Neurology® Clinical Practice

A peer-reviewed clinical neurology journal for the practicing neurologist
An Official Journal of the American Academy of Neurology

Neurology: Clinical Practice Publish Ahead of Print
DOI: 10.1212/CPJ.0000000000200081

Systematic review of accelerated long-term forgetting in children and adolescents with neuropediatric diseases

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Figure Count:1

Table Count:6

Search Terms:[199] All Neuropsychology/Behavior, [205] Neuropsychological assessment, [227] All Pediatric, [233] Adolescence, Accelerated long-term forgetting

Acknowledgment:

The authors would like to thank Tania Rivero, Information Specialist, University of Berne, for her support with questions concerning formal aspects of the systematic review. Furthermore, we would like to thank Susan Kaplan for her highly appreciated support with editing and formatting the manuscript.

Study Funding: The authors report no targeted funding

Disclosures:

N. Staehli reports no disclosures relevant to the manuscript. S. Bigi reports no disclosures relevant to the manuscript. S. Grunt reports no disclosures relevant to the manuscript. K. Lidzba reports no disclosures relevant to the manuscript. M. Studer reports no disclosures relevant to the manuscript.

Preprint DOI:

Received Date:2022-02-10

Accepted Date:2022-08-16

Handling Editor Statement:

Abstract

Purpose of review: Accelerated long-term forgetting (ALF) describes the phenomenon of normal learning and memory performance after short delays, but greater forgetting after longer delays which is not objectified in standardized memory tests. The topic is attracting increasing interest due to its clinical importance. Studies investigating pediatric ALF remain rare and no systematic review exists.
Recent findings: Based on our systematic literature search, twelve studies were found. Although most studies investigated ALF in children with epilepsy (n = 9), there is also evidence of ALF in children after traumatic brain injury (n = 1) and 22q11.2 deletion syndrome (n = 1).
Summary: To date, only a dozen of studies have investigated pediatric ALF. There is evidence that ALF is not an epilepsy-specific disorder, replicating findings of studies with adult patients. As ALF is missed using standardized assessments, we propose to add delayed time-points of testing memory performance.

List of Abbreviations

22q11.2DS = 22q11.2 deletion syndrome (= Di George's syndrome); ADHD = attention deficit hyperactivity disorder; AED =Anti-epileptic drugs; ALF = accelerated long-term forgetting; ASD = autism spectrum disorder; CMS = Children's Memory Scale; CVLT-C = California Verbal Learning Test for Children; IGE/GGE = idiopathic/genetic generalized epilepsy; FSIQ = Full-Scale Intelligence Quotient; LTM = long-term memory; NOS = Newcastle Ottawa Scale; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RAVLT = Rey Auditory Verbal Learning Test; TEA = transient epileptic amnesia;; TBI = traumatic brain injury; TLE = temporal lobe epilepsy; WRAML = Wide Range Assessment of Memory and Learning

Introduction

Accelerated long-term forgetting (ALF) is a recently identified memory phenomenon, describing an average memory performance after short delays (e.g., 30 min) followed by increasing forgetting of information over time (days to weeks).[1] Martin and colleagues (1991) first reported greater forgetting over a period of days in patients with epilepsy,[2] described as "long-term amnesia".[3] Blake and colleagues (2000)[4] subsequently introduced the term "accelerated long-term forgetting", which is now most commonly used. Most of the research on ALF has focused on adult epilepsy patients.[5] However, there is also evidence of ALF in patients with other neurological conditions such as hypoxic brain injury,[6] minor stroke,[7] traumatic brain injury,[8,9] or in the context of neurodegenerative disorders.[7,8,10–13] Thus, ALF does not seem to be an epilepsy specific disorder and exists in a variety of neurological impairments. Since standardized memory assessments investigate memory performance 20–30 minutes after learning, ALF may go undetected in clinical examinations using conventional memory tests.[5,14] Given that a delayed memory test may be a more sensitive measure than traditional memory assessments for detecting memory difficulties, it is important to include a delayed memory assessment in neuropsychological evaluation.

Despite the increasing number of studies on ALF, its underlying mechanism is still unclear, and findings remain debated.[15] Findings of impaired memory function at late delays are explained by problems of memory consolidation and it is assumed that ALF is caused by structural lesions or functional impairments or both.[15,16] However, there are also results supporting the hypothesis that ALF is rather a problem of memory retrieval[8] and may, therefore, be linked to executive functioning. Additionally, the influence of sleep on ALF is unclear. Given the fact that sleep, especially slow wave sleep, is known to be important for episodic memory consolidation by strengthening and stabilizing memories,[17,18] disrupted sleep might impair memory consolidation and might thus be associated with ALF. However, findings of studies analyzing associations between ALF and sleep remain controversial.[19,20] Furthermore, there are also inconsistencies in study findings about ALF due to methodological differences. Therefore, an earlier review emphasized the necessity for a systematic approach toward the evaluation of ALF, including standardized assessments and appropriate control groups.[5] Furthermore, there is no clear cut-off time after which ALF occurs and therefore long-delay assessments are performed at various time-points after learning. Numerous studies analyze the initial learning capacity and then memory performance after a delay of 30 min (as in standardized assessments) and after 7 days.[8,15] However, there is evidence that ALF may already occur 3-8 h[21] or 24h[22] after learning.

The core literature on ALF so far has focused on adults and several reviews on this topic have been published.[1,5,15] However, studies on pediatric ALF are still scarce, and to our knowledge, no review of ALF in children and adolescents has yet been performed. In light of the particular vulnerability to neurological conditions of the developing brain, the evaluation of ALF in the pediatric age group is of the utmost importance. Therefore, the aim of this systematic review was to assess published data on ALF in children and adolescents with neurological diseases. Based on previous findings in adults,[6–8,10–13,15] we hypothesized (1) that ALF in children and adolescents is not epilepsy-specific and (2) that ALF is not only a phenomenon of verbal memory.[15] Furthermore, we were

interested in whether delayed memory performance in children is associated with epilepsy variables, sleep or executive functioning.[15]

Methods

The review protocol was prospectively registered in the PROSPERO database for systematic reviews (protocol ID: CRD42021225706). This systematic review was carried out according to the PRISMA Guidelines, 2020.[23] Table 1 presents our search strategy based on the patient, intervention, comparison, outcome (PICO) framework.

Search Strategy

The literature search was performed within Embase (via Ovid), APA PsycInfo (via Ovid), and Ovid MEDLINE® on 12/07/2020, using the deduplication service provided by Ovid. To find further literature, we performed an additional search (on 02/20/2021) in Google Scholar, Web of Science Core Collection, the ProQuest Dissertation & Theses Global (PQDT)™ database, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), screening manually for duplicates. A repetition of the search on 12/05/2021 did not yield any additional results. The research question was divided into 3 concepts: children/pediatric/adolescents/teenagers, long-term forgetting, and consolidation. For each concept, we searched appropriate subject headings and synonyms for the free text search (e.g., "long-term amnesia" as a synonym for "long-term forgetting"[3]). To delimit search results and to ensure accessibility, publications had to comply with 3 limitations: human studies, publication date between 1990 and 2020, and full-text results. In the repetition of the search only the publication range was adjusted to 1990-2021. Table 2 illustrates the concepts of the search strategy and the limitations. Table 3 shows the exact search strategy and results for every step when searching the 3 databases via Ovid. The search strategy for additional sources can be found in Table 4.

Article Selection

After screening for duplicates, we retrieved 601 articles. Two reviewers (N.S. & M.S.) independently screened titles and abstracts for compliance with the defined eligibility criteria (see Table 5). In the case of uncertainty, the full article was assessed. Finally, the 2 reviewers screened the eligible articles independently for their reference lists. This backward citation search was done in Scopus, using the same eligibility criteria as for the initial search.

Data Extraction

Data extraction was done independently by the 2 reviewers, based on: underlying disease, sample size, time-points of testing, materials tested (verbal/non-verbal), outcome (recall/recognition), ALF found (yes/no), additional outcomes, strengths, and limitations. Each study was also assessed for information on the selection of participants (such as representativeness, recruitment process, comparability of patients and controls), the materials tested, and the methods used in the

assessments.[5] Quality of the nonrandomized studies included was evaluated using the Newcastle Ottawa Scale (NOS).[24]

The stepwise approach to potential inconsistencies was defined before starting the study and included first a discussion between the 2 independent reviewers and, in case of persistent inconsistencies, a consultation with other team members.

Results

Study Selection

Of the 601 articles initially identified, 12 were included in the final review. Details on the article selection process are given in Figure 1. All included articles were published after 2007 and investigated pediatric ALF in children with the following underlying conditions: epilepsy (n = 9), 22q11.2 deletion syndrome (n = 1), autism spectrum disorder (ASD, n = 1), and traumatic brain injury (TBI, n = 1). Details of these 12 articles are provided in Table 6.

Participants

Children with Epilepsy

Nine studies investigated ALF in children with epilepsy. In total, 255 children and adolescents with epilepsy were included (idiopathic generalized epilepsy [IGE]: n = 73, temporal lobe epilepsy [TLE]: n = 23, not further defined: n = 159). Six of these studies focused on genetic generalized epilepsies (GGE, or IGE respectively)[25–30] and one on TLE,[31] one compared IGE with TLE,[14] and one did not further classify epilepsy type.[32] Besides the etiology and medical treatment of the epilepsy, lateralization and severity[14,25,28–32] as well as EEG[14,31,32] and neuroimaging data[31,32] were analyzed to search for possible associations. Patients with other neurological conditions or a history of head injury were excluded,[28–30] as were patients with structural abnormalities seen on neuroimaging.[26,27] Four studies recruited patients from tertiary care institutions.[25,26,31,32] Controls were often recruited through peer networks and snowball systems[14,25,27,31] or via local schools.[25,28–30,32] One study did not state from where controls were recruited.[26] All but 2 studies excluded controls reporting seizures or with a family history of epilepsy.[25,32]

Two studies claimed a significant difference in sex ratio.[25,30] However, only Davidson and colleagues (2007) analyzed its influence on ALF.[30] One study provided no information on sex ratio.[28]

Children with other Diseases

Lah and colleagues (2017) investigated ALF in pediatric patients with TBI and reported their memory performance according to severity of TBI (mild/moderate or severe) in comparison to healthy controls. Williams and colleagues (2017) compared the memory performance of children with ASD to that of controls.[33] Maeder and colleagues (2020) grouped children with 22q11.2DS depending on their general cognitive functioning and compared a group with high global functioning (HIGH-subgroup) to a group with lower global functioning (LOW-subgroup). The cognitive performance of both groups was also compared with that of controls.[34]

Participants with a positive history of seizures[8] or other developmental, psychiatric, genetic, metabolic or neurological disorders (including prematurity), were excluded.[8,33] Two studies excluded controls who had a history of TBI, other developmental or neuropsychiatric disorder, or problems in school.[8,33] Other reasons for exclusion included medication usage and family history of ASD in first-degree relatives or further developmental or neurological disorders with a genetic component.[33]

In contrast, one study reported no further information about the neurological or psychiatric condition of controls.[34] Controls were community controls,[33] siblings of participants or of community controls, or were recruited via passive snowballing.[8,34]

The sex ratio of the participants in these 3 studies is comparable.[8,33,34]

Assessment

Materials

Episodic verbal recall was tested in every study using wordlists (modified CVLT-C,[35] modified RAVLT[36]) or stories (iter-SEIN,[32] CMS,[37] WRAML,[38] WMS-III[39]). Nine of the 12 studies also investigated verbal recognition.[8,14,25–30,34]

Figural memory recall was tested in 5 studies, all of which investigated children with epilepsy.[25,28–31] Four different assessments were used (scene memory,[40] spatial memory,[41] dot locations,[37] and the spatial object location task[29]). Figural recognition performance was not assessed.

Time-points and learning criteria

Ten of the 12 studies evaluated long-term memory performance after a 7-day delay.[8,14,27–31,33,34] One of them had a longitudinal design and followed up memory performance (including a delayed recall 1 week after learning) 2 years later.[26] Two studies used a different time-point to assess delayed long-term memory performance: One assessed long-term memory after 2 weeks[25] and, the other, patients were tested either after 2 days or 1 week, whereas controls were tested on both day 2 and day 7.[32] Four studies assessed recognition performance at more than one time-point.[28–30,34]

Learning criteria differed between the studies, spanning from 70–100% (see Table 6). Studies often examined the learning efficiency of their participants, meaning that the number of learning runs needed to reach the learning criterion were analyzed. Whereas, for verbal memory, 5 studies found comparable initial learning between patients and controls,[14,27–29,34] 4 studies found a significantly different number of learning runs needed.[8,25,30,31] A few studies did not mention initial learning performance,[26,32] or no learning criterion was defined.[33] In studies assessing figural memory, 4 studies found no difference in learning runs compared to healthy controls.[25,28–30] In contrast, one study found that significantly more children with TLE failed to reach the learning criterion compared with healthy control children.[31]

ALF Findings

Verbal Recall and Recognition

Six studies reported an impaired verbal recall performance in patients with epilepsy as compared to healthy controls at the delayed testing time-point.[14,26–28,31,32] One study found evidence for ALF;

however, statistical significance was not reached due to small sample size.[29] Two studies investigating children with GGE did not find ALF[25] or it was no longer observable after controlling for learning.[30] Additionally, Grayson-Collins and colleagues (2019) concluded from their longitudinal study in GGE patients, that ALF occurred at the follow-up time-point 2 years after initial assessment, but not at baseline testing. One study compared GGE with TLE patients and found ALF in children with TLE, but not GGE.[26] In studies of children with other diseases, ALF was found in those with 22q11.2DS and in children who had severe TBI, but not in children who had mild–moderate TBI.[8] Furthermore, no ALF was found in children with ASD.[31]

In 3 out of 9 studies there was evidence for impaired verbal recognition performance 1 week after learning.[14,27,34] In 5 studies, verbal recall at the delayed time-point was reduced while verbal recognition performance in these studies appeared to be intact.[8,26,28–30]

Figural Recall and Recognition

Of the 5 studies assessing ALF using figural material, 1 observed ALF[25] whereas the other 4 reported normal performance in tests of visual recall.[28–31]

Associated Findings

Some authors investigated additional factors associated with ALF. The findings of the 9 studies on epilepsy were conflicting: Whereas some found a negative correlation between recall performance and epilepsy severity,[26,32] 1 study found no such association.[27] Impaired long-term memory performance correlated with additional clinical variables, such as presence of status epilepticus,[28] abnormalities in MRIs,[8,31,32,34] longer duration of epilepsy,[26] and epilepsy activity.[27,32] Nevertheless, Grayson-Collins and colleagues (2019) found that seizure freedom can be linked to ALF as some participants were seizure-free at follow-up.[26] One study found that patients with left-sided TLE had an impaired verbal recall after short and long delays compared to healthy controls, but that patients with right-sided TLE did not.[31] However, these findings could not be replicated by other groups. A further correlation was reported between verbal recall performance 1 week after learning and temporal lobe resection.[31] As the performances immediately and 30 min after learning were comparable, surgery may be a further risk factor for the occurrence of ALF.

Cognitive and behavioral correlates of ALF were also reported. One study found a correlation between executive functioning and delayed figural recall.[25] Another study found an association between low full-scale intelligence quotient (FSIQ) and poorer recall performance after the 7-day delay but not after the 2-min and 30-min delay.[31] Furthermore, 1 study found an association between behavior problems and verbal recall performance 1 week after learning.[14] Additionally, Maeder and colleagues (2020) found the subgroup with lower global memory performance displayed significantly more positive psychotic symptoms than the subgroup with higher global memory performance or controls. No association with negative psychotic symptoms could be identified.[34]

Findings regarding age differ between studies: One study found older children showed better memory performance after longer delays.[32] However, Gascoigne and colleagues (2014) found a negative correlation between the age of children with TLE and recall performance after both short and long delays, meaning that older age may be associated with worse memory performance.[31] In pediatric TBI patients, the combination of lower Glasgow Coma Scale (GCS) and diffuse subcortical

injury was associated with greater declines in the proportion of words recalled from 30 min to 7 days.[17] Furthermore, patients with a steeper verbal memory decline showed significant reductions of left and right global hippocampal volume.[34]

Critical Appraisal

Study quality was limited for most studies reported since none of them achieved all 4 stars in the NOS (see Table 6). The main information missing related to the representativity of cases and controls. For example, no study reported the number of children initially contacted. Furthermore, it was not stated whether children who participated were comparable to those who refused to participate.

Discussion

ALF is a relatively recently identified memory phenomenon and describes accelerated forgetting over time after an initially normal learning and memory performance.[1] To date, most studies have investigated adult patients and information on the occurrence of ALF in childhood and adolescence is scarce. Our systematic review was based on 12 studies investigating pediatric populations and revealed the following main findings: The phenomenon of ALF does exist in children and adolescents. As expected from the literature on adults, 6 of 9 studies on children with epilepsy documented ALF.[14,26–28,31,32] However, evidence is emerging that other patient groups may experience ALF, such as children who have had severe TBI[8] or children with the 22q11.2 deletion syndrome,[34] while, in children with ASD, memory performance after 1 week was comparable to that of controls.[33] ALF was primarily found in studies using verbal recall assessments. Only 5 out of 12 studies investigated figural recall performance at a delayed time-point after learning, and only in one study ALF was found.[25]

As stated above, most studies investigated delayed episodic memory performance with verbal memory tests. Due to the variety of verbal memory assessments used, an overall comparison is not possible. However, ALF was detected with different assessments, indicating that it was not just a phenomenon associated with a particular test. Consistent with the definition of ALF, children would have been missed by a standardized assessment, as their learning and memory performance was comparable to controls at standardized testing times, but worsened after a longer delay.[8,31]

To date, none of the available standardized verbal and figural memory tests for children and adolescents provide normative data for a recall after more than 30 minutes delay. Delayed verbal memory performance was tested using standardized (CMS stories,[37] storytelling test,[42] WRAML story recall[38]) or adapted standardized verbal memory tests (modified CVLC-T,[35] modified RAVLT[36]) by adding a second delayed recall condition. However, figural memory performance was investigated in most studies using experimental tasks,[29,41] which were based on pilot studies with very small sample sizes.[29] Furthermore, encouraging participants to name the objects while learning could have led to an additional verbal consolidation, meaning that not only was visual memory tested but also verbal memory, which could have masked forgetting due to encouraging encoding in two modalities.[32.] ALF related to figural memory was only found using the Scene Memory task which might offer greater sensitivity due to higher ecological validity.[25] Consequently, possible impairment of visual memory performance in studies using other tasks could have been masked. More studies are therefore needed to investigate whether ALF also pertains to figural memory in children.

Six studies used a learning criterion of 100%,[8,14,25–27,31] meaning that material is presented repeatedly until the learned material is perfectly recalled. This procedure poses the risk of overlearning and may thus lead to underestimation of forgetting within the first hours after learning.[5] Furthermore, this kind of learning criterion may impede ability to detect ALF, as shown in one study using a learning criterion of a maximum of 12 learning runs.[25] Also, a learning criterion of 90% is still very likely to cover ceiling effects.[28,30,33] Besides potential overlearning, it could also be that the task was too easy. The approach to control for initial learning could help to hold learning performance constant, without inducing overlearning that could mask impaired memory performance after shorter delays.[30] In one study, although almost one quarter of children (4/17) failed to meet the learning criterion, they were tested as well, possibly distorting the results.[25] Only 3 studies tested long-term memory earlier than 1 week: either after one day[25,42] or after two days.[33] However, none of these studies found evidence for ALF at an earlier time-point than 1 week. Findings in children, therefore, contrast adult results where ALF was also detected at an earlier time-point.[21,22] Our results indicate that one week after learning seems to be an ideal time-point to assess delayed memory performance which appears clinically feasible. Furthermore, it should be considered, that repeated testing may prevent memory loss[5] and could therefore bias the results.

Studies investigating recall and recognition performance[8,14,25–30,34] sometimes reported impaired recall but preserved recognition performance,[8,25,26,28–30] which implies that ALF might be a problem of retrieval rather than a consolidation impairment.[8,25] However, recognition was only assessed for verbal but not for visual stimuli. Future studies should investigate recall and recognition for both modalities to gather more information to assess the hypothesis of ALF being a retrieval problem, rather than an issue of memory consolidation. If ALF reflects a retrieval impairment, it could be related to executive dysfunctions.[26] Although executive dysfunctions are known to be common in children with epilepsy,[43,44] only 1 study looked for and found a positive association between executive functions and delayed memory performance after 1 week in children.[25] It seems reasonable that better executive functions may lead to a better organization of the material that enhances encoding and may thus facilitate retrieval.[25] It is possible that epileptic discharge could interfere with memory consolidation and may thus reduce episodic long-term consolidation over time. Furthermore, there is evidence that epilepsy is related to impaired theory of mind, possibly affecting neural networks that underlie social cognition as well.[45] Thus, pediatric epilepsy could interfere with neural networks for memory consolidation and social cognition. Besides effects on social cognition, a recent study reported an association between behavior problems and ALF in children with epilepsy.[14]

So far, no data exists about the relation between sleep and ALF in pediatric samples, although it is known that sleep is a crucial factor for memory consolidation.[46] For example, children with 22q11.2DS are known to have more frequent sleep disturbances, which could impact memory consolidation over time.[47] In adults, there are only few studies in epilepsy patients investigating the association between sleep and ALF, with controversial findings. For example, one study of patients with transient epileptic amnesia (TEA) found enhanced ALF after sleeping,[20] while another study found beneficial effects of sleep on memory performance in patients with TEA[19] and even short naps.[48] Studies with findings of enhanced ALF after sleep described increased epileptic activity, that tends to occur during sleep and which in turn may disrupt important mechanisms strengthening memory traces

during sleep.[20,49,50] Thus, there is evidence that processes interfering with memory consolidation during sleep might increase the risk of ALF. However, there is also data indicating that ALF can occur already within hours after learning, contradicting the hypothesis that impaired sleep leads to ALF,[21] which outlines that further research in non-epileptic pediatric and adult patients investigating the influence of sleep on ALF is needed.

Knowledge about the neural foundation of ALF is scarce and it is not known whether ALF is caused by functional changes, structural damage or both.[15] In children who had had severe TBI, ALF was related to diffuse subcortical injuries in the acute stage, but not to frontal and temporal injuries.[8] Nevertheless, there was a tendency for children with frontal injuries to exhibit a greater decline in verbal recall over 1 week. Although these results were based on a brain scan shortly after the injury (while the psychological testing was nearly 5 years after the injury), ALF may occur not only as a result of focal damage in the cortex but also because of an impairment of the interactions between cortical regions.[8,51] Associations between the laterality of seizures and ALF were controversial.[14,31,32] Children with GGE did demonstrate ALF, contrary to findings in adults with GGE.[52] Children might therefore outgrow the phenomenon, supporting the findings of another study reporting a possible association between older age and better memory performance.[31] However, one study found a correlation of words recalled after a 7-day delay with epilepsy severity at baseline and younger age at seizure onset. It did not correlate with active seizure at follow-up.[26] These findings could suggest that ALF may not be seizure-related and that longitudinal studies are needed to investigate neuronal correlates and the impact of age on ALF.

Despite having scanned so many resources, our systematic literature search found only a few studies with small sample sizes, originating from a few research groups. Six articles (5 studies investigating ALF in children with epilepsy (IGE: n = 1;[27] TLE: n = 1;[31] IGE and TLE: n = 1,[14] GGE: n = 2 [25,26];) and 1 study investigating ALF in children after TBI[8] came from the research group of Prof. Sunica Lah, Australia. On request, we were informed that in the comparison study,[14] the initial sample of children with GGE[27] or the initial sample of children with TLE[31] were included. Furthermore, most children in the follow-up study[26] were from the earlier study investigating pediatric ALF in children with GGE.[27] The overlap of individuals exists also in controls. Therefore, the number of individuals included is rather small. In addition, although the intake of anti-epileptic drugs (AEDs) was considered, no study analyzed a possible association between AEDs and ALF. Moreover, in studies investigating non-epilepsy patients, no information about subclinical epileptiform discharges was available. Overall, sample sizes were very small, making it nearly impossible to do sub-analyses. Furthermore, Grayson-Collins and colleagues (2019) imputed missing data despite the small sample sizes, which can lead to biases.[26] Additionally, even though sex may influence memory performance,[53] only one study investigated its influence on long-term memory performance.[30] Future studies should assess the influence of sex on the memory performance after a 7-day delay.

Some limitations of the review process used should be mentioned. First, due to the limitation to full-text results in the databases accessed via Ovid, additional data might have been missed. Second, other sources were only scanned for the exact term “accelerated long-term forgetting”. However, by consulting 3 databases via Ovid and 4 additional sources (Google Scholar, Web of Science, ProQuest, WHO ICTRP), literature was searched in more sources than in numerous other

systematic reviews. Despite having scanned so many resources, only a small number of results were obtained due to relatively strict adherence to the predefined eligibility criteria. In particular, the time-points at which memory performance was assessed led to many exclusions: While clinical tests often did not exceed 30 minutes,[54] other studies were identified that lacked data on performance after a short delay and only assessed memory after a longer delay, e.g., 12 hours.[55] Nevertheless, due to the extensive literature search, we consider that the selected articles are a solid foundation for the systematic review – the limited number of research articles highlights that research on pediatric ALF has only just started.

Conclusion

ALF is not an epilepsy-specific disorder and it occurs in both children and adults[7,12] with various neurological disorders. However, research on pediatric ALF is still scarce and further investigation is needed. Nevertheless, we propose including the assessment of delayed long-term memory performance in standardized neuropsychological assessments by adding normative data for recall after delays longer than 30 minutes. With evidence not only for verbal, but also visual material, both modalities should be investigated in further studies. Since the underlying neural pathophysiology is not understood, future studies should assess the neural basis of ALF.

Take Home Messages

- ALF describes the phenomenon of impaired long-term memory despite normal learning and memory performance in standardized memory assessments. ALF occurs in children and adults with various neurological disorders and recent findings suggest that ALF is not a seizure dependent phenomenon.
- The origin of ALF needs further investigation as it is not yet understood whether ALF is caused by structural impairments or functional problems or a combination of both mechanisms.
- Future studies should investigate the influence of sleep and executive functioning to gather more information to determine whether ALF is a problem of memory consolidation or rather of memory retrieval.

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Tables

Table 1: PICO Framework

Population	Children and adolescents (aged 6 to 18 years) with neurological conditions or an acquired brain lesion
Intervention	Episodic memory performance at distinct points in time (immediate, 30 min delay, 24 h to 1 week delay)
Comparison	Healthy children and adolescents (aged 6 to 18 years)
Outcome	Forgetting between learning and free recall or recognition 30 min after learning and 24 h/1 week after learning

Table 2: Concepts for the Search Strategy

Concepts	Subject headings	Free text
Children, pediatric, adolescents, teenager	Child/ Pediatrics/ Adolescent/	(child* or p?ediatric* or adolesc* or teenager*).mp.
Long-term forgetting	*long-term memory/ o * = Focused subject heading Long-term memory/ o This was too broad, therefore the focus (*) Memory disorder/ o too broad, even if focused	(accelerated long-term forgetting or long-term amnesia or long-term forgetting).mp.
Consolidation	Memory consolidation/ o too broad, even if focused	(Long-term adj3 consolidation).mp.
Limitations		
o Human, excluding animal studies o Publication year: 1990–2020, as not described before o Full text only		

Table 3: Search Strategy for Embase (via Ovid), APA PsycInfo (via Ovid), Ovid MEDLINE ® ALL

Search History	Term	Results
1	(child* or p?ediatric* or adolesc* or teenager*).mp.	8372152
2	Child/ or Pediatrics/ or Adolescent/	5555643
3	1 or 2	8372152
4	(accelerated long-term forgetting or long-term amnesia or long-term forgetting).mp.	398
5	*long-term memory/	9801
6	(Long-term adj3 consolidation).mp.	1838
7	4 or 5 or 6	11607
8	3 and 7	1490
9	limit 8 to human	1415
10	limit 9 to yr="1990 - 2020"	1239
11	remove duplicates from 10	998
12	limit 11 to full text	552

Table 4: Search Strategies for Additional Sources

Source	Search strategy
Google Scholar	(children OR adolescents) AND "Accelerated long-term forgetting"
Web of Science	((Children OR Adolescents) AND "Accelerated long-term forgetting")
ProQuest	(children OR adolescents) AND "Accelerated long-term forgetting"
WHO ICTRP	(children OR adolescents) AND "Accelerated long-term forgetting"

Table 5: Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
1. Episodic memory tested immediately, after 30 min delay and after a delay of 24 h or longer 2. Children and adolescents, aged 6 to 18 years 3. Publication between 1990 and 2020	1. Memory performance not tested at distinct time-points 2. Animal studies 3. Outside specified age range (adults, preschoolers/infants/toddlers) 4. Conference abstracts 5. Reviews 6. Case reports

Table 6: Included Studies

Reference	Disease	Sample Size	Age (years)	FSIQ	Testing		Verbal			Non-verbal			NOS (x/4)
					Time-points	Learning Criterion	Test	Recall + ALF Findings	Recognition + ALF Findings	Test	Recall + ALF Findings	Recognition + ALF Findings	
[25]	GGE	17 P vs. 25 C	8–16	>79	Immediate, 30min, 1d, 2w	*Verbal*: 100% accuracy in one of max. 12 trials *Non-verbal*: 100% accuracy, max. 10 trials	Modified CVLT-C	X ALF: no	X (only at 2w) ALF: no	Scene Memory	X ALF: 1 day and 2 weeks	N/A	***
[26]	GGE	18 P vs. 29 C	5–18	>79	Immediate, 30min, 7 days + follow-up approx. 2 years later	100% recall on 2 consecutive trials or max. 12 trials	Modified CVLT-C	X ALF: at 7 days-delay at follow-up	X (only at 7 days) ALF: no	N/A			**
[14]	TLE & IGE	TLE 23, IGE 20, C 58	6–18	>80	2min0, 30min 7 days	100% recall on 2 consecutive trials or max. 12 trials	Modified CVLT-C	X ALF: at 7 days-delay	X (only at 7 days) ALF: yes	N/A			***
[32]	Epilepsy	59 P vs 126 C	4–10	>75	C: immediate, 20-30min, 24h, 1w P: immediate, 20-30min, 24h or 1w	Minimum number of presentation n= 3, max. = 4, if >90% is answered correctly, testing may be limited to 3 trials	iter-SEIN (Story telling test)	X ALF: at 7 days	N/A	N/A			***
[31]	TLE	23 P vs. 60 C	6–16	>80	immediate (learning), 2 minutes, 30min, 7 days	*Word recall and* design location: 100% recall on 2 consecutive trials or max. 12 trials	Modified CVLT-C	X ALF: at 7 days	N/A	Spatial memory task	X ALF: no	N/A	***

Table 6: Included Studies

Reference	Disease	Sample Size	Age (years)	FSIQ	Testing		Verbal			Non-verbal			NOS (x/4)
					Time-points	Learning Criterion	Test	Recall + ALF Findings	Recognition + ALF FIndings	Test	Recall	Recognition	
[27]	IGE	20 P vs. 41 C	6–16	>79	Immediate, 30 min, 7 days	100% recall on 2 consecutive trials or max. 12 trials	Modified CVLT-C	X ALF: at 7 days	X ALF: at 7 days	N/A			***
[28]	IGE	10 P vs 12 C	7–15	>70	Initial learning, 30 min, 7 days	*Verbal*: 90% accuracy over a min. of 2 following trials *Dot location*: minimum of 2 and maximum of 10 consecutive trails 83% accuracy, *Spatial object-locations task:* minimum of 2, max. of 10 consecutive trails, 70% accuracy (within 34mm range)	CMS Stories	X ALF: at 7 days	X (30min + 7 days) ALF: no	Dot location (CMS) + spatial object location task	X ALF: no	N/A	**
[29]	IGE	5 P vs 7 C	5–17	>70	Initial learning, 30 min, 7 days	*Verbal*: 90% accuracy over a minimum of 2 consecutive trials *Dot location*: minimum of 2 and maximum of 10 consecutive trails 83% accuracy, *Spatial object-locations task*: minimum of 2, max. of 10 consecutive trails, 70% accuracy (within 34mm range)	CMS Stories	X ALF: at 7 days, but not significant due to small sample size	X (30min + 7 days) ALF: no	Dot location (CMS) + spatial object location task	X ALF: no	N/A	**

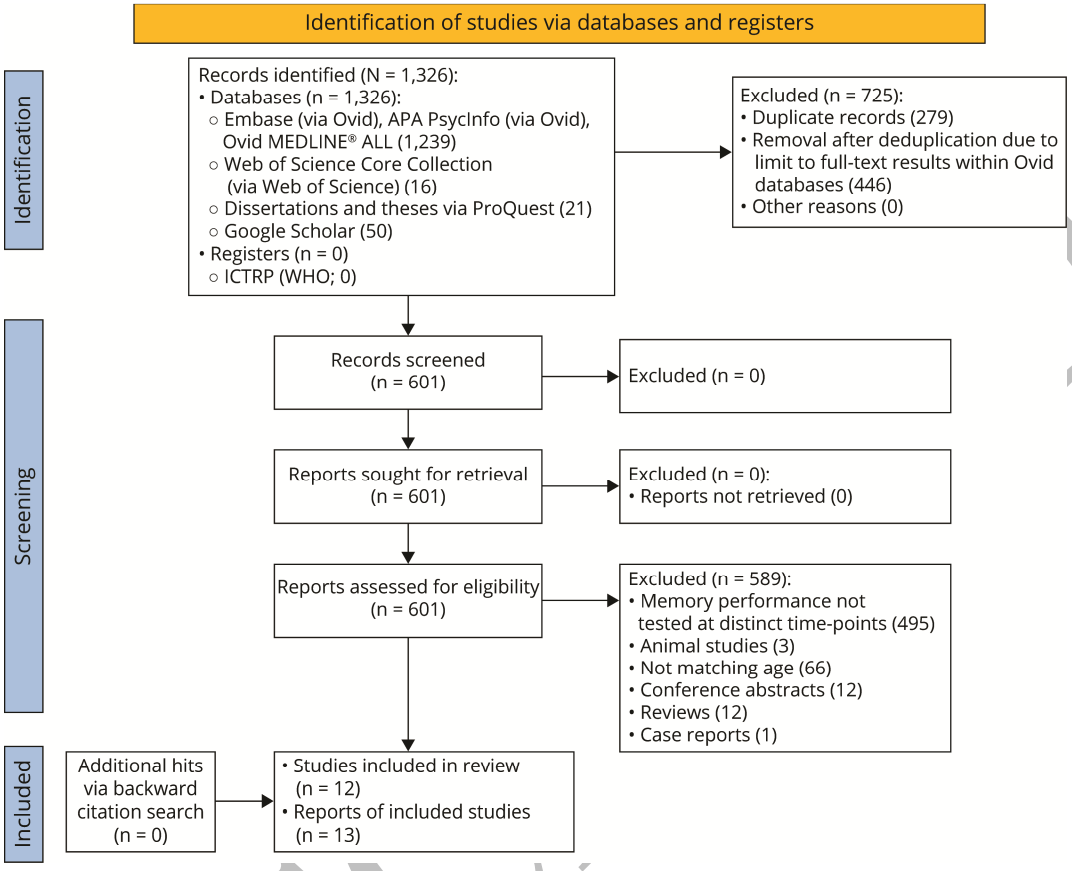
Table 6: Included Studies

Reference	Disease	Sample Size	Age (years)	FSIQ	Testing		Verbal			Non-verbal			NOS (x/4)
					Time-points	Learning Criterion	Test	Recall + ALF Findings	Recognition + ALF Findings	Test	Recall	Recognition	
[30]	IGE	21 P vs 21 C	6–16	>70	Initial learning, 30 min, 7 days	*Stories*: 90% accuracy *Dot location*: 82% accuracy Both on 2 consecutive trials over max. 10 trials	CMS Stories	X ALF: at 7 days, but not after correction for learning to criterion	X ALF: no	Dot Location (CMS)	X ALF: no	N/A	***
[34]	22q11.2DS	45 P vs 39 C	8–24	Tested No criterion	Encoding Recall 30 min, 1 day, 7 days,1month	80% success criterion or max. 6 trials	Adapted RAVLT	X ALF: at 1 day + 1 month	X (at all time-points) ALF: at 30 min + 1 month	N/A			***
[33]	ASD	47 P vs 31 C	9.19-16.96 (Mean 12.57) bzw. 16.93-52.26 (mean 25.44)	Tested No criterion	Immediate, 30 min, 2 days	N/A	WRAML (5–17 y) Story recall and WMS-III (16–89 y) logical memory I & II	X ALF: not significant	N/A	N/A			**
[8]	TBI	28 P (3 mild TBI, 12 moderate TBI, 13 severe TBI) vs 62 C	8–16	Tested No criterion	Learning, 2 min, 30 min, 7 days	100% recall on 2 consecutive trials or max. 12 trials	Modified CVLT-C	X ALF: x, sTBI already at 30 min (sTBI vs NC)	X ALF: no	N/A			***

22q11.2DS = 22q11.2 deletion syndrome (= Di George's syndrome); ADHD = attention deficit hyperactivity disorder; AED = anti-epileptic drugs; ALF = accelerated long-term forgetting; ASD = autism spectrum disorder; C = controls; CMS = Children's Memory Scale; CVLT-C = California Verbal Learning Test for Children; IGE/GGE = idiopathic/genetic generalized epilepsy; FSIQ = full-scale intelligence quotient; LTM = long-term memory; N/A = not applicable; NOS = Newcastle Ottawa Scale; P = participants; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RAVLT = Rey Auditory Verbal Learning Test; sTBI = severe traumatic brain injury; TBI = traumatic brain injury; TLE = temporal lobe epilepsy; vs = versus; WRAML = Wide Range Assessment of Memory and Learning; X = was assessed

Figure Legend

Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources[19]



Systematic review of accelerated long-term forgetting in children and adolescents with neuropediatric diseases

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Neurol Clin Pract published online October 12, 2022
DOI 10.1212/CPJ.0000000000200081