Memory Dysfunction

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ABSTRACT

Purpose of Review: This article highlights the dissociable human memory systems of episodic, semantic, and procedural memory in the context of neurologic illnesses known to adversely affect specific neuroanatomic structures relevant to each memory system.

Recent Findings: Advances in functional neuroimaging and refinement of neuropsychological and bedside assessment tools continue to support a model of multiple memory systems that are distinct yet complementary and to support the potential for one system to be engaged as a compensatory strategy when a counterpart system fails.

Summary: Episodic memory, the ability to recall personal episodes, is the subtype of memory most often perceived as dysfunctional by patients and informants. Medial temporal lobe structures, especially the hippocampal formation and associated cortical and subcortical structures, are most often associated with episodic memory loss. Episodic memory dysfunction may present acutely, as in concussion; transiently, as in transient global amnesia (TGA); subacutely, as in thiamine deficiency; or chronically, as in Alzheimer disease. Semantic memory refers to acquired knowledge about the world. Anterior and inferior temporal lobe structures are most often associated with semantic memory loss. The semantic variant of primary progressive aphasia (svPPA) is the paradigmatic disorder resulting in predominant semantic memory dysfunction. Working memory, associated with frontal lobe function, is the active maintenance of information in the mind that can be potentially manipulated to complete goal-directed tasks. Procedural memory, the ability to learn skills that become automatic, involves the basal ganglia, cerebellum, and supplementary motor cortex. Parkinson disease and related disorders result in procedural memory deficits. Most memory concerns warrant bedside cognitive or neuropsychological evaluation and neuroimaging to assess for specific neuropathologies and guide treatment.

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INTRODUCTION

Memory dysfunction can result from a wide array of neuropathologies that affect the distributed neural networks of several dissociable memory systems in the human brain. A convergence of data from molecular biology, neuropsychology, clinical neurology, and neuroimaging support the concept of clinically distinct memory systems: episodic memory, semantic memory, working memory, and procedural memory (**Table 2-1**). These systems represent tools for processing information for potential use after the passage of time, and their use may be either conscious (eg, explicit, declarative) or unconscious (eg, implicit, nondeclarative). Memory dysfunction is associated with the entire gamut of neurologic problems that affect brain function in disorders ranging from epilepsy to stroke and has growing clinical relevance as the population ages and Alzheimer disease and other neurodegenerative diseases increase in prevalence. In this context, the ability to make early and accurate diagnoses in patients with subtle memory dysfunction may facilitate the prediction of an underlying neuropathology and subsequent access to potential disease-modifying therapies currently in development.

EPISODIC MEMORY

Episodic memory refers to the ability to consciously recall personal episodes or experiences. Episodic memory is unique

TABLE 2-1 Clinically Relevant Memory Systems

Memory Subtype	Patient/Caregiver Early Concerns	Cognitive Testing Deficit	Relevant Neuroanatomy	Commonly Associated Neuropathology
Episodic (declarative, explicit)	Verbal: cannot remember breakfast this morning or the destination of most recent vacation Visual: cannot recall the cabinet in which the dinner plates are located or the side of the street of the local drug store	Verbal: recall of oral narrative, word list recall Visual: recall of figure copy, recall of figure location in space	Medial temporal lobes, Papez circuit Verbal: left greater than right Visual: right greater than left	Alzheimer disease, herpes encephalitis, thiamine deficiency, hippocampal sclerosis, hypoxic-ischemic insult, dementia with Lewy bodies
Semantic (declarative, explicit)	Cannot recall the number of weeks in a year or identify the breed of the family dog; identifies most household items as ''thing''	Fund of general knowledge, picture naming, category fluency	Anterior and inferior temporal lobes	Frontotemporal lobar degeneration, Alzheimer disease
Working (declarative, explicit)	Cannot recall a phone number immediately after hearing it; cannot perform a series of simple requests after traveling from one room to the next	Digit span, mental arithmetic	Prefrontal cortex, subcortical structures, parietal association cortex	Vascular insults, frontotemporal lobar degeneration, dementia with Lewy bodies, Parkinson disease dementia, traumatic brain injury
Procedural (nondeclarative, implicit or explicit)	Cannot recall technique for using a driver off the tee; cannot maintain a violin bow hold[a]	Not routinely tested	Basal ganglia, cerebellum, supplementary motor area	Parkinson disease, cerebellar degeneration, Huntington disease

[a] Not referable to motor deficits or novice abilities.

KEY POINT

- Episodic memory is the ability to recall personal experiences from one's life and involves a series of steps, which include encoding, consolidation, and retrieval.

among memory systems because it is distinctly related to both a sense of self and a sense of time.[1] Typically, dysfunction in this type of explicit, declarative memory brings patients to the neurologist for clinical evaluation of memory dysfunction.

Conceptually, episodic memory involves a series of steps including *encoding*, *consolidation*, and *retrieval*. Encoding describes the direction of cerebral resources to the processing of information via attentional mechanisms, whereas consolidation involves the storage of this information in a form that will be mentally accessible in the future. Retrieval refers to the act of remembering such information.

In 1957, episodic memory was clinically demonstrated to be distinct from other cognitive functions when Milner and Scoville[2] reported the now well-known case of Henry Molaison (H. M.), who lived from 1926 to 2008. A patient with intractable epilepsy, H. M. had undergone bilateral medial temporal lobe resections a few years before Milner and Scoville's seminal study. Although he suffered neither general intellectual loss nor perceptual dysfunction, H. M. did demonstrate profound *anterograde* amnesia (the inability to form new episodic

memories) for verbal and nonverbal material in all sensory modalities, as well as a lesser degree of *retrograde* amnesia (the inability to access episodic memories from the past).[2]

Neuroanatomy of Episodic Memory

While H. M.'s episodic memory deficit implicated the medial temporal lobes as critical to memory function, longitudinal neuropsychological testing and neuropathologic confirmation in other patients have similarly implicated bilateral damage to the CA1 region of the hippocampus as sufficient to create an isolated, albeit less severe, episodic memory deficit.[3] These findings highlight the complex anatomy of the medial temporal lobes, which include both hippocampal (subfields CA1 to CA3, dentate gyrus, and subiculum) and extrahippocampal (entorhinal, perirhinal, and parahippocampal cortices) structures (**Figure 2-1**). While the hippocampus is considered critical to memory consolidation, its role subsequent to consolidation and in nonepisodic memory tasks remains an area of controversy. Functional neuroimaging data in healthy individuals reveals that the dissociations so well defined in patients with brain injuries, like H. M., may be oversimplified.[4]

Damage to brain regions densely connected to the medial temporal lobes also results in variable degrees of episodic memory impairment. Disruption of the Papez circuit,[5] including the mamillary bodies, anterior nuclei of the thalamus, and fornices, produces anterograde amnesia. Injury to the posterior cingulate gyrus, which is functionally connected to the hippocampus, may also impair episodic memory. Functional neuroimaging supports this finding in patients at risk for developing Alzheimer disease due to either a genetic predisposition or amnestic mild cognitive impairment that demonstrates early alterations in the posterior cingulate and precuneus.[6] The frontal lobes also play an important role in episodic memory, primarily impacting encoding and retrieval functions. Additionally, thalamoprefrontal and thalamoretrosplenial connections contribute significantly to the episodic memory network and may make differential contributions to recollection and familiarity, concepts that remain challenging to operationalize.[7] Verbal and visual episodic memory functions also appear to be lateralized. Functional MRI (fMRI) in children reveals lateralization of activation to the left hippocampus with associated basal ganglia involvement for episodic verbal memory encoding.[8] Likewise, in healthy elderly subjects, structural MRI volumetry demonstrates a correlation between left hippocampal volume and verbal learning tasks, as well as right hippocampal volume and a visual, maze learning task.[9] Functional neuroimaging data suggest that the left medial temporal lobe may be more active in the recall of autobiographic memories, although adult patients with known medial temporal lobe pathology demonstrate compensatory increased activation in the ventral prefrontal cortex, precuneus, and lingual gyrus.[10] Conversely, correlation of right hippocampal function with visual memory has been demonstrated in patients with varying degrees of memory deficit due to mild cognitive impairment and Alzheimer disease.[11] Additionally, the right posterior hippocampal gray matter volume of London taxi drivers, whose job requires complex visual memory function, increases with the number of years of taxi driving and greater navigational expertise.[12]

Representative Neurologic Disorders Affecting Episodic Memory

The temporal profile of episodic memory disorders helps organize both the differential diagnosis and treatment plan. Episodic memory dysfunction from traumatic brain injury, including concussion,

KEY POINTS

- Anterograde amnesia is the inability to form new episodic memories. Retrograde amnesia is the inability to access episodic memories from the past.
- The hippocampal formation and medial temporal lobes are critical to episodic memory formation.
- Other cortical and subcortical structures that are clinically relevant in episodic memory include the diencephalon, limbic system, and posterior cingulate and precuneus regions.
- The temporal profile of episodic memory dysfunction is important for determining the causative neuropathology.

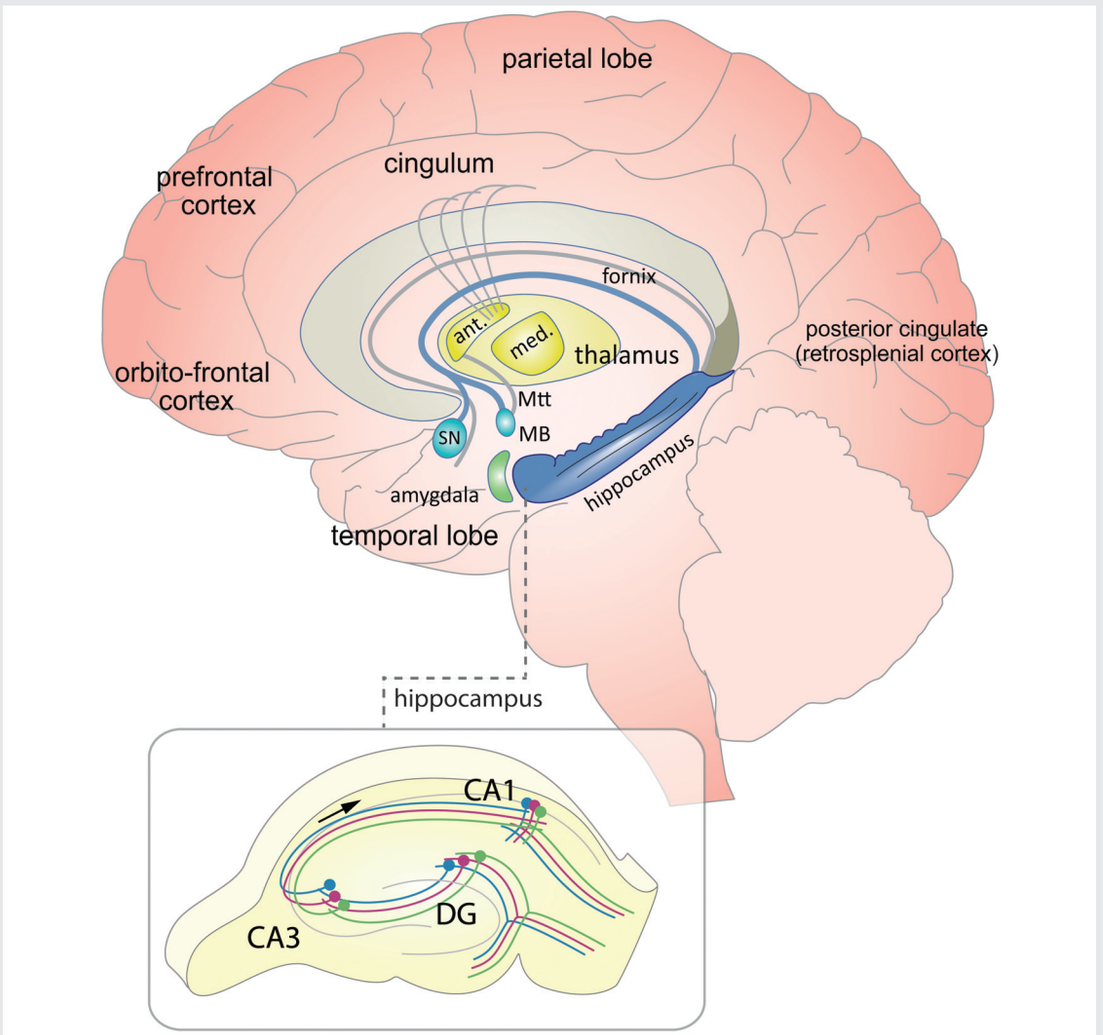

FIGURE 2-1 Neuroanatomic regions implicated in episodic memory dysfunction. Inset shows the feedforward, trisynaptic pathway involved in the processing of information within the hippocampus, known to be critical to the encoding stage of episodic memory.

ant = anterior thalamic nuclei; med = medial thalamic nuclei; Mtt = mamillothalamic tract; SN = septal nuclei; MB = mamillary bodies; CA = cornu ammonis; DG = dentate gyrus.

Courtesy of Thorsten Bartsch, MD.

and posterior cerebral artery distribution stroke affecting either medial temporal or thalamic structures[13] presents acutely and may slowly improve. Subacute presentation may suggest an infectious etiology such as herpes encephalitis,[14] an inflammatory condition such as paraneoplastic limbic encephalitis,[15] or a toxic/metabolic cause such as Wernicke-Korsakoff syndrome.[16]

Transient impairment of memory function can accompany complex partial or generalized seizures and is the hallmark of transient global amnesia (TGA), which is a profound anterograde and limited retrograde episodic memory impairment that may last up to 24 hours that can be associated with punctate diffusion-weighted MRI abnormalities of the CA1 region of the hippocampus, which are

most likely to be visualized on the second day after the episode.[17] Less commonly, transient epileptic amnesia can have features of both epilepsy (abnormal EEG, aura, automatisms, and response to antiepileptic medications) and TGA (transient anterograde and retrograde amnesia). Transient epileptic amnesia is distinct because the episodes are usually less than 1 hour in duration, recur monthly, and may be associated with an unusual loss of remote autobiographic memories, such as a wedding or graduation.[18]

Chronic memory dysfunction is most suggestive of a neurodegenerative disease, and anterograde amnesia is the most common syndromic presentation of Alzheimer disease dementia, although nonamnestic presentations of Alzheimer disease are increasingly recognized.[19] The patient in **Case 2-1** presented with chronic progressive visual greater than verbal memory deficits, a presentation suggestive of mild Alzheimer disease. Lewy body dementias, including dementia with Lewy bodies and Parkinson disease dementia, and frontotemporal dementias are less likely to present with early episodic memory impairment, but often progress to include memory dysfunction. Hippocampal sclerosis of aging may also present with chronic episodic memory deficits and is often clinically diagnosed as Alzheimer disease. The etiology of hippocampal sclerosis of aging remains elusive, although it is associated with advancing age and comorbid cerebrovascular pathology. Neuropathologic studies reveal the abnormal accumulation of TAR-DNA binding protein 43 (TDP-43) in a pattern distinct from frontotemporal lobar degeneration.[20] Of clinical relevance, patients with hippocampal sclerosis tend to have less significant functional impairment than patients with Alzheimer disease.[21]

Effective evaluation of a patient with an episodic memory concern requires a collateral historian. Both bedside mental status screening and formal neuropsychological testing, particularly tests of delayed recall of verbal and visual information, will confirm an episodic memory problem and clarify the severity of the clinical symptoms. During a brief clinical encounter, recall of a list of three to five words after a 5- to 10-minute delay is commonly included in standardized mental status assessment tools as a screening for verbal episodic memory dysfunction. To assess visual episodic memory, hiding personal objects around the examination room and asking the patient to recall the location is a quick and simple option. Commonly administered neuropsychological tests of episodic memory are detailed in **Table 2-2**.[22–28]

Neuroimaging helps confirm the involved neuroanatomy and may help predict neuropathology. Treatment should be directed toward the specific pathology. Targeted cognitive rehabilitation may be beneficial across the spectrum of memory dysfunction,[29] especially in mild impairment.[30] Pharmacologically, cholinesterase inhibitors are approved for use in the treatment of Alzheimer disease and Parkinson disease dementias, and memantine is approved for the later stages of Alzheimer disease.[31,32]

SEMANTIC MEMORY

Semantic memory refers to an individual's acquired knowledge about things in the world, their relationships, and their uses, including facts and concepts as well as words and their meanings.[33] The content of semantic memory is abstracted from experience and generalized without reference to a specific autobiographic episode. This subtype of explicit, declarative memory is dissociable from episodic memory, as mentioned previously in the classic example of H. M. The clinical presentation of semantic memory deficits most often involves the cognitive domain of language with presenting symptoms of

KEY POINT

- Evaluation of episodic memory dysfunction requires a collateral historian and cognitive assessment of delayed recall of verbal and visual information.

Case 2-1

A 79-year-old right-handed retired elementary school teacher reported 5 years of gradually progressive decline in her ability to recollect names and an increasing reliance on handwritten notes in order to accomplish her daily activities, such as shopping and cooking. Her husband of more than 50 years observed an increasing tendency for her to leave car doors and cabinets open and an uncharacteristic pattern of leaving tasks incomplete (eg, forgetting to turn off the faucet). Both denied her having any mood symptoms or behavioral features. Her husband had always managed the finances, and they attended to the household chores together. Although she was driving without any reported accidents or traffic infractions at the time of her initial evaluation, her husband reported escalating uncertainty regarding directions at intersections, and friends voiced concerns with her relative inability to properly park her car. During an on-road driving evaluation to investigate these concerns, she was unable to recall directions, adjust her rearview mirror properly, or to maintain the car within the appropriate traffic lane. Her past medical history was significant for treated hypertension, hyperlipidemia, and hypothyroidism. Her family history was significant for nonspecific dementia in a maternal aunt and cousin, both with onset in the sixth decade of life. On examination, the patient was socially appropriate and slightly anxious. Visual acuity was normal with correction, and visual fields were full to confrontation without extinction to double simultaneous stimulation. Smooth pursuit and saccadic eye movements exhibited normal speed and full excursions. The remainder of the neurologic examination was unremarkable. Formal neuropsychological testing revealed impaired visual memory and visual attention with a lesser degree of impairment in verbal memory and naming. Brain MRI demonstrated moderate generalized cortical volume loss with more regionally specific atrophy in the medial temporal lobes and hippocampal formations **(Figure 2-2)**. The patient was diagnosed with mild Alzheimer disease and initiated on donepezil therapy.

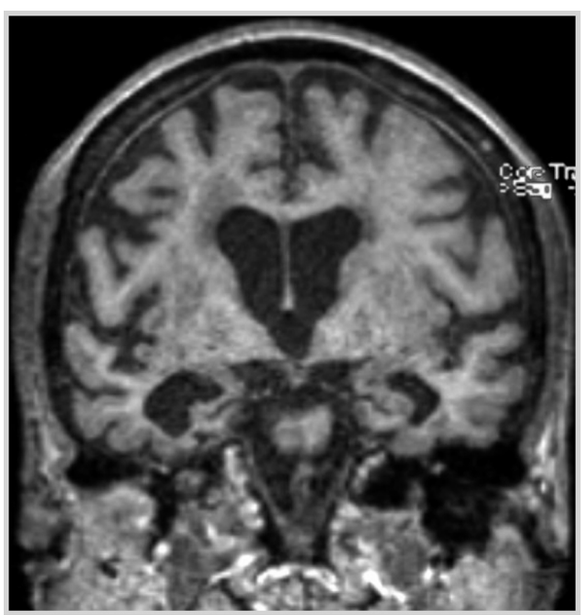

FIGURE 2-2 Imaging of the patient in **Case 2-1**. Coronal T1-weighted brain MRI showing moderate generalized cortical volume loss and regionally specific atrophy in the medial temporal lobes and hippocampal formations (right greater than left).

Comment. This patient presented with episodic memory problems and visuospatial dysfunction by history. Her neuropsychological testing confirmed that her episodic visual deficit was greater than her verbal memory deficit, which was reflected anatomically through greater atrophy of the right hippocampus and medial temporal lobe than the left hippocampus and medial temporal lobe. The patient's memory-predominant clinical syndrome in combination with her abnormal neuroimaging were consistent with a diagnosis of mild Alzheimer disease.

anomia. Low frequency words, such as proper names, may be impacted initially with the patient either making semantic paraphasic substitutions of higher frequency words or referencing supraordinate categories instead of more specific nouns

TABLE 2-2 Neuropsychological Tests of Memory

Memory Type	Examples of Neuropsychological Tests
Episodic (verbal)	Wechsler Memory Scale, Fourth Edition[22]: Logical Memory (recall of oral narrative)
	California Verbal Learning Test, Second Edition[23] (list learning with five encoding trials)
Episodic (visual)	Brief Visuospatial Memory Test, Revised[24] (recall of simple figures scored for accuracy of shape and placement)
	Rey-Osterrieth Complex Figure Recall[25] (immediate and delayed recall of copied complex figure)
Semantic (verbal)	Wechsler Adult Intelligence Scale, Fourth Edition[26]: Information Test (fund of general knowledge)
	Boston Naming Test[27] (naming line drawings)
Semantic (visual)	Northwestern University Famous Faces[28] (recognition and identification of famous faces)
Working	Wechsler Adult Intelligence Scale, Fourth Edition[26]: Digit Span
	Wechsler Adult Intelligence Scale, Fourth Edition[26]: Spatial Span
Procedural	Not commonly assessed with standardized tools

KEY POINTS

- Semantic memory dysfunction often presents clinically with anomia for low frequency words.
- The anterior and inferior temporal lobes are considered the region of greatest dysfunction in loss of object knowledge that crosses modalities.

(eg, ''dog'' or ''animal'' in reference to the pet guinea pig, "Belle"). In contrast to isolated anomia, semantic memory impairment persists even when patients are provided with the name of an object and asked for a definition as well as when they are asked to match conceptually related items. More profound impairment, manifesting as loss of object knowledge, can endanger patients, such as when they place non–food items in their mouths or inappropriately use common household or hygiene items (eg, using kitchen matches for toothpicks or shaving cream for toothpaste.)

Neuroanatomy of Semantic Memory

Given the depth and breadth of human conceptual knowledge, not surprisingly, the networks supporting the storage and retrieval of this information appear to be widely distributed throughout the brain. Indeed, neuroimaging evidence supports modality-selective, regional activation for motion, sound, olfaction, gustation, color, and even emotion-related concept comprehension. For example, in functional neuroimaging paradigms, comprehension of action-related concepts engages regions of the brain supporting the planning and execution of motor activity, with converging evidence of deficient comprehension of action verbs in patients with neurologic disorders affecting the motor system, such as Parkinson disease and motor neuron disease.[34] However, anterior and inferolateral temporal lobe regions are implicated as the major sites of pathology in patients with relatively isolated semantic memory deficits, including those with early semantic variant primary progressive aphasia (svPPA) (**Figure 2-3**[35]).[36] Recent structural and functional neuroimaging data from patients with svPPA support a model in which the anterior temporal lobe serves as an ''amodal hub,'' (not specific for one sensory or motor modality) linking the aforementioned modality-selective regions.[37]

As with episodic memory, lateralization of semantic memory function may also have clinical relevance. Patients with

KEY POINT

■ In early stages, the semantic variant of primary progressive aphasia provides a unique opportunity to observe semantic memory dysfunction in relative isolation.

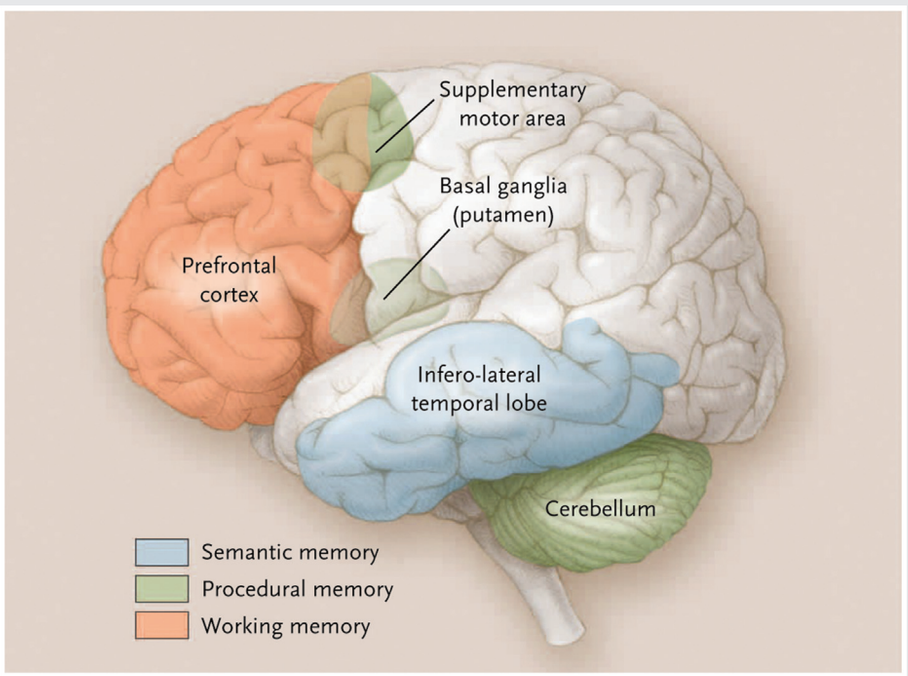

FIGURE 2-3 Neuroanatomic regions associated with semantic, working, and procedural memories.

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neurodegenerative dementia who have greater cerebral atrophy and reduced glucose metabolism in the left fusiform gyrus demonstrate poorer performance on verbal tasks of semantic knowledge, such as picture naming and category fluency (eg, number of animals generated in 1 minute), while those with similar structural and functional pathology in the right fusiform gyrus show greater deficits on nonverbal tasks of semantic knowledge, such as conceptual matching (eg, matching a nail to a hammer rather than a saw).[38]

Representative Neurologic Disorders Affecting Semantic Memory

The paradigmatic disorder affecting semantic memory is svPPA, characterized by anomic, fluent aphasia preceding a general loss of object knowledge with increasingly repetitive speech and eventual mutism. As described in **Case 2-2**, behavioral changes including prominent compulsivity emerge several years after language features in patients with more significant left anterior temporal atrophy at onset, but may be the presenting symptoms of patients with right temporal onset.[39] With an estimated prevalence of 1 to 5 out of 100,000 people between the ages of 45 and 64, sporadic svPPA is uncommon but scientifically compelling due to the consistency of the regionally specific atrophy of the anterior temporal poles and relatively predictable frontotemporal lobar degeneration neuropathology of ubiquitinated inclusions of TDP-43.[40] Semantic memory deficits are also common in Alzheimer disease,[41] although the trajectory of decline remains distinct from the more characteristic episodic memory deficits. Interestingly, the semantic categories most affected in svPPA and Alzheimer disease may be different when comparing

Case 2-2

A 64-year-old right-handed nurse educator retired from her position following 2 years of progressive difficulty recollecting names of students and colleagues. She subsequently left a volunteer position at a local charity due to the same concern. Her husband of 43 years reported that she was functioning normally as household and financial supervisor. She was driving without difficulty. Her behavior was characterized as compulsive, although this was a stable, lifelong adaptive trait during her 21 years of education. She had no significant medical history and was taking no medications. On examination, she was socially appropriate with the examiner and informant. She was fully oriented with normal verbal and visual memory performance. She had word-finding pauses with rare semantic paraphasic errors (category substitutions with related higher frequency words; eg, ''airplane'' for ''helicopter'') but no dysarthria or apraxia of speech. She had impaired naming on a modified Boston Naming Test (a score of 8 of 15) and was able to generate 10 ''D'' words, but only three animals in 1 minute. On further neurobehavioral assessment, she was noted to have surface dyslexia (inability to read phonetically irregular words; eg ''pint,'' ''yacht'') but not prosopagnosia (inability to recognize familiar faces). Her general neurologic examination was otherwise unremarkable. Initial brain MRI scan revealed focal atrophy of the left anterior temporal lobe **(Figure 2-4A)**. The patient was diagnosed with the semantic variant of primary progressive aphasia (svPPA). Over the next 5 years the patient's naming deficit worsened while her episodic memory declined to a lesser extent. She was increasingly rigid in her behaviors and played golf compulsively. She relied on picture catalogs to facilitate visual matching for grocery shopping and participation in social groups. Her follow-up head CT scan revealed bilateral anterior and inferior temporal lobe atrophy with preserved posterior brain regions **(Figure 2-4B).**

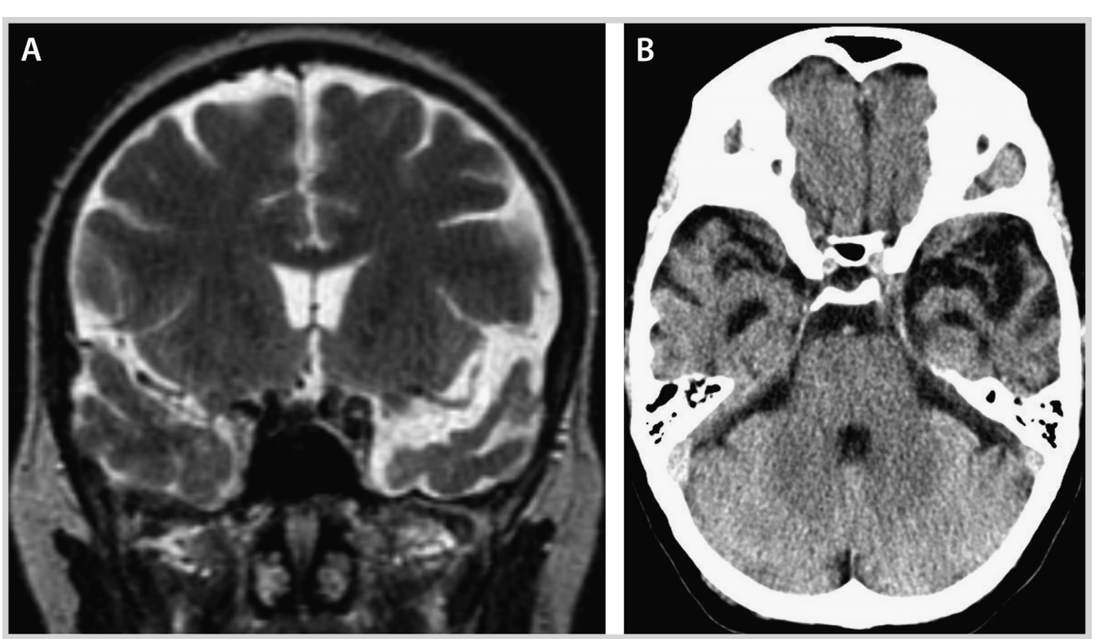

FIGURE 2-4 Imaging of the patient in Case 2-2. *A*, Coronal T2-weighted brain MRI showing focal atrophy of the left anterior temporal lobe. *B*, Axial head CT with bilateral anterior and inferior temporal lobe atrophy.

Comment. This patient initially had a mild deficit of semantic memory that predominantly affected her naming ability with relative sparing of her episodic memory. As the neurodegenerative illness progressed, her episodic memory was affected with relative preservation of her procedural memory (her golf game actually improved) and increasingly prominent behavioral features.

KEY POINTS

- Working memory is an explicit, declarative subtype of memory considered important to executive function.
- Procedural memory, the ability to acquire ''automatic'' skills, is unconscious and relies on motor systems including the basal ganglia, cerebellum, and supplementary motor cortex.

the identification of natural versus manufactured objects.[42] Another important group of neurologic patients with semantic memory dysfunction are those who have undergone temporal lobectomy for intractable epilepsy.[43]

As with episodic memory assessment, optimal assessment of a patient with semantic memory deficits requires a collateral historian for the patient. Similarly, either bedside mental status screening or formal neuropsychological testing, particularly assessing fund of general knowledge and naming, helps corroborate the clinical symptoms (**Table 2-2**). In a brief clinical encounter, listening carefully for semantic paraphasic errors and assessing low frequency object naming in the examination room (eg, asking the patient to name objects not commonly encountered in casual conversation such as the fluorescent light or door hinge) is informative. In patients with suspected svPPA, screening for surface dyslexia (the inability to read phonetically irregular words such as ''yacht,'' ''pint,'' and ''colonel'') may also support the diagnostic hypothesis.

Neuroimaging will be useful to confirm the involved neuroanatomy, and treatment should be directed toward the specifically identified pathology. Targeted speech therapy for compensatory strategies and alternative communication devices may be beneficial, especially in mild impairment.[44] Pharmacologically, selective serotonin reuptake inhibitors (SSRIs) may help reduce the behavioral features of svPPA,[45] while cholinesterase inhibitors and memantine are approved for use in the treatment of Alzheimer disease.[31,32]

WORKING MEMORY

Working memory refers to the active maintenance of verbal and nonverbal information in the mind for potential manipulation to complete goal-directed tasks and behaviors. Like episodic and semantic memory, working memory is an explicit, declarative memory subtype, but is generally considered a component of executive function. For more information on working memory, refer to the article ''Executive Dysfunction'' by Gil D. Rabinovici, MD, Melanie L. Stephens, PhD, and Katherine L. Possin, PhD, in this issue of CONTINUUM.

PROCEDURAL MEMORY

In contrast to episodic and semantic memory, procedural memory is nondeclarative, often implicit, and defined as the ability to acquire (with practice) cognitive and behavioral skills that subsequently operate automatically. Clinically relevant examples include learning the sequence of button pushes on a television remote to access a favorite program, driving a manual transmission car, and mastering the technical aspects of playing either a musical instrument or a sport. The neuroscience of implicit memory, described in studies as varied as those involving nonmammalian species such as *Aplysia* to classical conditioning in mammals, has elucidated important aspects of the neurobiology of human memory.[46] However, it remains conceptually challenging to extrapolate the classical conditioning of a rat freezing after a foot shock to the likes of either a virtuoso playing a Mozart piano concerto or a professional football player throwing a touchdown pass.

Neuroanatomy of Procedural Memory

Evidence from functional neuroimaging and neuropsychological task performance in patients with identifiable lesions converge to implicate the basal ganglia, cerebellum, and supplementary motor area of the cortex as the brain regions critical to learning a new procedure and habit formation (**Figure 2-3**[35]).

Representative Neurologic Disorders Affecting Procedural Memory

Procedural memory deficits are most commonly reported in patients with

Case 2-3

An 84-year-old right-handed retired attorney presented for evaluation of left hand tremor and cognitive concerns. He reported increasing difficulty recalling names of clients from his former law practice as well as difficulty rising from his recliner. His wife of 60 years was concerned with his hand tremor but reported no change in his memory during 15 years of retirement. The patient and his wife reported that he had mild depressive symptoms with daytime sleepiness and excessive movement during sleep, as well as reduced appetite. He continued to drive and managed the family finances and his medications without difficulty. He was an amateur violinist and was frustrated with his performance in weekly sessions with his instructor, which seemed to exceed the ''slowing down'' he had witnessed in chamber group peers. Past medical history was significant for treated hypertension and hyperlipidemia. Neurologic examination revealed hypophonia and hypomimia. There was no ideomotor apraxia. He had left upper extremity rest tremor with associated cogwheel rigidity. Finger tapping had mildly diminished speed and amplitude on the left. He used his arms to rise from the seated position and ambulated straightaway and on turns without difficulty. He had a subtly stooped posture and reduced left arm swing. There was no retropulsion on pull testing. Mental status screening at the bedside was normal, and formal neuropsychological testing revealed only psychomotor slowing. Neuroimaging was unremarkable. The patient was given a trial of low-dose levodopa, and his motor symptoms improved. He was diagnosed with Parkinson disease. His violin bowing ability deteriorated in spite of the medical management of his Parkinson disease, and he was forced to rely on his sheet music during performances. He was referred for physical therapy, but was unable to maintain his home exercise routine.

Comment. This patient had a procedural memory deficit involving his ability to play his violin with relative sparing of his episodic and semantic memory. Disorders that affect the function of the basal ganglia may result in procedural memory deficits that do not necessarily improve with treatment of motor symptoms and may impede responsiveness to nonmedical interventions such as physical and occupational therapy.

Parkinson disease, independent of other cognitive dysfunction or dopaminergic medication,[47] as illustrated in **Case 2-3**.

Other neurologic disorders that may present with procedural memory deficits include Huntington disease and cerebellar degeneration syndromes. The evaluation of procedural memory deficits will also require a collateral historian and neuropsychological testing, although procedural memory is not routinely assessed with standardized testing. Clinicians may need to request supplementary testing or devise an individualized task based on a patient's specific symptoms. Neuroimaging is valuable for identification of the neuroanatomic substrate of the procedural memory dysfunction and for predicting associated neuropathology. Although medications targeting motor symptoms may not be effective in treating these memory deficits, returning to an explicit approach to relearn a procedure may exploit the relative preservation of episodic and semantic memory function and highlight the interconnectedness of the memory systems.[48]

CONCLUSION

Although a variety of neurologic disorders may result in memory deficits, neurodegenerative diseases including Alzheimer disease, svPPA, and Parkinson disease provide useful models for investigating and treating the dissociable but interrelated systems of episodic, semantic, and procedural memory. Additional areas ripe for future investigation in an aging global population are memory processes that may engage multiple memory systems, such as prospective memory[49] (remembering to remember) and imagining the future[50] (remembering what is possible and probable).

KEY POINT

- Patients with Parkinson disease may manifest procedural memory dysfunction that does not respond to standard medical treatment, although explicitly relearning the procedure may be beneficial.

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REFERENCES

1. Tulving E. Episodic memory and common sense: how far apart? Philos Trans R Soc Lond B Biol Sci 2001;356(1413):1505–1515. doi:10.1098/rstb.2001.0937.
2. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 1957; 20(1):11–21.
3. Squire LR, Wixted JT. The cognitive neuroscience of human memory since H.M. Annu Rev Neurosci 2001;34:259–288. doi:10.1146/annurev-neuro-061010-113720.
4. Dudai Y, Morris RG. Memorable trends. Neuron 2013;80(3):742–750. doi:10.1016/j.neuron.2013.09.039.
5. Papez JW. A proposed mechanism of emotion. Arch NeurPsych 1937;38(4):725–743. doi:10.1001/archneurpsyc.1937.02260220069003.
6. Sperling RA, Dickerson BC, Pihlajamaki M, et al. Functional alterations in memory networks in early Alzheimer's disease. Neuromolecular Med 2010;12(1):27–43. doi:10.1007/s12017-009-8109-7.
7. Pergola G, Suchan B. Associative learning beyond the medial temporal lobe: many actors on the memory stage. Front Behav Neurosci 2013;7:1–24. doi:10.3389/fnbeh.2013.00162.
8. Maril A, Davis PE, Koo JJ, et al. Developmental fMRI study of episodic verbal memory encoding in children. Neurology 2010; 75(23):2110–2116. doi:10.1212/WNL.0b013e318201526e.
9. Chen KH, Chuah LY, Sim SK, Chee MW. Hippocampal region-specific contributions to memory performance in normal elderly. Brain Cogn 2010;72(3):400–407. doi:10.1016/j.bandc.2009.11.007.
10. Denkova EJ, Manning L. FMRI contributions to addressing autobiographical memory impairment in temporal lobe pathology. World J Radiol 2014;6(4):93–105. doi:10.4329/wjr.v6.i4.93.
11. Deipolyi AR, Rankin KP, Mucke L, et al. Spatial cognition and the human navigation network in AD and MCI. Neurology 2007;69(10):986–997. doi:10.1212/01.wnl.0000271376.19515.c6.
12. Woollett K, Maguire EA. Navigational expertise may compromise anterograde associative memory. Neuropsychologia 2009;47(4):1088–1095. doi:10.1016/j.neuropsychologia.2008.12.036.
13. Pergola G, Güntürkün O, Koch B, et al. Recall deficits in stroke patients with thalamic lesions covary with damage to the parvocellular mediodorsal nucleus of the thalamus. Neuropsychologia 2012; 50(10):2477–2491. doi:10.1016/j.neuropsychologia.2012.06.019.
14. Sabah M, Mulcahy J, Zeman A. Herpes simplex encephalitis. BMJ 2012;344:e3166. doi:10.1136/bmj.e3166.
15. O'Toole O, Clardy S, Lin Quek A. Paraneoplastic and autoimmune encephalopathies. Semin Neurol 2013;33(4):357–364. doi:10.1055/s-0033-1359318.
16. Kopelman MD, Thomson AD, Guerrini I, Marshall EJ. The Korsakoff syndrome: clinical aspects, psychology and treatment. Alcohol Alcohol 2009;44(2):148–154. doi:10.1093/alcalc/agn118.
17. Scheel M, Malkowsky C, Klingebiel R, et al. Magnetic resonance imaging in transient global amnesia: lessons learned from 198 cases. Clin Neuroradiol 2012;22(4):335–340. doi:10.1007/s00062-012-0140-7.
18. Bartsch T, Butler C. Transient amnesic syndromes. Nat Rev Neurol 2013;9(2):86–97. doi:10.1038/nrneurol.2012.264.
19. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7(3):263–269. doi:10.1016/j.jalz.2011.03.005.
20. Nelson PT, Schmitt FA, Lin Y, et al. Hippocampal sclerosis in advanced age: clinical and pathological features. Brain 2011;134(Pt 5):1506–1518. doi:10.1093/brain/awr053.

21. Brenowitz WD, Monsell SE, Schmitt FA, et al. Hippocampal sclerosis of aging is a key Alzheimer's disease mimic: clinical-pathologic correlations and comparisons with both Alzheimer's disease and non-tauopathic frontotemporal lobar degeneration. J Alzheimers Dis 2014;39(4):691–702. doi:10.3233/JAD-131880.

22. Wechsler D. Wechsler memory scale—fourth edition (WMS-IV) technical and interpretive manual. San Antonio, TX: Pearson, 2009.

23. Delis DC, Kramer JH, Kaplan E, Ober BA. California verbal learning test—second edition. Adult version. Manual. San Antonio, TX: Psychological Corporation, 2000.

24. Benedict RHB. Brief visuospatial memory test-revised: professional manual. Lutz, FL: Psychological Assessment Resources, Inc, 1997.

25. Stern R, Javorsky D, Singer E, et al. The Boston qualitative scoring system for the Rey-Osterrieth complex figure. Odessa, FL: Psychological Assessment Resources, Inc, 1994.

26. Wechsler D. Wechsler adult intelligence scale—fourth edition (WAIS-IV) technical and interpretive manual. San Antonio, TX: Pearson, 2008.

27. Kaplan E, Goodglass H, Weintraub S. Boston naming test. Baltimore, MD: Lippincott Williams & Wilkins, 2001.

28. Gefen T, Wieneke C, Martersteck A, et al. Naming vs knowing faces in primary progressive aphasia: a tale of 2 hemispheres. Neurology 2013;81(7):658–664.

29. Elliott M, Parente F. Efficacy of memory rehabilitation therapy: a meta-analysis of TBI and stroke cognitive rehabilitation literature. Brain Inj 2014;24(12):1610–1616. doi:10.3109/02699052.2014.934921.

30. Greenaway MC, Duncan NL, Smith GE. The memory support system for mild cognitive impairment: randomized trial of a cognitive rehabilitation intervention. Int J Geriatr Psychiatry 2013;28(4):402–409. doi:10.1002/gps.3838.

31. Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. J Intern Med 2014;275(3):251–283. doi:10.1111/joim.12191.

32. Wang HF, Yu JT, Tang SW, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. J Neurol Neurosurg Psychiatry 2015;86(2):135–143. doi:10.1136/jnnp-2014-307659.

33. Rogers TT, Lambon Ralph MA, Garrard P, et al. Structure and deterioration of semantic memory: a neuropsychological and computational investigation. Psychol Rev 2004;111(1):205–235.

34. Binder JR, Desai RH. The neurobiology of semantic memory. Trends Cogn Sci 2011;15(11):527–536. doi:10.1016/j.tics.2011.10.001.

35. Budson AE, Price BH. Memory dysfunction. N Engl J Med 2005;352(7):692–699. doi:10.1056/NEJMra041071.

36. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76(11):1006–1014. doi:10.1212/WNL.0b013e31821103e6.

37. Guo CC, Gorno-Tempini ML, Gesierich B, et al. Anterior temporal lobe degeneration produces widespread network-driven dysfunction. Brain 2013;136(pt 10):2979–2991. doi:10.1093/brain/awt222.

38. Mion M, Patterson K, Acosta-Cabronero J, et al. What the left and right anterior fusiform gyri tell us about semantic memory. Brain 2010;133(11):3256–3268. doi:10.1093/brain/awq272.

39. Seeley WW, Bauer AM, Miller BL, et al. The natural history of temporal variant frontotemporal dementia. Neurology 2005;64(8):1384–1390. doi:10.1212/01.WNL.0000158425.46019.5C.

40. Fletcher PD, Warren JD. Semantic dementia: a specific network-opathy. J Mol Neurosci 2011;45(3):629–636. doi:10.1007/s12031-011-9586-3.

41. Rogers TT, Ivanoiu A, Patterson K, Hodges JR. Semantic memory in Alzheimer's disease and the frontotemporal dementias: a longitudinal study of 236 patients. Neuropsychology 2006;20(3):319–335.

42. Libon DJ, Rascovsky K, Powers J, et al. Comparative semantic profiles in semantic dementia and Alzheimer's disease. Brain 2013;136(pt 8):2497–2509. doi:10.1093/brain/awt165.

43. Ives-Deliperi VL, Butler JT. Naming outcomes of anterior temporal lobectomy in epilepsy patients: a systematic review of the literature. Epilepsy Behav 2012;24(2):194–198. doi:10.1016/j.yebeh.2012.04.115.

44. Henry ML, Beeson PM, Rapcsak SZ, et al. Treatment for anomia in semantic dementia. Semin Speech Lang 2008;29(1):60–70. doi:10.1055/s-2008-1061625.

45. Seltman RE, Matthews BR. Frontotemporal lobar degeneration: epidemiology, pathology, diagnosis and management. CNS Drugs 2012;26(10):841–870. doi:10.2165/11640070-000000000-00000.

46. Kandel ER, Dudai Y, Mayford MR. The molecular and systems biology of memory. Cell 2014;157(1):163–186. doi:10.1016/j.cell.2014.03.001.

47. Muslimovic D, Post B, Speelman JD, Schmand B. Motor procedural learning in Parkinson's disease. Brain 2007;130(pt 11):2887–2897. doi:10.1093/brain/awm211.

48. Foerde K, Shohamy D. The role of the basal ganglia in learning and memory: insight from Parkinson's disease. Neurobiol Learn Mem 2011;96(4):624–636. doi:10.1016/j.nlm.2011.08.006.

49. Zogg JB, Woods SP, Sauceda JA, et al. The role of prospective memory in medication adherence: a review of an emerging literature. J Behav Med 2012;35(1):47–62. doi:10.1007/s10865-011-9341-9.

50. Schacter DL, Gaesser B, Addis DR. Remembering the past and imagining the future in the elderly. Gerontology 2013;59(2):143–151. doi:10.1159/000342198.