

Neuropsychology and advances in memory function

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Recent developments in the functional and neural bases of several aspects of memory are described including long term cortical memory storage, the transition from immediate to permanent memory mediated by medial temporal structures, working memory, memory retrieval, and implicit memory. These are linked to current data on the nature of anterograde and retrograde amnesia in the degenerative diseases, and also to issues in the clinical diagnosis of memory impairments. Understanding the bases of memory can inform the diagnosis of memory impairments in degenerative diseases, and the patterns of impairment seen in the degenerative diseases can help contribute to knowledge of the mechanisms of normal memory.

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INTRODUCTION

Perry and Hodges (1996) focused on the different profiles of memory dysfunction in different degenerative diseases. This review of progress will focus on advances in understanding the components of memory function (and dysfunction) and will touch on the implications these may have for understanding, diagnosing, and treating the memory disorders caused by degenerative diseases.

Recent progress has emphasised several old lessons. Memory is the persistence of information. Mechanisms for the persistence of information appear to be broadly distributed throughout the nervous system, as would be expected for so basic a need. At every level in each neuronal processing stream, there appears to be mechanisms that can extend the duration of neural activity, or that work to ensure that the information carried by transient neural activity can be stored. This more permanent storage is long term memory at the neural level. It seems clear that entrapment of transient neural activity into long term, neural memory is not a single step, but itself entails a large number of different processes. Each of these different steps to permanence themselves have their own particular time scales and mechanisms, and perhaps regional differences as well (Castro-Alamancos and Connors, 1997). The fastest are biochemical; perhaps the slowest are neural sprouting and remodelling. Neural remodelling may continue into adulthood in mammals, and

may be brought on by experience (Kemperman *et al.*, 1997).

It is clear, therefore, that 'memories' may result from many different levels of nervous system function (e.g. DNA, synaptic, neural, and neural network), and from many different types of processes even within each level (e.g. transient versus more permanent changes in synaptic reactivity). There have been a number of attempts to carve this complexity into a basis set of theoretically meaningful categories and relationships between them. This review discusses results within a few of these categories. However, it should be appreciated that the boundaries between these categories are not always clear, and are subject to empirical and theoretical redrawing (Robbins, 1996; Eichenbaum, 1997; Mathews, 1997). Moreover, normal circumstances of learning and recall may engage several different memory systems at the same time (Thompson and Kim, 1996).

PERMANENT STORAGE OF INFORMATION AND THE EFFECTS OF DEGENERATIVE DISEASES

It is now widely assumed, with mounting evidence, that information is stored in essentially the same regions of the nervous system in which it is used. Hence, much of the information ordinarily considered important to

people – such as facts within language, knowledge of pictures and faces – is cortically stored in the specific regions or combinations of specific regions responsible for the underlying functions. This has been particularly well worked out in the case of primate vision and visual representations, as Ungerleider (1995) reviewed.

The effects of degenerative diseases upon these cortical regions are often treated as though they were focal lesions (albeit widespread focal lesions). This is often correct, at least to a first approximation [e.g. in the case of posterior cortical atrophy (Ardila *et al.*, 1997) or focal-onset Alzheimer's disease (Davous *et al.*, 1996)] but there are also many reasons why degeneration affecting a region may have different effects from a structural lesion of the same region. Degenerative conditions evolve over much longer periods of time. This slow evolution may allow the individual to develop functional and possibly neuroanatomic compensations. Some evidence for this has been found in Alzheimer's disease (Becker *et al.*, 1996).

At a more basic level, however, degenerative diseases may alter how the affected cortex processes information compared with the changes produced by structural lesions. Warrington and Cipolotti (1996) suggested this possibility in the context of trying to understand impairments of semantic representations. Warrington and Cipolotti pointed out that degenerative diseases (and also herpes encephalitis) have been associated with total loss, or partial degradation, of semantic representations (1996). In partial contrast, semantic representations may not be lost with focal lesions, but instead may be refractory to access, particularly at rapid rates of stimulation. Why this difference should occur is not clear, although there are many possible local mechanisms (for example, degenerative diseases may affect only subpopulations of neurons). Regardless, investigators need to exercise caution in treating degenerations as though they were focal lesions. This also suggests a new opportunity, however. Degenerative diseases may cleave neuronal processes in ways that other diseases or techniques cannot.

PERMANENT STORAGE OF DECLARATIVE INFORMATION

There is now general agreement that the hippocampus and related medial temporal structures mediate the translation of temporary cortical activity (for some material) into more permanent forms of storage in the cortex. There is, it must be admitted, marked disagreement about exactly what types of information are involved, what parts of the hippocampus and adjacent structures are actually doing what, and how long this

consolidation process takes (Hasselmo, 1994; Gluck, 1996; Granger *et al.*, 1996; Hasselmo *et al.*, 1996; McClelland and Goddard, 1996; Gluck *et al.*, 1997). However, the importance of the hippocampus and adjacent medial temporal structures in the general process of immediate to permanent translation cannot be doubted. Traditionally, much of the evidence for this role has come from lesion studies. A particularly illustrative lesioned case was reported by Broman *et al.* (1997). The authors described a 27-year-old who developed a severe anterograde amnesia caused by respiratory arrest at the age of 8 years. Magnetic resonance imaging showed damage limited to the hippocampal region bilaterally, as would be expected from the history. It was not just new learning of episodic information that was severely impaired; this patient's development of vocabulary, literacy, and some other language functions were also arrested by his deficit. This case reinforces the points noted earlier, that current categorizations of memory systems may be imperfect, and that real life learning situations may require the cooperation of several different memory systems.

The role of the medial temporal structures in new learning has also now been demonstrated *in vitro*, by functional imaging with position emission tomography (Nyberg *et al.*, 1996) and functional magnetic resonance imaging (Stern *et al.*, 1996; Gabrielli *et al.*, 1997).

The prominent, early involvement of medial temporal structures by many degenerative conditions, such as Alzheimer's disease, is presumably part of the basis for the marked deficits of new learning (anterograde amnesia) in these conditions. Atrophy of the hippocampal formation (as measured by magnetic resonance imaging) predicts decline in memory function in ageing (Golomb *et al.*, 1996). In addition, many degenerative conditions cause other damage that would be expected to potentiate the effects of the medial temporal involvement. Disruption of cholinergic output from the nucleus basalis could impair an important cortical learning mechanism (Bakin and Weinberger, 1996). The medial temporal region is also likely to be important in memory retrieval (Gabrielli *et al.*, 1997). The joint disruption of both new learning and retrieval may account for why memory testing that jointly assesses both memory components may be more sensitive and specific for Alzheimer's disease than more narrowly focused memory testing (Buschke *et al.*, 1997).

WORKING MEMORY

Working memory is the term now applied to the scratchpad capabilities that allow new and old

information to be briefly retained in active, manipulable form. In this formulation, working memory is not so much a memory system as it is a confederation of already existing memory and executive abilities, which are recruited to suit the task at hand. Interest in and investigation of working memory has exploded in recent years, in part because of its clear importance as the conduit for learning, recall, and reasoning and many other mental abilities (Conway and Engle, 1996; Goldman-Rakie, 1996; Goldman-Rakie, 1997), and in part because it has proven to be accessible to neuroimaging and electrophysiologic techniques (D'Esposito *et al.*, 1995; Baddeley, 1996; Cohen *et al.*, 1997; Courtney *et al.*, 1997; Ruchkin *et al.*, 1997).

Working memory clearly requires activation not only of the regions directly involved in memory storage, but also of multiple prefrontal regions that are probably involved in memory search, coordination, and temporary storage of information and intermediate byproducts of processing.

Degenerative diseases, because of their typically widespread cerebral involvement, would be expected to cause early, marked impairments in working memory capacities. Working memory impairments, in turn, may underlie some of the puzzling clinical presentations of these conditions. A recent study that may be related to this point examined the effects of talking while walking in ageing and Alzheimer's disease (Camicoli *et al.*, 1997). The speed of walking in individuals with Alzheimer's disease slowed more when they talked at the same time than did the speed of aged individuals. This, it was suggested, may contribute to the risk of falls in Alzheimer's disease.

MEMORY RETRIEVAL

To be useful, information must not only be stored; it must also be accessed. Access can take the form of recognition, which is theoretically fairly direct, in the same regions where the memory is stored. Or it can involve recall, which may be by part-whole cueing, associative cues, time tags, or other mechanisms for recreating the stimulus that was originally encoded. Recall in particular, therefore, could often be expected to require many brain regions, and perhaps a relatively long time period of iterative activity. Functional imaging has to some extent supported these notions, showing activation of posterior as well as prefrontal regions with recall (Fletcher *et al.*, 1997; Cabeza *et al.*, 1997). However, as lesion data had already suggested, neuroimaging studies have also shown that medial temporal structures play a role in memory retrieval (Fletcher *et al.*, 1997; Gabrielli *et al.*, 1997; Nyberg *et*

al., 1996). As noted above, the dual role of medial temporal structures in new learning and in memory retrieval may account for the magnitude of the memory impairments seen in degenerative conditions that affect these regions.

REMOTE MEMORY

Classically, memory for premorbid information in degenerative conditions with memory loss was described by Ribot's law (Ribot, 1881): the retrograde amnesia was more marked for more recent past events and knowledge, and less marked (if a problem at all) for the oldest remote memories. This description is now known to be too simplistic, empirically inaccurate, and theoretically contentious. Many different categories of remote knowledge have been distinguished, although the fundamental reasons why there should be distinctions between them (if any) are not always clear. Semantic memory, memory for famous faces, famous names, external events, and memory for personal information (what some categorise as autobiographical memory) have all been studied, both in the degenerative diseases (Greene and Hodges, 1996) and in other conditions (Barbarotto *et al.*, 1996; Campodónico and Rediess, 1996; Evans *et al.*, 1996; Markowitsch, 1996; Alexander, 1997; Schmidtke and Vollmer, 1997; Reinkemeier, 1997) including normal ageing (Jansari and Parkin, 1996). Widespread regions of the brain, particularly of the right hemisphere, are activated in response to personal autobiographical information (Fink *et al.*, 1996). Retrieval of semantic information is also associated with activation of many brain regions, with some differences found for types of items (Damasio *et al.*, 1996).

One reason the study of retrograde amnesia has become so active is that the nature and extent of retrograde amnesia helps test different theories of memory storage (Graham and Hodges, 1997; Snowden *et al.*, 1996; Kapur, 1997; Murre, 1997). In the modal theory of memory described earlier, information is initially processed in the cortex. Long term retention of that information in the cortex is dependent (in some fashion) upon the hippocampus and other medial temporal structures. For some variable period of time after initial exposure, cortical memories remain susceptible to fading or disruption. This disruption is prevented by the medial temporal lobe system(s). Hence, in this formulation, damage to the medial temporal lobe will not only prevent the formation of new memories, but also allow the dissipation of more recent old memories; the fate of old memories of different ages will show how long is required for the fixation process. Conversely,

direct damage to the cortical storage system should damage all memories dependent upon cortical storage alone (older old memories), but comparatively spare more recent old memories, which are still being supported by the hippocampal system. Such a dissociation was found by Graham and Hodges (1997) between the retrograde gradients caused by amnesic Alzheimer's disease (presumably, a variant with degeneration more limited to the medial temporal lobe) and that caused by semantic dementia (having, among other problems, a fluent aphasia probably caused by cortical degeneration of the temporal lobe).

IMPLICIT MEMORY

Implicit memory is the term applied to learning and memory that does not require an explicit statement, but which is revealed in the course of performance of a task. Examples include the ability to detect perceptually degraded pictures or words, or learning of a motor skill such as maze navigation. It is likely that implicit memory is not a memory system *per se*, but instead a common characteristic of a large number of different neural systems, which show a common ability to learn through repetition. As expected from this formulation, implicit learning is not dependent upon the medial temporal (hippocampal) system, but instead dependent upon the specific regions involved in the function. Visuo-perceptual implicit memory, for example, has been shown to be impaired in a patient with bilateral occipital lobe lesions (Keane *et al.*, 1995); learning a probabilistic classification was severely impaired in Parkinson's patients, but not in amnesic patients (Knowlton *et al.*, 1996).

Traditionally, implicit memory was not affected by Alzheimer's disease, although deficits in implicit memory (motor skill learning) could be found in another degenerative disease, Huntington's chorea (Knopman and Nissen, 1991). However, more recent studies have suggested deficits in abilities such as perceptual fluency in Alzheimer's disease, although there are considerable conceptual difficulties in comparing the 'degree' of learning across patient and control groups (Gordon, 1988). Regardless, d-cycloserine, which affects the *N*-methyl-D-aspartate subtype of the central nervous system glutamate receptor, has recently been shown to improve priming in a word identification task in Alzheimer's disease patients (Schwartz *et al.*, 1996). Deficits in implicit memory would be expected in a disease which directly affects the circuits responsible, as Alzheimer's disease quite plausibly could do. The Schwartz *et al.* finding is among the accumulating evidence that the efficiency of these

circuits can be enhanced by *N*-methyl-D-aspartate receptor modulation.

EDUCATION, ABILITY AND THE COURSE OF DEGENERATIVE DISEASE

As expected, higher education and ability can affect the presentation of conditions such as Alzheimer's disease. Higher levels of education are associated with higher levels of functioning on verbal measures in Alzheimer's disease, but not with nonverbal measures, as a study by Filley and Cullum (1997) recently confirmed. What has captured public interest is the possibility that higher levels of education and accomplishment in some way protect against the development or expression of the disease. This has been the conclusion reached from a study of nuns (Snowdon *et al.*, 1996) and from a large, community-based sample of African-Americans (Callahan *et al.*, 1996), among others. However, a fundamental flaw of both these studies was that the criteria for intellectual impairment (performance) for the diagnosis of dementia were the same across all education and ability levels; they were not themselves adjusted for premorbid intellectual ability. Even if the decline caused by Alzheimer's disease was independent of ability, higher premorbid ability will cause an apparent delay in reaching such criteria because the individual is starting from a higher level, as the Filley and Cullum (1997) study and other data suggest they should. Therefore, although there are many reasons to think that early and sustained intellectual activity is desirable for maintaining mental abilities in later life, there is no reliable evidence, as yet, that it can truly protect against the onslaught of a devastating condition such as Alzheimer's disease.

CLINICAL DETECTION

The degenerative diseases do not generally result in qualitative neuropsychologic differences from normal ageing, at least in their early stages (although it would be hoped that they would). Instead quantitative differences from normal memory and other neuropsychologic functions are more often found. Self reported complaints, the observations of family and friends, and the health care provider's suspicions and mental status testing are the three principal routes to detection of Alzheimer's disease and other dementing conditions.

Self reported problems

Self reported problems with memory and other mental abilities unfortunately usually correlate with depression rather than degenerative disease, as one recent

(Smith *et al.*, 1996) and many previous studies continue to demonstrate. Subjective complaints do sometimes presage development of dementia (Schmand *et al.*, 1996), as expected. Moreover, in nondepressed individuals, subjective memory complaints do correlate with actual memory performance (Jonker *et al.*, 1996). This correlation may be expected to lessen with individuals who have more definite disease, such as early Alzheimer's disease, because of the minimization or complete unawareness of problems (agnosagnosia) that is often a feature of this condition. Starkstein *et al.* (1996) drew a further distinction, between unawareness of deficits in memory, orientation, reasoning, and praxis (cognitive unawareness), and unawareness for irritability, selfishness, inappropriate emotionality, and disinhibition (behavioral unawareness). Behavioral unawareness was present early in the disease; cognitive unawareness was more likely later.

Family informants

Family reports have long been the mainstay of detection of dementia, with generally a high sensitivity and an inherent ability to correct for premorbid intelligence and education (Mulligan *et al.*, 1996). However, the false-negative rate of family informants can be appreciable. Problems with 'memory or thinking' were denied by family informants in 21% of elderly Japanese-American men who met criteria for dementia (Ross *et al.*, 1997). This was particularly true with borderline or very mild dementia (52%), and less likely with more definite dementia (13%). However, as the authors of this study pointed out, these percentages may be greater than those found in other populations (Ross *et al.*, 1997). Respect for the elderly and the social stigmatism of mental illness in this cultural group would have been expected to inflate the percentage of unrecognised dementia, as would the fact that this cohort of elderly Japanese-American men was typically not expected to do many of the daily household duties that might have more easily revealed their cognitive deficits.

Clinical detection

Given the relatively high frequency of Alzheimer's disease, and the prominence of memory deficits, relatively short mental status tests that focus on memory are often sensitive enough for clinical screening (Stuss *et al.*, 1996). This is also true in examining the subset of individuals who present with memory loss, and who are at risk of developing Alzheimer's disease, with its more florid memory impairments (Tierney *et al.*, 1996). However, more complete neuropsychologic evaluation is likely to be desirable in clinical settings where the

spectrum of presenting conditions is wider, and where the risks of individual false positives and false negatives must be kept as low as possible (Selnes, 1995). Crystal and colleagues (1996) used formal neuropsychometric test data, both cross sectionally and longitudinally, to assess a sample of originally nondemented older individuals. Level of performance at entry, and rate of change, were both important predictors of ultimate normality, pathologic ageing, or Alzheimer's disease. These data would have been unreliable or unavailable from shorter screening instruments.

CONCLUSION

Analysis of memory deficits in degenerative disease is clearly an ongoing process, and rewarding for a number of reasons. There is the constant refinement of our understanding of what comprise 'memory' deficits, both quantitative and qualitative, which allows these conditions to be differentiated from normal ageing, and from each other. More detailed knowledge of the neuropsychology and underlying pathophysiology will allow more rational and more effective therapies for these conditions. Knowledge of the deficits that occur in degenerative diseases may also help to refine knowledge of the processes and neuroanatomic substrates necessary for normal cognitive and memory functions.

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