The prefrontal cortex in sleep

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Experimental data indicate a role for the prefrontal cortex in mediating normal sleep physiology, dreaming and sleep-deprivation phenomena. During nonrandom-eye-movement (NREM) sleep, frontal cortical activity is characterized by the highest voltage and the slowest brain waves compared to other cortical regions. The differences between the self-awareness experienced in waking and its diminution in dreaming can be explained by deactivation of the dorsolateral prefrontal cortex during REM sleep. Here, we propose that this deactivation results from a direct inhibition of the dorsolateral prefrontal cortical neurons by acetylcholine, the release of which is enhanced during REM sleep. Sleep deprivation influences frontal executive functions in particular, which further emphasizes the sensitivity of the prefrontal cortex to sleep.

Recent data indicate that the prefrontal cortex is particularly sensitive to sleep and benefits from it in important ways. Here we review new findings, which, although heterogeneous, are consistent. Our central hypothesis is that the executive cognitive functions, provided by the prefrontal cortex, are particularly sensitive to the fatigue induced by prolonged waking. We propose that during sleep it enjoys what is at first a passive respite in nonrapid-eye-movement (NREM) sleep and later, in REM sleep, a more active one. As a consequence of deactivation of the dorsolateral prefrontal cortex (DLPFC) during sleep, executive functions such as self-consciousness and analytical thought are severely impaired in NREM sleep and are weak in REM sleep. By virtue of the respite provided by sleep, the prefrontal cortex recovers its crucial functional competence for use on waking.

It is our view that any study of the function of the prefrontal cortex must take its extreme state dependence into account and that more detailed study of such a state dependence should be richly rewarding.

The loss of self-conscious awareness in sleep

The loss of self-conscious awareness occasioned by the transition from waking to sleep constitutes one of the universal and robust changes in consciousness that humans can observe in themselves and others. Even when a form of awareness returns in sleep during dreaming, the self-conscious awareness is remarkably different from waking consciousness [1]. This is most notable when awakening from a dream. The sudden switch from the self-absorbed awareness of dream reality to an awareness of waking reality is remarkably rapid. With it comes our immediate sense of self as separate, in a causal and analytical sense, from other aspects of consciousness such as perception and emotion.

What is the physiological basis of this profound change in consciousness? The answer suggested during the first half of the 20th century – that the sensorily deafferented sleeping brain was quiescent and at rest – has been soundly disproved by the discovery of the brain-activated state of REM sleep [2]. The observation that the ascending reticular activating system of the brainstem, described in waking by Moruzzi and Magoun [3], is re-engaged during REM sleep [4] has added to the richness of the concept of brain activation.

Subsequently, the neuronal basis of REM activation has been found to result from reciprocal interaction of aminergic and cholinergic neurons in the pontine brainstem [5]. Thus, although brain activation during waking is associated with noradrenaline, 5-hydroxytryptamine (5-HT) and acetylcholine-mediated neuromodulation, brain activation during REM is exclusively cholinergic (although the dopaminergic system appears to be continuously active throughout the cycle [6]). The neuromodulatory status of NREM sleep is intermediate between waking and REM sleep. Far from being a quiescent state, NREM sleep involves vigorous hippocampal–cortical, thalamocortical and cortico–cortical oscillatory activity [7,8] that may have important roles in the processing of learning and memory [9,10]. Sleep physiology and psychophysiology is summarized in Box 1.

The prefrontal cortex: executive functions and sleep

Functions of the prefrontal cortex that are most relevant to the self-conscious awareness that is lost in sleep are commonly termed 'executive'. These include self-observation, planning, prioritizing and decision-making abilities, which are, in turn, based upon more basic cognitive capacities such as attention, working memory, temporal memory and behavioral inhibition [11,12]. These functions are subserved by the nonmotor anterior and medial regions of the frontal cortex that are referred to collectively as the prefrontal cortex (see Box 2 for an overview of the subregions and functions of the prefrontal cortex). In the frontal lobes, the prefrontal cortex shows the greatest change from waking to sleep [13]. In summary, the changes associated with the transition from waking to NREM sleep might be ascribed to a globally reduced level of activity. This is followed by the selective reactivation of the most posterior and medial prefrontal areas and continued deactivation of anterior and lateral portions at the onset of REM sleep.

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Box 1. Sleep basics

Rapid-eye-movement (REM; also known as 'paradoxical', 'active' and 'desynchronised') sleep and non-REM (NREM) sleep are clearly distinguishable types of sleep. By convention, they are defined by the electrophysiological signals detected using a combination of electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG). Collectively, these measurements are termed 'polysomnography' [a]. First described by Aserinsky and Kleitman [b], REM sleep is characterized by: (1) wake-like and 'activated' (high frequency and low amplitude or 'desynchronised') activity in the EEG; (2) singlets and clusters of rapid eye movements in the EOG channel; and (3) very low levels of muscle tone (or atonia) in the EMG channel. NREM sleep includes all sleep except REM and is, by convention, divided into four stages that correspond to increasing depth of sleep as indicated by the progressive dominance of the EEG by high-voltage, low-frequency (also termed 'synchronised') wave activity. Low frequency waves dominate the deepest stages of NREM (stages 3 and 4), which are also termed 'slow-wave' or 'delta' sleep (see Fig. I). See Hobson [c] for a comprehensive primer on sleep physiology.

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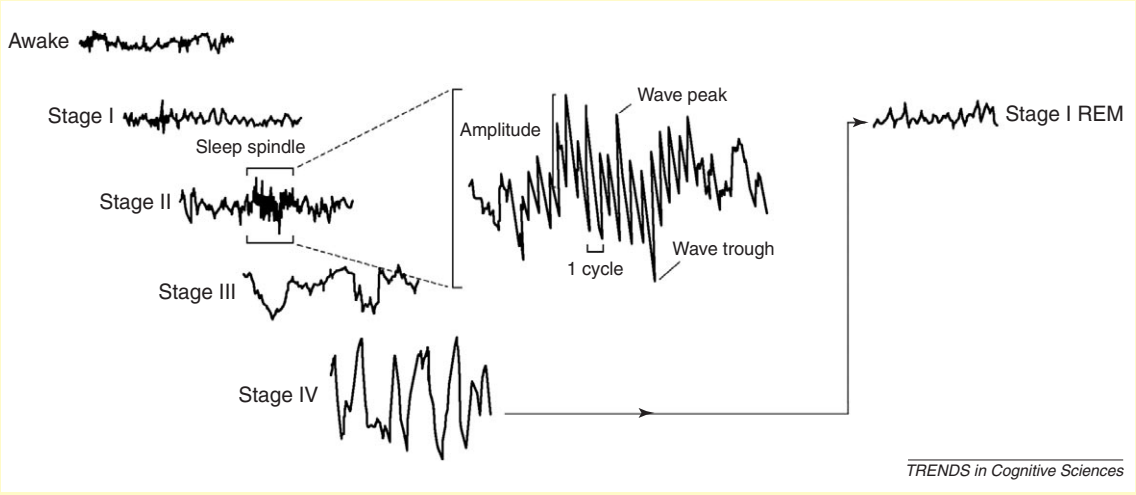

Fig. I. The changes in EEG activity throughout the sleep–wake cycle and their graphic representations in hypnogram. The awake state is dominated by beta frequency (>13 Hz), whereas in Stage I alpha waves (8–12 Hz) predominate. The major feature of Stage II is the appearance of sleep spindles and K-complexes. Delta waves (0.5–2ÿHz) make up 20–50% of the Stage III and more than 50% of Stage IV (Stage III and Stage IV being jointly named slow-wave sleep). REM phase is characterized by mixed but mostly high-frequency waves. Modified with permission from Ref. [d].

The prefrontal cortex during normal sleep: recent findings

Sleep-related deactivation of prefrontal cortices has emerged as a descriptive and explanatory factor in studies of sleep physiology and psychology. Here we summarize these findings, followed by a consideration of the role of the prefrontal cortex in dreaming. We are aware that increased delta activity does not always mean (complete) inactivity (see, for example, Ref. [14]). Rather than evaluating the absolute metabolism of the prefrontal cortex, we consider 'deactivation' of the prefrontal cortex in terms of relative activity.

The transition from waking to NREM is characterized by frontal deactivation as reported in positron emission tomography (PET) studies using either $H_2[^{15}O]$ [15,16] or ^{18}F deoxyglucose (^{18}FDG) [17] and quantitative EEG studies[18–20]. Deactivation increases with the deepening of NREM sleep [14] and is maintained in the transition from NREM to REM sleep [21]. However, with the onset of REM sleep, portions of the ventromedial, limbic-related prefrontal cortex and closely associated medial subcortex and cortex are reactivated, sometimes to levels that exceed those of waking [22].

For example, in a $H_2[^{15}O]$ PET study that specifically compares REM with NREM sleep, the prefrontal areas reactivated during REM include anterior cingulate (BA 32), caudal orbital and medial prefrontal (BA 10) cortices [13], but the DLPFC remained deactivated. Nofzinger *et al.* [23] have termed this frontal area the 'anterior paralimbic REM activation area' with the core structures being subgenual and pregenual anterior cingulate cortex, the amygdala and the insula. Nofzinger suggests that, in REM, these structures participate in '…the integration of neocortical function with basal forebrain-hypothalamic motivational and reward mechanisms.'

Activation of the anterior cingulate cortex is increased consistently in REM in other PET studies (e.g. Ref. [24]). Not only does the DLPFC remain

Box 2. Neuropsychology of the prefrontal cortex

Dorsolateral prefrontal cortex (DLPFC)
The involvement of the DLPFC (see Fig. Ia) in working memory has been studied intensively in monkeys. These studies indicate that the DLPFC has a role in the temporal order of information retrieval. A recent study in humans [a] described the area specialized for spatial working memory to be located 'more superiorly and posteriorly than in the monkey.'

Some psychological theories match what is known about the DLPFC from experience with patients. This is the case with Shallice's Supervisory Attention System (SAS), which intervenes when the routinized choice of behavioral schemata is confronted with a new situation [b]. Lesion studies confirm the prolongation of response-initiation times, and the appearance of difficulties in response suppression. The hypothesis of a central executive [c], where the outputs from a phonological loop and a visuo-spatial sketch pad are supposed to meet, could also be nested in the prefrontal cortex.

Ventromedial prefrontal cortex (VMPFC)
The VMPFC consists primarily of the orbitofrontal cortex and the anterior cingulate, and is also known as the 'limbic' cortex (see Fig. Ib). It has been demonstrated that the VMPFC plays a key role in decision making, social cognition and social judgement [d]. This concept is most clearly enunciated in Damasio's somatic-marker hypothesis, which ascribes to the VMPFC the role of 'marking' complex stimuli (such as social situations) with records of past autonomic and emotional responses and thereby makes possible high level social judgments, such as behavioral inhibition and assessment of complex social cues [e].

More complex clinical hypotheses of the prefrontal-cortical function have been advanced, but most of them still need to be tested: attention deficit disorder has been linked to the disturbance of prefrontal cortical inhibitory functions [f]; schizophrenia has been ascribed to deficits of the DLPFC [g]; obsessive-compulsive disorder has been related to a higher activity in the orbitofrontal cortex [h]: and the frontal pole (Brodmann area 10) was proposed to monitor the reward value of cognitive processes [i]. Functional magnetic resonance (fMRI) has shown that the right DLPFC supports planning [j]. Right medial frontal lesions, in particular, were shown to impair the ability to infer mental states in others ('theory of mind') [k], which is well matched by an fMRI finding of activation of the right anterior cingulum during similar tasks [l].

It is not by chance that neuroscientists are searching in the frontal lobes for the basis of the most sophisticated human abilities, because it is here that the roots of action as well as the roots of thought seem to intermingle.

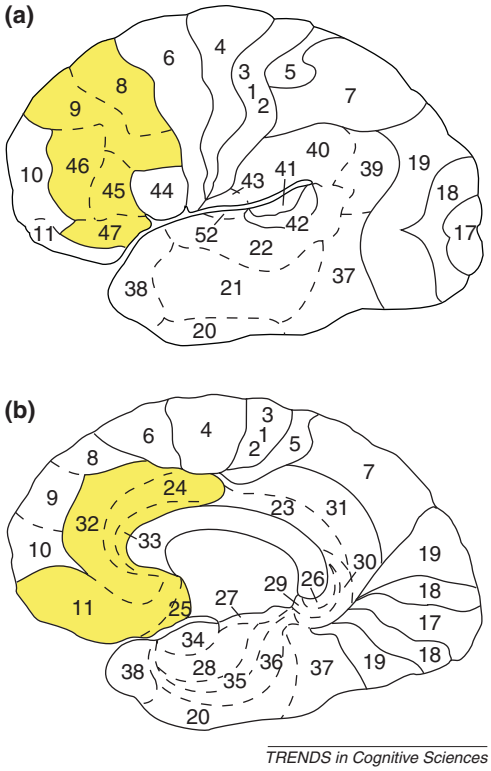

Fig. I. Approximate location of Brodmann areas (coloured yellow) considered to form (a) the dorsolateral prefrontal cortex (dorsal surface of the left hemisphere is shown), and (b) the ventromedial prefrontal cortex (median plane cut of the right hemisphere). Modified with permission from Ref. [m].

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deactivated in REM but, on waking, the prefrontal cortex lags behind other regions in achieving waking levels of activation [25]. Added to the observation of a frontal predominance of power in the low-frequency band [19] during the first NREM episode, the imaging evidence of the lag in activation on waking indicates a particularly high need for (recovery) sleep in the frontal region.

It is no wonder that cortical areas are relatively deactivated during NREM sleep compared to wakefulness: in NREM sleep, the thalamocortical input is disabled and the intrinsic synchronous

Box 3. An updated activation-synthesis hypothesis of dreaming

As in waking, activation of the forebrain occurs through ascending arousal systems located in the brainstem reticular activating system [a] and the basal forebrain [b]. Forebrain stimulation by such arousal systems in sleep probably facilitates the kind of consciousness typically encountered in dreaming (see Fig. I).

We hypothesize that the strong activation of the basal ganglia [c] contributes to the ubiquitous fictive motion of dreams [d]. Motor cortices might participate in dream movement, as evidenced by the expression of dreamed action in rapid-eye-movement (REM) sleep-behavior disorder [e]; and premotor areas of the anterior cingulate cortex might integrate dream movement and emotion.

Deactivation of frontal executive areas, such as the dorsolateral prefrontal cortex, during non-REM (NREM) sleep (e.g. Ref. [f]), followed by their failure to reactivate in REM (e.g. Ref. [c]) underlies the executive deficiencies that are prominent in dream mentation. In waking, prefrontal cortical areas are selectively activated during reasoning, episodic memory and working memory tasks (see Box 2). Our hypothesis is that, during dreaming, prefrontal deactivation leads to illogical thinking. Examples include *ad hoc* explanations [g], prominent mnemonic deficits [h] and bizarre uncertainties. Interestingly, hypoperfusion of the frontal cortex is associated with pathological temporal limbic activation in epilepsy [i], and reciprocal inhibition between frontal and limbic areas has been hypothesized to be involved in the etiology of depression and schizophrenia [j,k]. Thus REM sleep dreaming might be a normal physiological state of the brain that is analogous to psychopathological conditions in which limbic hyperactivation is combined with frontal hypoactivation [l].

At this early stage of research in dream neuropsychology, a few generalizations are beginning to emerge. First, ascending arousal systems activate the many forebrain regions involved in dream construction but do so in a manner chemically, and perhaps anatomically, different from waking arousal processes. Second, cortical areas activated in REM favor more medial circuits that link posterior association and paralimbic areas rather than circuits that include the primary sensory cortex and/or frontal executive regions [m]. Third, subcortical circuits that involve the limbic structures, striatum, diencephalon and the brainstem contribute strongly to regional brain activation in REM and, therefore, to the physiological substrate of dreaming (see Fig. I for a summary).

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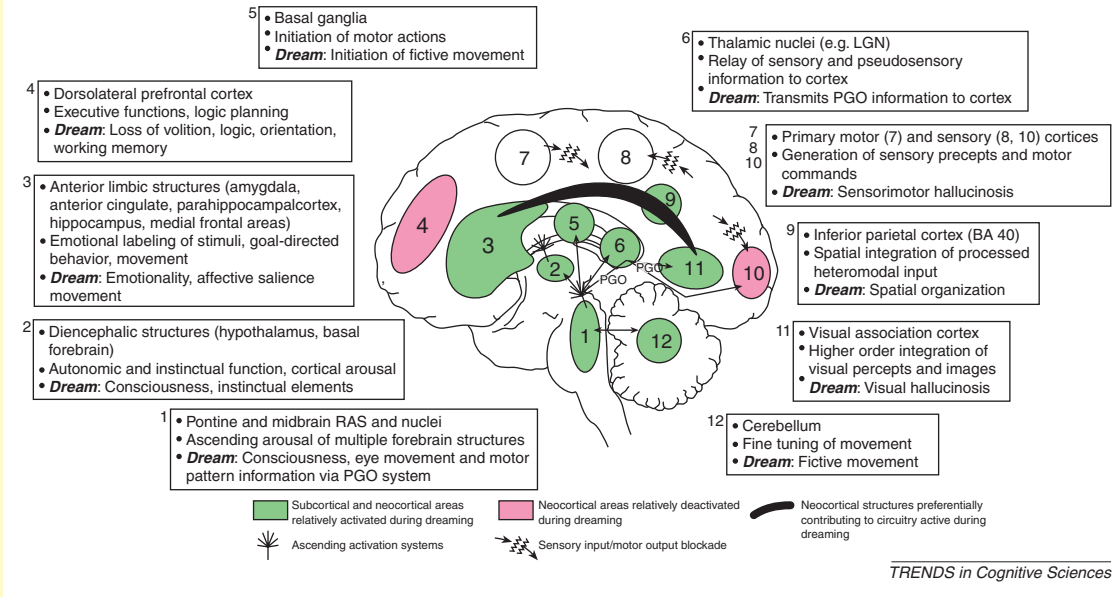

Fig. I. Forebrain processes in normal dreaming: an integrated model. Presented are various brain structures and their activity during REM sleep. In each box, the first bullet corresponds to the anatomical definition of the structure(s), the second defines the function the structure supports in waking, and the third bullet suggests the function the structure might support in the formation of dreams. Modified with permission from Ref. [l].

oscillations result in a significantly lower level of metabolism. At the beginning of the REM phase, however, activation of the acetylcholine system, starting from the pontine reticular formation, provokes a general increase in cortical activity [26]. We propose that the DLPFC remains relatively deactivated in REM sleep because it is directly inhibited by acetylcholine. Findings supporting this include a functional magnetic resonance study showing that acetylcholine-mediated enhancement increased the activity of extrastriate cortex but decreased the activity of the anterior prefrontal cortex [27]. It is possible that these differences are caused by differences in target neurons rather than the type of acetylcholine receptor activated because stimulation of muscarinic receptors can lead to either depolarization or hyperpolarization [28] and different subtypes of interneurons in the same cortical layer can react differently to acetylcholine-mediated stimulation [29]. The delay in achieving waking levels of activation in the DLPFC compared to other regions [25] might be explained by the finding that the DLPFC is scarcely innervated by noradrenaline-containing neurons and only moderately innervated by 5-HT-containing neurons. Thus it is possible that activity of the DLPFC is dependent mainly on other neurotransmitter systems, primarily those related to cortico–cortical pathways.

The prefrontal cortex and dreaming

Relevant to the deficits in self-reflective awareness, orientation and memory during dreaming are studies using $^{15}O_2$ PET [21] and SPECT [30] that show that a vast area of DLPFC undergoes significant deactivation in REM. However, DLPFC deactivation during REM was reported in a study using ^{18}FDG [22] and this discrepancy remains to be clarified. Nevertheless, it is likely that considerable portions of executive and association cortex that are active in waking are far less active in REM sleep, which leads Braun *et al*. [13] to speculate that '…REM sleep may constitute a state of generalized brain activity with the specific exclusion of executive systems which normally participate in the highest order analysis and integration of neural information.'

Taken together, these results indicate that the forebrain activation and synthesis processes that underlie dreaming, with selective activation of the subcortical and cortical limbic structures (which mediate emotion) and relative inactivation of the DLPFC (which mediates directed thought), are very different from those during waking (see Box 3).

The prefrontal cortex in sleep deprivation

Executive functions are not always easily measured. Agreement on the most appropriate tests and on their diagnostic value is not yet established. Thus, contradictory findings on the effects of sleep deprivation on prefrontal measures are not unexpected.

To date, the majority of sleep-deprivation studies have measured verbal fluency [31–33], temporal memory [34,35], logical reasoning [36], working memory [37,38] and planning [31]. However, a few studies have investigated inhibitory capabilities [33] and decision making [39], functions that are thought to be subserved by ventral (orbital) prefrontal areas [34,40].

One night's acute total-sleep deprivation reduces performance on neuropsychological tasks that are believed to be subserved by the prefrontal cortex [31–36,38,39,41–44]. Moreover, neuroimaging studies have found profound effects of one night's total sleep deprivation on the blood flow to prefrontal areas which correspond to the measured deteriorations in prefrontal task performance [37,45,46]. The majority of neuropsychological performance measurements and studies of regional cerebral metabolism use total sleep deprivation thereby depriving subjects of both NREM and REM sleep.

As in normal sleep [18,19], a frontal predominance in the delta (0.5–7 Hz) and alpha (8–12 Hz) band was noted during sleep deprivation; this frontal synchronization increased with prolonged waking [20] and was attenuated by sleep satiation attained with intermittent naps [47].

Some recent studies of groups of young adults failed to demonstrate deficits in executive function following one night's sleep deprivation [48–50]. One possible cause for this discrepancy might be the adaptation to a chronically sleep-deprived lifestyle in the young, healthy, collegiate populations that are studied traditionally [51]. In support of this, Friedmann *et al*. [52] found no behavioral effects in subjects who had undergone 6–8 months of gradual sleep restriction (down to 4.5–5.5 h sleep per night). Similarly, Blagrove *et al*., [36] report that reducing sleep to 5.2 h each night for 4 weeks (or 4.3 h each night for 4 nights or 5.3 h each night for 18 nights) produced no change in logical reasoning. In a meta-analysis, Pilcher and Huffcutt [53] conclude that sleep deprivation affects mood more than cognitive functions.

In the case of patients with obstructive sleep apnoea, findings more consistently indicate significant executive dysfunction (reviewed in Ref. [54]). However, in these cases, there is also the possibility of a direct effect of hypoxia on cerebral tissue.

An additional explanation for the negative results of some sleep-deprivation studies is the suggestion from Harrison and Horne [55] that in the simple tasks that are usually applied, the motivation of the subjects is typically low and the monotony of the tasks high, whereas the highly motivating complex tasks that are related to financial and other gains in everyday life dampen the effects of short-term sleep-deprivation.

Better-controlled studies as well as thorough meta-analyses are necessary to resolve these conflicting findings. The development of prefrontal tasks that have a higher degree of reproducibility and allow the same subjects to be studied repeatedly (see, for example, Ref. [56]) is one approach that should be useful in resolving these discrepancies.

Conclusion

The concept of hypofrontality, often in the presence of accentuated limbic or posterior perceptual cortical activity, may offer a convergent explanatory principle that links dreaming with a wide variety of psychopathological conditions [57–59]. In this review, we have advanced the idea that the deactivation of the prefrontal cortex during REM sleep is the result of direct acetylcholine-mediated inhibition of this cortical region. According to our proposal, cholinergic pathways are responsible for the reactivation in REM sleep of the prefrontal limbic cortex, but not of the DLPFC, thus depriving dream mentation of logical reasoning capacities.

Defective frontal functioning is also observed after sleep deprivation. The parallel slowing of EEG activity, which increases after prolonged waking and recovers after the subsequent sleep period, sheds additional light on the particular sensitivity of the prefrontal cortex to rest and sleep.

Acknowledgements
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Robots that imitate humans

Cynthia Breazeal and Brian Scassellati

The study of social learning in robotics has been motivated by both scientific interest in the learning process and practical desires to produce machines that are useful, flexible, and easy to use. In this review, we introduce the social and task-oriented aspects of robot imitation. We focus on methodologies for addressing two fundamental problems. First, how does the robot know what to imitate? And second, how does the robot map that perception onto its own action repertoire to replicate it? In the future, programming humanoid robots to perform new tasks might be as simple as showing them.

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The study of the mechanisms that enable an individual to acquire information or skills from another individual has been a seminal topic in many areas of cognitive science. For example, ethologists attempt to understand how bees communicate the location of food sources, to describe how successive generations of blue-tits learn to open milk cans, and to categorize the spread of tool use in chimpanzee troops. Developmental psychologists study the emergence of social learning mechanisms in human infants from the very early (but simple) imitative responses of the newborn [1] to the complex replication of task goals that toddlers demonstrate [2].

Research in robotics has focused on social learning for many reasons. Commercial interest in building robots that can be used by ordinary people in their homes, their workplaces, and in public spaces such as hospitals and museums, invoke social learning as a mechanism for allowing users to customize systems to particular environments or user preferences. Research in artificial intelligence has focused on social learning as a possible means for building machines that can acquire new knowledge autonomously, and become increasingly more complex and capable without requiring additional effort from human designers. Other researchers implement models of social behavior in machines to gain a deeper understanding of social learning in animals (including humans).

Differences between the study of social learning in animals and machines

The methods for studying social learning in artificial systems differ significantly from methods used to study social learning in biological systems. When studying animals, researchers attempt to determine the minimal set of capabilities required to produce an observed behavior. Precise taxonomies of the types of required skill have been developed; however, none of these is universally accepted (see Box 1). Although these descriptions often focus on cognitive skills, they do not completely capture the ways in which these skills can be constructed or combined to produce the observed behavior.

Whereas biological studies tend to be descriptive, studies of social learning in artificial systems are primarily generative; researchers attempt to construct a desired behavior from a minimal set of capabilities. These studies often use imprecise definitions of the external behavior (often using the word *imitation* to mean any type of social learning), but can precisely specify the underlying mechanisms of the system (see Box 2). Although these methodological differences do produce terminology problems between these related disciplines, on the whole, the literature on social learning in animals is a very accessible source of inspiration for robots, both physical and simulated (see Box 3).

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