Memory: A Marvel of nature

Dr David Weintrob
Senior Clinical Neuropsychologist in the Department of Neuropsychology at Austin Health, Melbourne, Australia.

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Thank you to the conference organisers for the opportunity to talk to you about memory.

As with walking and breathing, we often take our memory for granted and barely spend time marvelling at the astounding evolutionary feat it represents. I have three aims in this talk: (1) to remind you of the marvel that is memory; (2) to take you on a brief journey through the recent history of memory research and to outline the vital contribution that people with epilepsy have made to our modern understanding of how the brain makes memory possible, and; (3) to leave you with a sense of the nature and cause of memory dysfunction in epilepsy. That is, what are the kinds of things people with epilepsy forget and why.

At the outset, we need to understand what memory is. For most of us, it reflects the ability to remember an event that occurred in the past. Our 21st. Our marriage. The birth of our child. And, indeed, this is how memory is often defined by respected dictionaries. For those who study memory, however, memory is a much more diffuse, and indeed nebulous, phenomenon.

In general, for the neuroscientist, memory reflects the capacity of the organism to benefit from experience. It is, therefore, a ubiquitous presence in many very different life forms and assumes many different guises. For example, the ability of the earthworm to habituate to its environment represents a legitimate memory. So too is a dog's conditioned salivation in response to a bell.

In humans, memory ranges from simple ("his name is David") to complex ("she can recite all Shakespeare's sonnets"), from highly specific ("The talk starts at 11am") to the most general ("A lion is a kind of animal"), from the trifling ("I need to buy milk") to the vitally important ("which button launches the nuclear missile?"), from the visual (face recognition/painting recognition) to verbal (remembering a poem) to the spatial ("How do I get …there?") to the musical ("I can hum 20 different Beatles songs") to the active (I can kick a footy without even thinking about it). It underpins our ability to ride a bike, obey traffic signals, identify objects by name, use language, and behave appropriately when in church.

Moreover, and perhaps even more astoundingly, it encompasses the ability to be consciously aware now of an event that occurred seconds-minutes-hours-years-decades ago, and to re-experience that event – even if it occurred decades ago - with

a vitality and full reawakening of the colors, textures, and emotions we felt at the time...and to recall when and where the event occured.

In that it underpins our personal autobiographies, memory is integral to personal identity. That is, it is integral to our sense of who we are.

Note too, that a special kind of consciousness accompanies memory. When we recall events from our past, our consciousness awareness of that experience is different from our ordinary 'online' awareness of our environment. We seldom confuse the feeling that we are remembering an event with the feeling that we are admiring a sunset, dreaming, solving a Sudoku problem, or wondering what we should have for lunch. We are certainly conscious while doing those activities, but that consciousness is plainly and recognizably different. Endel Tulving, one of the doyens of memory research, has used the term "autonoesis" to refer to the special kind of consciousness that allows us to be aware of the subjective time in which events occurred.

Paradoxically, therefore, not only does memory allow us to travel back in time, it allows us to recollect future arrangements and to project ourselves into the future. That is, it seems to be closely linked with our ability to perceive the present moment as a continuation of preceding events and as a prelude to future activities. This last ability is probably unique to humans and is a vital precondition for human cultural evolution - awareness of the existence of a past is a necessary precondition for changing the future.

Memory is truly a remarkable evolutionary achievement.

THE COMPLEXITY OF MEMORY: REFINING THE QUESTION

In all its variety and glory, memory is being investigated across many different species, at many levels of analysis (molecular – cellular – anatomical – cognitive), using many different and often highly sophisticated techniques. Novel findings are reported almost daily in journals devoted solely to memory research. Any literature search will yield literally tens of thousands of studies.

What is indisputable is that memory did not evolve for the convenience of the neuroscientist. While significant progress has been made, Endel Tulving – one of the doyens of memory research- has noted rather prosaically that the main finding is that memory is "extraordinarily complicated".

EPILEPSY AND MEMORY

Nonetheless, the study of memory in people with epilepsy, and temporal lobe epilepsy in particular, has been enormously influential in attempts to impose scientific order on this amazing ability. It has also played a vital role in helping us understand how the brain makes memory possible. This is because in TLE, epilepsy and memory co-habit the same space. Indeed, Snyder has commented that the study of memory in individuals with temporal lobe epilepsy has provided "the most singularly important natural laboratory for uncovering the neuroanatomic bases of

human memory." (Snyder, 1997). The remarkable patient H.M. is regarded as the index case and our story really starts with him.

H.M.

After being introduced to the medical world in 1957, H.M. went on to become one of the most studied of all patients in medical and psychological history. In 1953, aged 27, H.M. underwent surgery in Canada to relieve his severely disabling epilepsy. In what his surgeon described as a "frankly experimental procedure", H.M. had the front-most end of both his temporal lobes removed. H.M's epilepsy was substantially improved by this operation. However, it soon became apparent that he'd sustained a "striking and totally unexpected" disturbance of memory. By way of illustration, he would re-read the same newspaper or magazine several times, seemingly unaware that he'd done so before; he was unable to remember the names of any doctor he met after his surgery, nor could he recognise them as familiar from one day to the next; if he left his room he was immediately lost.

In 1996, over forty years after his operation, the enduring severity of H.M.'s memory impairment was described by the New Zealand neuropsychologist Jenny Ogden as follows:

> "He does not recognise anyone he has met or seen since 1953 and cannot even recognise current photographs of himself. He cannot say what he was doing 5 minutes ago; with whom he lives; what day, month, year, or season it is; or his age."

And, by the way, just as a quick mental exercise, contrast that with your own memory for all the myriad episodes that you can remember from just this morning (e.g., from waking up, to making breakfast, to driving to work, to walking into this building etc.

Tragically, after his surgery, H.M. was locked into a permanent present that he described as "like waking from a dream…everyday is alone in itself"; in Ogden's words, he was "marooned in the moment."

THE HIPPOCAMPUS

Intriguingly, however, H.M.'s difficulties were "curiously specific to the domain of recent memory". His intellect, his personality, his ability to negotiate the niceties of social interaction, and his ability to speak and use language were all unchanged. This observation laid the basis for a critical insight, namely, that memory could be dissociated from other cognitive and behavioural domains. Critically, this in turn suggested the existence of a brain region whose principal function is memory formation.

Comparing H.M.'s operation and memory disturbance with other patients who'd had comparable, albeit less extensive, resections, logic dictated that the hippocampus was a critical structure. That hypothesis was subsequently confirmed and today the hippocampus is recognised as a critical component of the memory system, even if its

precise role remains a subject of intense debate. The centrality of the hippocampus to memory is why temporal lobe epilepsy, which is often associated with damage to the hippocampus, has played such a central role in memory research.

MULTIPLE MEMORY SYSTEMS

However, there was one other critical observation. Although H.M. was unable to retain any memory for the activities he'd personally undertaken minutes-hours–days beforehand, he was nonetheless capable of some learning. For instance, he could retain in mind a string of numbers, such as telephone number, and accurately recite them back to the examiner; he was capable of learning new motor skills, even though he was unable to recall doing the task before. Priming was also intact – e.g., if H.M. was shown a word such as 'DEFINE' and was later given the stem 'DEF' and asked to complete it with the first word that came to mind, he usually responded with the word shown earlier. If asked whether he'd seen the word 'DEFINE' beforehand, however, he'd deny any such memory. Similarly, with repeated exposure, he became faster at recognising incomplete line drawings even though he had no memory for seeing the drawing previously.

These observations underpinned a major insight, namely that memory is not a single, monolithic structure – instead, memory represents a range of different learning systems reliant on different parts of the brain. As a result of these observations, the following model holds great currency today…

[Diagram of the declarative versus non-declarative distinction]

DECLARATIVE VERSUS NON-DECLARATIVE MEMORY

In this model, a distinction is drawn between **declarative** and **non-declarative** forms of memory**.**

Declarative memory is concerned with memory for specific facts, i.e., with **"knowing what"**. It is so called because one can bring to consciousness and declare the content of this memory. That is, we are able to think about these sorts of memories, talk about them, and manipulate them in the spotlight of full awareness that it is a 'memory'. It allows us to declare, for example, that on my 21st birthday we had a beach party and that my brother made an embarrassing speech. Or, it allows me to declare that I remember that the chemical formula for salt is NaCl. This knowledge can be used flexibly across different situations. The declarative memory system is capable of rapid, one-trial learning. It is severely impaired in H.M. and other cases with bilateral hippocampal damage. In contrast, non-declarative memory is spared.

Non-declarative memory refers to memory for skills or procedures, i.e., it is concerned with **"knowing how"**. For example, the skill needed to ride a bike represents one kind of non-declarative memory – as we all improve our bike riding prowess over time some form of memory must be involved. However, this kind of skill memory cannot be "declared" – rather memory output is manifest by *performance* of the skill. Similarly, the ability to read a friend's handwriting because we have encountered it several times in the past is an example of non-declarative

memory. Priming and the formation of habits and emotional predispositions are other examples. This sort of memory cannot be used flexibly – rather it is a memory of sorts that can only be utilised under very particular conditions that very closely resemble the original learning episode. Most often, multiple exposures to the stimulus are required for this sort of memory to develop slowly and incrementally.

Declarative memory is further divided into 2 systems:

1. **Episodic memory**, i.e., memory for specific, personally-experienced events located in space and time. This system forms memories that are unique to the individual, define individual life histories, and ultimately contribute to the sense of self. These sorts of memories are inextricably bound up with a specific time, place, and emotional state in the individual's life history. Collectively, the amalgam of this information constitutes a memory episode. For example, being able to recall that last summer on the first night of my vacation in Bali I met a retired ship's captain over dinner whose company was very enjoyable is a form of episodic memory. It provides, in other words, an autobiographical framework that permits recollection of personally-experienced activities and the time and context in which they occurred. This is what most of us mean by memory – so too did the famous philosopher William James who wrote "Memory requires more than mere dating of the fact in the past. It must be dated in *my* past";
2. **Semantic memory**, i.e., memory for facts or general information about the world. It is impersonal, i.e., the content of this kind of memory is not specific to the individual but may be shared by literally billions of people. Moreover, it contains no record of the context in which the memory was formed. It encompasses, for example, our knowledge of the meaning of the word 'testify', the usual colour of a banana, the taste of an apple, the chemical formula for table salt, the knowledge that the summer months in Brisbane are usually quite humid, and how to behave when you enter a restaurant. Billions of people know and can declare this kind of memory without remembering the occasion on which it was learned.

To reinforce the distinction: Being able to state that Princess Diana died in Paris in a car accident reflects semantic memory; being able to state that one was eating breakfast at 7am in the kitchen and that you felt very sad when you learned this from the TV news broadcast reflects episodic memory.

AN EVOLUTIONARY ASIDE

BTW, semantic memory is the kind of memory that makes it possible for organisms to store a kind of "general knowledge" of the world and then use this information flexibly and appropriately. All kinds of animals have excellent semantic memory – that is, they know a lot about the kind of world they live in. Our evolutionary ancestors were like this, but at some point in human evolution, possibly rather recently, episodic memory emerged as an embellishment of semantic memory. As far as we know, no species other than humans has episodic memory of the kind just

described. That is, no other species has any subjective sense of self as existing in time with the ability to re-experience discrete events in one's personal history.

H.M. REVISITED

In respect of TLE, it is really declarative memory we're concerned with. More specifically, and particularly in light of its significance for everyday life, it is episodic memory that is usually of most concern to neuropsychologists and people with TLE.

As we've seen, episodic memory was profoundly impaired in H.M. After nearly 40 years he could recollect few, if any, events he'd personally experienced since his operation. Fortunately, however, unlike H.M., the overwhelming majority of people with TLE have damage confined to one temporal lobe. Consequently, any accompanying memory impairment tends to be very much milder than that of H.M's.

This is not to downplay the significance of memory impairment for patients and family, but fortunately we don't see the dense, disabling gaps in memory for recent personal activities that H.M exhibited. Having said as much, however, what kinds of memory difficulties do patients with TLE typically experience?

THE NATURE OF FORGETTING IN TLE

The paradox of H.M. is that through him we have learned a great deal about human memory, but because of the unexpected tragic results of his surgery the sample size of one will never increase. That is, no one has ever attempted removal of both temporal lobes again.

Following H.M., however, attention turned to patients with epilepsy who'd undergone unilateral resections of one temporal lobe only. These patients also showed memory impairments, albeit very much milder than that of H.M. Moreover, the nature of the deficit varied as a function of side, with memory for verbal information, i.e., information conveyed through the medium of language, being most affected by surgery on the left temporal lobe and memory for non-verbal information, i.e., information with a prominent visual or spatial emphasis that is not easily represented in language, being affected by surgery on the right temporal lobe. For example, the ability to learn a list of 15 words was depressed in people who'd undergone a left temporal lobectomy, but normal in those who'd had a right-sided operation. In contrast, the ability to remember an abstract geometric figure was depressed in people who'd had a right temporal lobectomy, but normal in those who'd had a left-sided operation.

Subsequent studies showed that, even prior to any temporal lobe surgery, similar problems affected people with either left or right temporal lobe epilepsy. These observations led to the **material-specific model** of memory, a theoretical framework which, although questioned in more recent times, still guides practice in many epilepsy centres around the world.

To summarise: Unlike H.M., people with unilateral TLE retain the ability to lay down personal memories and therefore generally retain an ongoing and coherent

autobiographical record. Against this backdrop, however, the individual with unilateral TLE may well have difficulty remembering the fine details of events they experience and new information they encounter. This is most pronounced for verbal information when the left temporal lobe is involved and most pronounced for non-verbal (i.e., visual and spatial information) when the right is involved.

Thus far, I've been referring to memory as it applies to a person's performance on a standardised, objective test of memory. That is, I've been referring to their performance on tasks that require them, for example, to learn a list of words or memorise an abstract figure. Relatively little work has been done attempting to understand how memory impairment on testing translates into deficits in everyday life. As broad pass, however, the kinds of things people with temporal lobe epilepsy tend to struggle with include:

Left temporal lobe epilepsy and hippocampal damage: retrieve skeletal autobiographical memories for which the gist of the memory is maintained, but some of the specific details are lost (St-Laurent et al, 2010; Thaiss and Petrides, 2008); they may remember having the conversation, but find that their memory for the details of what was spoken about is unreliable; details of instructions; details of information read in books and newspapers.

Right temporal lobe epilepsy: memory complaint less frequent; route around the city centre or local shopping centre; the layout of their local supermarket; location of their car on leaving the supermarket; less often, facial recognition

In both, there may be a denser and more encompassing disruption of memory for events that occurred shortly before or after a seizure.

TLE, memory, and some general observations
At this point, I will segue briefly and canvass a few other pertinent issues:

Severity – what determines the severity of memory impairment in TLE? Earlier age at onset of seizures, longer duration of epilepsy, and greater seizure frequency tends to be associated with a somewhat more severe impairment of memory (although exceptions are seen, raising the possibility that in some patients memory has transferred to the other temporal lobe);

Memory decline after temporal lobectomy – this issue is always taken extremely seriously and is always very carefully considered. The first point to note is that for most people with right TLE, a right ATL does not cause any discernible change in memory on specific testing. However, given that the left hemisphere of the brain is typically dominant for language, and given that most of what we need to remember is embedded in language, left ATL is usually much more of a concern. Again, however, as a general principle the damage, so to speak, is often done by the time a left ATL is contemplated and removing a part of the temporal lobe does not place people at great risk of a further disabling decline in memory. A recent study (Williams, Martin, & McGlone, 2009) looking at the subjective experience of memory

change after surgery found that most patients denied any significant change in their memory after temporal lobe surgery. Indeed, a small number of patients report (Williams, Martin, & McGlone, 2009) and exhibit (Baxendale et al, 2008) a modest improvement in memory. This converges on our experience at Austin Health.

In a small number of patients, however, the possibility of a significant change in verbal memory does exist. This is true especially of people with late-onset left TLE, no or only very mild hippocampal pathology, or normal or only mildly impaired verbal memory beforehand. The guiding philosophy in our program is that this needn't rule out surgery. Rather, any risk to memory needs to weighed against the benefits of seizure freedom and, moreover, needs to be understood in terms of what the likely functional consequences of memory decline will be. That is, although we might expect to see a change for the worse on our memory measures, this doesn't automatically translate into difficulties in everyday life. For example, a QC who relies very heavily on verbal memory might be a different prospect to someone with a more routine or repetitive occupation, even if the decline seen on our tests is equivalent.

Decline with time – there is evidence that refractory TLE may be associated with a slow but progressive decline in cognitive abilities (e.g., Jokeit & Ebner, 2002; Hermann et al, 2002; Cascino, 2009). That is, poorly controlled seizures may cause cumulative cognitive deficits over time. There is, therefore, a growing belief that epilepsy surgery may not be a procedure of last resort in suitable candidates. Time may mean neurons.

Immediate, short-term, working, and long term memory

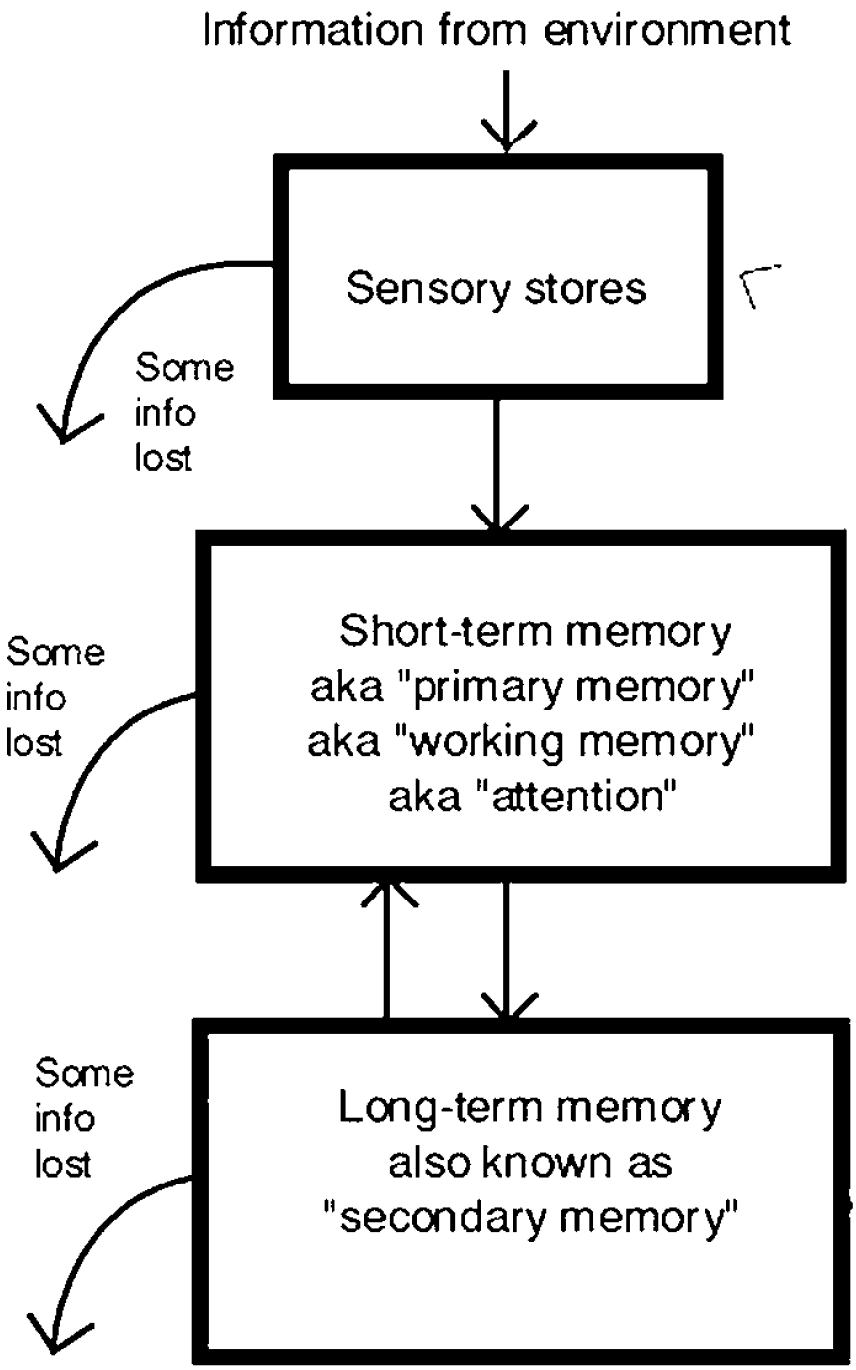
Up until now, we have considered memory in terms of the nature of the information to be remembered. That is, whether its verbal or spatial or musical or autobiographical or semantic. However, memories can also be distinguished in terms of the time interval across which the information needs to be remembered. When we consider this time dimension, memory can again be divided into categories. In particular, a distinction is drawn between immediate, working, and long-term memory.

Immediate memory refers to a system that makes it possible to store small amounts of information over very brief periods of time. Its capacity is very limited – e.g., it cannot deal with more than one or two sentences or about 6-9 digits at a time – and its contents decay rapidly to make way for the next items in the continuous stream of information that enters our awareness. For example, if I read out 7 digits and ask you to repeat them, you've engaged immediate memory. In real life, taking down a telephone number from a friend is a prime example of immediate memory – as your friend speaks the number, you transiently keep the digits online while writing them down and, once that is completed, you promptly forget them as your attention is engaged by the next item in the ongoing stream of consciousness. Indeed, one might speculate that this sort of task has become more important of late because of the increasing use in our society of digit and letter sequences, in the form of telephone numbers, post codes, ATM PINs and internet passwords.

Allied with immediate memory is **working memory**. This system not only facilitates the temporary maintenance of information in mind, but provides the mental workspace that allows us to simultaneously manipulate that information for some purpose. For example, if I read out a series of 7 digits and ask you to repeat them in reverse order, you have engaged working memory. Similarly, if I ask you to multiply 27 by 3, you need to simultaneously hold and manipulate various bits of information in mind until the answer is provided. Once you've done so, however, the mental workspace of working memory will be taken up by some other demand.

Immediate and working memory are crucial systems that make possible our ongoing awareness of the environment and all the events therein. It is closely allied, if not actually synonymous with, the concept of **attention.** Indeed, many neuropsychologists regard these processes as a part of the attentional system, rather than memory per se. As noted, they are characterised by the brief duration of the memory trace and by limited storage capacity. In contrast, **long-term memory** is a system or systems that underpin the capacity to store information over minutes-hours-months-years-decades-a lifetime. Storage capacity is virtually unlimited. The **declarative** and **non-declarative** memory systems I referred to earlier are forms of long-term memory.

A model proposed by Atkinson and Shifrin in the 1970s and that is probably still useful for our purposes links these different memory systems and suggests how information that reaches us from the environment flows through these various systems to end up as a permanent memory. Critically, information from the environment is first processed by immediate memory before it enters a more durable long-term store. In short, we need first to attend to information if we are to ever hope that it enters permanent storage.



[DIAGRAM]

Why am I at pains to mention this? The answer is that under this model, disruption of this intervening attentional/memory system can render long-term memory systems less efficient. How is this relevant to present discussion? The answer is that in people with epilepsy several factors and co-morbid conditions can impact, sometimes quite significantly, with this intervening system. Chief among these factors are medication and mood.

Anti-convulsant medication

At its simplest, epilepsy represents an abnormal electrical discharge between nerve cells in the brain. The aim of drug treatment is to suppress this excitability. While AEDs are often effective at doing just that, they unfortunately also suppress normal patterns of neuronal excitability more diffusely in the brain. The cognitive manifestation of that is sedation, a state in which normal levels of energy, arousal, attention, vigilance, and mental processing speed give way to drowsiness, slowness of thought, and lapses in focus and concentration. I often use a jogging analogy to make this point – for the person with epilepsy on medication, thinking can often feel like wading through mud rather than sprinting on dry bitumen. Similarly, imagine you've been sleep-deprived for a few days and you're asked to subtract 17 from 35 – the challenge that would pose is what matters are chronically like for some people with epilepsy on medication. In short, the common experience of sedation can disrupt the intervening attention/memory system and result in inefficiencies of memory.

BTW, different AEDs have different effects in this regard. Certain medications are more likely than others to cause sedation. The chance of sedation is also increased with rapid initiation, higher doses, and polytherapy.

Clearly, disruption of this intervening system can further compound memory disturbance in people with temporal lobe epilepsy whose long-term memory system is already compromised. However, disruption of this intervening system might also cause attentional and memory inefficiencies in people whose epilepsy arises from outside of the temporal lobe. Indeed, I'd go so far as to suggest that disruption to this intervening system is perhaps the principal source of cognitive difficulties in people with extra-temporal lobe epilepsy. Fortunately, those difficulties tend to be much less disabling.

An important point: This is not to say, however, that people should cease taking AEDs. Ongoing seizures of themselves can be detrimental to both cognition and quality of life and clearly the need to take AEDs to suppress seizures most often trumps any sedating effect they may have. However, I raise this issue because it is important if we are to fully appreciate the factors that can affect cognition in people with epilepsy.

Mood

I will touch briefly on the question of mood disturbance because it too has the potential to disrupt the intervening immediate/working memory system and cause or exacerbate cognitive dysfunction.

The incidence of mood disturbance, i.e., either depression and/or anxiety, is elevated in people with epilepsy. This may be a direct biological consequence of their condition, it may reflect the often significant psychosocial fears and restrictions that accompany the condition, or it may be some combination of the two. Regardless of cause, cognitive disruption frequently accompanies both disorders.

In people who are anxious, excessive and uncontrollable worry and pre-occupation with fears that are irrelevant to the task they need to complete in the 'here-and-now' crowd the mental landscape to the point where focussed attention on other matters is compromised. The tendency to transiently forget one's intention when walking into a room is a common manifestation of this. So too is the realisation that on reaching the bottom of a page one has failed to absorb what you've just read. So too is the phenomenon of losing track of what one wishes to say mid-sentence. Not surprisingly, people often interpret these sorts of attentional lapses as forgetfulness. Not surprisingly too, however, actual long term memory becomes unreliable in these contexts.

Similarly, low energy levels and associated amotivation make it difficult for some people with depression to invest the effort needed for effective attention and concentration. Again, long term memory can become unreliable in this context.

Indeed, in general neuropsychological practice, and I'm not referring just to epilepsy, anxiety and depression are among the most common causes of a memory complaint.

Language

One final consideration is worth mentioning. As I've already indicated, memory impairment is often present in people with TLE because their epilepsy and memory co-habit the same part of the brain. In addition to memory, another important cognitive domain that is partially housed in the temporal lobe, usually the left, is language. Not surprisingly, therefore, some patients with left TLE experience mild language difficulties. Typically this manifests as a word finding difficulty, that is, difficulty retrieving the name for a particular item. Naturally, this can compound any co-occurring memory deficit.

Closing

H.M. died in December 2008 aged 82. He was a quiet and courteous man with a sense of humour who, referring to his neurosurgeon, once said "What he learned about me helped others, and I'm glad about that."

The early descriptions of H.M.'s memory impairment ushered in the modern era of memory research. They showed that memory could be dissociated from other intellectual and perceptual domains, that memory itself can be subdivided into different domains, and that memory for the episodes of everyday life is critically dependent on the hippocampus and adjacent structures. Subsequent studies showed that people with damage confined to one temporal lobe also have memory deficits, albeit much milder than that of H.M. Typically, people with unilateral damage retain memory for the event, and thus retain a coherent autobiographical record. Frustratingly for them, however, they often experience a tendency to forget the fine details of events they experience and new information they encounter. This is usually most apparent when the damage is on the left and it can be a major contributor to the burden of epilepsy. It can also contribute to the restrictions that epilepsy sometimes imposes on academic achievement and employment.

Medication and mood may compound underlying memory impairment through their impact on attention/concentration, focus, and motivation.

[END]