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Perspective

Memorable Trends

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The current neuroscience of memory takes on board the remarkable achievements of molecular neurobiology and merges them with findings from systems neuroscience and cognitive psychology. This results in a highly dynamic depiction of the memory trace, appreciating its restlessness and incessant assimilation into accumulating knowledge. With an armamentarium of amazing methodologies at hand, and more around the corner, we still lack dictionaries of neuronal codes, able to translate spatiotemporal patterns of brain activity into behavioral tokens. But the path to getting there continues to fascinate, to be accompanied by fresh challenges and new approaches.

The past is a foreign country: they do things differently there. L.P. Hartley's poetic ode to nostalgia (*The Go-Between*) shrinks to a bare factual statement upon comparing memory research reported in *Neuron* in its first days and now. The first experimental paper to explicitly target putative memory-related research in *Neuron* used acute single microelectrode recording in hippocampal slice (Kauer et al., 1988). Twenty-five years and 8,000 articles later (over 400 of which are research papers with learning or memory in their title, with many more on neuronal plasticity at large), a study of memory in the mammalian brain reported in *Neuron* may already combine chronic tetrode recording arrays and precise optogenetic perturbation in the freely behaving rat (Smith and Graybiel, 2013).

That the contemporary tools of the trade are first and foremost options that creative scientific minds use in new ways is evident from the fact that both of these papers can be considered groundbreaking at their time. Expanding the toolbox available to the discipline, which has perhaps happened most strikingly in the last decade, enables neuroscience to take new steps forward. Imagine, for example, human memory research now in the absence of noninvasive functional imaging; the advances in our understanding of our own brain machinery is even more impressive given that this popular capability was unavailable only a rather short scientific-while ago (the first positron emission tomography [PET] study of human memory to appear in *Neuron* was in 1996 [Schacter et al., 1996], with the first fMRI paper following shortly thereafter). When *Neuron* started almost a decade earlier, cognitive neuroscientists really did do things differently.

The technology has changed and with it some of the questions that can be tackled more successfully. But has the evolution of methods, concepts, and data blended with creativity to advance the character of memory research in the past 25 years? Our view is that they are doing so, and we now reflect on the future implications of the current state of the art. We attempt to chart patches of the changed terrain of the science of memory and how it has changed and propose a few idiosyncratic conclusions on where it might be going.

Time Present and Time Past

The Trace Goes Dynamic

Psychological conceptions of learning and memory have long distinguished the acquisition or "encoding" process, from that of "trace storage" and the subsequent processes of "consolidation" that somehow enable storage to be lasting. Efforts to translate these concepts into the neurobiological domain distinguish the very rapid events associated with memory encoding in one-shot learning, such as activation of the glutamate NMDA receptor in neurons of the hippocampus, with those associated with the subsequent creation of biophysical, biochemical, or structural changes thought to mediate lasting trace storage. A memory "trace" or "engram" is a hypothetical entity that refers to physical changes in the nervous system that outlast the stimulus. However, while the trace may be created and sustained for a while, that is no guarantee that it will last. All too often, as in long-term potentiation decaying back to "baseline" levels, experience-induced perturbations of structure and function are short lasting. However, a key idea was that a consolidation process can be engaged to enable these physical changes to be sustained and then to last indefinitely (McGaugh, 1966).

Specifically, much of the research in the neuroscience of memory in the past century was embedded in the conceptual framework of a "dual-trace" model (Hebb, 1949): a short-term trace, which dissipates rapidly unless converted by consolidation into a long-term trace. It was generally thought that consolidation occurs just once per item and that the long-term trace would be stable and essentially permanent unless the areas of the brain that store the memory were damaged or the ability to retrieve the information somehow impaired. This conceptual framework was strongly influenced by the view that the neurobiological mechanisms of consolidation and maintenance of long-term memory are similar or even identical to those operating in tissue development, in which the cells become committed to their fate for the rest of their life unless struck by an injury or pathology. Indeed, much in the models and terminology of the highly successful molecular neurobiology of memory (Kandel, 2001) resonates with the reductionist world of the molecular biology of development. The influence and the interest of developmental neurobiologists in memory mechanisms continues to

this day, although with a corresponding sense that things may be less fixed than they once seemed (Hübener and Bonhoeffer, 2010).

The initial reductionist approach to neurobiology (Benzer, 1967; Kandel and Spencer, 1968) resulted in portrayal of a dynamic microcosmos within synapses and neurons. This was in regard to the encoding of the memory and its possible transition from a short-term to a long-term trace. The proposed molecular and cellular mechanisms of encoding and consolidation in even the simplest forms of learning, such as habituation, sensitization, and classical conditioning, were depicted as interacting signal-transduction cascades of synapse-to-nucleus-to-synapse communication, each shaped by state-dependent checks and balances of facilitation and repression. Particularly influential has been the research program of reflex modification in *Aplysia* (Castellucci et al., 1970; Kandel and Schwartz, 1982; Bartsch et al., 1995; Byrne and Kandel, 1996; Martin et al., 1997; Bailey and Chen, 1988; Shobe et al., 2009). A complementary picture emerged from the neurogenetic analysis of memory in *Drosophila* (Dudai et al., 1976; Dubnau and Tully, 1998; Waddell and Quinn, 2001; Keleman et al., 2007), in which lines such as *amnesiac* remain memorable for their failure to make this short-to-long transition coupled to some missing aspects of these cascades. These and studies in other organisms and model systems (e.g., Etcheberrigaray et al., 1992; Malenka and Bear, 2004; Gao et al., 2012) unveiled a rich molecular toolbox of neuronal plasticity that has been conserved and elaborated in evolution to permit memory traces to be formed (Kandel, 2001; Glanzman, 2010).

Yet the outcome—the "stored" long-term trace—was still conveniently considered by many as "fixed." The flexibility of behavior was appreciated, even championed, but a conceptual distinction was nonetheless made between the postulated permanence of the memory trace and its flexible use in providing the organism with capacity to vary its response to the world (McGaugh, 1966). This dissonance between the assumed engramatic stability and the observed behavioral mutability was even insightfully considered embarrassing (McGaugh, 1966) and hence in need of resolution.

On this point, some views in early cognitive and social psychology were arguably rather different. Here, the reconstructive but frail nature of real-life memory was an engine of excitement rather than of embarrassment (Bartlett, 1932) and served as a basis for influential experiments (Deese, 1959) that decades later found their way into brain research (Schacter et al., 1996). A major trend in the evolving science of human memory is bridging the gap between cognitive psychology concepts and the molecular and cognitive neuroscience views of memory. Whereas the cognitive psychology of memory opens out to biological interpretations of behavioral phenomena (e.g., retroactive memory interference interpreted as memory consolidation; Wixted, 2004), molecular and cognitive neuroscience is at last beginning to appreciate the restless, ever changing, and reconstructive nature of memory cherished by cognitive psychology (Dudai, 2012). In this respect, neuroscience is coming of age; we have moved away from the silos of thinking that permeated separate departments of psychology, physiology, and molecular biology to recognition that different levels of analysis have things to say to each other (Roediger et al., 2007).

Four examples illustrate this trend toward a more dynamic conception of the trace and of memory processing in general. The first refers to the ostensible and now questionable *permanence of the consolidated trace*; another to the *veracity* of memory; a third to the nature of the representations formed and the *assimilation* of new information into previously stored representations; and a fourth to the supposition that retrieval may represent a *transient alliance* of representations.

The Trace Reboots

The view that consolidation occurs just once per item was challenged in the late 1960s by reports that presentation of a "reminder cue" rendered a seemingly consolidated long-term memory item again labile to amnesic agents (Misanin et al., 1968). This reactivation-induced reopening of a consolidation-like window called into question the supposition that consolidation produced immutable stability and so came later to be termed "reconsolidation" (Sara, 2000). Some methodological concerns combined with the capricious nature of the history and sociology of science pushed reconsolidation under the radar for many years. A major step forward came with a study that replicated Misanin's observation of reconsolidation but did so by applying an amnesic agent directly into the identified amygdalar circuit that mediates long-term fear conditioning (Nader et al., 2000). This single paper had an unprecedented influence on the popularity of reconsolidation as a process to study, with the annual number of papers that describe and analyze the phenomenon soaring 50-fold within a few years. Besides providing new insights into the molecular and brain mechanisms of memory, the initially subversive concept of reconsolidation was rapidly subsumed into mainstream neuroscience. There has been extensive work on specifying the boundary conditions of reconsolidation, on pharmacological and molecular dissociations between consolidation and reconsolidation, and on the possible relevance of reconsolidation to cognitive and behavioral therapies for diverse conditions (Alberini, 2005; Nader and Hardt, 2009; Dudai, 2012).

The Trace Errs

In the classical neurobiological sequence of memory processes, operating in a healthy nervous system, there is seemingly little room for error. What will later be retrieved from the passive attic of stored traces must, of necessity, be what was put there in the first place. It took decades for the normal imperfections of memory to be considered by brain scientists as natural and research-worthy phenomena (Schacter, 2001). This may sound surprising to the biological ear, even if only because modern biology rests on the shoulders of molecular genetics, which uses imperfections (mutations) as its most effective and successful research tool. In early cognitive neuroscience as well, brain damage that caused abnormalities of function was the gateway to understanding the key attributes of memory systems that should ordinarily work as they evolved to do, but the supposition was that subjects without such damage would display memory processes that behaved in a well-brought-up manner.

Again, bibliometrics illuminates the trend. Between 1985 and 1999, only 63 papers in the Science Citation Index (*Thomson Reuters*) had "[brain AND memory AND false]" in their title,

compared to 575 in the period 2000–2012; correcting for the doubling of the number of papers having brain as their topic between these periods, this still yields a 5-fold increase in the interest of the neuroscience community in the inaccuracies inherent in our memory.

A particular contribution to this trend was provided by the introduction of noninvasive functional imaging methods, mainly fMRI, that collectively permit convenient investigation of the brain of healthy participants. Coupled to adaptation of classic protocols used in cognitive psychology to the scanner environment, imaging has confirmed that the brain does indeed deserve its renewed reputation as an occasionally mischievous mnemonic device. All in all, the emerging picture is that recollection is a reconstructive process that is naturally prone to various types of intrusions, modifications, and even illusions (Schacter and Addis, 2007). This apparent sloppiness includes, among others, mistakes in identifying the source of the information ("misattribution"), incorporation of misleading and superfluous external or internal information, and bias by previous knowledge and belief (Schacter, 2001)—all indicating that either the trace is far from being a static replica of the original experience or that the recollective process acts on a veridical trace to produce a memory of questionable veracity. That these "sins of memory," as Schacter aptly describes them, may have a selective advantage should not be forgotten; for example, one could suggest that retaining the gist without remaining bound for too long to the full details of an experienced episode may facilitate anticipation of future different scenarios and promote creative imagination (Bar, 2009; Moulton and Kosslyn, 2009).

Studies involving multiple techniques have identified a number of potential mechanisms by which memory might have the opportunity to drift from the ostensibly exact coordinates of real events. One might envisage that this could happen, for example, in the immediate offline fast compressed replay of an episode (Davidson et al., 2009), during reactivation and consolidation of episodes in sleep during the night after (Diekelmann and Born, 2010), in slow systems consolidation that trims representations and converts episodic into semantic knowledge (Winocur et al., 2010; Furman et al., 2012), in fast systems consolidation in which new information is assimilated into existing mental schemas (Tse et al., 2007; see below), and, finally, in updating during reconsolidation (Wang and Morris, 2010).

Assimilation of the New with the Old

The classic approach to laboratory experimentation on learning and memory, certainly in animal laboratories, is the conduct of the study with subjects that are considered to have either no previous experience with the specific task or, at least, equivalent but well-controlled experience. This simplicity has long been thought to be the best way to identify the quintessential mechanisms of encoding, storage, consolidation, and retrieval. The problem is that this is artificial, because adult organisms will typically have a great deal of prior knowledge, and its possession may change the manner in which these processes occur.

The impact of prior knowledge is greater or lesser for certain forms of representation. In cases in which the emotional or affective value of a stimulus is strongly changed by a conditioning experience, prior knowledge will generally have little influence. An innocuous stimulus may have a long history of being innocuous, but the sound of the weekly fire alarm coupled to visible flames and the smell of smoke changes things forever. However, in cases in which learning involves forming an association, whereby one stimulus can evoke the memory of another, or where one is a label or even the meaning of another, prior knowledge is likely to have a critical impact.

Contrast two cases. Certain forms of associative learning studied in the standard way are quite well understood with, for example, the specific role of the amygdala in cued fear conditioning now worked out at the level of the neural circuits, receptors, and molecules involved. Conveniently, the amygdala is positioned such that the changed activity of its neuronal output pathways has a direct effect on heart rate and numerous other sympathetic and parasympathetic expression systems. Thus, behavioral (freezing) and other changes (heart rate) are readily observed. From a representational perspective, this form of associative conditioning may only require a change in the value of the predicting conditioned stimulus (CS) such that it now has access to output pathways useful in circumstances of danger. The past history of CS neutrality may result in some degree of "latent inhibition" but does not otherwise affect this capacity for learning.

In contrast, the parallel-distributed associative machinery of the neocortex is able to store "associations" of the representational form that CS1 evokes a memory of CS2 (Holland, 1990; for an earlier discussion of such type of associations, see Konorski, 1950). This form of learning is likely different from cued fear conditioning in that CS1 now does not change value to be quantitatively like that of CS2 but, rather, enters into a network of associations that will ultimately come together as a system of knowledge. Paired-associative learning of this form has long been recognized, both within the animal learning community in studies of intentional actions (Dickinson, 1980) and in neuroscience starting with the seminal studies of Miyashita on the electrophysiological signature of fractal pairings (Miyashita et al., 1993). Research on "systems consolidation" at the memory circuits level, which is distinct from research on "cellular consolidation" at the single-cell level (Dudai and Morris, 2000), has led to the idea that the distributed circuitry of the hippocampus performs a variety of encoding-related operations to stimuli such as pattern separation and pattern completion before subsequently creating event-event or event-context associations that may then be subject to consolidation in neocortex (McClelland and Goddard, 1996). The hippocampus and neocortex are hence considered as complementary learning systems (CLSs; McClelland and Goddard, 1996). Whereas the hippocampus is good at putting anything together with anything, and particularly with spatial information in the case of rodents, the neocortex readily forms representations of individual stimuli but is more restricted functionally in its capacity to link disparate information (e.g., information in distinct sensory processing systems). The neuroanatomical connectivity required may be present, but the strength of connections is initially weak, with experience being the guide as to what gets functionally connected to what. The combined forces of flexible hippocampal-dependent learning, systems consolidation, and the vast storage capacities of the neocortex collectively realize the "binding" task of understanding and representing the world around us and not just changing behavior adaptively to deal with specific types of association.

However, this systems consolidation process is now revealed as one that is influenced by what has gone before. One recent example that combines thinking about prior knowledge with representational associations is the idea of forming ''schemas'' around related paired associates that then alter the rate at which new paired associates can be learned and consolidated (Tse et al., 2007). Specifically, animals are trained to enable one of several flavors of food to be associated with and thus predict the location where more of that foodstuff is available. In this case, neither the different flavors of food nor the locations change ''value'' in the manner that a context does in context fear conditioning; what changes is the ability of one set of cues (flavors) to evoke a memory of the other (places). The use of places also enables the animals to gradually build up a representation of the testing space, over several weeks of training, such that they may be thought to have a mental schema that connects these otherwise independent associations into some kind of framework. Interestingly, once this had been achieved, the encoding, storage, and consolidation of new paired associates can become very rapid—even though it was shown to entail consolidation in the neocortex that had previously been thought to require weeks to accomplish (Tse et al., 2011).

This work was originally suggested as a challenge to the CLS approach, but new work by McClelland (2013) indicates that these findings can be readily accommodated by this framework. Whereas catastrophic interference can occur when new information conflicts with prior associations, necessitating two separate but interdependent learning systems, the new analysis suggests that synergistic effects are seen when the new information to be assimilated is concordant with past associations. This animal and computational work on paired-associate learning is also being considered in elegant human fMRI studies of schema-associated assimilation that point to critical interactions between the medial temporal lobe, prefrontal cortex, and other neocortical regions (van Kesteren et al., 2010) and new models of processing that suggest a differential role for the hippocampus and prefrontal cortex as a function of prior knowledge (van Kesteren et al., 2012).

Trace Alliances

Data from both animal and human studies support the notion that the expression of memory involves a transient alliance of representations (Buzsáki, 2010; Watrous et al., 2013). The notion of highly distributed representations, raised over the years by both theoretical and experimental programs (Hebb, 1949; Lashley, 1950; Rumelhart and McClelland, 1986), hence gains an invigorating new twist. In it, the embodiment of memory items is portrayed as dynamic, ad hoc global network interactions, perhaps mediated by frequency-specific connectivity.

A recent example on how this may happen in episodic memory in the human brain is provided by Watrous et al. (2013). They employed simultaneous electrocorticographical (ECoG) recordings in patients undergoing seizure monitoring and recorded from areas in the medial temporal lobe (MTL), prefrontal cortex (PFC), and parietal cortex, which are the main components of the brain network that is activated in retrieval. The patients were engaged in retrieving spatial and temporal contexts associated with an episode. Phase synchronization was used as a measure of network connectivity. Watrous et al. (2013) found that successful retrieval was associated with greater global connectivity among the sites in the 1–10 Hz band, with the MTL acting as a hub for the interactions. Notably, spatial versus temporal context retrieval resulted in differences in the spectral and temporal patterns of the network interactions: while correct spatial retrieval was characterized by lower-frequency interactions across the network along with early and prolonged increases in connectivity, temporal order retrieval was characterized by faster-frequency interactions, a more delayed increase in network connectivity, and a lower temporal coherence across the network compared with the spatial retrieval. Thus, an alliance of brain regions, with frequency-specific connectivity between them, rather than regionally mediated activity alone, could be central to many instances of retrieval and probably to the formation, maintenance, and updating of episodic memory. Furthermore, it appears that frequency-specific patterns of interregional phase synchronization in large-scale networks can provide insight into how multiple contexts underlying a single episode can be recreated in the same network.

Candidate coalitions of memory-related representations are also unveiled by methodologies tapping into longer temporal intervals. Methods for assessing functional connectivity in human fMRI data unveil sets of coactivations of regions subserving episodic recollection (e.g., Greenberg et al., 2005; Maguire et al., 2000; Burianová et al., 2012). Within the animal domain, immediate early gene (IEG) mapping offers another opportunity to examine the coactivation and possible coordination of neurons in multiple brain areas during memory retrieval—as reported by Wheeler et al. (2013) for context fear conditioning. Whereas we used to think of plasticity-related gene activation as triggered solely by encoding and necessary for storage, research on reconsolidation (see ''trace rebooting'' above) has alerted us to the phenomena of gene activation during and after a retrieval session. While the timescale of IEG expression is at least three orders of magnitude slower than that studied in ECoG, obscuring whether gene activation is triggered by, required for, or is some epiphenomenon of memory retrieval, it nonetheless offers an opportunity to examine the dynamics of trace activation across the brain. Wheeler et al. (2013) establish that the network interactions that are seen in IEG expression change as a representation consolidates over time.

Time Present and Time Future

T.S. Eliot, whose insights into memory infiltrate our subtitles, saw that life had its retrospective, immediate, and prospective elements. The last of these applies even to memory itself, with a growing number of investigators considering planning from the perspective of memory (Schacter and Addis, 2007; Thom et al., 2013). The prospective aspect of memory research is also intriguing. Given our argument that contemporary conceptions of memory processing are diverting from our dual-trace and fixed storage heritage, we can usefully ask, ''Where are we going''?

In Search of the Engramatic Code

Memory is traditionally measured in terms of the change in an individual's behavior that results from their behavioral experience. This change reflects the encoding and retention over time of experience-dependent internal representations in the brain or

of the capacity to reactivate or reconstruct such representations (Dudai, 2002). Representations, unless possibly of very elementary reflexes, are commonly postulated to be encoded in the spatiotemporal activity of neural circuits, ensembles, or Hebbian ''cell assemblies'' (Buzsáki, 2010). The number of neurons required for a physiologically meaningful representation need not be big (Shadlen and Newsome, 1998), but it is important to recognize that it is commonly assumed to be more than one neuron, even though mechanisms are often discussed as if change happens at a small subset of synapses in a single neuron. The influential reductionist revolution in memory research (Kandel, 2001) focused initially on the molecular mechanisms of synaptic plasticity that are hypothesized to allow memory to take place in the first place (Martin et al., 2000). Hence, the search for the engram in major parts of the discipline tilted for a while more toward the search for the identity and function of the molecular and cellular ''nuts and bolts'' of engramatic machinery rather than the issue of how circuit activity represents the cognitive and behavioral content encoded in the trace. But the ever swinging pendulum of science is now reverting to a more active consideration of the place of circuits, including microcircuits, and how they may mediate diverse aspects of cognitive function. Already we see growing interest in inhibitory neurons as well as excitatory neurons and regulation of the balance of their influence on processing via homeostatic regulation (Turrigiano, 2008), in the selective role of synapses at specific parts of a dendritic tree, on the soma, or on axons (Somogyi and Klausberger, 2005), and the contribution that synaptic integration and clustered plasticity may make to representations (Govindarajan et al., 2006; Branco and Häusser, 2011). This circuit revolution takes on board the earlier understanding of activity-dependent synaptic plasticity (Bliss and Collingridge, 1993; Kandel, 2001) and deploys some of the same neurobiological tools as in the past, but there is a growing sense that the mechanisms of memory will not be satisfactorily understood in the absence of elucidation of the circuit code(s) of internal representations for which some of the new tools available will be invaluable.

Progress continues to be made through novel theoretical ideas and via incremental refinements to long-established techniques coupled to elegant behavioral paradigms and fresh analysis methods. Notable, though definitely not exhaustive, examples include the development of multivoxel pattern analysis techniques in cases in which a qualitative rather than a quantitative change in the blood oxygen level-dependent (BOLD) signal is expected as in episodic memory encoding and retrieval (Chadwick et al., 2012; Kuhl et al., 2012); the use of long-established tetrode recording techniques to discover yet more about place cells, head direction, and grid cells and their role in providing a spatial framework for navigation and the anchoring of event memory (Burgess et al., 2002; Taube, 2007; Moser et al., 2008); new twists to the hippocampal tale such as ''time cells'' in the rat hippocampus (Kraus et al., 2013); the combination of tetrode recording in the macaque with fMRI in humans to unveil conserved patterns of neural activity across the medial temporal lobe during associative learning (Hargreaves et al., 2012); and the exploitation of advanced molecular biology to unveil the role of epigenesis in plasticity and memory (Day and Sweatt, 2011), for example, the involvement of small RNAs in epigenetic control of persistent synaptic facilitation in *Aplysia* (Rajasethupathy et al., 2012).

However, recent outstanding technical developments add significant power to the reductionist approach to memory but also permit more effective approaches to the identification of the representational content and dynamics of memory items in the behaving organism at the circuit level. The technological advances augment and feed the realization that circuit research will move us to the next stage of understanding perceptual, attentional, and mnemonic codes. An emerging assumption is that understanding the patterns of firing of identified neurons in specific macro- and microcircuits will constitute the level of detail to which we must turn. But how? It is now becoming possible, using combinations of advanced electrical recording, miniaturized in vivo chronic microscopy, conditional genetic switches, and optogenetics, both to monitor the activity of such neurons and circuits and also to perturb selected elements of this activity with a view to making causal inferences about mechanisms. Activating and inhibiting these elements will play an increasingly critical role in establishing sufficiency with respect to expressing the elements of memory.

Much of this type of work is conducted on the hippocampus, long implicated in multiple aspects of mammalian memory (Buzsáki and Moser, 2013), although the amygdala, subserving fear conditioning, is also a favorable target (Zhou et al., 2009; Johansen et al., 2010). The neocortex, commandingly positioned above the fray, is gaining the renewed interest it deserves (Gilmartin et al., 2013). Selected examples in animal models include: (1) identification in the behaving mouse of neuronal traces of specific fear-context associations and the generation of synthetic memory traces of such associations by selective activation of neurons engineered to carry receptors exclusively activated by designer drugs (Garner et al., 2012); (2) labeling of specific ensembles contributing to the fear-context engram with channelrhodopsin and subsequent optogenetic reactivation of the ensemble (Liu et al., 2012); and (3) identification by hippocampal recording with chronic tetrode arrays of compressed activity signatures during sharp-wave ripples that may represent specific spatial memory information (Pfeiffer and Foster, 2013). Whether the activity signatures unveiled in these and other studies are or are part of the neural code of active memory representations still awaits further investigation, e.g., on how these messages are read and construed by downstream brain circuits (Buzsáki, 2010). But these findings represent a significant step forward on the road to decipher the neuronal language of memory.

In humans, still limited at the time of writing by the lower temporal and/or spatial resolution of current noninvasive functional imaging and the relatively crude methods of ''noninvasive'' intervention (e.g., transcranial magnetic stimulation and direct current stimulation), the pace of advance is a bit slower but still highly noticeable. Classifier multivoxel pattern analysis, noted above, already permits identification of BOLD signatures of some types of visual categories (though not tokens within these types) in candidate memory representations (Rissman and Wagner, 2012). Intracranial electrophysiology in human patients is inherently limited in terms of scope and experimental design, but the expanding use of this approach, ranging from ECoG

(see above), single-unit recording, and microstimulation, is likely to provide further information on the correlation, and ultimately necessity and sufficiency, of neuronal memory representations (Suthana and Fried, 2012).

The trend, made possible by the fast development of advanced techniques, is to tap further into the network alliances, global circuits, and microcircuit processes and cellular mechanisms that process information for effective encoding, create suitable representations, and maintain information over time. This trend is likely to gain further momentum in the forthcoming decade, driven by research questions in basic science but also by potential clinical applications involving brain-machine interface (BMI) and the development of neuromorphic technology (see below).

Increasing Realism

The scientific era in human memory research began with an intentional and systematic disregard to the meaning of the information to be remembered by selecting nonsense syllables as memoranda (Ebbinghaus, 1885). In animal learning also, there had been a supposition early on that an abstract and mathematical account of all there was to know about learning could be realized from studying the behavior of a rat at the choice point of a maze—culminating in the formalisms of Hull (1951) that are now, perhaps fortunately, lost to time. The dominance of simple, quantifiable, yet artificial and often meaningless, memoranda provoked Neisser (1978), almost a century later, to question whether psychologists were studying interesting or socially significant aspects of memory. Part of the Ebbinghausian tradition was carried into the human fMRI protocols, e.g., strings of paired associates composed of normally unrelated words or arbitrary still pictures to model episodic encoding. This was highly productive, but in recent years, more realistic learning and memory paradigms are encountered in the scanner environment, including the use of movies as episodic memoranda (Hasson et al., 2008), of navigation by knowledgeable taxi drivers (Hartley et al., 2003), recollections modified by social interactions (Edelson et al., 2011), and the use of that universal engine of memory, fear, under strikingly realistic conditions (Sharot et al., 2007). In parallel, it is noteworthy that the outcome of research on brain and cognitive mechanisms of memory spills into key aspects of daily life and society (Schacter and Loftus, 2013). The growth of "social neuroscience" portends growing interest in social aspects of memory in both human and animal-based neuroscience.

Similarly, it seems that more attention is devoted to the effectiveness of realistic milieu in animal models used in memory research, with renewed emphasis on the real-life cognitive universe of rodents (particularly space, odors, somatosensory stimuli, and their interactions, e.g., Morris et al., 2006; Sauvage et al., 2008; Buzsáki and Moser, 2013). The general understanding, itself rooted in several older animal psychology schools and now resurrected, is that animals learn better when the memoranda make sense in their world. Hints of a similar trend seem to emerge in the primate literature as well (Paxton et al., 2010). It is likely that widespread use of novel consumer technology (such as Google-type glasses or personal activity monitors), miniaturization of noninvasive functional imaging devices for humans, and facilitated real-time web communication will render more realistic memory experiments easier and more popular.

Memory Systems Updated?

The dominant taxonomy of memory systems, echoing earlier philosophical notions (Ryle, 1949), was shaped by studies of "global amnesics" like H.M. and other patients (Scoville and Milner, 1957; Rosenbaum et al., 2005; Squire and Wixted, 2011), supported by lesion studies in animal models (Mishkin, 1982; Olton et al., 1979; Fanselow, 2010). It has long portrayed the brain as possessing two major types of memory systems—declarative (explicit) memory for facts and events, for people, places, and objects ("knowing that") and nondeclarative (implicit) memory, the memory for perceptual and motor skills ("knowing how"). Whereas declarative memory is held to involve particular types of representation and conscious awareness for recollection, it also requires an intact hippocampus—at least at the time that a memory is acquired. In contrast, nondeclarative memory is thought to be a heterogeneous collection of experience-dependent changes shown in behavior and not to rely on the hippocampus but on a number of other brain systems: the cerebellum, the striatum, the amygdala, and, particularly in invertebrates, simple reflex pathways themselves. This taxonomy was immensely useful as a conceptual framework for both human and animal studies, in teaching where it is little short of a blessing, and as an engine for new experimental programs.

Recent ideas and data, however, have raised questions about this taxonomy. One issue relates to what can be concluded from brain damage/lesion studies, which identify *necessity*, compared to physiological approaches, which measure *correlates* of a presumed process—be it in neural firing, BOLD, IEG activation, or in other ways. Specifically, the demonstration in double-dissociation lesion studies that the integrity of the hippocampus is not necessary for declarative memory retrieval after a long consolidation period (e.g., retrieval of semantic memory) need not imply, as perhaps it was taken to do so in the past, that it cannot or does not participate when functioning normally. Functional imaging data suggest, in contrast, that brain circuits traditionally considered to be the hallmark of declarative memory (hippocampus) or of procedural memory (basal ganglia) take part, in the healthy brain, in tasks in which they may not previously have been expected to play a role (Reber et al., 2012; Scimeca and Badre, 2012; see also Voss et al., 2012). There is also a growing realization that the classic temporal gradient of retrograde amnesia, challenged in the development of the multiple-trace theory of Nadel and Moscovitch (1997), may not be reliably secured in animal models. Related to growing uncertainty about the taxonomy is the question whether "conscious awareness" is indeed a natural type of classifier for memory systems (Henke, 2010).

This also raises the more general question of what memory systems are (Roediger et al., 2007). Are such systems rigidly interconnected sets of brain areas dedicated to specific types of mnemonic tasks? Or should they be considered as ad hoc coalitions of computational modules that are recruited per task (Cabeza and Moscovitch, 2013)? The latter view resonates nicely with the dynamic view of memory expression, discussed above. It is likely that in the forthcoming years our view of memory systems will become updated, not unlike memory itself.

Prepare for the Bionic Future

Coinciding with the 25th anniversary of *Neuron* is a new revolution in neuroscience. Not only have concepts of memory-in-brain changed over the past 25 years, partly in response to the astounding new methodologies that are altering the way brain research is done, but also the style of work is changing. The discipline itself is experimenting, not without intense debates, in "big science" projects that reflect the colossal demands imposed by the sheer complexity of the brain and the technological and cognitive resources required to tackle them effectively (Kandel et al., 2013). Whatever path this revolution takes, it is highly likely that some of the achievements of the multipronged new sciences of the brain will culminate in understandings and capabilities that not long ago were confined to fictional universes only, and some of these will be directly related to human memory.

One possibility is that the science of biological memory will make the leap from the vintage point of the curious observer to that of the active player. Some harbingers are already with us: new attempts to enhance memory, which have a long history (for a recent basic science example, see Alberini and Chen, 2012), or attempts to erase memory to ameliorate posttraumatic stress disorder (PTSD) in humans guided by research on reconsolidation (Schiller et al., 2010). But one should consider also the potential capabilities of brain-machine interfaces (BMIs, e.g., Hatsopoulos and Donoghue, 2009) not only to compensate for the deficits and retrain lesioned brain and bodies, but also, once noninvasive techniques are further developed, to augment the capability of intact brains. The potential ethical and social implications of such capabilities should not escape our notice.

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