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Title

Brain and memory: Old arguments and new perspectives.

Permalink

<https://escholarship.org/uc/item/5240w274>

Journal

Brain research, 1621

ISSN

0006-8993

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Publication Date

2015-09-01

DOI

10.1016/j.brainres.2014.12.052

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Brain Research

Editorial

Brain and memory: Old arguments and new perspectives

The question of how the brain stores, organizes, and retrieves memories is one of the longest running and intensely argued issues in the biological sciences. It is easy to find reasons why this should be so. Casual introspection, more than a century of research and debates tells us that an understanding of memory is an essential, early step towards a theory of mental life and the phenomenon is profoundly mysterious, a feature bound to attract scholars. Memories form quickly (albeit with a still poorly understood stabilization period), can be remarkably persistent, and the brain possesses an almost unbelievable storage capacity. Moreover, all lines of evidence point to the conclusion that memories are scattered throughout the brain and yet are (1) organized into computationally efficient structures, and along several dimensions, and (2) rapidly recalled even across different sensory modalities. Finding a unifying explanation for these qualities makes for a fascinating and challenging problem; this challenge, combined with the central role played by memory in all human experience, likely explains the continuing intensity of research in the field.

But the very nature of the properties of memories suggests that consensus definitions, conclusive experiments and convincing arguments will be hard to come by. The past 50 years of work has amply confirmed this prediction. Seen in this light, the many and sometimes acrimonious arguments associated with memory research were probably inevitable. However, scientific controversies often have useful outcomes and the question arises as to whether this has been the case for memory research. The contributions to this Special Issue were intended to address this question. They are organized into sections on a spectrum beginning with studies related to encoding mechanisms and ending with psychiatric disorders. The papers in each group deal with old arguments, including those related to the brain changes that encode new memory, how these are affected by events in the body, where storage occurs, and how all of these processes are integrated into higher cognitive functions. They describe the latest developments along with intriguing new perspectives.

1. Synapses and memory

The idea that connections between neurons are encoding and storage sites for memories is very old, and probably predates

the coining of the term 'synapse' by Sherrington in 1897. The French psychologist, Theodule Ribot wrote in 1882 that 'the physiological conditions of memory' must include 'an association, a specific connection established between a given number of elements'. Later, he speculates that the association will '... by repetition, become as stable as the primitive anatomical connections'. Ribot was worried that permanent changes in the state of a neuron ('permanently polarized' in his terminology) would limit storage capacity, an issue that continues to encourage the assumption that storage occurs at connections rather than through whole cell modifications. Today, of course, we have much stronger, experimentally grounded reasons for accepting the hypothesis that synaptic modifications are the substrate for encoding. The discovery of the long-term potentiation (LTP) phenomenon by Bliss and Lomo (1973) demonstrated that synapses possess characteristics required for a storage element; rapid changes in strength, triggered by physiologically reasonable stimulation patterns, and extreme persistence. Those first experiments also provided evidence that the changes were synapse specific, a point that was firmly established by studies using the then newly introduced hippocampal slice preparation. Later came results showing that drugs that block LTP cause amnesia (Morris et al., 1986) and clear demonstrations that the potentiation effect occurs at predicted synapses during learning (Roman et al., 1987). Ribot would have understood and been delighted by these discoveries.

But intense controversies soon erupted. The first, and perhaps most severe of these, concerned the locus of the synaptic modification underlying LTP was due to an increase in transmitter release or an enhanced post-synaptic response. This debate has subsided in part because the post-but not the pre-synaptic camp succeeded in identifying detailed mechanisms supporting their argument. But the signaling cascades leading to post-synaptic LTP have themselves become the subjects of considerable argument. Papers in Section A of this Special Issue review the canonical ideas and show that these are either questionable or far from complete. The next part of the section deals with a historical, and very contemporary, dispute about the reasons why LTP and memory endures for such remarkable periods. Three very different ideas have been advanced, including new synapse formation, self-regenerating chemical systems that

enhance EPSPs, or structural modifications of existing synapses. Also included in the section, and relevant to each of these arguments, is a reappraisal of the extremely contentious issue of how protein synthesis contributes to LTP and memory.

2. Peripheral modulation of central plasticity

The synaptic viewpoint on memory encoding has proven to be a powerful organizing idea. But there is a long-standing argument that this focus ignores the potent effects of events occurring outside of the brain. Life experiences engendering strong emotional responses can produce exceptionally vivid and persistent memories. This ‘flashbulb memory’ (Brown and Kulik, 1977) phenomenon was hypothesized to reflect emotional arousal and particular features of the experience (consequentiality, surprise) and, relatedly, were postulated to produce intense activation of the limbic system (Stark-Adamec et al., 1983). Later studies began linking activation of key limbic structures, most prominently in the amygdala, along with ascending biogenic amines projections, to the production of memory in cortex and hippocampus. But work starting at about the same time indicated that the adrenal responses produced by startling or significant events could have potent effects on memory (King, 1969). Possibly, then, hormones act directly in brain to regulate encoding mechanisms, an idea that ultimately received a great deal of experimental support (see Roozendaal and McGaugh, 2011). The question of peripheral vs. central mediation of the effects of cues and circumstances continues to be addressed today, with an increasing focus on interactions with mechanisms involved in synaptic encoding. Work described in Section B of this Special Issue describes some of the latest thinking on these problems.

Sex steroids have long figured prominently in discussions of hormonal influences on learning mechanisms, in part because of continuing controversies about the magnitude of memory changes during the estrus cycle and following the onset of menopause. There is considerable evidence for a positive action on memory of estrogen (E2) across species, including humans, and much work with laboratory animals has focused on the mechanisms underlying this effect. The possibility that the potent influence of E2 on gene expression present in peripheral tissues also occurs in brain received considerable attention as a possible explanation for the steroid's actions on learning and on behavior. But the discovery that the number of dendritic spines in hippocampus and certain regions varies with the estrus cycle led to a relatively direct structural hypothesis: E2 triggers synaptogenesis and thereby facilitates encoding of memory. A second possibility emerged with findings that E2 causes a rapid and pronounced facilitation of LTP, suggesting that the hormone acts directly on the substrates of memory. Reconciling structural and synaptic signaling hypotheses for E2-induced enhancement of memory is a major effort for current research, and chapters in this section deal with this question.

Growing evidence that E2 is synthesized within and released from terminals has added a new and critical dimension to the debate and raised the question of how peripheral

and central systems interact. The papers included in Section B also address this critical problem.

3. Synapses to networks (engrams)

Nineteenth century researchers recognized that memory, as a psychological phenomenon, would require coordinated activity of large numbers of brain cells: only in the context of cellular networks would synaptic plasticity gain real explanatory power. The German neurologist Richard Semon is generally credited with crystallizing these points into the idea of a memory trace or ‘engram’, a functional network assembled through learning that stores newly gained experience (Semon, 1921). While the idea proved popular and led to a protracted ‘search for the engram’, questions and disputes about the nature of the entity characterized much of 20th century research. Are engrams found throughout the brain or restricted to key ‘memory structures’? Do encoding elements occur at all stages of the trace or are there specialized, modifiable relays? It is curious that LTP research has done little to resolve these basic issues, perhaps because of a focus on mechanisms (see above) as opposed to functional significance.

Answers finally began to appear from work in a perhaps unexpected location: the cerebellum. Richard Thompson and colleagues identified a complete network for connecting a conditioned stimulus to a learned response, and then obtained strong evidence that the necessary modifications were localized to a particular region and collection of neurons (see Poulos and Thompson, this issue). This research, which took place over a span of 5 decades, was the first to reach the goal of describing an engram. Research on cerebellum has since led to a fascinating picture of a structure with multiple and unexpected forms of plasticity. These topics are discussed in papers included in Section C of this issue.

The search for memory traces in the telencephalon has been hampered by the extreme complexity of potential networks. The pathways from the periphery to the hippocampus, seemingly the most obvious place to look for an engram, are (excepting olfaction) tortuous and still poorly understood. The same can be said for the links between the hippocampus and observable behavioral responses. The great advantages of the cerebellum are clearly missing there. But other areas in the forebrain with established links to certain types of memory are more promising. In particular, the amygdala, with direct projections to brainstem effector nuclei, was found to receive monosynaptic inputs from the thalamus; these connections, along with intra-amygdaloid circuitry, proved to be networks required to associate stimuli with a behavioral fear response. While it has not yet been possible to study all the links in this network in the manner of Thompson's Engram, researchers have made great progress in describing learning-related plasticity within the amygdala (Section C).

As the engram idea was being developed near the turn of the 20th century, anatomists were describing what would today be called local circuits. It would take the evolution of modern technologies to translate the search for memory traces down to

this scale. But progress has been rapid, as can be seen by work also described in this section of the Special Issue.

4. From networks to higher order memory phenomena

Perhaps the most challenging conceptual problem facing the life sciences is to explain complex memory operations, as experienced in everyday life and as part of consciousness, in terms of brain processes (Crick, 1994; Edelman and Tononi, 2000; Lynch and Granger, 2008). One approach has been to use modern EEG and imaging methods to test for interactions between cortical regions as subjects are performing cognitive tasks heavily dependent on memory. This very large scale network strategy has yielded powerful insights into the way in which various regions form transient functional associations; it also provided evidence that trans-cortical networks constitute computational systems for processing, organizing and storing information. But the approach uses a broad temporal brush and so addresses the ‘where’ more than the ‘how’ memories are assembled into thoughts. The speed and enormous complexity of cognition seem to require ever changing interactions between discrete populations of neurons sometimes separated by considerable distances; events of this type are beyond the resolution of current imaging methods.

The above argument leads to a quite different strategy involving recordings from single neurons as an animal attempts to master a complex problem or environment. This is nowhere better illustrated than in work studying the contributions of hippocampus to spatial learning. Researchers studying this problem have determined that single neurons in the hippocampus and its entorhinal connection to cortex fire in response to particular spatial features. Notably, cells in different stages of the entorhino-hippocampal network are activated by different aspects of space and movement required for navigating an environment. Attempts to refine this information and place it in a network context are reported in this section of the Special Issue.

But some investigators have raised the possibility that spatial learning is a special case of a more general memory function of hippocampus. The question goes well beyond a particular body of research to impact on all efforts to study memory networks: are such studies using paradigms that overlook the essential features of mammalian memory? Tulving some 30 years ago made the seminal observation that an observer assembles sequential events into an episode, and argued that this is the dominant form of human memory (Stark-Adamec et al. 1983). This proved to be one of the most fruitful concepts in the history of the field, but it is only recently that researchers have applied it to network analyses of hippocampus. Work in Section D describes some of the more exciting recent results.

How to integrate the experimental results from imaging, spatial mapping, and time studies into a formal theory of higher order memory phenomena? modeling incorporating experimentally derived information certainly provides the most direct route. Network modeling began 70 years ago and has continued with varying degrees of intensity ever

since. Much of the work intended to explain particular psychological phenomena (e.g., language acquisition) in brain network terms but, it is probably fair to say that instead, it demonstrated that any number of computational designs and models could reproduce features of the phenomena being modeled. The emphasis appears to have gradually shifted to understanding how neurobiological features work together to produce recognizable outcomes. This new perspective, aided by steadily increasing computer power and very clever algorithms, has produced biologically realistic descriptions of the brain operations underlying higher order memory phenomena (also in Section D).

5. Memory and brain diseases

The eponymous Alzheimer was certainly among the first to recognize that memory is profoundly affected by brain diseases. Subsequent investigators confirmed this connection for multiple forms of degenerative and neuropsychiatric conditions. There have been many conflicting hypotheses about the factors responsible for this relationship, beginning with the idea that memory is a very complex process and so likely to be negatively affected by any generalized disturbance. This is intuitively attractive but the identification of cell biological pathways that produce LTP (Section A) led to an additional and more direct, mechanistic explanation. Specifically, recent studies using rodent models showed that a very broad range of conditions that negatively affect memory and cognition sever specific links in the LTP signaling cascades. The list of such conditions includes early stage Huntington's disease, Angelman Syndrome, Fragile-X, stress, loss of estrogen, and aging. Moreover, amyloid build-up in the most discussed instance of a memory disruptive brain disorder is widely reported to impair LTP, and there are impressive data indicating that inflammatory interleukins also interfere with the machinery that stabilizes the potentiation effect.

Results of these types raise the question of whether perturbations in synaptic plasticity observed in brain diseases, or with peripheral infections, not only affect memory but also actually contribute to their pathogenesis. This idea aligns with a hypothesis advanced a number of years ago stating that abnormal activation of the mechanisms associated with LTP-dependent memory causes neurodegeneration. Work on the effects of brain disorders on plasticity and how this relates to behavior and brain integrity is described in Section E.

Success in locating discrete sites of action where brain disorders interfere with synaptic plasticity led to renewed efforts at rescuing memory via targeted manipulations. Not surprisingly, most of work thus far has used drugs that affect basic components of the LTP machinery. Promising results have been obtained for agents that enhance the actions of Brain-Derived Neurotrophic Factor (BDNF), a releasable synaptic peptide that markedly influences the induction threshold and magnitude of the potentiation effect. Studies using compounds that increase BDNF expression, or that act as agonists at its receptor, have shown positive effects on memory and other behavioral manifestations of brain diseases in multiple animal models. But the rapidly increasing

evidence for peripheral modulation of central plasticity (Section B) points to the possibility of a more natural approach employing agents normally present in the body. Work on this exciting strategy is also covered in this section of the Special Issue.

5.1. An overview of particular arguments.

Progress is to be expected in any scientific field studied with the intensity applied to memory research. But viewed from the perspective of a now long history, can we say that basic arguments have been resolved or reduced to the point where the pathway to solution is clear? In the case of the nature of the encoding mechanism, one of the most hotly contested debates, the answer is probably yes. It does appear that a 'standard model' is beginning to coalesce, a model that will have considerable power for reducing behavioral phenomena to neurobiological terms. But we also note that so much of the relevant work has focused on one subfield (CA1) in one brain area (hippocampus). It remains to be seen whether big surprises are waiting in other regions. The old question of how and to what degree the periphery regulates memory seems only now to be coming into focus. While there has certainly been progress, issues involving genes, anatomy, and synaptic chemistry need to be dealt with before anything like a proposed solution can be considered. The famous argument about whether the brain uses 'mass action' independent of anatomical boundaries vs. discrete memory traces based on definable networks can be said to have been resolved in favor of the latter. Still, it is surprising that we have as yet only impoverished descriptions of engrams for the cortical forebrain.

The many arguments about how to proceed from networks and memory to the free flow of cognition remain largely intact. Highly successful paradigms, most notably for spatial learning in rodents, have produced impressive linkages between complex behaviors and the activities of neurons in the extended hippocampus. Continuing work promises to give a description that incorporates rhythms, local circuits involving multiple subclasses of interneurons, and detailed anatomical features. But, as noted earlier, the question must be faced of whether the agreed upon behavioral paradigm engages those features of memory that are fundamental to stream of consciousness. This is, of course, an unfair demand to place at this point in the evolution of the field. But it does serve to underline the question of whether current behavioral emphases are the fastest routes to understand higher order memory/cognitive operations. Other strategies, some developed over several years, stressing time and sequences are now reaching maturity, as can be seen in papers published here. One senses the emergence of new, and likely fruitful, debates relating to what have been since its inception the ultimate goals of memory research.

5.2. Postscript

The editors would like to express their appreciation first to the authors for their excellent contributions to this Special Issue, and then to the many reviewers who agreed to work under unreasonable time constraints, real evidence that professionalism is alive and well. Thank you. They also wish to dedicate this volume to the memory of Richard F. Thompson who created so many of the ideas and paradigms that shape our field. A giant who will be sorely missed.

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0006-8993/\$ - see front matter

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<http://dx.doi.org/10.1016/j.brainres.2014.12.052>

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