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Review

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The contribution of the study of neurodegenerative disorders to the understanding of human memory

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Summary

Memory impairment is one of the most common complaints affecting patients with neurodegenerative disorders, and its investigation has provided insights into the function and properties of human memory. The study of Alzheimer's disease has indicated the importance of mesial temporal structures and the hippocampus in episodic memory. In progressive supranuclear palsy, frontotemporal dementias, Parkinson's disease and Huntington's disease fronto-striatal networks are involved in working memory and higher level cognition. The study of semantic dementia, where there is lobar atrophy of the temporal lobe, has shown that the temporal neocortex has an important function in semantic memory. The investigation of human memory in neurodegenerative disorders suggests that the interaction of networks subserving episodic memory, semantic memory, and working memory contributes to higher level cognition and results in the fundamental homeostatic processes of recall and learning.

Introduction

Memory impairment is one of the most common complaints in patients in the early stages of dementing diseases such as Alzheimer's disease (AD). The study of memory is important, as it may be the initial symptom that alerts the clinician to the possibility of a brain disease. This review describes how the study of neurodegenerative disorders has contributed to the understanding of human memory, and how this information has been used to develop models of memory systems and networks.

Neurodegenerative disorders usually involve multiple neuronal systems, and have some limitations compared with lesioning, such as might result from a neurosurgical procedure, head injury or lesioning experiments in animals. Nevertheless, neurodegenerative disorders offer insights into the function of fragmented neuronal networks, as disintegration of distributed systems is the template upon which therapeutic measures operate.

Memory in its simplest form may be considered to have a number of basic functional components essential for homeostasis. This review will not involve itself in a detailed discussion of neuropsychological theories of memory, but will attempt to demonstrate the basic deconstruction of memory in neurodegenerative diseases and, after a brief consideration of theoretical issues, how this has contributed to our understanding.

Memory may therefore be considered the functional expression of neuronal networks that subserve the properties of learning, storage and recall. Short-term memory allows the retention of information for brief time periods, and is a sub-system of working memory.[1] Long-term memory involves

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the recollection of personal and public events unique to that individual, such as events that happened yesterday or last week. This is called episodic memory.[2] Material-specific or semantic memory represents the store of information of our knowledge base of the world.[3] For example *'what is a school?', 'what is a river?'.*

Short-term, episodic, autobiographical and semantic memory are components of an explicit memory system, which involves conscious activity (as opposed to implicit memory, which is automatic). Implicit memory relies on neuronal networks that allow us to perform procedures such as the knowledge to play the piano or kick a football.

In neurodegenerative disorders, the functional components of memory networks may be dissociated such that patients may have impaired episodic memory but preservation of autobiographic and semantic knowledge, or other combinations of abnormalities.

This review describes how neurodegenerative disorders involve the neuronal networks subserving the unique capabilities of human memory.

Theoretical considerations

Prior to an analysis of the effects of neurological disease on memory function, some discussion of the theoretical basis of memory systems is essential, especially in the light of recent studies. Some patients with neurodegenerative disorders will have an amnesic syndrome characterized by anterograde amnesia. That is, they are unable to learn new verbal and nonverbal information from the time the illness began. This contrasts with retrograde amnesia, in which patients have difficulty retrieving events prior to the onset of the illness. A popular model suggests that the medial temporal lobe is involved in the storage and retrieval of episodic and semantic memories (Figure 1). One investigation looked at three groups of patients with neurodegenerative diseases involving different structures. Patients with early AD, with involvement of medial temporal structures, were compared to patients with semantic dementia with involvement of the anterior temporal lobe, to patients with the frontal variant of fronto-temporal dementia (fv-FTD). These subjects were investigated with an autobiographical memory task to assess the entire lifespan. It was observed that patients with early AD had a temporally graded memory loss obeying Ribot's law: i.e. more recently laid down memories were rapidly eroded, in comparison with memories laid down in the distant past. Patients with semantic dementia (SD) had a reserve gradient, and there was no clear

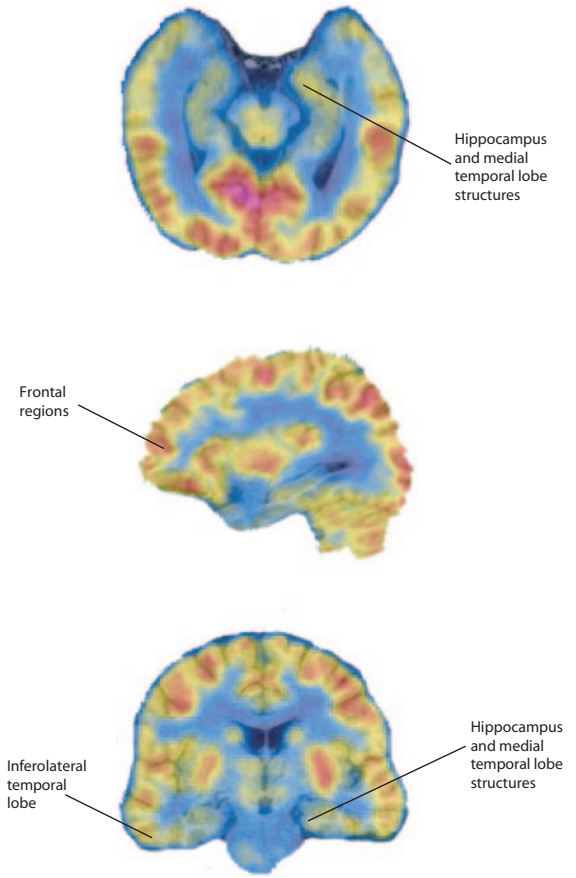

Figure 1. T1 weighted MRI images of normal brain with superimposed FDG PET scans, showing the important structures involved in human memory in the horizontal, sagittal and coronal planes.

gradient in patients with fv-FTD.[4] Episodic memory showed an ungraded loss in early AD and fv-FTD, and a temporal gradient in SD. Autonoetic consciousness, that is remembering, was defective in early AD and fv-FTD but preserved in SD. These observations suggested the multiple trace theory that the ability of the medial temporal lobe (MTL) to recollect episodic memory (EM) is more permanent, as opposed to the standard model, in which storage and retrieval of EM is limited for a number of years.

The investigation of the neural substrates of EM has been studied using MRI and 2-deoxy-D-glucose positron emission tomography (PET) in patients with mild cognitive impairment (MCI), thought to be the very early stages of AD, and reflective of involvement of the MTL.[5] In this study, encoding and retrieval were dependent on hippocampal grey matter density, encoding being a reflection of hippocampal glucose metabolism and retrieval of metabolism on the posterior cingulate, probably mediated by an indirect trans-synaptic mechanism.

Autobiographical memory (AM) refers to the recollection of events in the person's life. It may

be further characterized as lifetime events (when at university) or general events (going to a play). The structures subserving AM are multiple, and include the neocortex and limbic system.[6] The temporal lobes are thought to be important in the knowledge of people and events: the thalamus and MTL subserving memory for childhood and early adulthood, the MTL and diencephalon for processing early childhood and adulthood memory. The frontal lobes are postulated to provide general access to this system. The retrieval processes of AM are complex and mediated by the frontal lobe network, which samples knowledge networks in the temporal lobes. Event-specific knowledge, which recounts evidence of sensory experiences, is not organized conceptually, and is believed to be stored in the occipital and parietal regions. AM is a superordinate system that takes input from subordinate memory systems, and binds patterns of automation of lower order memory systems into mental representations of AM. In view of this superordinate nature, AM can be dissipated by lesions at different locations.[7]

Semantic memory (SM) is the neuronal network that stores and retrieves information about the meaning of words, concepts and facts. The studies of Hodges *et al.*[8] support the notion that SM is based in a network in the dominant inferolateral temporal lobe. These conclusions are founded on patients with SD, characterized by an aphasia syndrome with progressive erosion of word content. SD is also known as the temporal variant of frontotemporal degeneration (tv-FTD). The fv-FTD with atrophy of the frontal lobes is dominated by a behavioural syndrome characterized by disruptions in personality, disinhibition and executive functions.[8] Patients with SD have profound SM breakdown, which is unimpaired in the fv-FTD and only mildly involved in AD, in whom a defect in EM is dominant. In fv-FTD, SM is preserved and associated with mild abnormalities in EM and verbal fluency.[8] The study of AD and FTD supports the notion of the importance of MTL in EM and lateral TL in SM.

How might the systems of EM, WM, SM and AM interact to produce a functional memory system? One model proposed is the serial-dependent independent (SDI) model for the interrelation between these networks.[9] In this system, there is a hierarchical arrangement for different storage systems in which retrieval is independent. In this model, perceptual information cannot be encoded into EM and must be processed through the semantic system. In the multiple input model, EM derives input from the perceptual system of the semantic system.[10]

Alzheimer's disease

Alzheimer's disease is one of the commonest neurodegenerative disorders, and memory loss is one of its presenting symptoms. Alzheimer's disease is characterized by neuronal loss, neurofibrillary tangles and neuritic plaques. Studies by Braack and Braack[11,12] have identified that neurofibrillary tangles in the hippocampus and para-hippocampal regions occur early in disease, and correlate best with memory dysfunction. There has been increasing interest in the early symptoms of AD, as these patients probably qualify for treatment with drugs that might modify symptoms of AD, such as acetylcholinesterase inhibitors. Early AD may be characterized by impairment of verbal episodic memory, reflective of involvement of the hippocampal formation.[13] In a longitudinal study of early AD, episodic memory loss preceded widespread cognitive decline. This finding correlated with pathological involvement of the MTLs as found by Braack and Braack.[11,12] These findings, confirmed by magnetic resonance imaging (MRI), showed that in early AD, impaired verbal and episodic memory correlates with a reduced volume of the hippocampal formation and entorhinal cortex, which may be reduced by 25% using volumetric scanning.[14] The atrophy was most marked in the entorhinal cortex, superior temporal gyrus and extended to the anterior cingulate. Atrophy of the hippocampal formation also correlated with loss of verbal and visual memory, as found in studies of pre-symptomatic familial AD using longitudinal MR scanning.[15] Other studies supported the so-called 'preclinical phase' of AD affecting memory and involving the hippocampal formation.[16] Involvement of the MTL using volumetric MRI suggested that amygdaloid volumetric measurements provide a sensitive marker for verbal memory and visual memory, especially delayed recall in the early stage of AD.[17] Further studies of hippocampal volumes have shown that reductions in the left hippocampal volume best predict abnormalities of free recall and delayed free recall of verbal information, whereas atrophy of the right hippocampus was reflective of impaired recall and delayed recall of spatial location.[18,19]

Further analysis of episodic memory deficits in AD may reflect impaired learning rather than accelerated forgetting, on the basis of a study of 33 patients using the doors and people test.[20] Early studies have suggested that CT scanning, focussing on the MTL, would also be a sensitive tool and might be used in clinical practice to determine involvement of the structures in early AD.[21] MRI studies showed that reduced volume of the

amygdaloid and subiculum also correlated with memory performance. Atrophy of the right amygdaloid complex was associated with loss of visual and partial verbal memory and atrophy in the left subiculum with verbal memory.[22] The studies of Laakso *et al.*[23] also suggested that the volume of the left hippocampus correlated with abnormalities in the mini-mental state examination, and with impairment of immediate and delayed verbal episodic memory. The smaller the volume of the hippocampus, the more impaired was performance. The studies of Deweer *et al.*[24] contributed to the concept that the volume of the hippocampal formation correlated with the specific memory variables of episodic memory.

Short-term memory as a concept is difficult to define, and Baddeley has contributed much to this area by the development of the concept of working memory.[1] Working memory may be defined as a 'system' for the temporary holding and manipulation of information during the performance of the range of cognitive tasks such as comprehension, learning and reasoning. In a well-established model, working memory has a central executive, an articulatory loop and a visuo-spatial scratch pad.[1] Working memory may be affected in AD.[25] However, the component of working memory that is primarily affected has not been definitively resolved, but evidence suggests that it may be the central executive.[26]

More recent studies have suggested a role for the central executive process of working memory in visual rehearsal and vigilance performance.[27] The studies of Kempler *et al.*[28] suggested that impaired sentence comprehension in AD might be related to a deficit in verbal working memory. Patients with AD may experience difficulty with pronouns, which might be secondary to impaired working memory.[29] Other studies have suggested that involvement of working memory systems in AD might relate to a loss of the ability to map the understanding of a sentence onto depictions of world events.[30] Autobiographical memory deficit in AD might be secondary to impairment of retrieval (related to executive function) and loss of memory stores.[31]

Our knowledge of the world (semantic memory) appears to be stored in the temporal neocortex.[32] In AD, a pattern of retrograde amnesia has been found that obeys Ribot's law (1881), old memories being better preserved than recent ones. This observation, in light with other studies showing a reverse temporal gradient in SD, has suggested that the retrieval of recent declarative knowledge (episodic and semantic) is mainly subserved by the hippocampal complex, while the retrieval of more remote knowledge (from a few years to more than 10 years) depends on temporal neocortex. In 1990, it was shown that there was differential involvement of semantic vs. episodic memory in AD vs. Huntington's disease.[33] This finding had been suggested in earlier studies indicating that the semantic memory store may be affected in AD.[34,35] Memory impairment in AD results from involvement of automatic and effortful processing tasks.[36] The studies of Binetti *et al.*[37] suggest that the degradation of semantic knowledge in AD may be revealed by impaired category fluency tasks. Subsequent studies have revealed that semantic knowledge may be consistently affected in AD, and is probably a reflection of involvement of the temporal neocortex.[38] In a population of 52 patients with dementia of the Alzheimer type, patients had a profound deficit of episodic memory, characterized by delayed recall of new verbal and non-verbal material, with the transentorhinal region being consistently involved. Pathology at this site caused a disruption of the connection between hippocampus and other brain regions leading to the deficit of EM. Lesions in the transentorhinal region do not lead to impairment of SM. Semantic memory was affected when the pathology extended to the temporal neocortex.[38]

Studies have shown that identification of famous faces and famous names may be impaired in AD as part of the disruption of semantic knowledge stores. Patients with AD were impaired on both famous faces and name recognition, with a temporal gradient obeying Ribot's law, suggesting that face and name recognition units are from a semantic knowledge store eroded by the condition.[39] Semantic breakdown in AD, as determined by assessment of animate and inanimate objects, revealed that it might be secondary to storage access and a disruption of descriptive and phonological output systems.[40] This suggested that a number of different functional systems might be affected in the semantic memory impairment of AD. Other investigations found that abnormalities of semantic knowledge, as it pertains to famous persons, was a result of declining semantic knowledge stores, whereas retrieval abnormalities lead to anomia.[41] The studies of Lambon Ralph *et al.*[42] also suggested that semantic knowledge may be disrupted as a result of involvement of the temporal neocortex which may be activated by words and pictures, and that natural objects and artefacts may be stored differentially. These studies confirmed that the hippocampus was involved in new learning, whereas the temporal neocortex was involved in the storage of information. Encoding of recent events is initially dependent on the hippocampus and related structures.

Semantic dementia, a form of lobar atrophy involving the temporal lobe neocortex, has relative sparing of the hippocampal complex, and such patients have selective impairment of semantic knowledge, which supports the concept that the temporal neocortex is involved in the storage of semantic knowledge.[43] Single-photon emission computed tomography (SPECT) studies in patients with AD indicated that the superior temporal lobe and inferior parietal lobe were probably the structures subserving semantic processing.[44] The deficit of semantic knowledge in AD might be related to impaired ability in semantic relations.[45] Other studies indicated that semantic knowledge in the domain of natural objects or artefacts involved the temporal neocortex, whereas the fronto-parietal regions subserve perceptual and functional attributes.[46] In a study of 58 patients with AD, there was a significant advantage for artefacts, providing confirmatory evidence that different brain regions were associated with the storage of different categories of information.[46] The mechanism of involvement of SM might reflect involvement of a retrieval mechanism and of memory stores.[47] The deterioration of SM in AD might reflect a breakdown of organisation and structure of semantic knowledge stores as neurodegeneration spreads to associated cortical networks that store semantic representations.[48] The studies of Saykin *et al.*,[49] using functional magnetic resonance scanning, indicated that SM might involve the left superior temporal gyrus, the inferior and the mid-frontal gyrus. Functionally, the impairment of semantic knowledge in AD might involve abnormalities in the gain-decay mechanism in which information may be encoded and lost, with the velocity of loss dependent on the pathological process leading to impaired access to semantic representations.[50] The pattern of SM deficit in AD, with sparing of verbs but a selective deficit of nouns in the biological category, supported dysfunction in the temporal lobes, and is also observed in *Herpes simplex* encephalitis.[51]

The memory impairment of AD is characterized by early involvement of explicit memory, particularly those functions relating to episodic and working memory. Autobiographical memory will also be involved and possibly reflects impairment of retrieval (related to executive function) and loss of memory stores.[20] There is substantial sparing of implicit memory for visuo-motor skills, in comparison with Parkinson's disease.[52] This explicit memory loss involves the hippocampal-amygdaloid complex. The relative sparing of the primary motor and sensory cortical areas and the basal ganglia maintain the normal learning of visuo-motor skills in patients with AD. The involvement of the amygdaloid complex might reflect that emotional factors are important in recall in AD.[53] The rate of cognitive decline was more rapid in patients with AD with higher educational or occupational attainment, suggesting that functional reserve erodes faster in patients with more complex interconnections.[54,55] The involvement of episodic memory was specifically related to limbic diencephalic pathology and semantic impairment related to temporal and neocortical pathology.[56] Other studies suggested that preservation of perceptual priming in AD indicated relative preservation of the occipital regions and involvement of the medial temporal structures.[57] Visuo-spatial information may be impaired in AD and temporally graded in a retrograde fashion.[58] Short-term memory impairment in AD may involve a deficit in the rate of rehearsal.[59]

The study of memory in AD has been a fertile area of research, and confirms models of working memory as an expression of short-term memory processing, and the existence of explicit memory functions of episodic memory, autobiographical memory and semantic knowledge.[60] The elucidation of the nature of the memory deficit in AD is important in diagnosis, and contributes to our understanding of memory functioning. The neuropsychological approach to such patients will demonstrate patients with so-called mild cognitive impairment in whom there is symptomatic and objective memory impairment but do not fulfil criteria for the diagnosis of dementia.[61,62] Approximately 10–15% of such patients evolve to AD each year, and their conversion rate is dependent upon the series examined.[61] These patients will be the targets of future research, as it is in this population that agents which improve memory function and modify the natural history of disease offer the greatest hope.

Parkinson's disease

Parkinson's disease is a movement disorder characterized by bradykinesia, rigidity and tremor. Patients with Parkinson's disease may develop cognitive symptoms and even dementia.[63] Memory disorders in such patients are common. Mental processing in Parkinson's disease was shown to be slow in early studies.[64] Other studies suggested that Parkinson's disease patients might have a problem binding information into long-term storage, consistent with involvement of the entorhinal cortex and hippocampus.[65] Some studies indicated that procedural memory may also be impaired.[66] Cognitive decline in Parkinson's disease might be related to visuo-spatial disturbance, impairment

of memory and depression.[67] Early studies comparing Parkinson's disease and AD identified problems with episodic and semantic memory which are sensitive to pro-active interference.[68] The bradykinesia might be secondary to memory impairment.[69] The studies of Sagar *et al.*[70] suggested that impaired short-term memory processing in Parkinson's disease is possibly related to subcortical deafferentation of the frontal lobes secondary to striatonigral pathology.

Parkinson's disease patients perform better on explicit memory tests than AD patients, probably a result of the selective pathology of the mesial temporal structures in AD.[71] Other work has suggested that Parkinson's disease patients might have difficulty organizing new material and applying strategies.[72] There might also be a combination of reduced motivation and initiation behaviour, leading to cognitive deficits.[73]

Working memory may be impaired in Parkinson's disease, possibly secondary to involvement of the central executive as hypothesized by Baddeley's working memory model.[74–76] Cognitive deficits in Parkinson's disease have been explained in terms of frontal lobe dysfunction secondary to involvement of the basal ganglia.[77] Cognitive impairment in Parkinson's disease is probably multifactorial, and in some patients might be independent of subcortical dopaminergic pathways, and may involve neuronal abnormalities in the neocortex.[78] Controversy exists as to the contributions of subcortical vs. cortical pathology in the cognitive deficits of Parkinson's disease. Failure of verbal and visual memory might be a result of hippocampal atrophy in Parkinson's disease, whereas deficits in spatial working memory and intentional systems may be reflective of involvement of the frontal-striatal pathways.[79] Involvement of motor memory systems has been suggested as evidence of subcortical involvement in Parkinson's disease and Huntington's disease.[80] Studies showed that short-term memory deficit in Parkinson's disease correlated with deficits of working memory and involved attention and executive function, and were not secondary to a temporal ordering deficit.[81] An analysis of memory and learning strategies showed that Parkinson's disease patients were dependent on the order of the sequence presented.[82,83] Parkinson's disease patients may have involvement not only of the declarative memory, but also procedural memory. The modules involved in procedural memory include visual, auditory and tactile codes.[84]

Patients with Parkinson's disease may have a deficit in memory for spatial location with relative preservation of verbal memory, perceptual visuospatial and executive functions. This was interpreted as indicative of involvement of nigrostriatal dopaminergic pathways and the striatal-frontal neuronal circuits.[85] Learning and forgetting in Parkinson's disease may be impaired, and possibly a result of dysfunction in the medial prefrontal cortex.[86] Postle *et al.*[87] found that spatial learning and working memory were selectively impaired in early Parkinson's disease, suggesting that interactions between the basal ganglia and the pre-frontal cortex are important in higher level functioning. Knoke *et al.* [88] have shown that impaired learning in Parkinson's disease might be a result of dysfunction in the frontal executive control of intentional sources and encoding strategies. Impairment of temporal memories might be secondary to lowered dopaminergic input to the striatum.[89] Impairment of comprehension in patients with Parkinson's disease might be secondary to reduced syntactic-semantic link, leading to impaired working and syntactic processing.[90] The delay in recognition memory in Parkinson's disease was further evidence for involvement of working memory.[91] A study of event related potentials in Parkinson's disease patients showed that the auditory N-400 component in a repetition priming paradigm was abnormal in Parkinson's disease patients, suggesting a neurophysiological substrate to impaired memory function.[92]

Memory impairment in the absence of dementia was frequently found in a study of Parkinson's disease, where disorders of memory trace consolidation were dependent on the age of diagnosis rather than on its duration.[93] Interestingly, the reduced memory indices found in patients correlated with the degree of abnormalities in gait and postural reflexes. This implied that the cognitive deficits of Parkinson's disease were manifestations of the underlying pathological process. The cognitive deficits in patients with Parkinson's disease without dementia have shown impaired verbal memory, which may be a result of altered attention allocation and formulation of retrieval of effortful learning, suggesting frontal lobe dysfunction.[94] Disruption in short-term spatial memory has been correlated with reduced saccadic eye movements compatible with a disturbance in spatial memory representations in early Parkinson's disease.[95]A contribution to apraxic speech may lead to reduced memory span in Parkinson's disease.[96] The study of Howard *et al.*[96] found that patients with apraxic speech had lower memory span for longer words, indicative of involvement of speech planning and programming.

Thalamotomy and chronic thalamic deep brain stimulation may be used for the treatment of dyskinesias and tremor in Parkinson's disease. Some patients experience problems with language and memory after these procedures. A study of chronic

electrical stimulation of the left ventrointermediate (Vim) thalamic nucleus has revealed that Vim stimulation improved semantic verbal fluency but disrupted immediate recall of words, supporting the concept that the thalamus has a role in memory.[97]

Patients with Parkinson's disease have cognitive and memory disorders in the presence or absence of dementia. The memory profiles in Parkinson's disease may be variable and not homogeneous. In some patients, the pattern of cognitive abnormalities was more consistent with AD and, in others, more like Huntington's disease.[98] There is attractiveness in the hypothesis that impaired spatial learning and working memory are supportive of dysfunction in the interactions between the basal ganglia and prefrontal cortex. More work needs to be done to consolidate this hypothesis, as many of the studies in Parkinson's disease are underpowered to make conclusive statements.[87,99]

The pattern of cognitive abnormalities in early Parkinson's disease might reveal involvement of spatial learning and working memory, and indications of dysfunction in the basal ganglia and prefrontal cortex. The neuropsychological profiles of patients with Parkinson's disease, in comparison with those with AD, show overlap and dissociation. Speech, language and episodic memory are dissociable differences in the early stages of AD, in contrast to Parkinson's disease. Patients with Parkinson's disease are more likely to have cognitive slowing with absence of aphasia, indicative of a subcortical process. Visuo-spatial and executive functions may be impaired in both disorders. The diverse nature of the cognitive impairment in Parkinson's disease is probably a reflection of the variable nature of the underlying pathology. Patients with Parkinson's disease might have a subcortical process, and those who have associated Alzheimer pathology, more pervasive cognitive impairment.[100]

In conclusion, the study of Parkinson's disease contributes to the hypothesis that connections between the basal ganglia and prefrontal cortex are important for higher level cognition involving spatial and working memory.

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) or dementia represents a recently re-defined and complex group of disorders.[101] The diagnosis of FTLD is dependent on a combination of clinical, neuropsychological and imaging investigations. Patients with FTLD may be classified into frontal and temporal variants.[4,8,102,103] Patients with predominantly left-sided temporal lobe atrophy will have an aphasia syndrome, whereas those with right-sided temporal lobe atrophy will experience a behavioural syndrome characterized by instability, impulsiveness, bizarre behaviour, fixed ideas and decreased facial expression.[102] Semantic dementia is characterized by profound semantic memory breakdown, amnesia and surface dyslexia in patients with bilateral involvement of the polar and inferolateral regions of the temporal lobes. There is sparing of the mesial temporal lobes.[8,103] Visual recognition of faces and objects should also be affected, indicating involvement of the bilateral infratemporal areas and left hemisphere centres for language.[104] The frontal variant is characterized by behaviour abnormalities and executive problems arising from frontal lobe atrophy. There seems to be no consistent pattern of abnormality in memory function and the evidence so far suggests that there may be involvement of working memory.[105–107] The studies of Thomas-Anterion *et al.*,[108] in a series of 12 patients with AD and 12 with FTLD, showed that both groups exhibited a retrieval deficit in remote memory. Psychiatric features, especially mood disturbance, are common in comparison to AD.[106] Traditional neuropsychological tests are poor in differentiating FTLD from AD, and a combined approach using clinical, neurological, neuropsychological and imaging tests is necessary. FTLD patients have impaired working memory and executive functions related to the pathology affecting the frontal and temporal lobes in contrast to AD, where the mesial temporal structures are preferentially involved.

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterized by an extrapyramidal syndrome with a characteristic abnormality of eye movements, particularly in the vertical plane. PSP is the neurodegenerative disorder from which the concept of a subcortical dementing process evolved. Neuropathologically, there is loss of neurons in the peri-aqueduetal grey matter, superior colliculus, subthalamic nuclei, dentate nucleus, and the nuclei of ocular motor neurons. There is deposition of tau protein with neurofibrillary pathology in preserved neurons, which show 'whorl' tangles distinct from other neurodegenerative disorders. Neurons in the cerebral cortex eventually become involved. Patients with PSP exhibit slowness of cognitive and motor processing, impaired speed of information processing, and executive dysfunction, which differentiate the cognitive decline in PSP from other neurodegenerative disorders

such as AD.[109] PSP patients may have prominent recall deficits and forgetfulness with relative preservation of short-term and implicit memory processes, in contrast to AD where patients develop aphasia and apraxia.[110] Evidence suggested that deactivation of the frontal cortex was secondary to a subcortical processes in PSP.[111] In 1994, Pillon *et al.*[112] revealed that PSP patients had impaired memory deficits characterized by reduced immediate memory span, consistent with the notion that the cognitive deficits in PSP were due to involvement of frontal-striatal systems. More recent studies have added complexity to the cognitive decline in PSP, as long-term psychological and imaging studies suggested involvement of the cerebral cortex consistent with neocortical pathology.[113]

The investigation of the cognitive abnormalities in PSP has contributed to the hypothesis that subcortical structures such as the pallidum and mesencephalic reticular activation system, and their connections to the frontal cortex, are involved in working memory and speed of information processing. The published studies are limited and larger more long-term analyses are required.

Huntington's disease

Huntington's disease is an inherited neurodegenerative disorder characterised by chorea, dementia and psychiatric disturbances. It is caused by a trinucleotide CAG repeat mutation as found in other neurodegenerative disorders like the spinocerebellar ataxias. Huntington's disease may present with cognitive decline and dementia prior to the development of chorea and psychiatric disorder.[114] There is selective pathology in the basal ganglia, which eventually extends to the neocortex.[115]

The subcortical nature of the dementia in Huntington's disease is characterized by reduced speed of cognitive processing, with intact memory acquisition and retrieval. As the disease progresses other cognitive processes become degraded, consistent with the early pathological involvement of the corpus striatum.[116] A correlation between the severity of amnesia involving working memory and chorea has been observed, reflective of the pathological involvement of the basal ganglia and frontal lobes.[117] Huntington's disease patients may have impaired explicit memory associated with difficulty accessing semantic based knowledge.[118] The naming deficit in Huntington's disease might involve a disruption of perceptual analysis, whereas in AD there is a breakdown in semantic processing.[119] Procedural learning may be affected in Huntington's disease compatible with a role for the striatum in this function.[120] Explicit motor memory might be abnormal in Huntington's disease[71] and semantic memory may also be affected.[121]

Early studies suggested that patients with Huntington's disease have impairment in the coding of new information, consistent with reduced retrieval of learned material.[122] Further studies by Caine *et al.*[123] indicated that cognitive impairment in the early stages is not diffuse and homogeneous, but reflective of relative sparing of higher cognitive functions. Recently diagnosed patients may have retrograde amnesia with reduced remote memory.[124] Verbal recall, verbal recognition and procedural memory might also be impaired.[125]

Huntington's disease is distinguished by slowness of responses, and an impairment of working memory without aphasia, apraxia or agnosia. This is compatible with the role of subcortical structures, in particular the basal ganglia and their frontal lobe connections in psychomotor velocity and working memory. As Huntington's disease evolves, the cognitive deficit becomes more extensive paralleling the pathological involvement of the neocortex. The literature on Huntington's disease and cognitive changes is limited by the investigation of relatively small numbers of patients and further studies are needed.

Conclusion

The study of human neurodegenerative disorders offers the opportunity to understand the mechanisms involved in memory and to consider the cellular, chemical and molecular foundations of memory processing. Such considerations might lead to treatments to reverse the amnesic state. The analysis of neurodegenerative disorders involves the interface between clinical neurology with neuropsychology, neuropathology and neuropharmacology.

The study of neurodegenerative disorders provides evidence for the MTL in WM; the anterior, inferior and lateral portions of the temporal lobe in SM; a complex interactive network involving temporal lobes, thalamus, MTLs, diencephalon and frontal lobes in autobiographical memory; and the frontal-striatal network in working memory and speed of cognitive processing. The study of AD has provided insights into the role of forebrain cholinergic systems in learning and memory, not only relevant to AD, but also to the cognitive deficits of ageing.[126–128] Acetylcholinesterase inhibitors and muscarinic agonists are now available for the treatment of mild to moderate AD.[129] Hippocampal atrophy and the density of neurofibrillary tangles in the hippocampus correlated with EM disorder

and neuroimaging evidence for MTL atrophy in AD.[130] Abnormal phosphorylation of the microtubular associated protein tau in the entorhinal-hippocampal system correlated best with onset and degree of dementia.[131] It is possible the abnormal phosphorylation of tau is critical for the memory dysfunction of AD. The correlation with hippocampal neuritic plaques and amyloid load is less convincing.[132] The apolipoprotein E ε4 status correlated with EM disturbance and conversion to AD, probably as a result of apolipoprotein E ε4 allele being a significant risk factor for sporadic AD.[132] The neuropathological studies suggest that the abnormal phosphorylation of the tau protein may be the molecular basis for memory impairment in AD and offers scope for future therapeutic developments.

Neurotrophic factors may be important in memory function and neurotrophins, or drugs that act upon the neurotrophin pathways such as brain derived nerve growth factor, might also be potential treatments.[133] Other pharmacological strategies in the treatment of memory disorder might involve the use of glycine and polyamine agonists which act upon the N-methyl-D-aspartate (NMDA) receptor. It is possible that a combination of approaches using both cholinergic and glutamatergic agonists might have synergistic benefits. Agents acting on the nitric oxide system, which interact with glutamatergic pathways, might also prove useful.[134]

A number of novel gene systems are probably integral in the function of memory circuitry. Further research will provide functional insights as to the contribution of various molecular pathways to the networks of human memory and might provide new treatments. Nootropic agents (drugs that enhance memory) might work on the serotonin system or the cyclic AMP response element binding protein (CRE), which controls the expression of a number of genes and might be involved in long-term memory processing. Calcium-calmodulin-dependent protein kinase, protein kinase C, cyclic-AMP-dependent protein kinase, metabotropic glutamate receptors, adenylate cyclase and the NR1 subtype of glutamate receptor may all be important.[135]

The knowledge gained from the investigation of memory dysfunction in neurodegenerative disorders suggests the involvement of a number of networks in human memory processing (Figure 2). The study of AD suggests the importance of MTL structures and the hippocampus in episodic memory. Fronto-striatal systems are important for working memory and higher level of cognition as suggested through the analysis of disorders like PSP. The temporal neocortex has a role in SM. The interaction between these networks, their aberration in disease and their

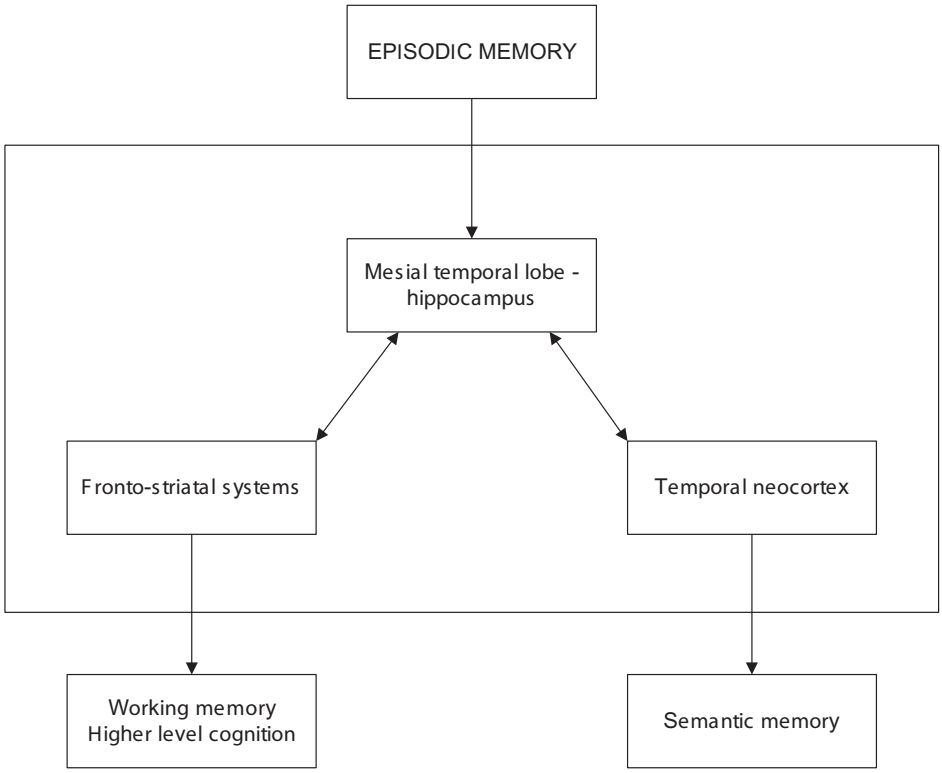

Figure 2. The networks of human memory.

modulation with therapeutic tools offers an opportunity to obtain further insights into the workings of human memory.

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