocampus, or amygdala. Disruption of glucocorticoid synthesis by administration of the drug metyrapone prevents the memory-enhancing effects of epinephrine. Thus, although epinephrine and glucocorticoid effects are initiated by different mechanisms, these adrenal stress hormones influence brain systems involved in processing memory and induce effects, as noted briefly above and discussed further below, that interact in modulating memory consolidation.

**Involvement of the Basolateral Amygdala**

It is well established that emotional experiences that induce the release of adrenal stress hormones also activate the amygdala. Further, there is considerable evidence that these stress hormones affect memory consolidation either directly by activating the amygdala or indirectly through influences that subsequently activate the amygdala. Lesions of the amygdala prevent the memory-enhancing effects of peripherally administered stress hormones. The basolateral amygdala (BLA) is the region of the amygdala that is critical for stress hormone influences on memory consolidation. The BLA is a cortical-like structure that has many reciprocal connections with other higher brain regions. Selective lesions of the BLA, but not lesions of other amygdala regions such as the central amygdala, prevent the memory-modulating effects of adrenal stress hormones. Further, memory consolidation is modulated by infusions of drugs affecting adrenoceptors or GRs administered selectively into the BLA. Adrenoceptor and GR agonists produce dose-dependent memory enhancement and antagonists of these receptors impair memory when infused directly into the BLA shortly after training. Infusions of these adrenoceptor and GR agonists and antagonists administered to other amygdala nuclei are ineffective.

**Role of Noradrenergic Activation of the BLA**

Noradrenergic activation of the amygdala by projections from the NTS and LC plays an essential role in the modulation of memory consolidation induced by both adrenergic and glucocorticoid effects. Infusions of β-adrenoceptor antagonists administered into the amygdala block the memory-enhancing effects of peripherally administered epinephrine that, as discussed above, are known to be mediated by activation of the noradrenergic cells of the NTS and LC. Further, β-adrenoceptor antagonists infused selectively into the BLA also block glucocorticoid-induced memory enhancement. Studies using in vivo microdialysis techniques to assess NE levels in the amygdala provide additional evidence that noradrenergic activation within the amygdala is involved in influencing memory. In rats, footshock stimulation of the kind that is typically used in fear-based training induces the release of NE in the amygdala, and the amount of NE released varies directly with the footshock intensity. Moreover, drugs and hormones known to enhance memory consolidation potentiate the increase in NE levels in the amygdala, induced by footshock stimulation. Further and importantly, in rats given inhibitory avoidance training, the magnitude of training-induced increases in amygdala NE assessed shortly after training correlates very highly with the rats’ subsequent long-term retention performance, providing additional evidence suggesting that amygdala NE regulates memory consolidation.

Noradrenergic activation of the BLA also appears to be essential in enabling glucocorticoid modulation of memory consolidation. Animal experiments investigating stress hormone and BLA involvement in memory consolidation typically use highly arousing training conditions, such as inhibitory avoidance or contextual or cued fear conditioning, that are known to induce amygdala NE release. There is evidence that such NE release is critical for glucocorticoid
enhancement of memory. When arousing training conditions are used, β-adrenergic antagonist antagonists administered peripherally or infused directly into the BLA block glucocorticoid-induced memory enhancement. Further, posttraining administration of corticosterone does not enhance retention of training experiences (e.g., object recognition) that induce relatively low emotional arousal. However, with such low-arousing conditions, administration of yohimbine, a drug that enhances NE release by blocking noradrenergic autoreceptors, enables glucocorticoid-induced memory enhancement.

Other findings indicate that corticosterone also does not directly induce activation of the BLA but, rather, influences BLA activity only when there is sufficient noradrenergic activation within the BLA. Such evidence strongly suggests that arousal-induced noradrenergic activation of the BLA is essential in enabling glucocorticoid-induced memory enhancement. These findings fit well with evidence from studies of human subjects indicating that glucocorticoid enhancement of memory consolidation may be limited to memories of information that is emotionally arousing. Such findings are also consistent with evidence that glucocorticoid-induced memory enhancement is blocked by intra-BLA infusions of β-adrenergic antagonist or Rp-cAMPS, a drug that blocks the NE signaling cascade, as well as evidence that GR antagonists do not prevent the memory-enhancing effects induced by intra-BLA infusions of the cAMP analog 8-Br-cAMP. This evidence clearly indicates that, in the BLA, cAMP activation is downstream from the interaction of glucocorticoids with β-adrenergic receptors. The interaction of glucocorticoids with noradrenergic influences in the BLA is summarized in Figure 1.

Most studies of the involvement of glucocorticoid and noradrenergic influences on memory consolidation have investigated the effects of hormones or drugs administered after the initial learning of tasks. As extinction consists of the learning of new consequences of cues, for example, that a cue that previously predicted footshock no longer predicts footshock, effects of these treatments on extinction should be comparable to those found with studies of

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**Figure 1** Interactions of adrenal stress hormones with the noradrenergic system in the BLA in modulating memory consolidation. Adrenal stress hormones are released during training in emotionally arousing tasks and are known to enhance memory consolidation. Epinephrine, which does not cross the blood–brain barrier, induces the release of norepinephrine (NE) in the BLA by activating vagal afferents to the nucleus of the solitary tract (NTS). Noradrenergic neurons in the NTS project directly to the BLA, and indirectly via the locus coeruleus (LC). NE binds to both β-adrenoceptors (β) and α1-adrenoceptors (α1) at postsynaptic sites and activates cAMP and protein kinase A formation. Glucocorticoids freely enter the brain and bind to glucocorticoid receptors (GRs) in brain stem noradrenergic cell bodies to potentiate NE release in the BLA, as well as postsynaptically in BLA neurons to facilitate the NE signal cascade. Glucocorticoids may influence the β-adrenoceptor-cAMP system via a coupling with α1-adrenoceptors. These stress hormone effects on noradrenergic activation in the BLA are required for regulating memory consolidation in other brain regions. PGi, nucleus paragigantocellularis; CREB, cAMP response-element binding protein. Reproduced from Roozendaal B (2000) Glucocorticoids and the regulation of memory consolidation. Psychoneuroendocrinology 25: 213–238, with permission from Elsevier.
original learning if the same modulatory systems are involved. The findings support this implication. When administered after extinction training, systemically or intra-BLA-administered glucocorticoids or NE enhance the consolidation of extinction memory.

**Effects of Corticotropin-Releasing Hormone (CRH) in the BLA on Memory Consolidation**

Although most studies examining emotional arousal or stress effects on memory consolidation investigated the effects of adrenal stress hormones, emotional arousal is known to induce the release of a variety of neuro-modulatory hormones within the brain, including opioid peptides, γ-aminobutyric acid (GABA), vasopressin, and adrenocorticotropic hormone (ACTH). Importantly, many findings have shown that intra-BLA infusions of drugs that either mimic or block the action of these transmitter systems enhance or impair memory for emotionally arousing training. Moreover, disruption of BLA activity prevents these drugs from influencing memory consolidation. One transmitter system that is of particular interest is CRH. CRH is a neuropeptide that is released by emotional arousal into the hypothalamus and plays a crucial role in regulating activity of the hypothalamic–pituitary–adrenocortical axis and circulating glucocorticoid levels. However, CRH is also released in extra-hypothalamic sites, including the amygdala as well as several other brain regions, in response to arousing or stressful stimulation. Blockade of endogenous CRH in the BLA with infusions of a CRH receptor antagonist impairs memory for emotionally arousing training, whereas infusions of CRH dose-dependently enhance memory consolidation. Furthermore, CRH is known also to interact with noradrenergic mechanisms in the BLA in influencing memory consolidation. Thus, this evidence indicates that BLA activation by emotional arousal is a general gateway in mediating stress hormone and neurotransmitter effects on memory consolidation.

**BLA Interactions with Other Brain Regions in Modulating Memory Consolidation**

Although the evidence summarized above clearly indicates that the BLA is a critical brain site for integrating adrenergic, glucocorticoid, and other stress-activated influences on memory consolidation, other evidence clearly indicates that the BLA is not the locus of the long-term memory processes modulated by stress hormones. Rather, the evidence indicates that BLA activation acts via efferent projections to influence memory processing in other brain regions. The BLA is richly interconnected with very many brain regions, including the hippocampus, caudate nucleus, nucleus accumbens, and cortical regions known to participate in different aspects or forms of memory. Posttraining noradrenergic activation of the amygdala influences memory in tasks known to involve functioning of different brain regions, including water-maze spatial and cued tasks, inhibitory avoidance, contextual and cued fear conditioning, conditioned taste aversion, and object recognition. Lesions of BLA efferent pathways block the memory-modulating effects of BLA stimulation. Additionally and importantly, lesions of the BLA, the nucleus accumbens or stria terminalis (a fiber pathway that connects the BLA with the nucleus accumbens) block the effects of glucocorticoids administered systemically after training.

The finding of many studies indicating that noradrenergic inactivation of the BLA or lesions of the BLA or its efferent pathways block the memory-modulating influences of drugs administered posttraining to other brain regions provides additional strong evidence that interactions with efferent brain regions are critical in mediating BLA influences on memory consolidation. The memory enhancement induced by a GR agonist infused into the hippocampus after training is blocked by selective lesions of the BLA or infusions of a β-adrenoceptor antagonist into the BLA. An intact and functioning BLA is also required for inducing memory modulation by adrenergic and muscarinic cholinergic drugs administered after training directly into cortical regions, including the entorhinal cortex, anterior cingulate cortex, prefrontal cortex, and insular cortex. The BLA also projects directly to the nucleus basalis (via the stria terminalis) that provides cholinergic activation of the cortex. Such activation is essential for learning-induced cortical plasticity. The evidence that stimulation of the BLA enhances cortical activation and that reversible inactivation of the nucleus basalis blocks the activation suggests that BLA activation may influence memory via such cholinergic activation of the cortex or that such activation is a corequirement. Findings indicating that lesions of the nucleus basalis-cortical projections block the memory enhancement induced by NE infused into the BLA posttraining support this hypothesis.

There is also considerable evidence indicating that the BLA regulates neuroplasticity in efferent brain regions. Stimulation of the amygdala enhances long-term potentiation (LTP) in thalamocortical synapses. Lesions of the BLA or infusions of β-adrenoceptor antagonists into the BLA prevent the induction of LTP into the dentate gyrus of the hippocampus as well as stress-induced influences on hippocampal and cortical LTP. In contrast, stimulation of the BLA facilitates LTP induction in these brain areas, whereas blockade of adrenergic or glucocorticoid mechanisms reduces this BLA effect on hippocampal neuroplasticity. Other
evidence suggests that synchronized oscillatory activity within the BLA may facilitate cortical processes involved in memory consolidation. A single footshock of the kind typically used in training increases the duration and synchrony of firing of BLA neurons lasting for up to 2 h. Such findings suggest that the increased firing may act to facilitate neuroplasticity underlying memory consolidation in efferent brain regions, including the cortex. Figure 2 summarizes the roles of adrenal stress hormones and BLA activation in modulating memory consolidation in other brain regions.

**Influence of Emotional Arousal on Human Memory: Stress Hormones and Amygdala Activation**

The findings of studies of the influence of stress hormones on human memory are highly comparable to those obtained in experiments with animals. Several studies have reported that epinephrine and glucocorticoids enhance memory and suggest that the effects are obtained selectively with emotionally arousing material. Cortisol administered to subjects prior to presentation of emotionally arousing words or pictures enhanced long-term memory. Similarly, epinephrine or cold pressor stress (known to induce the release of epinephrine and cortisol) administered shortly after subjects view emotionally arousing pictures enhanced their long-term memory of the pictures. In hospitalized patients undergoing intensive care treatment, the strength of subsequent memory of the experiences varied directly with the amount of cortisol and epinephrine they received during the treatment. Additionally, administration of a β-adrenoceptor antagonist prior to subjects’ viewing of an emotionally arousing series of pictures blocked the enhancing effect of emotional arousal on long-term memory.

There is also considerable evidence from human studies supporting the conclusions of animal studies indicating that the enhancing influence of emotional arousal on memory involves activation of the amygdala. In human studies, however, the experiments have not as yet investigated the possible selective involvement of the BLA. Evidence that in human subjects with amygdala lesions, unlike subjects with an intact amygdala, emotionally arousing stimulation does not enhance long-term memory supports the view that amygdala activation may be critical for emotionally enhanced memory. Alzheimer’s patients’ memory of a serious earthquake assessed months after the experience varied directly with the sizes of their amygdala, as examined by magnetic resonance imaging (MRI).
The involvement of amygdala activation in emotionally influenced memory has also been investigated in many studies using positron emission tomography (PET) and functional MRI (fMRI) in healthy humans. These studies reported that activity of the amygdala assessed during the presentation of emotionally arousing stimuli correlated highly with memory of the stimuli tested weeks later. Further, the relationship between amygdala activity during encoding and subsequent long-term memory was greatest for the most emotionally arousing stimuli and for subjects who showed a large increase in endogenous cortisol in response to the arousing stimuli. Importantly, β-adrenoceptor antagonists blocked both the increase in amygdala activity and the enhanced retention induced by emotional stimuli. Other findings are consistent with evidence from animal experiments, suggesting that amygdala activity modulates memory processing in other brain regions. Amygdala activity is highly correlated with the activity of hippocampal and parahippocampal regions during the encoding of emotional stimuli.

**Stress Hormone Effects on Memory Retrieval and Working Memory**

Although most studies investigating stress hormone effects on memory have focused on the neurobiological mechanisms underlying the consolidation of recent experiences, evidence indicates that these hormones also influence other memory functions. Stress exposure or glucocorticoids administered immediately after a learning session impair retention performance tested shortly after the session, that is, at a time when the memory trace has not yet been consolidated into long-term memory. Extensive evidence now indicates that glucocorticoids can affect such retention performance by impairing the retrieval of previously learned information. Stress exposure or glucocorticoids administered peripherally to rats shortly before retention testing, 24 h after training, impair retention performance. Likewise, administration of stress-level doses of glucocorticoids to human subjects shortly before memory testing impairs delayed recall on episodic memory tasks. Importantly, in contrast to stress hormone effects on memory consolidation, the impairing effects of emotional arousal on memory retrieval are temporary and subside when the hormone levels return to baseline. Extensive cognitive and neurobiological research indicates that the hippocampus is an important brain region implicated in memory retrieval. Glucocorticoid-induced memory retrieval impairment depends, in part, on GR activation in the hippocampus. Additionally, evidence from a PET study of memory in human subjects indicates that a stress-level dose of cortisone reduces activity of the parahippocampal gyrus, an effect that correlates with impaired episodic memory retrieval. The effects of epinephrine on memory retrieval have not been investigated.

The effects of glucocorticoids on memory retrieval are highly comparable to those obtained in studies of memory consolidation in that the effects depend critically on an interaction with noradrenergic mechanisms. Systemic administration of a β-adrenoceptor antagonist blocks the memory retrieval impairment induced by concurrent injections of corticosterone. Other evidence from animal studies indicates that the BLA interacts with the hippocampus in mediating glucocorticoid effects on memory retrieval impairment. BLA lesions or a β-adrenoceptor antagonist infused into the BLA block hippocampal glucocorticoid impairment of memory retrieval.

Such evidence clearly indicates that the role of BLA noradrenergic activity in regulating emotional arousal effects on hippocampus-dependent cognitive processes is not restricted to modulating memory consolidation but extends to memory retrieval. The evidence from animal studies is consistent with that from human studies examining stress hormone effects on memory retrieval. Glucocorticoids or psychosocial stress only impair retrieval of emotionally arousing information or during emotionally arousing test conditions. Further, the glucocorticoid-induced impairment of memory retrieval in humans is blocked by concurrent administration of a β-adrenoceptor antagonist. Findings of imaging studies indicate that successful retrieval of emotionally arousing information induces greater activity in and connectivity between the amygdala and hippocampus than retrieval of emotionally neutral information.

Stress exposure or glucocorticoid administration also impairs working memory, which is known to rely on the integrity of the prefrontal cortex. Mild uncontrollable stress impairs performance of rats on a delayed alternation task, a task commonly used to assess working memory in rodents. Such stress also increases NE (and dopamine) turnover in the prefrontal cortex. Excessive levels of NE in the prefrontal cortex are known to induce working memory impairment. Like stress, glucocorticoid administration impairs working memory. Stress doses of corticosterone or a GR agonist administered either peripherally or directly into the prefrontal cortex impair delayed alternation performance in rats. In addition, cortisol administration impairs working memory performance in human subjects. Importantly, glucocorticoids appear to interact with noradrenergic mechanisms in inducing working memory impairment. A β-adrenoceptor antagonist administered peripherally blocks the impairing effect of corticosterone on working memory in rats.
Further, animal studies have shown that glucocorticoid effects on working memory depend on functional interactions between the BLA and the prefrontal cortex. Disruption of BLA activity blocks the effects on working memory of a GR agonist administered into the prefrontal cortex. This evidence provides strong support for the hypothesis that BLA activity modulates stress or emotional arousal effects on working memory in other brain regions. There is also evidence from human studies supporting the hypothesis that glucocorticoids interact with noradrenergic mechanisms in inducing working memory impairment. Psychosocial stress impaired working memory only during conditions inducing concurrent activation of glucocorticoids and the sympathetic nervous system.

**Emotional Arousal and Traumatic Memory**

It is, of course, essential for our adaptation and survival that we record and retain lasting memories of our significant experiences. But can the activation of stress hormones and the amygdala by emotional arousal strengthen memories more than is necessary? Several kinds of studies have addressed this issue. In children who experienced traumatic injuries, elevated levels of epinephrine and cortisol measured immediately after the children were admitted to the hospital correlated with symptoms of posttraumatic stress disorder (PTSD) assessed 6 weeks later. Moreover, the administration of a β-adrenoceptor antagonist to recently traumatized patients attenuated the development of PTSD symptoms. Propranolol administered to patients (for 10 days) within 6 h after they experienced an acute psychologically traumatic event reduced the symptoms of PTSD assessed 3 months after the trauma. As with humans exposed to other types of extreme trauma, patients who have been treated in an intensive care unit often report traumatic memories. Extremely traumatic memories from intensive care treatment in some of these patients are associated with the development of PTSD. Many patients with stress-associated diseases, such as PTSD, show sustained neuroendocrine abnormalities, which include increased catecholaminergic activity and impairment in glucocorticoid signaling. Severely ill patients also often show insufficient endogenous glucocorticoid signaling which has recently been termed critical illness-related corticosteroid insufficiency (CIRCI). In several controlled trials in patients with suspected CIRCI, the administration of glucocorticoids (stress doses of cortisol) during intensive care treatment resulted in a significant reduction of PTSD symptoms in long-term survivors. Cortisol administration may help to surmount impaired glucocorticoid signaling from CIRCI during critical illness resulting in a downregulation of the stress response. Sustained cortisol administration might also prevent PTSD by interfering with memory retrieval.

As discussed above, high levels of glucocorticoids impair memory retrieval. Thus, low cortisol levels such as found in some patients after trauma at risk for PTSD or with established PTSD could lead to excessive retrieval of traumatic information. As it has been proposed that PTSD develops over time because of positive feedback mechanisms in which traumatic memories are constantly retrieved and restored; the administration of stress doses of glucocorticoids after a massive stress exposure could inhibit the recall of traumatic information and thereby reduce the probability of PTSD. In addition, glucocorticoid administration might also reduce the development of PTSD by facilitating the extinction of traumatic memories. Some evidence indicates that administering stress doses of cortisol might also be useful for the treatment of established PTSD as a result of major traumatic experiences of nonmedical origin. Thus, the findings of studies investigating memory of traumatic experiences offer support for the hypothesis that emotions can and do strengthen memories more than is necessary. And, the findings of the experimental studies provide some understanding of the neurobiological processes that underlie such strengthening as well as some possible implications for therapeutic intervention to ensure that significant events are well remembered, but not excessively remembered.

**Further Reading**


