

Editorial for Cortex Special Issue on 'Accelerated Long-term Forgetting'

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Accelerated long-term forgetting (ALF) has been gaining a good deal of attention recently from researchers and clinicians interested in human memory and its impairment in neurological disease. In its starkest form, ALF is present when an individual or group is able to learn and initially retain new information normally, but shows abnormally accelerated loss of that information from memory over subsequent days or weeks (Butler, Muhlert, & Zeman, 2010.; Elliott, Isaac, & Muhlert, 2014). The phenomenon as thus conceptualised is of clear importance both clinically and theoretically. Clinically, ALF goes 'under the radar', because standard neuropsychological tests probe newly acquired memories after relatively short delays (typically about 30 minutes). Theoretically, ALF could afford novel neuropsychological insight into the processes underpinning successful long-term memory retention in the healthy human brain.

Early descriptions of ALF came from dramatic single case reports of patients with epileptic seizures (De Renzi & Lucchelli, 1993; O'Connor, Sieggreen, Ahern, Schomer, & Mesulam, 1997), and were followed by studies showing the same phenomenon at a group level, prominently again amongst patients with epilepsy (Blake, Wroe, Breen, & McCarthy, 2000) (Butler et al., 2007; Martin et al., 1991). These discoveries prompted numerous investigations into the mechanisms of ALF in epilepsy, its clinical correlates and potential treatment. More recently, researchers claim to have demonstrated ALF in other neurological conditions including traumatic brain injury (Lah et al., 2017) and in pre-symptomatic people at enhanced genetic risk for Alzheimer's disease (Weston et al., 2018; Zimmermann & Butler, 2018). One aim of this Special Issue is to highlight the range of research already going on across disciplines and diseases, and promote further efforts in this important but nascent field.

Despite this justifiable wave of clinically oriented research on ALF, several authors have pointed out that fundamental conceptual and methodological questions remain unanswered (Butler & Zeman, 2008; Elliott et al., 2014). How should ALF be defined? Is ALF really qualitatively distinct or simply quantitatively different from the memory impairment usually described in brain disorders? Which sorts of testing protocol best capture ALF? Is ALF one thing or many? A second aim of this Special Issue is to bring these questions, and some of the answers, to the same table in an effort to build secure foundations for future ALF research.

The conceptualisation of ALF

To set the scene, two theoretical papers, by **Cassel and Kopelman** (2019) and by **Mayes and colleagues** (2019) debate the underlying nature and possible causes of ALF. Whereas the former argue that ALF represents a quantitatively different pattern to the forgetting typically seen in people with epilepsy, the latter put forward an argument supporting the idea that ALF is qualitatively different from classic, hippocampal amnesia. Issues related to factors such as recollection/familiarity and material specificity are considered in both papers

and both agree that a better understanding would help to shape clinical practice and remediation efforts.

Methodology of testing ALF

As several articles in this Special Issue demonstrate, there are numerous possible methods for testing and defining ALF. **Baddeley and colleagues** (2019) report data from two tests designed explicitly to overcome certain practical issues in the assessment of long-term forgetting: the Crimes test and the Four Doors test. In particular, these tests avoid repeated probing of the same material across multiple retention intervals. The authors show that, in healthy people, a single delayed probe revealed long-term forgetting that was remarkably similar across individuals regardless of the initial level of learning. In contrast, a multi-test protocol appeared to prevent forgetting, perhaps because the testing of individual features encouraged recollection of the whole episode and hence acted as a further reminder. The authors point out that further work is required to determine whether this ‘decelerated long-term forgetting’, may prove to be useful feature of an ALF test, since it avoids floor effects.

The study by **Hoefijzers and colleagues** (2019) reports “real-life” ALF using a controlled incidental memory test in patients with Transient Epileptic Amnesia (TEA). The examiner told the patients and control subjects a detailed and amusing story in a conversational manner before starting to administer a set of research experiments and then (without warning) tested their memory using recall and forced-choice recognition questions at 30 minute and 1-week delays. Patients and controls did not differ in their retention at 30 minutes, but patients were impaired on both recall and recognition testing at the 1-week delay. Over the two delay intervals, there was a greater drop in recognition scores compared to recall for patients. The authors argue that recognition testing may support memory retrieval in control subjects, but not in the TEA patients. Therefore, they suggest that this type of measure might be particularly sensitive for detecting ALF.

As yet, there is no widely agreed method for calculating an ALF score. **Helmstaedter and colleagues** (2019) examined long-term memory retention in patients with later-onset focal epilepsy, either as a result of limbic encephalitis or not, and compared their performance across three possible definitions of ALF: (a) unimpaired recall at 30 minutes and impaired recall at 1 week; (b) decline in absolute recall from 30 minutes to 1 week of $>1SD$ compared to controls; (c) decline in percentage recall from 30 minutes to 1 week of $>1SD$ compared to controls. Overall, patients with limbic encephalitis showed greater ALF than those without. No effect on ALF was found of seizures within the retention interval. Since methods (b) and (c) allow for the possibility of ALF even in patients who are impaired at earlier intervals, greater ALF prevalence was identified using these measures. Method (c) resulted in particularly dramatic ALF estimates, probably because percentage loss is greater for participants who start from a lower 30-minute baseline.

Neural mechanisms of ALF

To explore the neural correlates of ALF, **Audrain and McAndrews** (2019) tested patients with Temporal Lobe Epilepsy (TLE) on recognition of items and associations over delays of up to 72 hours and correlated behavioural performance with resting-state functional

connectivity between the hippocampus and other brain regions. Strikingly, patients showed normal forgetting for associative recognition, usually held to be highly hippocampus dependent, but ALF for item recognition, consistent with the Hoefelz and colleagues' finding described above. The authors suggest that patients were unable to utilise novelty to reject incorrect object-scene pairs. No clinical variables correlated with ALF. However, resting-state functional connectivity between the affected anterior hippocampus and the unaffected lateral temporal neocortex predicted forgetting of items over 72 hours. This result is interpreted within the framework of consolidation theory, which proposes that long-term persistence of memories requires post-learning interaction of the hippocampus with neocortical regions.

In the contribution from **Atherton and colleagues** (2019), short and long term memory was tested in patients with TEA. The patients showed ALF for a word list compared to a matched group of control subjects (i.e., normal short term memory, but impairments when recall was tested one week later). Recognition memory for visual scenes presented while subjects underwent fMRI showed a different pattern, with deficits in the patient group evident as early as 45 min (the first testing point). For the patients with TEA, subsequently forgotten stimuli were associated with reduced left hippocampal activation at encoding. When memory for Late test items (presented only at 4 day delay) was contrasted to memory for Early test items (presented only at 45 min delay), whole brain analysis at the time of encoding revealed a number of regions that exhibited a larger subsequent-memory effect for Late test items. These regions included the right post and pre-central gyri, the right insular cortex and the right amygdala. Hence, it was activity in these brain regions that was most predictive of the longevity of the memory.

Clinical scope, impact and interventions

Whilst most of the articles in this Special Issue address ALF in patients with epilepsy, **Geurts and colleagues** (2019) investigated whether ALF might underlie the subjective memory complaints of patients with transient ischaemic attack (TIA) or minor stroke, despite their normal performance on standard neuropsychological tests of memory. The patient group showed normal rates of learning and 30-minute recall/recognition of a word list. Unlike the findings in TLE patients, TIA was associated with significantly impaired recall after a 7-day delay but normal rates of decline in recognition memory. Whereas recall decline over 7 days correlated with subjective memory ratings in healthy controls, this association was lost in the patient group. The authors point out that standard delays may be inadequate for neuropsychological testing of memory in people following TIA or minor stroke.

Visser and colleagues (2019) found significant ALF in post-resection TLE patients using the Rey Auditory Verbal Learning Test. After matching patients to controls on initial learning, they found normal rates of forgetting at 30-minute recall but impaired performance at 1 week. While previous research reported ALF in non-resected TLE or in mixed groups of resected and non-resected patients, this is the first report examining post-resection patients exclusively. Existence of overt seizures did not predict ALF in this group, but was associated with poorer performance during learning and short delay recall. Subclinical seizures could not be ruled out, nor was it possible to determine whether ALF was the result of pre-surgical impairment or an outcome of surgery. While future studies could address these important

questions, the present report illustrates the prevalence of the phenomenon in conditions other than TEA and non-resected TLE.

Memory for the personal past has a recognised impact on emotional and social well-being. **Gascoigne and colleagues** (2019) explored whether ALF may therefore be associated with behavioural difficulties in children with epilepsy. They collected behavioural questionnaire data from 43 children with either idiopathic generalised or TLE, and found positive correlations between a variety of problem behaviours (including 'internalising' and negative social behaviours) and patients' forgetting of a word list over 7 days. In an interesting contrast, standard neuropsychological test results were not associated with behavioural patterns. The authors suggest that further work is required to elucidate the effects that ALF may have on emotional and social well-being of patients with epilepsy.

ALF was also not associated with overt seizures in a longitudinal study by **Grayson-Collins and colleagues** (2019). Children with genetic generalized epilepsy were followed over 2-3 years and tested on the California Verbal Learning Test. Seizures abated or completely resolved over the duration of follow-up for many of the children, yet ALF remained unchanged. The advantage of a longitudinal design is that it allowed the authors to investigate predictors of continued ALF in this population. Baseline epilepsy severity, early onset of epilepsy and severity of ALF at baseline all predicted ALF at follow-up. These findings appear not to support models of ALF that emphasize the role of seizures in destabilizing memory trace consolidation. Instead, they may be more consistent with suggestions of generalized cortical impairments, which reduce the capacity for long-term memory formation. That said, a critical test still missing is one that would rule out sub-clinical paroxysmal activity. Moreover, it may very well be that ALF reflects more than one mechanism of forgetting.

Contrary to the study by Grayson-Collins, the longitudinal research study by **Savage and colleagues** (2019) reported in the current issue found that ALF subsides over a period of 10 years concomitant with successful pharmacological control of seizures in patients with TEA. This was apparent when performance was examined at an individual patient level, reflected both in self-reports of long-term memory impairments, and laboratory measures of ALF. Interestingly, improvement was also seen in episodic autobiographical memory for events occurring after successful use of anticonvulsant medication. The contradictory results between this and the previously mentioned longitudinal study could reflect differences between clinical populations: TEA is an adult onset form of epilepsy while Grayson-Collins' study involved children with genetic generalized epilepsy. It may be that the underlying mechanisms of ALF associated with early onset epilepsy are different from those associated with late onset epilepsy, as also suggested by Grayson-Collins' finding that ALF at follow-up was associated with earlier onset epilepsy.

Finally, an attempt to use behavioural interventions to remediate ALF is reported. **Ricci and colleagues** (2019) tested whether multiple short-term, post-encoding retrievals (with and without elaboration), and/or a long-term recall booster session improved memory performance in 3 patients with ALF. The prospect of effective remediation of ALF through well-known behavioral interventions is intriguing, and in particular the observation that early rehearsal (within 30 minutes of initial encoding) can confer benefits up to 2 weeks

post-encoding. Recent ideas suggesting that repeated recall (i.e. ‘the testing effect’) enhances memory through activation of prior knowledge and direct cortical learning (Antony, Ferreira, Norman, & Wimber, 2017) may also explain the slight advantage of the recall plus elaboration condition in the Ricci et al. study and speak to the question of whether ALF reflects generalized cortical impairment.

Conclusions

Whilst there is much to ponder over in each individual contribution to this Special Issue, it is helpful sometimes to forget details and rather to abstract (Borges, n.d.). The curation of this collection of articles has distilled in our minds three research questions that we believe need particular attention:

- 1) *Is ALF just a mild form of ‘typical amnesia’ or is it neuropsychologically distinct?* The answer to this will motivate all subsequent mechanistic research. In our opinion, the quest must be for double dissociations between early and late forgetting in different neurological populations;
- 2) *What is the definition of ALF and the ideal method to detect it?* This issue may only be resolved by interested researchers coming together to establish definitions and best practice. An important goal of this process should be the development of a standardised neuropsychological test for use in clinical practice;
- 3) *Is ALF one, or more than one thing?* If the latter, then generalisations are likely to be simplistic or, worse, misleading. Examination of the cognitive and neural landscape of ALF across large patient cohorts will be crucial and should address whether the neural mechanisms of ALF are the same across different aetiologies and also how forgetting rates vary according to the stimulus modality and testing method.

We are grateful to all who have contributed to this Special Issue and hope that it will go some way towards smoothing a path for future ALF research that will be, in the best traditions of neuropsychology, both scientifically fruitful and clinically useful.

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