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Editorial

The enigma of long-term forgetting

Memory symptoms are common among people with epilepsy (pwe).[1] Their complaints are often corroborated by impairments on traditional tests of memory which assess learning and retention over delays of up to 30 min. Yet a substantial minority of patients report memory problems which are not identified on standard testing. This discrepancy has sometimes been ascribed to mood disorders.[2] There is, however, an alternative, or complementary, explanation: that established methods of memory testing fail to detect some genuine memory problems. Standard tests, for example, seldom assess autobiographical memory or retention of new information over delays greater than 30 min. A growing literature reports patients with epilepsy, usually arising from the temporal lobes (TLE), who show normal or near normal retention of information over 30 min delays, but increased forgetting over longer delays of days or weeks. This phenomenon has been described as 'accelerated long-term forgetting' – or ALF. Whilst there is growing evidence that ALF is measurable and clinically relevant, several key questions remain: (i) Is ALF a widespread phenomenon among pwe? (ii) Does ALF help to explain discrepancies between subjective memory complaints and results of memory testing? (iii) What are the underlying mechanisms of ALF? We consider these questions in turn.

(i) *Is ALF widespread among pwe*? There is now good evidence that ALF occurs among pwe, particularly in TLE.[3–8] It appears to be especially common in transient epileptic amnesia (TEA), a form of TLE in which episodes of amnesia are the principle manifestation of the seizure disorder.[9–11] However, some studies in patients with TLE have failed to identify ALF.[12–14] The explanation for these discrepancies is probably methodological. In studies which train subjects to a high learning criterion, ceiling effects and over-learning can obscure early forgetting, giving rise to the false attribution of ALF; conversely, in studies in which patients and controls start off with differing levels of retention, their forgetting curves are difficult to compare, and ALF may go undetected. Recent studies which take these methodological problems into account have confirmed the occurrence of ALF in TLE.[6,8] There is much less evidence regarding its occurrence in generalised epilepsy, though an early study suggested that it occurs following ECT.[15]

(ii) *Does ALF help to explain discrepancies between perceived and objective memory*? In people with TEA, two findings suggest that ALF is relevant to memory complaints. Butler et al.[10] reported more marked ALF among patients who spontaneously reported memory loss over weeks compared to those who did not. Butler et al.[16] found that ALF was a significant predictor of perceived memory on the Everyday Memory Questionnaire. However in other epilepsies, the picture has not been so clear. Muhlert et al.[6] found no significant correlation between perceived memory and ALF in patients with TLE. Blake et al. reported a significant correlation between memory complaints and ALF in people with left temporal lobe epilepsy, but "in the group as a whole, complaints of poor memory were actually more common than was failure on the very long-term memory test" (3(p482)). These mixed findings may reflect the small samples studied or differences in the frequency of ALF between subgroups of patients, as suggested by Blake and colleagues. The study in this issue of *Seizure* by Witt et al.[17] contributes to this debate. They found discrepancies between subjective and objective memory in half of their patients with epilepsy (47%). A substantial minority (24%) reported memory problems despite normal performance on standardised tests of memory. In these patients, forgetting over a four-week delay was a significantly better predictor of memory complaints than forgetting over 30-min or even one-week delays. This provides further evidence that traditional tests of memory fail to capture some genuine memory problems in epilepsy.

(iii) *What are the underlying mechanisms of ALF*? As the clinical phenomenon of ALF involves apparently normal memory acquisition and retention at short intervals, with impaired retention at longer delays, it is natural to suppose that it is due to a disorder of memory consolidation or storage. This may be correct, but it remains possible that memories are fragile from the outset in people with ALF. Learning is not always normal in patients who show ALF (e.g.6, 10), and subtle abnormalities in encoding may become more apparent over time. Yet if this were the main explanation for ALF, one would predict a direct relationship between retention over short and long delays. Muhlert et al.[11] found no evidence for this: while retention over 30 min was correlated with retention over 24 h in healthy controls, there was no correlation in patients with TEA. This suggests a disruption of normal memory processing in the interval between these time points.

Whichever stage of memory processing is implicated in ALF, current evidence suggests that the temporal lobes are the likely site of the underlying pathology. First, ALF affects declarative memory, which is thought to rely upon intact functioning of medial temporal and diencephalic structures, but not procedural memory, which relies on structures outwith the temporal lobe like the basal ganglia.[11,18] Second, several studies have found functional and structural abnormalities in the temporal lobes among patients with ALF, including hypometabolism in the right temporal pole with reduced neuronal density (inferred from a reduction in NAA/Cr on magnetic resonance spectroscopy) in the right hippocampus,[7] hippocampal gliosis (as shown by increased

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signal on T2 relaxometry[8]), and hippocampal atrophy.[8,19] However, none of these studies has yet demonstrated a correlation between these structural abnormalities and ALF.

This raises the possibility that the critical mechanism of ALF may be a functional rather than a structural disturbance. If so, disruption of sleep-related consolidation by subclinical epileptic activity is an intriguing candidate. Sleep is known to play an important role in memory consolidation,[20] sleep complaints are more common in patients with partial epilepsies than healthy controls,[21] and, prior to control of seizures through medication, patients with TEA who experience ALF often experience seizures upon awakening.[10] This possibility merits further investigation as it is a potentially treatable cause of memory impairment.

In conclusion, ALF is a moderately common cause of memory impairment in epilepsy, particularly in TLE and TEA. The work by Witt et al. in this issue demonstrates the clinical value of assessing ALF in patients with memory complaints who perform within normal levels on traditional tests of memory. Current evidence suggests that it is related to temporal lobe pathology or dysfunction, possibly dysfunction during sleep. Further work in this area should help us both to understand the symptoms of epilepsy in people plagued by memory loss and the mechanisms involved in memory processing in health.

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